Analyses prospectives de mortalité : approches actuarielle et biomédicale

Edouard Debonneuil

N°d'ordre NNT : 2018LYSE1096

THESE de DOCTORAT DE L'UNIVERSITE DE LYON

opérée au sein de

l'Université Claude Bernard Lyon 1

Ecole Doctorale N° 486

Sciences économiques et de gestion

Spécialité de doctorat : Sciences actuarielles

Discipline : Sciences de Gestion

Soutenue publiquement le 25/06/2018, par :

Edouard DEBONNEUIL

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Résumé

La durée de vie humaine tend à augmenter dans le monde depuis quelques siècles. Cette augmentation a été plus importante que ne le prédisaient les spécialistes qui ont énoncé des limites à l'âge humain et ces limites ont été régulièrement dépassées. La baisse de la mortalité a d'abord concerné les enfants en bas âge, puis les âges inférieurs à 65 ans, et maintenant les âges les plus avancés. Ces étapes se voient sur l'historique de la mortalité.

Malgré les incertitudes importantes sur l'avenir de la longévité, un moteur prometteur actuellement est celui de la biologie du vieillissement et ses applications. Une partie des travaux de cette thèse a consisté à documenter ces avancées, ce qui a fait l'objet d'un article (voir Moskalev (2017)) et à mettre ces avancées en perspective, avec des enjeux actuariels. L'industrie pharmaceutique prend conscience du potentiel des innovations biomédicales issues de la biologie du vieillissement et de grands acteurs de la pharmacie investissent en rachetant des biotechs et en développant leurs propres équipes internes. Ceci pourrait accélérer l'allongement de la vie.

En parallèle, les modèles des actuaires de type Lee Carter (1992) tendent à prédire une décélération de la longévité. Une partie de cette thèse a consisté à analyser les causes mathématiques de cette décélération artificielle. En partant d'un modèle ne produisant pas de décélération (voir Bongaarts (2014)), plusieurs modèles de mortalité future sont ici développés, qui produisent des augmentations constantes d'espérance de vie. Testés sur des pays de l'OCDE sur plusieurs décennies, il apparait qu'une augmentation voisine d'un trimestre par an était jusqu'à présent un meilleur prédicteur que les tendances de chaque pays. Les tables de mortalité généralement utilisées par les actuaires ne produisent pas ces tendances, et sont loin de représenter des avancées majeures issues de la biologie du vieillissement.

L'évolution de la longévité a bien sûr un impact significatif sur certains dispositifs de protection sociale, dont en premier lieu la retraite. Pour les systèmes de retraite par répartition le ratio actifs / inactifs diminue et met en risque l'équilibre de ces régimes ; les leviers d'action sont connus mais sensibles politiquement. Pour les régimes par capitalisation, le ratio durée de vie en retraite / durée de vie active augmente, ce qui rend difficile la constitution d'un capital suffisant pour assurer des rentes viagères. Au cours de cette thèse nous avons pu estimer des impacts, sur des réserves par exemple, en fonction de l'avenir de la durée de vie. Si les impacts sont importants, à moyen terme ils restent limités y compris dans le cadre d'un scenario d' "échappement de la longévité" où les espérances de vie dépassent significativement 100 ou 120 ans.

Les efforts pharmaceutiques en cours pour appliquer les résultats de la recherche biomédicale peuvent être craints du fait de leurs impacts sur les retraites. Cependant, le financement de ces efforts par les fonds de pension pourrait justement améliorer la performance des fonds et subvenir en partie aux besoins de financement des retraites. Un instrument permettant ces échanges financiers entre le monde biomédical et le monde actuariel a été décrit : le méga fonds de longévité. Il s'agit de financer un grand nombre de développements pharmaceutiques afin de bénéficier d'une mutualisation des risques cliniques et de capter financièrement les succès biomédicaux. Nous étudions ici dans quelle mesure un méga fonds de longévité peut répondre aux besoins.

Title in English

Prospective analysis of longevity: actuarial and biomedical approaches.

Summary

The human lifespan has been increasing in the world for several centuries. This increase was greater than predicted by specialists who set limits to human age, and these limits were regularly exceeded. The increase in mortality first involved infants, then the ages below 65 and now the more advanced ages. These stages are observed in the mortality history.

Despite the significant uncertainties about the future of longevity, a promising driver currently is that of the biology of aging and its applications. Part of the work of this thesis has been to document these advances, which was the subject of an article (see Moskalev (2017)) and to put these advances in perspective with actuarial issues. The pharmaceutical industry is becoming aware of the potential of biomedical innovations stemming from the biology of aging, and major players in pharmacy are investing in biotechs and developing their own internal teams. This could accelerate life extension.

In parallel, models of actuaries such as Lee and Carter (1992) tend to predict a deceleration of longevity. Part of this thesis was to analyze the mathematical causes for this artificial deceleration. Starting from a model that does not produce deceleration (see Bongaarts (2014)), several models of future mortality are developed here, which produce constant increases in life expectancy. Tested over OECD countries over several decades, it appears that an increase of around one quarter per year was, until now, a better predictor than the trends in each country. The mortality tables generally used by actuaries do not produce these trends, and are far from representing major advances stemming from biology of aging.

The evolution of longevity has of course a significant impact on some social protection schemes, in the first place on retirement. For pay-as-you-go pension systems the ratio of active to inactive decreases and puts the balance of these schemes at risk; the levers of action are known but are politically sensitive. For funded schemes, the ratio of retirement period to active life increases, making it difficult to build sufficient capital to provide life annuities. During this thesis we have been able to estimate impacts, for example on reserves, depending on the future of the life span. If the impacts are significant, in the medium term they remain limited, including in the context of a "longevity escape" scenario where life expectancy is significantly higher than 100 or 120 years.

Current pharmaceutical efforts to apply the results of biomedical research may be feared because of their impact on pensions. However, the financing of these efforts by pension funds could improve the performance of the funds and partially meet the retirement financing needs. An instrument allowing these financial exchanges between the biomedical world and the actuarial world was described: the longevity mega fund. It involves funding a large number of pharmaceutical developments in order to benefit from the pooling of clinical trial risks and therefore to financially capture biomedical successes. Here we study to what extent a mega longevity fund can meet the needs.

Mots clés

Longévité, vieillissement, taux de mortalité, biologie du vieillissement, industrie pharmaceutique, modélisation, Lee Carter, méga fonds, tendance, essais cliniques, développements biomédicaux.

Key words

Longevity, mortality rates, biology of aging, pharmaceutical industry, Lee Carter, megafund, trend, clinical trials, biomedical developments.

Cette thèse a été préparée au laboratoire LSAF: Laboratoire de Sciences Actuarielle et Financière (numéro EA2429)

Remerciements

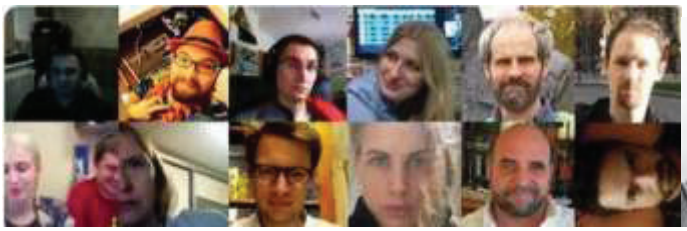
Je tiens d'abord à remercier mon directeur de thèse, Frédéric Planchet, pour son soutien et dévouement tout au long de la thèse. Toujours présent et toujours avec des solutions face à des sujets techniques parfois complexes, il m'a permis d'aller plus loin que l'objectif initial de la thèse sur bien des aspects.

Je tiens également à remercier mon co-directeur de thèse, Stéphane Loisel, pour son exigence et soutien simultanés, et son audace discrète pour provoquer la rencontre avec par exemple Ronald Lee (dernier survivant du fameux modèle « Lee Carter » (1992) de projection de mortalité), Nicole El Karoui (mathématicienne reconnue en matière de finance, démographie et processus aléatoires, qui rapidement m'a conforté dans l'idée de m'appuyer sur mes convictions personnelles dont l'importance de la santé, et l'intérêt de lier le risque de longévité à un système de financement de la santé), et Alexander Zhavoronkov (ami et créateur de Insilico Medicine, entrepreneur et visionnaire quant aux sujets relatifs à cette thèse, qui m'a poussé à avancer sur la thématique du méga fonds et m'a mis en relation avec des milieux très divers et complémentaires).

Je tiens à remercier les collectifs de recherche **côté actuariat** pour leur sympathie, bienveillance, et pour les échanges fructueux que nous avons pu avoir ensemble. Je pense notamment au laboratoires de Sciences Actuarielle et Financière à Lyon (SAF), au Laboratoire de Probabilités et Modèles Aléatoires à Paris (LPMA, aujourd'hui LPSM), et au groupe de recherche Lolita (Dynamic models for human Longevity with Lifestyle Adjustments, très à propos de cette thèse). Cette photo prise à Lyon lors de la conférence Longevity 11 et actuellement disponible sur http://lolita.isfa.fr/ illustre parfaitement ces liens. Mes amitiés à ces personnes.

Je tiens à remercier les collectifs de recherche **côté biomédical**, pour leur sympathie et bienveillance également, et les actions que nous avons pu réaliser ensemble. Et, « la

providence », qui m'a mis sur le chemin de ces aspects, en me faisant notamment brièvement travailler avec Cynthia Kenyon (à propos de tests de longévité sur nématodes, aujourd'hui responsable scientifique de CALICO, la branche antivieillissement de Google ou plutôt Alphabet), Barri Merriman (ex-professeur de UCLA, discret mais très technique et visionnaire, avec qui j'avais procédé à des analyses de données d'expression des gènes lors du vieillissement, aujourd'hui un responsable scientifique chez Human Longevity, Inc), Andrew Lo (professeur de finance au MIT, auteur et porteur du concept de megafund, en particulier le Cancer Megafund, structure proposée ici pour le financement de la santé et des retraites), Aubrey de Grey (ambassadeur et rassembleur international de la biologie du vieillissement ou plutôt d'ailleurs de la longévité), Alexander Zhavoronkov (que j'ai déjà remercié), Augustin Terlinden (ami et entrepreneur belge), Iryna Pishel et Dmitri Shytikov (du laboratoire de Gérontologie à Kiev avant que le laboratoire ne ferme du fait de la quasi guerre), les personnes de l'Institut Pasteur (à Paris et à Lille) qui développent avec énergie les solutions de santé et longévité de demain, ou encore les membres d'Epidemium et Challenge4Cancer. Je remercie également les personnes avec qui j'ai travaillé sur ces sujets à UCLA, l'Inserm, l'Institut Pasteur, ainsi qu'en assurance et en finance. Mes remerciements vont également tout particulièrement aux membres de GRG (Gerontology Research Group), Heales (Healthy Life Extension Society à Bruxelles), LongeCity (forum international), Longévité & Santé (à Paris), et surtout du board d'ILA (International Longevity Alliance, international) pour l'évolution de la recherche qu'ils ont accélérée depuis des années à travers le monde (Commission Européenne, Organisation Mondiale de la Santé, The Buck Institute for Research on Aging, etc.), menant aujourd'hui aux premiers développements importants chez l'homme. Voici quelques photos, actuellement disponibles sur http://longevityalliance.org :



Enfin, et tout particulièrement, je souhaite remercier ma famille pour m'avoir permis de me lancer dans cette aventure en plus de mon activité professionnelle, et pour me permettre plus généralement d'orienter ma carrière, afin qu'elle ait du sens et soit, au-delà d'une nécessité, l'occasion d'un accomplissement.

Table des matières

Introduction

Les actuaires calculent les besoins financiers pour faire face à des risques tels que ceux portés par les systèmes de protection sociale. Parmi ces risques, ceux de la santé sous diverses formes y compris maladie, invalidité, dépendance et retraite sont fortement liés à la durée de vie humaine. Or, la durée de vie humaine évolue rapidement depuis plus d'un siècle et diverses avancées biomédicales amènent à penser que la durée de vie en bonne santé pourrait augmenter très fortement dans les prochaines décennies. Si un tel scénario se produit, comment se comporteront les systèmes de protection sociale ? Comment les actuaires pourront-ils aider ces systèmes à s'adapter ?

Cette thèse aborde ces questions et tente de proposer des outils de mesure et de gestion du risque d'augmentation de la longévité exploitables dans ce contexte. Afin de travailler sur des éléments concrets, l'essentiel du travail est concentré autour de la mortalité et longévité plus que de la santé : le fait d'être en vie ou non est ici considéré de façon binaire. En comparaison, la frontière de la bonne santé est beaucoup plus difficile à définir et les aspects de santé amèneront dans ce manuscrit à des réflexions d'ordre qualitatif uniquement.

Dans une **première partie**, les avancées passées, présentes et futures de la longévité sont décrites et proposées, avec une approche fortement biomédicale. Ces aspects biomédicaux, qui y sont décrits, sont souvent peu connus des milieux actuariels alors qu'ils peuvent générer des impacts actuariels voire sociétaux majeurs. En ce sens, cette partie est essentielle pour appréhender les trois autres parties.

Dans une **deuxième partie**, différentes modélisations de ces avancées sont décrites et proposées, avec une approche fortement actuarielle. Nous soulignerons et expliquerons certains biais de modèles fréquemment utilisés, qui sous-estiment généralement les tendances de longévité à l'insu de l'actuaire qui les utilise. Nous proposerons un modèle paramétrique adapté à la tendance d'augmentation d'espérance de vie observée

empiriquement. Nous proposerons aussi des modèles avec d'autres tendances, en fonction des avancées biomédicales décrites en première partie.

Une **troisième partie** décrit la sensibilité des dispositifs actuels de protection sociale vis-à-vis des avancées de la longévité. Nous verrons notamment que les engagements de retraites estimés peuvent être très différents suivant que l'on s'appuie sur des scénarios envisagés au niveau gouvernemental, des tables de mortalité fréquemment utilisées par les actuaires, les tendances de longévité du moment, ou des scénarios issus de la première partie. Quelques possibilités classiques de gestion financière de ce "risque de longévité" sont présentées.

Une **quatrième partie** décrit les réflexions menées durant la thèse sur une autre forme d'accompagnement des avancées de la longévité, le "longevity megafund" (en anglais) ou "méga fonds de longévité" (en français). Combinant les approches biomédicales et actuarielles des avancées de la longévité, les moteurs économiques des milieux pharmaceutiques et les risques économiques des systèmes de retraite, ce type de structure pourrait à la fois soutenir les avancées biomédicales et réduire le risque financier de longévité. Nous tenterons d'évaluer dans quelle mesure le méga fonds de longévité peut réduire le risque de longévité.

I. Les avancées de la longévité

Durant un entretien en ligne face à 200 participants à l'été 2015, le bio gérontologiste Aubrey de Grey indique qu'il estime à 60 % la probabilité que les personnes âgées de 40 ans atteignent la "vitesse d'échappement de la longévité" - en anglais "Longevity Escape Velocity" (voir de Grey, (2015)). Ce terme désigne le scénario où les avancées biomédicales de réparation des dégâts du vieillissement, telles que des techniques facilitant la régénération des tissus, se développent suffisamment vite pour que la santé et l'espérance de vie *restante* de ces personnes augmentent dans le temps et ce, malgré leur avancée en âge. Comme nous le verrons **dans cette partie**, les avancées actuelles de la biologie du vieillissement et de la médecine régénérative semblent effectivement pouvoir conduire à ce type de scénario.

a) Divers indicateurs de longévité

La **longévité**, du latin *longaevitas*, désigne tantôt la durée de vie tantôt une longue durée de vie. Différents indicateurs sont utilisés pour quantifier la longévité, notamment l'espérance de vie, les taux de mortalité ou encore l'espérance de vie prospective.

L'**espérance de vie statique, de la population générale et à la naissance, est l'indicateur de longévité humaine généralement employé dans les communications publiques,** et est alors simplement nommée "espérance de vie". Précisément, l'espérance de vie statique à l'âge x (0 par défaut), à une période donnée t (généralement une année calendaire) et pour une population donnée (la population nationale par défaut), est la durée de vie moyenne restante pour les personnes d'âge x **si les conditions futures de mortalité sont inchangées** par rapport à celles mesurées durant la période t. Cet indicateur a l'avantage d'être peu discutable car il ne dépend pas d'hypothèses sur le futur. Les travaux de Pison (2005) rappellent que l'espérance de vie en France était de 25 ans en 1740, de 66 ans durant la période 1945-

1950 où les piliers du système de retraite français ont été créés (régime général de la Sécurité Sociale en 1945, retraite complémentaire Agirc en 1947, extension aux professions libérales en 1949), et est supérieure à 80 ans depuis 2004. Une **tendance de fond** se dégage ainsi pour l'espérance de vie (statique, à la naissance, pour la population générale) depuis plus de deux siècles : en excluant les périodes de guerre, l'espérance de vie augmente d'environ 20% à 23% année par an, soit un peu moins d'un trimestre par an.

Pour plusieurs raisons cette espérance de vie (statique, à la naissance, pour la population générale) sous-estime les durées de vie à considérer pour divers besoins de gestion financière. Tout d'abord, du fait que les personnes d'âge x n'aient déjà décédé, l'espérance de vie à la naissance est plus petite que la somme de leur âge x et de l'espérance de vie restante à l'âge x (ainsi une personne de 90 ans dépassera de fait l'espérance de vie à la naissance). Ensuite l'hypothèse de mortalité inchangée dans le temps, utilisée dans le calcul de l'espérance de vie, est totalement irréaliste comme l'indique la tendance de fond que nous venons de voir. En cela, l'**espérance de vie prospective**, qui intègre une hypothèse d'évolution des conditions de mortalité dans le futur – à la hausse si l'on poursuit peu ou prou la tendance de fond – est un bien meilleur indicateur. Ensuite encore, les inégalités sociales font que les personnes associées à des montants plus importants, les assurés typiquement, devraient avoir des espérances de vie plus élevées que nationalement. Enfin et similairement, divers contrats d'assurance excluent les personnes atteintes de **pathologies** particulières ; ces personnes ont en moyenne des durées de vie restantes plus courtes.

Pour ces raisons, et afin d'utiliser des indicateurs plus fins, **les actuaires ne s'appuient peu ou pas sur l'espérance de vie. Les actuaires utilisent des tables de mortalité statiques et prospectives, de population générale et d'assurés**. Ces tables sont des listes de **taux de mortalité** annuels. Le taux de mortalité annuel à l'âge x et l'année t, q_{xt}, est la proportion des personnes d'âge x en début d'année t qui est décédée durant

l'année. Les tables peuvent être spécifiques à un sexe (hommes, femmes) et une population. Les populations assurées ont généralement des taux de mortalité plus faibles que la population générale, du fait d'une sélection initiale, naturelle et renforcée notamment par la sélection médicale, de personnes avec relativement peu de problèmes de santé. Les tables statiques ne dépendent pas de t alors que les tables prospectives ont des "**améliorations de mortalité**" i_{xt}, qui sont des baisses de taux de mortalité pour l'âge x entre l'année t et t+1 ; nous verrons en partie II que l'utilisation du concept d'amélioration de mortalité a introduit des biais de modélisation dans la communauté actuarielle, lesquels apparaissent lorsqu'on mesure l'évolution de l'espérance de vie statique à partir des tables.

Notons que si les taux de mortalité et la longévité sont fortement liés à la **santé**, les actuaires connaissent peu les causes de mortalité des patients. Les risques d'incapacité, invalidité et dépendance sont suivis, mais généralement pas les risques liés spécifiquement à des pathologies. Les enjeux sont en effet essentiellement les primes d'assurance, qui sauf exception (couverture du risque maladie redoutée) ne sont pas spécifiques de pathologies particulières. De plus, une sélection médicale est effectuée pour divers contrats d'assurance: les actuaires ont donc peu d'information sur les patients.

La mortalité associée à des pathologies est étudiée dans les **milieux pharmaceutiques** par des "**biostatisticiens**" et non des actuaires, dans le cas des essais pré-cliniques et cliniques (chez l'animal et chez l'homme), pour tester l'efficacité de traitements. L'indicateur alors utilisé est celui des **courbes de survie longitudinale** des patients. Partant de 100% de patients en vie en début de suivi (t=0), ce nombre baisse plus ou moins vite suivant le groupe considéré et constitue une courbe de survie S_t. Chaque groupe contient une diversité d'âges, de sexes et d'autres facteurs, mais les groupes sont autant que possible constitués de façon à être comparables.

Outre les courbes de survie, la **recherche biomédicale** sur des animaux de durée de vie bien inférieure à la durée de vie humaine modélise des **taux de mortalité instantanés**

μ_t, parfois appelé **force de mortalité**. En effet, considérer des taux de mortalité annuels aurait peu de sens pour des animaux d'espérance de vie nettement inférieure à un an : ces taux vaudraient 1.

Bien que les milieux actuariel et biomédical utilisent des indicateurs différents, ces indicateurs sont des représentations différentes de mêmes phénomènes et tous peuvent par exemple être représentés en fonction du taux de mortalité instantané μ_t comme nous l'indiquons ici.

Commençons par la survie d'une population, que nous notons S_x. A un âge initial $x=x_0$, 100% de la population considérée est en vie: $S_{x0}=1$. A chaque durée infinitésimale dx, une proportion une μ_x des individus décède et la survie évolue de dS_x :

$$dS_x = - \mu_x S_x \, dx$$

En divisant par S_x et en intégrant suivant l'âge il s'en suit la formule :

$$S_t = S_{t_0} e^{-\int_{t_0}^{t} \mu_u \, du}$$

Si différentes personnes forment un groupe dans un essai clinique, chacune a une courbe de survie associée et la survie du groupe est la somme des courbes de survie individuelles, en multipliant par le bon S_{x_0} pour partir de 100% de personnes en vie en début d'expérience.

Les taux de mortalité annuels se déduisent de la survie suivie pendant un an. Pour un groupe d'âge x en début d'année t, la survie à un an est

$$\frac{S_{x+1,t+1}}{S_{x,t}} = e^{-\int_{x,t}^{x+1,t+1} \mu_u \, du}$$

Dans cette formule, x et t bougent en même temps à partir du point (x, t). Comme survivre correspond à ne pas décéder, elle vaut aussi $1-q_x$. Ainsi,

$$q_x = 1 - e^{-\int_{x,t}^{x+1,t+1} \mu_u \, du}$$

L'espérance de vie prospective restante à l'âge x_0 et la date t_0 est la moyenne des possibilités de durée de vie restante. Chaque possibilité de durée de vie $t - t_0$ s'obtient en

tirant un nombre aléatoire uniforme y entre 0 et 1 qui représente une survie S_t à laquelle l'individu décède. Ainsi, l'espérance de vie restante est l'aire sous la courbe de survie et du coup elle s'écrit :

$$e_{x_0,t_0} = \int_{x_0,t_0}^{\infty} \mathrm{e}^{-\int_{x_0,t_0}^{\mathrm{v}} \mu_{\mathrm{u}}\, \mathrm{du}}\, \mathrm{dv}$$

Nous voyons donc que ces indicateurs sont connectés entre eux. Pour les calculs actuariels qui sont liés à des populations humaines, comme nous le verrons en deuxième partie l'élément de base est le taux de mortalité annuel et les intégrales sont estimées par la méthode des rectangles jusqu'à un âge maximal théorique de durée de vie. Comme nous le verrons également en deuxième partie, des modèles peuvent s'appuyer sur ces indicateurs pour représenter des avancées de longévité futures potentielles. Comme nous le verrons en quatrième partie, dans le milieu pharmaceutique des gains financiers sont tantôt estimés suivant les améliorations de durée de vie, de patients, tantôt suivant les améliorations de durée de vie en bonne santé.

b) Une série de seuils de longévité formulés et toujours dépassés

La question d'un âge maximal humain est importante dans cette thèse car elle conditionne la vision des évolutions possibles de taux de mortalité y compris d'espérance de vie: si des personnes avaient aujourd'hui 200 ou 300 ans, imaginer que l'espérance de vie pourrait bientôt être de 150 ans dans certains pays semblerait beaucoup plus raisonnable que si nous pensons que l'être humain ne peut, de par sa constitution, dépasser les âges de 115 voire 125 ans.

L'âge maximal humain aujourd'hui recensé avec forte certitude est celui de 122 ans. Plus précisément, Jeanne Calment est née le 21 février 1875 à Arles et décédée dans la même ville le 4 août 1997, à l'âge de 122 ans, 5 mois et 14 jours. Dans la série des records vient ensuite le Japonais Shigechiyo Izumi décédé à 120 ans en 1986 puis l'américaine Sarah Knauss décédée à 119 ans en 1999. L'étude de tels chiffres et l'absence de record plus récent laisse penser à un seuil maximal de durée de vie de 125 ans ce qui mécaniquement limiterait l'espérance de vie future (Dong *et al.* 2016).

Cependant, que ce soit pour la durée de vie maximale ou pour l'espérance de vie, Oeppen et Vaupel (2002) rappellent que divers seuils ont ainsi été imaginés dans le passé et tous ont été franchis. Par exemple, en modélisant une baisse des taux de mortalité jusqu'à un niveau incompressible de mortalité modélisé dans le même temps, l'actuaire américain Louis Dublin a en 1928 prédit que l'espérance de vie à la naissance ne pourrait jamais dépasser 64.75 ans dans aucun pays. Soixante ans plus tard, un autre actuaire américain prédisait une espérance de vie à la naissance maximale de 85 ans (Olshansky *et al.* 1990), nombre aujourd'hui dépassé par les femmes japonaises.

Similairement, partout dans le monde les tables de mortalité utilisées par les actuaires sont régulièrement rectifiées à la baisse (baisse de mortalité et hausse de longévité), avec des intervalles typiques de 10 ou 15 ans entre deux révisions (Antolin and Mosher, 2014). Les actuaires n'ont donc cessé de sous estimer la longévité, ce qui naturellement crée des difficultés de gestion, pour le paiement des retraites notamment, comme nous l'étudierons en troisième partie. Et si des signes de non amélioration de longévité vers les âges de 110 ans apparaissent effectivement en ce moment, Gavrilov *et al.* (2017) rappellent que cela ne prédit en rien l'avenir, ni pour la durée de vie maximale ni pour l'espérance de vie.

[paragraphe ajouté quelques jours après la soutenance de thèse] Un très récent article dans Science (voir Barbi *et al.* (2018)) note que sur la base de données italiennes de bonne qualité, les taux de mortalité n'augmentent statistiquement plus à partir 105 ans, et que ce plateau de mortalité aux grands âges baisse suivant les cohortes. Cet article conclue qu'une limite d'âge n'a pas été atteinte. Le débat qui s'en suit dans Nature (voir Dolgin (2018)) montre à quel point la question d'un âge maximal chez l'homme aujourd'hui est dans les esprits associé à la possiblité d'améliorations futures importantes ou non de la longévité dans les esprits, malgré l'avertissement de Gavrilov *et al.* (2017) qu'il s'agit de deux sujets différents... Le débat n'est pas terminé comme le rappelle Jean-Marie Robine puisque l'étude de données de France, du Japon et du Canada est en cours.

c) Questions pour le futur et idées préconçues

La considération des tendances historiques et actuelles amène à hésiter entre l'**existence ou l'absence d'une limite proche** en termes de durée de vie humaine. Comme nous l'avons noté pour la France et comme noté pour les pays de forte longévité par Oeppen et Vaupel (2002), une tendance historique de fond a pu être notée pour l'espérance de vie d'environ **plus trois mois par an**, suggérant l'absence de limite d'espérance de vie proche. Mais cette tendance historique n'a en réalité pas été parfaitement constante. Ainsi, après les travaux de Pasteur (notamment) sur la théorie microbienne, pendant sept décennies l'espérance de vie a augmenté de plutôt **quatre mois par an**, vraisemblablement du fait de l'amélioration de l'hygiène de vie. Plus récemment, l'augmentation de l'espérance de vie semble plus liée aux avancées cardiovasculaires, et le rythme est un peu **inférieur à un trimestre** par an ; par exemple 0,23 année par an. A présent que la mortalité est très faible avant 65 ans, Vallin et Meslé (2010) notent que **l'avenir de l'espérance de vie dépend fortement des avancées médicales après 65 ans : une décélération ou accélération sont possibles suivant les avancées médicales.** L'espérance de vie est en effet un indicateur très macroscopique, qui cache des **différences importantes suivant les âges**. Comme le notent Robine et Cheung (2008), de plus en plus l'âge de décès chez les adultes semble concentré autour d'un **âge modal**. Cependant, ce phénomène prend des formes différentes aux Etats-Unis, en Europe ou au Japon, sans explication claire à ce stade. Au Japon, où les femmes bénéficient d'une espérance de vie supérieure aux autres pays, cette espérance de vie continue à augmenter fortement sans sourciller. De plus, le nombre de centenaires explose véritablement partout, ce qui suggère des possibilités encore très importantes en matière de durée de vie.

Au-delà de la longévité en tant que telle, ces dernières analyses s'accompagnent de questionnements sur l'**état de santé** des individus âgés. Si la santé était définie de façon très restrictive, comme la simple possibilité de se déplacer, si bien que la durée de vie en

bonne santé serait proche de la durée de vie, par construction la durée de vie en bonne santé augmenterait également fortement. A l'inverse, si la santé est définie de façon large, ces études observent une évolution lente, potentiellement positive ou négative, de la durée de vie en bonne santé, alors que clairement la durée de vie en mauvaise santé est en tendance haussière. De fait, les personnes décèdent aujourd'hui moins d'accident et plus de maladies chroniques. Des solutions contre ces pathologies chroniques, telles que la maladie d'Alzheimer, tardent à apparaitre. C'est pourquoi un allongement de la vie peut paraître synonyme d'une prolongation de la vie en mauvaise santé. Cependant, c'est l'état **chronique** des pathologies actuelles qui est en cause ici, et à chaque traitement trouvé contre ces pathologies chroniques correspondent des années de vie gagnées en bonne santé. Une recherche biomédicale qui aboutit à des solutions contre les pathologies chroniques devrait donc augmenter la durée de vie en bonne santé. Martin-Montalvo *et al.* (2013) observent notamment cette amélioration concomitante de la durée de vie et de la santé sur les résultats d'essais sur rongeurs. De fait, il est prévisible que les avancées de la longévité se matérialisent d'abord par plus d'années de vie **en bonne santé**, alors que c'est l'absence actuelle de solutions contre les pathologies chroniques qui caractérise aujourd'hui l'allongement de vie en mauvaise santé.

Une autre question est celle de la **pénibilité de l'application de solutions** pour rester en bonne santé. Comme nous le verrons plus loin dans cette partie, une forme de diète, la restriction calorique, est associée à une plus grande longévité. Entre ne pas fumer, ne pas boire, et être à la diète, il peut sembler intuitif que les débouchés de la biologie du vieillissement conduisent à rendre le quotidien difficile - à quoi bon tous ces efforts pour gagner des années de vie pénibles ? Or, comme nous le verrons, les développements pharmaceutiques issus de la biologie du vieillissement concernent des traitements, et non des styles de vie pénibles.

Au-delà des aspects de durée de vie et de santé, il peut sembler intuitif que l'allongement de la vie s'accompagne d'une augmentation de la taille des populations,

voire de **surpopulation**. Or, le contraire semble se produire, et c'est à la place un vieillissement de la population que nous observons : la population européenne aurait tendance ainsi à diminuer à cause de la baisse de la fécondité, mais la proportion de personnes âgées croîtrait sensiblement (voir Audet (2004)). Dans le cas de la Chine aujourd'hui la politique de l'enfant unique a été compensée par un allongement de la durée de vie, résultant en un taux de croissance démographique de 0,50% par an (voir PopulationData.net (2018)). Le vieillissement des populations est donc un effet majeur des avancées de la longévité. Les impacts sociétaux ne sont pas négligeables. Les besoins en logement resteraient forts pour loger des personnes âgées, les coûts de santé pourraient augmenter à moins justement que des solutions contre les pathologies chroniques ne soient trouvées.

Cependant, les avis divergent fortement quant aux **tendances de fond en matière même de longévité**. Certains, tels que Finch *et al.* (2014), considérant l'augmentation de la pollution notamment des nanoparticules, mais aussi l'obésité et les changements climatiques à venir, s'attendent à ce que l'espérance de vie baisse. D'autres, et en particulier de nombreux chercheurs en biologie du vieillissement et le prolixe de Grey (2015) pensent que nous sommes à l'aube d'une révolution et qu'il est possible que le premier homme qui vivra mille ans soit déjà né !

Plutôt que de s'opposer, il est possible que **les éléments considérés s'ajoutent** : que l'amélioration de certains facteurs tels que l'hygiène mène à une espérance de vie moyenne maximale : une limite. Cette limite devrait effectivement décroitre avec la pollution, l'obésité et des changements climatiques problématiques. Elle devrait croitre avec les améliorations biomédicales surtout **si des solutions face au vieillissement se développent** : le risque de mortalité chez l'homme double environ tous les huit ans d'âge, des thérapies contre le vieillissement pourraient donc typiquement diviser les risques par un facteur 2, 4, 8, 16 ou 32. Face à une telle amplitude de changement potentiel, le développement ou non de telles solutions, et la vitesse de développement de ces solutions, est donc clé pour envisager le futur de la longévité.

d) Avancées de la biologie du vieillissement

Une partie de cette thèse a consisté à suivre les avancées de la biologie du vieillissement, pour apprécier les possibilités d'allongement de vie de l'homme prochainement par ces approches. Devant la multitude d'avancées (des milliers, suivant leur découpage), une sélection d'éléments marquants est ici effectuée. Le lecteur souhaitant découvrir davantage à quoi ressemble les échanges entre experts du domaine pourra lire l'article en annexe 2 qui rapporte un échange entre experts sur les avancées biomédicales en cours pour allonger la durée de vie en bonne santé (voir Moskalev *et al.* (2017)).

Si vivre longtemps, voire devenir immortel, a pu être l'origine de rêves et mythes de tous temps, telle l'épopée de Gilgamesh, ou l'origine d'essais d'alchimie pour vivre longtemps par René Descartes par exemple (voir Grmek (1968)), l'approche scientifique et médicale de la longévité a vraisemblablement commencé en France, à la **fin du XIXème siècle**. Dans le champ des idées positivistes, Elie Metchnikoff, Charles-Édouard Brown-Séquard, Serge Voronoff et Jean Finot émettent l'idée que le corps humain est une machine qu'il convient d'alimenter par des compléments d'hormones pour vivre plus longtemps. A partir des années 1930, faute de résultats probants, la recherche de solutions se poursuit en considérant le corps dans sa complexité et la complexité de son environnement (voir Stambler (2011)).

Le concept de **restriction calorique** apparait alors, il s'agit de manger peu mais bien. Ce concept avait été découvert durant la première moitié du seizième siècle par un italien, Luigi Cornaro, qui après avoir mis sa vie en danger par excès de nourriture avait adopté l'attitude opposée. Il avait observé des bénéfices qu'il avait publiés dans quatre recueils et avait effectivement finalement atteint l'âge de 103 ans (âge rarement atteint à l'époque). En 1934, la restriction calorique est testée sur des rats et une longévité accrue de 40 % est effectivement observée (voir McCay et Crowell (1934)). Durant les décennies qui suivent, des résultats similaires sont observés sur des espèces animales de tout type, de la levure à la chèvre en passant bien-sûr par la souris, avec très peu d'exceptions à la règle. Plus récemment, deux principales études sur des singes sont

effectuées, avec des résultats positifs mais plus mitigés. Les explications biologiques de la restriction calorique restent floues, car multiples : la restriction calorique engendre un processus actif, et non pas passif, d'expression de nombreux gènes dans les tissus. Un recyclage et nettoyage de l'intérieur des cellules (autophagie) est notamment observé. La réaction du corps en restriction calorique est vraisemblablement un mécanisme issu de la sélection naturelle permettant de se renforcer pour survivre en période difficile. Sur les souris, des tests affinés observent que le degré de restriction alimentaire peut jouer positivement ou négativement suivant la souche de souris, leur âge et les variations de degré de restriction. Au global, même si la **prudence** est de mise quant au rythme, degré et type de restriction calorique, les résultats sont **positifs** (voir Fontana *et al.* (2010), Ingram et de Cabo (2017)) et récemment Pifferi *et al.* (2018) rapportent un allongement de durée de vie de 40% chez les Lémuriens (des singes, donc) et passe notamment par une réduction de près de 75% des risques de cancer. De plus, diverses études et observations chez l'homme indiquent que la restriction calorique améliore bien la santé (voir Most *et al.* (2017)), même si la privation alimentaire n'est pas compatible avec un impact à l'échelle des populations.

Du fait de la non applicabilité évidente de la restriction calorique à de larges populations, des **solutions "mimétiques" de restriction calorique** ("caloric restriction mimetics") sont activement recherchées depuis une à deux décennies, qui visent à obtenir des effets comparables sans passer par la privation alimentaire. Pour ce faire, l'absence d'explication biologique unique amène à tester des approches variées en comparant les effets en termes d'expressions des gènes dans divers tissus. Ces quelques dernières années, des résultats divers sont obtenus chez l'animal et certains sont testés par des essais cliniques. Par exemple, l'aspirine à faible dose aurait un effet de type restriction calorique (voir Pietrocola *et al.* (2018)) ainsi que les produits stimulant la production d'hydroxyde de souffre par le corps (voir Ng *et al.* 2018). Certaines de ces solutions pourraient bien déboucher sur des traitements chez l'homme dans la décennie à venir et nécessiter une gestion financière adéquate des dispositifs de protection sociale, comme le souligne l'article en annexe, de Zhavoronkov *et al.* (2012) .

Au-delà de la restriction calorique, de très nombreuses manières d'allonger la durée de vie sont découvertes chez l'animal depuis deux décennies, avec un rythme très clairement croissant. Les paragraphes qui suivent s'appuient sur une synthèse datant de 2010 (voir Kenyon (2010)) et sont complétés par d'autres références.

Le **nématode *Caenorhabditis elegans***, de durée de vie d'environ un mois en laboratoire, a fait l'objet de tests automatisés par milliers sur la durée de vie, avec des résultats positifs dans environ 10 % des cas et l'ensemble des résultats a permis de déceler quelques grands axes généraux. En tirant le fil de certains résultats et en ajustant les thérapies (thérapies géniques en particulier), des techniques ont été trouvées pour multiplier par dix la durée de vie de ces nématodes (voir Ayyadevara *et al.* (2008)).

Etant des mammifères, donc plus proches de l'homme, les **souris et rats** sont également très utilisés. Leur durée de vie en laboratoire de 2 à 3 ans rend les tests considérablement plus longs, coûteux et moins nombreux que pour les nématodes. Une longévité accrue de 50 % est découverte par hasard sur des souris initialement sélectionnées pour leur nanisme naturel (**souris "Ames"**). La mutation génétique est identifiée, rapprochée de nématodes vivant deux fois plus longtemps (mutation DAF-2) et de populations humaines – nains de Larrons, semble-t-il protégés contre le diabète et les cancers mais vivant dans la pauvreté en Equateur (voir Guevara-Aguirre *et al.* (2011)). Bartke *et al.* (2008) montrent que le couplage avec la restriction calorique donne une augmentation totale de durée de vie de 70 %. Ces souris amènent d'abord la recherche à considérer des souris naines, peu sensibles à l'hormone de croissance, pensant d'abord que la longévité vient forcément au détriment d'importantes caractéristiques telles que la taille et la fertilité. Puis il est découvert qu'au-delà d'une insensibilité à l'hormone de croissance, une insensibilité à un facteur de maturité des cellules (IGF1) a des effets similaires, et que **des augmentations de durée de vie peuvent être obtenues sans effet secondaire négatif évident** (voir Holzenberger *et al.* (2002)). Des mutations naturelles analogues (AKT, FOXO3A, FOXO1) sont trouvées chez des familles présentant une forte proportion de centenaires, suggérant que **ces effets sont transposables**

entre des souris de durée de vie de 2 à 3 ans et des hommes de durée de vie voisine de 80 ans.

Au début des années 2000, ces résultats globalement positifs mais liés à des thérapies géniques alors non acceptées pour l'homme (et présentant alors de forts risques) poussent à explorer l'**utilisation de traitements existants, donnés à des souris** de façon chronique et à petite dose. L'avantage de cette approche est de pouvoir rapidement s'appliquer aux populations du fait de l'utilisation de traitements déjà commercialisés (voir Barardo *et al.* (2017)). Différents traitements montrent alors des augmentations de durée de vie de 6 % à 26 %, notamment **l'aspirine** (voir Strong *et al.* (2008)), la **metformine** (voir Martin-Montalvo *et al.* (2013)) et la **rapamycine** (voir Harrison *et al.* (2009), Ye *et al.* (2013)). De façon indirecte les résultats sont corroborés par des observations chez l'homme, pour l'aspirine (voir Cuzick *et al.* (2014)), la metformine (voir Bannister *et al.* (2014)) et la rapamycine (voir Mannick *et al.* (2014)) qui depuis est devenue un anti-cancéreux, le plus utilisé aujourd'hui. De façon plus directe, des tests de durée de vie chez le chien sont en cours pour la rapamycine (voir Check Hayden (2014), Kaeberlein (2015)) et bientôt chez l'homme pour la metformine (essai clinique TAME organisé par l'université Albert Einstein College of Medicine à New York). Face à la compréhension que la persistance de cellules vieilles dans le corps, les **cellules "sénescentes"**, empoisonnent avec l'âge nos capacités de régénération des tissus (hypothèse "Senescence Associated Secretory Phenotype"), la recherche de traitements existants à détourner pour se débarrasser de cellules sénescentes est en cours, et j'ai eu la chance d'y participer en lançant une expérience en cours sur souris (International Longevity Alliance (2015)). Depuis, des développements pharmaceutiques de nouveaux médicaments sont en cours, visant à être plus efficaces, comme indiqué section suivante. Ces approches pourraient là aussi déboucher sur des traitements chez l'homme dans la décennie à venir et nécessiter une gestion financière adéquate des dispositifs de protection sociale.

A partir de l'année 2014 les techniques de **thérapie génique** s'améliorent grandement, avec des techniques telles que les "doigts de zinc" ou "Crisper-Cas9" permettant de faire

des couper-coller propres dans le génome des cellules, et une maitrise grandissante des méthodes ("vecteurs") pour distribuer ces thérapies au sein du corps. Initiée par la recherche sur des maladies rares, l'acceptation des thérapies géniques se fait progressivement. Il devient concevable de transposer à l'homme les nombreux résultats de longévité obtenus par mutations ponctuelles chez le nématode, le rat et la souris. C'est ainsi que des centres de thérapies géniques antivieillissement ouvrent en Asie et en Amérique (voir Mitteldorf (2015)), bien qu'il ne soit pas évident au jour d'aujourd'hui que ces thérapies aient des effets forcément positifs chez l'homme. Une des thérapies est ainsi d'ajouter une copie du **gène de la télomérase**, une enzyme qui évite l'érosion des extrémités des chromosomes ; une telle thérapie augmente la durée de vie de souris adultes de 13 % à 24 % suivant l'âge auquel le traitement est initié (voir Bernardes de Jesus *et al.* (2012)). Si ces traitements aujourd'hui incertains montraient des effets clairement positifs et se répandaient progressivement, cela nécessiterait une gestion financière adéquate des dispositifs de protection sociale.

Des approches se développent aussi qui ne sont **ni médicamenteuses ni géniques**. Par exemple, après avoir développé la méthode sur des rats et souris en vue de stimuler le système immunitaire de patients sidéens, un chercheur en Californie s'est injecté des hormones pour faire partiellement **repousser son thymus**, une glande qui produit les globules blancs et dont l'activité devient quasi inexistante passé la trentaine (voir Fahy (2003)). En lien avec la FDA, l'entreprise que ce chercheur a ensuite créée teste cela sur d'autres volontaires. Potentiellement, la faible activité du thymus durant des décennies pourrait expliquer en partie l'augmentation abrupte du risque de cancers et autres pathologies avec l'âge : le système immunitaire ne se serait pas développé suivant les besoins actuels.

Autre exemple : **l'injection de sang d'individus jeunes** à des individus âgés. Différents articles notent des bénéfices de composés de sang ou plasma d'individus jeunes (voir Conboy *et al.* (2005)), notamment sur la neurogénèse (voir Villeda *et al.* (2011)). Ces bénéfices sont jusqu'à présent observés sur un système biologique local, par opposition à l'organisme tout entier, ou sur une durée faible. Dans ce contexte, j'ai

échangé avec une équipe experte en circulation sanguine jointe entre animaux d'âge différents, et leur ai apporté mon expertise en prélèvements sanguins, organisation et suivi de tests de survie chez la souris et nécropsies pour l'analyse des causes de décès, pour tester les effets à long terme d'injections régulières de plasma de souris jeunes, à des souris âgées. Les résultats sont dans l'article en annexe (voir Shytikov *et al.* (2014)) : comme indiqué en Figure 1, sur la durée de vie, qui était l'indicateur majeur de l'étude, nous n'avons trouvé ni amélioration ni détérioration.

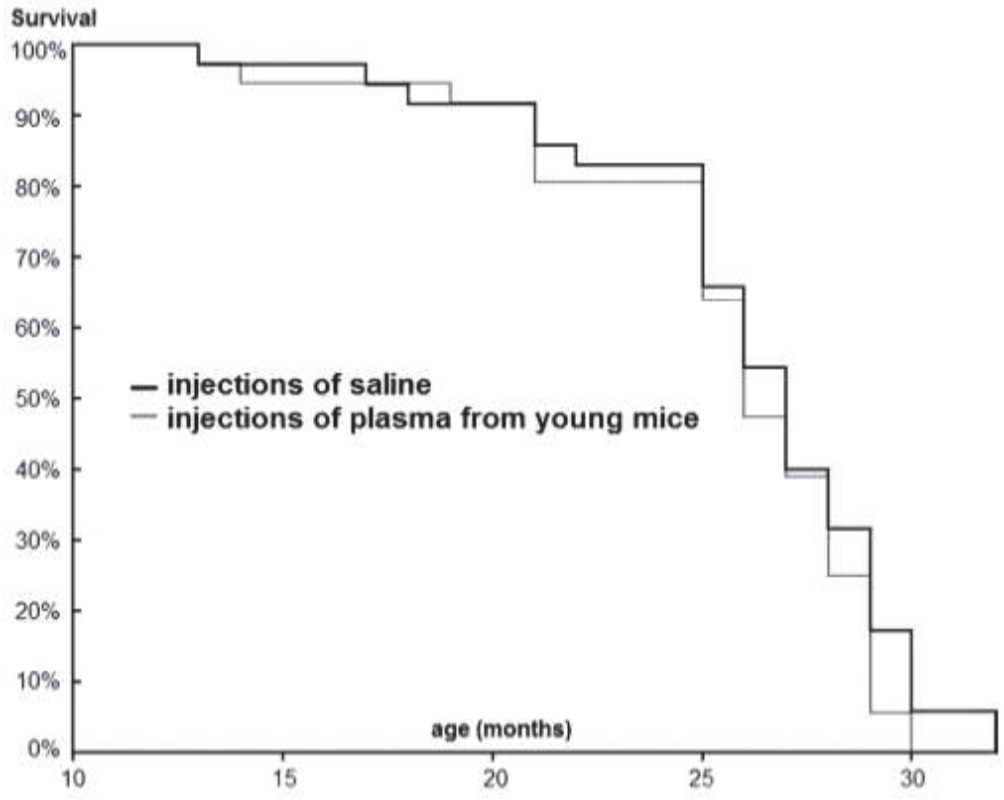


Figure 1 extraite de Shytikov et al. (2014).

Suite à l'article, des échanges avec une partie des auteurs des articles ayant publié sur des bénéfices ont conclu que cette absence d'effet était en effet troublante, que l'utilisation d'héparine pour nos prélèvements sanguins aurait pu neutraliser certains effets positifs – mais la dose utilisée était très faible donc c'est peu probable –, mais que d'autres personnes n'avaient également pu reproduire certains bénéfices préalablement publiés – dans notre étude nous n'avions pu vérifier ces bénéfices par manque d'expertise sur les technologies à employer – et que la quantité d'injection était peut-être

insuffisante bien que nous ne puissions expérimentalement faire mieux chez la souris. Ces échanges ont amené à conclure qu'il n'était pas impossible qu'il y ait des effets positifs locaux notamment cérébraux sans effet positif global sur la durée de vie. Certains indiquaient qu'ils allaient reproduire notre expérience. Nous n'avons pas vu cela mais une expérience similaire (voir Castellano *et al.* (2017)), ou du plasma de sang humain a été injecté au lieu de plasma de sang de souris - ce qui en soit est un biais important - avec au final des résultats clairs non pas sur du plasma d'individus mais de sang de cordon ombilical, et ces résultats concernent la mémoire et absolument pas la survie. Cependant, des documents de presse s'appuie sur ces résultat pour parler de fontaine de jouvence et de réjunévation de souris (voir Makin (2017)). Le fait d'obtenir certains résultats positifs est bien-sûr extrêmement positif, le fait que la réalité soit fortement tordue me semble à mettre en lien avec la création d'une entreprise, Alkahest Inc, à peu près en même temps avec une partie de ces personnes. Grâce notamment à un financement de 54 M$ (voir de Magalhães *et al.* (2018)) Alkahest a lancé un essai clinique correspondant contre la maladie d'Alzheimer : l'étude PLASMA, qui a tout récemment communiqué sur ses résultats de façon très positive auprès de la presse (voir Goldman (2017)) comparablement aux résultats de l'étude: des résultats positifs sont rapportés en termes de capacités à se déplacer chez certains patients mais une absence d'effet significatif est indiquée sur l'humeur et sur la mémorisation, mesures principales des bénéfices espérés. L'écart que nous observons sur cet exemple entre les discours, personnes et sommes en jeu d'une part, et la clarté des résultats scientifiques d'autre part, incite à la prudence lorsqu'il s'agit du passage à l'homme des résultats chez les animaux (médecine translationnelle): les faits doivent être étudiés avec bien plus d'attention que les discours.

Parmi les nombreux autres types de thérapies, une approche plus connue du grand public est la fabrication de **nouveaux organes** avant implantation. Les limitations sont qu'une chirurgie est alors nécessaire, et que hormis pour des cas simples comme la trachée les organes créés ont à ce stade des fonctionnalités insuffisantes (voir Ravnic *et al.* (2017) et Mir et Nakamura (2017)). Une approche au final quelque peu voisine laisse envisager

des perspectives importantes : des chercheurs dans des laboratoires à Paris, Madrid et Barcelone se sont inspirés d'animaux amphibiens (axolotls) dont les pattes repoussent parfaitement en cas d'arrachement et ont trouvé comment amener le corps à **régénérer des tissus** (voir Ocampo *et al.* (2016), Mosteiro *et al.* (2017)) après leur destruction partielle. La technique est à ce stade un peu brutale mais prometteuse. L'hydre, ou polype d'eau douce, est un animal qui se régénère fortement et qui ne montre pas de sénescence - son taux de mortalité ne semble pas dépendre de l'âge. Une estimation est que 5 % des individus sont encore en vie au bout de **1400 ans**, mais cette estimation dépend bien sûr du taux de mortalité associé aux conditions environnementales (voir Jones *et al.* (2014)). Un gène particulier, **FOXO** semble important dans la capacité de l'hydre de se régénérer tout en se débarrassant de ses cellules endommagées ; après avoir vu que des variantes de ce gène était importantes pour le nématode et plus fortement présentes chez des centenaires, la variante de l'hydre semble très prometteuse pour des thérapies (voir Martins *et al.* (2016)). Mais ce type de recherche ne débouchera certainement pas chez l'homme dans la décennie à venir.

Nous voyons ainsi que de **multiples approches prometteuses** sont en cours. Pratiquement aucune ne peut se réaliser en l'espace d'une décennie depuis son initiation mais de nombreuses approches semblent aujourd'hui **à quelques années ou une décennie du passage à l'homme**. Certaines touchent déjà quelques centaines de personnes sans que l'on puisse généralement à ce stade vérifier les effets sur la mortalité, comme la restriction calorique, l'utilisation prolongée de traitements existants à petite dose, et quelques thérapies géniques. Certaines approches suggèrent des augmentations de durée de vie de quelques années voire décennies, comme l'utilisation de traitements existants. Les dernières approches citées suggèrent des formes de rajeunissement par la **régénération** des organes et l'élimination des cellules problématiques.

Ce cumul de possibilités, y compris la possibilité de régénérer les tissus plutôt que de s'efforcer à ralentir le vieillissement, sont à l'origine du concept de "vitesse

d'échappement de la longévité" - en anglais "**Longevity Escape Velocity**" (voir de Grey, (2015)): si de premiers résultats sont remarquables chez l'homme dans les prochaines décennies, la **prise de conscience** qui en découlera amènera à développer les différentes approches à plus grande échelle et à régulièrement se débarrasser des cellules (ou tissus et agrégats) problématiques tout en stimulant la régénération des tissus, et à compléter les approches par celles nécessaires pour une forme physique de l'ordre par exemple de celle d'une personne de 30 ans aujourd'hui. Un taux de mortalité annuel constant de typiquement 0,1 % correspond à une espérance de vie de 1000 ans : si ce scénario de "Longevity Escape Velocity" se réalise effectivement la première personne de 1000 ans est peut-être déjà née. Il est toutefois bien difficile de saisir le degré de pertinence d'un tel scénario. Certes, il est possible de s'appuyer sur le passé pour **l'appréhender**: la chute de la mortalité infantile il y a 150 ans, appliquée aujourd'hui au grand âge. Mais ce scénario dépend des capacités futures de la recherche alors qu'à ce stade, l'essentiel des développements ne sont pas passés à l'homme. Le cas de l'injection de plasma d'individu jeune et Alkahest montre bien la difficulté d'estimer la possibilité de passage à l'homme.

e) Développements pharmaceutiques de solutions issues de la biologie du vieillissement

Il s'agit dans cette section de décrire le passage à l'homme qui s'effectue actuellement. Un premier passage à l'homme se fait **de façon minimaliste**, sans passer par des essais cliniques en double aveugle. Des personnes testent certains traitements sur elles-mêmes et des groupes de telles personnes se forment autour de thérapies. Tel est le cas actuellement pour la restriction calorique et autres diètes voisines, la metformine (traitement de base en cas de diabète sans complication), la rapamycine à petite dose, une combinaison de quercétine et dasatanib (pour se débarrasser de cellules sénescentes accumulées) ou encore les clients des premières entreprises de thérapie génique. Ces personnes prennent le risque d'occurrence d'effets secondaires sans suivi médical initial

individuel mais sont (à ma connaissance) bien informées. De façon plus organisée, une initiative effectue des essais cliniques dégénérés: les individus sont suivis par un médecin, mais il n'y a pas de groupe contrôle. Ces essais n'étant pas financés par un développement pharmaceutique, les participants paient eux même les frais. Ainsi RescueElders (2018) organise le traitement à la rapamycine pour 1800$ par an, l'injection d'un composant du sang de jeunes individus (GDF11) pour 7800$, la repousse du Thymus pour 28000$, et l'injection de plasma de jeunes individus pour 50000$.

A une échelle plus industrielle, le passage à l'homme se fait traditionnellement **à travers l'industrie pharmaceutique**: des investissements sont levés pour effectuer des essais cliniques avec groupes contrôles en double aveugle, pour obtenir des autorisations de commercialisation et des montants de remboursement par les autorités de santé (ou autre système adéquat, suivant le pays), pour pousser les ventes du traitement à travers des réseaux de commercialisation (ou information sur le traitement), et le retour sur investissement vient des ventes du traitement. Jusqu'à peu la biologie du vieillissement était uniquement à un stade expérimental (et de vente de poudres de perlimpinpin), et était peu connue des milieux pharmaceutiques, s'attachant aux processus du vieillissement et dégâts associés plutôt qu'aux pathologies spécifiques. Mais cela est en train de changer : les **start-ups biotechnologiques** issues de la biologie du vieillissement fleurissent, ainsi que les investissements associés, et divers essais cliniques sont en cours. Magalhães *et al.* (2017) décrivent cette transition de façon très concrète. Par exemple, leur tableau 1 indique qu'Alkahest Inc a été créé en 2014 et a fait une levée de 54 millions $ ou encore que Unity, une entreprise développant des produits contre les cellules sénescentes, a levé 116 millions $.

Alors que l'industrie pharmaceutique a du mal à percer contre les maladies dégénératives en utilisant des techniques développées pour des traitements aigus contre des pathologies aigues, et est en recherche de nouveau modèle sur ces aspects (voir Thiem *et al.* (2011), Roman et Ruiz-Cantero (2017)), divers **investisseurs** pensent que le passage à l'homme des avancées de la biologie du vieillissement est une "**ruée vers**

l'or" qui commence (voir Mellon (2017), Pratt (2016), Casquillas (2016)). En se concentrant uniquement sur le vieillissement de la peau et des cheveux, les estimations du marché sont de 122 milliard $ en 2013, 140 en 2015, 192 en 2019 et 217 en 2021 (voir Zion Market Research (2017), Transparency Market Research (2016)). Si effectivement les développements pharmaceutiques prennent le relais de la recherche contre le vieillissement à grande échelle, et augmentent fortement la durée de vie humaine, la gestion financière des dispositifs de protection sociale sera soumise à rude épreuve.

Récemment, la banque suisse UBS a lancé un **fonds d'investissement** de 458 millions d'Euros pour des développements biomédicaux contre le cancer (voir Tribune de Genève (2016)). Il est prévisible que d'autres fonds soient lancés pour d'autres pathologies majeures. Nous étudierons un tel cadre en quatrième partie de ce manuscrit.

II. Modélisation de ces avancées

Nous avons vu que les avancées actuelles de la biologie du vieillissement peuvent déboucher sur des augmentations importantes d'espérance de vie, en rupture potentielle avec le passé et les modèles actuariels habituellement utilisées. Cette section traite de modèles de mortalité pour le futur, relève des biais dans les modèles couramment utilisés et propose des modèles qui incorporent ou non ces avancées.

a) Le modèle de Lee Carter prédit des décélérations de longévité

L'essentiel du contenu de cette section se retrouve en anglais dans l'article en annexe 3 (voir Debonneuil *et al.* (2017) en annexe). De très nombreux actuaires travaillant sur les engagements de retraites utilisent le modèle de Lee Carter (voir Lee et Carter (1992)) ou ses dérivés et **pensent extrapoler de façon neutre la tendance du passé. Or, nous observons que le modèle de Lee Carter a plutôt tendance à produire une décélération des tendances de longévité.** Lors des recherches nous avons pu remarquer que ce biais avait déjà été rapporté (voir Bongaarts (2014)) sans que l'explication du biais ne soit donnée ni que la connaissance de ce biais soit généralement dans les esprits dans les cercles d'actuariat.

Nous avons trouvé l'explication du biais, que voici d'abord expliquée conceptuellement en deux temps. L'explication est produite sous forme mathématique après, et plus en détails dans l'article en annexe.

Premier temps : **le modèle de Lee Carter consiste à calibrer les taux d'améliorations de mortalité âge *par âge* et à appliquer sensiblement les mêmes améliorations de mortalité *par âge* dans le futur.** Expliquons déjà cela. En calibrant les taux de mortalité m_x (même définition que q_x sauf que le nombre de décès dans l'année est rapporté au nombre de personnes en milieu d'année et non en début d'année; ce qui n'est pas très différent numériquement si le rapport est bien inférieur à 1) sous la forme $\log m_x = \alpha_x + \beta_x \kappa_t + \varepsilon_{x,t}$: le dernier terme est aussi petit que possible

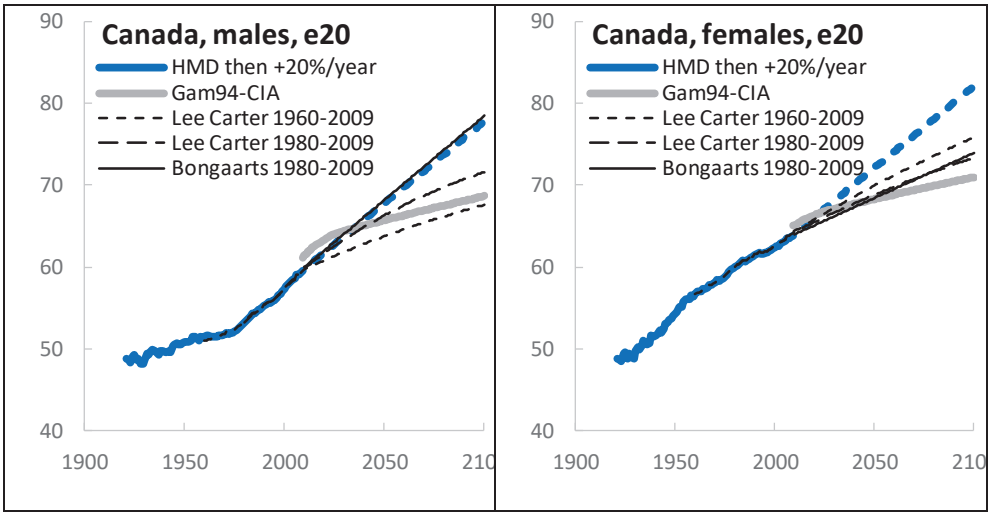
(suivant une distribution de l'erreur); arbitrairement (parmi les équivalences possibles de représentation), les β_x calibrés et les κ_t calibrés se somment respectivement à 1 et 0; α_x représente la mortalité en échelle log et $\beta_x (\kappa_{t+1} - \kappa_t)$ représente les améliorations par âge. Ces améliorations par âge sont alors utilisées pour les projections, avec la même amplitude par âge si κ_t est extrapolé linéairement, et approximativement la même amplitude sinon (modèles ARIMA).

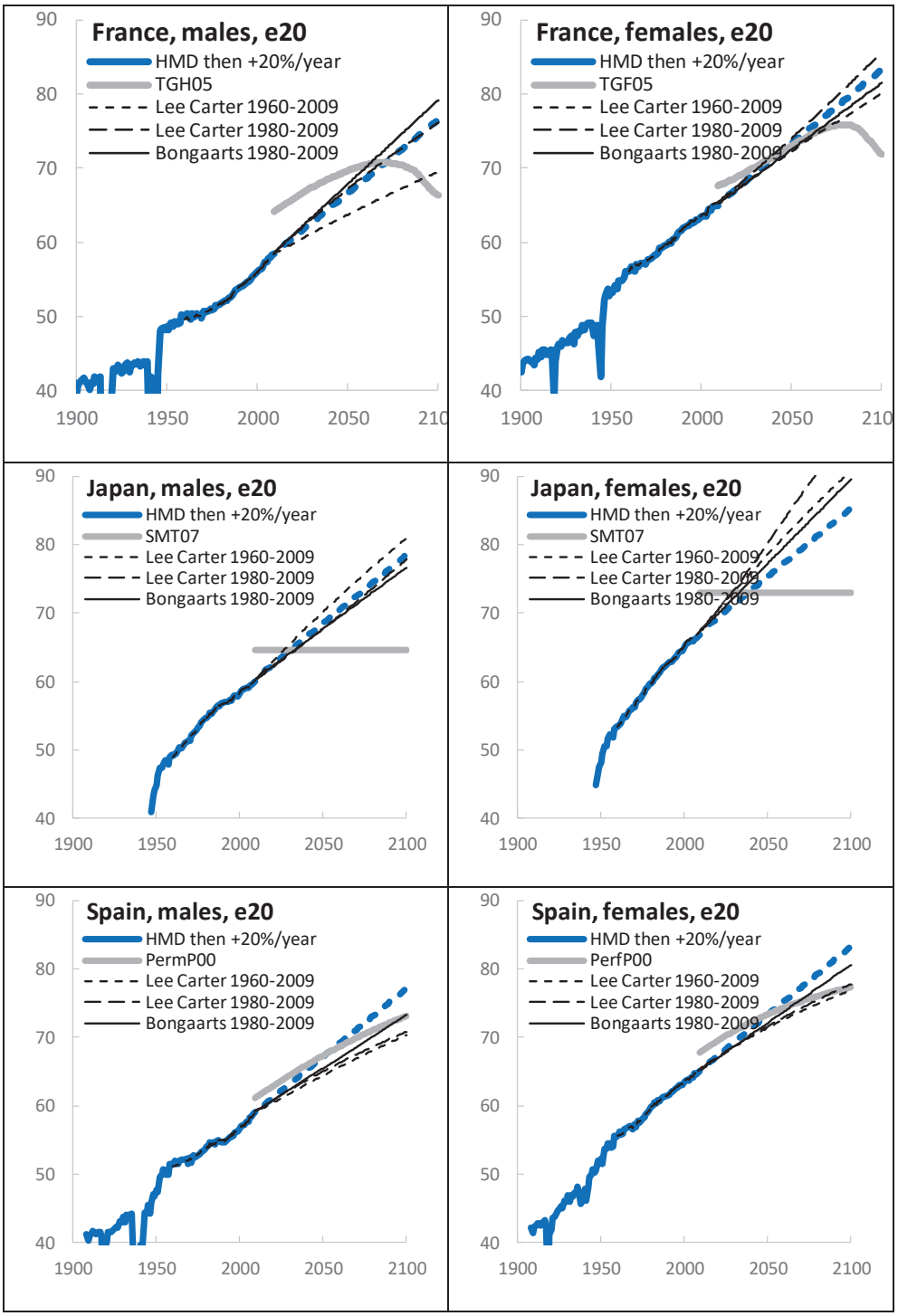
Deuxième temps : avec l'augmentation de durée de vie modélisée les âges auxquels les améliorations comptent le plus augmentent. **Lorsque les améliorations de mortalité calibrées décroissent à partir d'un certain âge jusqu'à devenir nulles** (cas standard, à moins d'historiques peu lisses suite à des changements brusques de mortalité ou un échantillon de faible taille), **les améliorations de mortalité qui comptent décroissent en conséquence jusqu'à devenir nulles**: l'espérance de vie croit de moins en moins vite jusqu'à stagner.

Le seul moyen d'éviter la décélération serait que les κ_t plongent fortement par rapport à leur évolution passée lorsque les améliorations de mortalité qui comptent décroissent. Si cela évitait la décélération de l'espérance de vie, cela provoquerait des améliorations très grandes aux plus jeunes âges calibrés et serait de ce fait fortement irréaliste. La réalité est que les améliorations historiques se sont déplacées des âges jeunes vers des âges de plus en plus élevés : la chute de la mortalité infantile a fait suite à une baisse de la mortalité adulte qui fait suite aujourd'hui à des développements biomédicaux face au vieillissement. Cela est naturel : la société développe des solutions de santé face aux problèmes principaux et non face à des conditions de santé qui surviennent dans la fraction de population la plus âgée.

Il nous semble de fait utile d'informer et d'alerter sur ce biais généralement introduit involontairement, d'autant qu'il est souvent appliqué aux engagements de retraites qui sont tout sauf négligeables.

Afin de montrer visuellement l'effet, pour différents pays l'espérance de vie est calculée à différentes dates passées pour la population générale et extrapolée linéairement suivant la tendance des pays développés avec une pente donnée (+20% par an) – c'est le scénario contrôle, sans le biais – et par modèle de Lee Carter, calibré sur diverses dates. Nous ajoutons un autre contrôle qui est le modèle de Bongaarts, c'est à dire en termes d'espérance de vie une tendance linéaire sur la base de l'historique du pays. Lorsque nous le pouvons nous ajoutons enfin l'espérance de vie des assurés telle que modélisée par une table de mortalité fréquemment utilisée par les actuaires pour ce pays. Point de détail, ces tables n'indiquant souvent pas les taux de mortalité avant l'âge adulte nous faisons tous ces calculs pour l'espérance de vie à 20 ans et non à la naissance. Le résultat pour quelques pays est indiqué figure 2, plus de résultats sont disponibles à la figure 3 de l'article (voir Debonneuil *et al.* (2017) en annexe).




France, males, e20
HMD then +20%/year
TGH05
Lee Carter 1960-2009
Lee Carter 1980-2009
Bongaarts 1980-2009
France, females, e20
HMD then +20%/year
TGF05
Lee Carter 1960-2009
Lee Carter 1980-2009
Bongaarts 1980-2009
Japan, males, e20
HMD then +20%/year
SMT07
Lee Carter 1960-2009
Lee Carter 1980-2009
Bongaarts 1980-2009
Japan, females, e20
HMD then +20%/year
SMT07
Lee Carter 1960-2009
Lee Carter 1980-2009
Bongaarts 1980-2009
Spain, males, e20
HMD then +20%/year
PermP00
Lee Carter 1960-2009
Lee Carter 1980-2009
Bongaarts 1980-2009
Spain, females, e20
HMD then +20%/year
PerfP00
Lee Carter 1960-2009
Lee Carter 1980-2009
Bongaarts 1980-2009

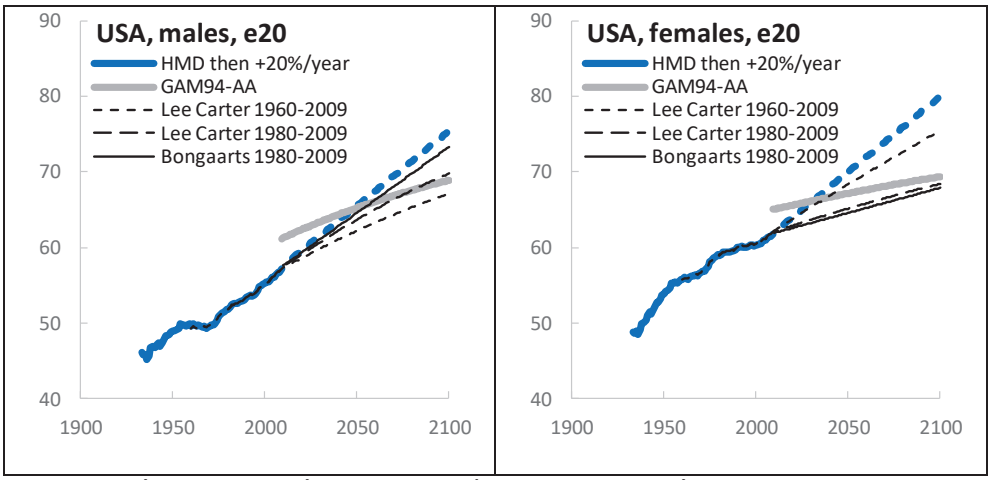


Figure 2. Prédictions d'espérances de vie à 20 ans pour différents pays, pour la population générale suivant divers modèles et pour les assurés. HMD: Human Mortality Database (mortality.org)

Nous observons donc **une décélération souvent produite par le modèle de Lee Carter**, ici dans tous les cas sauf celui du Japon pour les dates de calibration 1960-2009 et 1980-2009 — nous y reviendrons. Cette décélération est plus prononcée pour les tables de mortalité d'assurés, ce qui suggère que l'utilisation du modèle de Lee Carter ou de techniques similaires n'est qu'une des composantes de la décélération modélisée par les tables de mortalité dans le monde. Le cas des tables TGH05 et TGF05 (Tables Générationnelles Hommes et Femmes 2005) en France apparait particulièrement problématique en observant les espérances de vie produites, puisque de fortes décroissances apparaissent brutalement après 2070, mais cela provient d'une fermeture de tables particulière aux très grands âges qui n'a pas forcément tant d'impact lorsque des engagements sont calculés de façon prospective.

Toujours afin d'éclairer les esprits sur la non-extrapolation de la tendance du passé par le modèle de Lee Carter, nous **mesurons le biais rétrospectivement** : nous nous plaçons en 1989 et estimons l'espérance de vie à 20 ans et à 65 ans en 2009. Figure 3, nous voyons que sur un ensemble de pays cela amène **quasiment systématiquement** à sous estimer l'espérance de vie, de respectivement environ 2 ans et 1 ans en moyenne.

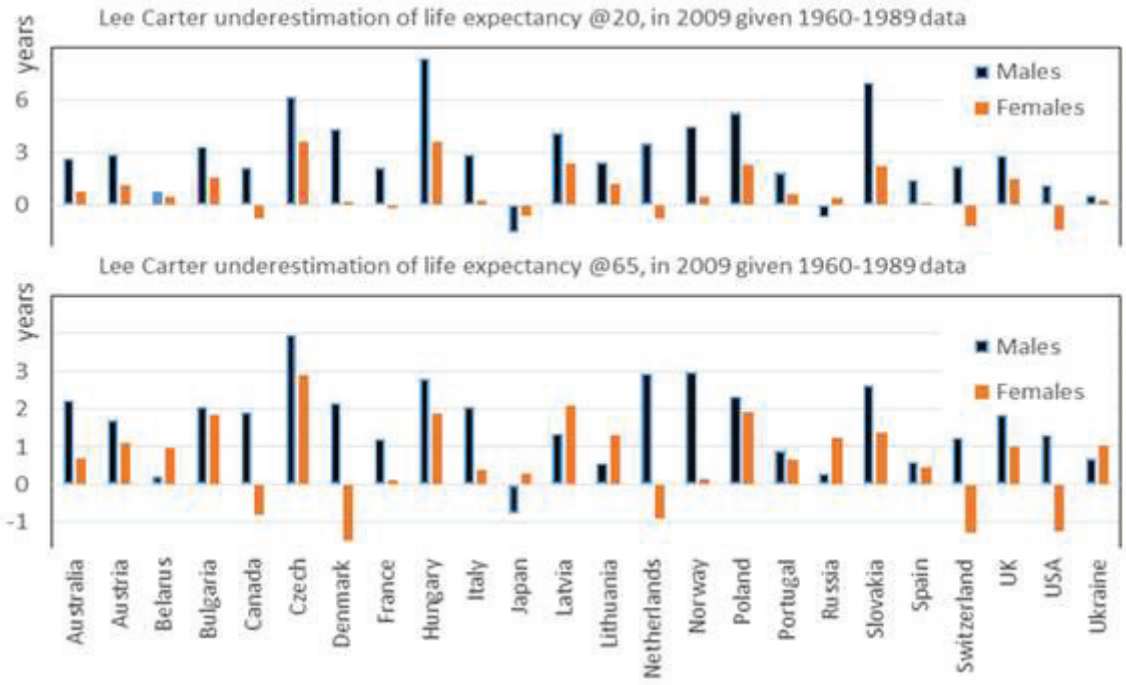


Figure 3. Sous estimations rétrospectives de l'espérance de vie par le modèle de Lee Carter.

Notons que **dans l'article initial de Lee Carter, la décélération naturelle du modèle était connue** et présentée comme un avantage du modèle (voir Lee et Carter (1992)), car à l'époque le franchissement systématiques des limites d'espérances de vie imaginées n'avait encore été décrit (voir Oeppen et Vaupel (2002)).

Reprenons l'explication avec un schéma et des équations, pour une explication complémentaire. La figure 4 schématise la forme des taux d'amélioration de mortalité en fonction de l'âge, et notamment ce qui compte pour comprendre le biais : leur décroissance à partir d'un certain âge.

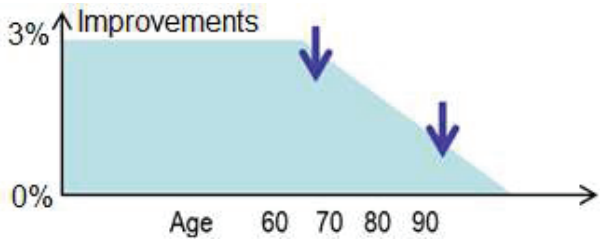


Figure 4. Schéma des améliorations par âge

Un développement mathématique détaillé dans l'article montre que ces améliorations sont le moteur linéaire de l'augmentation d'espérance de vie. Plus précisément, l'augmentation de l'espérance de vie d'une année à la suivante est une combinaison linéaire des améliorations i_{xt} :

$$e_{20,t+1} - e_{20,t} = \sum_{x=20}^{170} w_{x,t} i_{x,t}$$

Les poids $w_{x,t}$ sont donnés par :

$$w_{x,t} = q_{x,t} S_{20 \to x}\left(e_{x+1,t} + 0{,}5\right).$$

Aujourd'hui, les poids sont essentiellement centrés autour des âges 60-70 ans, le moteur de l'augmentation de l'espérance de vie est donc proche de 3 % si l'on suit la première flèche bleue du schéma. Lorsque l'espérance de vie aura augmenté, les poids seront décalés vers des âges plus grands et le moteur de l'augmentation de l'espérance de vie sera beaucoup plus faible : par exemple inférieur à 1 % comme indiqué par la flèche bleue de droite. Les améliorations aux très grands âges étant généralement considérées comme nulles, asymptotiquement **le modèle de Lee Carter produit une limite d'espérance de vie.** C'est ainsi que les espérances de vie produites ne sont pas linéaires en fonction de l'année future mais au contraire décélèrent jusqu'à ne plus évoluer. Si l'espérance de vie a cru ces dernières décennies (voire siècles, en faisant abstraction des périodes de guerre) approximativement linéairement, c'est justement parce que les améliorations par âge ont évolué. En les figeant, le modèle de Lee Carter provoque une décélération de l'espérance de vie.

Le cas du Japon, où le modèle de Lee Carter projette une espérance vie à 20 ans convexe, s'explique très bien d'après la figure 5 (extraite de la figure 5 de l'article). A gauche, nous voyons que suivant les dates de calibration du modèle, le modèle produit tantôt une espérance de vie inférieure à une extrapolation linéaire (modèle de Bongaarts) tantôt une espérance de vie supérieure. A droite, les taux d'amélioration par âge mesurés durant la période de calibration sont affichés avec les mêmes styles, et les poids $w_{x,t}$ en gris épais indiquent que les âges importants pour l'amélioration de l'espérance de

vie sont aux alentours de 85 ans. Comme indiqué par le cercle rouge, aux alentours de 85 ans les améliorations mesurées entre 1980 et 2009 sont très élevées avec notamment un saut étrange à 90 ans (potentiellement la conséquence d'une erreur de mesure de population 90 ans plus tôt); le modèle garde cette forme étrange pour le futur et produit l'espérance de vie encerclée en rouge. En haut à droite du graphe de gauche cette espérance de vie finit par redevenir concave car les âges où le poids $w_{x,t}$ est important augmentent progressivement, et car les améliorations considérées aujourd'hui aux âges de 95 ans et plus sont inférieures à celles autour de l'âge de 85 ans.

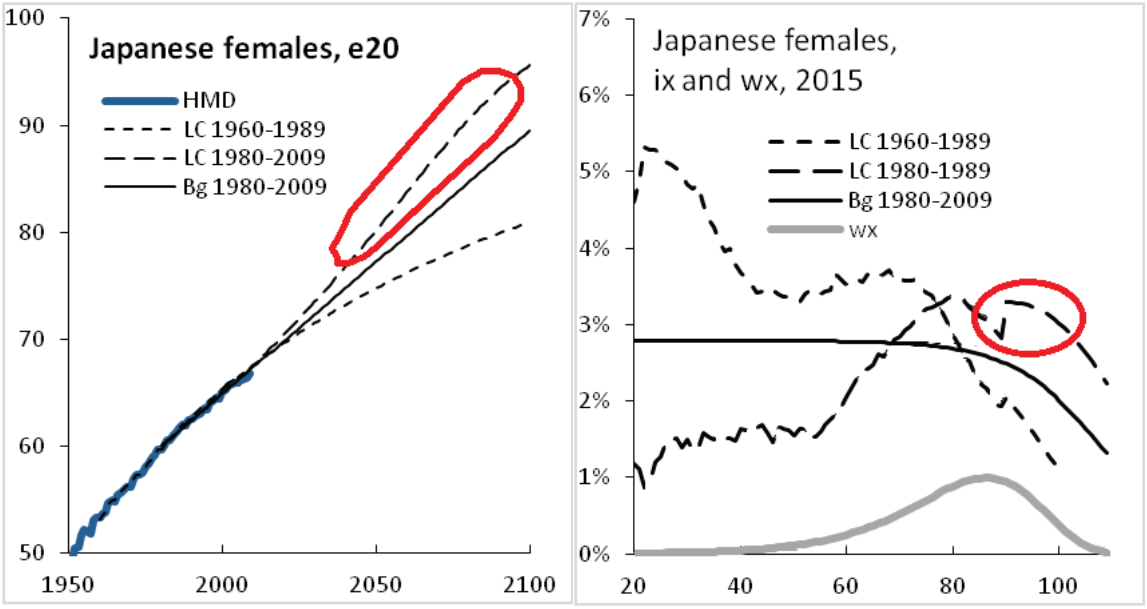


Figure 5. L'extrapolation tantôt concave tantôt convexe de l'espérance de vie des femmes japonaises par le modèle de Lee Carter (graphe de gauche) vient d'une forme particulière des améliorations en fonction de l'âge (graphe de droite). Le fait de projeter une espérance de vie tantôt concave ou convexe du fait de cette bizarrerie souligne d'autant plus l'attention à porter à ce biais du modèle de Lee Carter.

Nous pouvons de là généraliser : les modèles utilisant dans le futur des améliorations calibrées en fonction de l'âge auront une tendance à construire artificiellement une décélération, par non prise en compte de la dynamique de déformation temporelle des améliorations en fonction de l'âge. Cela inclue les modèles de type Lee Carter et Cairns Blake Dowd (voir Cairns *et al.* (2007)) à l'exception du modèle de Curie, généralement délaissé du fait de sa simplicité, car il épouse moins bien les taux de mortalité

historiques. Cependant, si l'objectif est de calculer des prix ou des réserves, la tendance de longévité est une composante qui devrait être prioritaire.

b) Des modèles qui ne produisent pas de décélération

Bongaarts (2014) propose un modèle qui, par construction, produit une espérance de vie qui augmente linéairement dans le temps. Plus généralement, et suite à notre analyse également, tous les modèles de type

$$\mu_{xt} = f(k_x x + v t)$$

ou bien

$$m_{xt} = f(k_x x + v t)$$

ou bien

$$q_{xt} = f(k_x x + v t)$$

produisent des espérances de vie linéaires. Debonneuil *et al.* (2017) utilise la deuxième formulation, plus précisément

$$logit\, m_{x,t} = A + B\,(x + s\,t)$$

où la tendance de longévité est par exemple s=20%. Debonneuil *et al.* (2018) utilise la troisième formulation, plus précisément

$$q_{x,t} = \frac{1}{1+e^{a-b(x-\varphi t)}}$$

où la tendance de longévité est par exemple φ=20%. Les deux modèles sont numériquement extrêmement similaires si s=φ, b=B et $e^{-a} = e^{-A}$. Aux très grands âges les taux de mortalité annuels tendent vers $1-e^{-1}=0.63$ avec le premier modèle et 1 pour le deuxième, mais cela a peu d'effet sur les calculs d'espérance de vie à 65 ans par exemple car il s'agit de très grands âges. Pour plus de similitude, le deuxième modèle aurait pu avoir un autre numérateur, mais 1 est plus esthétique et les taux de mortalité aux très grands âges ne sont pas précisément connus du fait du petit nombre de personnes à ces âges.

Un "**effet cohorte**" pourrait être ajouté de la forme "$+c_x\ g_{t-x}$", mais ce n'est pas forcément pour de bonnes raisons que ce type de modèle calibre souvent mieux les

données historiques : dans son mémoire, Debonneuil (2014) montre que les effets cohortes calibrés par ce type de modélisation sur les données françaises sont en réalité essentiellement des mesures de biais de recensement de population au voisinage des grandes guerres mondiales, et qu'utiliser cette modélisation de **soi-disant "effets cohortes"**, donc, pour le futur correspondrait à créer des biais de recensements imaginaires d'autres générations. Or, ces biais (appelés effets cohortes) semblent similaires pour d'autres pays (Allemagne et Angleterre notamment) : dans ces pays au moins, l'ajout de cette composante dite "effet cohorte" crée en réalité de faux effets cohortes.

La forme de ces deux modèles étant très simple, il peut être plus précis par exemple de prendre une fonction "f" paramétrique de type Heligman Pollard pour modéliser plus précisément la forme de la log mortalité en fonction de l'âge, comme proposé par Debonneuil (2004). Cependant, un avantage conceptuel de ces modèles simple est justement de pouvoir réfléchir simplement, notamment comme nous le verrons dans le cadre du méga fonds: le paramètre de tendance (s ou φ) est à la fois la tendance à la baisse de la mortalité et la tendance à la hausse de l'espérance de vie, qui augmente de s tous les ans.

c) Tendance de référence: tendance du pays ou "best practice trend"?

Comme nous l'avons souligné plus haut, les pays de grande espérance de vie ont une espérance de vie qui augmente ces dernières décennies d'un peu moins d'un trimestre par an. Il s'agit de la "best practice trend", dénomination plus précisément se rapportant à l'espérance de vie maximale d'espérance de vie dans le monde (voir Oeppen et Vaupel (2002)). Les pays de grande espérance de vie peuvent typiquement s'éloigner de cette best practice et y revenir, et donc avoir des tendances momentanément inférieures ou supérieures à la best practice trend. Dans ces cas, **la prédiction de la longévité future est meilleure en prenant la best practice trend qu'en poursuivant la tendance du moment**.

Cette intuition se vérifie en comparant les deux rétrospectivement, figure 6. Nous voyons que sur l'intervalle de 20 ans considéré l'utilisation d'une tendance centrale (Best Practice Trend) fournit de bien meilleurs résultats que la tendance historique des pays. Quelques pays échappent à cette bonne prédiction : des pays de l'ex-Union Soviétique dont l'espérance de vie n'a que très peu évolué dans la période. En considérant ces exceptions, la prédiction avec la tendance centrale a beaucoup de sens.

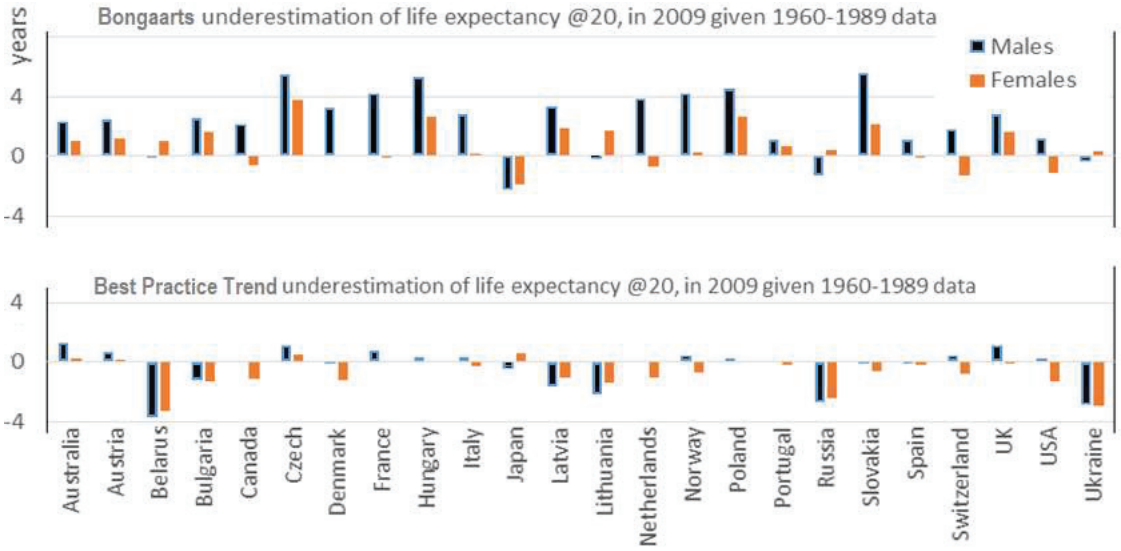


Figure 6. En haut: pour l'essentiel des pays testés, l'extrapolation de la tendance historique du pays de 1989 à 2009 (en s'appuyant sur les données des années 1960-1989) sous estime l'espérance de vie (espérance de vie à 20 ans ici). En bas: l'utilisation de la "best practice trend" (+20% d'espérance de vie à 20 ans chaque année) est un bien meilleur prédicteur sauf pour certains pays dont l'espérance de vie a évolué bien plus lentement que les autres pays: la Russie, l'Ukraine, la Biélorussie, et dans une moindre mesure la Lettonie et la Lituanie.

Cette analyse a potentiellement un biais du fait que nous savons aujourd'hui que l'espérance de vie dans le passé a globalement augmenté d'un peu moins d'un trimestre par an depuis longtemps pour un grand nombre de pays ; dans ces conditions nous avons en partie simplement vérifié ce que nous savons. Suite à la découverte toutefois que la tendance de fonds des pays de forte longévité est meilleure que l'utilisation de la tendance du pays lui-même, par la suite nous utilisons ce modèle :

$$q_{x,t} = \frac{1}{1 + e^{a-b(x-\varphi t)}}$$

Avec par exemple φ=20% pour une projection centrale, qui correspondrait à une absence de guerre majeure ou pollution majeure (ou autre situation similaire à la fin de l'ex-Union Soviétique) mais aussi une absence d'apparition de traitement majeur contre le vieillissement et ses pathologies (tout en supposant un maintien d'innovation biomédicale et d'amélioration de l'hygiène régulières). Suivant ensuite le niveau d'amélioration envisagé, φ peut prendre des valeurs plus petites ou plus grandes.

Le coefficient b=0.1 vient du fait que la calibration de cette forme (une régression logistique) en fonction de l'âge donne 0.1 à 1% près pour les pays développés, il est donc ici mis en dur. Le coefficient « a » dépend de la population, il pourrait par exemple se décomposer en « a'+b'*sexe » où « sexe » vaut 0 ou 1 suivant qu'il s'agisse d'hommes ou de femmes. Par la suite nous n'aurons pas besoin de faire de distinction entre hommes et femmes, et utiliserons a=10.5 ce qui à t=0 donne une espérance de vie de 84.4 ans, ce qui est légèrement supérieur à l'espérance de vie française actuelle et peut typiquement représenter l'espérance de vie d'assurés.

Nous poursuivons avec ce modèle qui nous semble adapté pour fournir des ordres de grandeur financiers raisonnables. Pour des besoins de prédiction de taux de mortalité à court terme, cette forme de mortalité en fonction de l'âge pourrait être inadaptée et un modèle de Lee Carter (par exemple) préférable, ou ce modèle pourrait être ajusté pour calibrer des formes de mortalité en fonction de l'âge plus subtiles comme indiqué par Debonneuil (2014).

d) Distribution de tendances possibles de longévité

Nous avons vu en première section que les avis divergent fortement quant à la tendance future de la longévité humaine, certains imaginant que le premier homme qui vivra mille ans est né, d'autres imaginant que la longévité va diminuer.

Face à ces grandes incertitudes, **nous modélisons la tendance φ de façon simple afin d'étudier les grands ordres de grandeur**. Premièrement nous considérons une tendance φ **constante** dans le futur. Une meilleure modélisation aurait consisté à partir

de la tendance actuelle et à la faire dériver progressivement vers une autre tendance, mais il aurait fallu alors modéliser cette dynamique progressive. Cela serait revenu à modéliser "quand" des découvertes majeures contre le vieillissement auront lieu ou "quand" des catastrophes majeures (pollution, climat) décimeront les populations. Deuxièmement nous considérons une **distribution log normale** de φ, parce que l'augmentation de durée de vie pourrait être très grande mais que la probabilité d'avoir un φ proche de la tendance actuelle est importante. Par simplicité nous considérons que la médiane est 20% et le paramètre d'écart-type 1, ce qui correspond à la densité de fonction suivante, illustrée en Figure 7 :

$$\mathrm{pdf}(\varphi) = \frac{e^{-\frac{(\ln\varphi - \ln 20\%)^2}{2s^2}}}{\varphi s\sqrt{2\pi}}$$

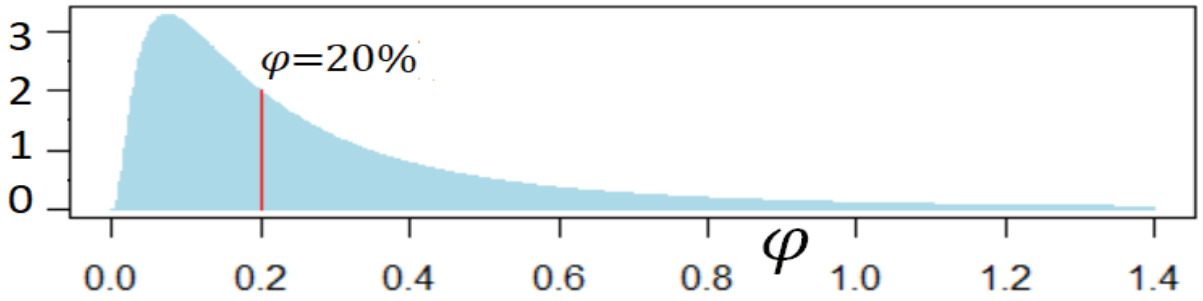


Figure 7. Densité de probabilité de φ, où φ est en axe des abscisses et la médiane φ=0.20 est la barre verticale rouge. L'aire sous la courbe vaut 1, l'aire sous la courbe pour φ>1 vaut 5%.

Suivant cette distribution, il y a autant de probabilité que φ soit plus petit que 20% que plus grand que 20%. Il y a aussi 5% de probabilité que φ>1(vitesse d'échappement de la longévité): sur de longues périodes de temps, cela signifierait que les personnes bénéficient d'une meilleure santé et d'un risque de mortalité qui diminue dans le temps, par exemple du fait de l'émergence et de la généralisation progressive de techniques de régénération des tissus. Certains trouveront ce 5% particulièrement élevé et d'autres particulièrement bas, comme indiqué en début de première section. C'est pourquoi nous allons aussi considérer des scénarios, notamment φ=50% et φ=80%. Pour une mise en perspective, nous pouvons rappeler qu'aux alentours de 1950 la tendance au Japon était clairement supérieure à φ=100% ce qui suggère que de grandes tendances sont

possibles lorsque l'hygiène, les avancées biomédicales et les contextes sociaux sont adéquats. Une autre mise en perspective est que ces dernières décennies l'espérance de vie a augmenté de plus de φ=50% d'année par an en Malaise, aux Philippines, au Vietnam, au Laos et au Bangladesh (voir Carbonnier *et al.* (2013)). Une autre mise en perspective encore est que durant près de 70 ans après la sensibilisation générale aux microbes par Louis Pasteur, φ était d'approximativement 30% dans les pays de plus grande espérance de vie (voir Vallin et Meslé (2010)) ; or, améliorer l'hygiène nécessite des changements culturels, technologiques et d'urbanisation complexes. Il est probable que l'adoption de thérapies antivieillissement une fois qu'elles existent soit un processus beaucoup plus rapide: un φ supérieur à 30% est assez probable.

e) Quelques scénarios

La Figure 8 présente quelques scénarios d'espérance de vie future pour la France (voir Debonneuil *et al.* (2017) en annexe).

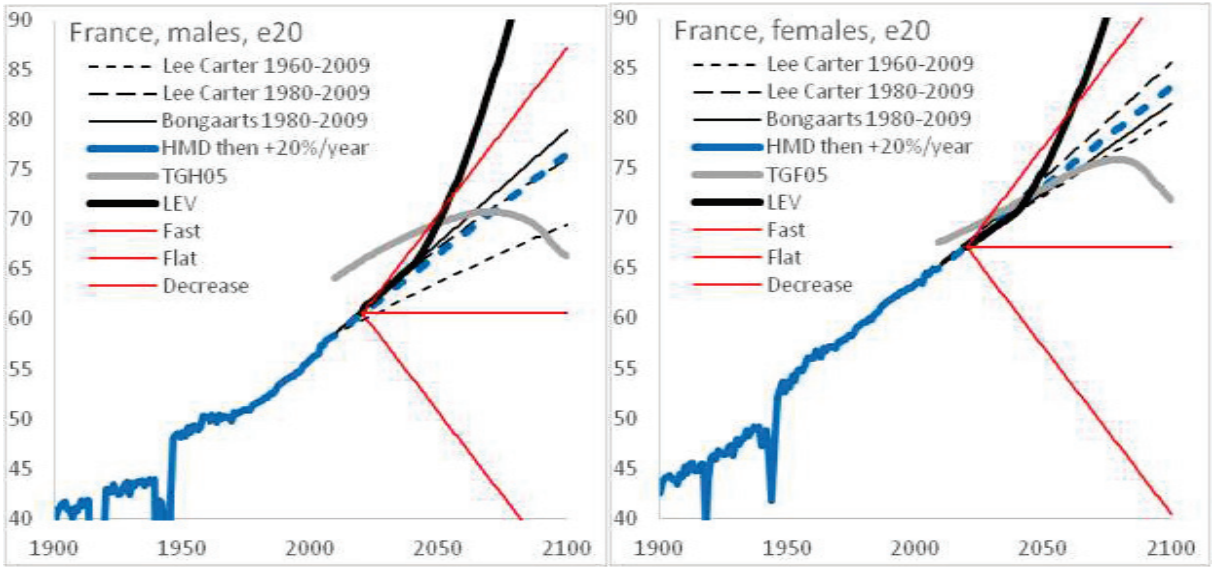


Figure 8. Exemples de scénarios de longévité pour la France, pour les hommes (à gauche) et pour les femmes (à droite). L'axe des ordonnées est l'espérance de vie à 20 ans. En ligne bleue épaisse continue, l'espérance de vie historique. En ligne bleue épaisse en pointillés, la poursuite à un rythme φ=20%. En ligne noire fine continue, la poursuite de la tendance des dernières décennies (modèle de Bongaarts). En courbe noire fine en pointillés, longs et courts, le modèle de Lee Carter suivant qu'il soit calibré sur 30 ou 50 ans d'historique. En

lignes rouges, φ=-20%, 0% ou 40%. En courbe noire épaisse, le modèle de "vitesse d'échappement de la longévité" tel que suggéré par Aubrey de Grey (voir de Grey, (2015)).

III. Des dispositifs de protection sociale sensibles aux améliorations de la longévité

Malgré la très grande couverture potentielle du titre de cette section, nous étudierons essentiellement ici le risque de longévité dans le cas de dispositifs de retraites. Nous commençons toutefois par lister divers dispositifs de protection sociale en France afin d'avoir un angle de vue plus large.

a) Divers dispositifs de protection sociale, plus ou moins sensibles aux améliorations de la longévité

En France, les risques couverts par la protection sociale sont ceux de la santé, la famille, la vieillesse et la survie, le logement, l'emploi, la pauvreté et l'exclusion sociale, et le risque de dépendance.

Une bonne partie de ces risques n'ont **pas de lien évident** avec les avancées de la longévité, même si des liens existent forcément mais qui ne sont pas clairement positifs ou négatifs financièrement.

Tel est le cas par exemple du risque d'**emploi**, qui comprend l'indemnisation du chômage, mais aussi des dispositifs liés à l'insertion et à la réinsertion professionnelle. Un exemple de lien est que vivre plus longtemps pourrait amener davantage à effectuer des formations professionnelles au cours de sa carrière pour s'adapter aux changements des besoins et des technologies, et réduire ainsi les risques de chômage. Cependant cette vision est certainement très parcellaire, par exemple le chômage n'est pas qu'une question d'adaptation de chacun aux besoins professionnels du moment. Un autre exemple de lien est que les personnes de plus de 65 ans et par exemple moins de 90 ans seraient amener à travailler, peut être sous forme d'insertion professionnelle au départ. Cela pourrait être positif pour l'emploi, ces seniors ayant des relations professionnelles

fortes établies au fil des années et pouvant alors être réactivées pour développer les activités.

Le risque de **logement**, plus précisément d'allocation au logement, n'est pas de façon évidente lié aux avancées de la longévité. Le risque de **pauvreté** et d'**exclusion sociale**, notamment des prestations pour des personnes démunies, ne l'est pas non plus.

Certains risques ont un lien beaucoup plus évident avec les avancées de la longévité. Les risques de **vieillesse et survie**, qui comprennent les pensions, sont évidemment les premiers concernés. Les autres risques ont des liens peu prédictibles.

Le risque de la **santé**, qui comprend la **maladie**, l'invalidité, les accidents et les maladies professionnelles, est concerné en particulier pour la **maladie**. Cependant le sens de l'impact n'est pas évident et dépend de l'allongement de la vie "en bonne santé" par rapport à l'allongement de la vie "en mauvaise santé". Si des solutions de santé majeures, à usage unique et rapide telles qu'une vaccination ou une thérapie génique unique, permettent de traiter rapidement ou d'éviter des maladies chroniques, le coût de l'application de ces solutions devrait être inférieur aux gains (comptabilisés au sein d'une même période) obtenus par évitement de coûts de remboursements pour traiter ces maladies. Par contre, si des solutions à usage chronique maintiennent les personnes en vie sans fortement améliorer la santé, les coûts de l'assurance maladie augmentent.

Les risques d'**invalidité** ont un lien faible avec les avancées de la longévité : les accidents et les maladies professionnelles correspondent à des âges jeunes pour lesquels les risques ne représentent pas l'essentiel des coûts face aux frais de gestion, si bien que l'amélioration des risques est loin d'avoir une influence aussi importante que pour les risques de vieillesse et survie. De plus, de fortes améliorations de santé pour les grands âges, tels que des traitements contre Alzheimer et les cancers, n'ont pas forcément des impacts majeurs sur les risques d'invalidité, qui concernent d'autres âges et majoritairement d'autres conditions. Pour les mêmes raisons et de façon plus évidente, les accidents et maladies professionnelles ont peu de lien avec la longévité.

Les risques de la **famille** ont vraisemblablement plus de liens, mais le sens global des liens n'est pas évident. Ainsi, les prestations liées à la maternité seraient réduites si le

nombre d'enfant par femme baisse avec la longévité, mais cela n'est pas totalement évident. Par exemple l'attention au risque de mortalité serait potentiellement renforcé ainsi que l'attention portée aux soins pour la mère et l'enfant. Les aides pour la garde d'enfants pourraient être réduites du fait de la disponibilité accrue des grands-parents, sauf s'ils sont moins disponibles du fait d'une activité professionnelle soutenue.

Les risques de **dépendance** ont, tout comme pour la maladie, un lien positif ou négatif avec l'allongement de la vie suivant qu'il se fasse majoritairement en bonne ou mauvaise santé. S'il s'agit d'une augmentation de durée de vie sans dépendance, et que la durée de vie en dépendance reste sensiblement constante, les cotisations sont collectées sur plus de durée pour des coûts constants. A l'extrême inverse, s'il s'agit d'une constante durée de vie sans dépendance et d'une augmentation de la durée de vie en dépendance, les coûts augmentent fortement mais pas les collectes.

Pour ces raisons, **nous nous concentrons par la suite sur le risque de longévité lié à la vieillesse et à la survie, ou plus précisément sur les systèmes de retraite.**

Les coûts de remboursement des soins et de l'aide humaine dans le cadre de la maladie et de la dépendance peuvent également augmenter fortement si les solutions de santé permettant de vivre significativement plus longtemps allongent en réalité surtout la durée de vie en mauvaise santé. Si l'explosion actuelle des maladies chroniques va dans ce sens, ce n'est heureusement pas le sens des résultats actuels de la biologie du vieillissement sur des animaux.

b) Différents systèmes de retraite ont différentes formes de risque de longévité

Suivant les pays, les retraites sont organisées très différemment.

En France par exemple, les retraites sont majoritairement financées par le système d'assurance public et par **répartition**. Ce dernier terme signifie que les cotisations versées par les personnes qui travaillent servent à brève échéance à payer les montants de retraite des retraités. Dans ces conditions, le ratio entre le nombre de retraités et le

nombre de travailleurs, et sa déformation, joue un rôle majeur. En cas d'avancée majeure de la longévité, telle qu'une augmentation des cotisations ne suffit pas à équilibrer le système, seule l'augmentation de l'âge de la retraite permet d'assurer des revenus acceptables pour les retraités ; sans cela, l'état ferait faillite.

Aux Etats-Unis et au Royaume-Uni, les retraites sont majoritairement financées par des **fonds de pension**, majoritairement privés. Deux grands types de fonds de pension se distinguent, les fonds de pension à contribution définie et les fonds de pension à prestation définie.

Dans les fonds à **contribution définie**, les ***cotisations sont définies à l'avance***, typiquement par un pourcentage du salaire ; elles sont investies dans des fonds; au moment du départ à la retraite, le capital ainsi accumulé est converti en montant de rente suivant une table de mortalité en vigueur. Le premier risque que les bénéficiaires craignent est que les rendements des fonds soient faibles ce qui amène à de faibles retraites. Le deuxième risque est que la durée de vie des populations à la retraite soit plus longue que prévue par les tables en vigueur et que le fonds de pension, ou l'assureur qui gère son risque, fasse faillite et que les populations ne reçoivent alors pas les montants de retraite prévus. Ce deuxième risque est exacerbé lorsque contractuellement la conversion s'appuie sur une table garantie et non pas sur une table en vigueur : non seulement les bénéficiaires vivront plus longtemps mais en plus leurs montants de rente annuels seront élevés du fait d'une table s'appuyant sur d'anciens taux de mortalité (voir Antolin et Mosher (2014), Oeppen et Vaupel (2002) et Debonneuil *et al.* (2017) en annexe).

Dans les fonds à **prestation définie**, les ***versements sont annuellement ajustés***, suivant les rendements du fonds et l'évolution des taux de mortalité, afin d'être capable de verser ultérieurement les ***montants de rente prévus*** contractuellement. Ces montants sont typiquement définis par un pourcentage des derniers salaires. Le premier risque qu'une entreprise craint – qu'elle gère le fonds de pension elle-même ou, plus couramment, s'appuie sur un fonds de pension externe – est que les cotisations à verser pour ses employés augmentent du fait des faibles rendements du fonds. Ce risque peut

aller à l'extrême jusqu'à la faillite de l'entreprise. Le deuxième risque est que les retraités vivent plus longtemps que prévu par le fonds ; que le capital prévu par le fonds se révèle alors insuffisant ; que le fonds fasse faillite et que les populations ne reçoivent pas les montants de retraite prévus. Un tel cas entraina par exemple la faillite de la ville de Détroit, aux Etats-Unis, en 2013 (voir Rauh *et al.* (2016)).

Les nuances entre ces deux types de fonds de pension apparaitront plus clairement lorsque nous étudierons l'intérêt d'investir dans un méga fonds de longévité.

c) Des enjeux financiers majeurs gérés avec des modèles sous-estimant les tendances actuelles de longévité.

Dans le monde, les montants à gérer dans les fonds de pension sont de l'ordre de **40 mille milliards de dollars** (voir Willis Towers Watson (2017)). Or, les tables de mortalité ont tendance à être insuffisantes devant des modèles de type Lee Carter (voir Antolin et Mosher (2007)). Or aussi, comme nous l'avons vu, les modèles de type Lee Carter ont tendance à projeter des tendances de longévité inférieures à celles du passé (voir Debonneuil *et al.* (2017) en annexe). Or aussi, comme nous l'avons vu, les améliorations de longévité pourraient être très supérieures à un trimestre par an. **Les enjeux sont donc importants et devront être gérés.**

Prenons l'exemple de la France. Le Conseil d'Orientation des Retraites (COR) conseille sur les ajustements à effectuer en France sur le système de retraite. Nous observons en Table 1 que les scénarios sur lesquels ils s'appuient (COR 2013) ont des tendances de longévité inférieures aux tendances de longévité que nous obtenons en appliquant un modèle de Lee Carter calibré sur 50 ans, elles mêmes inférieures à celles des tables actuarielles de référence (TGH TGF 2005), elles mêmes inférieures à celles du modèle vu plus haut avec φ=20%. La comparaison entre les modèles COR et Lee Carter sur 50 ans diffère entre les hommes et les femmes ; elle est à rapprocher de la figure 8 où l'on voit que le modèle de Lee Carter se comporte étrangement chez les hommes. De cette comparaison on déduit visuellement que **le modèle du COR n'allonge pas la durée de**

vie d'environ un trimestre par an mais plutôt d'environ un demi trimestre par an. Ainsi, les tendances de fond actuelles de longévité semblent insuffisamment prises en compte pour la bonne gouvernance du système français de retraite publique.

Example: France	e60,2010		e60,2060		Evolution	
	Hommes	Femmes	Hommes	Femmes	Hommes	Femmes
COR	22.2	27.2	28.0	32.3	**5.8**	**5.1**
LC 1960-2009	22.5	27.5	27.7	35.0	5.2	7.5
TGH TGF 2005	25.8	29.1	32.3	35.6	6.5	6.5
φ=20%	21.5	27.0	29.8	36.3	**8.3**	**9.3**
LC 1980-2009	22.6	27.6	31.0	37.5	8.4	9.9

Table 1, extraite de la table 3 de Debonneuil et al. (2017) en annexe. Espérance de vie à 60 ans des hommes et des femmes en France, en 2010 et 2060, suivant divers modèles, et différence entre 2060 et 2010 : cette évolution de l'espérance de vie à 60 ans sert d'indicateur simple pour trier les modèles de haut en bas dans le tableau.

Le système de retraite privé lui, s'appuie sur les tables actuarielles TGH TGF 2005. La table 2 indique que l'utilisation sous forme prospective de cette table n'est pas aussi biaisée que l'utilisation sous forme statique vue en Figure 2, où la fermeture particulière de la table amenait l'espérance de vie statique à diminuer fortement dans le futur. L'utilisation de φ=20% ou d'un modèle de Boongarts qui poursuit les tendances historiques d'espérance de vie amènerait à augmenter les provisions de peut-être 2%, quoique l'effet soit différent entre les hommes et les femmes et l'année considérée. Ainsi le système de retraite privé en France semble appliquer des hypothèses qui correspondent presque à la poursuite des tendances actuelles.

For people aged 65	In 2015		In 2025	
Trend/ Scenario	Males	Females	Males	Females
LEV	+4.3%	+6.5%	+13.6%	+9.8%
Fast	+3.6%	+5.4%	+7.7%	+6.2%
Bongaarts	+1.9%	+1.4%	+4.0%	-6.0%
φ=20%	+0.6%	+2.5%	+0.7%	-1.5%
THG THF 2005	0%	0%	0%	0%
Flat	-8.0%	-7.5%	-8.1%	-11.1%
Decrease	-18.7%	-19.5%	-18.9%	-22.7%

Table 2, extraite de la Table 2 de Debonneuil et al.(2017) en annexe. Impact sur les réserves d'un changement de modèle pour des annuités pour des personnes de 65 ans. Les modèles sont ceux décrits à la Figure 8.

Par contre, les tables actuarielles utilisées pour les retraites sont sensées contenir un certain degré de prudence. Si les avancées de la longévité se matérialisent fortement, les réserves calculées avec la TGH TGF05 sont insuffisantes, par exemple d'environ 5% aujourd'hui et 10% dans dix ans, si l'on suit l'exemple des deux premières lignes de la Table 2.

Comme l'indique la table 3, avec sa TGH TGF05 la France ne fait malgré tout pas partie des moins bons élèves. Cette table grise les indicateurs suggérant que des tables ont des tendances de longévité faibles comparé à une augmentation de φ=20% d'espérance de vie à 20 ans (Best Practice Trend). Le Canada, le Chili, Israël, l'Allemagne, le Japon (mais il s'agit d'un cas particulier de table actuarielle sans amélioration), l'Espagne et les USA utilisent des tables actuarielles a priori plus problématiques. Les pays pour lesquels ces calculs n'ont pas été effectués sont potentiellement plus à risque encore.

Country & tested table	Gender	Best Practice Trend $e_{g\,65}^{2009}, e_{g\,65}^{2015}, e_{g\,65}^{2020}$			Actuarial table $e_{g\,65}^{2009}, e_{g\,65}^{2015}, e_{g\,65}^{2020}$			Difference $\Delta e_{g\,65}^{2009}$	$\Delta e_{g\,65}^{2015}$	$\Delta e_{g\,65}^{2020}$	%Trend 2009→2020
Canada	Male	85.7	86.8	87.7	85.8	86.5	86.9	0.1	-0.1	-0.8	55%
GAM94-CIA	Female	89.2	90.4	91.4	88.2	88.7	89.0	-1.0	-1.7	-2.4	36%
Chile	Male	84.4	85.3	86.2	84.3	84.6	84.8	-0.1	-0.7	-1.4	28%
RV09	Female	87.9	89.1	90.1	89.2	89.4	89.6	1.3	0.3	-0.5	18%
France	Male	85.2	86.2	87.1	88.2	89.1	89.8	3.0	2.7	2.7	84%
TGHF05	Female	90.1	91.3	92.4	91.7	92.5	93.3	1.6	1.2	0.9	70%
Germany	Male	84.2	85.3	86.2	86.7	87.3	87.8	2.5	2.0	1.6	55%
DAV2004R	Female	87.8	89.1	90.1	90.4	91.1	91.6	2.6	2.0	1.5	52%
Israel	Male	86.2	87.3	88.2	86.6	87.0	87.3	0.4	-0.3	-0.9	35%
EMSSA09	Female	88.7	90.0	91.0	89.2	89.5	89.7	0.5	-0.5	-1.3	22%
Japan	Male	86.0	87.1	88.1	87.9	87.9	87.9	1.9	0.8	-0.2	0%
SMT07	Female	92.2	93.4	94.5	94.7	94.7	94.7	2.5	1.3	0.2	0%
Netherlands	Male	84.6	85.7	86.6	84.4	85.3	85.8	-0.2	-0.4	-0.8	70%
AGP10	Female	88.0	89.2	90.3	87.4	87.9	88.2	-0.6	-1.3	-2.1	35%
Spain	Male	85.2	86.3	87.2	85.1	85.7	86.1	-0.1	-0.6	-1.1	50%
PERMFC00	Female	89.8	91.1	92.2	89.5	90.0	90.5	-0.4	-1.1	-1.7	42%
Switzerland	Male	85.9	87.0	88.0	88.6	89.7	90.7	2.7	2.7	2.7	100%
ERMF09	Female	89.4	90.6	91.7	91.2	92.1	92.9	1.8	1.5	1.2	74%
USA	Male	84.5	85.5	86.4	85.0	85.5	85.8	0.5	0.0	-0.5	42%
GAM94-AA	Female	87.6	88.8	89.7	87.5	87.8	88.0	-0.1	-1.0	-1.7	24%

Table 3, copie de la Table 1 de Debonneuil et al. (2017) en annexe. Espérance de vie à 65 ans en 2009, 2015 et 2020, pour la population générale de divers pays, selon d'une part le modèle Best Practice Trend avec φ=20% et d'autre part la table actuarielle généralement utilisée. La différence d'espérance de vie devrait indiquer que les assurés vivent plus longtemps que la population générale, lorsque cela est insuffisamment respecté cette différence est grisée. L'évolution d'espérance de vie des assurés devrait a priori être voisine de celle de la population générale, lorsque cela n'est pas le cas la dernière colonne est grisée. Pour plus d'information, se référer à la table 1 de Debonneuil et al. (2017) en annexe.

d) Un risque financier majeur

Si, pour avoir un premier **ordre de grandeur** simpliste, nous multiplions les 40 trilliards de dollars d'en cours sous gestion de fonds de pensions dans le monde par 5% ou 10%, nous obtenons **2 à 4 mille milliards de dollars de risque de longévité dans le monde**. Ces 5% ou 10% sont ceux notés à partir de la Table 2, en considérant une population de 65 ans. En réalité le risque de longévité concerne des portefeuilles de personnes retraitées, à moindre risque proportionnel de longévité du fait d'une durée de vie restante plus courte, et des portefeuilles de personnes en âge de travailler, à plus grand risque mais ce risque peut être potentiellement mitigé par des actions de l'entreprise ou du fonds, ou du gouvernement, comme réduire les rentes ou augmenter l'âge de la retraite, ou encore augmenter les cotisations des actifs. De plus la Table 2 étudie le risque pour le relativement "bon élève" qu'est la TGH05 TGF05. Ainsi, au final cette estimation, très grossière, serait vraisemblablement le risque si celui-ci était aujourd'hui géré avec attention dans le monde.

Afin d'établir une mesure plus précise nous considérons un fonds de pension – à prestation définie par simplicité – et cherchons à savoir quel montant de capitaux propres il devrait avoir pour faire face au risque de longévité futur dans 90% des cas. Ce 90% considéré par appréciation personnelle peut être mis en parallèle avec Solvabilité II: Solvabilité II exige d'avoir le capital nécessaire pour faire face à ses engagements dans l'année dans 99.5% des cas. Si les chocs pouvant survenir chaque année étaient indépendants les uns des autres et identiquement distribués, l'objectif de Solvabilité II se traduirait en faisant face à ses engagements sur 21 ans dans $(99.5\%)^{21}$=90% des cas, sur 71 ans dans $(99.5\%)^{71}$=70% des cas et sur 92 ans dans $(99.5\%)^{92}$=63% des cas. En pratique, dans le domaine de la longévité un choc en cache une série qui suivent ; donc nous ne prenons pas une probabilité de 70% ou 63% mais 90%. Il ne s'agit pas non plus d'être plus prudent car sur la durée, dans le cas d'une série de chocs le système peut s'adapter.

Considérons donc une entreprise avec des employés de différentes tranches d'âge, salaires associés et contributions associées, et investissements associés comme indiqué Table 4.

Age	Individual annual contributions	Investment returns
[20-35[	3000	i1=5% ± σ1=2.7%
[35-50[	4500	i2=4% ± σ2=2.0%
[50-65[	6000	i3=2% ± σ2=0.7%

Table 4. Cotisations des employés d'âges 20-34, 35-49 et 50-64 ans, investies avec des rendements et risques différents. Extraite de la Table 1 de Debonneuil (2018).

Considérons d'abord que la tendance de longévité est celle attendue, φ=20%, ainsi que les rendements i1, i2, i3. Considérons que le capital accumulé de chaque génération correspond parfaitement aux engagements de retraite de la génération - ce qui revient à compter dans les engagements ce que l'entreprise doit verser de plus pour verser les prestations. Appelons C0 ce capital cumulé.

Supposons aussi, pour simplifier l'approche (ne pas avoir à simuler au delà de l'âge de 65 ans), que les montants de rente sont croissants durant la retraite avec un taux de croissance égal à celui du taux d'actualisation si bien que la duration des versements est égale à la durée à 65 ans, $D_{20\%}$. Ainsi, si la longévité évolue, le capital cumulé nécessaire pour servir les rentes devient $C = C0^* D_{\varphi}/D_{20\%}$.

Si φ<20%, il y a un surplus actualisé de $C0\ (1-D_{\varphi}/D_{20\%}) / [(1+i1)\ (1+i2)\ (1+i3)]^{15}$. Soit, proportionnellement au capital cumulé attendu,

$z = (1-D_{\varphi}/D_{20\%}) / [(1+i1)\ (1+i2)\ (1+i3)]^{15}$.

Si φ>20%, c'est un surplus négatif : la formule représente alors des fonds propres initiaux nécessaires pour faire face au scénario de longévité.

En faisant une simulation numérique sur 10000 tirages aléatoires (gaussiens) de i1, i2, i3 et φ, nous obtenons la Figure 9, qui indique z en ordonnée.

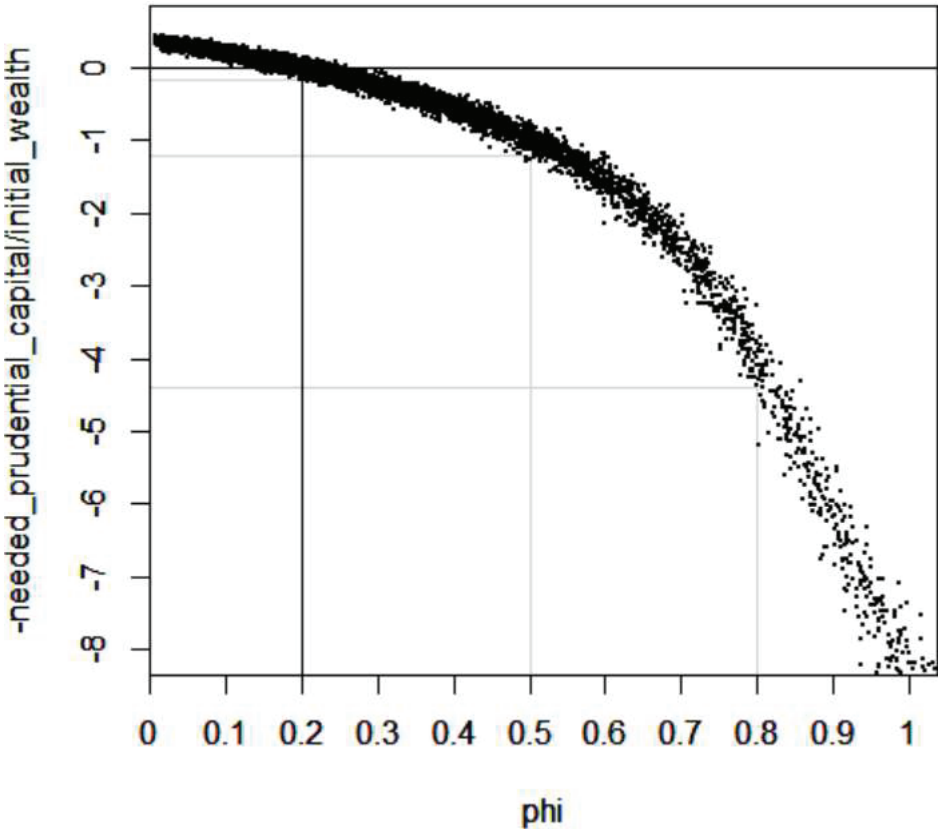


Figure 9. Valeur actuelle probable du gain sur le service des rentes exprimé en pourcentage du coût des rentes attendu, en fonction de la tendance φ de longévité (en abscisses). Ceci, pour 10000 tirages de φ, i1, i2 et i3.

Nous voyons que si l'espérance de vie augmente de 6 mois par an, pour ne pas faire faillite il faut un peu plus du double de cotisations supplémentaires à celles demandées aujourd'hui. Cette protection contre le risque de longévité peut de façon similaire s'obtenir en attribuant des montants de rente plus faibles, qui progressivement sont révisés à la hausse si le risque de longévité ne semble pas se matérialiser, ou en imposant initialement des capitaux propres plus élevés.

En utilisant la distribution log normale de φ, il faut 2,7 fois plus de cotisations qu'attendu pour faire face aux scénarios de longévité dans 90% des cas. Ce type de coussin est plus élevé que ceux calculés dans le cadre de Solvabilité II et suggère que les coussins actuels sont insuffisants ou que des ajustements importants des systèmes actuels doivent être mis en place pour accompagner la meilleure santé qui découlerait des recherches actuelles.

e) Des solutions pour gérer le risque de longévité

Les assureurs bénéficient d'une réduction du risque de longévité par la présence d'autres activités que l'assurance retraite, sensibles à une augmentation du risque de mortalité. Cependant, il s'agit essentiellement de risques de mortalité pour les personnes en âge de travailler, qui plus est de risques à court terme de mortalité. Du fait des courts engagements, les prix s'ajustent rapidement à une déviation prolongée de la sinistralité. Ainsi, cette couverture naturelle devrait en général être de faible efficacité.

Des contrats permettent de transférer le risque à d'autres acteurs, tels que des swaps de longévité qui transfèrent exactement le risque de longévité, ou des swaps de longévité indiciels qui transfèrent par exemple le risque de longévité d'un portefeuille modélisé par rapport aux évolutions de taux de mortalité ou de survie de la population générale, ce qui peut se décomposer par âge, sexe et date et donner lieu à des q-forward et S-forward (qui versent un notionnel fois le taux de mortalité ou survie au final réalisé d'une population moins le taux initialement prédit). Des exemples de telles transactions sont indiqués dans la littérature (voir Antolin et Mosher (2007)). Ces contrats, pouvant même aller jusqu'au transfert complet d'activité, ou à la titrisation du risque de longévité auprès d'un grand nombre d'investisseurs, permettent de diluer le risque. Pas de magie cependant : en cas d'avancée majeure de la longévité les différents acteurs auront des pertes plus importantes que les primes reçues pour prendre le risque.

D'autres solutions plus radicales correspondent à établir des lois qui augmentent l'âge de retraite et à revoir les contrats établis pour que les bénéficiaires ne reçoivent pas de montants de rentes trop importants qui mettraient en danger les systèmes de retraite. La mise en place de telles solutions serait nécessaire en cas d'avancées majeures de longévité et pourrait potentiellement améliorer en réalité la qualité de vie par la mise en place de périodes de longs congés et formations professionnelles (voir Vaupel (2010)). De tels changements sur des avantages acquis, et qui impactent de façon incertaine les taux de chômage, nécessitent beaucoup de courage politique. Leur mise en place préemptive serait idéale pour l'économie mais de tels changements sont difficiles à

actionner avant que les avancées de la longévité ne soient évidentes pour tous (voir Zhavoronkov (2013)).

Une solution différente et possiblement complémentaire se dessine dans la littérature depuis quelques années : le méga fonds de longévité. Il s'agit d'un fonds qui investit dans les développements cliniques contre les pathologies du vieillissement, à partir des recherches biomédicales les plus abouties dans le domaine, et vend les traitements produits ou au moins la propriété intellectuelle correspondante auprès d'entreprises pharmaceutiques. Le rendement est représentatif des gains de santé et longévité espérés chez les personnes âgées. Ainsi, ce type d'approche fournit des gains en cas d'avancées importantes de longévité au lieu de diluer les pertes ; ces gains sont reçus à l'avance ce qui permet de mieux piloter l'activité ; et les gains et pertes correspondent toutes deux aux âges de retraite ce qui devrait fournir une meilleure couverture naturelle que l'équilibre entre risque de mortalité et longévité. Face à ces espoirs, nous étudions le méga fonds de longévité en dernière partie de ce manuscrit.

IV. Analyse d'une solution potentielle d'accompagnement financier des systèmes de retraite: le méga fonds de longévité

Comme vu dans les parties précédentes, des avancées biomédicales actuelles, prometteuses pour gagner des années de vie en bonne santé, risquent en cas de réalisation d'impacter fortement les systèmes de retraites dans le monde. Diverses solutions permettent d'ajuster les systèmes de retraite et de réduire les risques, notamment l'investissement des cotisations dans un méga fonds de longévité, ce que nous étudions dans cette partie.

a) Au départ: le concept du méga fonds contre le cancer

En 2012, le laboratoire d'Andrew Lo au MIT propose de *vaincre le cancer par l'ingénierie financière* (voir Fernandez *et al.* (2012)). Face au faible taux de succès des développements pharmaceutiques contre le cancer et la difficulté correspondante de trouver des investisseurs pour poursuivre d'autres développements, il s'agit de mutualiser les risques de centaines de développements dans un fonds, un "megafund", structuré entre investissements en obligations et actions, voire de multiples manières afin d'attirer suffisamment d'investisseurs.

La clé d'un tel fonds réside dans l'effet d'échelle. Le financement d'un seul développement pharmaceutique est très risqué : si la probabilité n'est pas nulle d'obtenir un gain important, la plupart du temps les sommes investies sont juste perdues. Par contre, si le méga fonds s'appuie sur N développements suffisamment diversifiés, le rendement moyen est le même que pour un développement et le risque est réduit d'un facteur $\frac{1}{\sqrt{N}}$. Avec 250 développements cliniques, les caractéristiques financières d'un tel fonds ne seraient pas forcément extrêmement appétissantes mais pas non plus repoussantes.

Pour arriver à ces conclusions, un modèle de Markov est calibré sur des données pharmaceutiques pour représenter les transitions entre la recherche préclinique, les essais cliniques de phase 1, 2 et 3, les échecs ou les acceptations pour commercialisation, et la possibilité de vendre la propriété intellectuelle des thérapies à différents stades. Des simulations sont effectuées qui aboutissent au résultat.

Afin de simplifier la communication, un modèle simplifié est utilisé, où un investissement initial C_0 aboutit à un gain Y_{10} dix ans plus tard, avec une probabilité p. Le retour sur investissement sur 10 ans est alors

$$\rho = \frac{p \times Y_{10} + (1-p) \times 0}{C_0}$$

Le rendement annualisé est

$$r = \left(\frac{p \times Y_{10}}{C_0}\right)^{\frac{1}{10}} - 1$$

Deux versions numériques des paramètres sont présentées, une pour les traitements "blockbuster" qui génèrent au moins un milliard de résultat par an après la dixième année, et une pour les non blockbusters. Toutes deux aboutissent à

$$\rho \approx 3.1$$

et

$$r \approx 11.9\%$$

b) Extension: le méga fonds de longévité

Peu après, le principe d'un "méga fonds biomédical" est proposé, qui diversifie mieux les développements cliniques en couvrant un large panel de conditions de santé plutôt que de se concentrer sur le cancer, et qui intéresse les fonds de pension car il présente des gains de longévité (voir Stein (2016), Kahn (2015), MacMinn et Zhu (2017)). MacMinn et Zhu (2017) montrent que ce type de méga fonds couvrent mieux un portefeuille d'assurance vie que des q-forwards, instruments existants de couverture du risque visant

à recevoir la différence entre les q_x réalisés au sein d'une population et une valeur prévue contractuellement. Nous appelons ce type de méga fonds un "méga fonds de longévité" s'il investit plus particulièrement dans des thérapies contre les maladies liées à la mortalité (contrairement au développement de traitements contre la myopie ou les ongles incarnés par exemple).

c) Limiter les risques d'un méga fonds

Divers questionnements sont émis sur le principe de méga fonds, notamment le risque que les développements pharmaceutiques financés soient moins statistiquement indépendants que prévus, que l'orientation financière supplémentaire aux développements pharmaceutiques que donnerait un méga fonds ne vienne aggraver le risque que les aspects commerciaux l'emportent sur les aspects scientifiques et que les probabilités de succès soient alors d'avantage réduites que celles déjà observées dans le secteur pharmaceutique (voir Boissel (2013)).

J'ai réfléchi à ces risques avec des connaissances et nous avons fait un article sur la base de nos réflexions (voir Yang *et al.* (2016)), qui se trouve en annexe 5 et dont les principaux résultats sont ici présentés. Le découpage en obligations et actions semble effectivement nécessaire pour faciliter la collecte d'investissements. Le principe est que les gains remboursent en priorité les investisseurs en obligations en leur apportant un rendement prévu à l'avance, et que l'excès rembourse les investisseurs en action. Ce découpage, et un découpage plus fin selon les types de développements pharmaceutiques et leurs durées, amène cependant des risques.

Les probabilités de succès des développements pharmaceutiques sont faibles – dans le modèle vu quelques paragraphes plus haut, p=5% pour les blockbusters, ce qui indique une grande difficulté de discerner les bons projets des mauvais. Dans ces conditions, le découpage du méga fonds en de multiples entités – Special Purpose Vehicules, SPV – pour atteindre divers investisseurs met à l'épreuve l'impartialité des gérants du méga fonds. Ceux-ci, comprenant après quelques tests préliminaires que certains projets qu'ils

ont acquis sont meilleurs que d'autres, ont un intérêt financier personnel à regrouper les mauvais projets ensemble dans un mauvais SPV et à obtenir de bonnes performances sur d'autres SPV. Les gérants de fonds sont en effet en général intéressés sur la performance de la poche actions et ont intérêt à privilégier le rendement de cette poche.

Idéalement, les mauvais projets devraient être rejetés d'emblée et les probabilités de succès devraient être importantes. Autrement, il est important d'avoir des gérants fiables, qui distribuent aléatoirement les mauvais projets ressentis ("lemons") entre les SPVs. En cas de biais, le risque est qu'il y ait un regroupement. Nous étudions ces trois cas de figure en présence de 150 développements cliniques regroupés en 1 ou 6 SPV, suivant que les obligations soient définies sur la base d'un rendement de 8.5% ou 16.5%, et nous observons les rendements et probabilités de défaut pour les poches obligations et actions indiqués en Table 5. Mon apport sur cette partie a été de contribuer à affiner la réflexion, de définir les équations mathématiques et d'obtenir les résultats, qui se trouvent dans l'annexe de l'article.

Cas de rendement cible des obligations à 8.5%	Obligations		Actions	
	Rendement	Proba de défaut	Rendement	Proba de défaut
Gérants idéaux, 1 SPV	8.5%	<0.1%	27.1%	<0.1%
Gérants idéaux, 6 SPV	8.45%	0.4%	27.2%	<0.1%
Gérants ~~idéaux~~, 1 SPV	8.44%	1.6%	17.2%	5.0%
Gérants fiables, 6 SPV	7.78%	6.5%	17.5%	5.0%
Gérants biaisés, 6 SPV	5.85%	19.9%	27.7%	5.0%

Cas de rendement cible des obligations à 16.8%	Obligations		Actions	
	Rendement	Proba de défaut	Rendement	Proba de défaut
Gérants idéaux, 1 SPV	16.8%	0.2%	24.0%	0.6%
Gérants idéaux, 6 SPV	16.6%	2.8%	24.1%	0.6%

Gérants ~~idéaux~~, 1 SPV	14.8%	22.7%	12.2%	36.7%
Gérants fiables, 6 SPV	14. 8%	25.1%	12.2%	36.7%
Gérants biaisés, 6 SPV	11.7%	41.8%	25.9%	36.7%

Table 5, extraite de la Table 1 de (Yang et al. (2016)). Rendements et probabilités de défauts d'un méga fonds gérant 150 développements cliniques suivant le découpage en SPVs et la gestion visionnaire, impartiale ou non des gérants. Détails méthodologiques dans l'article (voir Yang et al. (2016)).

Nous voyons, bien-sûr, qu'en ne sélectionnant que des bons projets, les rendements sont bons et les probabilités de défaut faibles. Si les gérants ne sont pas si visionnaires (ou voyants ou devins) mais qu'il n'y a qu'un SPV, les probabilités de défaut sont plus importantes et les rendements moins bons. S'il y a 6 SPVs par contre, le regroupement ou non de mauvais projets dans des SPVs dope artificiellement les rendements des actions au global au détriment des obligations, lesquelles deviennent très risquées.

Outre le comportement des gérants du fonds, nous voyons l'importance d'être capable d'éliminer les mauvais projets dès le départ, avant constitution des SPVs. En supposant qu'investir une part du fonds dans divers filtres, tels que des essais précliniques sur animaux et cellules, l'obtention d'avis d'experts et des analyses de données diverses, puisse permettre d'éliminer une partie des mauvais projets, nous imaginons une loi entre la part d'investissement dédiée et l'efficacité de filtrage – laquelle reste à ce jour quelque peu arbitraire – et simulons les rendements et probabilités de défaut. Les résultats ainsi qu'un schéma d'organisation potentielle de filtrage sont indiqués Figure 10.

L'idéal est de combiner les deux approches: permettre aux investisseurs de demander des analyses parmi un ensemble d'analyses possibles, qui à la fois font office de filtrage et à la fois amènent un contre-pouvoir à la connaissance des gérants du fonds en termes de projets les plus prometteurs et les moins prometteurs.

Mon apport sur cette partie a été de faire fonctionner les simulations (sous Matlab, dérivées de l'article original du méga fonds contre le cancer, voir Fernandez *et al.* (2012)), de développer les équations mathématiques nécessaires au calcul précis de risque de défaut pour les cas complexes, et de contribuer à la réflexion globale pour

l'organisation du filtrage. L'article a été rédigé par l'ensemble des auteurs, mais principalement par Xianjin Yang.

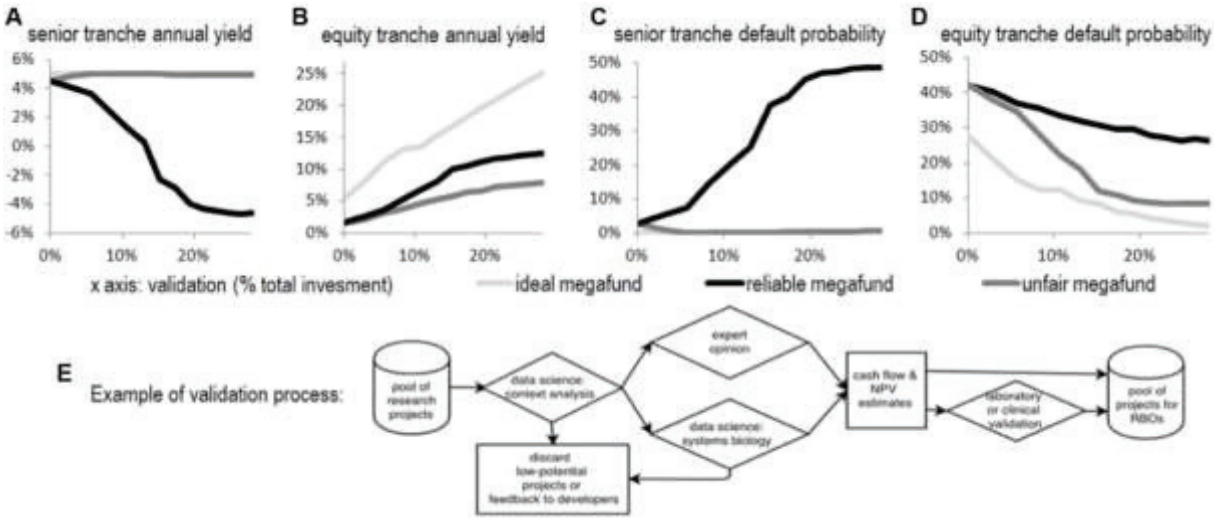


Figure 10, copiée de la Figure 1 de (Yang et al. (2016)).

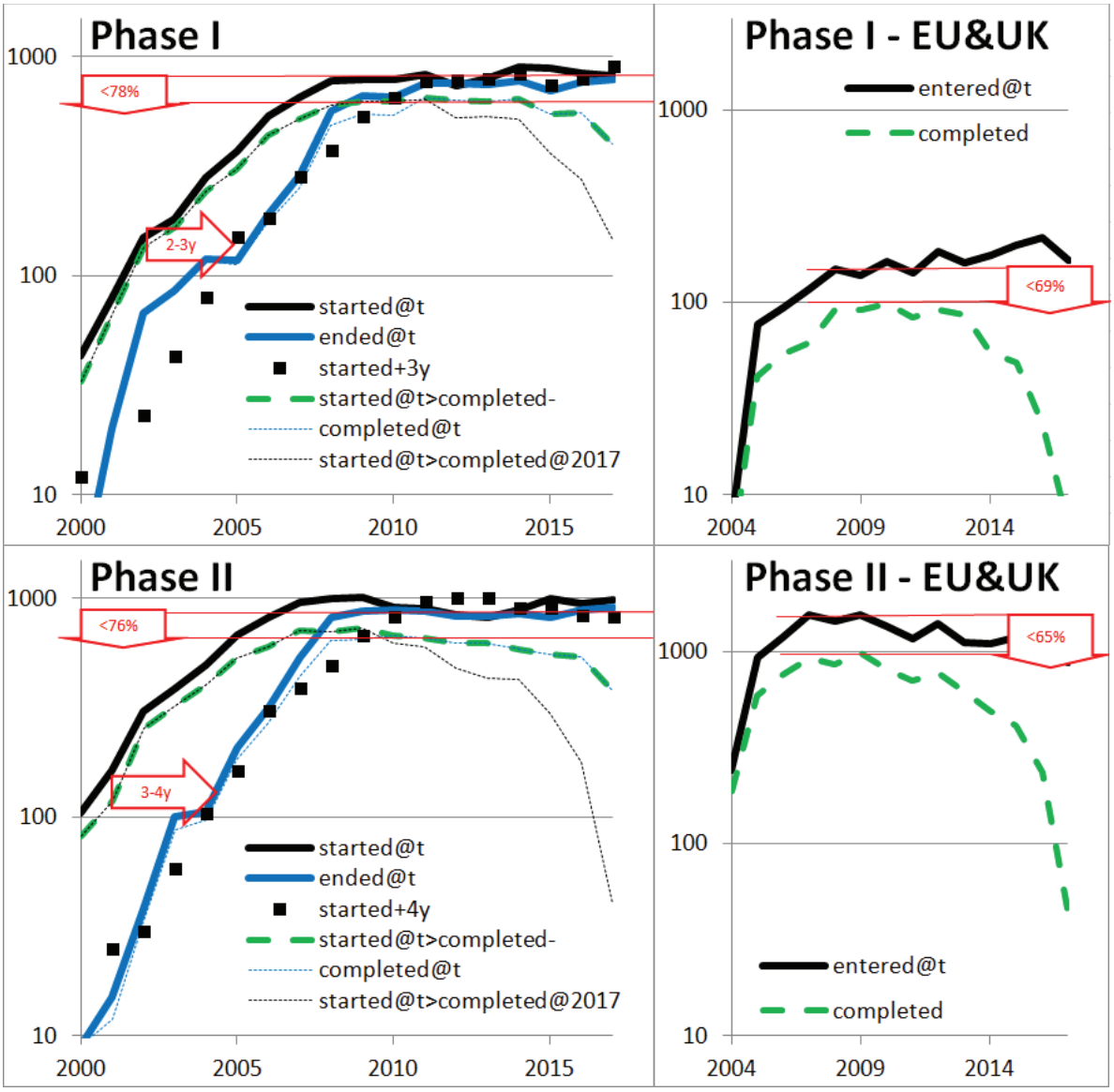
d) Equilibre entre risques et gains de longévité pour un fonds de pension

Muni de cette meilleure compréhension des risques et des points d'attention d'un méga fonds, cette question taraude alors : un méga fonds peut-il vraiment couvrir le risque de longévité des retraites ? Devant la complexité d'un tel équilibre, faisant intervenir des acteurs très différents, la question de bon sens qui se pose préalablement est la suivante : les gains issus d'essais cliniques réussis sont-ils à la hauteur des pertes liées au versement des rentes de personnes qui vivent alors plus longtemps ? Ceci fait l'objet d'un article avec des professeurs de l'ISFA (voir Debonneuil *et al.* (2018) en annexe) qui se trouve en annexe 6, dont les principaux résultats sont ici présentés.

Une difficulté pour cet article a été d'obtenir des ordres de grandeur de probabilités de succès et de gains liés aux essais cliniques et aux demandes d'autorisation de commercialisation, dans un contexte où les enjeux industriels et la pression gouvernementale pour réduire les remboursements et favoriser les génériques tendent à

obscurcir l'information. Grâce à l'open data sur les essais cliniques réalisés, nous avons dans un premier temps déduit que le nombre de développements pharmaceutiques par année et les taux de succès sont assez stables dans le temps, comme indiqué en Figure 11. Cela nous a aidé à nous guider dans la littérature scientifique aux résultats très variés et nous avons pu aboutir à ce que le modèle simple de rendement présenté dans l'article fondateur du méga fonds contre le cancer, et présenté en début de cette section, est pertinent et *a priori* prudent :

$$\rho = \frac{p \times Y_{10}}{C_0} \approx 3.1$$



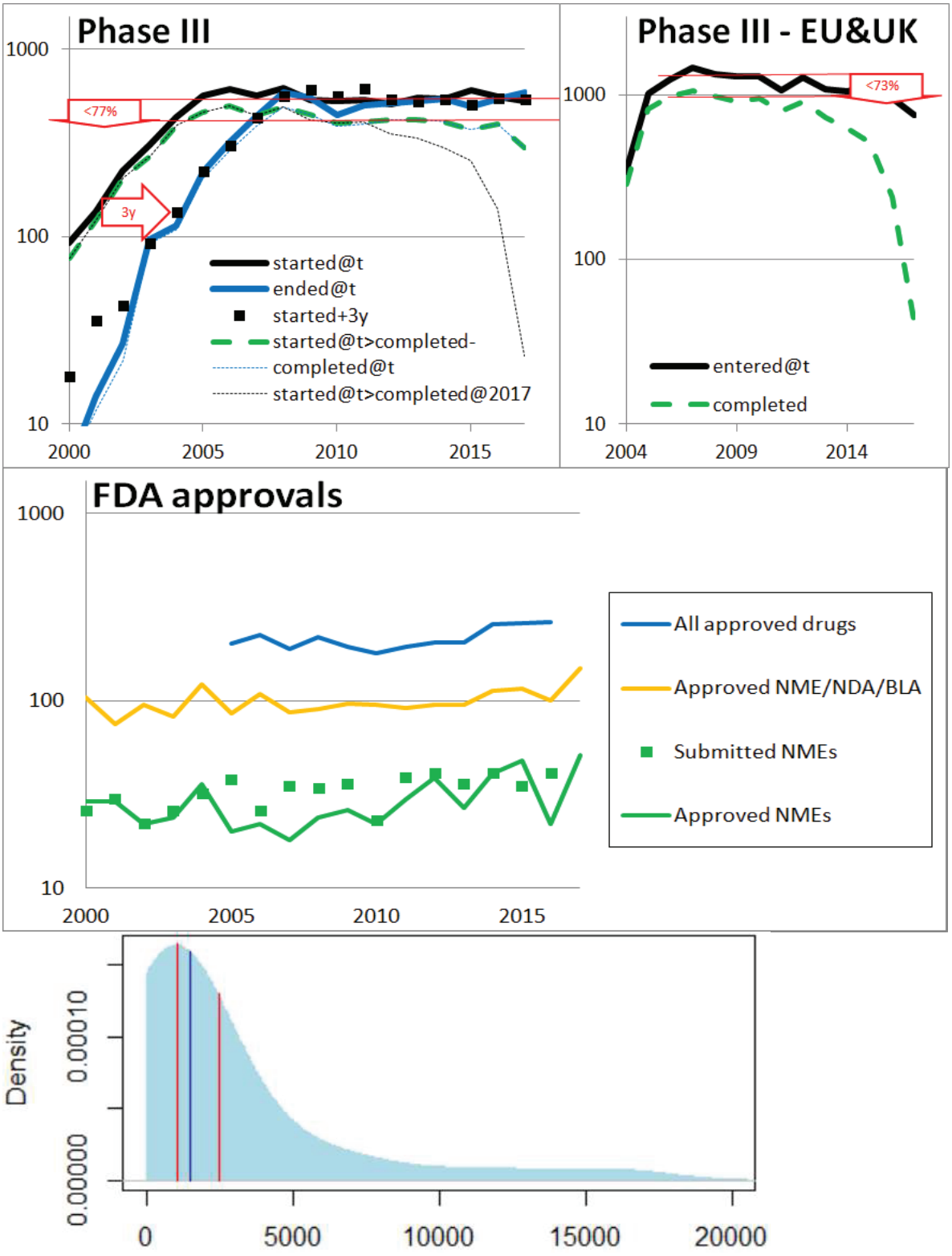


Figure 11, extraite des Figures 2 et 3 de l'article (Debonneuil et al. (2018) en annexe). Les trois graphes à gauche sont constitués à partir du moteur de recherche d'essais cliniques aux Etats-Unis clinicaltrials.gov. En noir, le nombre d'essais cliniques qui démarrent chaque année. Ces courbes montent d'abord, l'incitation à déclarer les essais cliniques étant récente, et se stabilisent, ce qui suggère que le nombre d'essais cliniques de phase 1, 2 et 3 est stable dans le temps. Il en est de même pour le nombre d'essais cliniques terminés, qui de

plus se stabilise au même niveau. Ceci renforce fortement la notion de stabilité: s'il y avait eu de plus en plus d'essais cliniques, les courbes noires auraient dû rester au dessus des courbes bleues. En vert, une estimation des nombres d'essais cliniques qui aboutissent correctement (avec un biais vers le bas à gauche et à droite, comme indiqué dans l'article) qui suggère là aussi une stabilité, et des taux de succès non négligeables. A droite, l'équivalent pour les essais cliniques en Europe; les courbes sont moins renseignées du fait des limitations de l'interface clinicaltrialsregister.eu et de l'incitation plus récente et moins forte qu'aux Etats-Unis de déclarer les essais cliniques, mais les courbes confirment les conclusions obtenues pour les Etats-Unis. En dessous, le nombre de traitements de différents types autorisés par la Food and Drug Administration aux Etats-Unis, et même le nombre de soumissions d'un certain type, sont globalement stables dans le temps (chiffres issus de Drugs@FDA et accessdata.fda.gov), et suggèrent des taux d'acceptation stables et non négligeables. En bas, la distribution des gains issus des développements cliniques (ici en millions de dollars, à partir du site de l'entreprise Royalty Pharma) montre par contre une grande disparité, ce qui justifie fortement de mutualiser un grand nombre de développements.

Une autre difficulté a été de calibrer un lien entre ces retours sur investissement ρ sur 10 ans et les tendances de longévité φ. Le lien est établi grâce aux éléments utilisés par les économistes de la santé côté entreprises pharmaceutiques et côté payeurs de santé pour négocier les remboursements des traitements. Ce domaine s'appuie majoritairement sur la notion de coût additionnel acceptable par gain additionnel de vie en bonne santé (Quality Adjusted Life Year) par patient, mais aussi de temps à autre par gain additionnel de vie (Life-Year ou Year-of-life). Nous avons aussi pu nous appuyer sur des statistiques de développements biotechnologiques ce qui a conforté l'utilisation d'un ratio prudent de 20 000 dollars pour le méga fonds par année de vie gagnée par personne aux Etats-Unis. Combinant cet élément avec l'idée qu'une faible amélioration de longévité est faiblement liée aux développements biomédicaux, nous formulons ce lien entre rendements ρ et tendances de longévité φ:

$$\rho = ln(exp(B\ \varphi) + A) + \varepsilon$$

A et B sont des coefficients caractéristiques respectivement du niveau actuel de rendement sur 10 ans (3.1) et de l'évolution de ce niveau suivant la tendance future de longévité φ (en lien avec un Year of Life de 20 000$ par année de vie gagnée). ε est un

bruit entre -1 et 1 représentant les éléments autres qui n'ont pu être modélisés. Exprimé en rendement annualité r, le lien est représenté Figure 12.

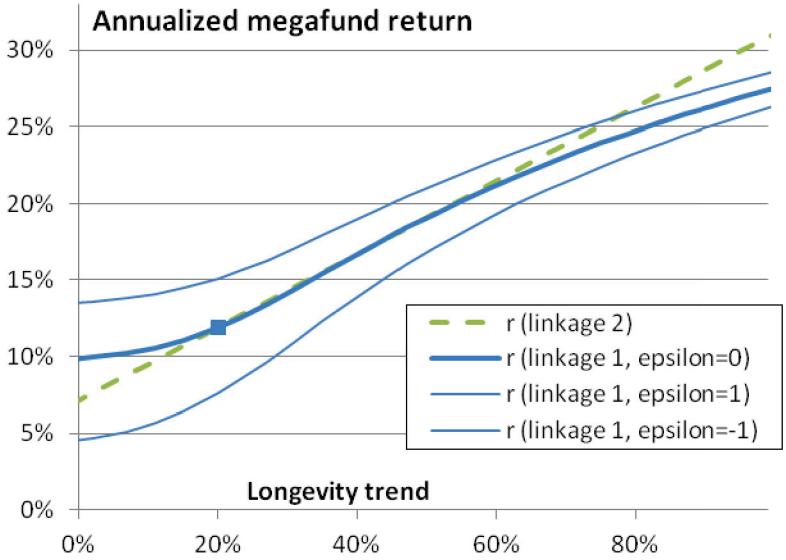


Figure 12, extraite de la Figure 3 de l'article (Debonneuil et al. (2018) en annexe). Le rendement annualisé global du méga fonds r est modélisé en bleu en fonction de la tendance de longévité φ. Le bleu épais représente le lien le plus probable. Le bleu fin représente des bornes estimées. Le carré représente la situation actuelle. En vert, une version linéarisée, pouvant représenter le comportement du méga fonds de longévité si, au lieu de représenter les avancées biomédicales globales, il se concentre sur les avancées issues de la biologie du vieillissement.

Tenant à présent compte de la structuration du méga fonds entre obligations et actions, nous supposons qu'une part α des investissements est pour la poche action et que le taux de rendement annuel cible des obligations est de 5%, ce qui donne la formule suivante pour le rendement annualisé de la poche actions, tant que le numérateur dans la parenthèse est positif (limité à i=-1 plus frais: alors tous les investissements action sont perdus, en plus de frais supplémentaires):

$$i = \left(\frac{\rho - (1-\alpha) \times 1.05^{10}}{\alpha}\right)^{\frac{1}{10}} - 1$$

Suivant la valeur de alpha, le comportement de i en fonction de la longévité est observé Figure 13. Assez logiquement, concentrer les surplus de rendement du fonds sur une

petite poche action peut créer de meilleurs rendements mais le risque est alors plus grand de ne pas obtenir de rendement positif.

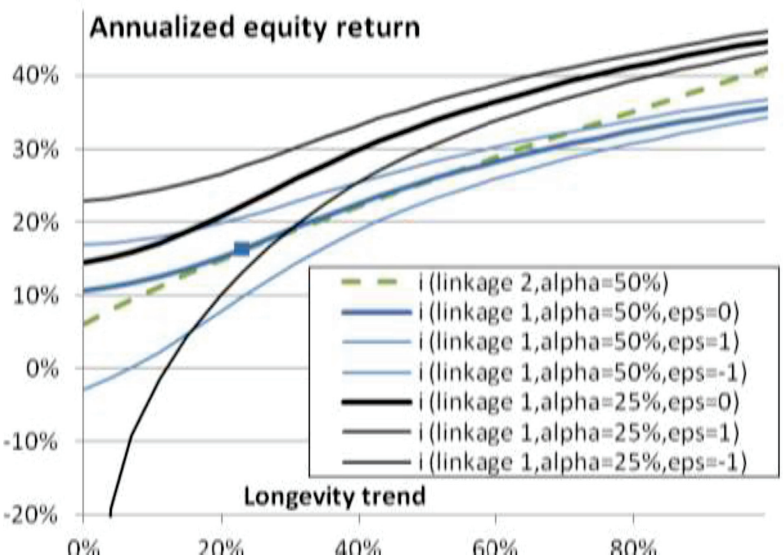


Figure 13. Modélisation du rendement annualisé de la poche action du méga fonds longévité en fonction de la tendance de longévité. Les styles sont ceux de la figure 12 mais en noir (au dessus) il est considéré que 50% des investissements sont en actions et en bleu (au dessous) il est considéré que 25% des investissements sont en actions.

Dans le cas du fonds de pension à prestations définies défini plus haut, ces gains peuvent être ajoutés aux pertes liées à la longévité en considérant une part d'investissement dans le méga fonds de longévité de 20% pour les âges de 20 à 34 ans, de 15% pour les âges de 35 à 49 ans, et de 10% pour les âges de 50 à 65 ans. Le résultat des simulations est présenté Figure 14.

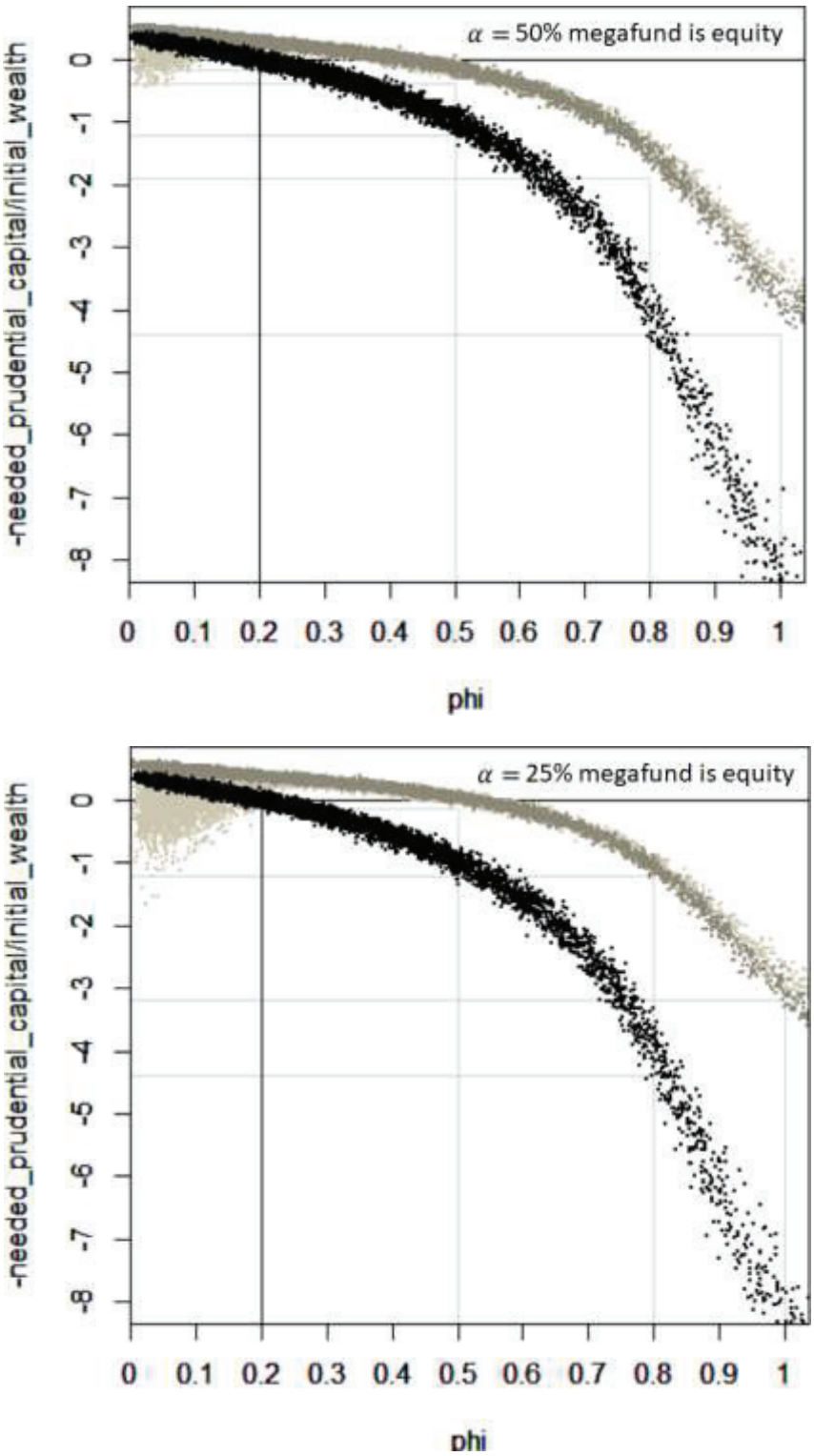


Figure 14, copiée de la Figure 5 de Debonneuil et al. (2018) en annexe. Styles identiques à ceux de la figure 9 mais l'investissement d'un méga fonds qui représente les avancées biomédicales générales est additionnellement en gris et l'investissement qui représente les avancées issues de la biologie du vieillissement est en gris clair. Qu'il y ait 50% (graphe du haut) ou 25% (graphe du bas) des investissements en action, nous voyons que les besoins en fonds propres supplémentaires pour faire face à des augmentations d'espérances de vie de deux (φ=0.50) ou trois trimestres par an (φ=0.75) sont considérablement réduits. Par contre, en cas

d'avancées plus importantes encore de la longévité, l'investissement dans le méga fonds reste insuffisant. De plus, le méga fonds qui investit spécifiquement dans les développements issus de la biologie du vieillissement prend un risque au cas où la vague d'avancées de longévité ne se produit pas (points épars dans la partie gauche des graphes).

La conclusion très positive présentée Figure 14 concerne la comparaison entre les ordres de grandeurs de gains de longévité produits par un méga fonds de longévité et les ordres de grandeurs de pertes pour un fonds de pension à prestations définies. Elle passe toutefois outre certains points d'organisation importants qui restent à préciser.

Considérons par exemple que le méga fonds obtienne des gains du fait que certains essais cliniques sont positifs et que des autorisations de commercialisation sont obtenues, par exemple pour des mimétiques de restriction calorique, pour une thérapie génique empêchant la perte musculaire (sarcopénie) avec l'âge, pour une thérapie hormonale permettant la repousse du thymus pour possiblement renforcer le système immunitaire des seniors, ou d'autres solutions de santé plus ou moins innovantes. Des premiers patients en bénéficient mais les effets sur la réduction de mortalité, de long terme, ne seront pas visibles. Seuls des essais sur souris par exemple permettent d'avoir une idée empirique des effets de longévité si l'utilisation des traitements se répand dans les populations humaines. Dans ce cas, un assureur en charge de prendre le risque de longévité pour servir des retraites saura-t-il mettre le gain du méga fonds en réserve pour les besoins de rentes à servir plus longtemps que prévu? Ou la vision sera-t-elle que jusqu'à preuve du contraire que la tendance de longévité est inchangée, i.e. φ=20%? Dans ce dernier cas, le gain sera vraisemblablement considéré comme une aubaine pour que l'entreprise n'ait pas à abonder pour que le fonds de pension génère le capital accumulé nécessaire; quelques décennies plus tard cependant, les taux de mortalité auront bien baissé car les personnes ne perdront plus leur masse musculaire comme avant, et il sera demandé à l'assureur de verser des rentes qu'il n'aura pas prévues; ou bien, suite à diverses discussions, les rentes des assurés seront réduites.

Le cas d'un fonds de pension à cotisation définie est plus problématique. Si le méga fonds performe bien mais que l'assureur garde une vision φ=20%, le capital accumulé, plus important que prévu initialement, sera converti en montants de rentes plus importants. Quelques décennies plus tard, il faudra non seulement verser des rentes plus longtemps mais des rentes avec ces montants plus importants.

Ainsi, nous le voyons, la bonne gestion du risque de longévité nécessite, au-delà de bons ordres de grandeurs de gains et pertes, une bonne articulation de ces équilibres.

Conclusion

Les avancées récentes de la biologie du vieillissement semblent en passe de se traduire par une augmentation significative de la durée de vie, au-delà de la tendance historique. Le monde pharmaceutique est un moteur financier fort d'un tel scénario.

Contrairement à l'intuition que les systèmes de retraites ne peuvent que souffrir d'un allongement de la vie, les conséquences pourraient être bénéfiques pour les systèmes de retraite : le ratio « durée de vie active / durée de vie inactive » pourrait augmenter. A court terme cependant, les systèmes établis présentent un risque de longévité : que ce soit pour les systèmes par répartition ou par capitalisation, une durée de vie accrue entraine d'avantage de versements de retraites mais pas forcément d'avantage de collecte pour cela. Etant donné les conditions de retraites actuelles, nous avons étudié ce risque de longévité pour les systèmes par capitalisation, à travers différents modèles. Ces études montrent qu'en cas d'avancées biomédicales majeures il faudra faire évoluer ces systèmes de retraite.

Des trois leviers bien connus pour ajuster les systèmes de retraite – âge de départ à la retraite, montant des cotisations et montant des rentes – l'augmentation de l'âge de départ à la retraite est certainement déterminant lorsqu'on considère des augmentations significatives de longévité. Mais ces changements sont toujours délicats à mettre en œuvre. Dans ces travaux de thèse, nous avons étudié un quatrième levier, qui concernerait les fonds par capitalisation : ils investiraient dans des fonds dont le rendement dépend de la longévité. Les simulations effectuées sont prometteuses : dans les cadres modélisés, les gains de rendements seraient comparables aux besoins de versement des rentes. Cependant, de nombreux aspects sont à considérer pour la mise en place de telles solutions. Ainsi, les gains produits par de bons rendements seront-ils utilisés pour anticiper l'accroissement de longévité ou simplement considérés comme une surperformance habituelle ? Quand saurons-nous reconnaitre que les éléments d'une longue vie des populations sont présents ?

Voilà là une face parfois oubliée de l'actuariat et de la gestion économique, par impossibilité de tout connaitre : les risques qui sont gérés, au-delà des aspects mathématiques et financiers, ont des fondamentaux qui parfois ne se voient pas au bon moment dans les chiffres. Le risque de longévité est particulièrement représentatif de cet aspect : des développements actuels peuvent entrainer de grands enjeux sociétaux et financiers dans 80 ans, qu'il conviendrait idéalement de prévoir et de gérer maintenant alors que les signaux sont actuellement faibles voire nuls, pour qui observe les taux de mortalité.

Un jour prochain peut-être le voisin d'un actuaire reviendra d'un mois de congés en pleine forme et expliquera qu'il vient d'activer temporairement la destruction de ses vieilles cellules et la régénération de ses tissus. L'actuaire aura beau avoir extrapolé toutes sortes de tendances issues du passé, la réalité ne collera pas à ce modèle. Le futur est parfois l'extrapolation du passé, mais pas toujours. Nous sommes parfois noyés dans des modèles de Lee Carter ou des modèles plus sophistiqués, noyés dans des systèmes sociaux complexes, et il n'est pas évident de réagir à ces avancées de la longévité. Devant la possibilité que celles-ci ne soient qu'un mirage, tant que les faits ne seront pas patents les avancées de la longévité seront un risque de longévité. Ceci, d'autant que les enjeux pour les systèmes de protection sociale sont importants.

Mais les enjeux pour l'industrie pharmaceutique sont également importants, et à plus court terme. Pour l'industrie pharmaceutique, les avancées de la longévité sont une aubaine à saisir, et bien des investisseurs l'ont compris. Aussi, il est possible que le moteur des changements soit l'industrie pharmaceutique. Novartis, Sanofi, Pfizer et bien d'autres ont à présent des départements "aging" (vieillissement) et s'intéressent de près à des développements issus de la biologie du vieillissement. Dans ce cadre, lier les investissements des fonds de pension à ceux de l'industrie pharmaceutique fait sens, mais cela nécessite encore quelques efforts pour mettre en place ce type d'innovation.

Il sera particulièrement intéressant dans quelques décennies de regarder en arrière et de considérer dans quelle mesure les éléments ici présents ont une once de vérité et quels

chemins la société, la biologie, la médecine et les systèmes sociaux auront emprunté entre temps.

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Annexes

Les annexes sont constituées des articles réalisés durant la thèse.

ANNEXE 1. ARTICLE: A REVIEW OF THE BIOMEDICAL INNOVATIONS FOR HEALTHY LONGEVITY

Alexey Moskalev[1],[10],[27],[38], Vladimir Anisimov[2],Aleksander Aliper[3], Artem Artemov[3], Khusru Asadullah[4], Daniel Belsky[5], Ancha Baranova[6], Aubrey de Grey[7], Vishwa Deep Dixit[8], Edouard Debonneuil[9], Eugenia Dobrovolskaya[10], Peter Fedichev[11], Alexander Fedintsev[1], Vadim Fraifeld[12], Claudio Franceschi[13], Rosie Freer[14], Tamas Fülöp[15], Jerome Feige[16], David Gems[17], Vadim Gladyshev[18], Vera Gorbunova[19], Irina Irincheeva[20], Sibylle Jager[21], S. Michal Jazwinski[22], Matt Kaeberlein[23], Brian Kennedy[24], Daria Khaltourina[25], Igor Kovalchuk[26], Olga Kovalchuk[26], Sergey Kozin[27], Alexander Kulminski[5], Ekaterina Lashmanova[1], Ksenia Lezhnina[3], Guang Hui Liu[28], Valter Longo[29], Polina Mamoshina[3], Alexander Maslov[30], Joao Pedro de Magalhaes[31], James Mitchell[32], Arnold Mitnitski[33], Yuri Nikolsky[34], Ivan Ozerov[3], Elena Pasyukova[35], Darya Peregudova[10], Vasily Popov[36], Ekaterina Proshkina[10], Evgeny Putin[37], Evgeny Rogaev[38], Blanka Rogina[39], Jane Schastnaya[3], Andrey Seluanov[19], Mikhail Shaposhnikov[10], Andreas Simm[40], Vladimir Skulachev[41], Maxim Skulachev[41], Ilya Solovev[10], Stephen Spindler[42], Natalia Stefanova[43], Yousin Suh[30], Andrew Swick[44], John Tower[45], Andrei V. Gudkov[46], Jan Vijg[30], Andrey Voronkov[1], Michael West[47], Wolfgang Wagner[48], Anatoliy Yashin[5], Nadezhda Zemskaya[10], Zhaxybay Zhumadilov[49], and Alex Zhavoronkov[3]

1 Moscow Institute of Physics and Technology, Dolgoprudny, 141700, Russia
2 Department of Carcinogenesis and Oncogerontology, N.N. Petrov Research Institute of Oncology, St. Petersburg, Russia
3 Pharmaceutical Artificial Intelligence Department, Insilico Medicine, ETC, B301, Johns Hopkins University, Baltimore, Maryland 21218, USA
4 Bayer Global Drug Discovery, Berlin, Germany
5 Social Science Research Institute, Duke University, Durham, NC 27708, USA
6 School of Systems Biology, George Mason University, VA 20110, USA
7 SENS Research Foundation, 1 Beaconsfield Terrace, Cambridge, CB2 3EH, UK
8 Department of Immunobiology, Yale School of Medicine, New Haven, CT 06520, USA
9 ActuRx, 92330 Sceaux, France
10 Institute of Biology of Komi Science Center of Ural Branch of Russian Academy of Sciences, Syktyvkar, 167982, Russia
11 Gero Limited, International Commerce Center, Kowloon, Hong Kong
12 The Shraga Segal Department of Microbiology, Immunology and Genetics, Center for Multidisciplinary Research on Aging, Ben-Gurion University of the Negev, POB 653, 8410501, Beer-Sheva, Israel
13 Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Bologna, Italy
14 Department of Chemistry, University of Cambridge, Cambridge CB2 1EW, UK
15 Department of Medicine, Research Center on Aging, Graduate Program in Immunology, Faculty of Medicine and Health Sciences, University of Sherbrooke, Sherbrooke, Quebec, Canada
16 Nestlé Institute of Health Sciences, EPFL Innovation Park, 1015 Lausanne, Switzerland
17 Institute of Healthy Ageing, and Department of Genetics, Evolution and Environment, University College London, London, UK
18 Division of Genetics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA
19 Department of Biology, University of Rochester, Rochester, NY 14627, USA
20 Nutrition and Metabolic Health Group, Nestlé Institute of Health Sciences, CH-1015 Lausanne, Switzerland
21 Open Research Department, L'Oreal, 93600 Aulnay-sous-Bois, France

22 Tulane Center for Aging and Department of Medicine, Tulane University Health Sciences Center, SL-12, New Orleans, LA 70112, USA
23 Department of Pathology, University of Washington, Seattle, WA 98195, USA
24 Buck Institute for Research on Aging, Novato, CA 94945, USA
25 Department of the Integrated Prevention Programs, Federal State Institution "National Research Center for Preventive Medicine" of the Ministry of Healthcare of the Russian Federation, 101990, Moscow, Russia
26 Department of Biological Sciences, University of Lethbridge, Lethbridge, Alberta, T1K 3M4, Canada
27 Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow, Russia
28 National Laboratory of Biomacromolecules, CAS Center for Excellence in Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences, Beijing 100101, China
29 Longevity Institute and Davis School of Gerontology, University of Southern California, Los Angeles, CA 90089, USA
30 Department of Genetics, Albert Einstein College of Medicine, Bronx, NY 10461, USA
31 Integrative Genomics of Ageing Group, Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, UK
32 Department of Genetics and Complex Diseases, Harvard School of Public Health, Boston, MA 02115, USA
33 Department of Medicine, Dalhousie University, Centre for Health Care of the Elderly-Suite 1305, 5955 Veterans' Memorial Lane Halifax, Nova Scotia, B3H 2E1 Canada
34 Biomedical Cluster, Skolkovo Foundation, Skolkovo, Russia
35 Institute of Molecular Genetics of Russian Academy of Sciences, Moscow, Russia
36 Voronezh State University, Voronezh, Russia
37 Computer Technologies Lab, ITMO University, St. Petersburg 197101, Russia
38 Vavilov Institute of General Genetics RAS, Moscow, Russia
39 Institute for Systems Genomics, School of Medicine, University of Connecticut Health, Farmington, CT 06030, USA
40 Centre of Medical Basic Research, Medical Faculty, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany
41 Department of Bioengineering and Bioinformatics, Lomonosov Moscow State University, Moscow, Russia
42 Department of Biochemistry, University of California at Riverside, Riverside, CA 92521, USA
43 Institute of Cytology and Genetics of Siberian Branch of Russian Academy of Sciences, Novosibirsk, Russia
44 Life Extension, Ft. Lauderdale, FL 33308, USA
45 Department of Biological Sciences, University of Southern California, Los Angeles, CA 90089, USA
46 Department of Cell Stress Biology, Roswell Park Cancer Institute, Buffalo, NY 14263, USA
47 BioTime, Inc., Alameda, CA 94501, USA
48 Helmholtz-Institute for Biomedical Engineering, Stem Cell Biology and Cellular Engineering, RWTH Aachen University, Aachen, Germany
49 Center for Life Sciences Nazarbayev University, Astana, Kazakhstan
Correspondence to: Alexey Moskalev; amoskalev@ib.komisc.ru

CONTENT

The field of biogerontology and regenerative medicine is rapidly evolving with many new advances in aging research promising to transform healthcare and extend healthy productive longevity. Recent breakthroughs in epigenetic, transcriptomic and multimodal biomarkers of aging, discovery of new and validation of old geroprotectors and advances in gene therapy provide an optimistic outlook. However, the propagation of laboratory

advances into clinical practice has been comparatively slow with few focused investment and technology integration programs worldwide.

To evaluate the technological readiness of the biomedical advances in biogerontology and accelerate the translation from laboratory to clinical and commercial setting, a community of scientists with support from the innovative investment companies organized the third bi-annual international conference titled "Biomedical Innovation for healthy longevity" in Saint-Petersburg, Russia in 25-27 of April 2016. The conference was organized by **Alexey Moskalev**, A**lex Zhavoronkov**, **Vladimir Anisimov**, **Olga Tkacheva** with support from the Fomenko family including **Andrei Fomenko**, **Lada Fomenko** and **Isabel Fomenko** acknowledged in this paper and attended by over 400 scientists from over 20 countries, representing the largest biomedical centers and presenting their work.

The conference included two parallel tracks covering research and translational aspects of aging research and three open round tables on longevity journalism, new methods of financing aging research and classifying ageing as a disease in the context of International Classification of Diseases 11th Revision (ICD-11) chaired by **Alex Zhavoronkov**, **Alexey Moskalev** and **Daria Khaltourina** with over 30 prominent scientists and medical doctors present. While most roundtable participants agreed that it is important to classify ageing as a disease to attract attention and resources to the field and make preventative treatments reimbursable with specific codes, there was major disagreements on the research, medical, ethical, regulatory and business issues. Two main approaches for classifying ageing as a disease were considered: assigning ageing a separate actionable code and developing a taxonomy of age-associated conditions with separate codes. The roundtable concluded with the proposal to develop an open community-managed discussion group using a common MediaWiki engine at http://www.ICD-11.org to explore the various approaches, aggregate the proposals and engage in international collaboration on both the ICD-11 and other disease classification registries.

Over 60 scientists gave talks, presented posters and submitted abstracts for the conference.

Brian Kennedy (Buck Institute for Research on Aging, USA) presented "Gender-specific effects of the mTOR pathway on metabolism and aging". **Claudio Franceschi** (University of Bologna) reported "Decelerated aging in semi-supercentenarians and their offspring according to the epigenetic clock". **Andrei V. Gudkov** (Roswell Park Cancer Institute) presented "Origin, biological significance and pharmacological targeting of senescent cells in vivo". **Vishwa Deep Dixit** (Yale School of Medicine) presented "Inflammasome and age-related inflammation".

Igor Kovalchuk (University of Lethbridge) in his report "Epigenetics of aging – from mechanisms to preventative strategies" presented an epigenetic theory of aging and the novel modes of epigenetic anti-aging interventions. Cells in the aging body exhibit extensive differences to cells in the juvenile organism, ranging from changes in gene expression and DNA methylation patterns, shortened telomeres, to the deteriorating genome maintenance mechanisms. At the tissue, organ and systemic level, cells are exposed to the altered stromal milieu caused by the altered secretory profiles of senescent cells and the deteriorating immune system which is not equally able to mount an immune response towards new antigens. The combination of these factors may facilitate the malignant transformation of cells and prevent the efficient recognition and clearance of transformed cells, thus leading to cancer predisposition.

Wolfgang Wagner (Helmholtz-Institute for Biomedical Engineering) presented "Simple Epigenetic Biomarkers for Biological Age". Aging is reflected by specific modifications in the DNA-methylation (DNAm) pattern. These epigenetic changes are enriched in developmental genes and can be reversed by reprogramming into induced pluripotent stem cells (iPSCs). Apparently, iPSC-derived cells remain epigenetically rejuvenated.

Age-associated hyper-methylation seems to be coherently modified in cancer and may reflect chromosomal reorganization that favors tumor-initiating genomic mutations. We established a simple signature based on DNAm levels at only three specific CpG sites (associated with the genes *PDE4C*, *ASPA*, and *ITGA2B*). This approach facilitates age predictions of blood samples with a mean absolute deviation from chronological age (MAD) of less than five years. The method is also applicable for buccal swabs, which facilitate non-invasive harvesting of DNA. However, the models need to be adjusted for this different specimen and the precision of age-predictions can be increased by using an additional cell-type specific signature - a "buccal-cell-signature" - that reflect the composition of buccal epithelial cells and leucocytes. Notably, there is evidence that simple epigenetic signatures can also be indicative for of all-cause mortality in later life. These results hold the perspective that simple epigenetic biomarkers, based on few or individual age-associated CpGs, can assist estimation of biological age.

Jan Vijg (Albert Einstein College of Medicine) "Genome instability: A conserved mechanism of Aging?". DNA mutations in somatic cells have since long been considered as a possible causal contributor to aging. However, since somatic mutations are rare they can only be detected in clonal lineages, such as tumors or organoids. We developed a reliable, validated assay to detect mutations across the genome in single cells or nuclei after whole genome amplification. Using this assay we discovered that mutation frequency in somatic cells is much higher than in the germline, confirming the disposable nature of the soma. Our results also show an age-related increase in somatic DNA mutations in human white blood cells. We plan to use the single-cell genomics assay to study the landscape of somatic mutations in different organs and tissues of aging humans.

Yousin Suh (Albert Einstein College of Medicine) reported "Functional genomics approach to develop targets for slowing aging in humans". The discovery of evolutionarily conserved pathways with major impact on lifespan and health span in animal models has suggested a potential to identify therapeutic targets for interventions that could favorably influence age-related outcomes in humans. Identification of gene variants that protect humans against crippling diseases at old age is likely to help find novel strategies for prevention and therapy. With the advent of novel high-throughput genomic technologies, discovery of functional pathways that influence lifespan or health span in humans is now feasible through identification of genetic variants associated with these outcomes. Since longevity is associated with diminished risk for diseases and pathologies, novel potential therapeutic targets could be identified based on knowledge of functional pathways of gene variants associated with longevity. We have been conducting systematic multidisciplinary studies to discover functional gene variants associated with longevity in the conserved pathways of aging, including (epi)genome maintenance, using functional genomics approach. To understand molecular mechanisms underlying the association with longevity, functional consequences of gene variants on age-related parameters are assessed in cell culture and in vivo animal models. The results may open up the possibility of targeted and personalized intervention strategies, ultimately leading to improved quality of life of the elderly population.

Guang-Hui Liu (Institute of Biophysics of Chinese Academy of Sciences) presented "Using stem cell and gene editing techniques to study and treat human genetic disorders". Gilford progeria syndrome (HGPS) and Werner syndrome (WS) are two human premature aging disorders with features that closely recapitulate the features of human ageing. Mutations in *LMNA* and *WRN* genes lead to aberrant splicing product progerin and protein loss in HGPS and WS, respectively. Study on how genetic alteration leads to the cellular and organismal phenotypes of premature aging will provide clues to the molecular mechanisms that underlie physiological ageing and increase our understanding of molecular pathways contributing to healthy aging. We have generated induced pluripotent stem cells (iPSCs) from fibroblasts obtained from patients with HGPS. Further, using targeted gene correction technology, we successfully corrected the mutated *LMNA* gene in HGPS-iPSCs. Finally, by using targeted "knock-out" and "knock-

in" technique, we also created WS-specific human embryonic stem cells (hESCs) with *WRN* mutation as well as Parkinson's disease (PD)-specific hESCs with *LRRK2* mutation. Upon differentiation of these "diseased" human pluripotent stem cells into different somatic cell types, they demonstrated aging-associated tissue-specific disease phenotypes. Together, these tools offer unprecedented platforms to study the pathogenesis of human aging and aging-related diseases.

Vadim Gladyshev (Harvard Medical School) "Lifespan control across species and model systems". Many human diseases are associated with aging, which is often their most significant risk factor. The aging process can be regulated during evolution, e.g. mammals show >100-fold difference in lifespan. We employ this diversity to shed light on mechanisms that regulate lifespan. For this, we apply comparative genomics to short- and long-lived species and carry out analyses across panels of mammals. We sequenced the genomes of several mammals with exceptional lifespan and identified genes that may contribute to their longevity. In addition, we carried out analyses of gene expression, metabolites and elements across large panels of mammals. We also analyzed gene expression across different cell types that are characterized by different longevity (cell turnover). These studies point to both unique (to cells, lineages) and common adaptations to longevity involving various pathways. It is our hope that a better understanding of molecular mechanisms of mammalian lifespan control will lead to a better understanding of human diseases of aging.

Andrey Seluanov (University of Rochester) "Longevity mechanisms in the naked mole rat and other long-lived mammals".

John Tower (University of Southern California, Los Angeles) "Sex-specific regulation of life span in Drosophila". Aging in Drosophila is associated with up-regulation of the innate immune response, the oxidative stress response, and the proteotoxicity response, including the mitochondrial unfolded protein response (UPRmt); these changes suggest an aging-associated failure in mitochondrial maintenance that limits life span. Accordingly, we found that transgenic reporters for genes of innate immune response (antimicrobial peptide/AMP genes), cytoplasmic UPR (Hsp70) and UPRmt (Hsp22) are predictive biomarkers of life span. Mifepristone/RU486 is a glucocorticoid receptor antagonist and progesterone receptor antagonist with human female contraceptive and abortifacient activities, reported to reduce inflammation. In female Drosophila, mating increases reproduction and inflammation and decreases life span. We found that mifepristone/RU486 acts in Drosophila females to decrease reproduction, delay inflammation and increase median life span up to +68%. Long-lived females had normal or increased food consumption based on dye-uptake and capillary-feeding assays, arguing against a dietary restriction mechanism. Both mating and mifepristone/RU486 changed median life span by altering initial mortality rate. High-throughput RNA sequencing was used to identify genes up-regulated or down-regulated upon mating, and where the change was reduced by mifepristone/RU486. Several candidate positive regulators of life span were identified that are conserved in humans, including dosage compensation regulator Unr and the Dopamine 2-like receptor. Candidate negative regulators included neuropeptide CNMamide and several involved in protein mobilization and immune response, including the AMP gene Drosocin. Analysis of Drosocin-GFP reporters in live flies recapitulated the aging-associated inflammation, including the effects of mating and mifepristone/RU486. The results implicate steroid hormone signaling in regulating sex-specific trade-offs between reproduction versus immune function and longevity.

Vadim Fraifeld (Ben-Gurion University of the Negev) "Mitochondria: a bottleneck of aging and longevity?" Nuclear-mitochondrial relationships could be characterized as "enslaving" rather than symbiosis. Indeed, mitochondria are the most "hard-working" organelles in the animal cell, which have delegated the vast majority of the genes to the nuclear genome. This situation inevitably brings about to a "conflict of interests", with far-reaching consequences. Unsurprising-ly, mitochondria-associated variables (mtDNA

GC content, metabolic rate, metabolic score, body temperature) are powerful predictors of mammalian longevity, and thus could be considered the main targets for longevity-promoting interventions.

Vera Gorbunova (University of Rochester) "The mechanisms of more efficient DNA repair in long-lived mammals: the role of SIRT6".

Blanka Rogina (University of Connecticut Health) "*Indy* reduction maintains fly health and homeostasis". *Indy* (*I'm not dead yet*) encodes the fly homologue of a mammalian transporter of the Krebs cycle intermediates. Reduced *Indy* gene activity has beneficial effects on energy balance in mice, worms and flies, and worm and fly longevity. In flies, longevity extension is not associated with negative effects on fertility, mobility or metabolic rate. Others and we show that *Indy* reduction extends longevity by mechanism similar to calorie restriction (CR). Some of the hallmarks of these changes are altered intermediate nutrient metabolism, increased spontaneous physical activity and increased mitochondrial biogenesis. These changes have been found in fly heads, thoraces and the midguts. The observed changes in midgut energy metabolism, specifically decreased production of free radicals, results in preservation of intestinal stem cell (ISC) homeostasis and midgut integrity. Our studies show a direct link between changes in energy metabolism, caused by the *Indy* reduction and preservation of ISC homeostasis. The data suggest that *Indy* reduction preserves homeostasis in tissues that contribute to extended health and longevity.

Elena Pasyukova (Institute of Molecular Genetics of Russian Academy of Sciences, Russia) "Neuronal transcriptional regulators of lifespan in Drosophila melanogaster".

Irina Irincheeva (Nestlé Institute of Health Sciences) presented "Why don't we all lose weight equally on Caloric Restriction?" Proteomics explanation to weight loss variability on a low-calorie diet in overweight and obese subjects" Obesity is characterized by a state of metabolic inflexibility and chronic inflammation leading to the development of comorbidities like type 2 diabetes, dyslipidemia or certain cancers and generally to a decreased life expectancy in obese individuals. Low calorie diets (LCD) (<1000 kcal per day) have been shown to be very effective in improving many of the metabolic dysfunctions. However, the capacity to lose weight and the associated metabolic improvements show significant variability in humans, even under the same controlled dietary regimes. To understand the molecular basis for these differences we screened the plasma expressions of over twelve hundred proteins in 500 overweight and obese subjects to determine whether we could predict at baseline the weight loss outcome of 8 weeks LCD diet (800 kcal per day). As discovery data to construct a weight loss predictive model we used the Pan-European cohort DiOGenes (Diet, Obesity and Genes, Larsen et al., 2010). To select weight loss predictive proteins we deployed elastic net bootstrap estimation of high-dimensional regression (Chatterjee and Lahiri, 2011) adjusting for gender, age and BMI at baseline. We evaluated the accuracy of our predictive model on the data set of 500 independent subjects from Ottawa Hospital Weight Management Clinic using LCD for weight loss. The accuracy of the predictive model was significantly higher than random in the independent data set.

To identify functional relationships and biochemical pathways shared between the predictive proteins we performed network analyses. The results allow us to formulate a first hypothesis on biological processes leading to successful weight loss for overweight and obese subjects on a low-calorie diet.

Alexander Kulminski (Duke University) presented "Uncoupling associations of risk alleles with endophenotypes and phenotypes: Insights from the Apolipoprotein B locus, lipids, myocardial infarction, and survival". Traditionally, genome-wide association studies (GWAS) have emphasized the benefits of large samples in the analyses of age-related traits rather than their specific properties. We adopted a realistic concept of genetic susceptibility to inherently heterogeneous, age-related traits driven by the elusive role of evolution in their properties. We analyzed in detail the associations of

rs693 and rs562338 polymorphisms representing the Apolipoprotein B locus with endophenotypes (total cholesterol [TC] and high-density lipoprotein cholesterol) and phenotypes (myocardial infarction [MI] and survival) in four large-scale studies. We showed that a strong, robust predisposition of rs693 and rs562338 to TC (beta=0.72, p=7.7×10-30 for rs693 and beta=-1.08, p=9.8×10-42 for rs562338) is not translated into a predisposition to MI and survival. The rs693_A allele influences risks of MI and mortality for MI patients additively with lipids. This allele shows antagonistic effects -- protecting against MI risks (beta=-0.18, p=1.1×10-5) or increasing MI risks (beta=0.15, p=2.8×10-3) and mortality for MI patients, in different populations. Paradoxically, increased TC concentrations can be protective against MI for the rs693_A allele carriers. Our results uncouple the influences of the same alleles on endophenotypes and phenotypes despite potential causal relationships among the latter. Our strategy reveals an overall highly significant association of rs693 with MI (p=5.5×10-8) that is contrasted with a weak estimate following the traditional, sample-size-centered GWAS strategy (p=0.16) in the same sample. These results caution against the use of the traditional GWAS strategy for gaining profound insights into genetic predisposition to healthspan and lifespan.

Vladimir Skulachev (Moscow State University) in his lecture "Naked Mole Rats and Humans: Highly Social Creatures Prolonging Youth by Delay of Ontogenesis (Neoteny)" considered some physiological mechanisms responsible for longevity of eusocial mammals, i.e. a rodent (naked mole rat) and a primate (human). It is concluded that both naked mole rat and human are no more affected by dynamic natural selection due to specific organization of the socium (naked mole rat) and substitution of fast technical progress for slow biological evolution (human). Since aging is supposed to be a program stimulating evaluability by increasing pressure of natural selection upon an individual, such a program became a harmful atavism for naked mole rat and human. This is apparently why aging as a reason for death is very rare in naked mole rats younger than 30 years and humans younger than 55 years. Such an effect is achieved, at least partially, by prolongation of youth (neoteny). The numerous facts are described indicating that The Master Biological Clock responsible for timing of ontogenesis is retarded both in naked mole rat and in human. In these species, numerous traits of youth do not disappear (or disappear enormously slowly) with age. For a long time, in naked mole rat, this point of view was supported mainly by morphological observations, such as absence of hair, auricles and scrotum, underdevelopment of lungs, etc. Recently, numerous physiological features of neoteny in naked mole rat were described. Among them are (i) long gestation, (ii) long maturity time, (iii) strong delay in brain development, (iv) regeneration and elongation of neurons during entire life span, (v) extremely high resistance of adult mole rat neurons to anoxia/reoxigenation, a property inherent in newborn and young, but not adult mammals, (vi) resistance to H2O2 - induced apoptosis of cell culture, (vii) absence of age-linked decay in levels of antioxidants (in particular, due to very high concentration of extracellular antioxidant hyaluronan), (viii) absence of any increase in peroxidation index of lipids with age, (ix) no age-linked increase in ROS production, (x) retarded postnatal development of mitochondrial reticulum in skeletal muscles, (xi) absence of decay in the amount of mitochondria with age, (xii) no age-induced decay in proteasome level, (xiii) no indications of aging of immune system, (xiv) low transcription of genes and activity of insulin and IGF1 and high transcription and activity of IGF2, etc. These and other specific features of the naked mole rats explain their resistance to cancer, infections, cardiovascular and brain diseases, diabetes, and, as a result, their long maximal lifespan, which is more than 30 years vs. 3.5 years for mice (a rodent of the similar size).

For humans, it is generally accepted that embryo, neonatanal and young organisms have features similar to other primates, thereby the listed morphs resemble very much human, not ape. As to the ape-specific traits (a lot of hair on the body, construction of the skull, large superciliary arches, etc.), they appear in adulthood of animals and do not appear in humans. Recently, studies of brain transcriptomes of humans, chimpanzees and rhesus macaques revealed that in humans, just like naked mole rats, transcription of

large group of genes is strongly retarded compared to the great apes. Comparison of pairs of highly and lowly social mammals (naked mole rat vs. mouse and human vs. chimpanzee) is very interesting. In both pairs, highly social representative (i) is long-lived, (ii) its age-dependent mortality during first 30-55 years is so low that its contribution to the total mortality is negligible, (iii) gestation and maturation times are longer, (iv) brain development is strongly retarded but without negative effect on the final mass of the organ, (v) skeletal muscle development is also retarded resulting in lowering in the final mass.

Demonstration of neoteny in humans at physiological and genetic levels is very important for understanding of physiological, pathological and therapeutic aspects of aging. In particular, prolongation of youth by delay of aging is impossible to imagine within the framework of the concept of stochastic (non-programmed) aging but can easily be explained if aging is programed and controlled by The Master Biological Clock, like other main steps of ontogenesis. Arrest of operation of aging program in humans by an antiaging medicine seems to be a promising approach to prolong our healthspan.

David Gems (University College London) spoke on "The origins of senescent pathology in *C. elegans*". The biological mechanisms at the heart of the aging process are a long-standing mystery. An influential theory has it that aging is the result of an accumulation of molecular damage, caused in particular by reactive oxygen species (ROS) produced by mitochondria. This theory also predicts that processes that protect against oxidative damage (involving detoxification, repair and turnover) protect against aging and increase lifespan. However, recent tests of the oxidative damage theory, some using the short-lived nematode worm *C. elegans*, have often failed to support the theory. This motivates consideration of alternative models. One new theory, conceived by M.V. Blagosklonny and based on the antagonistic pleiotropy theory of G.C. Williams, proposes that aging is caused by the non-adaptive running on in later life of developmental and reproductive programmes. Such quasi-programmes (i.e. that are genetically programmed but non-adaptive) give rise to hyperfunction, i.e. functional excess due to late-life gene action, leading via dysplasia (including hypertrophy and hyperplasia, and atrophy) to the age-related pathologies that cause the late-life increase in mortality. Here we assess whether the hyperfunction theory is at all consistent with what is known about *C. elegans* aging, and conclude that it is. In particular, during aging *C. elegans* show a number of changes that may reflect pathology and/or hyperfunction, including oocyte hypertrophy to form tumor-like masses, proximal gonad atrophy and disintegration, massive yolk accumulation, cuticular hypertrophy and neurite outgrowth. Such changes are retarded in long-lived mutants, and can contribute to mortality. We demonstrate how futile run-on of yolk synthesis, conversion of intestinal biomass into yolk, and germline apoptosis generate late-life pathology. Our assessment implies that the hyperfunction theory is sufficient to explain the origins of major senescent pathologies in *C. elegans,* i.e. is a major cause of aging in this organism. The relative importance of hyperfunction and molecular damage as causes of different senescent pathologies in different organisms, and the interactions between these two major senescent etiologies are important topics for future investigation.

Vadim Gladyshev (Harvard Medical School) "The rising deleteriome". Understanding the nature of aging is an important step in developing approaches to manipulate it. Various theories posit that aging may be caused by molecular damage, genetic programs, continued development, hyperfunction, antagonistic pleiotropy alleles, mutations, trade-offs, incomplete repair, etc. I will discuss that these ideas can be conceptually unified as they capture particular facets of aging. Living is associated with a myriad of deleterious processes, both random and deterministic, which exhibit cumulative properties, and represent the indirect effects of biological functions at all levels, from simple molecules to systems. From this, I derive the deleteriome, which encompasses cumulative deleterious age-related changes and represents the biological age. The organismal deleteriome consists of the deleteriomes of cells, organs, and systems, which change along roughly synchronized trajectories and may be assessed through biomarkers of aging. Aging is

then a progressive decline in fitness due to the increasing deleteriome, adjusted by genetic, environmental, and stochastic processes. I will discuss how the deleteriome can be analyzed by following increased molecular damage in the form of low molecular weight species, somatic mutations derived from the analysis of cancer genomes, and dietary approaches.

Arnold Mitnitski (Dalhousie University) reported "A dynamical network model for age-related accumulation of health deficits and mortality". How long people live depends on their health, and how it changes with age. Individual health can be tracked by the accumulation of age-related health deficits. The fraction of age-related deficits is a simple quantitative measure of human aging. This quantitative frailty index is as good as chronological age in predicting mortality. It has been shown that the accumulation of deficits is related to age associated imbalance between damage and repair processes, at the different levels of the organism. What causes such an imbalance was not clear. In order to answer this question, we developed a dynamical network model of aging. An individual was represented by a network of connected deficit nodes (n=800), each of which has two stable states corresponding to health and damaged. In our model, damage and repair rates have no explicit time-dependence, but do depend on the state of connected nodes. Transitions between the states were governed by: (i) interactions between the nodes, i.e. network connectivity, and; (ii) the environment, with a general stochastic mechanism (white noise) representing the environment. With this model, we observed upward curvature of the frailty index and broadening the distribution of the frailty index with age. We use a simple mortality criterion, where mortality occurs when the most connected node is damaged. In this way, we qualitatively reproduce Gompertz's law of exponential increasing human mortality with age. No explicit time-dependence in damage or repair rates was needed in our model. Instead, implicit time-dependence arose through deficit interactions - so that the average deficit damage rates increased, and deficit repair rates decreased, with age. We discuss the implication of our computational model that will allow us to start with high-quality model data, before we test our insights against current and emerging clinical data.

S. Michal Jazwinski (Tulane University Health Sciences Center) presented "Metabolic and Genetic Markers of Biological Age". Biological and chronological age are not the same, as individuals depart in health from the average. Taking a systems approach, we developed an objective measure of healthy aging, a frailty index (FI34) composed of 34 health and function variables. FI34 is a much better predictor of mortality than is chronological age; therefore, it directly reflects biological age. It increases exponentially with chronological age, but it does so more slowly for offspring of long-lived parents. FI34 is also heritable (h2=0.39). Thus, it can be used in genetic analyses. The patterns of aging described by the variables in FI34 are very different for offspring of long-lived and short-lived parents. We have examined the association of the components of energy metabolism with FI34 in the oldest-old. Surprisingly, there is a positive association of FI34 with resting metabolic rate (RMR). This points to the rising cost of maintenance of integrated body function with declining health during aging. There are differences between males and females, however. In males, circulating creatine kinase (CK) increases with FI34. A decline in fat-free mass (FFM) is found instead in females. The CK increase in males is associated with variation in the genes XRCC6 and LASS1. These genes have in common a role in cell death, suggesting tissue damage as a source of increased energy costs of maintenance with declining health in males. In females, there is an association of variants of UCP2 and UCP3 with FI34, which is not found in males. These genes encode mitochondrial membrane transporters that impact cell metabolism. An interaction of a functional variant of UCP3 with RMR explains the association with FI34. We have used FI34 in an unbiased screen for genomic variation associated with healthy aging. This uncovered a region on chromosome 12 associated with this phenotype. Fine-mapping dissects this into three sites, which bear marks of regulatory function and association with longevity. Supported in part by grants from the National Institutes of Health (NIH).

Aubrey de Grey (SENS Research Foundation) spoke on "Longevity escape velocity: incorporating technological progress into extrapolation". Predictions of future longevity have historically failed, by and large, to prove accurate. I will argue that this is because they are in one or another way based on pure extrapolation of past trends, a method that incorporates the implicit assumption that it does not matter *how* we contrived to achieve longevity improvements. I will explain how a careful examination of the medical and other advances that led to increased longevity could have resulted in much better predictions of their impact. I will then focus on the future, and especially on the initially counterintuitive but ultimately inescapable conclusion that regenerative medicine applied to the health problems of old age will at some point, probably within the next few decades, create a sharp discontinuity - which others have termed the "Methuselarity" - in the longevity of successive cohorts. This discontinuity will be so dramatic that period life expectancy will literally cease to be calculable, because mortality rates for all ages so far attained will become so low that survival probabilities will multiply to more than 50%.

Daniel Belsky (Duke University) presented "Quantification of biological aging in young adults". Population aging threatens to bring a tidal wave of disease and disability (1). Strategies to prevent or treat individual diseases will be inadequate to contain costs and preserve economic productivity; interventions that address the root cause of multiple diseases simultaneously are needed. Such "geroprotective" interventions are emerging from model organism studies. Translation of these interventions to humans is slowed by the need for lengthy follow-up to evaluate effectiveness. This is especially true in the case of interventions that will need to be applied to young humans free of age-related disease, for whom prevention is still possible. Thus, surrogate endpoints for trials of geroprotective interventions are needed. Because most human aging research examines older adults, many with chronic disease, little is known about aging in young humans. We studied aging in 954 young humans, the Dunedin Study birth cohort. To quantify biological aging in these individuals, we tracked multiple biomarkers across three time points spanning their 20s and 30s. We devised a longitudinal measure that quantifies the pace of coordinated physiological deterioration across multiple organ systems (e.g., pulmonary, periodontal, cardiovascular, renal, hepatic, and immune function). This measure, the "Pace of Aging," showed substantial variation in young, healthy adults who had not yet developed age-related disease. Young adults with faster Pace of Aging were, by midlife, less physically able, showed cognitive decline and brain aging, self- reported worse health, and looked older. The number of assays and repeated measurements required to assess Pace of Aging make it impractical for large-scale geroprotector trials. Biological aging measures that can be implemented in a single cross-section of data at baseline and follow-up are needed. We examined Pace of Aging alongside several, more scalable cross-sectional measures of biological aging. These measures were based on clinical biomarker and genomic data, including two recently published clinical-biomarker algorithms, telomere length, and epigenetic clocks. We asked two questions: (1) Do different measures of biological aging measure the same thing? and (2) Do different measures of biological aging capture different information about healthspan? Findings suggest promise and challenges in research to develop surrogate endpoints for trials of geroprotective interventions.

Andreas Simm (Martin Luther University Halle-Wittenberg) presented "Biomarkers of Ageing: the what-where from-when questions".

Tamas Fülöp (University of Sherbrooke) presented "Are there any reliable biomarkers for immuno-senescence?". Aging is accompanied by many physiological changes including those related to the changes in the immune system. These changes are called Immunosenescence which is accompanied by the Inflamm-aging phenomenon. Many biomarkers have been proposed to describe these age-associated changes in the immune system. One of the most consistent is the chronic Cytomegalovirus infection. Most of the elderly are affected in developed countries which about 70% and in developing countries about 100% at the age of 80. Despite the numerous studies there is no consensus which role the recurrent CMV infections play in the alterations of the immune system namely in

the Inflamm-aging process and in the more consistent phenotypic alterations of T cells. Many experimental evidence supports that changes observed with aging (increase of memory CD8+ T cells, increase in pro-inflammatory cytokine mediators) may be related to chronic CMV infections. However, this infection was also showed to be a promoter of a better immune response in some cases e.g. vaccination. There is still debate whether CMV infection causes the immuno-senescence which in this case would suggest that aging of the immune system is nothing else, but just a viral infection. In contrast, if this is just a concomitant phenomenon thus in this case we should target other biomarkers which would represent the immuno-senescence. There is much confusion between diseases and biological aging, thus one of the main tasks is to define biological aging. Longitudinal studies combined with healthy very old elderly persons studies may give some clue to this and may help to find earlier biomarkers to reflect biological aging changes and eventually modify them.

Joao Pedro de Magalhaes (University of Liverpool) presented on "Gene expression profiling for the discovery of biomarkers of ageing". There is widespread interest in identifying biomarkers of ageing in order to accelerate basic and translational research. Our lab has employed various gene expression profiling approaches to identify molecular signatures that can be used as biomarkers as well provide functional insights on ageing and its manipulation. We performed a meta-analysis of ageing gene expression profiles using microarray datasets from multiple mammalian tissues, which revealed several conserved molecular signatures of ageing. We also applied our network and meta-analysis methods to dietary manipulations of ageing, in particular caloric restriction (CR), and identified candidate genes and processes strongly associated with CR in mammals. Moreover, we have been employing whole transcriptome profiling (RNA-seq) to study ageing and its manipulation by diet, which has significant advantages when compared to microarrays. Lastly, to catalogue and help understand ageing changes, we developed the Digital Ageing Atlas (http://ageing-map.org/), a one-stop collection of human age-related data covering different biological levels (molecular, cellular, physiological, psychological and pathological).

Arnold Mitnitski (Dalhousie University) reported "Indices of biological aging as indicators of heterogeneity of people's health". There is an increasing interest to assessing biological aging - the aging rates are different in individuals of the same chronological age. Some found attractive an idea that these differences reflect differences in "biological age". How to estimate biological age is a matter of ongoing debates. The techniques differ also depending on which biomarkers are used to calculate of biological age. We discuss the different approaches to estimation of biological age based on biomarkers of aging of different nature: from the sub-cellular level to the level to the whole organism. We consider this issue from the heterogeneity of people at the same chronological age perspective, from which the index of biological age is only one of possible measures of such heterogeneity. We illustrate some challenges in assessing biological age, by comparing a few measures of heterogeneity: the indices of biological age, defined with and without chronological age, and the frailty indices. By providing head-to-head comparison of these measures we demonstrated that inclusion of chronological age in the measure of biological age is unnecessary, and also (at least in the data sample we present) inferior to the frailty indices. The latter are based on the higher number of biological and clinical data therefore more likely capture the essential characteristics of health and its changes during aging, than a rather restricted set of biomarkers used to calculate biological age score. Also, the items used to calculate the frailty indices are readily available (either from the routine blood tests or/and from clinical assessments), the algorithm of its assessment is simple, in contrast to the obscured statistical techniques of calculating the biological age scores from a relatively restricted number of continuous biomarkers. Extensive comparisons across different databases are required. We discuss the problem of integration of various biological/clinical in a unified index of biological age.

Alexander Kulminski (Duke University) reported "Can age-specific genetic effects be relevant to biological age?". Living organisms are getting older and eventually die at a certain age. The actual time an organism has been alive refers to chronological age (CA). However, not all organisms die at the same chronological age even if they are of the same species. The idea of biological age (BA) is that the differences in lifespan of these organisms can be due to an internal clock. For humans, BA refers to how old that human seems. A problem, however, is how to quantify BA. A promising approach could be to express BA in terms of measurable phenotypes such as biomarkers. As phenotypes, biomarkers represent endpoints of a cooperative work of genes in an organism. Accordingly, BA could readily have a genetic origin. Does it necessarily imply that there should be specific genes regulating BA? The answer is not straightforward. Associations of BA with telomere length seems to support existence of BA-specific genes. However, studies of laboratory animals show that even genetically the same organisms can have dramatically different lifespan even if they are in the same, perfectly controlled environment. These and other findings suggest that BA can be modulated not only by the BA-specific genes but also by changes in the effects of other genes over CA. Studies show that epigenetic modifications can modulate the effects of genes over CA. What about genes themselves, do they influence the same phenotypes differently at different ages? It is often assumed that genes have age-independent effects on phenotypes. In this presentation, we will discuss evidence of the changing role of genes in human phenotypes with age.

Alex Zhavoronkov, Evgeny Putin, Alex Aliper, Mikhail Korzinkin (Pharmaceutical Artificial Intelligence Department, Insilico Medicine, Inc.) presented a talk on "Gamification of data collection for deep learning and biomarker development". Since the publication of Horvath's epigenetic aging clock in 2013, the field of aging biomarkers is rapidly evolving with epigenetic and transcriptomic markers developed to accurately predict chronological age of the patient. However, since these tests are reasonably new and expensive, the number of samples with clinical outcomes is still low making it difficult to assess the biological relevance and facilitate for rapid clinical propagation.

One data type, medical professionals have a lot of experience with, which is abundant, cost-effective and actionable is clinical blood and urine tests commonly including basic blood biochemistry and cell counts. Millions of clinical profiles with blood biochemistry data are available worldwide providing sufficient number of samples to train deep neural networks.

We obtained a large data set of standard blood tests with 41 parameters linked to age and sex of the patients from Invitro Laboratories, one of the largest providers of laboratory services in Eastern Europe. The data set contained over 60,000 samples coming from routine checkups and excluded sources of patients with diseases like hospitals and medical institutions. We trained 21 single class deep neural networks ensembled using a stacking model to predict the patients' chronological age with 83.5% epsilon-accuracy r of 0.91 with R(2) of 0.82 and mean absolute error (MAE) of 5.55 years.

Following on the footsteps of Microsoft's http://www.how-old.net, we built a website http://www.aging.aiinviting people from all over the world to submit their test results in order to guess their age. From January 15 to March 31st over 1,500 people participated in the study. In addition to blood tests we asked to provide height, weight and smoking status, the new parameters that are being evaluated for the future studies. We plan to expand Aging.AI system to work with urine, transcriptomic and imaging data and welcome collaborations in building comprehensive and actionable biomarkers of aging.

Ivan V. Ozerov (Senolytics Department, Insilico Medicine, Inc.) presented "iPANDA identifies the pathway signature in senescent cells: a step forward to development of novel senolytic drugs". Cellular senescence combined with an inability of immune system to effectively eliminate senescent cells leads to persistent accumulation of senescent cells

in an aging organism. On the other hand, senescent cells represent a constant danger to the cell population as far as they partly lose their functions and induce malfunctioning of surrounding cells. As senescent cells accumulate in even greater numbers over the years, the whole tissues gradually loose their specific properties. Such process results in developing of aging phenotype and encourages the risk of malignant transformation in the affected cells. Hence therapies aimed to selectively eliminate senescent cells have a potential to slow down age-related changes in tissues and body in whole as well as to reduce the risks of cancer generation. Recently three low-molecular compounds which demonstrate an ability to selectively eliminate senescent cells in various tissues were proposed. This novel class of prospective drugs is referred to as senolytics.

In this study, we apply our recently-developed approach to large-scale transcriptomic data analysis in silico Pathway Activation Network Decomposition Analysis (iPANDA) to identify pathway signatures of senescent cells in various tissues and pathway signatures of known senolytic drugs. iPANDA algorithm is specifically designed to obtain robust results when analyzing transcriptomic data from multiple sources. Thus, we were able to extract the common tissue-independent features of senescent cells including downregulated anti-apoptosis signalling networks as well as several tissue-specific features of cellular senescence. In order to find novel compounds with senolytic properties we utilized this information for obtaining a list of prospective protein targets. A list of about 100 low-molecular senolytic candidates was derived partly from the pharmacophore-based scanning of proposed protein targets and partly from a list of known drugs which selectively affect the identified pathways involved in cellular senescence. At present moment, the validation process of these compounds in cell culture experiments is on the way.

Ksenia Lezhnina and colleagues (Insilico Medicine, Inc.) presented "Signaling pathways signature of sarcopenia identified by iPANDA algorithm." Sarcopenia is a losing muscle mass and function with aging. Decreased strength and power of muscle function may contribute to higher risks of accidents among older people and affects quality of life. Until recently sarcopenia was not even considered as a pathological condition and as a consequence clinical definition and diagnostic criteria is poorly developed. Mechanism underlying sarcopenia is extensively investigated but still not fully understood. In order to study this we compare transcriptomic profiles of muscle tissues from young and old people, both women and men. We assume that aging process starts from the fourth decade of life. We apply a new algorithm in silico Pathway Activation Network Decomposition Analysis (iPANDA) to transcriptomic data to find signaling pathway signatures of aging in muscle tissues. Common pathway signatures can be considered as a target for development of new approaches for sarcopenia treatment.

Artem Artemov and colleagues (Insilico Medicine, Inc.) presented "*In silico* screen for drugs increasing cancer immunotherapy success rates". Cancer immunotherapy has been shown to be extremely efficient. Unlike traditional targeted therapy, it can lead to a complete remission rather than a few months increase in lifespan. Unfortunately, it is beneficial for only a small subset of patients. In this work, we performed *in silico* screening of compounds which can be administered in combination with anti-PD1 immunotherapy to increase immunotherapy success rate. We collected publicly available transcriptome data for tumours responding and not responding to immunotherapy. Next, we applied iPANDA, Insilico medicine pathway analysis algorithm, and deep-learning based approach to identify a transcriptomic signature predicting the success of immunotherapy in a particular tumour. Finally, we analyzed drug-induced transcriptome effects to screen for the drugs which could robustly drive transcriptomes of tumour cells from non-responsive state to the state responsive to immunotherapy. Among the top-scoring drugs we found known compounds used in combination with cancer immunotherapy. Interestingly, we also found a compound which was a close chemical analog to a compound used in cancer immunotherapy, but hadn't itself been studied for this indication. This approach, after preclinical and clinical validation, may lead to improved cancer care and dramatic lifespan increase of cancer patients.

Polina Mamoshina and colleagues (Insilico Medicine, Inc.) presented "*In silico* modeling of human skin permeability of compounds with possible geroprotective activity" Despite the fact that many chemicals demonstrate potential skin rejuvenating activity, skin aging is still an incurable process. The major problem is that most of the anti-aging compounds have low skin penetration level and so bioavailability. Dermal absorption rate could be estimated by *in vitro* and *in silico* approaches. We utilized a set of Machine Learning techniques to predict skin permeability coefficient (Kp) of compounds with skin geroprotective activity. K-nearest neighbors algorithm showed the best performance with r=0,94, R^2=0,86, *MAE*=0,29. This new approach may lead to a development of new effective remedies that could slow down or even reverse skin aging.

Jane Schastnaya (Insilico Medicine, Inc.) presented "iPANDA for biomarker identification in aging-associated hair loss". In silico Pathway Activation Network Decomposition Analysis (iPANDA) is a novel biomathematical method, which has a potential to be a universal tool for pathway activation analysis in the treatment of anti-aging diseases and for the identification of actionable targets for therapy. It can be used for the analysis of any physiological, stress, malignancy and other perturbed conditions at the molecular level. We showed the results of a qualitative analysis of signaling pathway activation state in androgenetic alopecia. Some of these signaling pathways may serve as targets for the treatment of hair growth disorders. For example, recent findings demonstrated that inhibition of JAK-STAT signaling pathway can promote hair growth. Further progress in research will lead to the increasing insight into pathways involved in pathological hair cycling.

Alexander Fedintsev and **Alexey Moskalev** (Moscow Institute of Physics and Technology) presented "Markers of cardiovascular health for human chronological and biological age estimation". The aging process is unavoidably associated with a decline in functional physical capacity. A lot of anti-aging interventions are known but they were tested only on model organisms so it is very important to develop simple, cheap and accurate method of biological age estimation which can be used to control anti-aging therapy efficacy. To develop such a method, we performed analysis using machine learning approach to reveal parameters which are mostly associated with chronological age and selected four of them. These four predictors which showed highest importance are: complex intima media thickness, arterial stenosis, augmentation index, and pulse wave velocity. The combined index composed of these four parameters explained up to 61% of variance in age, more than other biomarkers of age like telomere length or glycans. We also measured median absolute error which was 5.12 years for women and 5.46 years for men. These four parameters reflect aging of cardiovascular system. Cardiovascular diseases are the major cause of age-related mortality so we assume that our method is good estimation not only of chronological but also of biological age. In addition, this method uses medical equipment which is widely represented in modern clinics.

Peter Fedichev (Gero, Inc.) in his report "Target and biomarker identification platform to design new drugs against aging and age-related diseases" studied fundamental aspects of aging to develop a mathematical model of gene regulatory network. We show that aging manifests itself as an inherent instability of gene network leading to exponential accumulation of regulatory errors with age. To validate our approach, we studied age-dependent omic data such as transcriptomes, metabolomes etc. of different model organisms and humans. He builds a computational platform based on our model to identify the targets and biomarkers of aging to design new drugs against aging and age-related diseases. As biomarkers of aging we choose the rate of aging and the biological age since they completely determine the state of the organism. Since rate of aging rapidly changes in response to an external stress, this kind of biomarker can be useful as a tool for quantitative efficacy assessment of drugs, their combinations, dose optimization, chronic toxicity estimate, personalized therapies selection, clinical endpoints achievement (within clinical research), and death risk assessments. According to the

model were proposed a method for targets identification for further interventions against aging and age-related diseases.

Anatoliy Yashin (Duke University) reported "Lack of Replication in GWAS of Complex Traits: Insights for Efficient Analyses of Human Aging and Longevity". The genome-wide association studies (GWAS) performed during the last decade detected a large number of SNP loci that influence variability of human aging, health, and longevity related traits. While many of these findings were confirmed in analyses of independent populations many other identified associations remain non-replicated. The persistent non-replication of the research results indicates a problem that needs immediate attention. The purpose of this paper is to investigate the possible contribution of population genetic structure to this problem. We reviewed the results of recent GWAS of longevity related traits and investigated forces and mechanisms that form genetic structures of human populations. We found that these structures may differ in populations used in genetic association studies. We investigated the role of linkage disequilibrium (LD) between functional SNPs on estimates of the effects of these SNPs on mortality risks. We found that the estimates of genetic associations of minor allele in the first locus with lifespan as well as age trajectories of mortality rates for carriers and non-carriers of this allele are strongly modulated by the levels of LD between the two loci. Depending on the LD levels between these SNPs the same genetic variant may have positive, negative, or no association with longevity related trait. The estimated associations may also change with increasing age from positive to negative and vice versa. The results of these analyses indicate that the difference in LD between the two functional SNP loci in the two study populations may contribute to the lack of replication of the results of genetic association studies of human longevity related traits. These results also show that studying LD patterns around functional SNPs, as well as effects of haplotypes on longevity related traits may contribute to better understanding the genetic nature of these traits.

Alexander Maslov (Albert Einstein College of Medicine) presented "Quantitative assessment of genome integrity by high-throughput sequencing: application for aging research". Aging is a complex trait governed by both genetic and environmental factors. While environmental exposure promotes genome instability, a major driver of the aging process, genetically determined mechanisms of genome maintenance act in the opposite direction and promote longevity. The idea that environmental hazards promote aging is not novel. Twin studies have demonstrated that environmental factors play an important role in the development of degenerative diseases associated with aging and that the relative contribution of non-genetic factors increases in advanced ages. However, until recently these studies had a mostly descriptive character; now since the advent of new technologies in genetic research, predominantly next-generation sequencing, we are capable of taking this a step further and directly assess genome integrity in primary cells or tissues of any species.

Matt Kaeberlein (University of Washington) presented "Effects of transient mid-life rapamycin treatment on lifespan and healthspan". The FDA approved drug rapamycin increases lifespan and improves measures of healthspan in rodents [1]. Nevertheless, important questions exist regarding the translational potential of rapamycin and other mTOR inhibitors for human aging, and the optimal dose, duration, and mechanisms of action remain to be determined [2]. Here I will report on studies examining the effects of short-term treatment with rapamycin in middle-aged mice and dogs. We find that transient treatment with rapamycin is sufficient to increase life expectancy by more than 50% and improve measures of healthspan in middle-aged mice. This transient treatment is also associated with a remodelling of the gut microbiome, including dramatically increased prevalence of segmented filamentous bacteria in the small intestine, along with a dramatic shift in the cancer spectrum in female mice. In dogs, we have defined a dose of rapamycin that is well tolerated, and initial results are consistent with improvements in age-associated cardiac function similar to those observed in rapamycin-treated mice. These data suggest that a transient treatment with rapamycin may yield robust health benefits in mice, dogs, and perhaps humans.

Stephen Spindler (University of California, Riverside) presented "Flies, mice and humans, and the search for longevity therapeutics".

James Mitchell (Harvard T.H. Chan School of Public Health) reported "Increased endogenous hydrogen sulfide as a conserved mechanism of longevity extension".

Maxim Skulachev (Moscow State University) presented "Development of mitochondrially-targeted geroprotectors: from the molecular design to clinical trials and marketing strategy". Research and development of geroprotectors is always challenging when the project passes from theoretical and laboratory work to routine drug development (preclinical and clinical trials and medical authority approvals). In this talk, we present an example of an anti-ageing RnD project aimed on creation of geroprotector drugs on the basis of rechargeable mitochonrially-targeted antioxidants. Our strategy is to get the potential gero-protector approved as a drug against a certain age-related disease, and then to expand the list of indications for this pharmaceutical to other traits of ageing. We synthesized a series of novel organic compounds, namely, cationic, membrane-permeable derivatives of plastoquinone. Preclinical studies gave very promising results in several animal models of age-related diseases, including eye-diseases, neurodegeration and inflam-mation. Our first pharmaceutical was designed for local administration (in the form of eye-drops) to speed up the process of clinical development and to get the clinical data faster. At the current stage of the project our first drug Visomitin (Rx eye drops with antioxidant SkQ1 helping in such age-related diseases as dry eye syndrome and cataract) has been approved and marketed in Russia and successfully passed phase II clinical trials in US. Systemic oral form of SkQ1 has entered clinical trials in Russia and completed preclinical program in US and Canada. We consider our project to be a valuable attempt to slow down human aging by a mitochondrial approach.

Sibylle Jager (L'Oreal) presented "Longevity compounds for skin anti-aging: promising strategy or false hope".

Andrey Voronkov (Moscow Institute of Physics and Technology) presented "Polypharmacological geroprotectors for healthy longevity". In modern drug discovery, the concept of polypharmacology has attracted substantial attention. In this concept one multi-targeting drug, or drugs combination is used for targeting of several, complementary biotargets, which can result in synergistic effect. Synergism results from increase of the efficiency due to the complex interactions between biotargets and networks, regulated by them. Synergistic effects can assist the reduction of the therapeutic dose and correspondingly reduce the side effects. Therefore multi-targeting represents a very prospective direction for the drug discovery, which can be used for the treatment of the complex and difficult for the treatment diseases, while the side effects of such therapies will be reduced in comparison to single-targeting drugs combinations. One example of such diseases are oncologic diseases without cures. Another example of such condition is aging. We are working on the universal methods and approaches for design of the small molecules, capable to regulate complex biological processes, such as aging and cancer, while at the same time such therapies will expose organism to minimum of the possible side effects.

Alexey Moskalev (Institute of Biology of Komi Science Center of Russian Academy of Sciences) presented "Geroprotectors study on Drosophila model". To date, more than 200 substances that prolong the life of model organisms have been reported in the literature (geroprotectors.org). Reducing the cost and improving the efficiency with which increasingly large amounts of data from model organisms can be applied to humans will be critical to progress in the development of human geroprotectors. For this purpose, we have to come to an agreement what should be considered applicable to human geroprotectors. Primary selection criteria for potential geroprotector:

1. Increased lifespan in models or human. The increase in lifespan is not always accompanied by positive changes in the quality of life, and additional criteria for geroprotectors is needed, and discussed below
2. Amelioration of human aging biomarkers (http://ageing-map.org)
3. Acceptable toxicity
4. Minimal side effects
5. Improving health-related quality of life
6. Secondary selection criteria for potential geroprotector:
7. Evolutionary conservatism of target or mechanism of action (agingchart.org)
8. Reproducibility of geroprotective effects on different model organisms
9. Simultaneous influence on several aging-associated causes of death in mammals
10. Increase of stress resistance

Vladimir Anisimov (N.N. Petrov Research Institute of Oncology) presented "Light desynchronosis, cancer and aging". Light-at-night has become an increasing and essential part of modern lifestyle and leads to a number of health problems, including excess of body mass index, cardiovascular diseases, diabetes and cancer. Exposure to constant illumination was followed by accelerate aging and tumorigenesis in female CBA, 129/Sv and transgenic HER-2/neu mice. Male and female rats were subdivided into 4 groups and kept at various light/dark regimens: standard 12:12 light/dark (LD); natural lighting of the North-West of Russia (NL); constant light (LL), and constant darkness (DD) since the age of 25 days until natural death. Exposure to NL and LL accelerated estrous function switch-off, induced metabolic syndrome and tumors, reduced life span rats as compared to the standard LD regimen. Melatonin given in nocturnal drinking water prevented adverse effect of LL and NL. The LL regimen accelerated colon carcinogenesis induced by 1,2-dimethylhydrazine (DMH) in rats whereas DD or the treatment with melatonin alleviated the effect of LL. The LL regimen accelerated whereas the DD regimen inhibits both mammary carcinogenesis induced by N-nitrosomethylurea in rats. Nocturnal drinking of melatonin increased the mean life span in female CBA, SHR, SAMP-1 and transgenic HER-2/neu mice. Melatonin inhibited spontaneous or chemically induced carcinogenesis in mammary gland, colon, uterine cervix and vagina, lung, skin and soft tissues. Gene expression profile study in the heart and brain of melatonin-treated CBA mice has shown that genes controlling the cell cycle, cell/organism defense, protein expression and transport are the primary effectors for melatonin. Melatonin has also increased the expression of mitochondrial genes, which correlate with its ability to inhibit free radical processes. Meta-analysis of clinical data has shown positive effect of melatonin in treatment of cancer patients. Thus, we believe that melatonin may be used for prevention of premature aging and cancer development.

Mikhail Shaposhnikov, **Alexey Moskalev** (Institute of Biology at Komi Science Center of Russian Academy of Sciences) and **Peter Fedichev** (Gero Ltd., Hong Kong) presented "Effect of Sun/klaroid gene deletion on lifespan, stress resistance, locomotor activity and fertility in Drosophila melanogaster". Accumulation of the inner nuclear envelope the Sun1 protein leads to severe tissue pathologies with decreased lifespan in mice with Hutchinson-Gilford progeria syndrome. Progeroid animals that are deficient for Sun1 show markedly reduced tissue pathologies and enhanced longevity. However, the role of SUN1 in normal aging is not clear. Here we studied the effect of Drosophila melanogaster klaroid/Sun gene deletion, on lifespan, stress resistance (to starvation, paraquat, hyperthermia, and ionizing radiation), age dynamics of locomotor activity and fecundity. It was found that hetero- and homozygous for the klaroid/Sun deletion Drosophila melanogaster males and females have increased median and maximum lifespan. It was noted that lifespan in flies homozygous for studied deletion was longer than in heterozygotes flies. The effect of the klaroid/Sun deletion on stress resistance depends on the genotype and the sex. In males, the klaroid/Sun deletion leads to an increase in locomotor activity, while in females there were no changes in locomotor activity. The increased female fecundity was detected in individuals with the mutation in the klaroid/Sun gene for both homo- and heterozygote. Thus, the increase in lifespan in

klaroid/Sun Drosophila melanogaster mutants is not accompanied by the negative effects on fecundity, stress resistance and locomotor activity.

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Ekaterina Proshkina with co-authors (Institute of Biology of Komi Science Center of Russian Academy of Sciences) presented "The influence of the activity of DNA damage recognition and repair genes on the lifespan of Drosophila melanogaster". DNA damage commonly occurs in the course of normal metabolic processes and accompanied aging. At the same time, a number of facts evidenced the relationship between DNA repair efficiency and longevity of organisms. In the present research authors focused on the determination of lifespan by activity of different DNA damage recognition and repair genes using the fruit fly D. melanogaster as a model object. In the most cases, mutations in genes, which encode proteins providing DNA damage recognition (ATM and ATR homologues), regulation of stress response (p53 and Gadd45), DNA excision repair (XPC, XPF, PCNA homologues), and double-strand break repair (BLM, Rad50, Rad54, XRCC3 homologues), sufficiently decreased D. melanogaster lifespan. Thus, dysfunction of DNA repair genes impairs organism vitality and reduces lifespan. An alternative approach is the screening for genes the overexpression of which increases the lifespan. Overactivation of DNA repair genes encoding enzymes that coordinate the recognition of DNA damage (HUS1, CHK2 homologues), base and nucleotide excision repair (AP-endonuclease-1, XPF and XPC homologues), double-strand break repair (BRCA2, XRCC3, KU80 and WRNexo homologues) led to both the positive and negative effects on D. melanogaster lifespan dependent on driver, stage of induction, gender and the role of a gene in the DNA repair process. Conditional ubiquitous and constitutive neuron-specific overexpression of investigated DNA repair genes negatively changed lifespan. Constitutive ubiquitous and conditional neuron-specific overexpression of genes involved in DNA damage recognition and repair mainly prolongs lifespan. Most beneficial effects were found out for homologous of genes HUS1, CHK2, XPC and XPF, that execute regulatory functions and provide the excision repair process. At the same time, negative effects of the stimulation of DNA repair genes can be associated with the absence of appropriate epigenetic regulation and the excessive energy expenditure.

Ekaterina Lashmanova and colleagues (Moscow Institute of Physics and Technology) presented "The effects of novel 2-selenohydantoin derivatives on lifespan and stress resistance of nematodes". Selenium is an essential element for human health. It plays an important role in thyroid hormone metabolism and immune system. It also possesses antitumor effects. Furthermore, selenium is present in the enzyme glutathione peroxidase, which detoxifies peroxides and hydroperoxides, and selenium availability regulates enzyme's activity. Recently, 12 novel 2-selenohydantoin derivatives were synthetized and their antioxidant activity was revealed using electrochemical methods (Ivanenkov et al., 2016). The goal of the present study was to investigate the effects of these compounds on lifespan and stress resistance of nematodes.

The experiments were performed using the wild type N2 Caenorhabditis elegans. Nematodes were cultured in liquid medium at 20°C in 96-well plates. Selenium-containing compounds were added in final concentrations 100, 10 and 1 μM on the first day of adulthood. Each experiment was performed five times. In addition, the effects of these compounds on the survival of nematodes under stress conditions was studied.

The addition of 2-selenohydantoin derivatives didn't significantly effect resistance of nematodes to oxidative stress (100 mM paraquat) and heat shock (33°C). Eleven 2-selenohydantoin derivatives out of twelfth did not have any significant effects on median and maximum lifespan of nematodes or effects were not stable. At the same time, one of the studied compounds in concentration 1 μM significantly increased the median lifespan of *C. elegans* by 11%. However, the effects of this compound in other concentrations were not detected.

These results indicate the prospects of search of geroprotectors among 2-selenohydantoin derivatives.

Ilya Solovev, **Eugenia Dobrovolskaya** with co-authors (Institute of Biology of Komi Science Center of Russian Academy of Sciences) presented "Effect of neuron-specific circadian clock gene overexpression on *Drosophila melanogaster* lifespan". Genes of circadian rhythms change their expression during aging of different organisms. We analyzed available transcriptomic data from different on-line bases and compared circadian genes' expression profile changes in animals (*Caenorhabditis elegans*, *Drosophila melanogaster*, *Mus musculus, Homo sapiens, Heterocephalus glaber, Strongylocentrotus purpuratus* and *Balaena mysticetus)* showing various aging rates. We investigated from the datasets that expression profiles of circadian genes in heads of old *Drosophila melanogaster* are almost identical with the profiles in young imagos after ingestion of prooxidant, with the exception of *tim* and *pp2A-B'* genes. In addition, such genes as *clk, per, cry, pdp1, vrille, cwo* decreased their expression levels in normally aging individuals, when *cyc, tim, bdbt, sgg, pdf* showed an increase. These findings have led us to an idea of normalizing expression profiles of circadian oscillator elements to compensate potential aging-associated changes during all lifespan. Primarily, we overexpressed *clk, per, cry, cyc* and *tim* using neuron-specific RU486-inducible system, this resulted in the increase of median life expectancy (10%) in *tim-* and *cry12*-overexpessing females. Median lifespan of female fruit flies overexpressing *per10* was 5.4% longer than in control group. Noteworthy, overexpression of *clk* shortened (−10%) only female's lifespan. 4% augmentation of median life expectancy was observed for males overexpressing *per24* and *cyc*.

Eugenia Dobrovolskaya, Ilya Solovev with co-authors (Institute of Biology of Komi Science Center of Russian Academy of Sciences) presented "Effects of caloric restriction on lifespan of *Drosophila melanogaster* individuals with tissue-specific overexpression of circadian clock genes". The aging process is associated with changes in the expression level of various genes. Genes forming a system of "biological clock" of the body are not an exception, it evidenced by the worsening with age in physiological rhythms and aperiodizm of sleep and wakefulness cycles in old individuals. The molecular clock found in each cell of the peripheral tissues of multicellular organisms. A main environmental factor connected to the rhythms of biological processes is light, with daily and annual variations in the light intensity are associated with such phenomena as sleep, physical activity, rest, growth, reproduction, sexual behavior, moult and migration. Most human genes of circadian rhythms are evolutionarily conserved and have orthologs in the fruit fly *Drosophila melanogaster*. It was found that adults of *D. melanogaster* show the decrease in gene expression of photosensitive protein Cryptochrome with age, while its overexpression in old flies slows down the rate of aging. On the other hand, fruit flies with mutations in the genes of circadian rhythms are characterized by a reduced life span. The purpose of this study was to investigate wheather caloric restriction affected the life span of Drosophila melanogaster with overexpressed circadian rhythms' genes (Period, Timeless, Clock, Cycle, Cryptochrome). We chose UAS / GAL4 system to ensure

conditioned (mifepristone-inducible) gene overexpression in flies' muscules, fat body and gut. Drosophila lines were placed on standard media with different caloric values and life span had been being observed once a day. The results of this study demonstrate the relationship of circadian rhythms' gene regulation mechanisms and caloric restriction response pathways.

Darya Peregudova with co-authors (Institute of Biology of Komi Science Center of Russian Academy of Sciences) presented "Chemical (formaldehyde, toluene, tcdd) and physical (ionizing radiation) factors influence on the physiological and genetic *Drosophila melanogaster* characteristics". The changes of living organisms' physiological characteristics caused by various stressors are based on the cellular and molecular alterations. The reason for changes in the gene expression may be caused by the direct gene damage due to exposure, or activation of different mechanisms of an organism's biological structures damage recognition and stress response promotion. The actuality of the formaldehyde, toluene, TCDD and irradiation low doses effects studying is their widespread occurrence and negative impact on living organisms.

The aim of this work was to study changes in expression of stress response genes (Hsp70, Mus209 (PCNA), Mus210 (XPC), Rrp1, Brca2, spn-B, Ku80, PARP-1, Gadd45, Wrinkled / Hid, Sod1, Sod2, Catalase, MST-1, Cyp4e2), immune response genes (Drosomycin, Defensin, Metchnikowin) and genes associated with aging (dSir2, FOXO, JNK), caused by the exposure to low doses of dioxin (0.822 and 1.644 μmol/L), toluene (50 and 100 μmol /L), formaldehyde (7%, 14%), and irradiation (20 and 40 cGy), and to study the attendant changes in physiological characteristics (life span, locomotor activity, fertility) in Drosophila melanogaster male and female (*Canton-S* wild type strain). As a result of this work, it was showed that the above-mentioned impacts cause a significant increase in median life span of Drosophila melanogaster wild type strain *Canton-S* individuals (by 2-4%), there were no changes in female fertility, the locomotor activity in males was significantly increased. It is also have been shown that the biggest part of the studied genes increases its expression after exposure to low doses of formaldehyde, toluene, dioxin and irradiation.

Nadezhda Zemskaya (Institute of Biology of Komi Science Center of Russian Academy of Sciences) with co-authors presented "The relationship of lifespan and stress resistance of different *Drosophila* species". The relationship of stress resistance and longevity was described based on the results of experiments with various lines of certain biological species. As a rule, long-lived lines are more resistant to various kinds of stress, and short lived mutants of various model organisms are hypersensitive to adverse environmental factors. Similar links can be determined by comparing different species with each other. However, this is a lack of most current research in this area, that comparisons are made between evolutionarily far-spaced species (rodents, bats, man, whales), and many identified patterns associated with aging may actually be only distantly related to the problem.

The aim of this work was to study the differences in stress resistance of several species of the *Drosophila*genus, which are significantly different in lifespans. We investigated 12 *Drosophila* species (*D. ananassae, D. austrosaltans, D. biarmipes, D. erecta, D. kikkawai, D. melanogaster, D. pseudoobscura, D. saltans, D. simulans, D. virilis, D. willistoni, D. yakuba*) provided by Dr. V. Gladyshev (Harvard Medical School, USA), and estimated their lifespan as well as resistance to oxidative stress (20 mM paraquat), hyperthermia (35°C) and starvation. Correlation analysis of stress resistance and longevity data was performed. Studied *Drosophila* species demonstrated different reaction to stressors. The extremely long lifespan and enhanced resistance to all investigated stressors was found for *D. virilis*. Additionally, relatively high survival was shown for *D. melanogaster* under oxidative stress, for *D. kikkawai* and *D. pseudoobscura* under hyperthermia, for *D. biarmipes* in the starvation condition. Obtained data revealed relationship between maximum lifespan and stress-resistance of *Drosophila* species.

Evgeny Rogaev (Vavilov Institute of General Genetics RAS) "Aging, Genomics, Alzheimer' Disease".

Sergey Kozin (Engelhardt Institute of Molecular Biology, Russian Academy of Sciences) presented "Aged isoform of β-amyloid as biomarker and drug target of Alzheimer's disease". Alzheimer's disease (AD) is closely associated with ageing. In view of the amyloid hypothesis, the key molecular event of AD is a structural transition of β-amyloid (Aβ) from the physiologically normal monomer state to soluble neurotoxic oligomers accumulating in the form of insoluble extracellular aggregates (amyloid plaques) in brain tissues. Zinc ions as well as 'aged' Aβ species present in the plaques are known to play a crucial role in triggering pathological conversion of endogenous Aβ. Isomerization of Asp7 is the most abundant age-related spontaneous non-enzymatic modification of Aβ. Our in silico, in vitro and in vivo studies have shown that Aβ species with isomerized Asp7 (isoAsp7-Aβ) significantly differ in their properties from healthy (non-modified) Aβ molecules. We have found that isoAsp7-Aβ might constitute a nucleation seed and initiate formation of the neurotoxic zinc-dependent Aβ oligomers, thus inducing development of cerebral amyloidosis and other pathological processes characteristic of AD. Moreover, the role of the Aβ metal-binding domain (the N-terminal region 1-16) as the minimal necessary and sufficient pathogenic unit of isoAsp7-Aβ has been strongly suggested. These findings allow to link the emergence of isoAsp7-Aβ due to Aβ ageing with the onset of age-related pathology, and to use isoAsp7-Aβ species as potential biomarkers and drug targets of early diagnosis and therapy of AD.

Anatoliy Yashin (Duke University) presented "Genetics of Alzheimer's Disease: Insights for Studying Connection among Health, Aging, and Longevity". A number of independent genome-wide association studies (GWAS) of Alzheimer's disease (AD) detected highly significant associations of genetic variants from APOE and TOMM40 genes with this disorder. Epidemiologic studies detected connections of AD with other diseases such as cancer, Parkinson disease, type II diabetes, CVD, and others. A number of studies link AD with presence of viral and bacterial infections (e.g., herpes simplex type 1 virus). Other studies find association of AD with processes developing in aging brain. The existence of such connections indicates that GWAS of AD may also detect genetic variants associated with other diseases and help investigate common genetic mechanisms that link AD and related pathologies. This may contribute to better understanding of the origin of AD and improve efficiency of corresponding preventive and treatment strategies. We performed GWAS of Alzheimer's disease (AD) using LOADFS data available from dbGaP. The analyses showed strong (genome-wide significant) genetic signals for SNPs from several genes on chromosome 19. These include CTB-129P6.4, CTB-129P6.7, PVRL2, TOMM40, APOE, APOC1 and BCAM. Associations of SNPs from HLA-DQB2, LINCO1006, DKFZp779M0652, RNASE11, RP11-14J7.6, MIR7154 were close to genome-wide significance. These results are obtained in joint and separate analyses of male and female data. SNPs detected in these analyses were also found in studies of human longevity (e.g., rs2075650). This SNP is downstream gene variant of the PVRL2 characterized as "poliovirus receptor-related 2 (herpes virus entry mediator B)". This SNP is also an intron variant of TOMM40 gene. We reviewed evidence from other studies of AD and its connection with other health disorders and compared them with our findings. The results of these analyses indicate that development of AD involves several genetic pathways that have connection to development of other chronic pathologies.

Rosie Freer (Cambridge University) presented "A protein homeostasis signature in healthy brains recapitulates tissue vulnerability to Alzheimer's disease". In Alzheimer's disease, the aggregation of amyloid-beta and tau in plaques and tangles spreads progressively across brain tissues following a characteristic pattern. Over two decades after the characterization of the progressive development of this disease, the mechanisms that govern the selective vulnerability of these tissues remain under debate. Using transcriptional analysis of healthy brains, we identify an expression signature that predicts – well before the onset – the tissue-specific vulnerability to disease. We obtain

this result by finding a quantitative correlation between the histopathological staging of the disease and the specific expression patterns of the proteins that co-aggregate in plaques and tangles, together with those of the protein homeostasis components that regulate amyloid-beta and tau. Since this expression signature is evident in healthy brains, our analysis provides an explanatory link between a tissue-specific environmental risk of protein aggregation and a corresponding vulnerability to Alzheimer's disease.

Natalia Stefanova (Institute of Cytology and Genetics of Siberian Branch of Russian Academy of Sciences) "Prefrontal cortex transcriptomic indices of sporadic Alzheimer's disease in human and in a rat model". Alzheimer's disease (AD) is the most prevalent neurodegenerative disease. We showed that senescence-accelerated OXYS rats represent a promising model of sporadic form of AD with the typical signs of disease: degenerative alterations and death of neurons, synaptic and mitochondrial dysfunction, hyperphosphorylation of the tau protein, accumulation of amyloid β, and the formation of amyloid plaques. Here, we aimed to compare the gene expression profiles of the prefrontal cortex from OXYS rats and Wistar rats as controls to identify the molecular mechanisms and the factors underlying disease progression. The transcriptome analysis was conducted at three stages of the disease (pre-symptomatic, symptomatic and progressive stage) in OXYS rats, using RNA-Seq technique. We identified marked differences in the prefrontal cortex transcriptome between the two rat strains already at the pre-symptomatic disease stage (> 600 genes), with an increasing of gene expression in the symptomatic stage (> 900 genes) and at the progressive stage (> 2 000 genes) in OXYS rats compared with age-matched Wistar rats. Gene ontology analysis of the transcriptional profile from OXYS rats showed marked changes of specific pathways involved in AD molecular pathway, as well as in mitochondrial and synaptic functions, protein phosphorylation, Ca2+ homeostasis, hypoxia, immune processes, and apoptosis. Then, we compared the gene expression profiles of the prefrontal cortex from human AD and OXYS rats. We demonstrated that transcriptional profile changes in the cortex as in human AD as well in OXYS rats, primarily due to mitochondrial dysfunction, synaptic plasticity and Ca2-signaling pathway. This study highlights a set of key genes and molecular pathway indices of disease which may prove useful in identifying potential disease modifiers responsible for the heterogeneity of human sporadic form of AD and which may represent valid therapeutic targets for ameliorating the disease course in humans.

Olga Kovalchuk (University of Lethbridge) presented "Chemo brain and aging – is there a link?". It is projected that by 2030 newly diagnosed cancer cases will reach 21.7 million worldwide. The development of new chemotherapeutic agents and regimens for cancer therapy has led to increasing rates of survival in cancer patients and, therefore, it is important to ensure that cancer survivors suffer minimal side effects and have good life quality. Despite of undisputed benefits, chemotherapy causes a wide array of side effects, including central nervous system (CNS) toxicity. Chemotherapy-induced CNS side effects impact the cognitive domains of attention, memory, processing speed, and executive function, causing a condition that has been termed chemo brain. While the molecular and cellular mechanisms of chemo brain are not well investigated, the frequency and timing of its occurrence and their persistence suggest that chemo brain may be epigenetic in nature. We analyzed the effects of two commonly used cytotoxic chemotherapy drugs—cyclophosphamide (CPP) and mitomycin C (MMC) - on transcriptomic and epigenetic changes in the murine prefrontal cortex (PFC) and hippocampal regions. The key findings of our study are: (i) chemotherapy altered the gene expression profiles in the brain; (ii) MMC treatment resulted in accumulation of 8-oxodG, decreased global DNA methylation, and increased DNA hydroxymethylation in the PFC tissues of female animals; and (iii) the majority of the changes induced by MMC in the brain tissues resembled those that occur during the aging processes. This is the first study that suggests a link between chemotherapy-induced chemo brain and brain aging, and provides an important roadmap for future analysis.

Vasily Popov (Voronezh State University) presented "Methylene blue rejuvenates behavior and induces brain mitochondria biogenesis in aging mice". Age-related brain dysfunctions are believed to be associated with deregulation of mitochondria functions increasing risks to develop neurodegenerative diseases (ND). Recently, mitochondria – targeting drug methylene blue has been drawing considerable interest as a potential treatment for ND. Despite well studied effects of MB at the level of isolated mitochondria and cells in several ND models, its effects on the functioning of non-diseased brain remains unexplored. We have compared the effect of per oral MB treatment on the behavior, mitochondria reactive oxygen species generation, and gene expression in adult and aged mice. We found that 15 month old mice manifested a decrease in physical endurance, spontaneous locomotor activity, and exploration concomitant with an increase in anxiety-related behavior, as compared to 7 month old mice. A 60 day MB treatment slow down these changes in 15 month old mice. There was no significant body weight change, oxygen consumption rate and RQ index in either adult or aged MB-treated mice. MB significantly increased the rate of ROS production in isolated brain mitochondria. The expression of several genes relevant to mitochondria biogenesis, bioenergetics, and antioxidant defense (NRF1, MTCOX1, TFAM, SOD2) was greatly suppressed in aged mice; it was restored by MB treatment. We hypothesize that the effects of MB may be mediated by its ability to increase H2O2 production in brain mitochondria, which in turn activates Nrf2/ARE signaling pathway and mitochondria biogenesis.

Khusru Asadullah (Editor in Chief of Advances in Precision Medicine) presented "Trends in translation medicine: the value of external innovation". Collaborations between academic institutions and the diagnostics/pharmaceutical industry are increasingly being initiated and executed. It's assumed that these relationships could help to improve research and development productivity in industry, as well as enable academic institutions to better exploit the translational potential of their research. Identification and validation of targets and biomarkers, key elements of successful drug discovery, are challenging. Unfortunately, according published data are frequently irreproducible. Thus, we must not rely on published data only. Extensive joined efforts of multiple partners seem crucial to foster progress. Different models are used and required for different stages of the drug discovery and development process as well as for different kinds of targets and biomarkers.

ACKNOWLEDGMENTS

The authors, organizers and participatnts would like to thank the Fomenko Family including Andrei Fomenko, Lada Fomenko and Isabel Fomenko, iVAO corporation and Bioprocess Capital Partners for their support of the conference.

ANNEXE 2. ARTICLE: AGED MICE REPEATEDLY INJECTED WITH PLASMA FROM YOUNG MICE: A SURVIVAL STUDY

Dmytro Shytikov,[1] Olexiy Balva,[1] Edouard Debonneuil,[2] Pavel Glukhovskiy,[3] and Iryna Pishel[corresponding author 1]

1. D.F. Chebotarev State Institute of Gerontology NAMS, Lab Pathophysiology and Immunology, Kyiv, Ukraine.

2. Heales (Healthy Life Extension Society), Paris, France.

3. National University, Department of Mathematics and Natural Sciences, Los Angeles, California.

corresponding authorCorresponding author.

Address correspondence to : Iryna Pishel, PhD, D.F. Chebotarev State Institute of Gerontology NAMS, Lab Pathophysiology and Immunology, 67 Vyshgorodska Street, 04114 Kyiv, Ukraine,

E-mail:iryna.pishel@gmail.com, ira_pishel@geront.kiev.ua

ABSTRACT

It was reported using various biological models that the administration of blood factors from young animals to old animals could rejuvenate certain functions. To assess the anti-aging effect of young blood we tested the influence of repeated injections of plasma from young mice on the lifespan of aged mice. One group of 36 CBA/Ca female mice aged 10–12 months was treated by repeated injections of plasma from 2- to 4-month-old females (averaging 75–150 µL per injection, once intravenously and once intraperitoneally per week for 16 months). Their lifespan was compared to a control group that received saline injections. The median lifespan of mice from the control group was 27 months versus 26.4 months in plasma-treated group; the repeated injections of young plasma did not significantly impact either median or maximal lifespan.

Key words: aging, immunology

INTRODUCTION

The deterioration of various organs and system functions with age is well documented. Numerous dysfunctions in metabolism, the cardiovascular system, and the immune system lead to the development of specific diseases associated with aging that are the main cause of death in older age groups.

Various studies have reported health improvements in old mice that were treated with blood factors from young mice, either through heterochronic parabiosis, plasma, or mesenchymal stem cell engraftment (see Conboy *et al.* (2005) and Shen *et al.* (2011)). This potentially life-extending therapy could occur in humans with blood transfusions, so gathering statistics in humans and identifying the "good" factors in plasma could be key for improving health in an aging population. Positive effects may be seen during injections of plasma from young donors to old recipients. In particular, injections of the platelet-rich plasma (including autologous injections) seemed to have positive effects in

countering cell senescence, promoting skin rejuvenation, and improving several pathologic conditions (see Cheng *et al.* (2012), Kim *et al.* (2011), Shin *et al.* (2012) and Chen *et al.* (2013)).

However, opposing data have also been reported. In a classical work by Carrel and Ebeling (1921), serum from old animals was found to inhibit the growth of cell cultures. More recently, Villeda *et al.* (2011) showed that injection of plasma from older animals to young animals can cause age-related changes in the nervous system of the young recipients. Effects of contact with systemic environments between young and old animals have also been studied (see Villeda *et al.* (2011)). This and other works suggest that transferring of plasma from old animals can induce age-related changes in different organs in young animals.

Such reports suggest that the old animals contain factors that control the rate of aging, and that transferring plasma from young animals can be beneficial for aging mice and induce some type of rejuvenation.

Here, aged mice were repeatedly injected with plasma from young mice, and we observed the effects on lifespan and on markers of aging (CD4/8 ratio in peripheral blood and plasma thyroxine level).

MATERIALS AND METHODS

Two groups of aged mice followed for survival

Long-lived CBA/Ca mice were selected for the experiment to eliminate the effect of young plasma injections on the development of certain types of age-related pathologies and to assess the impact on the species life span of mice generally.

Seventy-two CBA/Ca female mice aged 10 months (n=7), 11 months (n=34), and 12 months (n=31) were randomly divided into two groups of equal age distribution and size (n=36). The treatment group was repeatedly injected with young heparinized plasma, and the control group was repeatedly injected with saline with the same heparin concentration. All manipulations were carried out in accordance with the guidelines established by the D. F. Chebotaryov State Institute of Gerontology Administrative Panel for Lab Animal Care. The mice were housed in nine cages, with each cage containing approximately the same number of treated and control mice, for better comparability. Mice received food and water *ad libitum*. Temperature was 21±1°C.

Deaths were checked every 1–3 days. Necropsies of dead animals were made to assess the presence of visible pathologies, with a particular focus on the following internal organs: lungs, liver, kidneys, thymus, spleen, and intestine. Any deviation from the norm was recorded, such as the expansion of tissue, tumors, cysts, tissue atrophy, and hemorrhage. Posthumous investigations were not done in cases of great body damage or prolonged time at room temperature.

Injections of young plasma or saline

Design. The two groups were treated by injections on the same days, with the same method of administration (intravenous or intraperitoneal); the two methods were used to minimize injury to veins and to maximize the chance of delivering possible "youth factors." On average, there was one intravenous (75 µL) and one intraperitoneal (150 µL) injection per mouse per week for 16 consecutive months. For each injection of plasma in the treatment group, the control group was injected with an equal volume of heparinized saline. The injection volume was 225 µL of plasma per mouse per week, or 900 µL per

mouse per month in total. According to generally accepted estimates, 80%–100% of the blood plasma volume of the whole organism was injected monthly.

Plasma. Blood plasma is composed of a complex mixture of transport proteins, growth factors, and small molecule compounds as well as the transport vesicles, which have a wide range in terms of their biological effects and half-lives. This makes the search for rejuvenation factors extremely difficult and requires a careful approach to selecting the method of blood sample isolation. For this purpose, we used blood plasma for injection since the process of blood coagulation leads to a sharp increase in the amount of transport vesicles with blood coagulation factors in the serum, changes the levels of some amino acids and proteins, and lowers blood serum composition stability (see Yu *et al.* (2011)). To obtain plasma, we used the heparin, which is suitable for use *in vivo*, in contrast to anticoagulant citrate dextrose and EDTA. Heparin has several side effects during chronic use, but in this experiment, we used concentrations that were 1/10 of the therapeutic dose. This approach was expected to negate the occurrence of side effects and to minimize binding with blood proteins in the mice of control group. We injected freshly isolated blood to minimize the loss of short-lived blood factors that are destroyed during dialysis and long-term storage.

Plasma was aseptically prepared on the day of injection. Blood from 2- to 4-month-old CBA/Ca female mice was collected retro-orbitally and pooled in one standard heparinized BD Vacutainer® (90 USP units/7 mL of blood; the final concentration of sodium heparin was 12.9 USP units/mL). Plasma was obtained via centrifugation (1500 g for 15 minutes). The control group was injected with saline (NaCl, 9 g/L) with the same concentration of heparin as in the plasma-treated group.

Injections. This experiment involved a chronic course of injections, which can be a traumatic procedure. To minimize the traumatic effect and stabilize the route of administration in case of venous thrombosis, we used a combined approach for injecting plasma: one injection intravenously and one injection intraperitoneally weekly. Intravenous and intraperitoneal injections are the two most widely used administration routes. Intraperitoneal injection has several disadvantages, including a lower rate of absorption compared with the intravenous injection. On the other hand, the intraperitoneal route is often considered to be effective for tumor therapy (see Wong *et al.* (2011) and Dou *et al.* (2013)). Some studies even concluded that this route was slightly preferable to others (see Miyagi *et al.* (2005) and Buijs *et al.* (1998)).

Prior to injection, the tail was warmed, and tail vein injections were performed with 30-gauge needles. To minimize potential bias of injury, subsequent injections were made to the alternate tail vein, and starting from the 13th month of the experiment, the mice received only intraperitoneal injections, twice a week. After the 16th month of the experiment, no further injections were given. Injections were done in parallel for control and experimental animals by a single operator at the same time of the day.

Throughout the experiment, investigators carrying out procedures and making observations were blinded with regard to whether animals belonged to the treatment or control group.

CD4/CD8 measures by flow cytometry To assess changes in peripheral T-cell composition, the $CD4^+/CD8^+$ ratio was measured with flow cytometry. For this study we used eight animals from each group at each time point. For the first two time points, the same animals were used. However, after some animals died, we used additional animals for studies of this parameter.

Peripheral blood for analysis was taken five times during the experiment, at 3.2, 5.9, 7.7, 8.9, and 13.5 months. Twenty-five microliters of blood were taken from eight mice of

each experimental group from the tail vein and placed in phosphate-buffered saline (PBS) with 1% fetal calf serum and 1.9 mM EDTA. Blood samples with EDTA were kept cold until staining with antibodies: anti-CD8α/Lyt-2 (Texas Red conjugate, clone 53-6.7) and anti-CD4/L3T4 (PE-Cy7, GK1.5) (PickCell Laboratories). Briefly, single-cell suspensions were resuspended in PBS with 2% fetal bovine serum (Sangva) at 2×10^7 cells/mL. Cells were incubated with antibodies for 30 min on ice in the dark. After incubation red blood cells were lysed with RBC Lysing Solutions. After lysis, cells were washed with PBS and fixed with 1% paraformaldehyde in PBS (pH 7.0). Events were analyzed using a BD FACSAria™ (BD Biosciences). Dead cells were excluded based on forward and side light scattering.

Thyroxine measures by enzyme-linked immunosorbent assay

Twenty-five microliters of blood were taken from the tail vein of eight mice from each experimental group in heparinized capillaries four times during the whole experiment, at 5.9, 7.7, 8.9, and 13.5 months. After centrifugation, 10 µL of plasma was frozen at −20°C until analyses. Total thyroxine (T_4) level in the plasma of experimental animals was measured by enzyme-linked immunosorbent assay (ELISA; Thyroxine ELISA kit, Diagnostic Systems) according to the manufacturer's instructions.

Statistical analysis

Comparison of changes in $CD4^+/CD8^+$ ratio and T_4 level between saline- or plasma-treated groups were done by Mann–Whitney *U*-test (U). Analysis of animals' survival was done by Kaplan–Meier estimates and the logrank statistic. Analysis of pathology frequencies was done by Fisher exact test. All operations were done with the help of STATISTICA 7 software (StatSoft Inc.).

RESULTS

Control group survival

The median lifespan of the control group was 27 months. This is in line with a reported median lifespan of 27.5 months for CBA/Ca females (Harlan Laboratories) and suggests that the multiple injections with heparinized saline did not affect lifespan.

Treatment does not impact lifespan

The lifespans of the two experimental groups were very similar (Fig. 1), including median and maximal lifespan ($p>0.05$). We had hoped to observe a lifespan increase because available scientific evidence suggests that the treatment with some factors from young systemic environments may improve stem cell functioning in old animals and should have some beneficial effect in them. Therefore, we wondered if frequent injections of plasma from young animals would provide some "youth factors" that would increase the lifespan of aged animals. However, we did not observe such an effect.

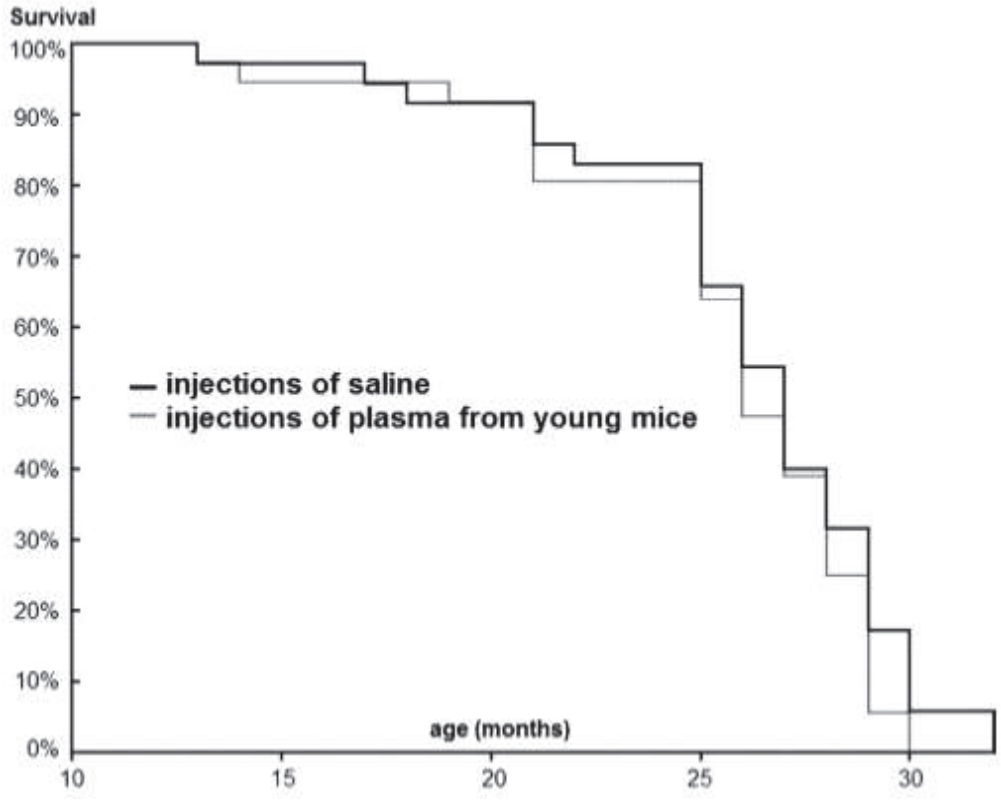

FIG. 1. Survival rate of CBA/Ca female mice treated either heparinized plasma from young animals or heparinized saline. Injections were started while mice were 12.6±0.7 months old and lasted for 16 months of the experiment. After 16 months, injections were stopped as we considered harm from the injection itself. Survival in both control and experimental groups was assessed during the whole experiment.

The CD4+/CD8+ ratio is decreased in plasma-treated group

According to existing evidence (see Discussion), a positive effect of young plasma injections could be expected for some immune parameters in plasma-treated mice; in particular, the CD4+/CD8+ ratio in the blood. It is known that T-cell immunity is subject to significant changes during aging, and the CD4+/CD8+blood ratio is one of the key markers of immune status assessment (see Larbi *et al.* (2008)). This parameter is routinely used by different laboratories and is easily reproducible. Therefore, the aim of this study was to evaluate the change in the ratio relative to a control group of animals of the same age. Data are reported as percent change versus the control group. In young animals, the typical CD4+/CD8+ ratio usually exceeds 2 and is sharply reduced with age (Fig. 2B). We assessed this ratio at 3.2, 5.9, 7.7, 8.9, and 13.5 months of treatment (Fig. 2A) and did not find any significant differences in the first two measures. Conversely, we observed a decrease in the blood CD4+/CD8+ ratio in the plasma-treated mice compared with the saline-treated group at 7.7 and 8.9 months. These changes were statistically significant only at 7.7 months ($p(U)<0.001$ and $p(U)=0.1$, respectively). The late gradual restoration of the CD4+/CD8+ ratio to the level of the control group appeared in peripheral blood at 8.9 and 13.5 months (Fig. 2A).

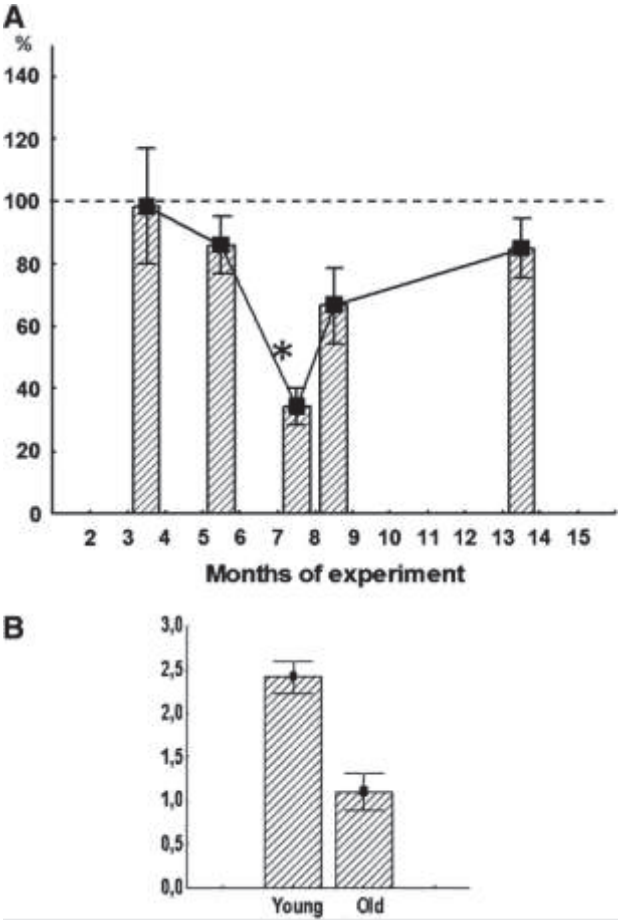

*FIG. 2. Changes in the CD4+/CD8+ ratio in peripheral blood of CBA/Ca female mice treated either with heparinized plasma from young animals or heparinized saline. Measurements were performed five times during the experiment. Dashed line: the CD4+/CD8+ ratio of control animals taken as 100%. Data are reported as percent change versus the control group. Each group had eight animals. (A) Typical ratio of CD4+/CD8+ in young (2–3 months) and aged (22–24 months) females mice CBA/Ca strain. (B) Central marker is the mean value and whiskers are the standard error from the mean value. *p(U)<0.001 comparing to saline-treated group.*

Changes in the T4 level

We wondered if the transfer of hormones or other young blood-borne factors could have explained the lower CD4+/CD8+ ratio. T4 is one of the factors that are the most impacted by aging. It is well documented that its concentration becomes lower with age (see Brown-Borg (2007)). Clinical consequences are generally controversial. It is thought that a low T4 level is connected to multiple age-related metabolic and immune system disorders (see Yeap (2013) and Sarati *et al.* (2012)). Further, considerable evidence suggests a beneficial effect of additional thyroid hormones to the health of elderly individuals (see Mooradian (2011)).

We measured the total T4 level by ELISA at 5.9, 7.7, 8.9, and 13.5 months (Fig. 3). As expected the T4level was first stable and then gradually decreased with age in the control group (the time point at 8.9 months was not significant). The plasma group appeared to have a different trajectory, despite the low statistical significance. At 5.9 months the plasma-treated group had a slightly lower total T4 level compared to the saline-treated groups (p(U)=0.52). At 7.7 and 8.9 months the T4 level was higher but did not reach statistical significance compared to the control group (p(U)=0.23 and p(U)=0.14, respectively).

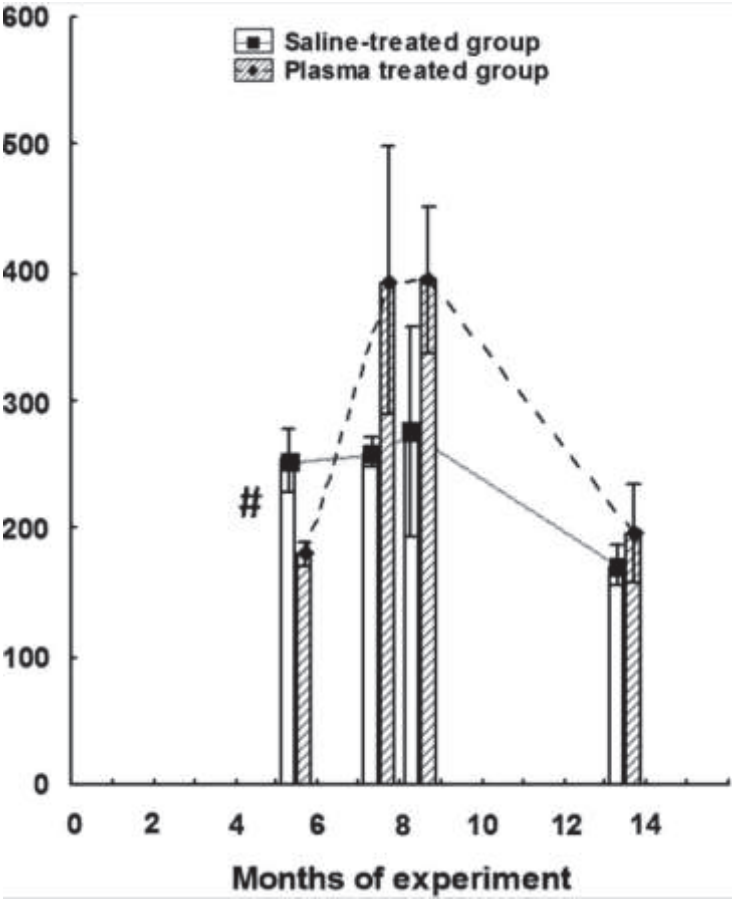

FIG. 3. Changes in the total thyroxine level (nmol/L) in peripheral blood of CBA/Ca female mice treated either with heparinized plasma from young animals or with heparinized saline. Measurements were performed four time during the experiment. Each group had eight animals. Central marker is the mean value and whiskers are the standard error from the mean value. #p(U)<0.1 comparing to the saline-treated group.

Necropsies

The CBA/Ca strain is well known for its longevity, which is due to a low tumor frequency in females.

We performed necropsies on undamaged mice no more than 24 h after death, which accounted for half of the animals in each group (n=16). We limited our analysis to visible organ pathologies in the peritoneum and the thoracic chest. Each necropsy was analyzed with an anatomo-pathologist to ensure correct conclusions.

Results of necropsies are shown in Figure 4. Given the relatively small number of necropsies, statistical significance was difficult to reach. We observed a tendency for a slightly higher frequency of oncologic pathologies (total number of visible tumors in organs; Fisher exact test, p=0.067) in the plasma-treated group; differences between both groups were in the 90% confidence interval (90% CI), 0.036–0.932. There was a tendency for a slightly lower frequency of ovarian cyst (Fisher exact test, p=0.144, differences between both groups were in 90% CI 0.54–0.041) in the plasma-treated group.

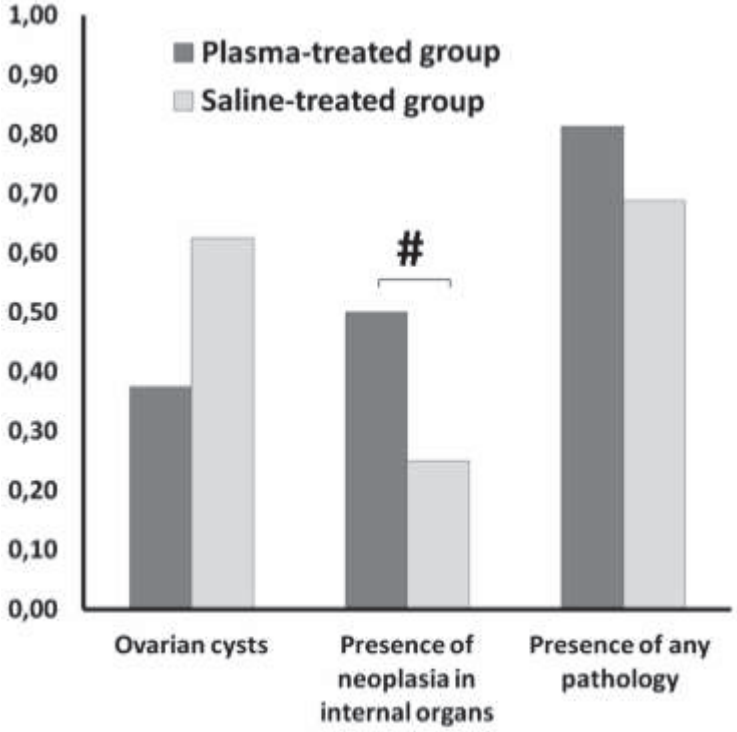

FIG. 4. Frequency of different pathologies in CBA/Ca female mice treated either heparinized plasma from young animals or heparinized saline. Dead animals were investigated only if their bodies were undamaged and they had not been dead for more than 24 h. During necropsy, visual investigations for presence of any type of pathology were made. Each group had 16 animals. #p=0.067 (Fisher's exact test)

DISCUSSION

Aging is for now an irreversible process that affects multiple organs and is the leading cause of age-associated mortality and morbidity. The search for an efficient way to counter age-related changes in an organism is a task of high importance.

Recently, scientific evidence of a rejuvenating effect of young blood on different tissue and organ functions was published. Among these studies, heterochronic parabiosis was particularly interesting: the model demonstrates the possibility of constant exchanges of cellular and humoral factors through the blood between animals of different ages (see Conboy (2013) and Gibney *et al.* (2012)).

The coexistence of animals for 5 weeks in parabiosis was shown to lead to improved cognitive function in old heterochronic partners and positive effects on regeneration in the brain (see Villeda *et al.* (2014)). Reverses in age-related cardiac hypertrophy were reported by Loffredo *et al.* (2013), Ruckh *et al.* (2012) as well as Villeda *et al.* (2011 and 2014). Irina Conboy's laboratory found some evidence of possible positive effects on aged cells in vitro and on several organism's systems, including muscle and liver regeneration (see Conboy *et al.* (2005)). Mesenchymal stem cell transplantation was reported to have rejuvenating effects on aged hosts, but the results of such studies of stem cell transplantation in aging are quite contradictory (see Shen *et al.* (2011)). Furthermore, a number of clinical studies on autologous platelet-rich plasma injection to correct some health conditions can fall in the category of introducing young factors (see Davis *et al.* (2012)).

Still, after such mostly positive reports, the question of the overall beneficial effect becomes extremely intriguing: Instead of looking at a specific parameter or a short period of time, is maintaining a young milieu globally beneficial over time? This can be asked through a simple measure: Does it increase lifespan? In previous experiments, we looked at the survival of mice following temporary isochronic and heterochronic parabiosis (unpublished data). It was found that aged mice tended to live longer after a period of heterochronic parabiosis than isochronic parabiosis, suggesting a globally beneficial effect of the young milieu. However, the difference was not statistically significant, and lifespans were not in the range of those of untreated animals, possibly due to the traumatic condition of parabiosis. Therefore, general conclusions were very uncertain regarding "anti-aging" effects, and another model for long-term effects was sought, namely, plasma injections.

Injection of plasma from one animal to another animal of a different age is a particularly interesting model. Unlike heterochronic parabiosis, it is unidirectional, and it avoids the risk that arise from bidirectional partners. It is less traumatic. Further, it is realistically applicable to humans—it is happening every day with blood transfusions, making its study potentially particularly meaningful for current patients.

Continuous perfusions—modeled by parabiosis—could have much stronger effects than occasional injections—modeled by plasma injections. However, Wyss-Coray's laboratory reported that in addition to neurological findings from heterochronic parabiosis, negative results were obtained by injecting plasma from old animals to young ones. Positive results were obtained by injecting plasma from young animals to old ones, and injecting, GDF11, a specific protein present in high concentration in young plasma, also yielded positive results (see Villeda *et al.* (2011 and 2014)).

In our study, we used a similar scheme and dosage for young plasma injection, but with some differences. To maximize preservation of the young blood composition, we used freshly isolated heparinized plasma and, accordingly, heparinized saline in the control. The control group that received saline injections had a very normal lifespan curve. Certainly, heparin has a number of side effects during chronic use. However, we used a low concentration of the drug, and this approach should negate the occurrence of side effects. It is disappointing that administration of young plasma to middle-aged female mice did not affect their lifespan in comparison with the control group.

While young blood may not extend lifespan, the lack of life extension in our study could be specific to factors within it. We do not suggest it could be a (non-detected) disease, as both groups (saline and plasma) were represented in every cage. We wondered if the difference in plasma collection could explain the positive short-term findings from Wyss-Coray's laboratory, while we did not find positive long-term results. Contrary to them, we collected the plasma on heparin and not on EDTA, and we injected plasma on the same day rather than after freezing it (see Villeda *et al.* (2011)). The reason for using heparin is simply that, in contrast to EDTA, it is suitable for use in vivo. We also injected freshly isolated blood to minimize the loss of short-lived blood factors that are destroyed during dialysis and long-term storage. Of course, differences in strain, sex, and exact ages could be such that some beneficial effects are not observed. Short-term beneficial effects were reported by various teams with various models, so we would be surprised if these differences had an effect; here again, testing a short-term effect on our commonly used model of mice would be reassuring.

Given current results, our best hypothesis is that administering young plasma simply does extend lifespan in the proposed design of the experiment. It is possible that the reported short-term beneficial effects may well happen but are insufficient to affect the lifespan. It is also possible that the administration of heparinized young plasma introduces some disequilibrium as well.

To analyze the possible changes that occur in an old organism receiving young plasma, we tested some blood parameters. One was the CD4+/CD8+ ratio in the peripheral blood. Indeed, age-related changes in the immune system play important roles in pathogenesis of many disorders associated with age (see Loffredo *et al.* (2013)). It is well known that T cells are one of the most affected units during aging, and age-related changes in T cells have been amply documented, with an increase in the number of CD8+ cells and a decrease in number of CD4+, causing the CD4+/CD8+ ratio to shift with age. Further, there is a decrease in the proliferative capacity of T cells from aged persons as well as an increase in the number of T cells with memory phenotype, which have defective functional properties (see Holland and van den Brink (2009) and Tsukamoto *et al.* (2009)). All these changes are seen as negative predictive factors. However, the CD4+/CD8+ ratio is commonly used as a marker of immune system aging and as a prognostic factor for human longevity (see Larbi *et al.* (2008)).

We found that the CD4+/CD8+ ratio decreased in the peripheral blood of experimental mice in comparison to the control group at 8 months of plasma injection (Fig. 2A). This reduction was due to an increase in the number of CD8+ cells in the blood. Such changes in the subpopulation of T lymphocytes have been found in our previous experiments on the model of heterochronic parabiosis (see Pishel *et al.* (2012)). We suggest that these changes are due to the ability of young plasma to stimulate the homeostatic proliferation of CD8 cells in the old organism, which normally should be suppressed. However, subsequent measurements revealed no significant differences for this parameter as compared with the control group at 9 and 13 months. This fact implies the absence of a stable positive effect of young plasma injection to maintain a balance between CD4 and CD8 cell populations in the blood of aging animals in our experiment design.

The total T4 level in plasma-treated mice was not statistically significant in comparison with the control group (Fig. 3).

Analysis of pathologies occurring in experimental animals upon aging shows a double effect. On the one hand, a slightly higher, but nonsignificant prevalence of cancer pathology was identified in the plasma-treated mice, which suggests the possibility that youth factors may perturb the aged host. The development of malignancies due to the uncontrolled influence of some enrichment in "youth stimuli" in an aged systemic environment have been previously suggested (see Meehan *et al.* (2013)). Such stimuli seem to exist: Conboy *et al.* (2005) reported an increase in the stem cell proliferation from old donors when the cells were cultured in media containing serum from younger animals; however, such stimuli may have some undesired effects for the whole body in vivo. On the other hand, we observed the opposite effect when assessing the occurrence of ovarian cysts—their frequency tended to be lower in plasma-treated mice (Fig. 4). These facts suggest no effect of prolonged administration of young blood plasma on the development of age-related pathologies in female mice CBA/Ca in our study design.

In the present study, we tested the possible positive effect of humoral factors present in young plasma on middle-aged female CBA/Ca mouse lifespan. In our study design, the administration of young plasma did not affect lifespan. We did not find any significant effect of young plasma on the blood CD4/CD8 ratio, plasma T4 level, and the development of age-related pathology of internal organs. The absence of any effect of young plasma in our study may be due to the peculiarities of the mouse strain, sex, or dose and regimen of plasma injection. Given the potential importance of the question we addressed, and of the beneficial short-term effects reported in the literature, further research is planned to investigate the question with another design.

ABBREVIATIONS USED

ELISA enzyme-linked immunosorbent assay

PBS phosphate-buffered saline

T4 thyroxine

AUTHOR DISCLOSURE INFORMATION

No competing financial interests exist.

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ANNEXE 3. ARTICLE: DO ACTUARIES BELIEVE IN LONGEVITY DECELERATION?

Debonneuil, E., Loisel, S., & Planchet, F. (2017). Do actuaries believe in longevity deceleration?. Insurance: Mathematics and Economics.

DO ACTUARIES BELIEVE IN LONGEVITY DECELERATION?

Edouard Debonneuil[α] **Stéphane Loisel**[*] **Frédéric Planchet**[*]

Univ Lyon - Université Claude Bernard Lyon 1,

ISFA, Laboratoire SAF EA2429, F-69366, Lyon, France

Prim'Act, 42 avenue de la Grande Armée, 75017 Paris, France

ActuRx

Version 2.0 du 05/08/2017

ABSTRACT

As more and more people believe that significant life extensions may come soon, should commonly used future mortality assumptions be considered prudent? We find here that commonly used actuarial tables for annuitants – as well as the Lee-Carter model – do not extrapolate life expectancy at the same rate for future years as for past years; instead they produce some longevity deceleration. This is typically because their mortality improvements decrease after a certain age, and those age-specific improvements are constant over time. As potential alternatives i) we study the Bongaarts model that produces straight increases in life expectancy; ii) we adapt it to produce best-practice longevity trends iii) we compare with various longevity scenarios even including a model for "life extension velocity". iv) after gathering advances in biogerontology we discuss elements to help retirement systems cope with a potential strong increase in life expectancy.

Introduction

During an online interview with more than 200 attendants, the bio gerontologist Aubrey de Grey indicated that he estimates at 60% the probability that people currently aged 40 reach "Longevity Escape Velocity" (de Grey, 2015), a set of scenarios where one's remaining life expectancy increases as one ages, because therapies gradually come to restore health faster than the rate of body deterioration due to biological aging (de Grey, 2010). There is so far evidence of strong life expectancy improvements in animal models (see for example Bartke *et al.* 2008 or Bernardes de Jesus *et al.* 2012) but little (Bannister *at al.* 2014) or no evidence of such medical advances in humans so far. We are still far from curing some diseases where one single gene is the source of the problem. Therefore, it may take longer than de Grey's estimate to strongly slow or reverse ageing. Besides, one would need to think more about the social and economical issues that would appear in such a world and about their negative impacts on longevity improvements. Nevertheless, given the increasing number of scientists who believe that the human lifespan may soon increase at an

[α] Edouard Debonneuil is founder of ActuRx. Contact: edebonneuil@yahoo.fr

[*] Stéphane Loisel and Frédéric Planchet are researcher at SAF laboratory (EA n°2429). Frédéric Planchet is also consulting actuary at Prim'Act. Contact: stephane.loisel@univ-lyon1.fr / frederic@planchet.net. Their work benefited partially from the financial support of the ANR project "LoLitA" (ANR-13-BS01-0011).

unprecedented pace, one may wonder if retirement systems are built in a way that could cope with such scenarios if they were to take place. In particular, currently used mortality projections for retirement systems are very different from the concept of Longevity Escape Velocity:

A widely used basis for mortality projections is the Lee-Carter model (Lee and Carter, 1992). It has led to the development of numerous models (Cairns *et al.*, 2011). In their original paper, Lee and Carter (1992) present a forecast of US life expectancy that first continues at the historical trend and then decelerates over time. Their confidence intervals are presented that are below a linear extrapolation of life expectancy. The authors write: "While many methods assume an upper limit to the human life span (…) our method allows (…) the deceleration of life expectancy (…) without any special additional assumption". At that time indeed, a sort of "longevity deceleration" was expected.

A widely known view is that life expectancy grossly increases by one quarter per year. Such a view was introduced by Oeppen and Vaupel (2002) ten years after the publication of the Lee-Carter model, in the context of maximal life expectancy across countries. They indicate that it has increased fairly linearly for more than 150 years – a "best practice line"– and has broken various predictions and limits imagined by actuaries, such as a 1928 computation of a putative ultimate human life expectancy of… 64.75 years (Dublin, 1928). Along those lines, Bongaarts (2004) questions longevity decelerations embedded in the Lee-Carter model and develops a simple mortality projection model that produces straight life expectancy increases.

Vallin and Meslé (2010) recomputed maximal life expectancy with other data and find that it is better represented by several portions of lines than by one line: the trend can change over time in particular due to various medical and social progresses. As they indicate, maximal life expectancy has increased by up to 4 months per year during several decades after the work of Louis Pasteur, the trend is now lower than "one quarter per year" and is more and more driven by improvements at later ages, in particular depending on how age-related frailty and age-related pathologies are addressed. Along those lines, Li *et al.* (2013) produce an extended version of the Lee-Carter model that allows for age patterns of mortality decline to rotate in the future towards higher ages, thereby reducing the longevity deceleration of the Lee-Carter model. Note that Ronald Lee was one of the coauthors of that paper.

One might interpret the latter as a convergence of views that a decelerating pattern of the Lee-Carter model is inadequate and that a trend of linear increases of life expectancy, which would be slower than one quarter per year for the next decades to come, makes sense. In this paper we name such a scenario the "Best Practice Trend" following the strong-worded vocabulary of Oeppen and Vaupel (2002), even if it is of course not clear at all what the best practice is, and we model it in this paper. However, views are far from uniform. There have typically been debates whether general improvements will outweigh changes in lifestyle, pollutions and climate, whether age-specific risks of chronic diseases will increase or decrease for a given age, and whether lifespan should consecutively increase or decrease and also whether a limit of human lifespan exists (Aubert *et al.*, 2010; Cambois *et al.*, 2010; Debonneuil *et al.* 2011).

Facing uncertainty, actuarial assumptions should be prudent rather than aggressive. Antolin and Mosher (2014) review the sufficiency of actuarial mortality tables that are commonly used for retirement systems, country by country. For that purpose, they compare mortality tables with projections obtained with models that extrapolate log-mortality rates, such as the Lee-Carter model.

They find in most of the cases that the mortality table leads to lower provisions than the model (Antolin and Mosher, 2014) – thereby generating a general warning: are actuarial mortality tables sufficient? Antolin and Mosher (2014) also suggest that governments help set up a framework to financially hedge longevity risk.

Here, further than comparing commonly used mortality tables with commonly used actuarial models, we compare them with models that extrapolate life expectancy linearly. Placing then the results in the context of potentially even far different futures than generally investigated we gather facts of advances in biogerontology and elements of solutions to help retirement systems cope with strong increases in human lifespans.

Mortality projection methods

Overview

We here limit the modeling scope in order not to disperse into too many aspects. Complex longevity risk estimations that would consider country-specific and system-specific risk absorption mechanisms and amounts at stake are not considered. Rather, the quantitative parts of this paper focus on life expectancies (period and generational life expectancies starting at different ages) and values of immediate annuities for people aged 65. The sole data we use here are general population data and actuarial tables, the results of which are compared without modeling complex basis risk between general and insured populations. Similarly, results for males and females are superimposed without modeling correlations between the two. For the sake of simplicity, we consider life expectancy at age 20 (and above) rather than at birth because some actuarial tables do not provide mortality rates for lower ages. Of course, this oversimplification would prevent one from accurately estimating longevity risk. However, it enables us to illustrate our conclusions with little complexity.

The interest of the analysis then lies in the use of models with various trends and some first order comparison with commonly used actuarial assumptions.

Briefly, for a given country and a given gender, five mortality projection models (“Lee-Carter”, “Bongaarts”, “BestPractice”, “Fast”, “Flat”, “LEV”). Indicators are calibrated from the general population data. Indicators are then computed for various dates, both based on those models and based on an actuarial table for the same country and gender: [period] life expectancy at age 20 and 65, generational life expectancy at age 65 and immediate annuity value at age 65.

Standard methods

Regarding data, the general population data consist in deaths and expositions taken from the Human Mortality Database for various countries (Human Mortality Database, 2015). It is split by gender, age “x” and calendar year “t”. We consider data up to calendar year 2009 only as more recent data is currently only available for a limited number of countries. The actuarial mortality tables are those commonly used in insurance according to a recent report from the OECD about the insufficiency of current actuarial assumptions (Antolin and Mosher, 2014).

Regarding indicators, annual mortality rates $q_{x,t}$ are computed from central mortality rates $m_{x,t}$ using

$$q_{x,t} = 1 - e^{-m_{x,t}}$$

The remaining [period] life expectancy at age x is computed using$e_{x,t} = 0.5 + \sum_{y=x}^{170} \prod_{z=x}^{y} (1 - q_{z,t})$

The expected lifespan of people aged 65 at year t is computed using

$$e_{g\,65}^{t} = 65.5 + \sum_{x=65}^{\infty} \prod_{y=65}^{x} (1 - q_{y,t+(y-65)})$$

In practice we replace ∞ by 170 (except for the LEV model where we use 10000). Immediate annuities at age 65 are calculated similarly, with an interest rate of 2%:

$$\ddot{a}_{65}^{t} = 65.5 + \sum_{x=65}^{\infty} \frac{\prod_{y=65}^{x} (1 - q_{y,t+(y-65)})}{1.02^{x-64}}$$

We will compute them with standard mortality tables ($\ddot{a}_{65(table)}^{t}$) and various models ($\ddot{a}_{65(model)}^{t}$).

Regarding the Lee-Carter model, parameters are calibrated for ages 0 to 89 with the LifeMetrics "fitmodels.r" functions (see Cairns *et al.*, 2007), which is an implementation of an adjustment of the original Lee-Carter model (see Brouhns *et al.*, 2002). The longevity trend is obtained by extrapolating kappa with a simple linear regression (slope defined by least square linear regression, and applied to the last known kappa; for further refinements, it could be possible to apply trends to an average of the last 3 years for example): we obtain central mortality rates $m_{x,t}$ for ages 0 to 89 and at any future date. For any given date t we then extrapolate $m_{x,t}$ from ages 60-89 to ages 90-170 using a logistic regression: $logit\, m_{x,t} = a_t x + b_t$. This is simple and sufficient for the gross indicators that we use in this paper such as life expectancies at age 20 and 65. To smooth mortality rates along age and time one may extrapolate mortality rates at high ages in a coherent manner across consecutive years following Planchet (2006).

Regarding the "Bongaarts" model, sometimes called "shifting logistic", we carry out a standard logistic regression on deaths and expositions with respect to age and time: $logit\, m_{x,t} = A + B\, x + C\, t$. Similarly, to the application of the trend to the last kappa for the Lee-Carter model, we recalibrate the mortality level (A) on the data of the last year $logit\, m_{x,t} = A' + B\, x + C\, t$ and we apply trends to the last year. Bongaarts (2004) demonstrates that the model naturally produces linear life expectancy at birth (or low ages for which mortality rates are small).

Best practice trend model

To define the strong-worded "Best Practice Trend" model, we first compute the "best practice" life expectancy at different ages based on all countries available in the Human Mortality Database since 1900. For retrospective projections that are based on data up to the year 1990, we use a second order polynomial fit between 1900 to 1989 of the best practice life expectancy at age 20 ($BP_{20,t} = \alpha_{20} t^2 + \beta_{20} t + \gamma_{20}$) and 65 ($BP_{65,t} = \alpha_{65} t^2 + \beta_{65} t + \gamma_{65}$) to directly extrapolate "Best Practice Trend" life expectancies of any country between 1990 and 2009 at age 20 or 65 at the same polynomial pace: $e_{x,t} = e_{x,t0} + (BPT_{x,t} - BPT_{x,t0})$. Results are shown in Figure 1.

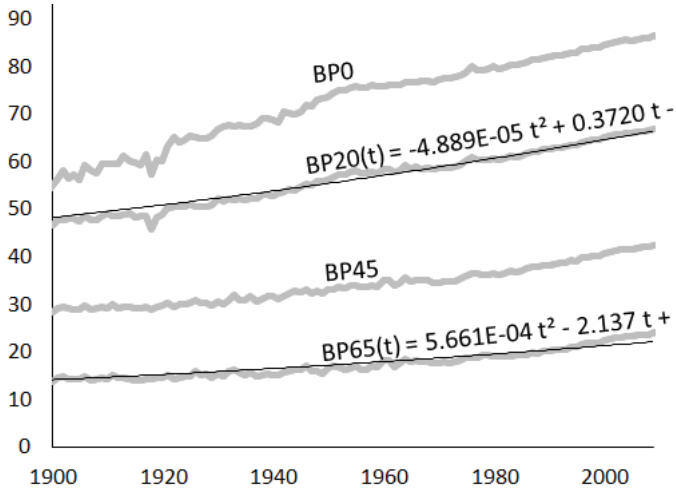


Figure 1. Best practice life expectancy at ages 0, 20, 45, 65 (in years) across all countries and genders available on the Human Mortality Database, between 1900 and 2009. Second order polynomial fits between 1900 and 1989 for ages 20 and 65.

For future predictions that are based on data up to the year 2009 for each country and gender, we define the "Best Practice Trend" model as a Bongaarts model that is constrained to have a desired trend in terms of life expectancy: $logit\ m_{x,t} = A + B\ (x + s\ t)$. A and B are calibrated by maximum likelihood, as a standard logistic regression. We choose the trend s=20%, since the polynomial fit between 1900 and 2009 of the best practice life expectancy at age 20 yields roughly linear increases of 20% per year (from 19% to 21% between 2010 and 2100; less than "one quarter per year" which would be s=25%); keeping in mind that mortality rates produced by the model from birth to age 20 have little impact on the computed life expectancy (Bongaarts, 2004). As a verification of the assumption, for every country and gender and every year from 2000 to 2100 we have measured that the year slope of the resulting $e_{20,t}$ is between 0.199 and 0.20 per year.

Of note, we could certainly have used a unique model for both retrospective and future analyses $logit\ m_{x,t} = A + B\ (x + \alpha_{20}t^2 + \beta_{20}t)$, but to avoid complex interpretations of results we did not want the model used for future analyses to produce life expectancy accelerations.

Extreme projections

During seven decades following the work of Louis Pasteur, the best practice life expectancy has accelerated by 4 months per year (Vallin and Meslé, 2010). Based on that historical pace we define a "Fast" model that uses the Best Practice Trend model until 2025 and that then increases life expectancy by 4 months every year: $logit\ m_{x,t} = A + B\ (x + 0.2\ 2025 + (t - 2025)/3)$. Similarly, in order to consider scenarios of non-increasing life expectancies, we define a "Flat" model where the Best Practice Trend model is used until 2025 and then mortality rates do not evolve anymore. We also introduce a "Decreasing" model where life expectancy decreases at the pace of 4 months per year starting at 2025: $logit\ m_{x,t} = A + B\ (x + 0.2\ 2025 - (t - 2025)/3)$. The choice of 2025 is arbitrary but the reason of starting the change of trends later than 2015 is that we are not aware of signs that would indicate that such a change of trend should happen now. As an attempt to model the Longevity Escape Velocity (LEV) announced by de Grey (2015), we define a "LEV" model that is first a Best Practice Trend model and then performs adaptations: for ages 85 and above starting at 2040, 84 and above starting at 2041, 83 and above starting at 2042, and so on, mortality rates are

defined by annual mortality improvements of 5%: $q_{x,t+1} = q_{x,t}\,(1 - 5\%)$. Starting with the Best Practice Trend model for France for example (men and women combined), that model respectively gives a 61% and 85% probability for people currently aged 40 and 20 to reach Longevity Escape Velocity: close to the announced 60% and 80%. The underlying real life scenario – whether realistic or not – would be that a set of medical or pharmaceutical procedures would first reach a mass usage at ages 85 and above in 2040 and would then gradually reach younger ages. Given improved research guidance after first successful results, as well as a consequent increased awareness and attention to improve health, such procedures would on average decrease age-specific mortality rates by 5% per year. Sustained mortality improvements of 5% at high ages may at first not seem extreme but they actually lead to life expectancies of more than 1000 years for people currently aged 40! Sustained mortality improvements of 4% would also lead to Longevity Escape Velocity but to approximately match the announced probabilities they should start within the next few years.

Commonly used mortality tables produce decelerating life expectancies

Decelerating common actuarial tables, by country

In order to compare common actuarial mortality tables with various projection models, for every country available at the Human Mortality Database for which a commonly used annuity table is studied in the OECD report (Antolin and Mosher, 2014) we computed the life expectancy at age 20 up to year 2100: i) historically, ii) with the actuarial tables and iii) various models: Lee-Carter (with two calibration periods), Bongaarts, Best Practice Trend ("+20%/year"). The results are shown in Figure 2 and Figure 3

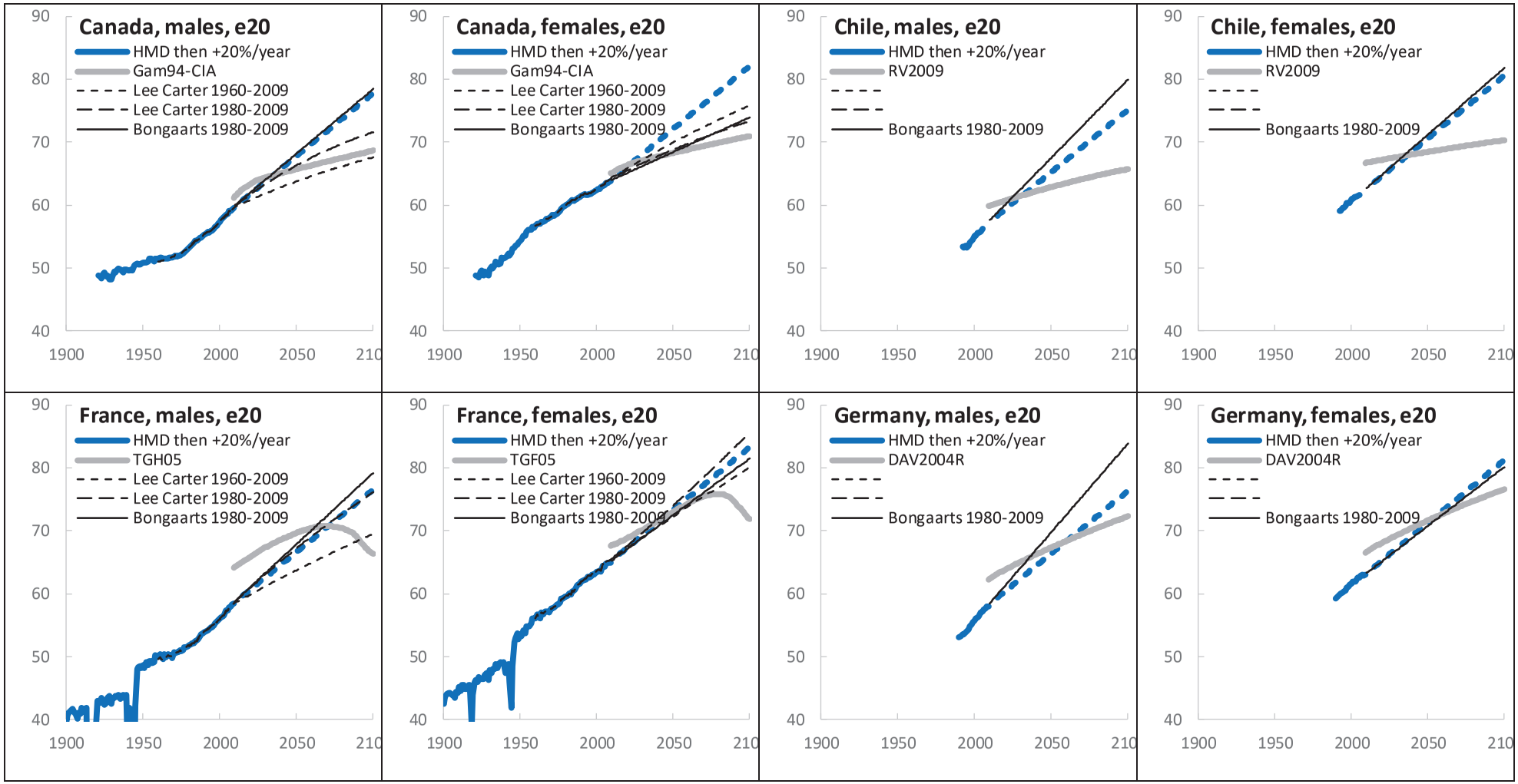
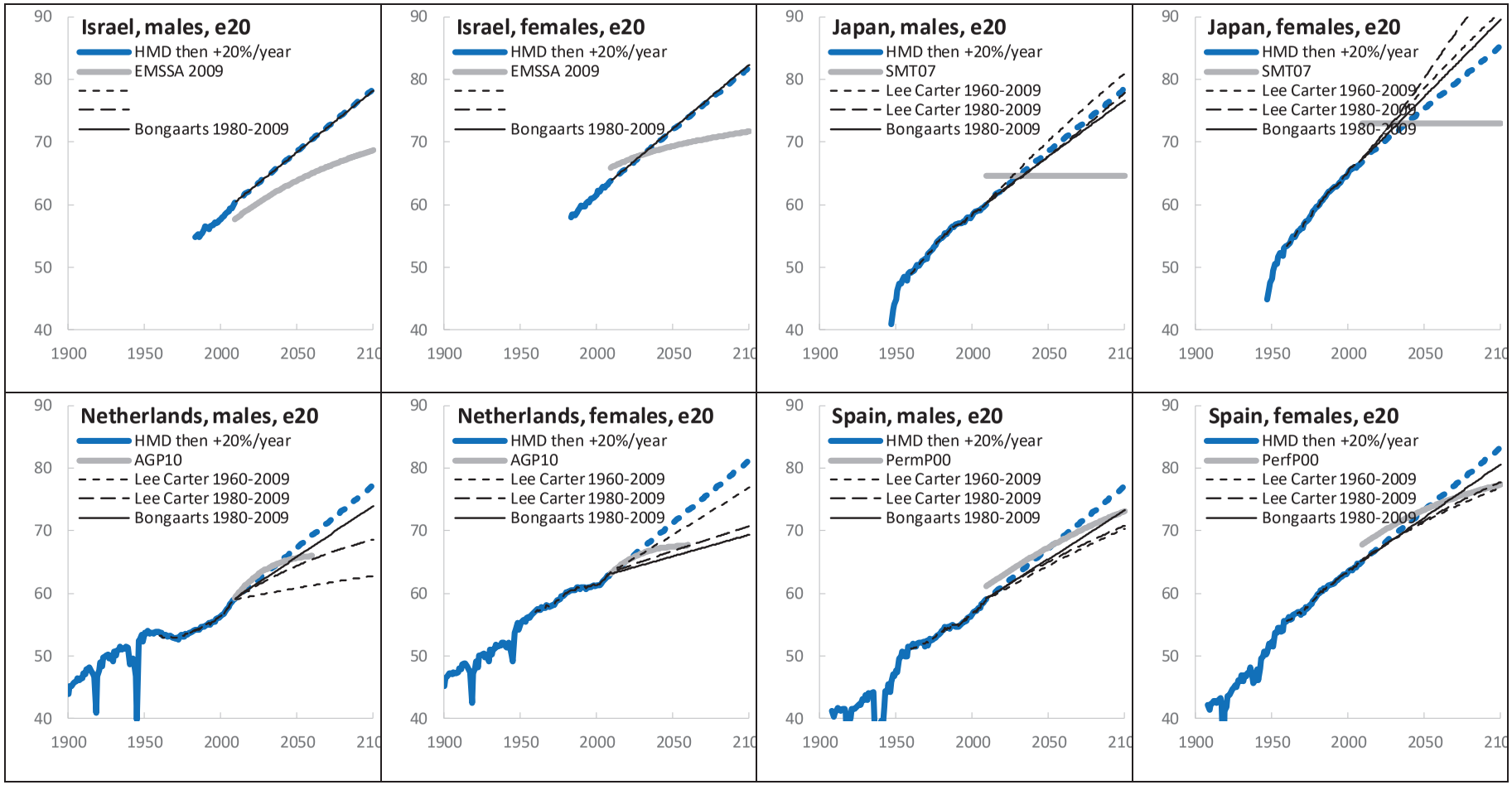


Figure 2. Comparison of past and projected life expectancy at age 20 for males and females according to commonly used actuarial tables and general population models for Canada (actuarial table GAM1994-Scale CIA), Chile (RV2009), Germany (DAV2004R). Historical life expectancy is shown in thick continuous blue lines and extended with a linear slope of 20% (Best Practice Trend method) in thick dashed blue lines. In contrast, actuarial tables are in thick continuous grey lines and are observed to have a much lower trend. The thin black lines correspond to models that aim at extrapolating the historical trend of the country: the Lee-

Carter model in dashed lines (fitted on years 1960-2009 (rapidly dashed lines) and 1980-2009 (slowly dashed lines) and the Bongaarts model (continuous lines). When one of those could not be correctly computed, it is not shown (lack of convergence in the fitting program of Lee-Carter).



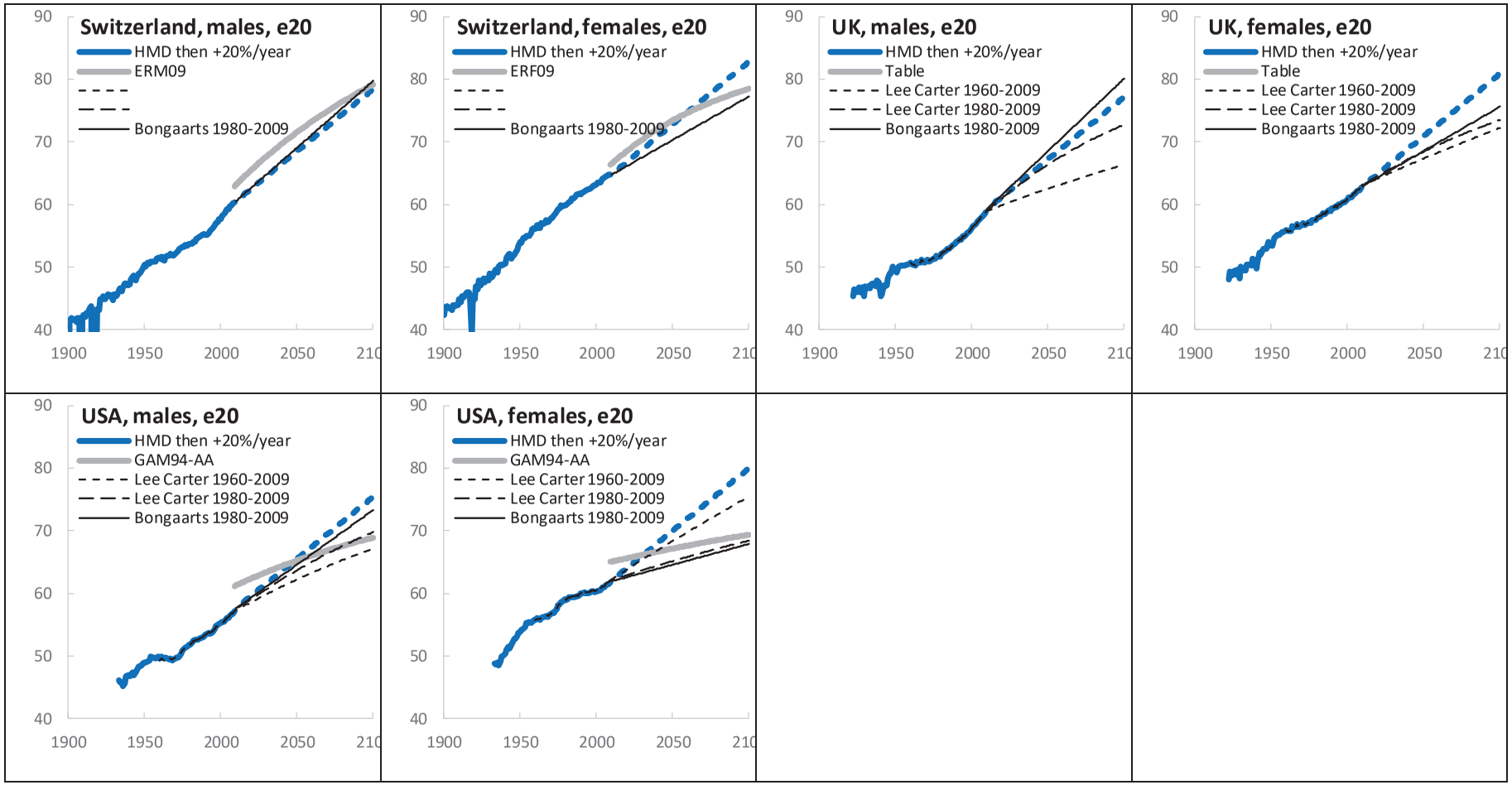


Figure 3 (continuation of figure 2). Comparison of past and projected life expectancy at age 20 for males and females according to commonly used actuarial tables and general population models for Israel (EMSSA 2009), France(TG2005), Japan (SMT2007), Netherlands (AGP2010), Spain (PERMC), Switzerland (ERM2009), UK, USA (GAM1994-Scale AA).

Let us for example consider the case of Canada (first two graphs of Figure 2). For males, the Best Practice Trend and the Bongaarts models for linear life expectancy extrapolation are aligned. The Lee-Carter models start similarly but very rapidly produce lower life expectancies: they produce longevity deceleration (to a stronger degree when not focusing on recent data). Compared to those models, the common actuarial projection table (Gam94-CIA) starts with higher life expectancies – it makes sense as insured persons tend to live longer than the general population – but rapidly produces lower life expectancies than modeled for the general population with linear extrapolation models (Best Practice Trend, Bongaarts) and even here lower than the Lee-Carter model calibrated with recent data. It could be interpreted as a warning for the commonly used actuarial table: are provisions for retirement sufficient? It could also be seen as individuals with lower life expectancy catching up with favored individuals. To avoid this crossing, two-population models have been proposed (see Salhi and Loisel 2012 and Cairns *et al.* 2015). If such a population mix would lead to a life expectancy deceleration, it would be unexpected however to lead to low remaining lifespans of retired persons as seen further below.

For females, results are visually more complex as the Bongaarts projection is much lower than the Best Practice Trend. This is not surprising as life expectancy has particularly low increases during the calibration period of the Bongaarts model. The Lee-Carter models seem to start similarly to the Best Practice Trend but they rapidly produce lower life expectancies, still greater though than the (again here low) Bongaarts predictions. As for males, compared to those models, the common actuarial projection table starts with higher life expectancies and rapidly down crosses other curves. Again, it could be interpreted as a warning for the commonly used actuarial table: are provisions for retirement sufficient?

Overall, Figure 2 and Figure 3 show a variety of cases. The following common features appear:

i) Except for the Japanese tables that do not attempt to project trends, all commonly used actuarial tables studied here project decelerating life expectancies – with longevity trends that are globally smaller than in the past. This explains the title of this paper: “Do Actuaries believe in longevity deceleration?”. In most cases, within a few decades, the life expectancy of the actuarial table becomes lower than here modeled for the general population, although it would be expected that insured populations keep higher life expectancies than general populations: are provisions for retirement sufficient?

Given the potential amounts at stake, we highlight below some mathematical explanations of why the commonly used assumptions behave that way. We further investigate the likely insufficiency of the tables, and we discuss the gravity of the situation in the discussion section. In the documents describing the methodologies pursued to obtain those tables, we have not read that there was a voluntary deceleration.

ii) While using the actuarial tables, we have noticed that for most of the tables studied here (all except for the UK, Japanese and French tables), the construction of the actuarial table is similar to a Lee-Carter model: mortality rates at a given age decrease exponentially with time at an age-specific rate (similar rather than identical because Lee-Carter produces an exponential decrease of $t \to m_{x,t}$ rather than $t \to q_{x,t}$). For some tables (such as DAV 2004R), there is a short, initially different, transition period, but it then becomes again is similar to a Lee-Carter model too.

This might be one of the explanations of the deceleration as for all those countries the Lee-Carter models shows life expectancy deceleration. Below, we investigate the mechanism of such deceleration produced by the Lee-Carter model and such tables. We also explain why the Lee-Carter models here produced longevity acceleration in France and Japan.

iii) The French and Japanese actuarial tables are not built similarly to Lee-Carter models. Japanese tables are mortality rates that do not evolve over time: it is transparently hoped that the initial prudence of these mortality rates is sufficient to compensate the absence of trend in the table, until the next table. The French table has a complex construction: the decrease of life expectancy at age 20 that is produced after 2070 should not be a warning in itself as it comes from a specific closure that is applied for generations for which no data is available (Planchet 2006) rather than a limitation for current generations. Therefore, for these two countries more than for others, sufficiency or insufficiency should rather be analyzed with generational life expectancies, which is done below.

iv) In most cases the Bongaarts predictions are close the Best Practice Trend. In the other cases, the trend was particular during the fitting period used for the Bongaarts model. There are actually many reasons for the latter to happen. We have already seen that for Canadian females life expectancy increases varied much over time. Fitting over a longer period here leads to much closer results (data not shown), but for some countries like France fitting over long periods leads to strange results due to the impact of wars. For Chile and Germany, due to the limited availability of data, the Bongaarts model was fitted on short periods of time (1992-2009 and 1990-2009 respectively). On such small periods the measure of the trend is of course delicate. In both cases, the Best Practice Trend model cannot be discarded.

Moreover, the case of Japan highlights some 'neutral' aspect of the best practice trend approach: many developing countries have fast life expectancy increases as they 'bridge the gap' towards longest lived countries (World Health Organization, 2015). Countries of ex-USSR have in the contrary 'created a gap'. For those countries with particular current trends, it is not obvious whether current trends are likely to continue or even 'reverse' (creating or bridging the gap back). Using the trend of the best practice is then a way to choose a neutral view, in the absence of country-specific contextual knowledge. Of course, socio-economic forecasts are of first-order relevance for longevity prediction in those countries.

Therefore, for the sake of simplicity, in what follows we shall use the best practice trend as a reference to estimate possible insufficiency of tables. We shall keep in mind however that specific knowledge about each country (*i.e.,* whether their specific ongoing trend is temporary or likely to continue) would likely adjust views, including for example population dynamics such as birth patterns (Boumezoued, El Karoui and Loisel, 2015).

Why do common actuarial tables and models produce life expectancy deceleration, mathematically speaking?

Here we try to understand the longevity deceleration embedded in commonly used actuarial tables. In fact, most tables studied above behave similarly to Lee-Carter in that by construction they have age-specific mortality improvements $i_{x,t} = (q_{x,t+1} - q_{x,t})/q_{x,t}$ that differ by age but are constant with time. This is sufficient to create longevity deceleration – as schematized in Figure 4 – if age-

specific mortality improvement rates diminish after a given age. For the sake of simplicity we mention the Lee-Carter model but some widely used similar models like the Cairns Blake Dowd models (Cairns *et al.*, 2011) also create mortality improvements that vary by age (roughly linearly, by construction) and are roughly constant with time; they therefore have the same behavior.

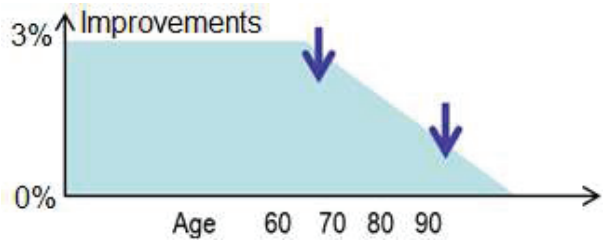


Figure 4: Schematized explanation of the longevity deceleration. Mortality improvements are here schematized by age. What matters is that they decrease past a certain age (here past 60-70 years of age). The arrow above age 60-70 typically indicates the ages where mortality improvements currently drive life expectancy the most. As time passes, mortality rates become lower and people live longer. Most important ages to remain alive or not decay to the right, as symbolized by the arrow above age 90. At that age, mortality improvements are very low which means that the drivers of longevity are then very low: a 'longevity deceleration' has been modeled. Ultimately, if important ages to remain alive decay to ages with negligible mortality improvements then there is no more driver of longevity and life expectancy reaches a ceiling.

To be more precise than in Figure 4, we can check that some ages are more important than others for life expectancy, in terms of mortality improvements. For consistency let us consider life expectancy at age 20.

Let us split the probability to live from age 20 to age y (>x) into three probabilities: the probability to live until age x, the conditional probability to then remain alive until age x+1 and the conditional probability to then remain alive until age y:

$$S_{20\to y} = \prod_{z=20}^{z=y-1} (1-q_z) = S_{20\to x}(1-q_x)S_{x+1\to y}$$

This allows decomposing the life expectancy in a way that highlights its dependence on q_x:

$$e_{20} = 0.5 + \sum_{y=20}^{170} S_{20\to y} = 0.5 + \sum_{y=20}^{x} S_{20\to y} + \sum_{y=x+1}^{170} S_{20\to x}(1-q_x)S_{x+1\to y}$$

The first two terms do not involve q_x. Regarding the last term, $(1-q_x)$ can be factored out. So we get the following derivative:

$$\frac{de_{20}}{dq_x} = -\frac{de_{20}}{d(1-q_x)} = -S_{20\to x}\sum_{y=x+1}^{170} S_{x+1\to y} = -S_{20\to x}(e_{x+1}+0{,}5)$$

Since we want to see the changes of life expectancy driven by relative variations of q_x (mortality improvements) rather than absolute variations, we multiply by q_x and we get

$$e_{20,t+1} - e_{20,t} = \sum_{x=20}^{170} w_{x,t} i_{x,t}$$

where

$$w_{x,t} = q_{x,t} S_{20 \to x}\left(e_{x+1,t} + 0{,}5\right)$$

The formula provides weights by which improvement factors must be multiplied to compute increases in life expectancy. Figure 5 tests it for Japanese females: it is an interesting case because depending on the period on which the Lee-Carter model is fitted it can produce accelerating or strongly decelerating longevity – visualizing the shape of mortality improvements past age 60 provides the explanation. Also, it shows that very strange extrapolations of kappa would be needed for the naturally decelerating Lee-Carter model not to produce decelerating life expectancy. This would not be achieved with usual ARIMA extrapolation of kappa. In Figure 6, visualizing the mortality improvements of the various actuarial tables studied above explains the deceleration as well.

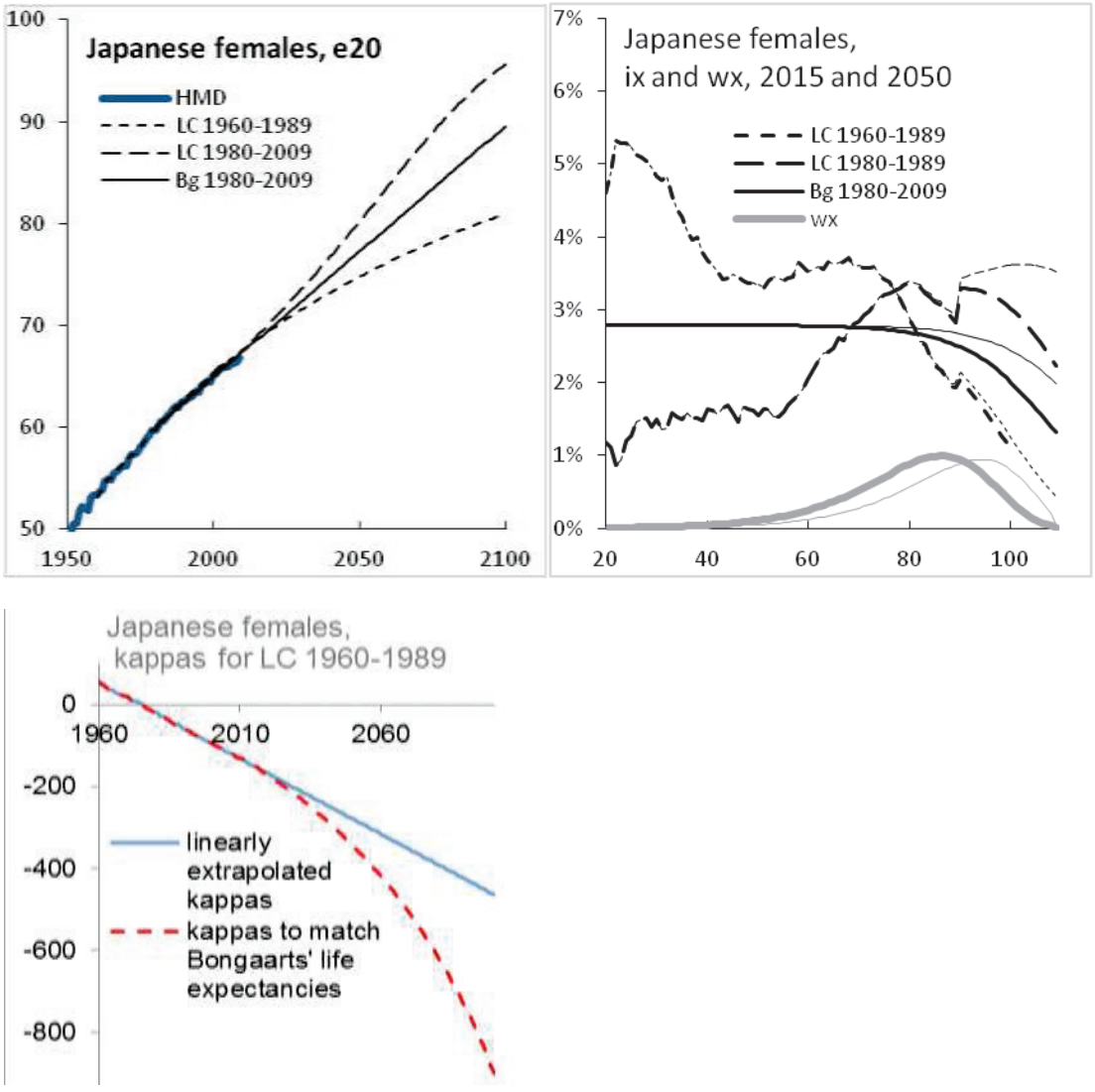
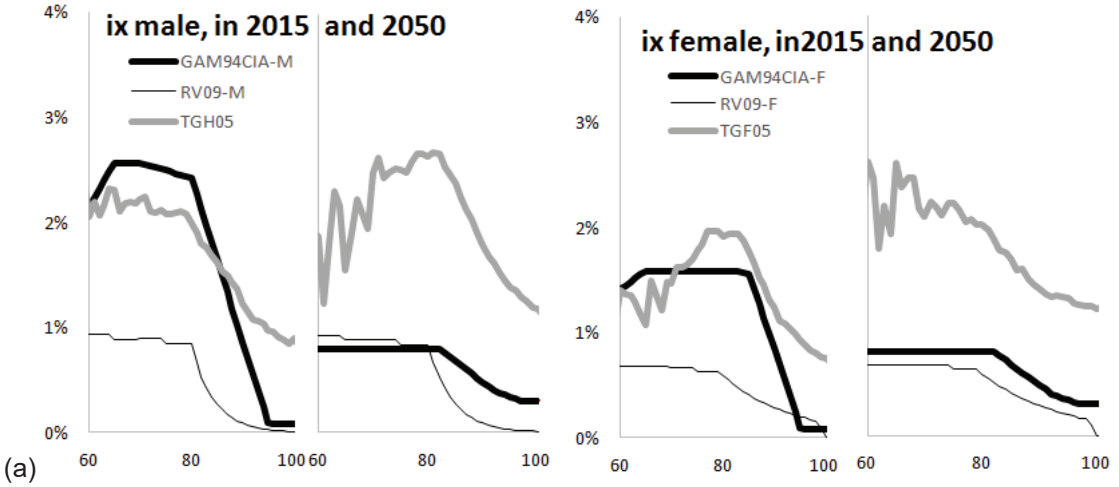
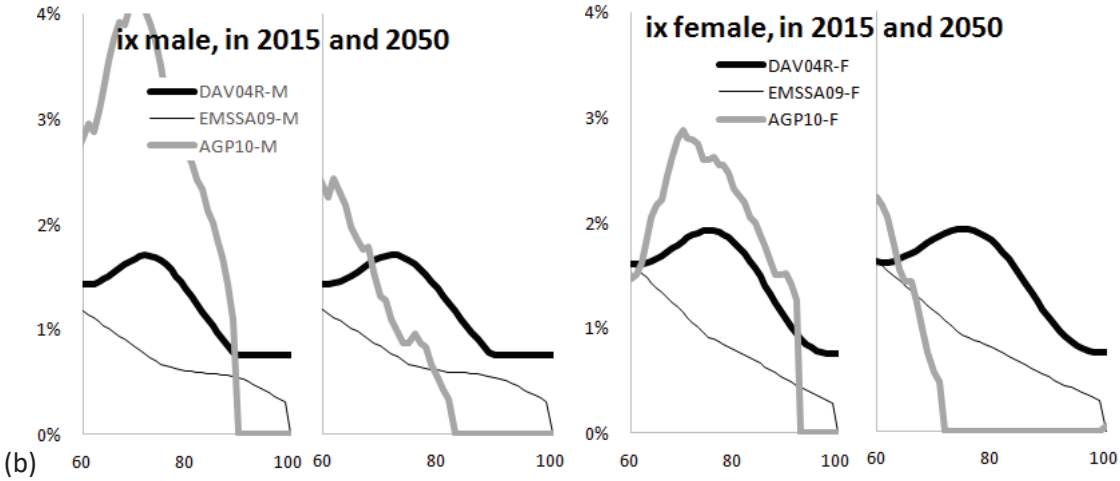


Figure 5. Deciphering accelerating and decelerating longevity mechanisms. The graph on the top left shows historical life expectancy at age 20 and its projection with 3 models. The case of

Japanese females is taken because out of the 3 projection models, one produces an acceleration (Lee-Carter model fitted on years 1980-2009; long dashes), one extrapolates life expectancy linearly (Bongaarts model, solid line in the middle) and one produces a deceleration (Lee-Carter model fitted on years 1960-1989; short dashes). The graph on the bottom highlights that the difference between the two latter projections is important by indicating which kappa extrapolation of the Lee-Carter 1960-1989 model would be needed to move, in the top left graph, the decelerating short dashes to the non-decelerating solid line (it was obtained by calibrating kappa in order to reach the desired life expectancy): such kappa are far from a linear or even simple ARIMA extrapolation of past kappa. The right-hand side panel attempts to explain why the Lee-Carter model sometimes decelerates or accelerates life expectancy. It shows the corresponding mortality improvements with the same lines style as the top left graph and the weights in a thick gray line (thinner lines for the year 2050 than the year 2015). In 2015, what matters is improvements for ages 60-100 with a focus on ages 80-90 (thick gray curve). It explains that life expectancy increases faster with the 1980-2009 Lee-Carter calibration than the 1960-1989 Lee-Carter calibration. In 2050, what matters is improvements about 7 years later. The decreasing improvements by age of the 1960-1989 model explain the deceleration; the globally increasing then globally decreasing mortality improvements by age of the 1980-2009 model explain the acceleration then deceleration. Similarly, for each country the shape of improvements by age after age 60 explain the more or less pronounced deceleration of the Lee-Carter model (data not shown). The Bongaarts model has decreasing mortality improvements after a certain age but no deceleration is produced as they decay to the right with time.



(a)



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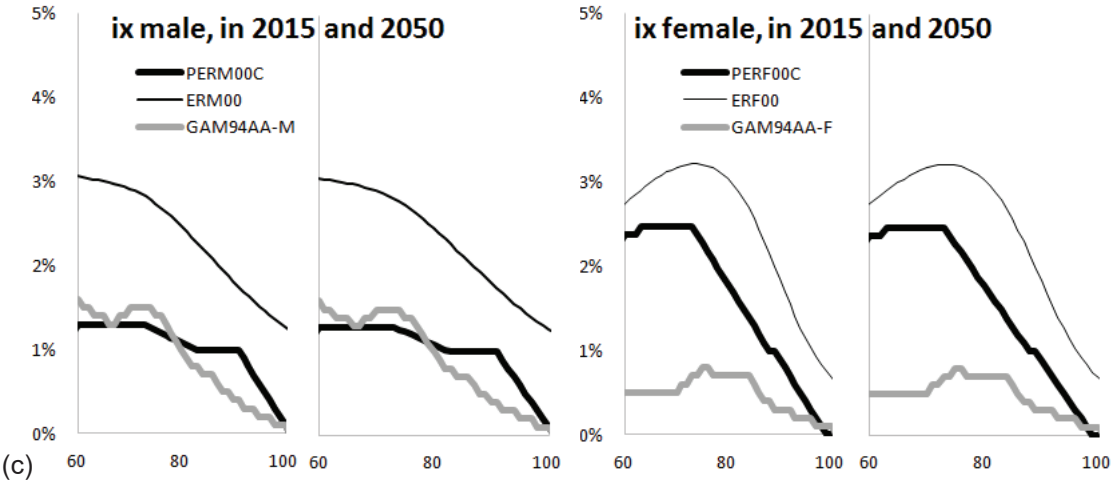

(c)

Figure 6. Mortality improvements by age for the various tables studied, in 2015 and 2050. SMT07 is not represented since it has no improvement. The x-axis is only shown from age 60 to 100 in order to focus on mortality improvements that materially impact lifespans. The 9 tables are put in 3 groups of 3 by alphabetical order of the country: (a), (b), (c). It is immediate to detect the tables that behave like Lee-Carter and those that do not, depending on whether the same curves appear in 2015 and 2050 (left and right parts of each panel). All curves plunge down after age 80, which, according to the explanations given above leads to longevity decelerations. Some plunge to zero, which leads to life expectancy ceilings over time. Between age 60 and 80, some curves increase, which counterbalances the deceleration for some time. Visually, those graphs explain the shapes observed in Figure 6 for actuarial tables up (except for the French TGHF05 after 2080: a specific closure leads to strong decelerations).

We hope that such visualization will help the reader rapidly realize that some model have decelerating behaviors. Of course, if the model contains no mortality improvement after a certain age then in the long term life expectancy will even tend not to increase anymore. From a social and biomedical point of view, a "longevity-optimistic" person may think that there would rather be people to investigate and find solutions with respect to the most important reasons to get ill and die.

As this section explains the longevity deceleration embedded in actuarial tables, one should also note that an additional late longevity deceleration factor comes from the closure of tables. To make the point particularly clear, while it is today rare to reach the age of 100, it could become quite common in a few decades. Tables that give a 100% mortality rate at age 100 will produce an additional longevity deceleration compared to a table that instead does so at age 130 (or 170!).

A retrospective analysis argues for non-decelerating, non-extrapolative trends

So far, the paper has been looking at future predictions. One can get additional insight from a retrospective analysis. We here use the Lee-Carter, Bongaarts and Best Practice Trend models to compute remaining life expectancies at age 20 and 65 at year 2009 based on data up to 1989. We do so for the 24 countries for which this is possible for males and females (i.e. data is available at those dates and the Lee-Carter fitting method converges) out of the 37 countries of the Human Mortality Database. The results are shown in Figure 7.

Figure 7. For 24 countries, difference between actual and predicted life expectancy in 2009 based on general population data up to 1989. It is computed for life expectancies at age 20 and 65 (alternating graphs), for males and females, and with the following prediction models: the Lee-Carter model (first two graphs), the Bongaarts model (two next graphs) and the Best Practice Trend (last two graphs). The fitting period for the Lee-Carter and Bongaarts models is 1960-1989.

The results of Figure 7 indicate that:

i) The Lee-Carter model globally underestimated longevity: predictions underestimated life expectancy in 86% of the cases (83 among 96) and the few prudent cases were not prudent by much compared to the lack of prudence otherwise.

ii) However, the longevity deceleration of the Lee-Carter model is not the major culprit here. Indeed, the Bongaarts model, that produces straight life expectancy increases, produced similar patterns (Figure 7).

iii) The Best Practice Trend model produced much better results, but also much better understanding of the results, that holds in two aspects: it slightly underestimated the longevity of most developed countries and overestimated the longevity trend of ex-USSR countries that was particularly not important during that period.

Results seem in favor of the Best Practice Trend when one does not have a more precise view that would come from country specificities or specific expected advances in longevity improvements. Of course, even if longevity ends up decelerating after some time, such improvements, if prolonged long enough, may threaten pension schemes.

Consequent longevity risk

The above [period] life expectancy at age 20 is an indicator that takes some snapshot of mortality rates at a given year. But the 'longevity risk' faced by insurers and pension funds largely depends on mortality rates for a generation rather than of a given year, especially when individuals enter retirement, close to age 65. The amounts they shall receive for the rest of their life indeed depend on their accumulated capital and on how long the actuarial tables expect them to live on average.

As a second indicator, we therefore compute expected generational lifespans for people aged 65. In Table 1 we do so for insured persons using actuarial tables and for general populations using the best practice model. We compare the two and we gray results that suggest that a table would be insufficient if the best practice trend scenario occurred. If one believes in this scenario, then the results seem worrying as i) none of the tables studied has a comfortable difference today of lifespan between insured and general populations ii) the issue is expected to get worse as most tables project surprisingly low improvements (last column) and indeed iii) in 2020 two thirds of the tables even project lower lifespans for insured than for the general population. Given the weight of retirement in economics, the gray results therefore suggest probable large increases of debt to come, year after year as people enter retirement, if life expectancy continued to increase by nearly one quarter per year and if nothing were done to compensate that longevity risk.

Country & table tested	Gender	Best Practice Trend $e_{g\,65}^{2009}, e_{g\,65}^{2015}, e_{g\,65}^{2020}$			Actuarial table $e_{g\,65}^{2009}, e_{g\,65}^{2015}, e_{g\,65}^{2020}$			Difference $\Delta e_{g\,65}^{2009}$	$\Delta e_{g\,65}^{2015}$	$\Delta e_{g\,65}^{2020}$	%Trend 2009→2020
Canada	Male	85.7	86.8	87.7	85.8	86.5	86.9	0.1	-0.1	-0.8	55%
GAM94-CIA	Female	89.2	90.4	91.4	88.2	88.7	89.0	-1.0	-1.7	-2.4	36%
Chile	Male	84.4	85.3	86.2	84.3	84.6	84.8	-0.1	-0.7	-1.4	28%
RV09	Female	87.9	89.1	90.1	89.2	89.4	89.6	1.3	0.3	-0.5	18%
France	Male	85.2	86.2	87.1	88.2	89.1	89.8	3.0	2.7	2.7	84%
TGHF05	Female	90.1	91.3	92.4	91.7	92.5	93.3	1.6	1.2	0.9	70%
Germany	Male	84.2	85.3	86.2	86.7	87.3	87.8	2.5	2.0	1.6	55%
DAV2004R	Female	87.8	89.1	90.1	90.4	91.1	91.6	2.6	2.0	1.5	52%
Israel	Male	86.2	87.3	88.2	86.6	87.0	87.3	0.4	-0.3	-0.9	35%
EMSSA09	Female	88.7	90.0	91.0	89.2	89.5	89.7	0.5	-0.5	-1.3	22%
Japan	Male	86.0	87.1	88.1	87.9	87.9	87.9	1.9	0.8	-0.2	0%
SMT07	Female	92.2	93.4	94.5	94.7	94.7	94.7	2.5	1.3	0.2	0%
Netherlands	Male	84.6	85.7	86.6	84.4	85.3	85.8	-0.2	-0.4	-0.8	70%
AGP10	Female	88.0	89.2	90.3	87.4	87.9	88.2	-0.6	-1.3	-2.1	35%
Spain	Male	85.2	86.3	87.2	85.1	85.7	86.1	-0.1	-0.6	-1.1	50%
PERMFC00	Female	89.8	91.1	92.2	89.5	90.0	90.5	-0.4	-1.1	-1.7	42%
Switzerland	Male	85.9	87.0	88.0	88.6	89.7	90.7	2.7	2.7	2.7	100%
ERMF09	Female	89.4	90.6	91.7	91.2	92.1	92.9	1.8	1.5	1.2	74%
USA	Male	84.5	85.5	86.4	85.0	85.5	85.8	0.5	0.0	-0.5	42%
GAM94-AA	Female	87.6	88.8	89.7	87.5	87.8	88.0	-0.1	-1.0	-1.7	24%

Table 1. Expected lifespan of people aged 65 in 2009, 2015 and 2020: computed on the best practice trend approach for general populations and on commonly used actuarial tables insured population, for males and females of various countries. It would be expected that insured people live longer than the general population: when this is not the case, the difference is highlighted in gray. It is highlighted in light gray when the difference is particularly low (less than 3 years for males and less than 1 year for females). The last column compares the longevity improvements of the actuarial table with those of the best practice trend: $(e_{g\,65}^{2020} - e_{g\,65}^{2009})_{actuarial\ table} / (e_{g\,65}^{2020} - e_{g\,65}^{2009})_{best\ practice\ trend}$. One may imagine that insured persons should not have too different improvements from the general population, *i.e.* that the indicator should not be too different from 100%. We have therefore grayed the indicator when it is lower than 70% (arbitrary value).

We could precisely compute some risks in terms of potentially insufficient reserves for the different countries, but this would require estimating the degree of prudence of current mortality rates for each table. We rather do such an analysis below for the sole case of France, in presence of extreme longevity scenarios.

Dealing with the risk of extreme longevity

Longevity risk with regards to other scenarios of future longevity

Figure 3 focused on comparing commonly used assumptions with linear increases of life expectancy. There are however obviously a whole range of possible scenarios of future life expectancy as

highlighted in Figure 8. It illustrates that trends of commonly used actuarial assumptions are actually not so different from linear extrapolations of life expectancy when compared with very different potential trends.

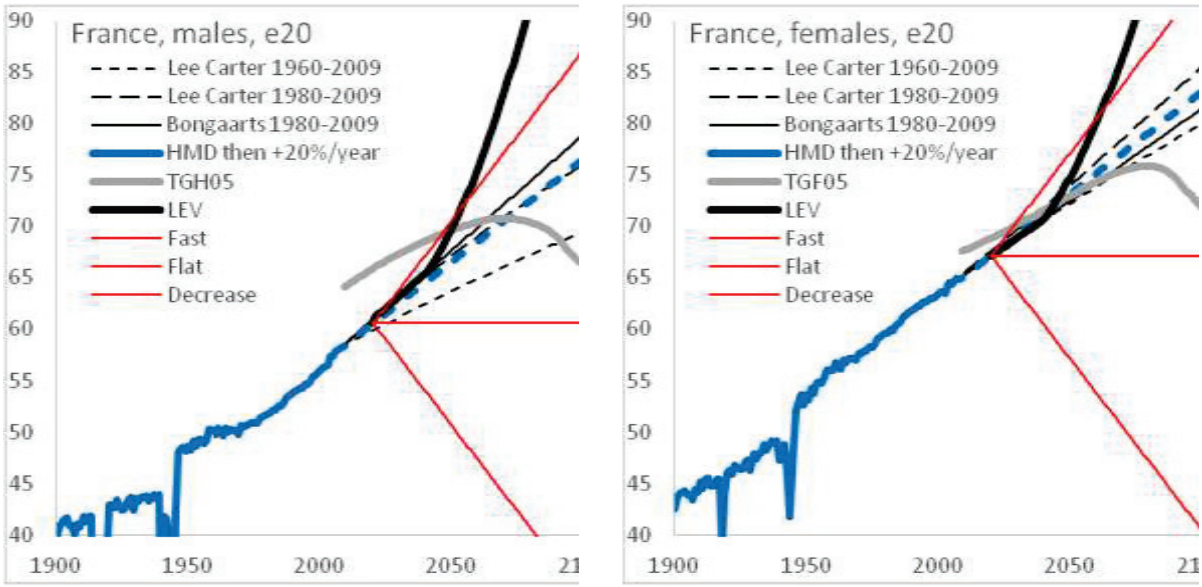

Figure 8. Historical as well as projected life expectancy at age 20 for French males (left) and females (right). It includes contents from Figure 2 *i.e.* historical values and Best Practice Trend ("+20%/year", thick line), regulatory prospective tables (here TGH/F05, gray decelerating thick line), Lee Carter models (dashed lines) and Bongaarts model (solid line close to "+20%/year). It also represents more extreme scenarios: a decrease of life expectancy at the pace of 4 months per year ("Decrease", decreasing straight line), a stable life expectancy ("Flat", horizontal line), an increase of life expectancy at the pace of 4 months per year ("Fast", increasing straight line), and an accelerating life expectancy ("LEV" for Longevity Escape Velocity, thick black line).

In order to compute corresponding financial risk estimates we not only need to deal with longevity trends but also with the initial mortality level of actuarial tables. As a working hypothesis we consider that the [period] life expectancy at age 65 produced by actuarial tables in 2015, $e_{65,2015}$ is exact. In terms of trends for insured populations, we use the models we derived from the Bongaarts model and we adjust their mortality level (parameters 'A' in section 2) to match the $e_{65,2015}$ of the table. The indicator of longevity risk is then the percentage of reserves that should be added if reserves were computed with that adjusted model instead of the actuarial table: $\frac{\ddot{a}^{t}_{65(BPT)}}{\ddot{a}^{t}_{65(table)}} - 1$, in absence of interest rate and inflation risk. The results are shown in Table 2. Of course, the effect is more important in a long interest rate context and financial risks are important factors that we do not consider here.

For people aged 65	In 2015		In 2025	
Trend/ Scenario	Males	Females	Males	Females
LEV	+4.3%	+6.5%	+13.6%	+9.8%
Fast	+3.6%	+5.4%	+7.7%	+6.2%
Bongaarts	+1.9%	+1.4%	+4.0%	-6.0%
Best Practice Trend	+0.6%	+2.5%	+0.7%	-1.5%
Actuarial Table	0%	0%	0%	0%
Flat	-8.0%	-7.5%	-8.1%	-11.1%
Decrease	-18.7%	-19.5%	-18.9%	-22.7%

Table 2. Impact on reserves when modifying the trend of existing actuarial tables

Table 2 gives an order of magnitude of the financial risk. In practice the true financial risk might not be well characterized by a single number. If the present value of losses compared to existing reserves were considered for a current portfolio it could be greater or lower depending on the considered retirement system and therefore ages to be considered, on absorption mechanisms, and in particular on the presence of guaranteed tables or not (the latter being obviously problematic if scenarios like Fast or LEV were to take place in the future). Besides such important considerations, Table 2 reveals that if life expectancy increased at the same rate as in the past the financial impact would be moderate (less than 2% impact on reserves for people aged 65 in 2015) and that more diverse scenarios can have more severe impacts. Regarding the Fast and LEV scenarios, the impacts are much stronger ten years ahead than today.

It is certainly easier for retirement systems to adapt to lower than to higher life expectancy than planned. Therefore, high life expectancy scenarios such as the “Fast” and “LEV” scenarios should be considered with care, especially as they differ from currently used tables or even from the Best Practice Trend in a substantial manner: if they were credible then it would be adequate that the long term nature of retirement liabilities leads society to preemptively build solutions to face such scenarios in a serene manner. On the other hand, using them blindly could lead to inappropriate conclusion regarding pension funds solvency. As an attempt to help judge the credibility of such scenarios, given that LEV scenarios are mentioned by bio gerontologists and given that bio gerontologists and actuarial scientists do not generally naturally work together, we further try to gather and investigate concrete advances in biogerontology.

How serious is biogerontology about strong life extensions?

Biogerontology can be defined as the science that studies aging from a biological perspective. The following text attempts to briefly gather biomedical advances and views that can be found in biogerontology circles such as in the specialized mailing-list Gerontology Research Group or the International Longevity Alliance (group of biogerontology associations from more than 50 countries).

First, as an attempt to briefly explain views, increasing in life expectancy can be schematized in two phases. The first phase has mostly dealt with microbes and the second phase deals with biological aging.

i) The action of Louis Pasteur is typical of the first phase: convincing the world that microbes are everywhere, even if invisible, and that they can be avoided or treated through various techniques.

Some of those techniques are hygiene (e.g.: boiling water, washing hands, the development of refrigerators and cold chains), vaccines and antibiotics. As noted by Vaupel (2010) such techniques have contributed to a drop of infant and young adult mortality rates.

ii) Currently biomedical actions of society are typical of the second phase: convincing the world that the pathologies that we get as we grow older can be avoided and treated, at least to some extent, through various techniques. This includes advances against cancer, cardiovascular diseases, stroke, and dementia. It goes beyond as the increased rate of such diseases with age as when as frailty is believed to set from common processes and accumulation of deteriorations that can be mitigated with lifestyles including regular physical activity, drugs, genetic therapies and regenerative medicine. It is believed that the unprecedented awareness about the topic, exploration of first results, increased communication across researchers and the rapid development of stem cell, organ generation, health information technology and other technologies will help lead to a drop of mortality rates at late adulthood within a few decades.

Secondly, here are some concrete results to help judge current progress.

Due to one gene change, some naturally-dwarf mice ('Ames dwarf mice') were found to live about 50% longer than their siblings and their lifespan is further increased with some specific lifestyle known as 'caloric restriction' (Bartke, 2008). **Equivalently mutated people are naturally found, known as 'Laron dwarfs'**, who seem to be resistant to diabetes and cancer; they are generally rejected from society which so far doesn't allow to possibly measure longer lives (Guevara-Aguirre, 2011). It has not yet been tested whether performing the mutation once mice are adults extends their lifespan; if so, human applications would possibly not be far.

Several human drugs were showed to prolong the life – and healthy life – of adult mice by 6% to 26% when given chronically and at low doses; such as aspirin (Strong 2008), metformin (Martin-Montalvo, 2013), rapamycin (Harrison 2009, Ye 2013). The latter has included successful results when starting at a late age and a projects are starting to test rapamycin versus placebo in dogs and various companion animals (Check Hayden 2014, Kaeberlein 2015). Since people generally do not currently take treatments when not ill equivalent results are difficult to find in existing human data. However, some relatively close circumstances indicate that those drugs – low dose aspirin (Cuzick 2014), metformin (Bannister 2014), rapamycin (has since become a first-line treatment in oncology), everolimus (Mannick JB 2014) – are also generally beneficial with respect to human health as we grow older. In 2015, a clinical trial is started to test on one thousand non-diabetic people whether metformin is globally beneficial (TAME study, Albert Einstein College of Medicine).

As gene therapy in adult individuals starts to become safe, and possibly have better benefit-risk balances than drugs, a 'telomerase' gene therapy was performed in adult mice and increased their lifespan by 13% to 24% depending on the age at start (Bernardes de Jesus 2012). In April 2015, in a Mexican hospital and a Colombian hospital, renowned scientists of that field have started to commercialize a similar human 'telomerase' gene therapy as well as another gene therapy that helps, according to them, muscles grow in spite of advancing in age (Mitteldorf, 2015). One of those scientists has tested the latter on himself in 2010.

Non-drug, non-genetic interventions are being put in place too. Recently, a renowned scientist published that he grew a new thymus on himself, after the method was developed in rats and for

AIDS patients (Fahy, 2003). The thymus is an organ that develops our immune system and that shrinks at adulthood. A company, Intervene Immune, has since been started to treat other persons similarly, the hope being to typically better protect from viruses and cancer.

On the quest to tackle underlying joint solutions to age-related frailty and various age-related diseases, progress is moving from small-scale companies to pharmaceutical companies such as the Calico company created by Google, Human Longevity, Navitor Pharmaceuticals or others (McGreevey 2015). Attempts are being done to officially define aging as a disease in order for such research to find corresponding funds for the pharmaceutical industry and for treatments to be covered by health insurance (Hayden 2015, Zhavoronkov and Bhullar 2015, Bulterijs *et al.* 2015, Gems 2013).

At the individual level forecasts are not to increase long term needs but rather to help the body repair, regrow, restore and maintain vitality; at collective level consequences are debated such as risks of overpopulation or unequal access to corresponding healthcare (Alexandre 2011, Coeurnelle 2013). As a result, for both technological and social reasons it is difficult to judge in what timeframe results would extend the lifespan of populations. They seem however sufficiently massive by people in the field to be more important than the forces that would instead tend to decelerate longevity, and to be worth communicating to actuaries that a best estimate scenario could rather be that life expectancy accelerates in the future.

We shall remind that considering such views is important for retirement systems in the sense that it allows to prepare for such cases but that various other views exist including the possibility to reach a maximum life expectancy ceiling or even to see life expectancy decrease (Aubert *et al.*, 2010; Cambois *et al.*, 2010; Debonneuil *et al.* 2011).

How do governments position themselves?

The authors of this paper live in France and have therefore searched for assumptions used by French public authorities. The longevity trends used by French public instances (the “Conseil d’Orientation des Retraites”, COR) to define adjustments in the public retirement systems are significantly lower than the standard French actuarial tables TGH TGF 2005 (Table 3).

Example: France	e60,2010		e60,2060		Difference	
	Males	Females	Males	Females	Males	Females
LC 1980-2009	22.6	27.6	31.0	37.5	8.4	9.9
Best Practice Trend	21.5	27.0	29.8	36.3	**8.3**	**9.3**
TGH TGF 2005	25.8	29.1	32.3	35.6	**6.5**	**6.5**
LC 1960-2009	22.5	27.5	27.7	35.0	5.2	7.5
COR	22.2	27.2	28.0	32.3	**5.8**	**5.1**
LC 1960-1989	21.1	27.1	26.1	32.3	5.0	5.2

Table 3. Life expectancy at age 60 and its increase between 2010 and 2060 according to assumptions used by the Conseil d’Orientation des Retraites (COR) (COR, 2013) and according to other assumptions in France (Lee-Carter model fitted on different periods, regulatory tables for insured TGH TGF 2005 and Best Practice Trend model). The increase in life expectancy of the COR assumption is in particular significantly lower than that of the regulatory tables (last 2 columns).

We have not investigated if government instances of other countries also use assumptions that have lower life expectancy trends than the country-specific commonly used actuarial tables. Certainly,

dealing with complex social systems adjustments (such as pressure not to increase retirement age by much) makes it difficult to take prudent assumptions. This is in fact a sensitive political issue, where myopic view often favors short-term effects and postpones discussions about inter-generational risk transfers.

More prudent tables to envision solutions

Mortality projections are elements that help adjust retirement systems. Mentioning more prudent mortality assumptions, such as using the Best Practice Trend, the "Fast" or the "LEV" scenarios at least to envision the behavior of existing systems, may help be aware of non-decelerating life expectancy potentials impacts, and not think that volatility is limited to the one of the noise in Lee-Carter type models. Typically it may further reduce the use of guaranteed tables may. It may also help consider structural changes that may be globally better in a vast range of future scenarios.

For example, it may be possible to apply methods on such scenarios that statistically detect that mortality rates do not follow expectations (see Croix *et al.* 2015 and El Karoui, Loisel and Salhi 2015) of new trends and to estimate how longevity risk was mitigated if then retirement age was increased at a given realistic pace. If longevity risk was not mitigated enough, then retirement age should be preemptively increased. The latter was already suggested without such technique (Zhavoronkov *et al.*, 2012; Zhavoronkov, 2013). Such approaches could now help build quantified analysis for more concrete discussions.

A general increase of retirement age is of course only one of many levers. Using such scenarios may help study other approaches. While presenting perspectives of linear increases in life expectancy, James Vaupel for example used such perspectives to estimate that working less per week in exchange of working more years might be some appealing solution (Vaupel, 2010).

Not all boils down to actuarial assumptions. In the latter investigation, working less per week may for example mean working one day less per week, earn less as well and be encouraged to use the extra day for familial activities (taking care of children or parents) or new economic activities but it may as well lead to distortions of competitions and relocation of businesses. However, citizen behaviors may also be studied based on similar situations (Forget, 2011). In contrast, today's longevity-decelerating scenarios seem unlikely to help be ready in case of accelerations of life expectancy.

Financial hedges to help mitigate longevity risk

In addition to reviewing the sufficiency of commonly used actuarial tables much literature suggests that governments establish solutions to hedge longevity risk (Antolin and Blommestein 2007, Antolin and Mosher 2014, Blake et a. 2014).

Substantial work has been produced to price longevity risk and to propose financial tools such as bonds and swaps to transfer the risk to specific stakeholders or even capital markets (Barrieu *et al.* 2012, Bauer *et al.* 2010, Barbarin 2008, Blake *et al.* 2006, Coughlan *et al.* 2011, Hunt and Blake 2015, Kogure and Kurachi 2010, Lane 2011, Ngai and Sherris 2011, Olivieri and Pitacco 2008, Wan and Bertschi 2015).

Some natural hedge may be found by associating longevity risk with mortality risk. Product design (Richter A and Weber 2011), reverse mortgages (Wang *et al.* 2011) and protection insurance (Cox and Lin, 2007) may provide some longevity hedge. The natural hedge remains however partial (Zhu and Bauer 2014).

There might be opportunities to invest in assets that are very different from mortgages or insurance and that make profits with longevity increases. If biogerontology scenarios investigated here can happen, it might be better for retirement funds to invest into such developments and manage longevity profits rather than suffer from such scenarios (Fagnan *et al.* 2013, Fernandez *et al.* 2012, MacMinn *et al.* 2015, Yang *et al.* 2016).

Discussion

We have highlighted that commonly used actuarial assumptions tend to produce life expectancy deceleration and found underlying mathematical explanations as well as elements that suggest that governments may be unwilling to consider non-decelerating longevity assumptions, thereby putting retirement systems at risk.

We have developed some models that produce non-decelerating life expectancies. With the increasing prospects of strong increases in human lifespan, for example through the arguably promising field of biogerontology, such models may help be prepared in case biogerontology promises come true. Considering advances in biogerontology and associated scenarios may help find solutions; detecting changes early enough to act or even investing into biogerontology companies might even be parts of solutions, even if it necessarily takes very long, often too long before one may react on a firm statistical background.

In a few decades, it may well be that a pandemic, resistance to antibiotics, a war, social instability or individuals preferring a reasonably long, happy life to a very long life with a lot of invasive monitoring, or some other event, causes longevity improvements to decline or vanish, and that our descendants laugh at us and at our crazy concerns about longevity risk.

It might also happen that longevity improvements develop further, and that biogerontology science finally impacts strongly life expectancy. In that case, our descendants would blame us for not anticipating this scenario early enough, and according to the most optimistic gerontologists, we might even sit in the court in person if we are still alive then!

There is currently no evidence that this science will produce results in the near future. The authors of this paper have different views, either believing in longevity acceleration and deceleration. However, the authors share the conclusion that the different scenarios should be presented and considered by decision makers, like climate change scenarios investigated by GIEC.

It would be inappropriate and impossible to adopt the LEV scenario as the new best estimate oof course. But it is important to make governments, politicians and risk managers of insurance companies, pension funds, reinsurance companies and banks aware that the uncertainty on future longevity developments is much greater than the volatility accounted for in the Lee-Carter model and its subsequently developed models. Understanding and managing this risk requires an interdisciplinary approach.

Given the potential size of the risk we support the conclusion of Antolin and Mosher (2014), who suggest that governments further investigate how to make retirement systems resilient to such scenarios.

Acknowledgement

We thank Alexander Zhavoronkov for discussions on refreshing solutions for retirement systems. We are grateful to active leading members of the International Longevity Alliance for having reviewed the section on biology of aging: Didier Coeurnelle, Anton Kulaga, Daria Khaltourina, Elena Milova, Liz Parrish, Avi Roy, Paul Spiegel, Daniel Wuttke.

Acknowledgment. This work benefited from the financial support of the ANR project “LoLitA" (ANR-13-BS01-0011), research chair "Management de la modélisation" sponsored by Cardif, and research chair "Actuariat Durable" sponsored by Milliman Paris.

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ANNEXE 4. ARTICLE: EVALUATING THE IMPACT OF RECENT ADVANCES IN BIOMEDICAL SCIENCES AND THE POSSIBLE MORTALITY DECREASES ON THE FUTURE OF HEALTH CARE AND SOCIAL SECURITY IN THE UNITED STATES

Zhavoronkov, A., Debonneuil, E., Mirza, N., & Artyuhov, I. (2012). Evaluating the impact of recent advances in biomedical sciences and the possible mortality decreases on the future of health care and Social Security in the United States. Pensions: An International Journal, 17(4), 241-251.

ABSTRACT

Social Security and Medicare programs are contributing to the rapidly increasing public debt and continuous budget deficits. The extent of the fiscal imbalance attributed to these programs may substantially exceed the forecasts of the Social Security Administration (SSA) and the most aggressive projections of other organizations. The many advances in biomedical sciences may significantly extend the longevity of the aging population that will by far outpace the planned increases in the retirement age. In this article, we evaluate three hypothetical scenarios where all other factors affecting the demographic distribution remain unchanged, but the mortality rates are decreased taking into consideration the progress in science and technology. Our estimates reveal that if deaths caused by cardiovascular diseases and cancer are eliminated, the fiscal imbalance may be as high as USD 87 trillion in present value. Given the current pace of biological innovations, the likelihood of elimination of those diseases is not improbable, and if that happens the welfare programs may no longer be sustainable. We propose that the forecasting methods of fiscal imbalance should incorporate the progress in medical sciences. The US and other governments may consider proactively increasing the retirement age and accelerating research in biomedical sciences with the goal to extend healthy working life span to keep pace with the decreases in mortality.

Keywords: longevity mortality life expectancy

INTRODUCTION

The structural imbalance of Social Security and Medicare programs

Social Security provides enrollers, their spouses and, in some instances, their child dependants retirement and disability insurance, as well as other benefits. Primarily, however, Social Security provides a fundamental source of income to retirees and it has played a significant role in the reduction of elderly poverty within the country (see Engelhardt and Gruber (2004)). Social Security is primarily financed through payroll taxes contributed by both employers and employees. After a number of years, participants who are fully insured are legally entitled to the proceeds of the funds to which they and their employers have funded. Practically, individuals are eligible to receive Social Security funds after 40 calendar quarters (see Gokhale and Smetters (2005)).

Although the program is a hugely important safety net for Americans, the financial future of US Social Security and Medicare programs is subject to serious issues that could ultimately lead to the insolvency of the Social Security Fund. The Social Security

Administration (SSA)'s trustee report (2012) noted that actuarial deficits of Social Security and Medicare programs substantially increased in 2012 and attributed this deficit increase to the possible increase in Medicare costs, coupled with changes in Social Security, resulting from decreased payroll tax revenue. The SSA raised serious concerns that Social Security and Medicare programs, which accounted for approximately 36 per cent of the 2011 federal expenditure, are likely unsustainable under prevailing financial conditions and legislative policies. Similar concerns have been extensively discussed by Brown *et al*. (2011), Kotlikoff (2006), and Gokhale and Smetters (2003 and 2005) among many others.

The receipts-expenditure imbalances of the Social Security program primarily occur because of the dramatic demographic changes engendered by the retiring Baby Boomer population. Over the next 50 years, a significant portion of this population will be entitled to collect benefits, which will increase the dependency ratio. Although this generation significantly contributed to the labor force, their retirement will drastically decrease the revenue available to provide payouts. Subsequently, the taxpaying base will drastically dwindle upon Baby Boomer retirement.

The equation goes far beyond the Baby Boomer phenomenon. Indeed, biomedical advances have significantly reduced mortality rates, and over the last 50 years life expectancy has increased by more than 10 years. However, retirement age has not changed much: the consequence is a strong imbalance from longer retirements.

In addition, and possibly in line with the reduced mortality rates, global fertility decreased from five to two and a half children per female (see Bloom *et al.* (2011)). This has strong implications for Social Security as the present social structure is based on a generational framework in which individuals' payroll taxes are used to pay for retirees' benefits.

Last but not least, and again probably in line with longer lives, the length of education has increased, as well as the average age to enter workforce (see Fullerton (1997)). Therefore, improved longevity – the direct result of innovative medical sciences – and other elements that to a large extent are probably a consequence of improved longevity have generated this difficult situation: too few citizens providing receipts during too little time and too many citizens generating expenditures during increasing durations.

Assessing the current state of Social Security

When Social Security was enacted in 1935, this development was not anticipated. At present, the current SSA trustee report (2012), coupled with some earlier findings by Gokhale and Smetters (2003 and 2005), provides evidence on the state of imbalance of Social Security and Medicare programs. Figure 1 shows the increasing trend in historical and projected Social Security and Medicare expenses as percentage of GDP.

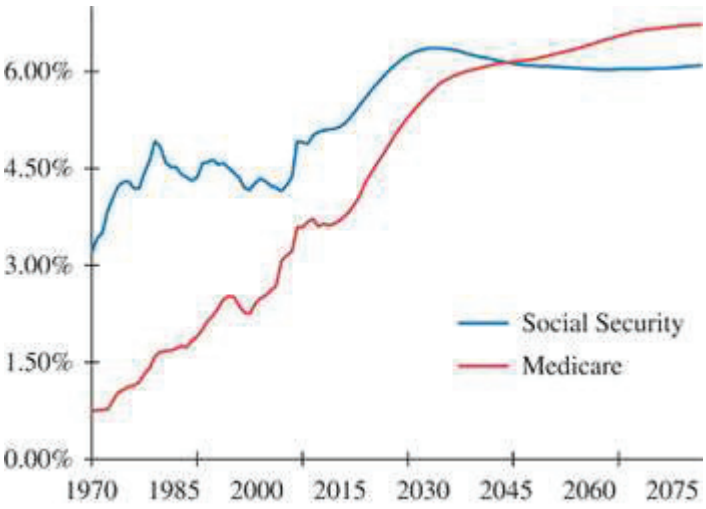

Figure 1. Social Security and Medicare cost (as a percentage of GDP) (1970–2086). Source: SSA Trustee Report (2012).

One solution is to increase receipts. The SSA expects this percentage of GDP to normalize at least by mid-century; given the current state of economic and political affairs, the additional burden of this imbalance will be borne by the working generation.

However, in this article, we propose that greater consideration and changes are needed to address the situation before deficits start to triple. Indeed, most of the actuarial assumptions related to costs and revenues for Social Security and Medicare programs are based on population growth using historical trends. These projections might be seriously flawed as developments in the medical and health sciences, especially in the mid- to late twentieth century, have started to increase longevity past retirement age, faster than in the past. This trend is likely to continue in the future with further advancement in the biological sciences, which will likely create a significant variance between population projections and actual beneficiaries in the future. The 2011 SSA projections expected the Trust Fund to be depleted by 2036; however, after accounting for actual beneficiaries in 2012, that same trust fund is now expected to be depleted in 2033: simple extrapolations of the past do not seem to be sufficient.

Recent biomedical advances and declining mortality rates

Much of the world's breakthroughs in science and technology that led to the advent of the digital age and globalization occurred in the second half of the twentieth century. The most notable technological advances such as portable electronics and the Internet were widely adopted in the past two decades. Biomedical sciences largely benefit from such advances: research articles accessible to a few on paper are being replaced by online articles accessible to everyone. Research and clinical practice is now communicated and coordinated via online papers, emails, forums, at an unprecedented speed. As a result, there has been considerable progress in biomedical sciences with advances in advanced biomaterials, diagnostics methods, cell, tissue and organ engineering and regeneration, genomics, proteomics and bioinformatics.

We are only starting to see concrete applications because the road to market is much more difficult for biomedical technologies than it is for computer science because they require rigorous validation via the heavily regulated medical industry. Consequently, many of the recent technologies that possess the potential to significantly extend healthy life spans remain at the laboratory level. However, with the help of aging populations in particular, the amount of funding in the biomedical sciences has been increasing at an unprecedented rate.

Figure 2 illustrates well the rate at which knowledge and funding in biomedical sciences is progressing. It is reasonable to expect that these investments will yield longevity dividends in the form of decreases in mortality and increases in healthy life spans in the near future.

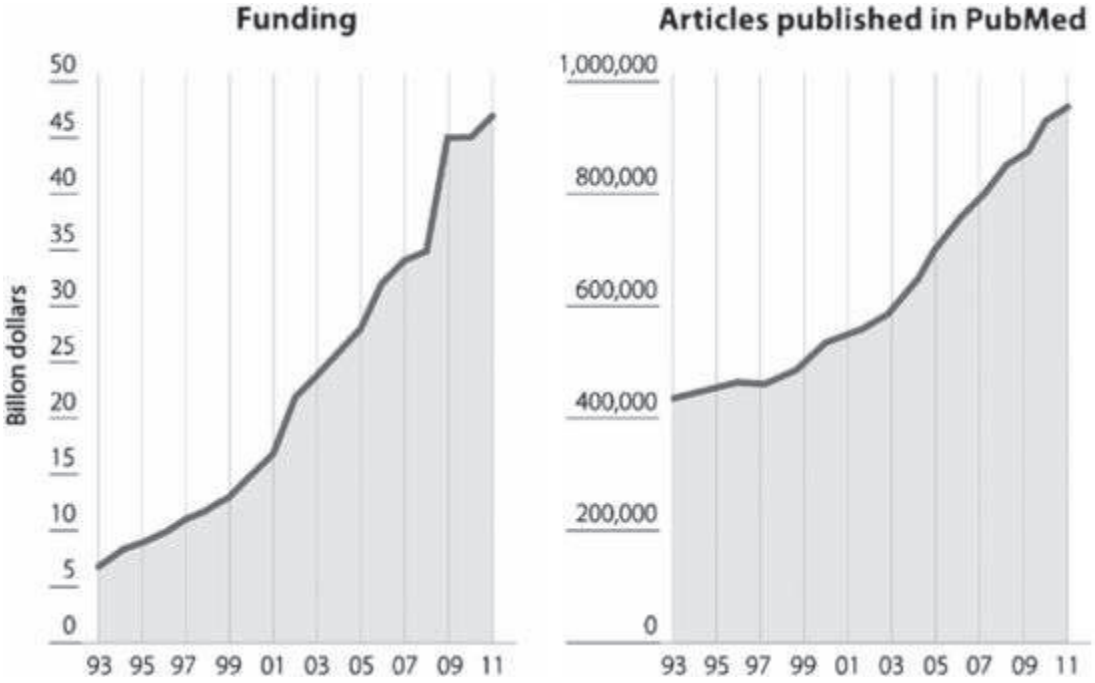

Figure 2. Increases in government funding and research articles 1993–2011.Source: These calculations were made using the International Aging Research Portfolio. 9 They include NIH, NSF, European Commission, CIHR IRSC Canada and AHR Australia grant data on biomedical sciences.

Some life-extending technologies are already in or nearing mainstream clinical use. Statins, beta-blockers, vasodilators and other pharmaceuticals that significantly extend the survival of patients with cardiovascular conditions became blockbuster drugs with tens of billions of dollars in revenue. The mainstream clinical use of many of these drugs and procedures started less than three decades ago and focused on treating the patient. The focus on patients is a natural starting point, to make health technologies marketable. However, the greater effect is likely to come, when those technologies will be used to prevent the development of the medical condition, before symptoms become troublesome (Table 1).

Survival Time	***Survival rate (%) by year***						
	1975–1979	***1990***	***2000***	***2005***	***2006***	***2007***	***2008***
1-year	69.9	75.6	79.5	80.7	81.3	81.6	81.8
2-year	60.1	67.1	73	74.4	75.4	75.7	—
3-year	55	62.7	69.7	71.2	72.2	—	—
4-year	51.6	59.8	67.6	69.2	—	—	—
5-year	49.1	57.9	66.1	—	—	—	—
6-year	47.2	56.2	64.9	—	—	—	—
7-year	45.5	54.7	63.8	—	—	—	—

Survival Time	*Survival rate (%) by year*						
	1975–1979	*1990*	*2000*	*2005*	*2006*	*2007*	*2008*
8-year	44.2	53.5	62.8	—	—	—	—
9-year	43	52.4	62	—	—	—	—
10-year	41.9	51.4	—	—	—	—	—

Table 1. Relative survival (per cent) by the year of diagnosis (all cancer sites, all races, males and females) in the United States (1975–2008). Cited from the National Cancer Institute's SEER Cancer Statistics Review 1975–2009.

At present, owing to the relatively short time that such novel drugs and treatments have been available, and because they are still primarily targeted to people with serious health conditions, the effects on life expectancy and demography in general are not yet quantifiable. Consequently, it may take another decade for the longevity revolution to set new standards in life expectancy planning. However, the analogy with strong investments for faster computer chips might become better every year. Indeed, many more potent life-extending technologies are being developed in the R&D arena that require investments to go through validating procedures and reach general population health. The strong pressure of aging populations is likely to provide the required investments and to lead to shorter paths towards marketability.

In this article, we argue that because of increases in the biomedical sciences, and consequently, human longevity, we should expect a significantly higher proportion of aging citizens, which will likely produce additional severe burdens to dwindling funding for Social Security and Medicare programs. The next section will highlight the methodology we will employ to ascertain population projections and provide estimation for the requisite revenue levels to pay out benefits. The subsequent section will provide a discussion of our findings. Summarily, the last section will provide concluding remarks.

METHODOLOGY

Population projections

For the sake of clarity, we will define three simple mortality scenarios in the future, and will keep other assumptions such as fertility and immigration unchanged across the three scenarios. As mentioned in the introduction, increased longevity would actually reinforce the imbalance indirectly, but some associated decisions would be undertaken as a consequence: instead of modeling such details, we will take three clear different scenarios. Depending on what associated actions may be undertaken in the future, the results of the scenarios could be revised up or down.

Our first scenario is a simple extrapolation of the past, where the speed of hygiene and curative medical improvements remain the same as the past despite the unprecedented rate of discoveries of the last decades that are for many still in the lab. We model it with a Lee-Carter model (1992), where the exponential decrease of mortality rates for any given age continues at the same pace: 'mortality improvements of the past remain the same in the future'. We fit the improvement rates for males and for females aged 20 to 100 from 1951 to 2007, based on general US population data extracted from the Human Mortality Database (HMD), and apply them up to 2080.

In the second scenario, we assume that in the period from 2013 to 2030, there would be a decrease in the overall mortality rate by 50 per cent, following a considerable reduction in the risk of most common cardiovascular diseases and some other common ailments.

To be clear, the quantification of impacts on mortality by some specific biomedical progress is still more art than science. Owing to co-morbidity and disease interactions, some models predict that the elimination of mortality from heart disease could increase life expectancy by 7.5 years (see Somerville and Francombe (2005)). Therefore, the calibration of scenario 2 comes from a more global appreciation: a division of mortality rates by two corresponds to an increase of life expectancy by 8 years, or to biomedical improvements of slightly less than four decades so far. The next paragraph gives examples of ongoing biomedical breakthroughs, and we will let the reader judge whether this is sufficiently exceptional in terms of probable impacts to represent in itself several decades of past progress.

Thus, here are examples that may correspond to scenario 2. In a strong technological form, scenario 2 may result from current developments in the growing of vessels and tissue engineering, and the reprogramming of cells after infarction scar formation in full cardiac muscle cells. This would have been science fiction 10 years ago but we now see the first applications in the clinics. Apparently less exceptional but far from insignificant, scenario 2 may also correspond to the application of current life-extending drugs to secondary prevention, instead of limiting the use to patients. That is an ongoing path with the generalization of the use of vasodilators and beta-blockers following light cardiovascular symptoms; or the use of metformin in low educated populations at risk of diabetes. In its much wider form, the concept becomes one of a cheap polypill for anyone aged 55 and above: small doses of medications to reduce blood pressure, blood glucose and LDL cholesterol. Such a strategy was predicted to reduce cardiovascular disease by more than 80 per cent (see Wald and Law (2003)) and some of the first implementations so far confirm the predictions (see Sanz and Fuster (2009), Zeymer *et al.* (2011), Wald *et al.* (2012)).

In scenario 3, we assume that during 2013-2030, the mortality rate will be reduced by 80 per cent. This corresponds to an increase of life expectancy of 18 years and could typically occur with drugs that slow aging (see Martin *et al.* (2003)), although targeting diseases does not necessarily lead to slowing aging.

Here are some concrete examples in the form of a 10-year retrospective synthesis. We start with the worm *C elegans* because, owing to fast life span screenings, it has generated numerous guiding results that apply to mice and humans. Life extension is found to be so plastic that even randomly silencing genes can significantly extend life span; in 2005, 89 such genes are counted (see Hamilton *et al.* (2005)). Some genes are studied and greater life extensions are observed – up to 10-fold (see Ayyadevara *et al.* (2008)). In mice that are also mammals, lifespan can be doubled by a mix of gene change and diet restriction (see Bartke and Brown-Borg (2004)). And some long-lived human families are found to naturally have some gene mutations (in genes called 'FOXO3A', 'IGF-1', 'AKT') that were previously shown to extend the life span of mice (see Kenyon (2010)). A large focus is now on drugs, with a starting point in already approved drugs. In 2009, the drug rapamycin was found to increase the life span of mice even when started late in life (see Harrison *et al.* (2009)). That drug was approved for cancer and other conditions and is widely used in clinical practice. It might be that taking the drug would prolong human life span by 10-30 years, but it has many side effects 'meanwhile' and in the end it might also be that it does not prolong life span. Other drugs with very little side effects are very promising and are being tested in various ways. Metformin, the widely used, cheap, anti-diabetic drug, showed promising results in cancer and cardiovascular prevention. Here, we find that scenarios 2 and 3 overlap when considering the assessment of the long-term-health impact of existing drugs (see Debonneuil (2012)). Scenario 3 may also correspond to more disruptive impacts from regenerative medicine and tissue engineering in particular.

For the purpose of our estimation, all three scenarios come with complementary assumptions: the birth rate was assumed to be proportional to the total number of women aged between 20 and 45 years where the coefficient of proportionality is taken to the ratio in 2007. Furthermore, we assumed that migration stabilized at the level of a million people a year, causing sex and age structure not to likely differ from that of the general population. The algorithm for the population estimation is reported in Appendix.

Estimation of benefits and revenues

We model SSA-based fiscal imbalance as simply the difference between government revenue and expenses related to both Social Security and Medicare programs. The differentiating point between our estimates and those of the SSA (and previously reported in the literature) will be the impact of the aging population with a higher life expectancy and increased health-care costs. Mathematically, the imbalance between receipts and benefits will be represented as:

$$PV(\text{Fiscal Imbalance}) = PV(\text{Benefits}) - PV(\text{Receipts})$$

The present value (PV) of benefits is expected to be greater than the present value of revenues, causing a deficit in already costly and increasingly underfunded Social Security and Medicare programs. Therefore, it is only logical that sweeping policy changes must be made in order to engender the sustainability of these important programs.

In order to estimate this imbalance, we adapt the two population cohorts used and reported by the SSA in their trustee report; these are 20–65 years for the working population, and 65 and older for the beneficiaries. Our projections for these cohorts are a function of an increase in longevity adjusted on a yearly basis. Consequently, we adjust benefits and receipts for Social Security and Medicare programs. The benefits are based on outlays for Social Security and Medicare. The Social Security expenses are calculated for the segment receiving the benefits after the age of 65. The expenses are adjusted for those members of the population who will retire before regular FRA. Medicare expenses will accommodate for both Part A and Part B Medicare facilities. Similarly, the receipts for Social Security are calculated by simply taking the contribution of the working population from payroll taxes and any income taxes paid by the Social Security beneficiaries, Medicare receipts, taxes on benefits, premiums, general revenue and state transfer and drug fees. All estimates for receipts and benefits are extracted from the SSA's website, and we simply adjust for our population projections.

FINDINGS AND DISCUSSION

Size of the imbalance

The decade-long comparative population projections based on our three scenarios and the SSA Trustees Report (2012) are reported in Table 2.

Year	*SSA Trustee Report*		*Scenario 1 (Lee-Carter)*		*Scenario 2 (−50%)*		*Scenario 3 (−80%)*	
	20–64	*65+*	*20–64*	*65+*	*20–64*	*65+*	*20–64*	*65+*
2013	192.68	44.79	188.21	43.58	188.21	43.58	188.21	43.58
2020	198.20	55.64	191.54	54.87	191.84	55.86	192.03	56.47
2030	202.78	72.75	192.92	73.92	194.48	82.42	195.43	88.70
2040	213.34	80.01	198.91	84.02	201.24	102.08	202.64	117.72

Year	*SSA Trustee Report*		*Scenario 1 (Lee-Carter)*		*Scenario 2 (–50%)*		*Scenario 3 (–80%)*	
	20–64	*65+*	*20–64*	*65+*	*20–64*	*65+*	*20–64*	*65+*
2050	224.29	83.81	205.08	89.57	207.57	113.26	209.01	135.97
2060	232.47	90.30	210.43	95.01	212.74	119.81	213.97	144.41
2070	242.38	97.10	218.33	99.66	220.42	124.14	221.44	147.79
2080	251.87	104.15	224.31	106.73	226.07	131.45	226.81	155.20

Table 2. Comparative population projections in age cohorts (in millions). Source: SSA Trustee Report 2012 (intermediate assumptions) and authors' estimations.

Under scenario 1, the total population is approximately 429 million[1] by 2080, of which 106 million (~25 per cent) are aged 65 or older, and 224 million will be of working age. The SSA estimates for intermediate assumptions project that the working population will increase to 251 million, while beneficiaries will be approximately 104 million. In scenario 1, throughout the projection period, our estimates for beneficiaries are similar to those of SSA estimates; however, we observe a variance within working population. This variance will result in a reduction in estimated receipts *vis-à-vis* the SSA, for Social Security and Medicare, mainly via payroll taxes, which will result in a relatively larger imbalance for these two programs.

In scenario 2, the general population shows a rather moderate increase (~456 million by 2080, against the ~429 million in the baseline scenario). There is almost no change in the number of affected children and teenagers (up to 19 years), and we observe only a slight affect in the major category of workers (20–64 years). This is because mortality rates in the categories are already quite low. Conversely, we project that the number of people of retirement age (65 years and older) will increase significantly to 131 million compared with 106 million in scenario 1, and 104 million for SSA estimates. We project that beneficiaries will account for approximately 29 per cent of the total population by the terminal year. In this scenario, where we expect a 50 per cent decline in mortality owing to the elimination of cardiovascular diseases, we expect a significant increase in unfunded Social Security and Medicare benefits liabilities compared with what is currently anticipated and reported in the recent SSA Trustee Report.

Our third scenario is the worst-case scenario for United States. In this scenario, where we expect mortality to decline by 80 per cent owing to the development of geroprotectors, we expect the total population to grow moderately to 480 million by 2080. As mortality rates within the working population are already low, there is no significant change in our estimates for the working-age group. However, the number of people of retirement age will rise significantly to approximately 155 million, accounting for 32 per cent of the total population. If this scenario prevails, we expect that the provision of these vital public goods programs either will cease or be dramatically undercut.

Timing of the imbalance and aggravating factors

On the basis of SSA and our three scenario population estimates, we project the fiscal imbalance of Medicare and Social Security programs as outlined in section 'Estimation of benefits and revenues'. These comparative figures are presented in Table 3. The SSA reports a surplus of USD 2.8 trillion in 2013 that decreases to a deficit imbalance of USD

[1] For space constraints, we are not reporting year-wise total population estimates and focus on population in two age cohorts. All estimates that are not reported are available on request.

5 trillion (917 billion in present value) by 2080. On the basis of the official estimates, the Social Security program has a surplus of receipts over projected benefits with net present value[2] of USD 9.5 trillion. An important factor in this estimation is the expectation that the trust fund will continue to support the benefits before it is exhausted in 2033. It is important to note that last year, the SSA expected the fund to be exhausted by 2036.

Year	*SSA estimates*		*Scenario 1*		*Scenario 2*		*Scenario 3*	
	Imbalance	*PV imbalance*	*Imbalance*	*PV imbalance*	*Imbalance*	*PV imbalance*	*Imbalance*	*PV imbalance*
2013	−2815.1	−2745.6	−2953.3	−2880.4	−2953.3	−2880.4	−2953.3	−2880.4
2020	−3078.4	−2520.7	−3174.6	−2599.4	−3105.5	−2542.9	−3062.9	−2507.9
2030	−753.5	−480.6	−56.0	−35.7	860.8	549.0	1044.3	666.0
2040	854.6	424.5	1202.5	597.4	1951.8	969.6	2608.2	1295.8
2050	1231.3	476.5	1934.7	748.7	3370.7	1304.3	4765.3	1844.0
2060	1924.9	580.2	2929.3	882.9	5087.2	1533.3	7254.9	2186.7
2070	3078.7	722.8	4346.5	1020.4	7422.6	1742.6	10 435.3	2449.9
2080	5019.1	917.8	7090.2	1296.6	11 622.9	2125.4	16 031.2	2931.6
NPV imbalance		−9556.0		4320.5		36 971.8		66 363.5

Table 3. Comparative imbalance (decade wise and present value) of Social Security benefits and receipts (in billions). For Present Value the discount rate is effective yield on 10-year US Treasury Bonds discounted back to 2012. Negative (positive) number represents Surplus (Deficit) of receipts over benefits. Source: SSA Trustee Report 2012 (intermediate assumptions) and authors' estimations.

The situation is particularly suboptimal when we incorporate population mortality factors to estimate the resulting Social Security imbalance. In the first scenario, we expect an imbalance of USD 4.3 trillion in present value that increases to USD 36.9 trillion if mortality decreases by 50 per cent. Further, if we expect the innovation in medical sciences to reduce mortality by 80 per cent, the deficit in present value will rise to USD 66.4 trillion. We expect the trust fund to be exhausted by 2030, 2029 and 2028 for scenario 1, 2 and 3, respectively. For Medicare (Part A and B), official estimates reveal a net present value imbalance of USD 13.3 trillion, whereas in our base case we expect this deficit to trail around USD 13.8 trillion. In scenario 2, we project the deficit to be USD 17.6 trillion, while in the extreme case of 80 per cent decline in mortality we report an expected net imbalance of USD 22.2 trillion. The Medicare-based comparative imbalances are presented in Table 4.

Year	*Official estimates*		*Scenario 1*		*Scenario 2*		*Scenario 3*	
	Imbalance	*PV imbalance*	*Imbalance*	*PV imbalance*	*Imbalance*	*PV imbalance*	*Imbalance*	*PV imbalance*
2013	−459.0	−447.7	−459.1	−447.8	−459.1	−447.8	−459.1	−447.8
2020	−410.5	−336.1	−407.4	−333.6	−406.5	−332.9	−406.0	−332.4
2030	267.8	170.8	268.5	171.3	293.8	187.4	312.5	199.3

[2] For present value calculation we used effective yield on US Treasury Bonds of various maturities. The results remained similar representing no impact of maturity premium. We are only reporting results for 10-year bond yield discounted back to 2012.

Year	*Official estimates*		*Scenario 1*		*Scenario 2*		*Scenario 3*	
	Imbalance	*PV imbalance*	*Imbalance*	*PV imbalance*	*Imbalance*	*PV imbalance*	*Imbalance*	*PV imbalance*
2040	455.5	226.3	469.2	233.1	555.3	275.9	629.7	312.8
2050	759.3	293.8	789.6	305.6	965.7	373.7	1133.9	438.8
2060	1125.9	339.4	1168.2	352.1	1448.0	436.4	1724.9	519.9
2070	1820.0	427.3	1852.6	434.9	2281.4	535.6	2695.4	632.8
2080	2658.7	486.2	2733.3	499.8	3379.2	618.0	3999.9	731.5
NPV Imbalance		**13 392.0**		**13 875.8**		**17 631.6**		**21 182.3**

Table 4. Comparative imbalance (decade wise and present value) of Medicare benefits and receipts (in billions). For Present Value the discount rate is effective yield on 10-year US Treasury Bonds discounted back to 2012. Negative (positive) number represents Surplus (Deficit) of receipts over benefits. Source*: SSA Trustee Report 2012 (intermediate assumptions) and authors' estimations.*

The total liability for Social Security and Medicare programs is presented in Table 5. The official estimates for these unfunded liabilities remain around USD 3.4 trillion. However, we predict that these liabilities will remain between USD 18.1 trillion and USD 87.5 trillion based on various mortality scenarios. The results for Social Security and Medicare imbalance are not surprising in our scenarios. We observe a larger impact in Social Security as compared with Medicare because Social Security benefits are continuous cash flows that will increase with increases in population that is in retirement age. Conversely, Medicare benefits are paid when they are incurred, and in our extreme scenarios, where we expect a drastic decline in mortality rate due to innovation in clinical knowledge, we should also expect a regressive increase in benefit payments related to Medicare, stemming from the elimination of some common but expensive to treat diseases.

Net present value	*Official estimates*	*Scenario 1*	*Scenario 2*	*Scenario 3*
Social Security	−9556.0	4320.5	36 971.8	66 363.5
Medicare	13 392.0	13 875.8	17 631.6	21 182.3
Total	3836.0	18 196.2	54 603.4	87 545.8

Table 5. Present value of total liabilities from Social Security and Medicare (2012–2080) in billions. For Present Value the discount rate is effective yield on 10-year US Treasury Bonds discounted back to 2012. Negative (positive) number represents Surplus (Deficit) of receipts over benefits. Source: Authors' estimations.

Our results are more alarming than earlier evidence by Gokhale and Smetters (2003 and 2005), and Kotlikoff (2006) who reported likely variance in the financial position of the trust fund and the sustainability of these programs for the public welfare. Gokhale and Smetters (2005) forecasted a fiscal imbalance of USD 65.9 trillion based upon fiscal and generational imbalance. Our prediction on fiscal imbalance only stands at USD 87.1 trillion for the worst-case scenario[3]. None of these earlier studies incorporated the likely

[3] It must be noted that effective yield used by Gokhale and Smetters (2005) was slightly less than the discount rate we have used, so our estimates are more conservative.

scenarios when longevity could increase at a higher pace than is anticipated by SSA population experts owing to dynamic development in the medical sciences.

CONCLUSION

In this article, we interconnect the impact of technological enhancements in the medical sciences on the unfunded liabilities of US Social Security and Medicare programs. We base our findings on three different scenarios that assume varying mortality rates that are linked with the elimination of particularly lethal diseases such as cardiovascular diseases and cancer. If health conditions improve, and these diseases are eliminated Baby Boomers will have a higher longevity and we should expect a fiscal imbalance that can be as high as USD 87.1 trillion in present value. If this occurs, it will raise two questions. First, how can the United States support unfunded liabilities of this scale? Second, will the United States become insolvent if there is a default on these liabilities? Given the present legislation, concerning Social Security and health care, US solvency, and the sustainability of these public programs is critically important but also virtually impossible with the *status quo*.

Currently, there have been no serious efforts to prepare against the mounting deficit. It is imperative that this issue is addressed via drastic changes to the funding and administration of Social Security via the tax code. It seems inevitable that the retirement age must be immediately increased to significantly over 65 years or even 70. In addition, inroads should be made so that Baby Boomers can be reemployed if ideal fiscal conditions are not met and reality dictates that they must return to work.

Some corrective actions are described. Increasing the age of retirement is not a desirable solution from the personal point of view of most workers. But if governments can accelerate the ongoing longevity revolution, shift the priorities to increasing healthy working life span instead of keeping the patient alive for as long as possible in the later years, and simultaneously increase the age of retirement, the benefits will become obvious. Governments, policy organizations and health-care providers should work together to proactively increase the pension age, promote and foster lifelong learning and career planning, accelerate aging research and make preventative and regenerative medicine readily available. Financial institutions and pension funds should incorporate the effects of the recent biomedical breakthroughs into the forecasting models and, in the short term, consider developing financial vehicles to hedge against increases in longevity to maintain solvency until decreases in mortality turn from a source of economic burden to a source of economic growth.

The strong potential deficit of the Social Security and the Medicare should not be ignored and urgent actions should be taken to prevent the coming crisis.

ACKNOWLEDGEMENTS

The authors would like to thank Dr Ayesha Afzal for assistance in preparing the financial model and Hugh Gallagher of Insurope and IEBA and Geoffrey Furlonger of SPARK Pensions and HR consulting for their valuable advice.

APPENDIX

Algorithm

1 The starting values for the population $N_{g,x,t}$ are the values in 2007. The fraction β_g of male to female newborns is calculated using the number of males B_g and females F_g in 2007.

2 The central mortality rate $m_{x,t}{}^{g}$ is calculated using a Lee-Carter model: $\log m_{x,t}^{g} = \alpha_x^g + \lambda_x^g \cdot t$

It is transformed into an annual mortality rate with the formula $q_{x,t}{}^{g}$=1-exp($m_{x,t}{}^{g}$) In scenarios where mortality is reduced with a coefficient **k**, $q_{x,t}{}^{g}$ is further multiplied by (1−*k*).

3 The population exposure and mortality for age *x*>0 in the following year is calculated using:

$$N_{x+1,t+1}^{g} = N_{x,t}^{g} - M_{x+1/2,t+1/2}^{g}$$

$$M_{x,t}^{g} = R_{x,t}^{g} \cdot N_{x,t}^{g}$$

4 The number of fertile women is calculated using: $F_t = \Sigma N_{x,t}^{F}, 19 < x < 45$

5 The number of live birth is calculated using: $B_t^g = \beta^g \cdot F_t$

6 The number of births (for *x*=0) in the following year is calculated using: $N_{0,t+1}^{g} = B_t^g$

7 Migration is assumed to be +1 million; the adjustment for the population in cohorts is calculated using: $N_{x+1,t+1}^{g} \rightarrow N_{x+1,t+1}^{g} \cdot (1 + 10^6 / N_t)$

8 Return to step 1.

Legend

t	Year	
x	Age	
g	Gender	$g \in \{'F', 'M'\}$
N_t^g	Population of gender **g** at year **t**	$N_t^g = \Sigma N_{x,t}^g$
$N_{x,t}^g$	Number of those of gender **g** and age **x** at year **t**	
$M_{x,t}^g$	Number of cases of death of those of gender **g** and age **x** at year **t**	$M_{x,t}^g = R_{x,t}^g \cdot N_{x,t}^g$
$R_{x,t}^g$	Death rate among those of gender **g** and age **x** at year **t**	
α_x^g, λ_x^g	Regression coefficients	$m_{x,t}^g = \exp(\alpha_x^g + \lambda_x^g \cdot t)$
F_t	Population of fertile women at year **t**	$F_t = \Sigma N_{x,t}^F$, $19 < x < 45$
B_t^g	Number of births with gender **g** at year **t**	$B_t^g = \beta^g \cdot F_t$, $\beta^g = B_{2007}^g / F_{2007}^g$

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ANNEXE 5. ARTICLE: CANCER MEGAFUNDS WITH IN SILICO AND IN VITRO VALIDATION: ACCELERATING CANCER DRUG DISCOVERY VIA FINANCIAL ENGINEERING WITHOUT FINANCIAL CRISIS

Yang, X., Debonneuil, E., Zhavoronkov, A., & Mishra, B. (2016). Cancer megafunds with in silico and in vitro validation: accelerating cancer drug discovery via financial engineering without financial crisis. Oncotarget, 7(36), 57671.

Xianjin Yang[1], Edouard Debonneuil[2], Alex Zhavoronkov[3], and Bud Mishra[4]

1. King Abdullah University of Science and Technology, Jeddah, Saudi Arabia

2. Universite Lyon 1, Laboratoire SAF, France

3. Insilico Medicine, ETC, Johns Hopkins University, Baltimore, MD, USA

4. Courant Institute and Tandon School of Engineering, NYU, NY, USA

Correspondence to: Bud Mishra, mishra@nyu.edu

ABSTRACT

Advances in financial engineering are radically reshaping the biomedical marketplace. For instance, new methods of pooling diversified drug development programs by placing them in a special purpose vehicle (SPV) have been proposed to create a securitized cancer megafund allowing for debt and equity participation. In this study, we perform theoretical and numerical simulations that highlight the role of empirical validation of the projects comprising a cancer megafund. We quantify the degree to which the deliberately designed structure of derivatives and investments is key to its liquidity. Research megafunds with comprehensive *in silico* and laboratory validation protocols and ability to issue both debt, and equity as well as hybrid financial products may enable conservative investors including pension funds and sovereign government funds to profit from unique securitization opportunities. Thus, while hedging investor's longevity risk, such well-validated megafunds will contribute to health, wellbeing and longevity of the global population.

Keywords: megafund, in silico validation, cancer megafund, research-backed obligation, RBO

INTRODUCTION

Biomedicine faces a dilemma. Despite many recent scientific breakthroughs demonstrating a clear potential for combating cancer, there has been no significant private investment in cancer drug R&D. Both constantly rising costs and increasing rates of failures in the late stages of clinical trials have made the pharmaceutical R&D unappetizingly risky from a financial perspective (see Scannell *et al.* (2012)).

In particular, there are two main challenges. First, on average the success rate of clinical trials is low so that the average financial yield is low. Second, the large investments required to bring a single treatment to the market lead to an all-or-nothing result: the risk is high. To increase funding for cancer research while providing adequate financial

returns to investors with wide ranging risk profiles by investing in multiple clinical trials at once thereby mutualizing investments and diluting risks, the concept of a "cancer megafund" was proposed (see Fernandez *et al.* (2012)). A massive amount of investment capital would support a portfolio of many drug development projects in order to spread the risks associated with any stand-alone biomedical project. The resulting lowered default probabilities could make returns attractive to investors. By issuing Research-backed Obligations (RBOs), it could be also possible to attract both fixed-income and equity investors.

In parallel, a comprehensive multi-period, multi-state program was developed to simulate the behavior of the megafund entity over time and stress test the conceptual framework. Fagnan *et al.* (see Fagnan *et al.* (2013)) extended it in a way that demonstrated that third-party guarantees can improve the economics of RBO transactions at very low costs. The megafund concept was then extended to orphan diseases (see Fagnan *et al.* (2014)) and to longevity hedge instruments (see MacMinn *et al.* (2014)). The approach received criticism with calls made for more mathematically rigorous and faithful modeling, which could result in structuring and simulating the megafund entities to better elucidate and engineer risk profiles (see Boissel (2013)).

One alternative is to group investments to attract a diverse investor base. The original cancer megafund concept proposed offloading assets into one (SPV), a commonly used type of legal structure to make the link between investors and the users of investments such as pharmaceutical companies, without considering the heterogeneity of the drug development programs. In practice, drug development programs may typically be housed under different SPVs to attract diverse investors. For example, some investors may prefer investing in immunotherapy and others may prefer investing in small molecules tethered to nanoparticles. Another major challenge of operating in the real world is the presence of "lemons" (see Akerlof (1995)) in drug development programs, where projects have flaws known to their promoters but not to the buyers which can be modeled as information asymmetric games with potential for deceptive Nash equilibria. It is suspected that drug discovery and development is a "lemons" market, where over half of results may be non-reproducible in part due to the complexity of experimental conditions, the pressure to publish, low statistical powers and difficulty to publish negative results (see Mobley *et al.* (2013)). Therefore, while there are many efforts to consolidate knowledge (see Errington *et al.* (2014)), it might be expected that lemons are a practical important factor to consider when devising a megafund.

Through stylized examples, this study demonstrates how the introduction of "lemons" and their distributions influence the profits gained from different tranches: an "ideal" megafund discarding lemons before they are included into SPVs, a "reliable" megafund distributing the lemons evenly in the megafund and an "unfair" megafund greedily maximizing short term profit by placing lemons into toxic SPVs. Because proposed drug development projects are not a typical financial asset, we demonstrate that careful "validation" of their quality can in the best case lead to a better selection of what programs to develop and in the worst case lead an unfair megafund to better create toxic SPVs.

Our stylized "ideal" megafund does not fund any lemon at all. This is a hypothetical fund utilizing rigorous validation mechanisms and enough substantial time and resources to scrutinize every project before including it into an SPV. Table 1 shows that an ideal megafund has very low risks and very high financial returns and that making several SPVs of about 50 drug development programs enjoys many attractive traits. In addition to attracting different types of investors, it is optimal from the financial perspective.

150 assets, serving 8.5% to senior tranches	Senior tranches in practice		Equity tranches in practice	
	Yield	Default Probability	Yield	Default Probability

150 assets, serving 8.5% to senior tranches	Senior tranches in practice		Equity tranches in practice	
	Yield	Default Probability	Yield	Default Probability
Ideal megafund, 1 SPV	8.5%	< 0.1%	27.1%	< 0.1%
Ideal megafund, 6 SPVs	8.45%	0.4%	27.2%	< 0.1%
Reliable megafund, 1 SPV	8.44%	1.6%	17.2%	5.0%
Reliable megafund, 6 SPVs	7.78%	6.5%	17.5%	5.0%
Unfair megafund, 6 SPVs	5.85%	19.9%	27.7%	5.0%

"150 assets, serving 8.5% to senior tranches	Senior tranches in practice		Equity tranches in practice	
	Yield	Default Probability	Yield	Default Probability
Ideal megafund, 1 SPV	16.8%	0.2%	24.0%	0.6%
Ideal megafund, 6 SPVs	16.6%	2.8%	24.1%	0.6%
Reliable megafund, 1 SPV	14.8%	22.7%	12.2%	36.7%
Reliable megafund, 6 SPVs	14.8%	25.1%	12.2%	36.7%
Unfair megafund, 6 SPVs	11.7%	41.8%	25.9%	36.7%

Table 1. Summary statistics of different biomedical megafunds

Our stylized "reliable" megafund does not perform extensive due diligence like the ideal megafund but will randomly choose "lemons" alongside other projects and distribute them evenly among SPVs. The case of a single SPV then corresponds to the case studied by Fernandez *et al.* (2012) and indeed Table 1 shows that low risks and potentially sufficient returns can be obtained when pooling 150 assets. Making several SPVs to attract diverse investors generates non negligible risks in senior tranches, thus making one naturally wonder if returns can be high enough to attract investors.

Our stylized "unfair" megafund shows that the situation can rapidly deteriorate with multiple SPVs as after diligent examinations the managers of the megafund may identify the set of lemons and be incentivized to not pool assets completely randomly. As indicated by Sanjeev Arora *et al.* (2011), a strategy is to over represent the number of lemon projects in a few SPVs, thereby skewing the probability of default while making it computationally intractable to detect the toxic SPVs. Other SPVs would be handled in the same way as with the reliable megafund. Table 1 shows that equity tranches would then perform better than in the reliable megafund but that senior tranches would massively default. If the megafund managers hold shares of equity tranches, as generally done for the sake of credibility and responsibility, when facing lemons they would actually be tempted to manage the fund in an unfair way.

Average annual yield and probability of loss of senior and equity tranches, for a megafund of 150 drug development programs that aims to serve a respectable return to senior tranches, strongly depend on the type of megafund. These statistics suggest using validation mechanisms to get closer to an ideal megafund. The underlying mathematics and parameters are in the next section.

The results in Table 1 clearly indicate that it would be ideal to eliminate lemons beforehand. Such a validation-based strategy may actually be feasible at a certain cost: initial *in vitro*, *in vivo* and *in silico*intense "validation" could filter some lemons out. It could also improve the knowledge on how to develop non-lemons: what population to target, the way of administration and the dosage all jointly maximizing some measures of benefit/risk. It can therefore be expected that investing in such validation methods can greatly improve the performance of megafunds.

In order to investigate such aspects, we used the simulation framework of Fernandez *et al.* (2012) and its extension by Fagnan *et al.* (2013). We further extended it to model multiple SPVs, to distinguish lemons from non-lemons, to model the three behaviors of

megafunds described above and to model the impact of initially investing in validation. The results are in Figure 1.

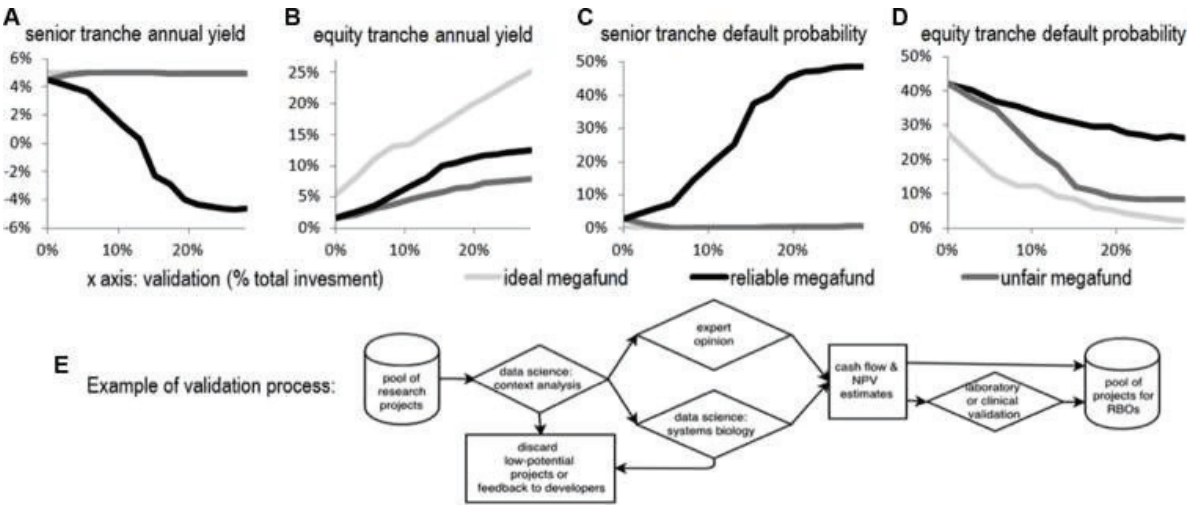

Figure 1. The relations between average yields and the degree of validation

Figure 1 shows the average yields (A and B) and default probabilities (C and D) for respectively senior and equity tranches over 20,000 simulated paths for an ideal megafund (light gray lines), a reliable megafund (dark gray lines) and an unfair megafund, depending on the degree of validation (as a percentage of the total investment; x-axis). As expected, validation reduces risks and improves returns for ideal and reliable megafunds; here, it turns some poorly attractive fund into strongly attractive funds. In case of an unfair management however, the knowledge of where lemons are lead the fund managers to collect them into toxic SPVs, which makes the corresponding senior tranches very risky. Using a portion of the investments for a validation process that could for example be strongly data driven (E) may significantly improve the performance of the fund by reducing the number of lemons.

To allow readers to analyze their own preferred parameters, we uploaded the simulation software in the public domain with an open-source license to run, modify and distribute the code and provided the mathematical model in the next section. One can choose higher returns for senior tranches or otherwise adjust other parameters or mechanisms. Figure 1 however already points to the main conclusion of the paper: the behavior of a cancer megafund strongly depends on the science behind its assets and on the transparency about lemons; treating lemons flippantly can be catastrophic.

As for Akerlof's original model of used car markets (1995) or even the 2008 credit crunch crisis, knowing the quality of assets and behaving in an informed manner with respect to bad assets are crucial practical aspects of a megafund. As a market of megafunds emerges, investors, lacking means to distinguish the type of a megafund (see Arora *et al.* (2011)), may choose either not to participate or to demand lower prices. Similarly to the "lemon" market for used automobiles, ideal and reliable megafunds that perform costly investigations will then be expelled from the market by low cost deceptive megafunds that fund deceptive biomedical research.

MATHEMATICAL APPROACH

Overview

We start by modelling a reliable megafund with several SPVs. A series of stylized assumptions are taken for simplicity. Examples of parameters are given for clarity.

Having a single SPV ($M = 1$) is then simply a special, but particularly interesting case. An ideal megafund (no lemon: $n = 0$) is another interesting special case.

The unfair megafund can be viewed as a combination of two reliable megafunds for the senior tranches and as a reliable fund with slight adaptations for the equity tranches.

Modelling a reliable megafund

Drug development programs, lemons and SPVs. As an example, out of 300 investigated drug development programs a reliable megafund selects N = 150 of them, and distributes them uniformly across M = 10 SPVs of D = 50 drug development programs each. Let us consider for simplicity that each drug development program is shared across the same number of SPVs, which is then $M\,D/N$.

Out of all, we assume that n = 75 drug development programs are in fact lemons and that for simplicity their success rate is 0. The other half is non-lemons, their success rate is p = 10% (so that the combined average success rate is 5% as in [2]). In case a non-lemon succeeds it generates B = 12.3 millions of present value at T = 10 years (for simplicity). We assume that the upfront investment is I = 0.2 million for every drug development project, whether a lemon or not.

Senior tranche and equity tranche. In order to attract both fixed-income and equity investors, s = 50% of the investment capital of any SPV goes to a senior tranche and the remaining part ($1 - s$ = 50%) to an equity tranche. For simplicity, each SPV contains two tranches. After ten years, the senior tranche pays the gains of the SPV up to the initial investment plus an interest that corresponds to an r = 5% annual interest rate. We say that the senior tranche "defaults" if it is not able to pay that interest rate.

The remaining gains are spread to the equity tranches of all SPVs as if it was a unique equity tranche (method that reduces the risk of equities). The equity amount is then paid to its investors. If it is below the capital invested in the equity tranche we say that the latter "defaults".

Computing financial characteristics of a reliable megafund

Payoff of senior tranches. The total investment in the megafund is NI: the product of the number investments N and the amount invested in each I. It is split across SPVs and across tranches so the investment for a senior tranch is $I_{senior} = \frac{NI}{M} s$.

Isenior=NIs/M. The senior tranche pays $I_{senior}\,(1 + r)^T$ to its investors if there are enough successes in the SPV to do so. If there are not enough successes, i.e. if the senior tranche defaults, the few successes each pay BN/MD to the investors (because as seen above each drug development program is split across MD/N SPVs).

Default of senior tranches. The frontier between the two cases determines the probability of default d_{senior} : when k successes that pay as much as what the senior tranche shall pay in the absence of default i.e. $k\frac{BN}{MD} = \left(NIs/M\right)\left(1+r\right)^T$.
The number of successes must be an integer so we round k up to the nearest integer above $K = \lceil k \rceil$ and the senior tranch defaults if the number of successes is less than

$$K = \left\lceil \left(NIs/M\right)\left(1+r\right)^T \frac{MD}{BN} \right\rceil = \left\lceil DIs/B\left(1+r\right)^T \right\rceil.$$

The default probability of the senior tranche is then

$$d_{senior} = \sum_{k=0}^{K-1} \binom{NL}{k} p^k \left(1-p\right)^{(NL-k)},$$

where $NL = D\frac{N-n}{N}$ is the number of non lemons in the SPV.

Yield of senior tranches. The average value generated by the senior tranche is the average of what it pays weighted by its probability:

$$V_{senior} = \left(1-d_{senior}\right) I_{senior} \left(1+r\right)^T + \sum_{k=0}^{K-1} \binom{NL}{k} p^k \left(1-p\right)^{(NL-k)} k\frac{BN}{MD}.$$

The average annual yield is then expressed from the investment and the average return:

$$y_{senior} = \left(\frac{V_{senior}}{I_{senior}}\right)^{\frac{1}{T}} - 1.$$

Yield of equity tranches. All equity tranches receive the same investment Iequity=NIM(1−s). Also, all equity tranches receive the same values: for every SPV, the values in excess of a senior tranche are spread over all equity tranches. So all equity tranches are in the same state and it is easier to consider them together as one large equity tranche that receives the known amount $I_{equities} = NI(1 - s)$ and pays the value of all successes in the megafund minus the payments of all the senior tranches. On average the megafund has $(N - n)p$ successes so that aggregate equity tranche pays

$$V_{equities} = \left(N-n\right) pB - MV_{senior}.$$

The average annual yield is then

$$y_{equity} = \left(\frac{V_{equities}}{I_{equities}}\right)^{\frac{1}{T}} - 1.$$

Default of equity tranches. That calculation is complicated in the general case so we performed case by case calculations.

The calculation is simple in the case of a megafund with a single SPV: the reasoning is that of d_{senior} with a K that is the minimal number of successes to pay $P_{senior} + I_{equity}$:

$$d_{equity}^{M=1} = \sum_{k=0}^{K'-1} \binom{N-n}{k} p^k \left(1-p\right)^{(N-n-k)},$$

where

$$K' = \left\lceil \frac{\left(NIs\right)\left(1+r\right)^T + NI\left(1-s\right)}{B} \right\rceil.$$

In the case of multiple SPVs, a long formula could be established for the equity default probability by considering the two-dimensional enumeration of how many senior tranches default and how many excess successes are generated in the group of SPVs whose senior tranches do not default. We used an intuitive approximation instead.

A number k of successes occur within the whole megafund and generate a value kB. On average MV_{senior} must be subtracted from that value in order to consider how much value remains for equity – that is where the approximation is done: we consider MV_{senior} as given whereas it is a random variable. The equity tranches default if that remaining value is insufficient to pay the equity investments i.e. if $kB - MV_{senior} < I_{equities}$. So the default is when $k < K'$ where

$$K' \approx \left\lceil \frac{MV_{senior} + NI\left(1-s\right)}{B} \right\rceil.$$

That is,

$$d_{equity} = \sum_{k=0}^{K'-1} \binom{N-n}{k} p^k (1-p)^{(N-n-k)}.$$

We will use a more intuitive estimation of K':

$$K' \approx \left\lceil \frac{M(NIs)(1+r)^T + NI(1-s)}{B} \right\rceil.$$

Indeed it is a simple formula that matches the exact formula in the case of a single SPV and that is otherwise numerically close to the formula above and comparatively prudent.

Computing financial characteristics of single SPV and ideal megafunds. The analysis for single SPV megafunds can then be slightly simplified by setting $M = 1$ and $D = N$ in the above equations. The equity default probability in particular is simple as indicated in the previous section.

Modelling unfair megafunds and computing associated characteristics

Modelling. The N assets are now split in two types of SPVs: M_1 SPVs have d_1 lemons each and M_2 toxic SPVs have d_2 lemons each with $d_2 > d_1$.

Senior default probability. It is as if we have two reliable megafunds: a non-toxic megafund with $N_1 = N\frac{M_1}{M_1+M_2}$ assets and M_1 SPVs and a toxic megafund with $N_2 = N - N_1$ assets and M_2 SPVs.

Each of them has a default probability

$$d_{i,senior} = \sum_{k=0}^{K-1} \binom{D-d_i}{k} p^k (1-p)^{(D-d_i-k)},$$

where $i = 1, 2$ and $K = \lfloor \mathrm{DIs}/B(1+r)^T \rfloor$ is the same for the two megafunds. The overall default probability is then of course the weighted average

$$d_{senior} = \frac{M_1}{M} d_{1,senior} + \frac{M_2}{M} d_{2,senior}.$$

Senior yield. Similarly,

$$y_{senior} = \left(\frac{M_1 V_{1,senior} + M_2 V_{2,senior}}{MI_{senior}} \right)^{\frac{1}{T}} - 1,$$

where

$$V_{i,senior} = (1-d_{i,senior}) I_{senior} (1+r)^T + \sum_{k=0}^{K-1} \binom{D-d_i}{k} p^k (1-p)^{(D-d_i-k)} k \frac{BN}{MD}.$$

Equity yield. The same reasoning as for a reliable megafund leads exactly to the same formulas.

Equity default probability. A long formula could be established by considering the three-dimensional enumeration of how many senior tranches default in the two sub-megafunds and how many excess successes are generated in the group of SPVs whose

senior tranches do not default. We instead use the approximation concept used for a reliable megafund, it leads to the same formula.

Numerical application

The following Table 2 is a detailed version of Table 1 presented earlier in the paper. In all cases, N = 150, I = 0.2, B = 13.6 and s = 50%.

Reliable 1	'a la Fernandez et al.'	Reliable 2	'a la Fernandez et al.'
Parameters	$n=0,\ p=5\%,\ M=1,\ r=3.8\%$	Parameters	$n=0,\ p=5\%,\ M=1,\ r=5\%$
Senior	$K=\lceil 1.8\rceil,\ d=0.4\%,\ y=\mathbf{3.8\%}$	Senior	$K=\lceil 1.99\rceil,\ d=0.4\%,\ y=\mathbf{5.0\%}$
Equity	$y=\mathbf{19.0\%},\ K'=\lceil 2.99\rceil,\ d=1.8\%$	Equity	$y=\mathbf{18.6\%},\ K'=\lceil 3.2\rceil,\ d=5.5\%$
Reliable 3	'a la Fernandez et al.'	Reliable 4	'a la Fernandez et al.' on
Parameters	$n=0,\ p=5\%,\ M=1,\ r=8.5\%$	Parameters	$n=0,\ p=5\%,\ M=1,\ r=9.4\%$
Senior	$K=\lceil 2.8\rceil,\ d=1.8\%,\ y=\mathbf{8.3\%}$	Senior	$K=\lceil 2.99\rceil,\ d=1.8\%,\ y=\mathbf{9.3\%}$
Equity	$y=\mathbf{17.3\%},\ K'=\lceil 3.98\rceil,\ d=5.5\%$	Equity	$y=\mathbf{16.8\%},\ K'=\lceil 4.2\rceil,\ d=12.6\%$
Reliable 5	Reliable 3 lemons/non-lemons	Reliable 6	5 or 50 SPVs
Parameters	$n=75,\ p=10\%,\ M=1,\ r=8.5\%$	Parameters	$n=75,\ p=10\%,\ M>1,\ r=8.5\%$ $\boldsymbol{D=52}$ (previously $N=D=150$)
Senior	$K=\lceil 2.8\rceil,\ d=1.6\%,\ y=\mathbf{8.4\%}$	Senior	$K=\lceil 0.96\rceil,\ d=\mathbf{6.5\%},\ y=7.8\%$
Equity	$y=\mathbf{17.2\%},\ K'=\lceil 3.98\rceil,\ d=5.0\%$	Equity	$y=17.5\%,\ K'=\lceil 3.98\rceil,\ d=5.0\%$
Reliable 7	5 or 50 SPVs	Idea 1	1 SPV
Parameters	$n=75,\ p=10\%,\ M>1,\ r=\mathbf{16.8\%}$ $D=52$	Parameters	$\boldsymbol{n=0},\ p=10\%,\ \boldsymbol{M=1},\ r=16.8\%$
Senior	$K=\lceil 1.99\rceil,\ d=\mathbf{25.1\%},\ y=14.8\%$	Senior	$K=\lceil 5.8\rceil,\ d=\mathbf{0.2\%},\ y=16.8\%$
Equity	$y=12.2\%,\ K'=\lceil 6.98\rceil,\ d=\mathbf{36.7\%}$	Equity	$y=24.0\%, K'=\lceil 6.98, d\rceil=\mathbf{0.6\%}$
Ideal 2	5 or 50 SPVs	Ideal 3	
Parameters	$n=0,\ p=10\%,\ M>1,\ r=8.6\%$ $\boldsymbol{D=52}$	Parameters	$\boldsymbol{n=0},\ p=10\%, \boldsymbol{M>1}, r=16.8\%$ $D=52$
Senior	$K=\lceil 0.96\rceil, d=0.4\%,\ y=8.5\%$	Senior	$K=\lceil 1.99\rceil, d=2.8\%, y=16.6\%$
Equity	$y=27.2\%,\ K'=\lceil 3.98\rceil,\ d\le 0.1\%$	Equity	$y=24.0\%, K'=\lceil 6.98\rceil,\ d=0.6\%$
Unfair		Unfair	
Parameters	$n=75,\ p=10\%,\ D=52,\ r=8.6\%$ $M_1=M_2=3,\ d_1=9,\ d_2=43$	Parameters	$n=75,\ p=10\%,\ D=52,\ r=16.8\%$ $M_1=M_2=3,\ d_1=9,\ d_2=43$
Senior	$K=\lceil 0.96\rceil,\ d=19.9\%,\ y=5.9\%$	Senior	$K=\lceil 1.99\rceil,\ d=41.8\%,\ y=11.7\%$
Equity	$y=27.6\%,\ K'=\lceil 3.98\rceil,\ d=5.0\%$	Equity	$y=25.9\%,\ K'=\lceil 6.98\rceil,\ d=36.7\%$

Table 2. Detailed summary statistics under different configurations

SIMULATIONS

As with the work of Fagnan *et al.* (2013), we focused only on early-stage investment (Preclinical and Phase I), which is the most risky portion of the drug development process and where funding is scarce. We selected one semester as the time step of the study and 6 years as the duration of the drug development process. During

one semester, drugs have probabilities to move to another stage of the drug development process. At the end of each semester, current cash reserves will increase through the compound interest transferring to the next stage. We used the same methods as those used by Fernandez to make upfront payments and periodic payments and also to compensate the developers for successful completion of key milestones. If a drug successfully transfers into Phase II or other later stages, we sell it and realize profits immediately. For every drug, we used the same methods and parameters to evaluate it and calculate its cost as in the previous work.

It should be noted at this point that lemons have a different transition probability matrix from non-lemons. For non-lemons we use the same matrix as Fernandez *et al.* (2012) as a reasonable assumption in the absence of validation (impacts of validation are described below). We designed the transition probability matrix of lemons based on the principle that lemons have much higher probability of failures and that the more stages they reach, the higher is the probability and cost of failure.

We introduce multiple SPVs and the behavior of the megafund: ideal, reliable or unfair. By default we start with 200 assets and consider that half of them are lemons. The ideal megafund starts by eliminating the lemons and therefore starts with $N = 100$. The reliable fund eliminates some of the lemons depending on the amount invested in validation and therefore starts with N between 100 and 200. The unfair fund keeps the $N = 200$ assets; in the absence of validation it behaves like the reliable fund (not able to distinguish between lemons and non-lemons) but the more the validation, the more it distributes lemons into some SPVs, the toxic SPVs. $M = N / 4$ SPVs are built. Each SPV randomly chooses $D = N / 2$ assets, where some asset will be distributed across a few SPVs, others across many SPVs: the only constraint is that each asset goes to at least one SPV. The unfair megafund uses a quarter of its SPVs as toxic SPVs.

The probability to detect that an asset is a lemon is modelled depending on the percentage of investments used for validation: $p_{detection} = 1 - e^{-10v}$. With that formula it is 0 in the absence of validation and close to 95% when 30% of investments go to validation.

With validation also comes improvements of non-lemon probabilities. Indeed performing preliminary analysis on drugs should allow to better target a dose, way of administration and target population with a high benefit to risk balance.

The mechanism of tranches is minimally modelled for the sake of clarity of analysis. No junior tranche is used: we only model the senior tranche and the equity tranche. In case a senior tranche does not default it pays at the end of the period and the senior tranche pays nothing if it defaults.

CONCLUSIONS

In conclusion, the megafund concept based on modern securitization techniques and debt and equity financing may provide another mechanism to accelerate drug discovery in cancer and other diseases. However, for the concept to be effective, it needs to consider the economics of the lemons market in cancer research. Considering the amount of irreproducible research published in high-level journals, it is fair to assume that asymmetry of information will exist between scientists, managers and investors. Introducing stringent *in silico* and laboratory validation techniques prior to enrolling projects into SPVs may improve the odds of clinical trials. A potential security mechanism would be that regulators impose that a significant percentage of the upfront costs go to drug discovery program validation and that results of investigations are openly shared with both debt and equity investors – this might also improve the reproducibility of biomedical research.

ACKNOWLEDGMENTS AND FUNDING
B.M. is supported by an NCI PSOC grant# U54 CA193313.

CONFLICTS OF INTEREST
The authors declare that they have no conflicts of interest.

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ANNEXE 6. ARTICLE: CAN PENSION FUNDS PARTIALLY MANAGE LONGEVITY RISK BY INVESTING IN A LONGEVITY MEGAFUND?

Edouard Debonneuil [1,*,†] Anne Eyraud-Loisel [1,†] Frédéric Planchet [1,2,†]

[1] ISFA, Laboratoire SAF EA2429, Univ Lyon—Université Claude Bernard Lyon 1, F-69366 Lyon, France; anne.loisel@univ-lyon1.fr (A.E.-L.); frederic@planchet.net (F.P.)
[2] Prim'Act, 42 Avenue de la Grande Armée, 75017 Paris, France
* Correspondence: edebonneuil@yahoo.fr, Tel.: +33-6-5207-6562

† These authors are researcher at SAF laboratory (EA n°2429). Frédéric Planchet is also consulting actuary at Prim'Act.

Received: 19 March 2018; Accepted: 22 June 2018; Published: date

ABSTRACT

Pension funds, which manage the financing of a large share of global retirement schemes, need to invest their assets in a diversified manner and over long durations while managing interest rate and longevity risks. In recent years, a new type of investment has emerged, that we call a longevity megafund, which invests in clinical trials for solutions against lifespan-limiting diseases and provides returns positively correlated with longevity. After describing ongoing biomedical developments against ageing-related diseases, we model the needed capital for pension funds to face longevity risk and find that it is far above current practices. After investigating the financial returns of pharmaceutical developments, we estimate the returns of a longevity megafund. Combined, our models indicate that investing in a longevity megafund is an appropriate method to significantly reduce longevity risk and the associated economic capital need.

Keywords: longevity; mortality; longevity risk; pension fund; megafund; biomedical; biology of aging; pharma; model; needed capital

1. Introduction

In 2012, Fernandez et al. (2012) presented the concept of “cancer megafund”, a financial solution to stimulate the financing of potential solutions to cancer. It is an alternative to the current pharmaceutical development model where dramatic decreases in profitability are described (see Scannell et al. 2012) that make investors reluctant to bet on biomedical innovation. In essence, the concept is about risk mutualization: the expected rate of return of 150 diverse and carefully selected biomedical drug developments is similar to that of a few carefully selected developments but, owing to the law of large numbers, the risk is considerably smaller. Since investing in many developments requires many investors, the megafund concept includes securitization techniques to attract enough investors, notably pension funds and insurance companies. The fund is split between two financial instruments: “Research Backed Obligations” (RBOs), which provide investors with fixed returns, backed by clinical trials, and equity, which captures the remaining profits.

The concept is rapidly proposed for other applications than cancer, such as Alzheimer’s disease (see Lo et al. 2014), orphan diseases (see Fagnan et al. 2014), and general biomedical innovation in large, in London, the USA, Australia, or Sweden (see Swedish Agency for Growth Policy Analysis 2017). In parallel, Boissel (2013), Marko (2013), Tenenbaum (2013), Fagnan et al. (2014, 2015), Lo and Naraharisetti (2014), Lo (2015), Yang et al. (2016), and Hull (2016) underline both the broad potential applications and risks of the megafund structure. Essentially, in order to finance many “long shots”, whether health-related or not, the projects should be largely uncorrelated as opposed to all focused on the same disease or set of diseases. There are additional considerations to take into account for a megafund to mitigate risk: according to Hull (2016) and Yang et al. (2016), each individual project should have a minimum probability of success; according to Yang et al. (2016), the megafund should not be structured in too many financial components to align investors’ interests.

In 2014, the concept emerges that targeting various diseases has an additional desirable effect than a better diversification: as described by Stein (2016) and MacMinn and Zhu (2017), it can hedge longevity risk, i.e. the financial loss if people live longer than planned. They suggest that "biomedical RBOs" can hedge longevity risk. The link would not be perfect. For example, some life-extending drugs may be developed in which the megafund has not invested. Still, it would provide a better longevity hedge than alternative longevity-linked securities (see MacMinn and Zhu (2017)). This is unexpected good news as Pension funds and insurance companies are essential stakeholders for a megafund to reach its critical mass. This becomes even better news as Pension funds and insurance companies are not prone to finance treatments that lead to longer pensions to be paid.

Given such impressive conclusions that a megafund could both support medical discoveries and the financing of pensions, this paper gets back to basics and checks some foundations for such an interest in pension funds to invest in a longevity megafund. The analysis of fine hedging adjustments, as in MacMinn and Zhu (2017), is beyond the scope of this article. Instead, we investigate more fundamental aspects of the equation that were partly ignored, such as the magnitude of longevity risk and the magnitude of rates of returns. Focusing on the link with longevity risk, we name the structure "longevity megafund" rather than "biomedical megafund" when it invests into solutions to life-threatening diseases rather than all kinds of diseases.

The paper is organized in three main sections. In Section 2, and with greater details in Appendix A, we model the potential size of longevity risk. We conclude that the necessary prudential capital to cover longevity risk is significantly higher than what is common practice in the industry today. In Section 3, and with greater details in Appendix B, we model the expected rate of return of a biomedical megafund and a longevity megafund. We attempt to quantify key factors in the equation such as the cost and success rate of clinical trials, the profitability of pharmaceutical developments, both under the current longevity trend and with scenarios of increasing human longevity. In Section 4, we cross both longevity risk and rate of return to assess the attractiveness of a longevity megafund to pension fund asset managers. We then conclude and discuss some remaining aspects that we could not study here.

In order to ease the understanding, Appendix C at the very end of the article lists figures, tables, and variables by theme: “Longevity model”, “Returns of pharmaceutical developments”, and “Pension fund needed capital”.

2. Potential size of longevity risk

Stein (2016) and MacMinn and Zhu (2017) highlighted that pension funds may be interested in investing in a longevity megafund to manage some of their longevity risk. Longevity risk is generally directly or indirectly estimated by how well models match historical mortality data. However, as described by Debonneuil et al. (2017), not only do frequent actuarial models unknowingly project decelerating life expectancy trends, advances on the largest source of longevity risk are largely ignored: a likely forthcoming wave of biomedical solutions to old age conditions that comes from biology of aging and animal models. Here, we therefore aim to take into account such advances, and we suggest a simple model that does not produce decelerating life expectancy trends to generate longevity scenarios. We then use a model of a pension fund to estimate the needed prudential capital with respect to longevity risk.

2.1. Solutions Derived from Biology of Aging Are Reaching Clinics

In the 19th and 20th centuries, infant mortality rates and young adult mortality rates have dropped so that the future trend of life expectancy is now to a large extent a matter of solutions to old age conditions (see Vallin and Meslé 2010 and Debonneuil et al. 2011).

In the beginning of the 21st century, a series of biomedical discoveries suggest that mortality rates may drop at old age as well. The series started with animal models of human aging and is now turning to humans. In 2008, Ayyadevara et al. (2008) were able to extend the lifespan of laboratory nematodes by circa ten times with one single gene change and Bartke et al. (2008) were able to extend the lifespan of laboratory mice by 70% with a combination of gene change and diet. Since then, a vast range of successful methods in animals were reproduced at the level of cells and tissues in humans and human trials are now being discussed (see Barardo et al. 2017 and Moskalev et al. 2017). The translatability to humans is supported by several discoveries. In particular, some mutations that increase the lifespans of rodents are seen in long-lived human families (see Kenyon 2010). Also, low-caloric diets, that can extend the approximate 2-year lifespan of rodents by more than 40%, extend the approximate 6-year lifespan of primates by more than 50% (see Pifferi et al. 2018), without observed sign of physical nor mental health deterioration. The graft of bio-printed

organs (see Ravnic et al. 2017; and Mir and Nakamura 2017) and the in vivo degradation of old tissues that the body then naturally replaces by younger tissue (see Fahy 2003; Ocampo et al. 2016; Mosteiro et al. 2016; and Mendelsohn et al. 2017) are already being tested in specific clinical settings. The latter advances show that science is not only on its way to slow down human aging but also to restore youthful characteristics to the body once old.

One may then expect much better health at old ages, which in turn means lower mortality rates and longer lives. By how much? The life expectancy impact of curing diseases is inconsistently estimated because beyond each disease itself there is a largely unknown associated global burden on the body (see Martin et al. 2003; Arias et al. 2013; and Guibert et al. 2017). Where models or parameters are to be chosen, psychological ceilings lead to underestimate parameters. This is how in 1928 Dublin (1928) predicted an ultimate average life expectancy limit of 64.75 and how in 1990 Olshansky et al. (1990) increased that estimate to 85, which is already less than the woman life expectancy in Japan.

Keeping maximum human lifespan around the age of 115 is one of those arbitrary ceilings. It seems to be such lately and this leads for example Vig and Le Bourg (2017) to consider that it will necessarily remain as such. But the latter is not a proof, as noted by Gavrilov et al. (2017) who even observes a constant centenarian mortality since 1940. Comparing the effects of current interventions in various animal species and humans Ben-Haim et al. (2017) suggests a further increase of 30% of lifespan, i.e., 150 years of maximal lifespan may be at reasonable reach based on ongoing developments.

Until a few years ago, the field of biology of aging was only about fundamental research and largely away from pharmaceutical developments. The pharmaceutical industry used to apply methods developed for single, acute diseases to multiple, chronic diseases (see Thiem et al. 2011; Roman and Ruiz-Cantero 2017) instead of targeting the underlying aging and regenerative processes as described above. Since about 2015, various biotech companies have raised funds to bring biology of aging results to the clinics (see De Magalhães et al. 2017; and Debonneuil et al. 2017). Various investor reports, books, and conferences consider that current retired persons may be the first populations to benefit from such advances (see Mellon and Chalabi 2017; Pratt 2016; and Casquillas 2016). When essentially focusing on hair and skin aging, which were the main anti-aging industry drivers until recently, estimated sizes of the anti-aging market are $122 Bn in 2013, 140 in 2015, 192 in 2019, and 217 in 2021 (see Zion Market Research 2017; Transparency Market Research 2014) which explains why the financial industry is starting to drive this move.

Of course, these advances may also require non-negligible adjustments in retirement systems: retirement systems face the “longevity risk” that retirements must be paid longer than financially planned. Current retirement systems essentially stem from the middle of the 20th century, when most young workers were not expected to reach retirement age, and they depend on various mortality tables that are regularly updated but that empirically under-estimate historical life expectancy trends (see Antolin and Mosher 2014; and Debonneuil et al. 2017). In the USA only, if deaths caused by cardiovascular diseases and cancer were eliminated, the fiscal imbalance of Social Security and Medicare programs may be as high as $87 trillion in present value (see Zhavoronkov et al. 2012).

2.2. Model of longevity risk

We choose a model, derived from Bongaarts (2005) and Debonneuil et al. (2017), that is simple enough to be traceable and understandable but incorporates key features that are rarely encountered in actuarial sciences: as we will see, it generates non-decelerating life expectancies and is relatively universal owing to its simplicity. It is defined by this logistic formula for the annual mortality rate of someone aged x in t years:

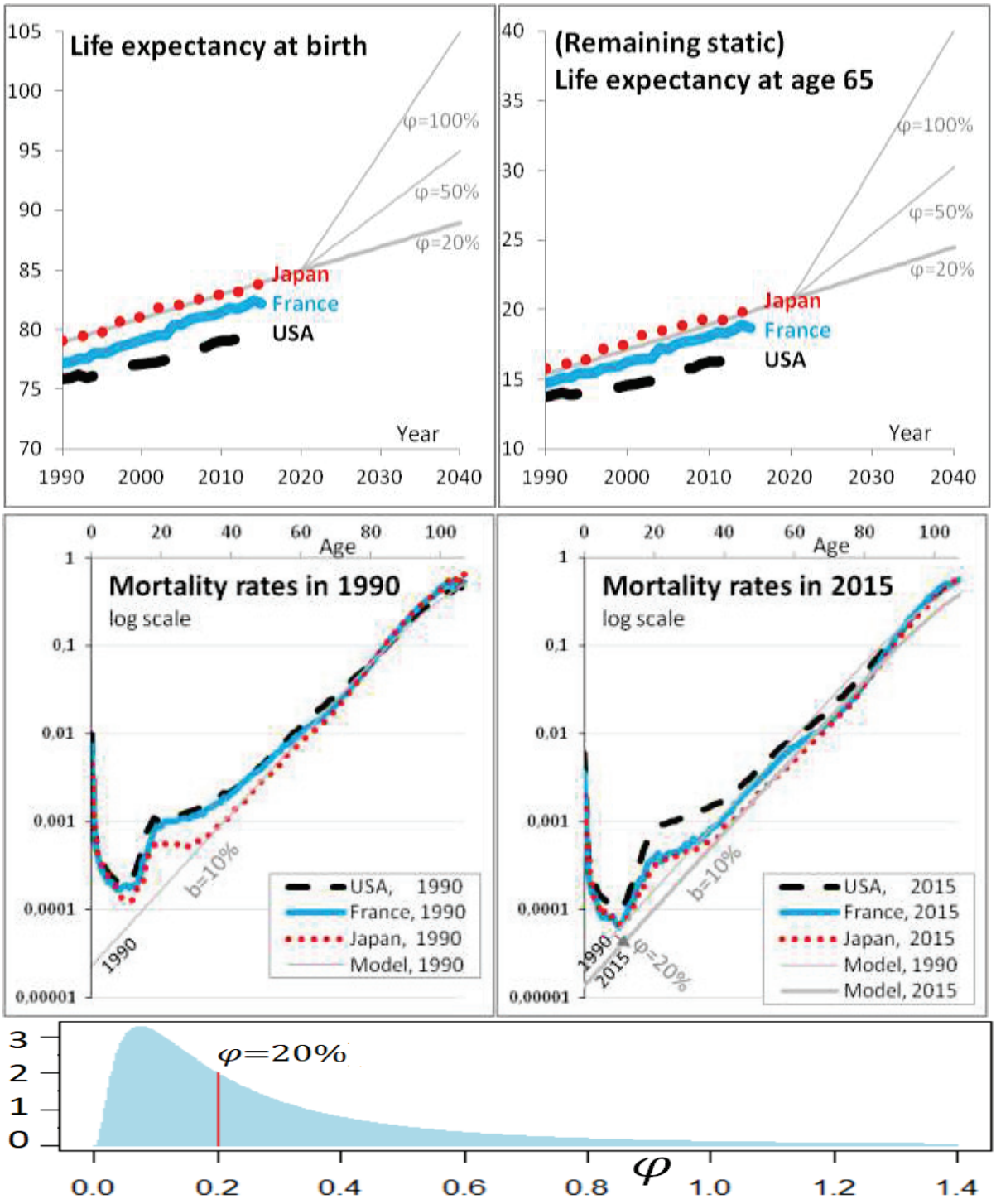
$$q_{x,t} = \frac{1}{1 + e^{a-b(x-\varphi t)}} \quad (1)$$

where t = 0 corresponds to 1 January 2020, as explained in Appendix A, ϕ represents the annual increase of life expectancy at birth, for t < 0 it is set to the current ϕ = 20% trend and for t ≥ 0 it is randomly selected based on a probability density function to describe various possibilities in the future:

$$\mathrm{pdf}(\varphi) = \frac{e^{-\frac{(\ln \varphi - \ln 20\%)^2}{2s^2}}}{\varphi s\sqrt{2\pi}} \quad (2)$$

Appendix A describes in greater details the reasons for choosing this model and how the parameters are calibrated (a = 11.3, b = 10%, ϕ=20% up to t = 0 then s = 1 to draw a random ϕ). It notably defines remaining life expectancy at age x and time t, e_(x,t), that is used for the calibration. Overall, the model and its parameters are chosen to fit mortality rates and life expectancy in Japan, as indicated in Figure 1, as a representation of the life expectancy of pensioners weighted by amount (that are higher than the general population as higher amounts are correlated with lower mortality due to social inequalities). The longevity level at time t = 0, a, can of course be adjusted to model specific populations of pensioners, but what mostly matters for what follows is the range of possible longevity trends for t > 0.

Fig 1. Characteristics of the chosen longevity model



In the first two graphs, remaining life expectancy at respectively birth and age 65 is computed from year 1990 to 2040 based on the model (see Equation (1)), in gray lines using different values of φ as written, and from 1990 to 2015 for specific countries based on historical data (more precisely based on the mortality rates estimates provided by the Human Mortality Database): Japan in (red) short dashes, France in (blue) continuous lines, and the USA in black long dashes. As expected, life expectancies are greater in Japan than in France and lower in the USA. The model fits life expectancy and mortality rates of Japan. The same style of lines is used for the next two graphs, that represent the mortality rate at different ages in log scale, for the years 1990 and 2015, respectively. The model matches the Japanese mortality well from age 40 to 85; mortality rates at these ages are important to model life expectancy at age 65 and below (see Debonneuil et al. 2017). In the fourth graph, the model at 1990 is additionally shown to provide a visual reference on how mortality rates have evolved from 1990 to 2015. The fifth graph shows the chosen lognormal probability density of φ.

2.3. Implication for a Pension Fund in Terms of Needed Prudential Capital

Let us use a simple model of a pension fund to apply the longevity model and compute capital needs.

Population studied. We consider the following cohort defined as such at time t = 0: 300 employees of age 20, 300·(1-q_20,0) employees of age 21, 300·(1-q_20,0)(1-q_21,0) employees of age 22, etc. until an age 64 and no retired persons. This provides a distribution of the population across ages that is roughly natural. When applying the mortality model, this corresponds to 13,000 people at time t = 0 (year 2020). We follow this closed portfolio over time (t = 1, 2, etc.) and every year people die according to mortality rates. For the sake of simplicity, we do not model arrivals nor departures. The number of people aged x at time t is then:

$$N_{x,t} = \left(300 \prod_{v \geq 20}^{v<x-t} (1 - q_{v,0})\right) \prod_{v \geq x-t}^{v<x} (1 - q_{v,t+v-x}) \quad (3)$$

The formula is valid for workers aged 20 to 64 at t = 0, i.e., for t ≥ 0 and x < 65 + t and x ≥ 20 + t. Otherwise, this is not the cohort, so N_(x,t) = 0. Summing over ages, numerically at t = 0 the cohort is composed of 13,295 employees.

Contributions and investments. Using Asset Liability Management (ALM) practice standards, we consider employees of different age tranches, each with different salaries per tranche, a contribution of 10%, and different returns per tranche, as shown in Table 1.

Tab 1. Contributions by age tranche

Age	Salaries	Individual annual contribution	Annual investment return rate
20 to 34	30,000	3,000	i1=5% σ1=4%
35 to 49	45,000	4,500	i2=4% σ2=3%
50 to 64	60,000	6,000	i3=2% σ3=1%

The table lists the assumptions used to model contributions. For example, employees from age 20 to 34 earn 30,000 each year, provide 3,000 to the pension plan, this contribution has an annual return of $i_{1,t}$=5%±4%.

The increasing contributions of persons aged 20–34, 35–49, and 50–64 that are invested in decreasing degrees of risk. This is based on practice where younger people invest in more risky and potentially more profitable assets, whereas older people invest in safer assets with less profitability. For each of the three funds, dedicated to an age tranche, the annual return rate (i1, i2, i3) is normally distributed, which corresponds to a lognormal distribution of wealth. The volatilities σ are chosen with a Sharpe ratio of 1 (personal experience with such a level), a risk-free rate of 1% and a 2-by-2 correlation of 50% between the three fund return rates:

$$\sigma_k = \frac{i_k - 1\%}{1.0} \quad (4)$$

$$\langle i_{k,t}, i_{l,t} \rangle_{l>k} = 50\% \quad k, l = 1,2,3 \quad (5)$$

We consider that in the past, the annual returns were exactly 5%, 4%, and 2% (depending on the age tranche). In order to avoid modeling complex contractual clauses we consider that the accumulated capital of a worker who dies serves as accumulated capital C_(x,t) for the group of persons aged x at t (no removal of capital).

Under such assumptions, at t=0:

$$C_{x,0} = \begin{cases} \sum_{u\geq 20}^{u<35} N_{u,0} 3000 \cdot 1.05^{x-u}, 20 < x \leq 35 \\ C_{x,35} \cdot 1.04^{x-35} + \sum_{u\geq 35}^{u<50} N_{u,0} 4500 \cdot 1.04^{x-u}, 35 < x \leq 50 \\ C_{x,35} \cdot 1.04^{x-35} + \sum_{u\geq 50}^{u<65} N_{u,0} 6000 \cdot 1.02^{x-u}, 50 < x \leq 65 \end{cases} \quad (6)$$

We also have C_(x,0) = 0 for x ≤ 20 (no contributions yet) and x ≥ 65 (at time 0 we only consider workers). Then, year after year between t − 1 and t,

$$C_{x,t} = C_{x-1,t-1} + c_{x-1,t-1} \cdot N_{x-1,t-1} \cdot i_{x-1,t-1} \quad (7)$$

where c and i are the contributions and annual investment returns as defined by Table 1 and Equations (4) and (5).

Initial wealth. By initial wealth we mean the total accumulated capital at t=0:

$$W_0 = \sum_x C_{x,0} \quad (8)$$

Numerically, this leads to an initial wealth of approximately 2 Bn (1,995, 578, 577). In what follows, we will express the needed prudential capital by amount of initial wealth.

Benefits at retirement. Retirement benefits depend on the accumulated capital at age 65, that is here converted in a lifelong annuity by an insurer who is responsible for paying corresponding benefits throughout the life of the pensioners.

Instead of having to model interest rates and increases of annual benefits during retirement, we take the simplifying assumption that increases are such that the two compensate: the duration of benefit payments is then the remaining lifespans at age 65. If $B_{65,t}$ is the annual benefit paid to the workers who retire at time t, the present value of benefits at time t is then $B_{65,t} \cdot L_{65,t}$.

At time t however, a longevity trend is not necessarily observed. We consider that the conversion from the accumulated capital $C_{65,t}$ to the benefit amount B_t is done based on the mortality model with φ=20%. Since actuarial tables generally have decelerating trends (see Debonneuil *et al.* (2017)) insurers would consider it prudent compared to existing practices. If longevity increases much, the use of φ=20% remains a plausible base since actuarial tables do not evolve immediately after observing overestimations of mortality rates (see Vaupel (2010)).

In order to face risks, the insurer may convert only a part π of $C_{65,t}$, where π is between 0 and 1. For the sake of simplicity, we consider π=1.

$$B_t = \frac{\pi \cdot C_{65,t}}{N_{65,t} \cdot L_{65,0|\varphi=20\%}} \quad (9)$$

With that definition of benefit amounts, if the future longevity trend is φ=20% then the mechanism in place to collect contributions and investment returns provide the right amount of money to pay all pensions. However, additional wealth is initially needed to face higher longevity trends.

Needed prudential capital. We define the needed prudential capital by the amount of money initially needed, in addition to initial wealth, to pay the pensions of the workers with a high probability.

In order to assess the needed prudential capital $K_{\varphi,\{i_{x,t}\}}$ at t=0 under the assumption of a given future scenario defined by the longevity trend φ and the investment returns $i_{x,t}$ ("$\varphi, \{i_{x,t}\}$"), we allow wealth to become negative (instead of claiming bankruptcy) and we measure wealth after all benefits were paid. $-K_{\varphi,\{i_{x,t}\}}$ is the present value of that final wealth, so that $K_{\varphi,\{i_{x,t}\}}$ is the additional initial wealth that would have been needed to provide the right amount to pay retirement benefits in the future, without reaching bankruptcy. For the sake of simplicity, the discounting is performed along investments done, i.e. the wealth is divided by the value of an initial investment of 1 when invested in the different funds in the same proportion of contributions. In practice, long term investment choices and associated discounting may be optimized through the use of progressive utility (see El Karoui *et al.* (2014)).

$$-K_{\varphi,\{i_{x,t}\}} = \sum_{t>0} \frac{C_{65,t} - B_t \cdot L_{x,t}}{\prod_{0<u<t}(1 + \frac{\sum_x C_{x,u} i_{x,u}}{\sum_x C_{x,u}})} \quad (10)$$

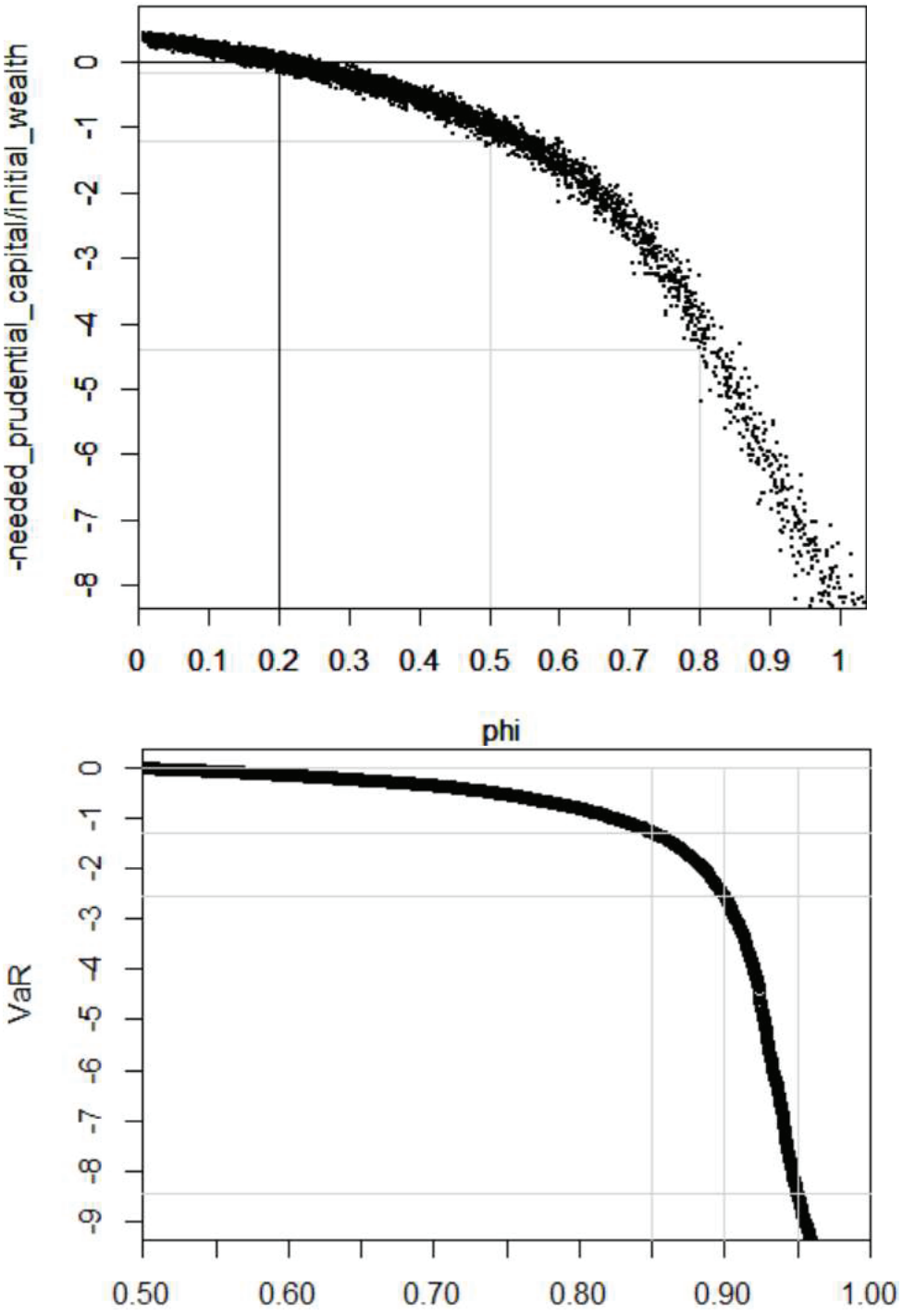
We generate 10,000 future scenarios of longevity trend φ and investment returns $i_{x,t}$, using a Cholesky decomposition of the covariance matrix $\langle \sigma_k, \sigma_l \rangle$ to simulate correlated returns. We compute 10,000 corresponding values of $K_{\varphi,\{i_{x,t}\}}$ to compute the needed prudential capital, that we arguably define as being sufficient to pay retirement benefits in 90% of the simulated scenarios: a 90% VaR (Value at Risk).

$$K = VaR^{90\%}_{\varphi,\{i_{x,t}\}} K_{\varphi,\{i_{x,t}\}} \quad (11)$$

This would mean that there is a 10% risk of not fully paying retirement benefits. The risk may be lower because adjustments may occur. For example, in case of difficulties new business contributions would probably be used to some extent to pay the benefits of the older business. However, events can be worse than modeled and reactivity can be questioned with respect to retirement systems. In what follows, we will also compute the 85% VaR and 95% VaR as this choice has a material impact.

Results. Figure 2 shows the needed amount of additional initial wealth, expressed as a proportion of the initial wealth, depending on the future longevity trend.

Fig 2. Needed prudential capital depending on the future longevity trend (or lack of) expressed as a proportion of the initial wealth



In the two graphs, the y-axis shows the present value of remaining wealth after paying retirement benefits for current employees, divided by the initial wealth of the pension fund: "-1" means that 100% of additional wealth would be needed today, i.e. a needed prudential capital of the size of the initial wealth. In the first graph, the x-axis shows different scenarios for the longevity trend φ and each dot in the graph is the result of a scenario. In the second graph, the x-axis is the level at which to compute the VaR that represents the needed prudential capital: for example, a 90% VaR over all scenarios.

If the current longevity trend continues (φ=20%) an additional capital of circa 15% of the initial wealth may be considered. Such is due to the uncertainty of the fund returns – the thickness of the

curve in Figure 2. Taking the average (the center of the black curve) instead of a VaR shows a perfectly neutral initial wealth.

However, if the longevity trend is $\varphi = 50\%$ the needed prudential capital should be slightly more than the initial wealth. If the longevity trend is $\varphi = 80\%$, the needed prudential capital should be more than 4 times the initial wealth.

In practice however, one does not know the future of longevity, so the prudential additional wealth shall cover a wide range of possible longevity trends. Using the lognormal distribution of longevity trends, our simulation suggests that the needed prudential capital is approximately 1.4 times, 2.7 times or 8.4 times the initial wealth depending on whether a 85%, 90% or 95% VaR is respectively considered. One might have expected that longevity risk is handled with a prudential capital of 10% or 30% of the initial wealth. Such is not the case here because we consider the type of breakthroughs that were described at the beginning of the article and that are burgeoning. It is worth noting that in a Solvency II environment the solvency capital requirement is estimated with a short-term view of risks; here we consider the needed current capital with a long-term view of risks given that pensions represent long term liabilities.

2.4. Conclusion of This Section

Longevity risk is not small, which could incentivize pension funds or other retirement payers to invest in the equity tranche of a longevity megafund provided it brings enough return, including enough return in a wide range of longevity scenarios.

3. Potential rate of return of a longevity megafund

In this section we first discuss the rates of return of pharmaceutical developments, we then estimate their evolutions in case of longevity scenarios and we then investigate corresponding rates of return for the equity tranche of a longevity megafund.

3.1. Rate of returns of pharmaceutical developments today

There has been much debate on the rate of return of pharmaceutical developments. For example, the average research and development cost per pharmaceutical development has been reported to be USD 2558M by DiMasi *et al.* (2016) but less than USD 59M by Light and Warburton (2011). Appendix B navigates through such inconsistent historical reports, but also consistent open data and recent investigations, and concludes that the pharmaceutical development returns have been relatively stable. The return of a large portfolio of pharmaceutical developments can be put in a model defined by Fernandez *et al.* (2012) where an initial investment C_0 leads ten years later to a gain Y_{10} with a probability p(success rate): the 10-year return is

$$\rho = \frac{p \times Y_{10} + (1-p) \times 0}{C_0} \qquad (12)$$

and the annualized return is

$$r = \left(\frac{p \times Y_{10}}{C_0}\right)^{\frac{1}{10}} - 1 \qquad (13)$$

Based on the analysis in Appendix B, the success rate p from undertaking a first small clinical trial to commercial approval would typically be about 12%. The average research and development cost would typically be C_0=USD 50M, let us consider C_0=USD 55-60M due to megafund management fees, and the average 10-year gain when selling results to pharmaceutical companies Y_{10}=USD 1.5 Bn. The corresponding annualized returns are then 11.6%-12.5%. In fact, returns may be quite different depending on the strategy of the megafund so the numbers initially chosen by Fernandez *et al.* (2012) for a cancer megafund seem reasonable to us for a longevity megafund under current conditions (i.e. the current longevity trend φ=20%): ρ=3.1 and r=11.9%.

The next two sections investigate how megafund returns evolve with longevity trends, for a generic biomedical megafund and for a longevity megafund.

3.2. Evolution of biomedical megafund returns with longevity: "Linkage 1"

This section investigates how megafund returns evolve with longevity trends, for a generic biomedical megafund that invests in all kinds of pharmaceutical developments.

In the 19th and 20th centuries, infant mortality rates and young adult mortality rates have dropped. Now, the future of life expectancy will more and more become a matter of solutions to old age conditions (see Vallin and Meslé (2010)). We apply that latter view in the context of how much successful pharmaceutical developments are paid when they extend lives.

Currently, biomedical developments and longevity are poorly linked: the approximate 3 months of increase in life expectancy per year are still largely a matter of improved lifestyles and many biomedical innovations address health needs that do not relate to longevity – for example, migraine or glaucoma treatments. The OECD estimates that 37.2% of the current longevity trend is due to health care spending, other factors being improved education, improved income and decreased smoking and alcohol consumption (see OECD (2017)). This means that biomedical innovation accounts for less than an additional month of life every year: out of approximately **35 new molecular entities and biologicals per year** some may add one week but others zero day. Under such circumstances with longevity trends $\varphi < 30\%$ the profitability of a biomedical megafund, that invests in very diverse pharmaceutical developments, should be close to the one described above: $\rho = 3.1$ and $r = 11.9\%$.

However, it is difficult to imagine that life expectancy may become much higher than the age of 100 only with lifestyle improvements (see Gavrilov *et al.* (2017)): **health care improvements will *de facto* be the main driver for large longevity increases**. A longevity scenario is for example that 35 new molecular entities and biologicals are still produced per year but now they mostly address critical life limiting conditions, such that each therapy on average adds one week of year to life expectancy. Under that scenario, biomedical innovations alone increase life expectancy by 35x7/(365/12)=8 months per year. The megafund gains would then depend on **accepted costs per year of life saved through biomedical intervention**.

Accepted costs notably increase with the perception of a critical need and with the ageing of populations (see Murphy and Topel (2006)). An analysis in **1995** of 500 life saving interventions suggested additional costs of **42** k$ per additional life-year but only **19** k$ for the specific case of medical interventions (see Tengs *et al.* (1995)). However, for cancer patients this number was **54**k$ in 1995 and it ramped up to **217**k$ in **2013** (see Howard *et al.* (2015)). In the UK the NICE used to accept biomedical innovation for 20 to 30k£ per additional healthy year of life (see Devlin (2003)). Elsewhere, **50k**$ has long been the common reference and higher numbers are now often used (see Neumann *et al.* (2014)). Based on all these numbers, we consider 50k$ as a reasonable accepted cost per life year gain, and since pharmaceutical companies would typically pay 40% of the value to the megafund (Stewart 2001) we consider that the gains provided by the megafund should be the order of **20k$ per additional year of life per person** (40% of 50k$).

Let us now design a model of megafund profitability that accounts for both low longevity scenarios and high longevity scenarios with some smooth intermediate shape. We use the following formula for the 10-year profitability ρ :

$$\rho = ln(exp(\rho_L) + A) + \varepsilon \qquad (14)$$

where the coefficients, ρ_L, A and ε are defined as follows.

ρ_L is a function of longevity that increases the profitability ρ with longevity. Under strong longevity scenarios, the parameter A is small compared to $exp(\rho_L)$ and then $\rho \approx \rho_L + \varepsilon$: ρ_L represents the evolution of ρ with longevity. Historically, this evolution can be estimated via the annual 35 new molecular entities and biologicals described above, that are taken by approximately 10 M patients in the years under patent:

$$\rho_L = \frac{p \times Y_{10}}{C_0} = B\varphi \qquad (15)$$

with $B = \frac{p \times (Y_{10}/\varphi)}{C_0} = \frac{10\% \times (20{,}000\ k\$/\varphi) \times 10M}{35 \times 50M\$}$ =11.4. The 10M patient is an estimate provided by experts but it corresponds for example to 21% of 48.5M of Americans over age 65 (see Human Mortality Database) which is half of those taking polypharmacy (see Kantor et al (2015)), a proxy for using one of the 35 drugs.

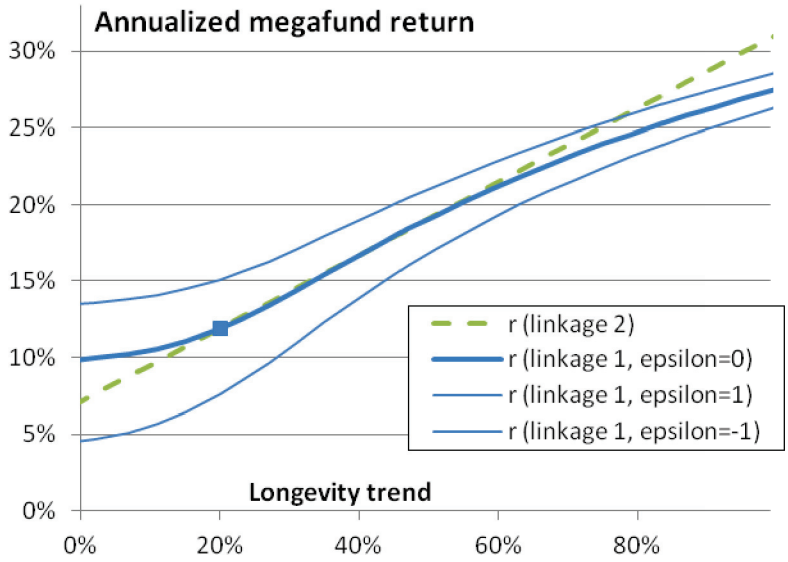
A is a coefficient to set profitability at the right level. Historically, $\varphi = 20\%$ and $\rho = 3.1$ so we take $A = exp(\rho) - exp(\rho_L) = e^{3.1} - e^{11.4 \times 20\%}$=2.48 to get $\rho = 3.1$ for $\varphi = 20\%$.

The residual performance ε of the megafund, due to factors not present in the equation such as the quality of the fund managers, is a uniform random number between -1 and 1 given that the measure of p=10% is unsure by approximately 5% (see Thomas *et al.* (2016), Wong *et al.* (2018)) and that prices are unsure too (as seen with the Royalty Pharma density above).

We call that link between longevity and returns "linkage 1"; it is for a megafund that invests in a large set of biomedical developments like the 35 new molecular entities and biologics mentioned above. Figure 3 shows the corresponding annualized profitability $r = \rho^{\frac{1}{10}} - 1$. With ε=0, 1 and -1 the annual return under the current longevity trend is respectively 11.9%, 17% and 7.6%. The curve is concave.

As we have seen, various assumptions have lead to this link. This may lead to slightly higher or lower returns, which can be taken into account in ε definition. In practice, a megafund could have its own development strategy and have consequently greater or lower returns and document it for investors. In any case, as we will see, a pension fund could then adjust its share of investments in the megafund accordingly.

Fig 3. Megafund annualized return r as a function of longevity trend φ



The square represents the central scenario with a future longevity trend of 20% and an annualized return of 11.9%. If the megafund target a very wide variety of pharmaceutical developments, returns are expected to depend on the longevity trend as show by the continuous (blue lines; the thick line is the best estimate, the thin lines represent a range of uncertainty): "linkage 1". If the megafund targets mortality-linked diseases, the expected link with longevity is the (green) dashed line.

3.3. Evolution of longevity megafund returns with longevity: "Linkage 2"

This section investigates the link between megafund returns and longevity in case the megafund invests in solutions against aging processes and life-threatening diseases.

Various considerations could further strengthen or weaken the concavity of the curve observed in Figure 3. On the one hand for example, the longevity wave may mostly occur via an improved success rate as many biology of aging discoveries may enter hospitals and offer various new ways to treat the aging and chronic diseases that are currently difficult to treat. On the other hand, as the accepted cost depends on the perceived criticality of needs (see Howard *et al.* (2015)) it may be possible that new health treatments are not perceived as critical in a longevity scenario and the accepted cost may not necessarily increase.

Let us now consider a longevity megafund: a biomedical megafund that is particularly focusing on conditions that are linked with mortality and longevity. The return may be lower in case of low longevity trend and higher in case of high longevity trend, due to the returns provided by biology of aging solutions. Obviously and as we will see, this provides a better longevity risk management tool.

Mathematically, the link between longevity and return would be less concave and we model it with a linear approximation of "linkage 1":

$$r = 7.1\% + 24\% \times \varphi + 4\% \times \varepsilon \qquad (16)$$

This "linkage 2" is chosen to fit the approximately linear part of the "linkage 1" curve seen in Figure 3. With ε=0, 1 and -1 the annual return under the current longevity trend is respectively 11.9%, 15.9% and 7.9%.

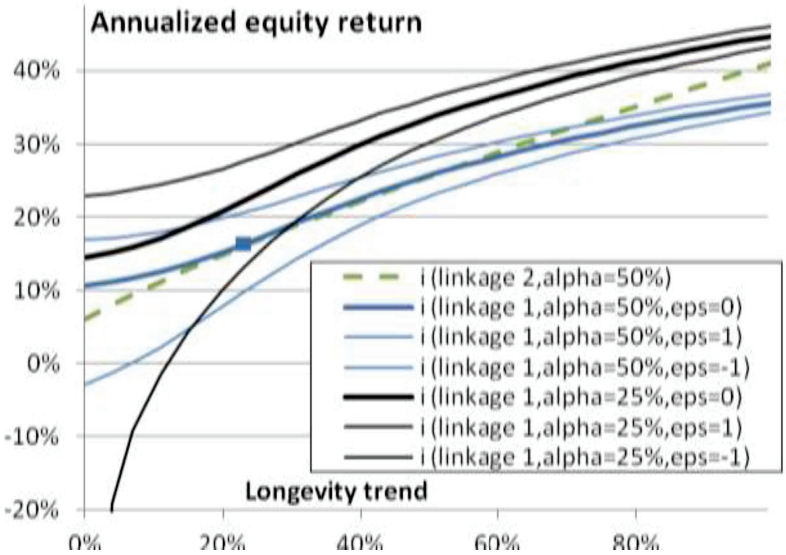
3.4. Evolution of megafund equity returns with longevity

In practice, a pension fund may invest in the equity tranche of the megafund rather that in the whole megafund. A megafund must be structured into debt and equity (non-debt) because without the debt part it would be difficult to find enough investors to have enough drug development programs financed for the megafund risk to become small compared to returns, hence to be financially attractive. The debt part, composed of "research-backed obligations" (RBOs), provides fixed annual returns: it cannot hedge longevity risk. Therefore i, the annualized return of the equity part of the megafund, that provides gains in excess of RBOs, is the rate that matters to possibly cover longevity risk:

$$i = \left(\frac{\rho - (1-\alpha) \times 1.05^{10}}{\alpha}\right)^{\frac{1}{10}} - 1 \qquad (17)$$

where α is the equity percentage of investments in the megafund and where we supposed that the annual interest rate of the RBOs is 5%. Indeed, if I is the total of investments received by the megafund αI is the investment in the equity tranche, ρI is the gain generated 10 years, it first pays $(1-\alpha)I \times 1.05^{10}$ to the RBOs investors – who invested $(1-\alpha)I$– and so that equity investors receive the reminder, $\rho I - (1-\alpha)I \times 1.05^{10}$: this must be compared to the initial αI investment 10 years earlier. When the 10-year return of drug developments is $\rho = 3.1$, having $\alpha = 50\%$ or 25% of investments dedicated to the equity tranche leads to $i = 16.4\%$ or $i = 22.3\%$, respectively: the equity share can be used as a lever to obtain higher returns if there are enough successful drug development programs (at the cost of reducing returns if there are not enough). Figure 4 shows the corresponding equity return as a function of longevity trend. Greater returns are found except with the stronger lever ($\alpha = 25\%$) and lowest longevity ($\varphi < 7\%$ here): here, strongly negative returns are found, highlighting that the lever effect bears risks. Even though a pension fund should make gains when longevity is high, it should make sure these are sufficient in such a scenario.

Fig 4. Annualized equity return i as a function of longevity trend φ



This graph is similar as Figure 3 except that (black) curves are superimposed to should annualized equity returns: the annualized returns of investing in the equity part of the fund, rather than the whole megafund annualized return.

4. In which cases will a pension fund benefit from investing in a megafund?

We have seen that a longevity megafund can provide high equity returns in case of longevity, suggesting an interest for pension funds to invest in a longevity megafund. This part analyses the conditions of interest, starting by deciphering different types of pension funds and other types of retirement systems.

4.1. What type of retirement systems would benefit from investing in a longevity megafund?

Retirement systems are mainly composed of defined benefit plans, defined contribution plans, pay-as-you-go plans, and voluntary insurance retirement contracts (see US Department of Labor (2016), House of Commons Work and Pensions Committee (2016) and Broadbent *et al.* (2006)).

So far, to our knowledge the literature suggests that longevity megafunds may hedge longevity risk, without investigating what type of plans would best benefit from investing in a longevity megafund.

4.1.a. "Defined benefits" means that the pension benefits are defined and guaranteed by the pension fund. The fund is reponsible for the investments and bears the longevity risk. The capital may be handed over to an insurance company which will bear the longevity risk. The benefits are typically defined as a percentage of the pensionable salary, for example 20% of the average salary over the last three years of work. Investing in a longevity megafund could be a way for defined benefit pension funds to partially hedge their longevity risk: in case of strong longevity improvements, investment returns should be greater so that the accumulated capital can pay benefits longer than the prospective life expectancy calculated at time of retirement.

4.1.b. In defined contribution plans, employer and employees provide contributions during their working years. Often, employees make investment choices to build their capital for retirement. The amount of accumulated capital depends on how well investments perform. Often, the accumulated capital is transferred to an insurance company that pays annuities and bears the longevity risk. The risk can also be at the level of the pensioners in case of a lump sum, but they can also buy annuities. In recent decades, a shift has occurred from defined benefit plans to defined contribution plans in order to avoid the financial risk borne by the fund during the capital build up period.

If the pension fund or the employees decide to invest in the longevity megafund, the accumulated capital should increase with longevity. This is interesting for the employees but if they decide to annuitize their wealth the annuity amounts would consequently be greater and the longevity risk borne by the pension fund or the insurer would actually be greater in the same proportion. Therefore, and paradoxically, investing in the longevity megafund during the capital build-up period is good the employees but probably not for the pension fund or the insurer (it depends on whether employees decide to annuitize their wealth). Investing in the megafund in the retirement period remains a way to reduce longevity risk, but it is not customary to invest the retirement capital in exotic funds.

4.1.c. In pay-as-you-go pension plans there is no, or very little, investment: the contributions from employers and employees directly pay the benefits to retired persons. In such a system, that is for example widely used in France, the lack of investment makes the longevity megafund of no use for the pay-as-you-go pension plan itself. However, retirees may ask an insurer to annuitize their wealth and the insurer would benefit from investing it in a longevity megafund.

4.1.d. In conclusion, from a first qualitative perspective the equity part of a longevity megafund makes sense for defined benefit pension plans and for the investment of retirement capital by any stakeholder, but a priori not for the investment of contributions by defined contribution pension plans that bear the longevity risk, as it would be increased.

Our analysis is somewhat simplistic as numerous retirement systems exist and risks can be transferred to stakeholders who have distinct characteristics. For example, insurers providing deferred annuities may transfer their longevity risk to reinsurers who might benefit from investing in a longevity megafund. Also, various practical aspects such as counterparty risk, basis risk and megafund returns – of course – may require to adapt the conclusion.

4.2. Impact of investing in a megafund on needed prudential capital

We here extend the simulation of the needed prudential capital seen at the end of the second part of the paper, by having the pension fund invest a percentage of contributions in the equity part of a megafund.

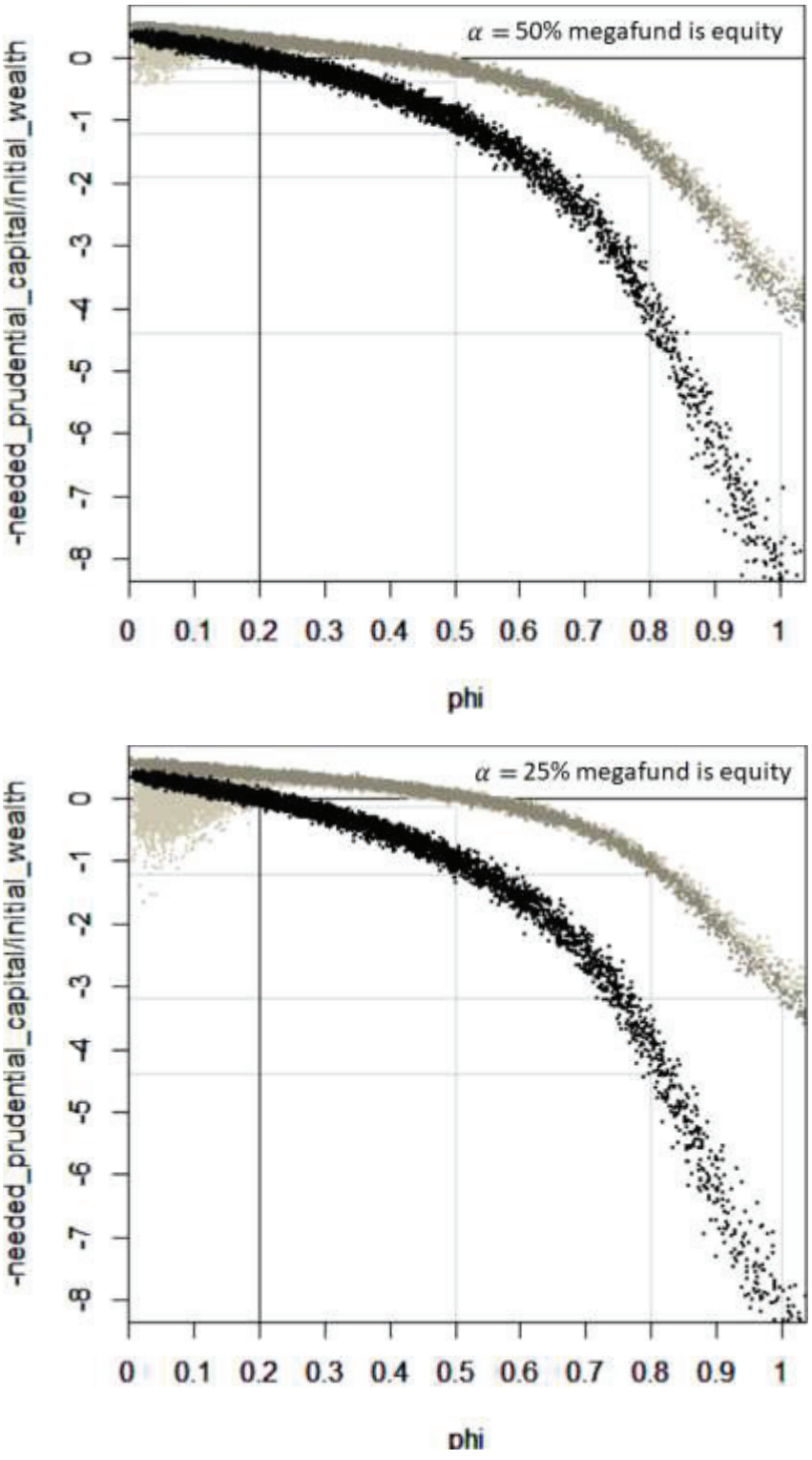
Let p1, p2, p3 be the percentage of contributions invested in the equity part by age tranche, with the age tranches described in Table 1. The equity part of a megafund offers a higher expected risk and return than investments performs when approaching retirement, as seen in Table 1. For that reason we consider p1>p2>3: p1=20%, p2=15%, p3=10% and we name it a "material investment". Since the megafund is a new type of structure we think that pension funds would not invest more in the coming decade, even if it significantly reduces longevity risk.

The differences in simulations are that at t=0, the residual performance of the megafund (ε) is a new variable that is randomly chosen between -1 and 1 for each simulation and that the contributions to the megafund and the gains from the megafund are computed.

Figure 5 shows the needed prudential capital, expressed as a proportion of the initial wealth, depending on the future longevity trend. A first result is that much less prudential capital is needed when investing in the megafund but the longevity risk coverage becomes gradually limited with longevity trends φ >70%. A second result is that a biomedical and longevity megafund lead to approximately the same coverage when φ is between 20% and 70%, but a longevity megafund has a higher risk to create losses if φ<20% and greater longevity risk coverage if φ>70%. This is expected from the linear approximation performed in Equation 16 to model the return of a longevity megafund. It is also expected due to the nature of a longevity megafund, that focuses on more specific biomedical advances but that should better cover fundamental improvements of health as we age. A third result is that a megafund with a lower share α of equity investments leads to a better coverage in case of strong longevity trends but also a stronger risk of losses when investing in a longevity megafund and when φ<20. This is also expected: when the returns of the pharmaceutical developments are greater than the fixed return, the larger the fixed income share the greater the remaining profits, that are distributed to the equity share; and this leverage works both ways, when megafund returns are lower than 11.9.

One may wonder if the megafund still covers longevity risk well with a mild investment or without structuring the megafund between debt and equity (α=100%). We define a "mild investment" as half of the material investment: p1=10%, p2=7.5%, p3=5%. Table 2 explores the needed prudential capital with respect to diverse investment options. Clearly, longevity risk is reduced when investing more in the megafund, when investing in a megafund that has a reduced share of equity and when investing in a longevity megafund, that targets longevity-related pharmaceutical developments. However, it is also the option that bears risks if φ<20, as seen in Figure 5. Moreover, a basal prudential capital must exist due to aspects that we only approximately modeled with "ε" so the modeled 14-fold reduction prudential capital when materially investing in a biomedical megafund having 50% of equity is suspicious. An optimal megafund structure in these respects would be a mix between a biomedical megafund with 25% equity and a longevity megafund with 50% equity.

Fig 5. Needed prudential capital, expressed as a proportion of the initial wealth, depending on the future longevity trend and on investments in a longevity megafund



The first graph is for a megafund that uses 50% equity investments, the second graph is for a megafund that uses 25% equity investments. Each dot in the graph is the result of a scenario of the future. In black, no investment is performed in the megafund (p1=p2=p3=0). In light gray, the pension fund invests in the longevity megafund. In gray, the pension fund invests in the generic biomedical megafund.

Tab 2. Needed prudential capital, expressed as a proportion of the initial wealth, depending on investments in a longevity megafund

	85% VaR	90% VaR	95% VaR
No megafund	1.4	2.8	8.5
Longevity megafund that has 25% equity	0.3 0.6	**0.6 1.4**	**2.4 4.6**
Biomedical megafund that has 25% equity	**0.1 0.6**	**0.5 1.4**	3.3 5.1
Longevity megafund that has 50% equity	0.3 0.8	0.9 1.6	3.1 4.9
Biomedical megafund that has 50% equity	0.3 0.7	0.9 1.6	4.0 5.8
Longevity megafund that has 100% equity	0.5 0.9	1.2 1.8	3.9 5.4
Biomedical megafund that has 100% equity	0.5 0.9	1.2 1.9	4.6 6.4

Each line is a different way to invest contributions, and each column is a different definition of the needed prudential capital. Each cell contains two numbers (except for the first line that serves as a reference), with a precision of circa 0.1. The first number is the needed prudential capital in case of a material investment in the megafund (p2=15%), the second number in case of a mild investment (p2=7.5%). For example, taking a 90% VaR, a material investment in a megafund leads to a needed prudential capital that is less than the initial wealth instead of almost three times the initial wealth.

5. Conclusion

The current article studied the conditions in which investing in a longevity megafund can cover the longevity risk of a pension fund.

With assumptions that such a megafund is reasonably well managed, it appeared that the cover may work for defined benefit and to some extent for defined contribution pension schemes, however with some limitations if life expectancy starts to increase by typically 9 months per year.

The risk analysis performed at the end of the second section suggests that the short-term prudential capital risk approach that is currently proposed by diverse regulators, such as the Solvency Capital Requirement in insurance, may not lead to the right order of magnitude of prudence. We defined the notion of needed prudential capital to face long term risks, having in view likely upcoming significant discoveries in the biomedical, aging-related field. The amounts of needed prudential capital we compute is not 10% or 30% of the initial wealth but rather 140%, 280% or 850% depending on the desired level of value at risk (85%, 90% or 95%).

Investing 10% to 15% of assets in a longevity megafund, that invests in pharmaceutical developments with a particular focus on longevity-related developments, would typically divide the needed prudential capital by 3 (by 2 to 14 depending on conditions, as seen in Table 2). In case of rapid longevity increases, retirement systems should ideally be thoroughly adjusted. Since adjusting retirement systems is not easy, a longevity megafund may help accompany changes over time.

The longevity megafund remains at this stage a theoretical concept. If the biomedical discoveries described at the beginning of the article truly extend human lifespan in a very significant manner, it may be important to develop this longevity megafund solution early enough. It is therefore a good timing to perform more research on the predicted behavior of the megafund, that we could not study here in details.

For example, given the numerous pension funds, biomedical researchers and pharmaceutical developments worldwide, mechanisms may be investigated to favor their interaction towards a longevity megafund that favors both the financing of health and of retirement systems. Also, given that the longevity megafund concept fits defined benefits schemes better than defined contribution schemes, solutions for contribution schemes should be investigated.

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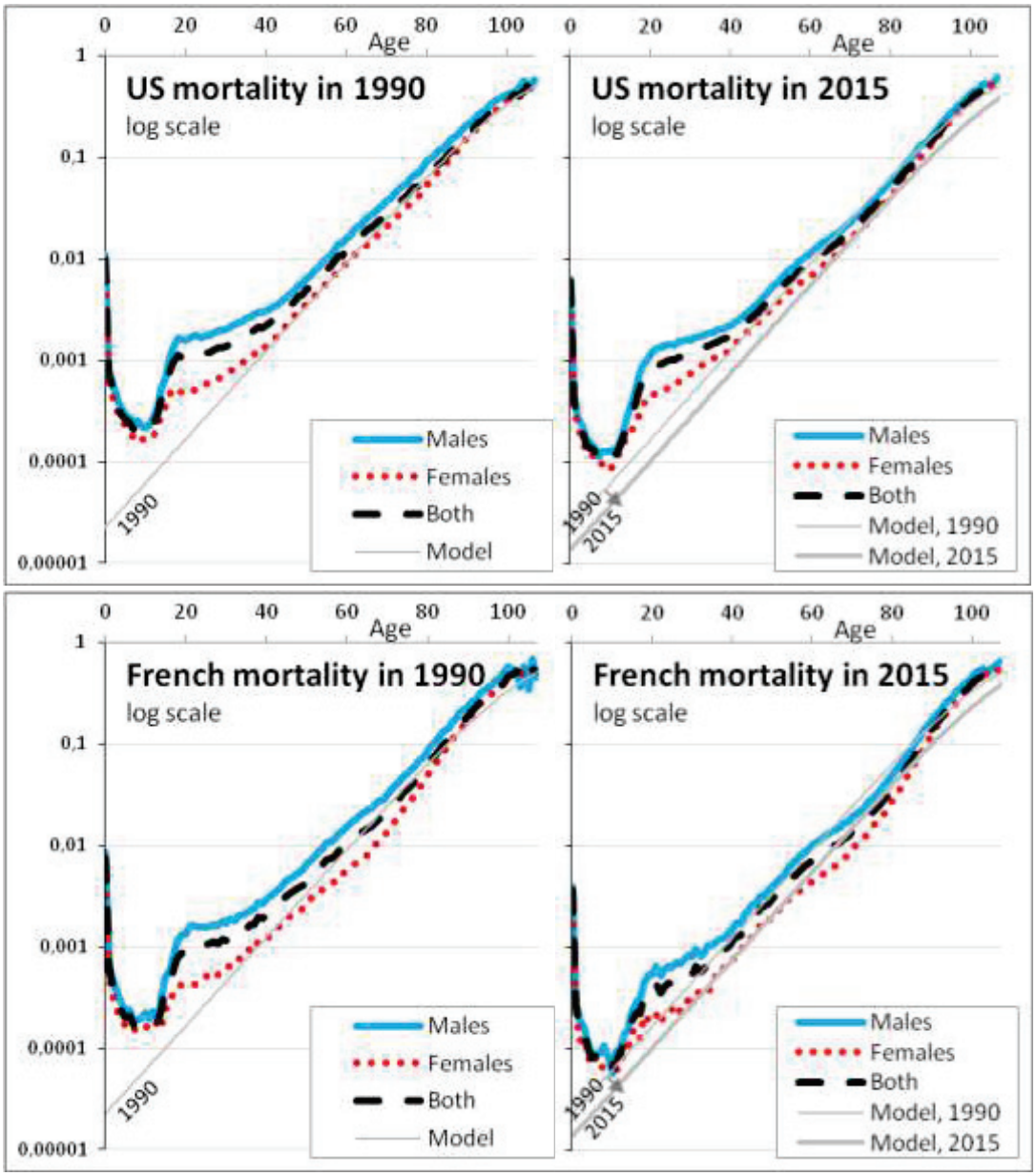
Appendix A - Choice of the mortality model

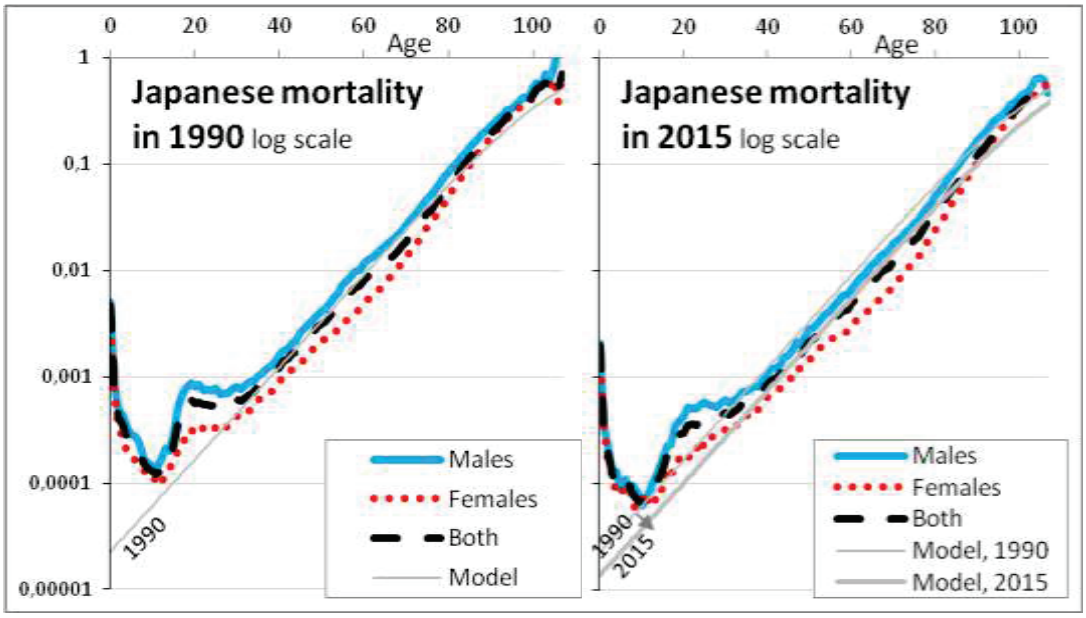
This part describes the choice of the mortality model described in Equations 1 and 2 with greater details than in part 2.

The time, **t**, is expressed in years and t=0 at year 2020: to compute capital needs we consider a population or workers in 2020 and study in parts 2 and 4 how to finance its pensions.

The parameter **b** can be understood as the natural relative increase of mortality with age. We take b=10%: this is approximately the historical slope of log-mortality rates between ages 40 and 90, as shown for France, Japan and the USA for the years 1990 and 2015 in the third and fourth graphs of Figure 1 and in greater details in Figure 6. Said differently, every increase of age by one year is associated with an increase of mortality risk by approximately 10% of its value.

Fig 6. Historical mortality rates, for three countries and as modeled





Annual mortality rates are shown in log scale as function of age, for the USA, France and Japan (graphs from top to bottom), in 1990 and in 2015 (graphs on the left and on the right). Each graph shows the mortality of males in a (blue) continuous line, the mortality of females in (red) dots, the mortality of both in (black) dashes and the mortality of the model used in this article in a gray line that is visually straight up to age 85. For the graphs on the right, the mortality of the model in 1990 is added to help visualize the change of mortality between 1990 and 2015.

Other parameters are defined using the concept of static and prospective life expectancy. The ***prospective*** **life expectancy** of a population aged x at time t, $L_{x,t}$, is how long that population lives on average if its mortality rates evolve according to a model. The ***static*** **life expectancy** of that population, $e_{x,t}$, is how long that population lives if mortality rates were not evolving after time t. The word "static" is generally omitted.

Mathematically, the static or prospective life expectancy is the area under the survival curve of the population. As generally done in actuarial science, we approximate that area by consecutive rectangles. The rectangles are centered at every round age (we here name u the age at which survival is estimated; u>x). They are of width one year except the first one, of height 1 and width 0.5 year. This leads to the following formulas where we indicate the computation of survival, S(u), for the sake of clarity:

$$L_{x,t} = 0.5 + \sum_{u>x} \underbrace{\prod_{v\geq x}^{v<u} (1 - q_{v,t+(v-x)})}_{S(u)} \quad (18)$$

$$e_{x,t} = 0.5 + \sum_{u>x} \underbrace{\prod_{v\geq x}^{v<u} (1 - q_{v,t})}_{S(u)} \quad (19)$$

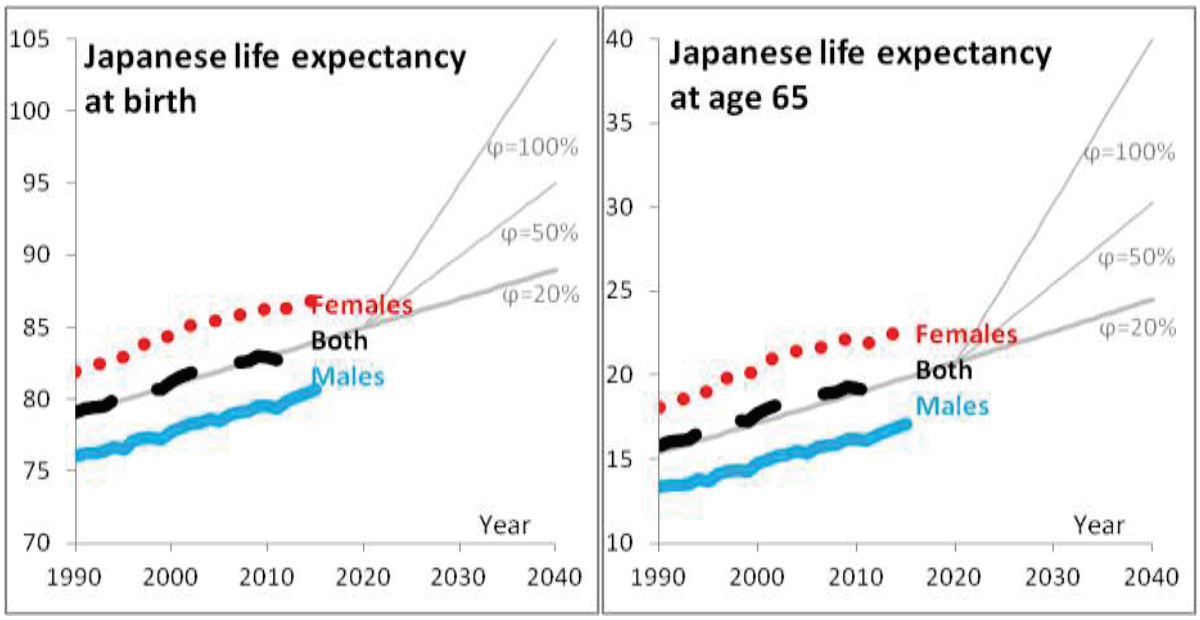
In the calculation, for practical reasons we must set a limit for u, rather than infinity. It must be an age that has a negligible probability to be reached according to the model. We arbitrarily take 300

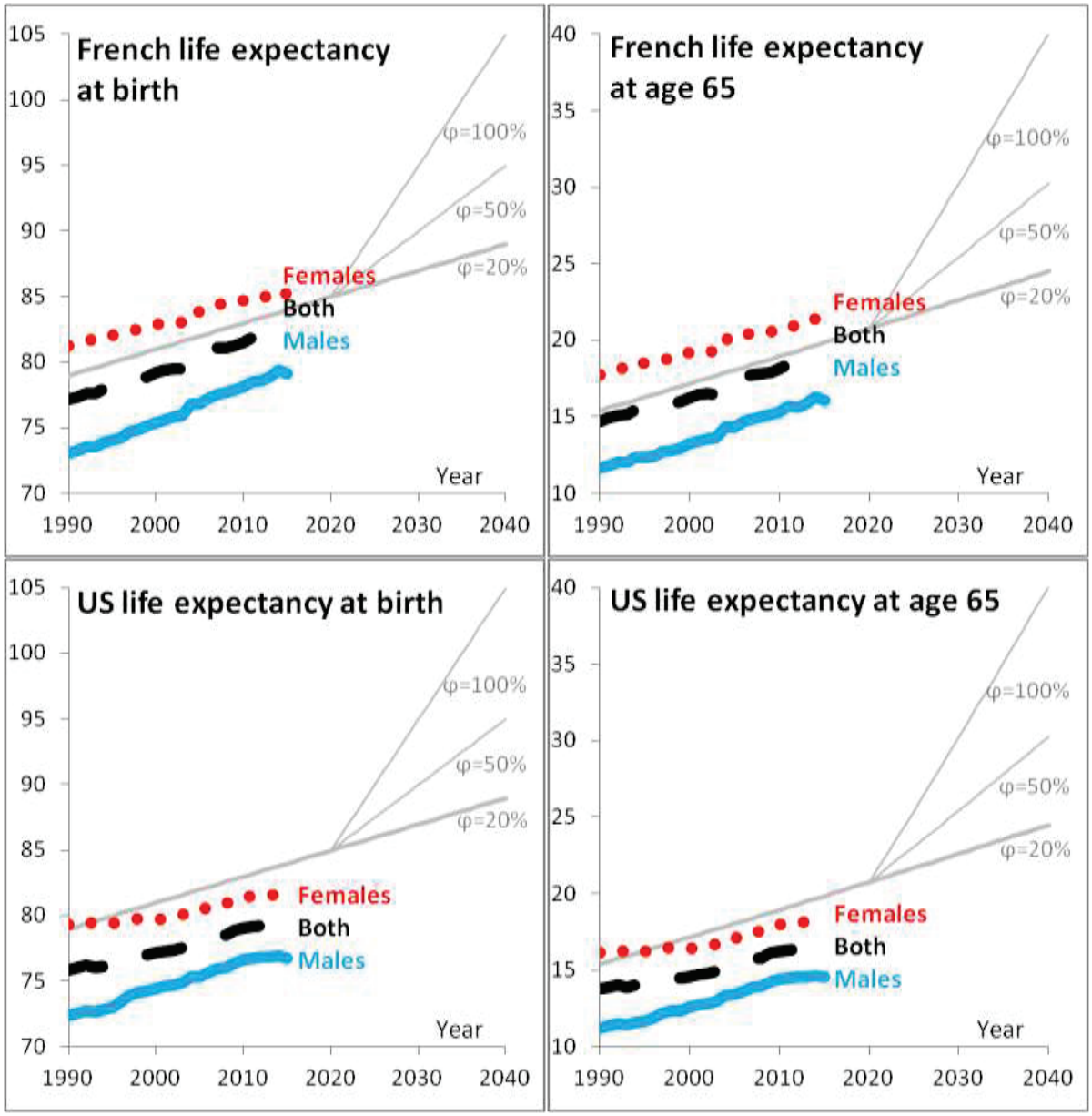
years and have checked that taking 300 or 400 years does not materially affect the estimates here performed.

The parameter **a** can be understood as the initial life expectancy level (or initial mortality level but mortality rates increase when a is decreased). Knowing that what matters most for the article is to simulate various longevity scenarios, we choose one reference country, Japan in our case, and we choose a=11.3: this provides a reasonable estimate of life expectancy at birth and at age 65 of the Japanese general population in 2020, as shown in the two first graphs of Figure 1 and in greater details in Figure 7.

For the reference country we choose **Japan** as it is a long-lived country. We do so because in most countries the mortality of pensioners would be expected to be lower than general populations owing to their socio-professional levels. This is all the more relevant as the model should represent mortality weighted by amounts (one would expect pension level, health and low mortality to be positively correlated due to social inequalities) to model capital needs. Still, the model could be adjusted to a particular population by using a different value for a. It is to be noted that further **refinements** could be made, such as a better mathematical shape of log-mortality as a function of age using for example an adaptation of the model of Heligman and Pollard (1980) as described by Debonneuil (2015). These refinements were deemed unnecessary in the context of this article.

Fig 7. Static life expectancy at birth and at age 65, for three countries and as modeled





Life expectancy at birth (graphs on the left) and at age 65 (graphs on the right) are shown as function of calendar year, for Japan, France and the USA (graphs from top to bottom). Each graph shows the mortality of males in a (blue) continuous line, the mortality of females in (red) dots, the mortality of both in (black) dashes and the mortality of the model used in this article in portions of gray straight lines. More precisely, φ=20% is used for the thick straight line and φ=50% and φ=100% is used for the two thin straight lines that start in 2020.

Let us now discuss φ, that represents the longevity trend. As explained for a broader range of models by Bongaart (2004), Equation 1 produces annual increases of life expectancy at birth by φ years because increasing t by 1 year produces the same mortality rates as decreasing x by φ year (and because at birth, where decreasing x does not make sense, the model produces negligible mortality rates compared to adult mortality rates). For example, to model life expectancy increases of a quarter every year we would consider $\varphi = \frac{3 \text{ months}}{12 \text{ months}} = 25\%$. This is a clear behavior compared to various actuarial models, such as the model from Lee and Carter (1992), that are often believed to extrapolate historical trends with a neutral view but actually tend to produce decelerating life expectancies and no longevity improvements ultimately (see Bongaart (2004) and Debonneuil *et al.*

(2017)). Another clear behavior of the model is to produce mortality improvements that are $\frac{\varphi}{10}$ at young ages (because we use b=1/10) so 2.5% in the example of an additional quarter per year. These mortality improvements gradually lower with age without forcing mortality improvements by age to be constant over time.

As highlighted in the first two graphs of Figure 1 for 3 countries and by Debonneuil *et al.* (2017) for a range of 24 countries, $\varphi = 20\%$ fits the current longevity trend. This why we consider **φ=20% before t=0**. Debonneuil *et al.* (2017) used a similar model, "Best Practice Trend", that is more complex to express in terms of annual mortality rates $q_{x,t}$ but that has the same longevity trend feature.

However, the **future longevity trend** may be different. A wide range of potential longevity increases can happen as we have seen, so we use a **lognormal distribution** of φ. Its median is 20% to have a 50% chance of greater or lower longevity trend. The probability density function is then the one shown in Equation 2. Considering a possible wave of solutions for age-related conditions in the coming decades we set the standard-deviation **s** to 1. This leads to a 5% probability that φ>1 (precisely, based on 10 million simulations of φ we measure a probability of 5.38%). Over long periods of time, the latter corresponds to people enjoying better health and reduced mortality risks as time goes, for example because of the emergence and progressive generalization of tissue regeneration techniques. The future is unknown and some authors may argue that this probability of 5% is not reflective of future longevity trends. This is why at times in the article consider four **specific longevity scenarios** that could be weighted as a mean to represent other distributions of longevity risk: φ=0% (no improvement in the future), φ=20% (historical trend), φ=50% (wave of anti-aging solutions) and φ=80% (strong solutions to ageing).

The relevance of the φ=50% and $\varphi = 80\%$ scenarios and the relevance of a 5% probability of having φ=100% can be partially appreciated in light of **historical annual increases of life expectancy** that followed large implementations of biomedical discoveries. We attribute a value of φ to them because φ models annual increases of life expectancy. Around 1950 Japan had a trend above φ=100%, suggesting that high trends are possible when solutions for better health are known and are implemented. In the last decades, south Asian countries of Malaysia, Philippines, Vietnam, Laos and Bangladesh (see Carbonnier *et al.* (2013)) have experienced an increase above 50%. During approximately 70 years after the microbial communications of Louis Pasteur, φ was around 30% in long-lived countries (see Vallin and Meslé (2010)). The Pasteur example is particularly interesting as improving hygiene requires complex cultural, technological and urbanization changes: it can be foreseen that using anti-aging therapies once available is a faster process.

Appendix B - Investigation of the current rate of return of pharmaceutical developments

Biology of aging may be reaching the clinics now and in the forthcoming decades, which should in principle boost the pharmaceutical industry. However, for now a crisis is declared on the pharmaceutical side, with reported strong increases in research and development investments in the last decades, high cost of risk for investors, but strong decreases in success rates of drug developments (see Scannel *et al.* (2012)). Reported estimates of average research and developments cost are 802M$ (see DiMasi *et al.* (2003)) per successful drug, including the cost of failures, or more recently 2558M$ (see DiMasi *et al.* (2016)). Such **numbers are debated** to be less than 59M$ and it is suggested that most publicly available data in the field are biased (see Light and Warburton (2011) and Lazonick *et al.* (2017)).

In this delicate context of non-communicated cost structure, the first megafund studies conducted sophisticated analysis of historical drug developments.

For the **cancer megafund** (Fernandez 2012, in Supplementary materials) a markovian model was developed for simulations as well as two very simple models to explain the orders of magnitude of profitability: a model for blockbusters (drugs with annual revenues of more than $1 billion) and a model for non-blockbusters. These two models consist in an initial investment C_0, 200M$ and 100M$ respectively, leading ten years later to a gain Y_{10}, 12.3B$ and 3.1B$ respectively, with a probability p, 5% and 10% respectively. When using Equation 13 it happens that with these numerical assumptions the two models lead to the same **annualized return r of 11.9%**.

For the case of a **megafund against rare diseases** one would expect smaller investments and smaller gains: small clinical trial sizes may be accepted given the reduced number of patients, and the drugs would be commercialized to less patients. After detailed analyses (see Fagnan *et al.* (2015)), including refinements to be less dependent on industry averages (see Fagnan *et al.* (2016)), the costs for preclinical trials, phase I, and II (elements of C_0) are respectively estimated at about 3, 3 and 8M$, the resulting values (elements of Y) are estimated at about 7, 23 and 57M$ and success probabilities (elements of p) at about 80%, 87% and 53%. Put together, the final annualized rate of return is estimated to be **between 12% and 15%** (see Fagnan *et al.* (2016)).

Recently, the average costs, probabilities of success and durations of clinical developments have become **much clearer** following articles in 2016, 2017 and 2018 from teams with large amounts of data and incentives to be fair (see Sertkaya *et al.* (2016), Martin *et al.* (2017), Wong *et al.* (2018)). As a result, it becomes easier to estimate the megafund profitability by distinguishing **cost, success rate and gains** of pharmaceutical developments. We perform this analysis with a particular focus on the USA as it is by far the country with the most clinical developments (see Thiers *et al.* (2008)).

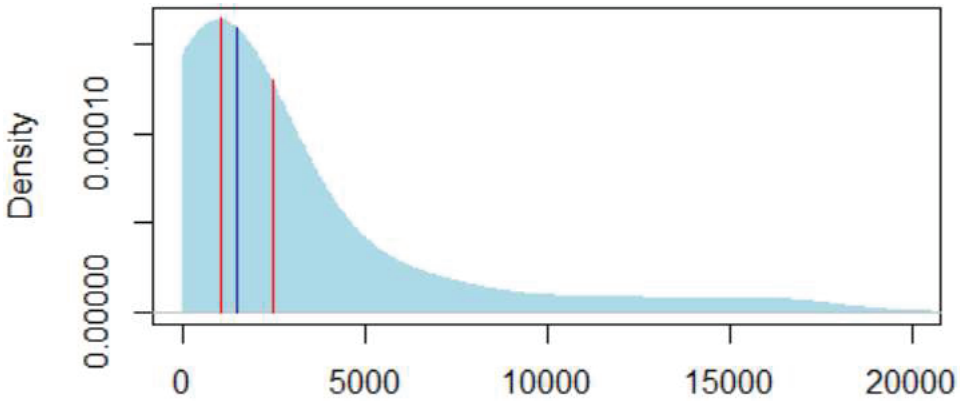
The average US **cost** of a phase I, II and III in the USA is respectively of 4, 13 and 20 M$ and the cost for the FDA approval step is smaller (see Sertkaya *et al.* (2016)). Similarly, the medium cost for major biopharma companies is respectively 3.4, 8.6 and 21.4M$ (not specific to the USA; see Martin *et al.* (2017)). When summing these numbers, in both cases **the cost of a drug development that goes through two phase I, two phase II, one phase III and one FDA approval is about 50M$**, or 0.05 bn$

(we considered two phases I and two phases II in this amount to represent additional costs such as reproducibility tests of biology of aging results). This order of magnitude is for all therapeutical areas on average as well as for the specific case of oncology (see Sertkaya *et al.* (2016)).

The **success rates** for a compound in phase I to reach the market is estimated by Wong *et al.* (2018) at **14%** (66.4% to reach phase II and then 58.3% to reach phase III and then 59.3% to reach approval; model that assumes at least 1 phase I, 1 phase II, 1 phase III if one of the phases is lacking in the data). It is greater than previous estimates at 9.1% (see Thomas *et al.* (2016)). It particular, it includes significantly higher success rates since 2013. Whether the later increase comes from a bias in their model or a real recent change, our further investigation based on open data does not confirm this trend very clearly so we will take a slightly **prudent** hypothesis in that respect.

We then estimate the megafund **gain of selling** the intellectual property to pharmaceutical companies by referring to the valuations obtained by Royal Pharma. Royal Pharma is a company that buys biomedical intellectual property and sells it to pharmaceutical companies. The sales amounts are reported online (Royal Pharma portfolio) and Figure 8 shows the distribution of amounts obtained. The median is 1.03 nb$. The average is 2.48 bn$. Two amounts are greater than 10 bn$, if removed the average becomes 1.66 bn$. With a margin of prudence as a megafund might not be as effecitient as Royal Pharma in optimizing sales, we considered a gain of **1.5 bn$** per successful pharmaceutical development.

Fig 8. Estimated gain per successful drug development based on Royalty Pharma sales



The x-axis of the two red vertical bars are the mean (2.48 bn$, on the right) and the median (1.03 bn$, on the left) of the sales amounts, in M$. The light blue shade is the density of the sales amount, using a smoothing gaussian kernel whose bandwidth is half of the sales standard deviation. The blue vertical bar, between the two red horizontal bars, is the gain we consider for investors in the megafund, under current longevity trends (1.5 bn$).

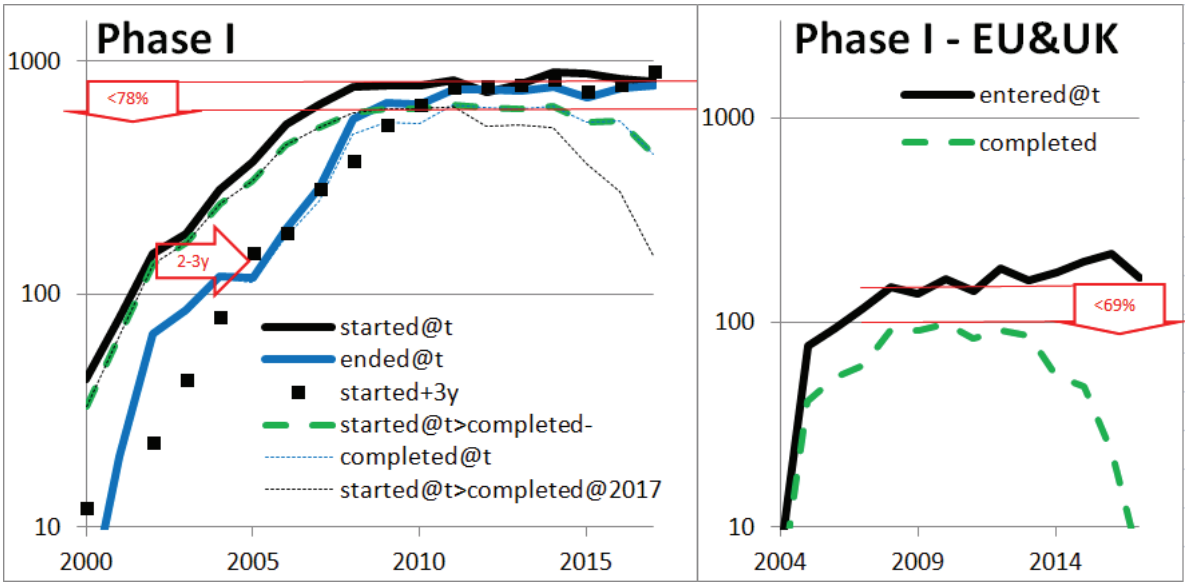
Combining costs of 50M$, a success rate of 14% and gains of 1500M$ in Equation 13 leads to an annualized return of $(14\%*1500/50)^{0.1}-1$ = **15.4%**. Using a slightly lower success rate as seen above, of 12%, and a greater cost to include management fees and carried interest as reminded by Phalippou (2010), of 60M$, leads to an annualized return of 11.6%. This is not far from the **11.9%** annualized return suggested by Fernandez *et al.* (2012) in the case of a cancer megafund.

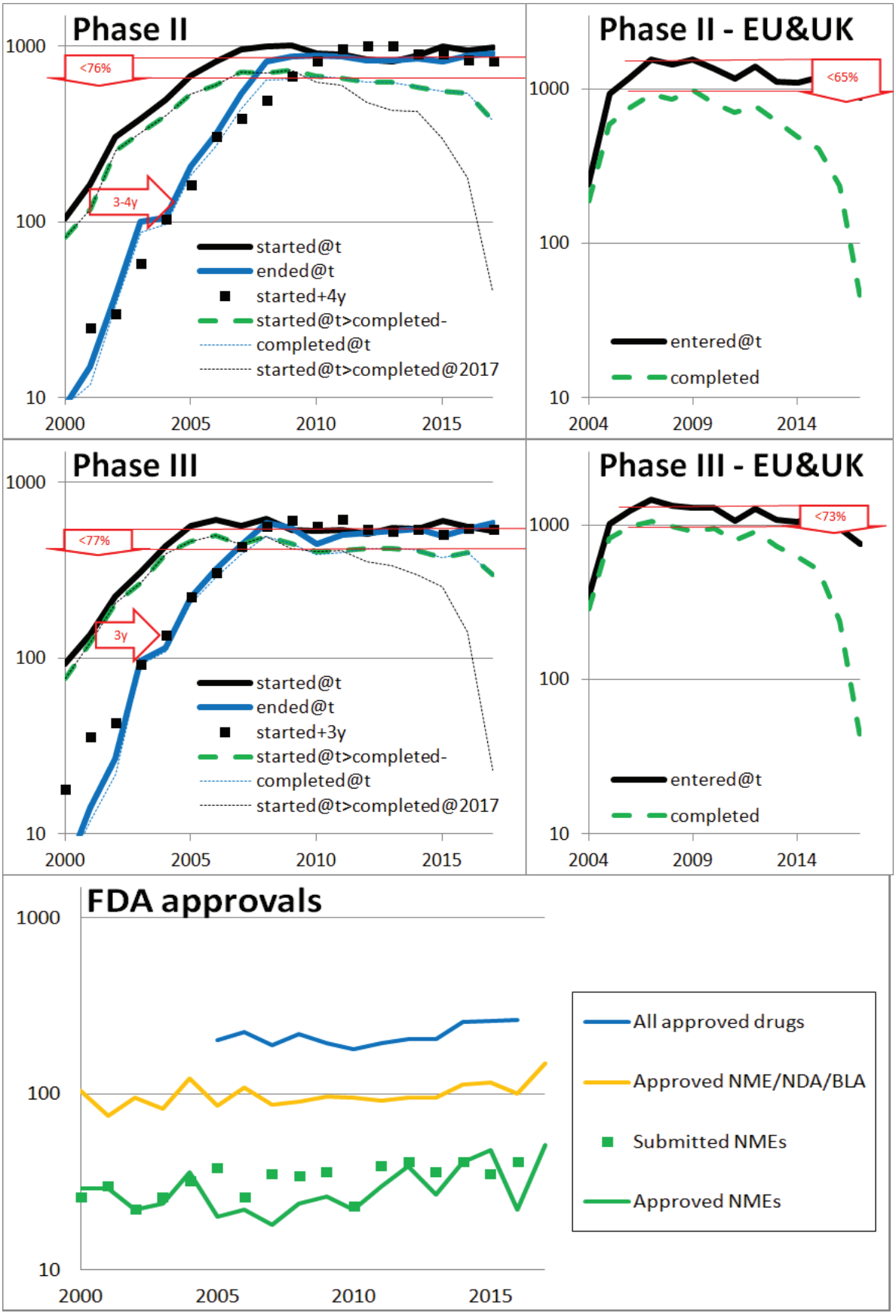
All these investigations are based on the literature. As we have seen there is conflicting data in the literature. In order to better decipher the right orders of magnitude, we analyzed the evolution of pharmaceutical developments based on open data. More precisely, we followed the evolution of

clinical trials and FDA approvals in the USA, Europe and the UK. We investigated the main types of clinical trials: Phase I, II and III. Phase I trials are conducted with a small number of patients (20-80) mainly to test safety and first side effects, phase II trials involve a larger group of patients (100 – 300) to determine efficacy against a placebo, and to further evaluate side effects, phase III trials are conducted with a large group of patients (1000-3000) to confirm efficacy and safety, and to compare the drug or treatment with existing ones. The results are shown in in Figure 9: various indicators of drug development are particularly stable which suggests that **the pharmaceutical research and development field is relatively stable**.

In particular, on the first 3 graphs on the left of Figure 9 the number of declared new clinical trials in the USA, according to clinicaltrials.gov, is stable since 2008 and roughly equal to the number of clinical trials ended: there are as many clinical trials starting than ending. Both the stability and the equality at a plateau suggest that, contrary to what one may read, **the number of clinical trials of each type has remained very stable**. Since declaring clinical trials in clinicaltrials.gov is needed to publish in the USA, it is a relatively reliable source.

Fig 9. Pharmaceutical drug development indicators based on open data: clinicaltrials.gov, clinicaltrialsregister.eu, Drugs@FDA and accessdata.fda.gov





The three first graphs on the left show numbers of USA clinical trials per calendar year t, for respectively Phase I, Phase II and Phase III reporting by the pharmaceutical industry according to clinicaltrials.gov. The Y-axis is in

*logarithmic scale. For each of them, the top (black) thick and continuous curve is the number of **clinical trials started** each year (first participant enrolled). The other thick continuous curve (in blue) is the number of **clinical trials ended** each year (primary completion data: last participant providing data for the primary outcome measure). A decay of 3 or 4 years of the first (black) curve is represented in (black) squares to see how well it compares with the second (blue) curve: the resulting estimated **length** of clinical trials is indicated in the (red) arrow pointing the right. The (black) thin dashed curve that plunges on the right side is the number of clinical trials started each year AND **completed** before 2018. The plateaus observed with the first two lines and the latter two lines, underlined (in red) differ due to the non-100% completion rate, as measured in the arrows pointing down (with a "<" sign with respect to success rate). The three graphs on the right side are equivalent slides but for **Europe and the UK**, based on clinicaltrialsregister.eu ; clinicaltrialsregister.eu is more recent than clinicaltrials.gov and does not provide the same filters so we only rely on clinical trials started each year, completed since or not. The last graph shows the **accepted drugs of different types in the USA**, by the FDA, every year. The top (blue) line represents any type of new drug accepted (United States Government Accountability Office, 2017). The middle yellow curve represents approvals for some specific types of treatments: New Molecular Entities (NME), New Drug Applications, Biologic License Applications (types 1 - 8 in Drugs@FDA, 2018). The bottom green curve represents NMEs only. The number of NME submissions (accessdata.fda.gov, 2018) is showed in green squares.*

Other observations on Figure 9 are less striking but they all similarly suggest a good stability of pharmaceutical developments, which contributed to our estimates of financial returns.

It is expected that the two curves are at a lower level before 2008 as clinicaltrials.gov is recent. The decay of the curves gives an estimate of the **duration** of the clinical trials including enrollment time: 2-3 years for Phase I, 3-4 for Phase II, 3 for Phase III.

The **rate of normal completion** of clinical trials (defined in clinicaltrials.gov as having the "last subject, last visit" occurred) is estimated by ratio between the number of completed trials and the number of trials. Even though the lines of completed clinical trials have bias both on the left (since clinicaltrials.gov is recent) and on the right (since not all trials have had the time to end), a plateau can again be seen. Looking at the difference of the plateaus (number of clinical trials and number of completed clinical trials), the data suggests that the rate of normal completion is stable for the different phases. These rates are approximately 15% greater than the success rate estimated by Wong et al. (2018), which is not incoherent.

The European and UK data suggests similar patterns although the more recent and not mandatory declaration in clinicaltrialsregister.eu make it less reliable: it is difficult to judge in what degree the results are different from the USA.

The last graph of Figure 9 indicates that the success rate from starting a Phase III – the costliest phase – to approval is greater than 50%: out of 400 annually completed phase III trials, 200 new drugs are accepted per year. This is more than is often perceived by communications in the field. Lastly, the squares are close to the curve and suggest that the FDA approval rate for new molecular entities is 89% over 1996-2016. All this is in factor of the non-negligible returns we estimated. The advantage of such open data is that anyone can reproduce the computation to appreciate that pharmaceutical successes are not rare and that investing in pharmaceutical developments is financially reasonably attractive.

Appendix 3 - List of figures, tables and variables in the article

In order to accompany the understanding of the concepts of this article, this part lists figures, tables and variables by theme: "Longevity model", "Returns of pharmaceutical developments", and "Pension fund needed capital".

Tab 3. Figures

Theme	Figure	Name
Longevity model	1	Characteristics of the chosen longevity model
	6	Historical mortality rates, for three countries and as modeled
	7	Static life expectancy at birth and at age 65, for three countries and as modeled
Returns of pharmaceutical developed	8	Estimated gain per successful drug development based on Royalty Pharma sales
	9	Pharmaceutical drug development indicators based on open data: clinicaltrials.gov, clinicaltrialsregister.eu, Drugs@FDA and accessdata.fda.gov
	3	Megafund annualized return r as a function of longevity trend φ
	4	Annualized equity return i as a function of longevity trend φ
Pension fund needed capital	2	Needed prudential capital depending on the future longevity trend (or lack of) expressed as a proportion of the initial wealth
	5	Needed prudential capital, expressed as a proportion of the initial wealth, depending on the future longevity trend and on investments in a longevity megafund

Tab 4. Tables

Theme	Table	Name
Pension fund needed capital	1	Contributions by age tranche
	2	Needed prudential capital, expressed as a proportion of the initial wealth, depending on investments in a megafund

Tab 5. Variables

Theme	Variable	Name	Definition
Longevity model	a	Level of longevity	Equation 1
	B	Ageing rate	Equ 1
	x	Age in years	Equ 1
	Φ	Longevity trend	Equ 1
	t	Year (t=0 corresponds to 2020)	Equ 1
	$q_{x,t}$	Annual mortality rate at age x and time t	Equ 1
	s	Standard deviation of potential longevity trends	Equ 2
	$L_{x,t}$	Prospective life expectancy at age x and time t	Equ 18
	$e_{x,t}$	Static life expectancy at age x and time t	Equ 19
	C_0	initial investment	Equ 12
	Y_{10}	gain ten years later	Equ 12
	p	probability of success	Equ 12

Returns of pharmaceutical developments	ρ	10-year return	Equ 12
	r	annualized return	Equ 12, 16
	ρ_L	evolution of ρ with longevity	Equ 14, 15
	A	parameter to ajust the expected level of ρ	Equ 14
	B	correlation between ρ and longevity	Equ 15
	ε	residual performance of the megafund	Equ 14
	i	annualized return of the equity tranche	Equ 17
	α	equity percentage of investments in the megafund	Equ 17
Pension fund needed capital	$N_{x,t}$	number of persons aged x at time t	Equ 3
	$C_{x,t}$	accumulated capital for the group of persons aged x at t	Equ 6, 7
	i1, i2, i3	expected annual return of contributions by age tranche	Tab 1, Equ 4
	σ1, σ2, σ3	standard deviation of the annual returns by age tranche	Tab 1, Equ 4
	$i_{k,t}$	annual return of contributions by age tranche and year	Tab 1, Equ 5
	W_0	initial wealth of the pension fund	Equ 8
	$B_{65,t}$	annual benefit paid to the workers who retire at time t	Equ 9
	$K_{\varphi,(i_{x,t})}$	needed prudential capital for a given scenario	Equ 10
	K	needed prudential capital	Equ 11
	p1, p2, p3	percentage of investments in the equity tranche by age tranche	Section 4.2