Prospective stochastic longevity modelling

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ABSTRACT
Mortality improvement has traditionally been analysed using an array of statistical methods, and extrapolated to make future actuarial projections. This paper presents a prospective forward-looking approach to longevity risk analysis which is based on stochastic modelling of the underlying drivers of mortality improvement, due to changes in lifestyle, health environment, and advances in medical science. The rationale for this approach is similar to that adopted for structural modelling of other types of dynamic insurance risk, e.g. natural catastrophes, where risk analysts construct a stochastic ensemble of events that might happen in the future, rather than rely on a retrospective analysis of the non-stationary and comparatively brief historical record. With any stochastic modelling of the future, the time evolution of the underlying dynamical processes is crucial. Understanding these processes is the key to longevity modelling, since they govern the time frame for mortality improvement. By developing meta-models for the underlying causes of medical and healthcare progress, insight is gained into the mechanisms by which significant levels of mortality improvement can be sustained for future decades.

KEYWORDS
Longevity risk; mortality improvement; medicine; geroscience; catastrophe modelling

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1. INTRODUCTION

Intensive actuarial research into longevity risk has evolved increasingly elaborate and sophisticated statistical projections of future mortality (see e.g. Pitacco et al., 2009). In these projections, no information other than previous history is taken into account. The tacit underlying assumption is that all of the information about the future is contained in the past observed values of the death rates. Projection credibility is limited by the retrospective use of past mortality data alone, which may not capture dynamic trends in future mortality improvement. Indeed, it is widely recognized within the biomedical community that, in the long-term, mortality change may be driven by very different forces from the recent past.

Furthermore, in the absence of a coherent probabilistic framework for modelling future mortality change, there may be little recourse but to reliance on subjective actuarial opinion on long-term improvement rates. As a basis for setting long-term mortality improvement rates, the decision to use an average over the past century, rather than a medium-term or recent decadal average, should be better informed by what is already known about the future of medicine and healthcare.

As a general inference principle, probability assignments of future mortality improvement should be conditional on all the information available: not just on past mortality data, but also on the considerable knowledge about future medical research programmes and public healthcare agendas. Stochastic models of longevity that do not recognize or access such knowledge will inevitably lack forecasting resolution. To give a specific example, if there is a drug which has been demonstrated in completed trials to be safe and effective in treating a disease, then the probability of an individual dying from this disease in the future will be lower than in the past.

If there were a global moratorium on medical research, or stagnation in scientific ideas, statistical forecasting would be much more static and clearer. However, the medical research field is highly dynamic, as indicated even by the language used to describe the realm of biomedical discovery. New vocabulary is a portent of dynamic longevity risk. An innovation in longevity risk is the coinage of a new word *geroscience* for the study of the interface between ageing and age-related diseases. Ageing is the most important risk factor for disease in the western world. In 2007, the US National Institutes of Health granted $25 million to the Buck Institute for Age Research in California to create the new discipline of geroscience. This is an innovative interdisciplinary initiative, bringing together molecular biologists, neuroscientists, cell biologists, geneticists, endocrinologists, pharmacologists and mathematicians, to understand better the processes of ageing, and to elucidate their role in the mechanics of disease. Ageing and disease are now perceived to have similar mechanisms, as endorsed by the award of the 2009 Nobel Prize for Medicine to the discoverers of telomerase, an enzyme important both for cell replication and cancer growth.

With the expectation of sustained progress, biologists of ageing at the Buck Institute have advised that we should be prepared to adjust for significant increases in lifespan during this century. There is an intriguing risk assessment parallel between
human geroscience and climate geoscience. Climate scientists anticipate significant increases in global temperature in the 21st century, causing major financial distress to the world economy, including to the insurance industry in respect of storms and floods. As a latent progressive global pensions peril, geroscience is also on the catastrophe risk horizon and may be regarded ultimately by life actuaries as the climate change of longevity risk. As with climate change, awareness and then preparedness are essential for prudent risk management.

1.1 A Review of Catastrophe Insurance Risk Modelling

Over the past several decades, probabilistic risk assessment of extreme insurance risks has been radically transformed from an academic pursuit in California to a major international business sector. Career specialization within the actuarial profession makes it helpful to review, for the benefit of life and pensions actuaries unfamiliar with property insurance, some key facts about catastrophe insurance modelling. Until the mid-1980s, the insurance risk management of natural hazards, such as floods, windstorms and earthquakes, was very simplistic, limited often to a crude deterministic estimation of Probable Maximum Loss. Information on a US property portfolio might not even have exposure data at state level, let alone city or address level, and there might be total ignorance as to building hazard vulnerability. Insurers who requested further information would lose market advantage to those unruffled by the exposure uncertainty. This dearth of information started to change with the advent of the desktop computer, when it became economically practical for better exposure information to be captured, and for the portfolio risk to be quantified probabilistically using the first generation of catastrophe insurance models run on personal computers.

A fundamental tenet of catastrophe modelling is that no historical time series of loss experience is adequate for catastrophe risk management. This has been an expensive recurrent lesson for the insurance industry. Both Hurricane Andrew, which swept through Florida in 1992, and the Northridge earthquake, which struck southern California in 1994, greatly exceeded prior Probable Maximum Loss estimates, and exposed the shortcomings of using finite historical time series of loss data for statistical projection of future loss. In the 1970s and 1980s, the annual California earthquake loss ratio was very small in most years, and peaked at about 130% in 1989. However, the loss ratio in 1994, the year of the Northridge earthquake, was a statistically surprising 2272.7% (Embrechts, Kluppelberg & Mikosch, 1997).

Catastrophe risk analysts approach risk assessment in a different methodological direction from statisticians, following the classic scientific paradigm in developing structural causal models of the underlying physical phenomena (Woo, 2011). In sequence, the underlying threat source is modelled, then the vulnerability to the threat is assessed, and the loss to an insurance portfolio is evaluated. Through construction of hierarchal event-trees, risk is disaggregated into its component parts, which then become more amenable to parameterization through objective technical analysis.

Rather than characterizing the historical time series by a single deterministic
projection, an ensemble of potential future events is constructed which collectively spans the range of future possibility. This involves teams of seismologists, meteorologists and hydrologists in developing stochastic models of earthquake, windstorm and flood occurrence, and mapping the damaging hazard footprints at a fine spatial scale. To complement the detailed modelling of the geographical footprints of future scenarios, insistent emphasis is placed on the acquisition of high resolution data on exposure geography and hazard vulnerability. Earthquake risk, for example, is sensitive to the proximity of a building to an active fault, and its standard of seismic design. Effort to capture spatial and engineering design information is necessary in reducing the epistemic uncertainty associated with portfolio risk, and has now become standard industry practice.

It is commonplace for graphic natural catastrophe metaphors to be used to describe all manner of extreme risks where historical information may have limited value for risk projection. For example, the hazard terms, seismic shock, tsunami and hurricane, have all been applied to financial crises on Wall Street (see e.g. Kansas, 2009). The conceptual framework and computational methodology for modelling natural hazards has broad financial risk application, and has already been applied to man-made dangers to life, such as terrorism, and has been extended to cover pandemic disease. Indeed, excess mortality risk to a life insurance portfolio can now be quantified using detailed structural models of the principal drivers of excess mortality, the most notable being pandemics. Quantitative epidemiological models of the spread of contagious disease are a major conceptual improvement over the historical analysis of sparse casualty figures from past pandemics. This methodological advance beyond the actuarial extrapolation of historical excess mortality experience has motivated its further development in structural mortality modelling.

1.2 Understanding Individual Mortality
In order to develop a structural model of population mortality, at the outset an understanding is required of the medical basis for the modelling of mortality at an individual level. Progress in this medical domain is expedited by longitudinal studies, which track the life course of individuals over decades through a succession of disease states until death. The most influential of these longitudinal studies has been the Framingham Heart Study, which began in 1948. The objective of the Framingham Heart Study was to identify the common factors or characteristics that contribute to cardiovascular disease, by following its development over a long period of time in a large group of participants who had not yet developed overt symptoms or suffered a heart attack or stroke. For this study, some 5,000 people from the US town of Framingham, Massachusetts, were enrolled and tracked over time, receiving medical examinations every two years.

As a result of such diligent protracted longitudinal health studies, replicated internationally, it is possible to quantify personal medical and lifestyle risk factors, e.g. blood pressure, cholesterol, diabetes, smoking, alcohol consumption, body-mass-
index etc. According to an individual’s lifestyle traits (e.g. smoker or not), and health status (e.g. diabetic or not), statistical survival curve projections can be constructed, being informed and validated by the extensive longitudinal medical studies of the principal life-threatening diseases.

Disease prevalence is markedly dependent on socio-economic class, and data might be mined down eventually to the geographical level of a doctor’s surgery. In the future, the supply and acquisition of physical and mental health factor data on pensioners may become no more unusual than gathering architectural data on property vulnerability. In the meantime, for very large pensions, there may be benefits in investing extra effort to enrich the individual data to increase the resolution on important risk factors that would refine the analysis, such as height and weight data, smoking, and other pertinent lifestyle information such as cognitive, psychological and social resilience that are the hallmark of successful ageing (Woo, 2013).

A pension portfolio can be characterized in terms of the relative frequency of individualized population segments with specific risk factor characteristics, for example smokers and non-smokers, etc.. Supplementary to base mortality data, the procedure for imputing risk factor distributions can make use of whatever information is made available, e.g. socio-economic class, postcode data, size of pension, as well as age and gender.

2. DRIVERS OF MEDICAL AND HEALTHCARE ADVANCEMENT

Since the Renaissance, every century has introduced medical innovation and advanced progress in medical science. With the medical research frontier extended collaboratively on a global scale, and expedited by online communication and data exchange, the degree of innovation in prospect for the 21st century holds particularly great promise. For mortality change to be projected into an uncertain medical future, the underlying stochastic process of medical advancement needs to be modelled. This requires construction of a meta-model of medical progress (Woo et al., 2010).

The unpredictability of the progress of medical research is a frustration for those whose lives depend on medical discovery. It has also been a conceptual stumbling block to the use of medical information by the international actuarial community (e.g. Actuarieel Genootschap, 2007), perplexed by the lack of consensus amongst renowned experts on the timescale for disease cures. Probabilistic longevity risk studies have been undertaken (e.g. RAND, 2005) that have attempted to elicit directly from medical experts the likelihood of disease cures within specified time windows. But however well such elicitations are facilitated, their forecasting skill level is disappointing. This reflects not so much the ignorance of experts as the significant degree of inherent randomness in medical discovery, which makes research funding an investment lottery for pharmaceutical companies. Guessing the timing of a disease cure has a sizeable irreducible aleatory component, akin to spinning a roulette wheel of discovery.

It is precisely this characteristic unpredictability of medical research which encourages the development of a prospective stochastic model. The formal analysis
of the scientific discovery process (Cheng, 2001) suggests that most computational models of discovery can be conceptualized as performing a recursive search of a space of possible states. Accordingly, over and above the smooth evolution of progress, there is a random walk component reflecting the serendipitous heuristic search aspect of scientific discovery; the haphazard progress of the clinical trials and regulatory process; the possibility of latent side-effects and litigation; medical research malpractice; and socio-ethical objections to the new dimensions in medical treatment.

Serendipity plays some part in all technological progress, no more so than in medical advancement. Serendipity has been defined as the art of finding what we are not looking for by looking for what we are not finding (Quéau, 1986). From penicillin to tomoxifen, the history of medical breakthroughs (e.g. Le Fanu, 2006) is replete with examples of accidental unforeseen discovery. Indeed, an entire book (Meyers, 2007) has been written on the role of serendipity in modern medical breakthroughs. As an example of complementary discovery, breast cancer research has led to new insights into brain development and vice versa.

Many of the most important breakthroughs in medicine have come from unexpected sources in seemingly unrelated fields, and have depended on luck, accident and error. But human sagacity is required to recognize an opportunity opened by serendipity. As Louis Pasteur said, chance favours only the prepared mind. Investigations that seemed totally irrelevant to any practical objective have yielded most of the major discoveries of medicine. Arthur Kornberg, Nobel Laureate in Medicine for his DNA discoveries, has graphically described the way that progress is actually made, ‘Medical research is still more a game of pool than billiards. You score points regardless of which pocket the ball goes into.’ A scatter-gun metaphor for medical progress is thus more apt than the linear model of steady advancement that is often the public perception. Progress does not follow a straight path from point A to point B. Rather, point X is reached in the course of looking to reach point Y.

2.1 Vitagions

To encompass the complete spectrum of potential mortality change developments, it has to be recognized that medical and healthcare advancements are themselves intrinsically stochastic processes, marked by a considerable degree of randomness. There are five generic categories of advancement: lifestyle, health environment, disease reduction, regenerative medicine and anti-ageing. These are weakly coupled and the latter three staggered in time, so allowing them to be modelled approximately as separate stochastic processes.

Each of these five categories is termed here a vitagion, i.e. an agent for prolonging life. The need to introduce new terminology reflects the novelty of structural longevity risk modelling, in which the principal agent categories of mortality improvement are explicitly identified and analysed. The five vitagions are now described.
[A] **Personal Lifestyle**

The behavioural sciences of social psychology, consumer marketing, and health economics provide guidance for alternative future projections of lifestyle. Government intervention in promoting healthier lifestyles is a significant external risk mitigating factor. Democratically elected governments are reluctant to prohibit dangerous lifestyles in which citizens may freely choose to indulge. However, mindful of the health interests of citizens, and state responsibility for healthcare, governments may adopt policies of libertarian paternalism that encourage but do not enforce healthier behaviour. This is the influential *nudge* strategy, expounded by the behavioural economist Richard Thaler and the risk lawyer Cass Sunstein (2009). Examples of government nudging include increasing taxes on cigarettes and alcohol, and pressurizing the food industry to reduce the salt and fat content of processed foods, and to label calorie content on food packaging and restaurant menus.

Given the diverse range of public policy tools for exercising control over excessively unhealthy behaviour, the population prevalence of obesity defines a stochastic process with a currently rising trend that must eventually downturn, as smoking prevalence has done. The turning of the obesity tide is not expected for a few decades, but social psychology provides a societal mechanism for a more rapid transition. To the extent that obese people tend to network socially with others who are obese, the spread of obesity might be slowed with the introduction of nudges judiciously targeted at community behavioural role models. This has proven successful in reducing the prevalence of smoking.

Extensive research into smoking trends (Future Foundation, 2005) and obesity trends out to 2050 (McPherson, Marsh & Brown, 2005) provide an informed basis for stochastic modelling of UK smoking and obesity. Regarding smoking prevalence, this research suggests that as the proportion of smokers in the population falls, public attitudes to government intervention may become more positive, providing a popular mandate for more draconian restrictions on where smoking is tolerated and permissible.

[B] **Healthcare Environment**

The historical record of public health until the middle of the last century attests to the role of the healthcare environment in lowering mortality rates. The healthcare environment covers hygiene, sanitation, pollution, knowledge of health and medical issues, availability of healthcare education, and attitude towards healthcare provision such as visiting the doctor. Differences in healthcare between socio-economic classes are marked, but may be narrowed with the adoption of policies that explicitly target public health services and expenditure at the less privileged in society (Gregory, Dixon & Ham, 2012).

Overall improvement of the healthcare environment is likely to be slowed by budget constraints on government spending, especially during episodes of economic crisis and financial austerity. The dependence of future longevity on macroeconomics is an exogenous factor that contributes to the volatility around this vitagion. Explicit
recognition of this factor aligns the prospective approach to longevity modelling with the philosophical view of the economist John Maynard Keynes that it is better to be approximately correct than precisely wrong. A prospective longevity model captures in an approximate manner the underlying drivers of future mortality, but it is intrinsically more challenging to parameterize than a retrospective statistical model that can be fitted with high numerical precision.

[C] **Medical Intervention**

This covers the medical discovery of new chemical entities, including medication and vaccines, improvement in diagnostics and the delivery of treatments. The pace of discovery is hastened by the broadening international dimension of scientific collaborative research, and escalating computational power for drug molecule design. However, progress is subject to the economic law of diminishing returns, which has become a major commercial hindrance for pharmaceutical companies yearning to achieve high returns from blockbuster drugs such as statins. Drug discovery is far from being a linear forecastable process, and the big pharmaceutical companies are increasingly looking beyond their own research laboratories to commercialize the discoveries made by successful biotechnology firms, or concentrate their research efforts by exchanging drug and healthcare business divisions with each other.

[D] **Regenerative Medicine**

This covers the new discipline of regenerative medicine, encompassing nanomedicine and stem cell therapy, potentially providing the means to replace cells damaged by trauma or devastating diseases such as Alzheimer's, Parkinson's, heart disease, cancer and diabetes. Rejuvenative biotechnology holds the future promise of progressive regular maintenance of the human body, including the growth of new organs, potentially including even the heart.

It is widely accepted by health officials that regenerative medicine will provide the next evolution of medical treatments. According to the leading American demographer, Jay Olshanksy, rejuvenative therapies could herald the most important revolution in public health in his lifetime. Most likely, the time scale for practical regenerative medicine is several decades away, but already some successes in organ renewal are impressive enough to justify confident expectation of future major discovery and significant impact on public health.

[E] **Anti-ageing**

This covers the molecular genetics of the ageing process, which is intrinsically related to disease. Just as the future lifespan of a vintage car depends not just on its chronological age but also on its state of upkeep and repair, and how many miles are on the clock, so possible biochemical and genetic techniques might have the effect of lowering an individual’s biological age below his or her actual chronological age. Given that age is the biggest risk factor for disease, such techniques raise the prospect of
notable human lifespan increases in the 21st century: hypothetically, an octogenarian may have the disease susceptibility of a seventy-year-old.

In 2014, Craig Venter, a pioneer in sequencing the human genome, established a corporation, Human Longevity Inc., to apply genetic sequencing to some of the intractable questions about health and ageing. Longevity analysis will become a big data problem. The technical and financial support for anti-ageing research offered by the information giant Google further encourages optimism over the sustained development of this frontier of the longevity research agenda.

3. MODELLING FRAMEWORK

In his history of the rise and fall of modern medicine, Le Fanu (op. cit.) has argued that the law of diminishing returns applies to medical research. This is manifest within the health econometric model of Lichtenberg (2005), where mortality improvement due to drug discovery is represented as a logarithmic function of medical progress, specifically the cumulative number of New Chemical Entities (NCE). This incorporates the law of diminishing returns in a transparent and tractable manner.

Not just with drug discovery, but for any vitagion, there is a fundamental ultimate limit to the mortality reduction benefit associated with it. This is calculated by aggregating a vitagion’s maximum impact on each cause of death. Denote by $V_{MAX,j,x}$ the maximum plausible mortality reduction at age $x$ due to the vitagion $j$. This can be traced back to the mortality reduction attainable for cancer, cardiovascular and other diseases. Disaggregation of the contributions from the various diseases allows $V_{MAX,j,x}$ to be estimated for each age and vitagion.

The percentage of $V_{MAX,j,x}$ achieved at time $t$ is written as $tr_{j,x}(t)$. The reduction in base mortality for vitagion $j$ at age $x$ and time $t$ is then:

$$ F_j(x,t) = 1 - tr_{j,x}(t) V_{MAX,j,x} $$

The random process $tr_{j,x}(t)$ is expressed, via a simple tapering exponential function, in terms of the expected trend $r_{j,x}$ towards $V_{MAX,j,x}$, starting out from initial time $t_0$:

$$ tr_{j,x}(t) = 1 - \exp \left[ -u_{j,x} r_{j,x} (t - t_0 + n_{j,x}(t)) \right] $$

The uncertainty structure of this random process is embedded within two factors. First, the vitagion trend volatility is represented as a lognormal distribution with unit mean $u_{j,x}$. The long-term trend is strictly positive and long-tailed, and a lognormal distribution provides a convenient and parsimonious approximate representation. Secondly, vitagion path volatility is represented by a Brownian motion with zero mean $n_{j,x}(t)$. The vitagion mortality reduction factors are correlated in respect of both trend and path volatility. The aggregation of these vitagion trajectories into an all-cause projection of mortality involves a decomposition of mortality improvement by cause of death.
3.1 Model Parameterization

The most widely used and influential model for mortality forecasting was developed by American demographers, Ronald Lee and Lawrence Carter in 1992. This model has been in general use by the US Census Bureau, the US Social Security Administration, and elsewhere within the international actuarial community. The Lee-Carter model represents age-dependent mortality rates $m(x,t)$ in terms of age-related effects $\alpha_x$ and $\beta_x$ and a random walk drift term $\kappa_t$:

$$\kappa_t = \kappa_{t-1} + d + \epsilon(t)$$

$$Log\left[m(x,t)\right] = \alpha_x + \beta_x \kappa_t$$

The functional form of this model was arrived at by Lee and Carter empirically through fitting US mortality data from 1933 to 1987, but may be motivated from a structural modelling perspective by considering the vitagion drivers of mortality improvement. In particular, the random walk with drift is a reflection of the volatility around the vitagion trends, and may be interpreted in terms of the inherent randomness in the impact of the fluctuation of population lifestyle and health environment, and the random walk of medical discovery.

The fact that the random walk drift term $\kappa_t$ in the Lee-Carter model is partially attributable to the random walk in medical discovery is a poignant footnote to the life of Lawrence Carter, who battled with multiple sclerosis for nearly twenty years before his premature death at the age of 68 in 2011. Whilst gradual progress has been made in understanding multiple sclerosis, especially the genetic basis for this debilitating disease, any cure will have come too late to prolong his longevity, and may well require a dose of serendipity. With a low population prevalence of about 1/1000, an eventual cure for multiple sclerosis would generate a downward fluctuation in population mortality rates.

The Renshaw-Haberman model (Pitacco et al., op. cit.) is an actuarial extension of the classic Lee-Carter model to include an additional cohort effect term $\gamma_{t-x}$, which ensures that historically observed differences in generational mortality are preserved in the projection:

$$Log\left[m(x,t)\right] = \alpha_x + \beta_x \kappa_t + \theta_x \gamma_{t-x}$$

The aggregate age-period trend arising from the vitagions can be constrained to match current mortality trends. Furthermore, the total path volatility around the age-period trend can be fitted from historical experience. This calibration procedure provides explanatory insight into the underlying rationale for the parameters of statistical models.

The mortality reduction factors from the five vitagions are combined multiplicatively with the base mortality $m(x,t_0)$ to produce a mortality forecast. The base mortality of a portfolio may reflect past experience, standard industry tables, or population
statistics, and is associated with a degree of estimation error that is captured by a log-normal factor.

\[ m(x, t) = m(x, t_0) \cdot \prod_{j=1}^{5} F_j(x, t) \cdot \text{cohort term} \]

4. MORTALITY IMPROVEMENT RISK METRICS

The prospective approach to longevity risk assessment is conceptually the future of longevity modelling. It takes account of knowledge already available of innovative research agendas such as geroscience, and provides a more informed and farther vista into the future than any statistical projection based on historical data.

In particular, the actuarial hunch that the long-term future mortality improvement rate would be similar to the average over the 20th century may be a manifestation of collective cognitive bias that has consistently underestimated mortality improvement. More reasoned projections informed by medical science should facilitate longevity risk transfer to the capital markets (Nakada et al., 2014).

The partition of the underlying sources of future mortality improvement into five vitagions allows the 21st century landscape of longevity increase to be charted as shown in Figure 1. Current mortality improvement arises from the three vitagions of lifestyle [A], health environment [B] and medical intervention [C]. Gradually, the contribution from regenerative medicine [D] will develop and flourish in the middle of the century, and then anti-ageing [E] will emerge as the major source of mortality improvement towards the end of the century.

![Figure 1 Percentage mortality improvement in future decades arising from the five vitagions: Lifestyle [A]; Health Environment [B]; Medical Intervention [C]; Regenerative Medicine [D]; Anti-Ageing [E]](image)
4.1 Solvency II

The stochastic modelling methodology outlined above lends itself to the computation of probabilistic risk metrics, insightful for longevity risk management. Where risk criteria or guidelines are expressed in terms of an extreme return period, e.g. 200 years, this methodology provides a coherent quantitative framework for prudent portfolio-specific risk management. In the absence of this type of probabilistic risk framework, the adequacy of a risk management strategy can be difficult to assess systematically. In particular, when the extreme stress values are selected rather arbitrarily, deterministic scenario analysis may be no more satisfactory in respect of mortality improvement in the 21st century than it has been for earthquake magnitude or hurricane landfall intensity in the last century, prior to the advent of catastrophe modelling.

The Solvency Capital Requirement (SCR) under Solvency II is set at 99.5% VaR over one year. The 99.5% criterion is equivalent to a 1-in-200 probability. Whereas various mortality risk models have been adapted for SCR analysis (e.g. Börger, 2009), the medically-based prospective approach proposed here is well suited not just to facilitate this computation in accordance with state-of-the-art medical knowledge, but to identify the key longevity factors which govern this tail risk. Furthermore, it is capable of relating back in risk terms the stipulated longevity shock of a 25% reduction of mortality.

REFERENCES


