Institut für Finanz- und Aktuarwissenschaften

Scanning the horizon: integrating expert knowledge into the calibration of stochastic mortality models

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- Amsterdam, Netherlands
- September 2024

Scanning the horizon: integrating expert knowledge into the calibration of stochastic mortality models

Agenda

Motivation

Why consider the field of "anti-ageing medicine"?

Two expert scenarios for the future of human life expectancy

A "driver-driven" calibration procedure

Risk analysis

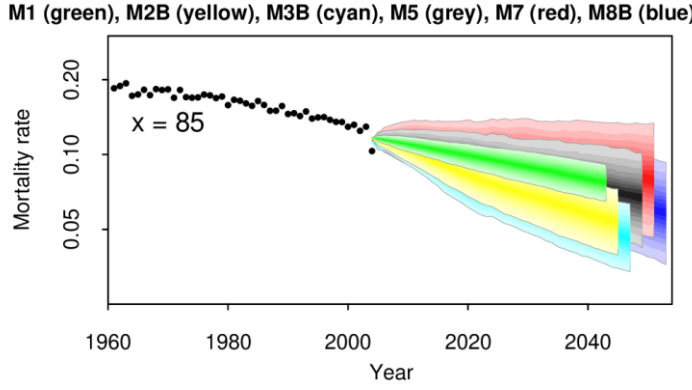
Conclusion

References

Motivation

Data-driven calibration

- Stochastic mortality models (like the Lee-Carter (LC) or Cairns-Blake-Dowd (CBD) model)
  - Essential tools for modeling, measurement, and management of longevity risk



Source: Cairns et al. (2011)

- Model parameters are typically calibrated to historical mortality data
  - past mortality patterns and dynamics are captured as closely as possible
  - and then stochastically projected into the future
- Suitable approach whenever there is no indication that the structure of future mortality fluctuations might be different than a structure observed in the past

Stochastic mortality models are generally calibrated by looking in the "data rearview mirror" → **"data-driven" calibration.**

Motivation

Driver-driven calibration

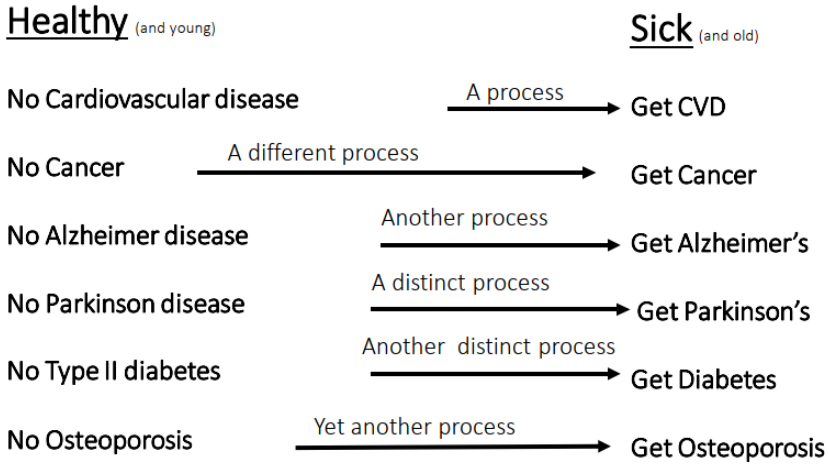
- Knowledge about potential scenarios that might impact the future development of mortality
  - exists in many different disciplines (like ageing research)
  - along with the potential for subject specialists to provide educated estimates for the potential impact, the timing, and the probability of occurrence.
- However, this knowledge is typically not considered in longevity risk management.
- A well-founded calibration should consider all available information.
- For illustration: Imagine the year is 1929 and Flemming discovered penicillin.
  - Contemporary expert judgement has anticipated that this will have an impact on life expectancy.
  - Of course, nobody could have precisely predicted the impact, the timing, and the probability.
  - But any "educated guess" by experts would have provided a better understanding of the uncertainty of (then) future human life expectancy than a purely data-driven approach.

Following an interdisciplinary approach, we develop a methodology how expert knowledge on the future of human life expectancy can be integrated into the calibration of stochastic mortality models → **"driver-driven" calibration.**

Why consider the field of "anti-ageing medicine"?

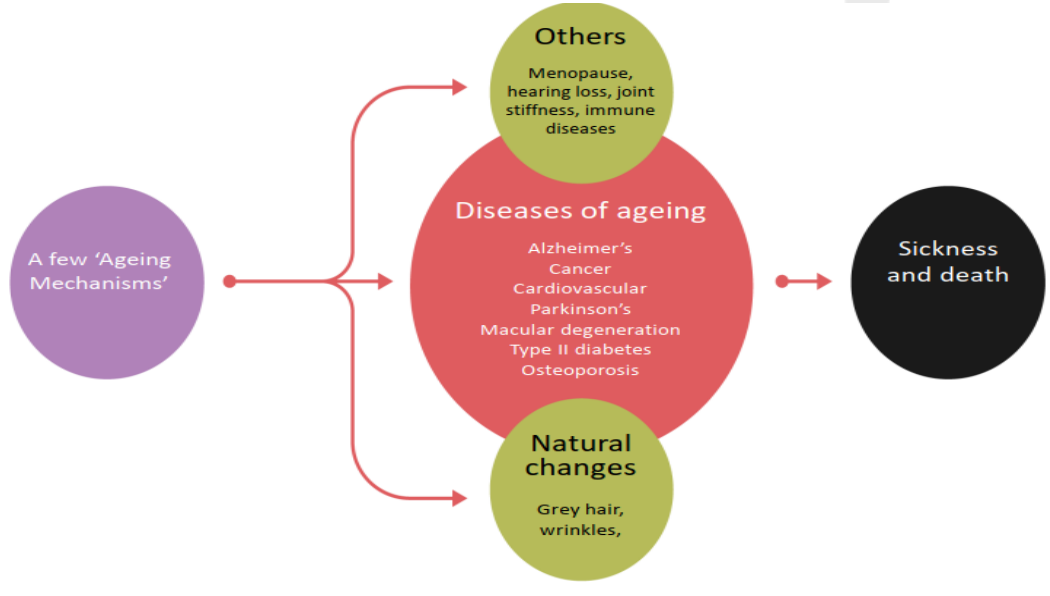
"***Mechanisms that cause ageing are known…*** " (Faragher, 2023)

Ageing does not work like this,…



Source: Faragher (2023)

but like this:



Why consider the field of "anti-ageing medicine"?

"***Mechanisms that cause ageing are known…and druggable***" (Faragher, 2023)

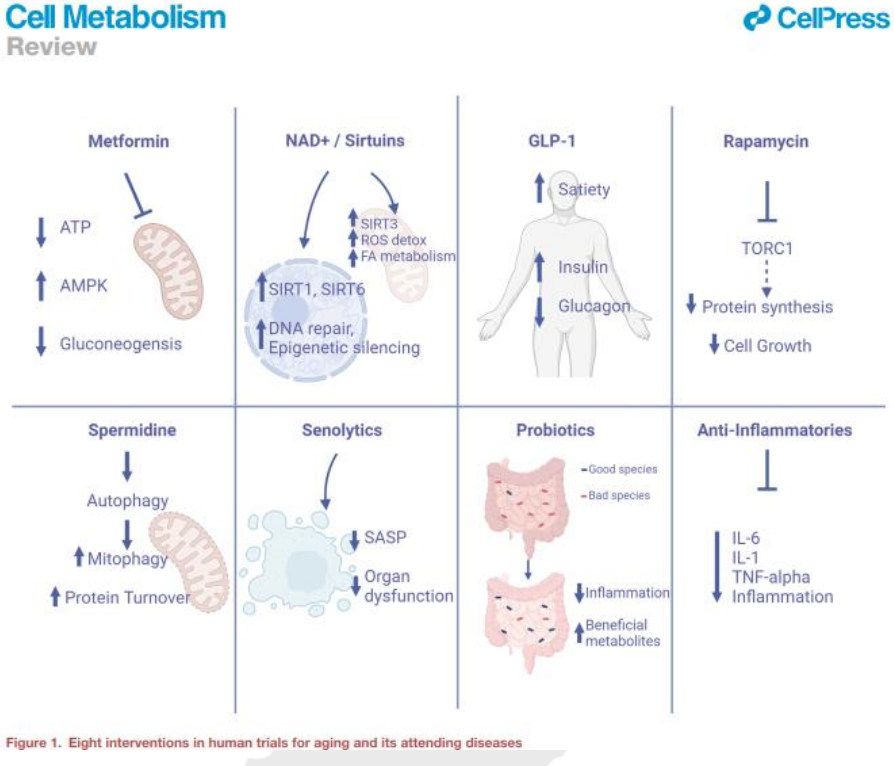


Figure 1. Eight interventions in human trials for aging and its attending diseases

Source: Guarente et al. (2024)

Eight promising drug classes, most of which have the potential to modulate hallmark mechanisms, are currently in clinical human trials.

Two expert scenarios for the future of human life expectancy

Some cautious but very important notes

- Our focus: longevity risk management
  - Only consider scenarios in the direction of an increase in life expectancy
  - Most relevant: “low probability / high impact” events
  - Focus on the model’s “volatility” rather than on the “best estimate”
- At this stage, nobody can know which interventions will prove most effective, at what point in time they will come to the market, and what the effect on human life expectancy will be.
  - In particular, determining a reasonable probability of occurrence is extraordinary tricky.
  - Any expert opinion will naturally be far from a perfect prediction!
- We are not claiming that our considered expert scenarios are the right ones.
- Rather, we
  - argue that we are currently at a point in time where uncertainties regarding the future development of life expectancy might be larger than a purely data-driven approach suggests,
  - propose a methodology on how to integrate expert knowledge into the model calibration, and
  - illustrate this using exemplary expert scenarios.

Two expert scenarios for the future of human life expectancy

- Two expert scenarios:
  - One scenario that is later used for the driver-driven calibration
  - A second scenario for validating the long-term uncertainty of the resulting model
- An expert scenario consists of three components:
  - **What** might happen?
    - What is the impact on a given reference figure?
    - For example, we consider the impact on the remaining cohort life expectancy (LE) at age 65.
  - **When** could it happen?
    - Over which time horizon does the scenario unfold?
  - **How likely** is it to occur?
    - What is the probability that this scenario (or something else with an impact that is at least as high as in the specified scenario) will occur?

Two expert scenarios for the future of human life expectancy

The scenario: Senolytics

- Senescent cells are cells that do not divide any more, but do not die.
  - Anti-cancer mechanism
  - Accumulate in the body over time and contribute to chronic inflammation, tissue dysfunction, and the progression of age-related diseases.
- Hence, their elimination clearly has the potential to slow down or even reverse ageing.
  - *Senolytics* are drugs that selectively eliminate senescent cells.
  - More than 60 human trials in progress, some already in Phase II.

More than 60 ongoing human trials

ClinicalTrials.gov Search Results 07/07/2022

	Title	Status	Study Results	Conditions	Interventions
1	Senolytic Agents &Osteoarthritis	Not yet recruiting	No Results Available	•Osteoarthritis	•Drug: Quercetin Cap/Tab :Fisetin Cap/Tab •Drug: Quercetin Cap/Tab:Fisetin Cap/ tab,Glycyrrhizin capsules •Other: Placebo
2	Senolytic Agent Improve the Benefit of Platelet-Rich Plasma and Losartan	Recruiting	No Results Available	•Femoroacetabular Impingement	•Drug: Fisetin •Drug: Placebo
3	Use of Senolytic and Anti-Fibrotic Agents to Improve the Beneficial Effect of Bone Marrow Stem Cells for Osteoarthritis	Recruiting	No Results Available	•Osteoarthritis, Knee	•Drug: Fisetin •Drug: Losartan •Drug: Placebo - Losartan •Drug: Placebo Fisetin
4	Senolytic Therapy to Modulate Progression of Alzheimer's Disease	Active, not recruiting	No Results Available	•Alzheimer Disease	•Drug: Dasatinib + Quercetin
5	Senolytic Drugs Attenuate Osteoarthritis-Related Articular Cartilage Degeneration: A Clinical Trial	Active, not recruiting	No Results Available	•Osteoarthritis, Knee	•Dietary Supplement: Fisetin •Drug: Placebo oral capsule
6	Senolytic Therapy to Modulate the Progression of Alzheimer's Disease (STeMPAD) Study	Recruiting	No Results Available	•Alzheimer Disease, Early Onset •Mild Cognitive Impairment	•Drug: Dasatinib + Quercetin •Other: Placebo Capsules
7	An Open-Label Intervention Trial to Reduce Senescence and Improve Frailty in Adult Survivors of Childhood Cancer	Recruiting	No Results Available	•Frailty •Childhood Cancer	•Drug: Dasatinib plus Quercetin •Drug: Fisetin
8	Senescence in Chronic Kidney Disease	Enrolling by invitation	No Results Available	•Chronic Kidney Disease	•Drug: Group 2: Dasatinib •Drug: Group 2: Quercetin
9	Cellular Senescence and COVID-19 Long-Hauler Syndrome	Recruiting	No Results Available	•SARS-CoV2 Infection	
10	Targeting Senescence to Reduce Osteoarthritis Pain and cartilageE Breakdown (ROPE)	Not yet recruiting	No Results Available	•Osteoarthritis, Knee	•Drug: High-dose/short-duration Fisetin •Drug: Low-dose/sustained-duration Fisetin •Other: Oral placebo capsule
11	Targeting Cellular Senescence With Senolytics to Improve Skeletal Health in Older Humans	Recruiting	No Results Available	•Healthy	•Drug: Dasatinib •Drug: Quercetin •Drug: Fisetin
12	COVFIS-HOME: COVID-19 Pilot Study of Fisetin to Alleviate Dysfunction and Decrease Complications	Enrolling by invitation	No Results Available	•Covid19 •Coronavirus Infection	•Drug: Fisetin
13	COVID-FIS: Pilot in COVID-19 (SARS-CoV-2) of Fisetin in Older Adults in Nursing Homes	Enrolling by invitation	No Results Available	•Covid19 •SARS-CoV Infection	•Drug: Fisetin •Drug: Placebo
14	COVID-FISETIN: Pilot in SARS-CoV-2 of Fisetin to Alleviate Dysfunction and Inflammation	Enrolling by invitation	No Results Available	•Covid19	•Drug: Placebo •Drug: Fisetin

Rule of thumb: About 90% of trials fail. But this is now a numbers game...

Clearance of p16^{Ink4a}-positive senescent cells delays ageing-associated disorders

Darren J. Baker[1,2,3], Tobias Wijshake[1,4], Tamar Tchkonia[3], Nathan K. LeBrasseur[3,5], Bennett G. Childs[1], Bart van de Sluis[4], James L. Kirkland[3] & Jan M. van Deursen[1,2,3]

Two expert scenarios for the future of human life expectancy

The scenario: Senolytics

- Potential impact on human life expectancy
  - Point of reference: up to 37% increase in remaining life expectancy for mice (cf. Baker et al., 2016; Yousefzadeh et al., 2018)
    - largely attributed to the suppression of cancer
  - However, cancer-related deaths are about a third lower in humans than in rodents
    → 37% upper estimate, (1/3)*37% ≈ 12% lower estimate
  - Various other arguments why the impact on humans might actually be higher than 12%
    - in particular effects resulting from potential "stacking" of interventions

    → our estimate: 25% (approximately midway between the upper and lower estimate)
- Estimated timing
  - Rule of thump: 16 years from phase 0 to licensing.
  - Our estimate: 10 years (2 more years for phase II + another 2 years for phase III + 1 year for licensing + 5 years to reach large parts of the population).

Our exemplary expert scenario used for calibration:

An increase in remaining LE at age 65 of *25%* over a time horizon of *10* years with a probability of occurrence of *1%*

Two expert scenarios for the future of human life expectancy

"Out-of-the-box": the killifish scenario

- Mankind has undergone an extended evolutionary bottleneck (cf. Hu et al., 2023)
  - essentially everyone alive on earth today descends from a population of less than 1000 individuals about 900,000 years ago
- Another genetically bottlenecked species is the *African turquoise killifish*

  - exhibits many typical signs of aging at the molecular, cellular, organ, and behavioral levels, similar to those seen in mammals
  - remarkable increase in life expectancy of 60% in response to *resveratrol*
- We consider the possibility that a similarly high increase in life expectancy could occur in humans through a simple, but as yet undiscovered, intervention.
  - Of course, an increase of 60% in LE at birth would lead to an even higher increase at age 65.
    → we exemplary assume an increase in remaining LE at age 65 of 100%.
  - Such an intervention, if it exists at all, has yet to be found.
    → assume rather long time horizon of 30 years

Our „out-of-the-box" expert scenario used for model validation:

An increase in remaining LE at age 65 *100%* over a time horizon of *30* years is highly unlikely, but within the realm of possibility.

A driver-driven calibration procedure

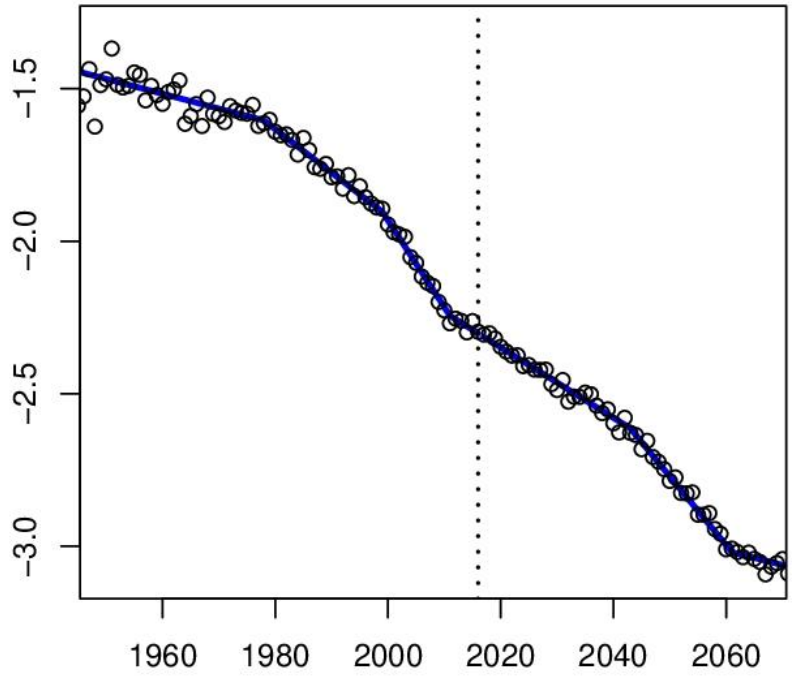
Considered stochastic mortality models

- CBD model structure of Cairns et al. (2006)

$$logit(q_{x,t}) = log\left(\frac{q_{x,t}}{1-q_{x,t}}\right) = \kappa_t^{(1)} + \kappa_t^{(2)}(x-\bar{x})$$

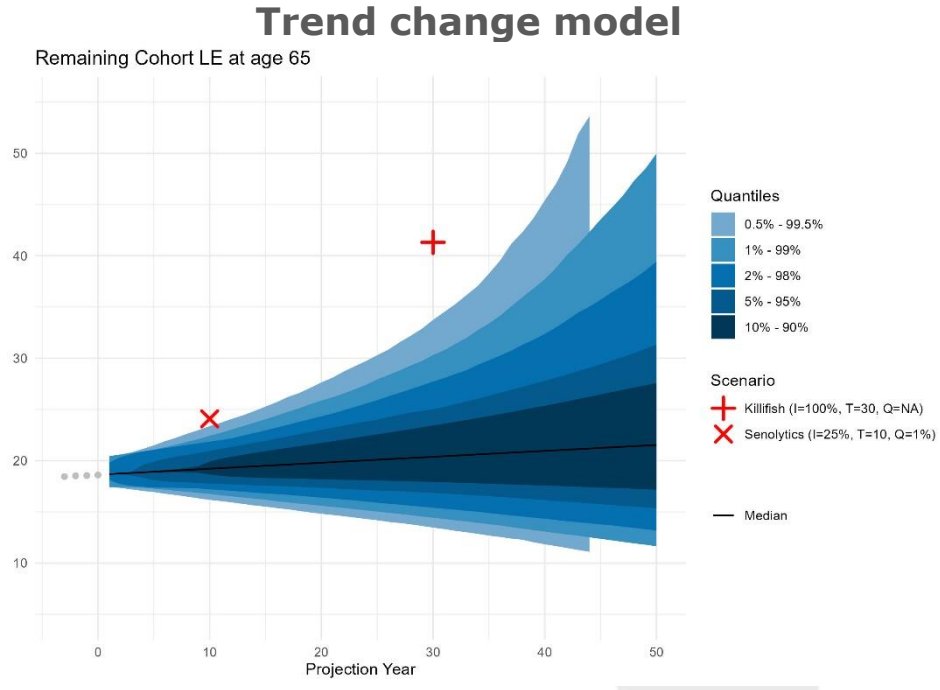
  - Trend change model of Börger & Schupp (2018) for the period effects $\kappa_t^{(1)}$ and $\kappa_t^{(2)}$:

Trend change model



A driver-driven calibration procedure

Step 1: Data-driven calibration as starting point



Model	Senolytics ℙ(%)	Killifish ℙ(%)
Trend (data-driven)	0.31%	0.20%

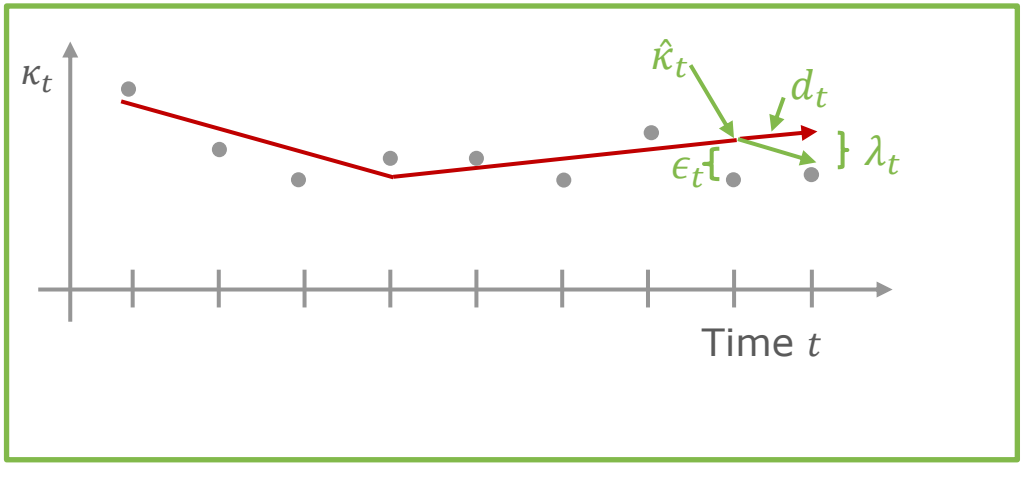
- The model provides a reasonable form of uncertainty that matches the assessment of long-term uncertainty in our expert scenarios.
- Nevertheless, the quantile for the senolytics scenario remains well below the specified value of 1%. → **model appears to underestimate uncertainty.**

A driver-driven calibration procedure

Step 2: Identification of a suitable volatility parameter for scaling

Technical details

The trend change model has several „volatility parameters“:



- Extrapolation of the current mortality trend:

$$\hat{\kappa}_t = \hat{\kappa}_{t-1} + d_t$$

- The trend can experience a change in any year in any direction with a trend change probability of p_t:

$$d_t = \begin{cases} d_{t-1} & with\ probability\ 1 - p_t \\ d_{t-1} + \lambda_t & mit\ probability\ p_t \end{cases}$$

- The trend change has an intensity of $\lambda_t = M_t \cdot S_t$
  - with sign $S_t^{(i)} \in \{-1,1\}$ and
  - magnitude $M_t \sim LN(\mu_M, \sigma_M^2)$
- Finally, we add annual fluctuations $\epsilon_t \sim N(0, \Sigma)$ around the trend: $\kappa_t = \hat{\kappa}_t + \epsilon_t$

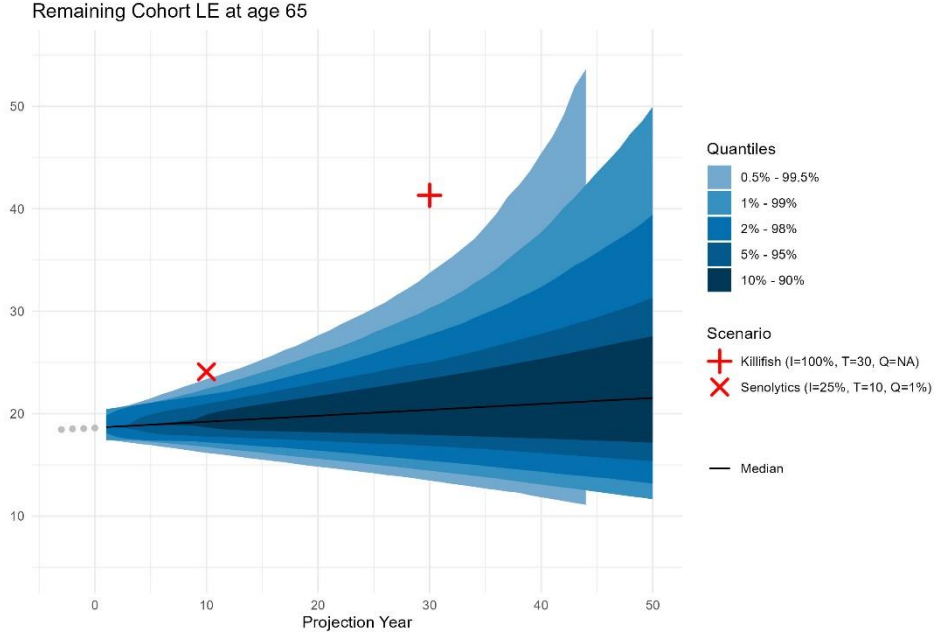
Most promising variant:

Calibrating the trend change intensity parameter μ_M for the first period effect $\kappa_t^{(1)}$ for trend changes that point in the direction of an increase in LE.

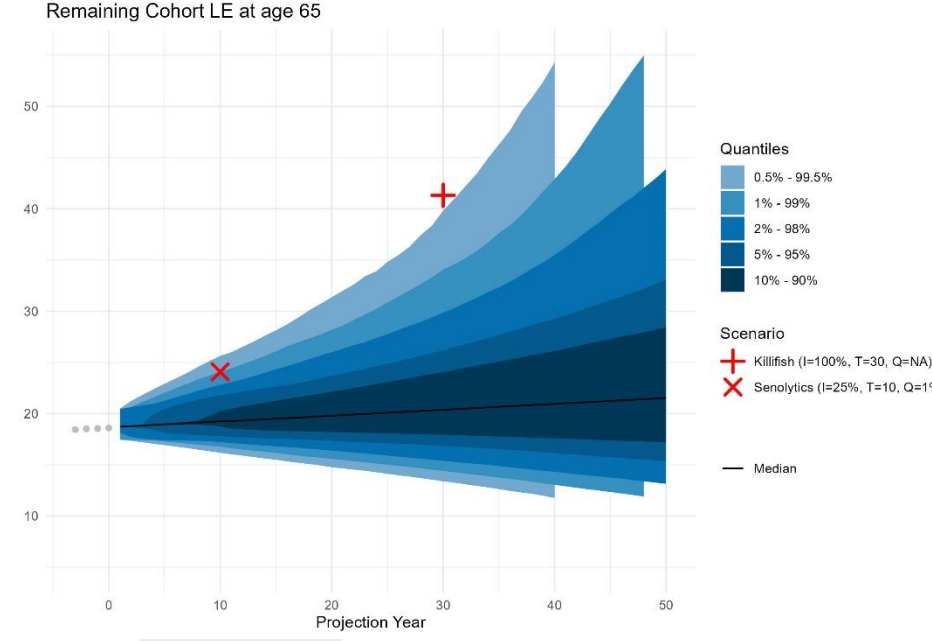
A driver-driven calibration procedure

Step 3: Resulting model calibration and validation

Data-driven



Driver-driven



Model	Senolytics $\mathbb{P}(\%)$	Killifish $\mathbb{P}(\%)$
Trend (data-driven)	0.31%	0.20%
Trend (driver-driven)	1%	0.43%

- Regime switch: driver-calibrated μ_M for 10 years, data-calibrated afterwards
- Driver-driven leads to wider confidence intervals reflecting higher uncertainty
- Validation of long-term uncertainty with regard to the killifish scenario

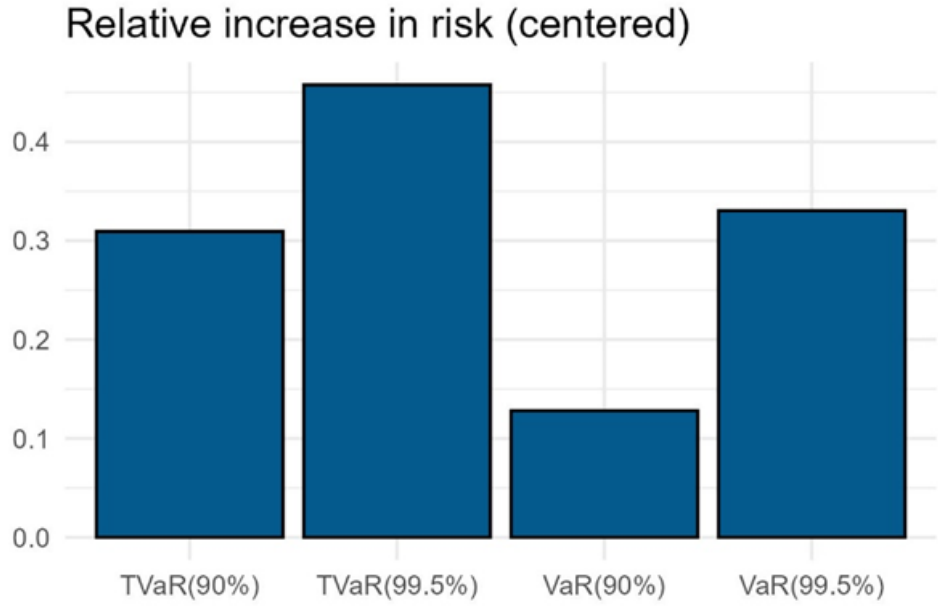
Risk analysis

A simplified case study

- Simplified closed portfolio of life annuities
  - Built up in the past by selling the exactly same type of contract to the same number of costumers at the beginning of each year.
  - Retirement age of 65, interest rate of 2%
- We analyze the distribution of the centered random present value of future liabilities (cf. Cairns et al., 2014; Börger et al., 2021)

$$L - \mathbb{E}(L)$$

  in terms of the 90%- and 99.5%
  - Value-at-Risk and
  - Tail-Value-at-Risk



- The driver-calibrated model leads to a significantly higher assessment of longevity risk than the data-driven approach, particularly with regard to tail risks.
- Hence, our proposed driver-driven calibration procedure offers a valuable complement to established data-driven approaches.

Conclusion

Summary and Outlook

- Currently, the uncertainty about the future development of human life expectancy is rather high.
- Expert knowledge from other disciplines is typically not considered in longevity risk management.
- We therefore propose a "driver-driven" approach for the calibration of mortality models.
  - Idea: model should match the prediction of an expert scenario
  - Particularly relevant when there are "low probability / high impact" scenarios on the horizon
- We motivate and propose two exemplary scenarios for the future development of life expectancy.
  - Interdisciplinary approach with an expert from the field of anti-ageing research
- Main finding: The "driver-driven" calibration can lead to a structurally different assessment of longevity risk than the traditional "data-driven" approach, especially with regard to tail risks.
- Several potential extension
  - joint consideration of multiple expert scenarios
  - different model structures (e.g. models with jump processes)
  - …

References

Börger, M. & Schupp, J. (2018) Modeling trend processes in parametric mortality models. *Insurance: Mathematics and Economics, 78, 369-380.*

Börger, M. & Freimann, A. & Russ, J. (2021) A combined analysis of hedge effectiveness and capital efficiency in longevity hedging. *Insurance: Mathematics and Economics 99, 309-326.*

Cairns, A.J.G., Blake, D. and Dowd, K. (2006) A two-factor model for stochastic mortality with parameter uncertainty: Theory and calibration. *The Journal of Risk and Insurance, 73(4), 687–718.*

Cairns, A.J.G., Blake, D., Dowd, K., Coughlan, G. D., Epstein, D., & Khalaf-Allah, M. (2011). Mortality density forecasts: An analysis of six stochastic mortality models. *Insurance: Mathematics and Economics*, 48(3), 355-367.

Faragher, R.G.A. (2023) Biology of Human Senescence, Talk of Richard Faragher, Professor of Biogerontology, at the „Living to 100 Symposium" 2023 in Orlando.

Fleming, A. (1929). On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of B. influenzae*. British journal of experimental pathology*, 10(3), 226.

Guarente, L., Sinclair, D. A., & Kroemer, G. (2024). Human trials exploring anti-aging medicines. *Cell Metabolism*, 36(2), 354-376.

References

Hu, W., Hao, Z., Du, P., Di Vincenzo, F., Manzi, G., Cui, J., ... & Li, H. (2023). Genomic inference of a severe human bottleneck during the Early to Middle Pleistocene transition. *Science*, 381(6661), 979-984.

Yousefzadeh, M. J., Zhu, Y. I., McGowan, ..., & Niedernhofer, L. J. (2018). Fisetin is a senotherapeutic that extends health and lifespan. *EBioMedicine published by THE LANCET*, 36, 18-28.

Appendix

Trend change model vs. random walk with drift

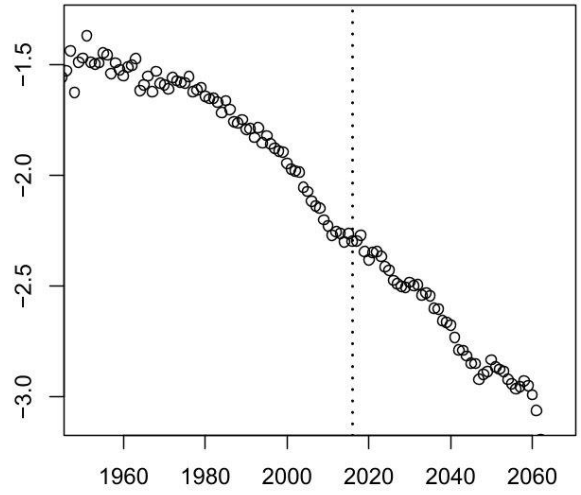
- CBD model structure of Cairns et al. (2006)

$$logit(q_{x,t}) = log\left(\frac{q_{x,t}}{1-q_{x,t}}\right) = \kappa_t^{(1)} + \kappa_t^{(2)}(x - \bar{x})$$

  - Two different models for projecting the period effects $\kappa_t^{(1)}$ and $\kappa_t^{(2)}$:

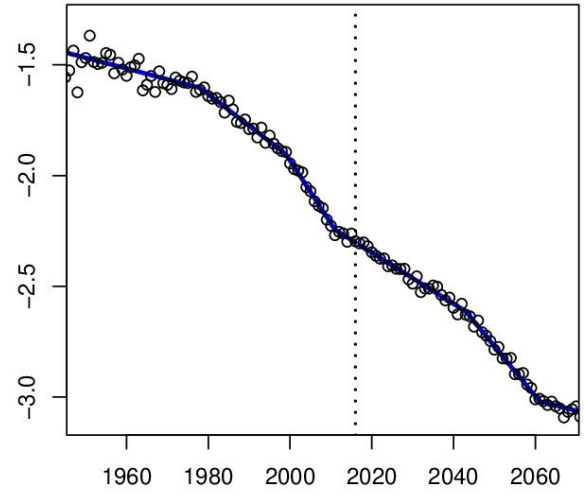
Random walk with constant drift

- Standard approach, cf. Cairns et al. (2006)



Trend change model

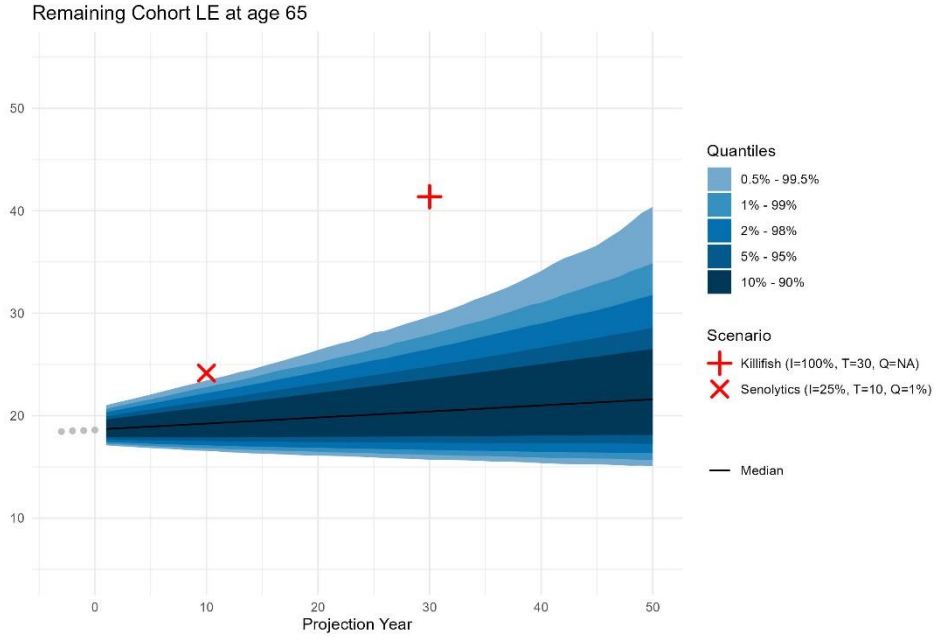
- cf. Börger & Schupp (2018)



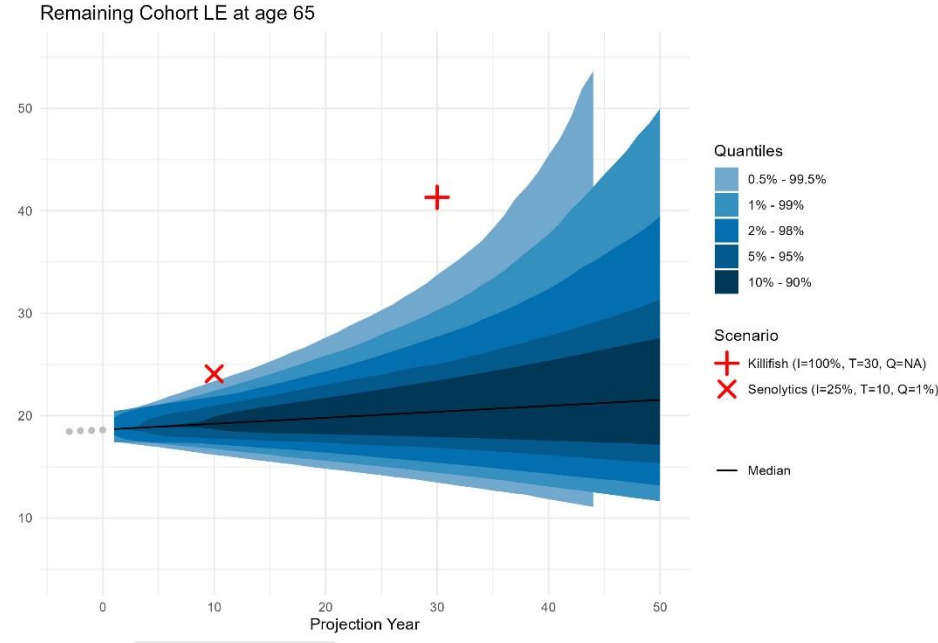
Appendix

Trend change model vs. random walk with drift

Random walk with constant drift



Trend change model



Model	Senolytics ℙ(%)	Killifish ℙ(%)
RWD (data-driven)	0.25%	0.07%
Trend (data-driven)	0.31%	0.20%

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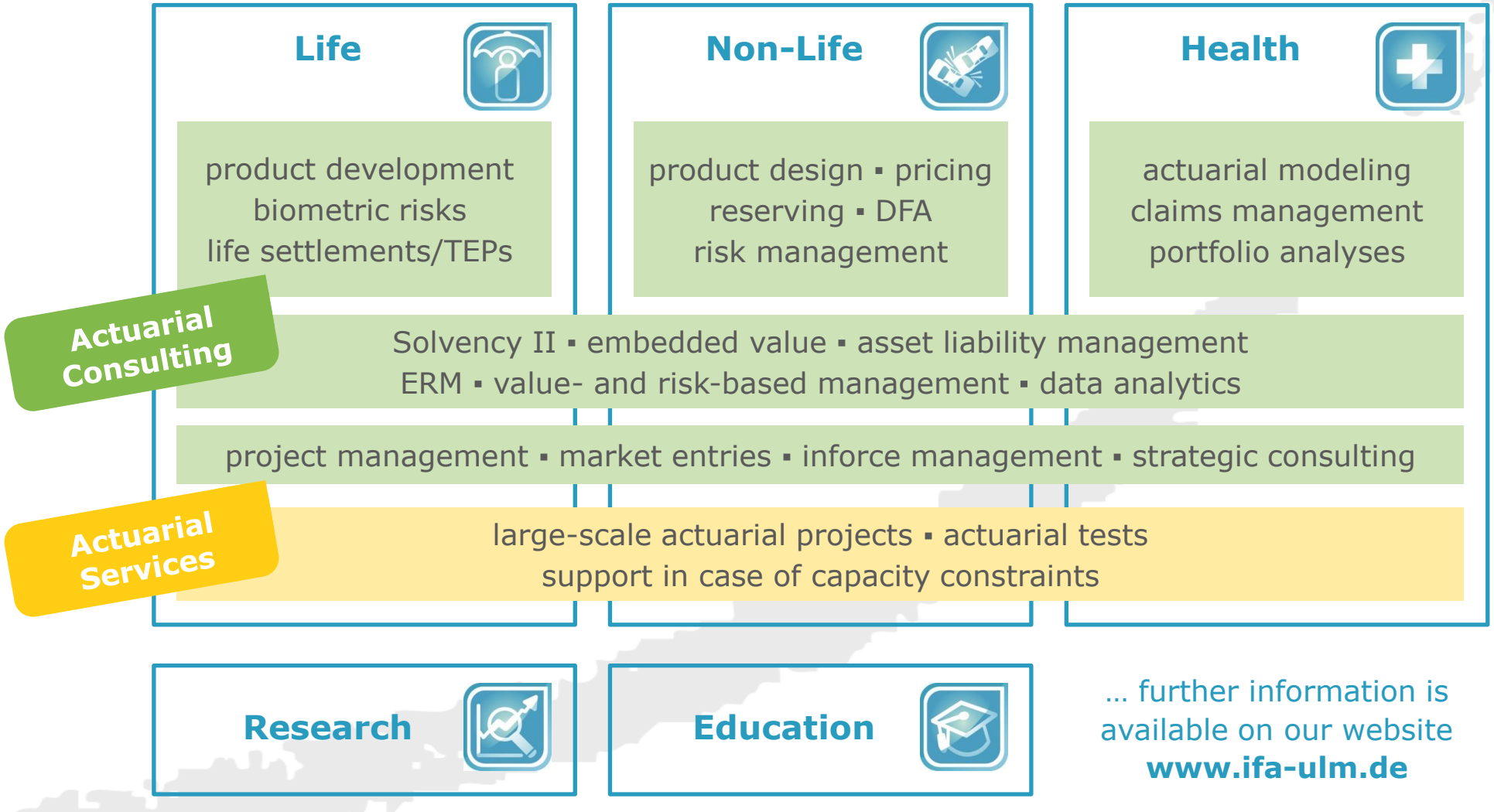

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