Chapter 10 - Long life in a pill? Compression of morbidity and the cutting edge in research and biotech

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Compressing morbidity

Human life usually begins with good health; old age brings increasing sickness and disability. Lets for simplicity call the period of general good health the **healthspan** and the period of illness and disability near the end of life the **sickspan**. Of course health is punctuated by illness, but let's for discussion consider this schematic concept of healthspan followed by sickspan.

Imagine how awful it would be if we extend lifespan by only extending the sickspan - adding years of illness and disability. clearly not optimal.

It is also not a great idea to stretch out lifespan and sickspan in proportion - stretching time like a rubberband. Ideally we want to extend life and compress sickspan (Fig 11.1).

This is the concept of **Compression of morbidity** proposed by James Fries in 1980. Fries predicted that advances in medical care and healthy living will
Reduce the period of illness and disability in an individual's life. Morbidity will thus be "compressed" into a shorter time span. Rather than living with chronic diseases for many years, individuals could experience a relatively long period of good health, followed by a brief period of illness or disability right before death.

But how can we compress morbidity? Most research in model organisms does not address this directly. Researchers often show that lifespan extension also improves health at a given age - say mice at 2 years of age are healthier with treatment than without.

But a single time point doesn't tell us if the sickspan is compressed. We need longitudinal data on health. This is currently rare, but will become available in the coming years thanks to mice longitudinal aging projects like SLAM.

In the meantime we need a theory to help us prioritize interventions that compress the sickspan.

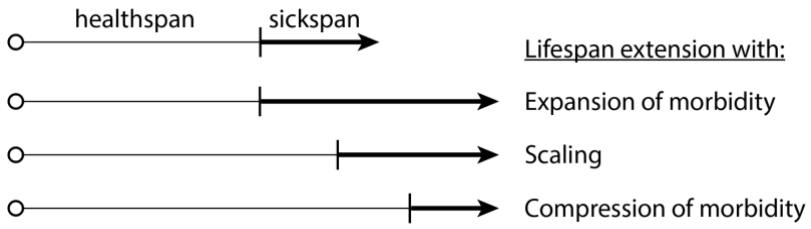


Fig 11.1

The SR model predicts that scaling interventions extend sickspan proportionally like a rubber band

We can make progress using the house-and-truck model. We will see that longevity interventions can have different effects on sickspan- some compress morbidity and others just stretch it out.

The model shows that slowing down the houses extends lifespan but also extends sickspan by the same factor. Such interventions stretch time like a rubber band, adding years of sickness. In contrast, extending lifespan by changes in any other model parameter - trucks, noise or threshold- compresses the sickspan. As a slogan, interventions that steepen the survival curve compress morbidity.

To see this requires a bit of algebra shown in the appendix. But we can understand the essence . Diseases occur when noise crosses the disease threshold Xd as we saw before. the disease threshold is lower than the death threshold Xc , otherwise the disease would occur after we die. Since threshold is lower, disease onset is more affected than death by random noise crossing the threshold early. Parameters that make the curve steeper effectively reduce randomness and thus prevent early disease more than they prevent early deaths. The net effect is a compressed average sickspan.

These compressing interventions include enhancing the trucks, reducing noise or simultaneously raising the death and disease thresholds (raising overall robustness). **Thus interventions that steepen the survival curve are predicted to compress morbidity.**

There is one exception where steepening of the survival curve *expands the sickspan* instead of compressing it. This is when you raise the death threshold X_c without raising the disease threshold X_d . This extends sickspan by a lot ! It's like a sick person in an intensive care unit that extends life artificially.

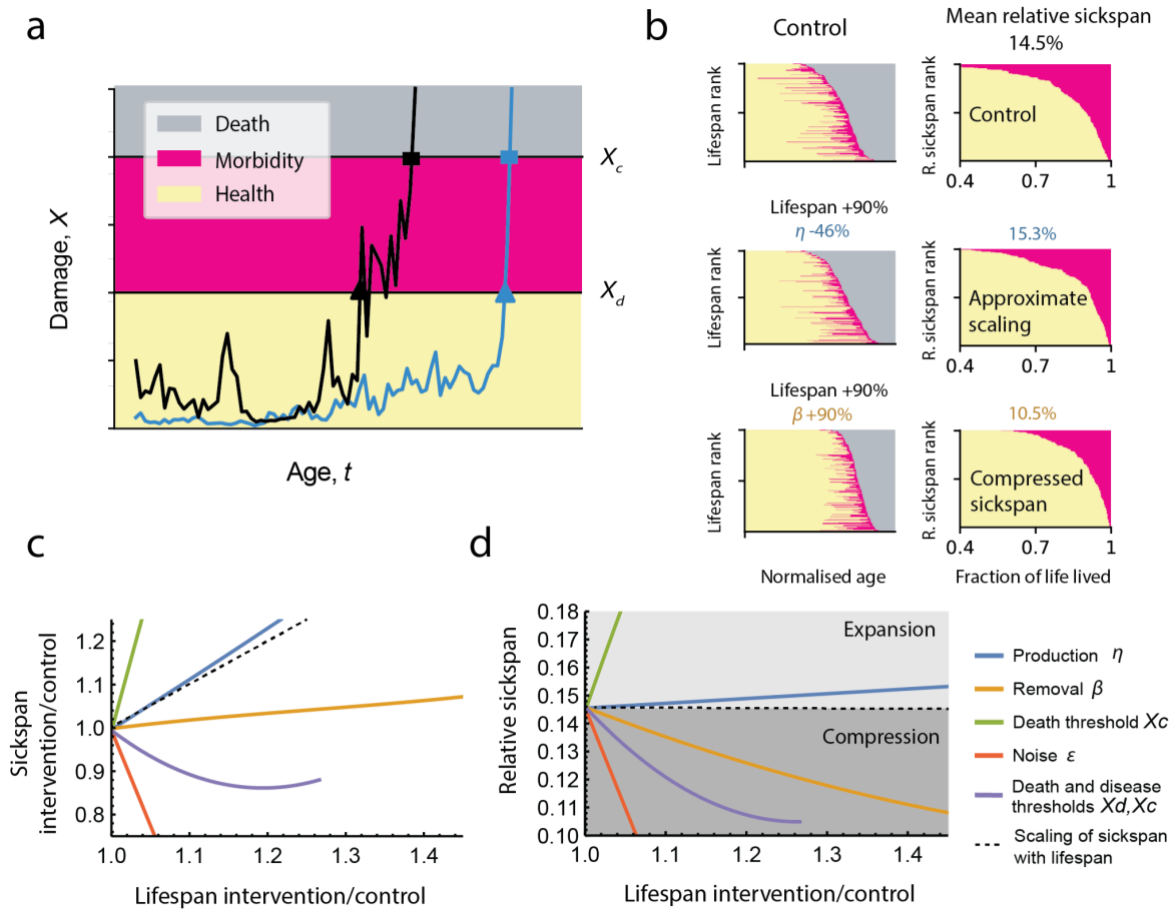


Fig 11.2 sickspan in the SR model is defined by crossing threshold Xd, and is compressed by interventions that steepen the survival curve. Source Yang et al 2025

Steepening interventions indeed compress relative sickspan in invertebrates and mice

Here is another case where the model has a clear prediction. A possibility to disprove the model. Remarkably, the prediction is supported by data on sickspan in model organisms treated by lifespan extending interventions.

These experiments were performed in mice, fruit flies *Drosophila melanogaster* and nematodes *Caenorhabditis elegans*.

In mice, Luciano et al followed mouse health by measuring their frailty index (sum of different deficits) at several time points in different longevity interventions. The experiment included dietary interventions (20% and 40% calorie restriction and two intermittent fasting schedules) in two strains (Diversity Outbred and C57BL/6). Sickspan was defined as periods of life with 4 or more age-related deficits in the mouse frailty index.

This data shows that relative sickspan decreased with steepness (Fig 11.3). Scaling interventions (steepness intervention/control of 1) showed approximately scaled sickspan (Fig. 11.3). These findings agree with the SR model predictions!

In flies, Gaitanidis et al measured longitudinal healthspan in *Drosophila* by quantifying age-related declines of motor functions. They assayed escape performance in response to gently banging food vials on the counter, i.e. “startle assays”. Each fly was scored for its jumping, climbing and flying responses to generate a frailty score for each individual by summing the number of functional deficits.

Sickspan was defined as the period where an individual has a score above a threshold value. The experiment was repeated for 5 dietary interventions (including protein restriction, superfood and curcumin- all well known in the fly longevity field) in males and females in two fly strains with different lifespans (Lausanne, Oregon).

Again, Relative sickspan decreased with steepness. Scaling interventions (steepness/control of 1) showed approximately scaled sickspan. predictions upheld!

In the worm *C. elegans* two studies evaluated healthspan. Statzer et al used a piezoelectric system to measure muscle power cross-sectionally throughout the lifespan for five different longevity-affecting mutants: daf-2(e1368), daf-2(e1370), glp-1 and eat-2, and defined sickspan by the period of life when muscle power is below 50% of wildtype. Analysis of this data shows that relative sickspan decreases with steepness.

Another method to define healthspan used the period of spontaneous movements- worms move for a few days and then slow down and stop. This method was used by both Oswal et al and Statzer et al, for several longevity interventions including temperature, food deprivation, food inactivation by UV, daf-2 (e1368 & e1370), eat-2, glp-1 (both studies), nuo-6.

Relative sickspan defined by voluntary movement also decreased with survival curve steepness, as predicted (Fig. 11.2). Scaling interventions scaled or slightly expanded relative sickspan.

In these experiments on invertebrates and mice, steepening interventions compress the relative sickspan, whereas scaling interventions approximately scale the sickspan.

It didn’t have to be this way- every time the model passes a test I’m relieved. **Let’s take a nice deep sigh of relief.**

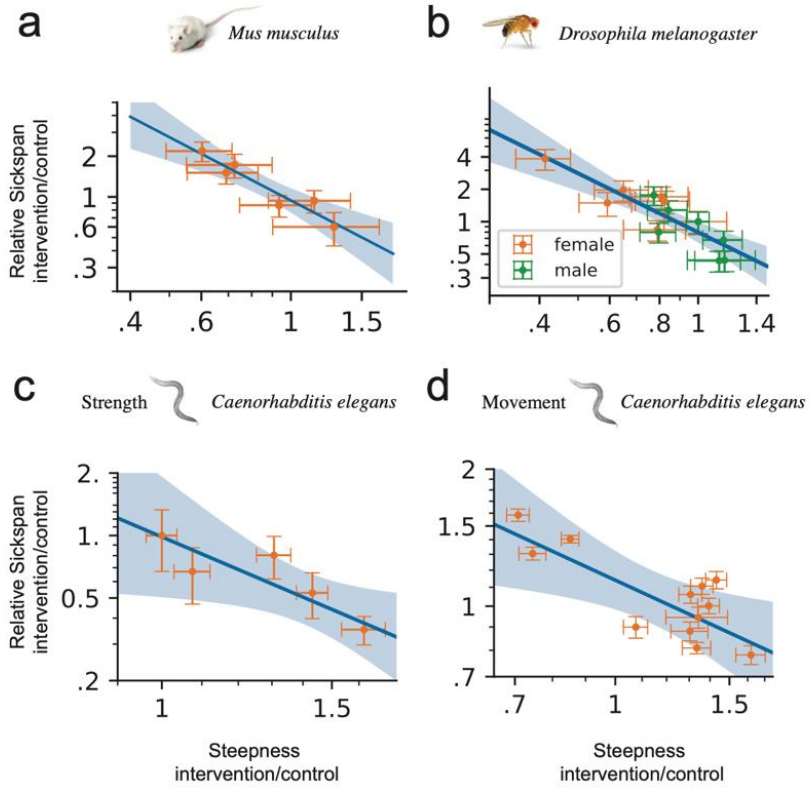


Fig 11.3 Steepening interventions compress the sickspan in worms, flies and mice. Source Yang et al 2025.

Several interventions in mice are predicted to compress sickspan

Whereas longitudinal health data is currently rare, death is much more commonly measured. Therefore survival curves of mice under longevity interventions are routinely reported in the literature. We can thus see which mouse interventions show scaled survival curves, and which steepen the survival curve. The latter are candidates for compressing morbidity.

The most rigorous study is by the National institute of aging Intervention testing program (ITP). They test each intervention in three separate locations, with hundreds of mice. And these are genetically diverse mice (so as not to get results specific to a single genetic background, such as the commonly used black 6 mice which are identical twins). So far they have reported 42 nutritional and pharmacological interventions. Other studies reported 26 additional interventions

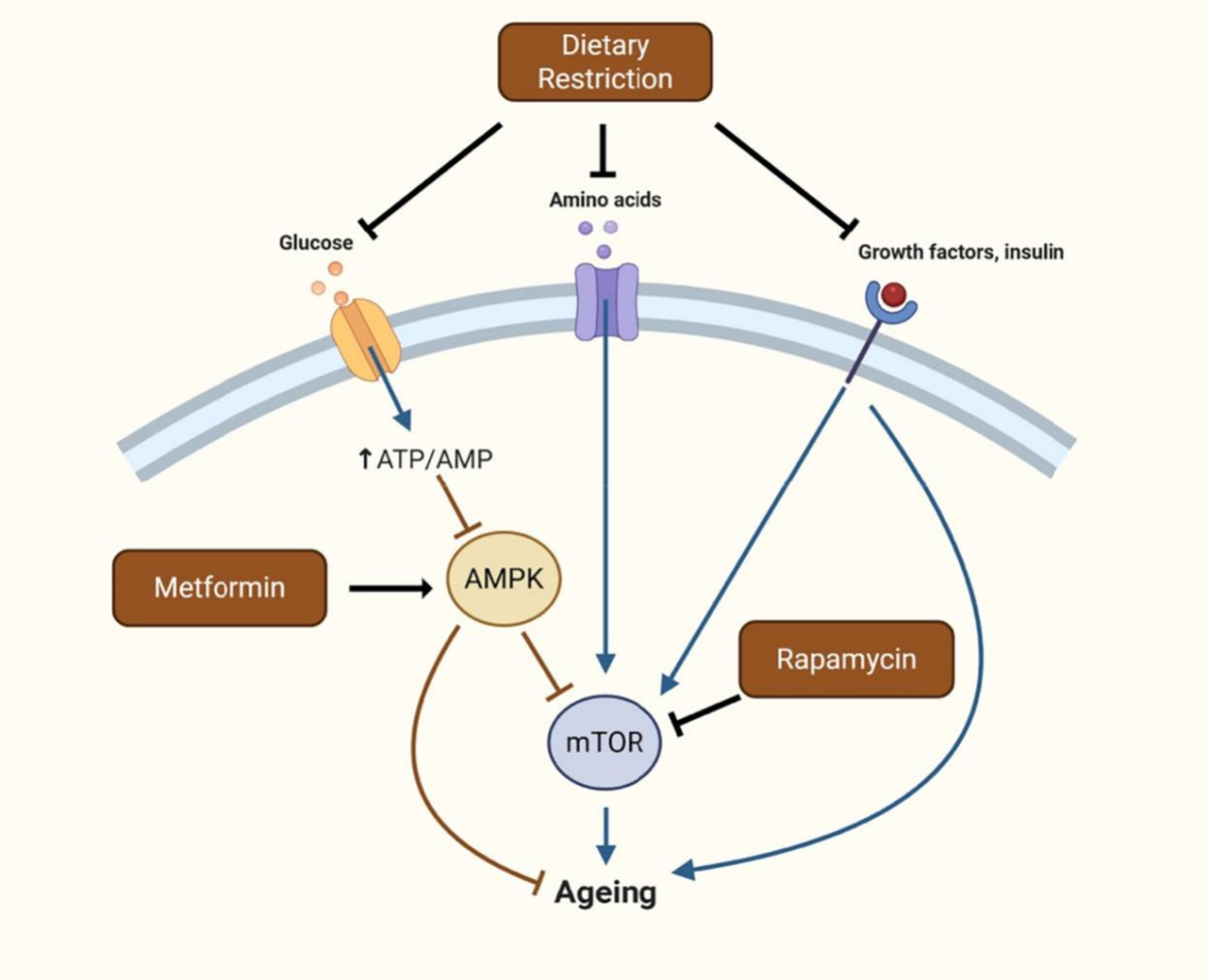
Among the 65 interventions (42 in NIA ITP, 26 outside of NIA ITP) most did not show significant effects. Some showed steepening effects - and others they showed approximate scaling according to bootstrapping tests.

One of the scaling interventions is rapamycin. A nice story is that when they tried rapamycin in 2009, they were frustrated that it broke down in the mouse gut and did not reach the bloodstream. It took many months to formulate the right coating to get it to the blood - by that time the mice intended for this study had aged.

But instead of throwing The mice away, Rich Miller insisted on trying even though they did not believe old mice can be affected. To everyone's surprise and delight , rapamycin extended lifespan in the old mice,

9% in males and 14% in females (this is the 90% survival extension, roughly maximal lifespan extension). This turned into a historic paper- the first demonstration in mice of late age life extension.

According to the SR model, since rapamycin scales the survival curve it should also scale sickspan - a prediction waiting to be tested on mice. So should caloric restriction which scales the survival curve (both rapamycin and CR primarily affect mTOR).



In contrast, there were several classes of life-extending interventions with steep survival curves (Fig 11.4) .

Senolytics extend lifespan and steepen the survival curve, as noted by Kowald and Kirkwood who analyzed data from two types of senolytic drugs and from genetic ablation of p16 positive cells. In our analysis, the effect of senolytics resembles increasing trucks - the removal rate β in the SR model. This strengthens the hypothesis that in mice, senescent cells (and more generally pro-inflammatory damaged cells) may play the role of the driving damage X in the SR model, as suggested by Karin et al.

Preventing glucose spikes An intriguing class of steepening interventions includes cyclic ketogenic diet in two different studies, the ketogenic agent 1,3-butanediol (BD) and the diabetes drugs acarbose and canagliflozin. These interventions share a common mechanism: they all lower glucose spikes, the fraction of time where the sugar glucose is at high levels in the blood. The drug acarbose inhibits an enzyme that

releases glucose from complex carbohydrates in the gut, and canagliflozin is an SGLT2 inhibitor that releases glucose to the urine by inhibiting kidney glucose reabsorption. These interventions extend median lifespan in male but not female mice.

Glucose spikes are thought to primarily damage blood vessels. Damage to blood vessels is a major pathology in diabetes - whose definition is high blood glucose - causing cardiovascular and renal disease. Endothelial cells that line the blood vessels are damaged by high glucose in several ways including reactive oxygen species, glycation of proteins and activation of signaling pathways.High glucose causes senescence in endothelial cells .

Judging from the shape of the survival curves, these vasculature-protecting mechanisms appear to increase damage removal rate *β - that is, to enhance the trucks*. One interpretation is that damaged microvasculature reduces access of immune cells to the senescent and damaged cells in tissues. Interventions that protect microvasculature may thus enhance the 'roads' for immune clearance, and hence increase the removal rate *β*. This can contribute to their steepening effect on the survival curves.

The notion of *vascular protection* as a mechanism for the steepening interventions is consistent with a VEGF longevity intervention that promotes vascular repair and slows the age-related loss of microvasculature . Mild VEGF overexpression from mouse liver showed a 45% life extension and 148% increased steepness for females. Senescent cells in the endothelium are reduced. Vasculature protection may also be relevant for captopril, a hypertension drug which increases steepness with a mild longevity gain in mice.

The ITP is currently (2026) testing glp1 receptor agonists (semaglutide and its friends) with results expected soon. Other studies found that the drug improves grip strength and organ health in old mice at doses that do not lower weight.

Non-feminizing estradiol 17-α-estradiol, steepens survival curves and extends lifespan even when administered late in life in male mice; it has no longevity effect in females. The longevity effects of this estradiol are reported to depend on testicular hormones. It is plausible that it has protective roles on the vasculature.

R*apamycin in females* One experiment with rapamycin at high dose shows a steepening effect in females, particularly on the part of the survival curve that corresponds to very old ages. It may thus have a secondary effect at high doses on older individuals.

antioxidants and anti-inflammatory agents cause steepening but with milder longevity effects (NDGA in males, green tea extract - a rare one that works in female mice) .

In the SR model, strong steepening with mild lifespan extension characterizes coordinated increases in the mortality and morbidity threshold X_c and X_d. One may hypothesize that these thresholds are affected by tolerance to inflammatory damage which is a major causal factor in aging [86,87]. Indeed, a deleterious effect of senescent and damaged cells is secretion of inflammatory factors [88].

It's like it's like a term what's gonna happen strategy strategies with ass like making the garbage with stinky 50% reduction I don't know this removal. It's a personal thing I don't know if detail more be honest

we talked with her. We can ask a question about

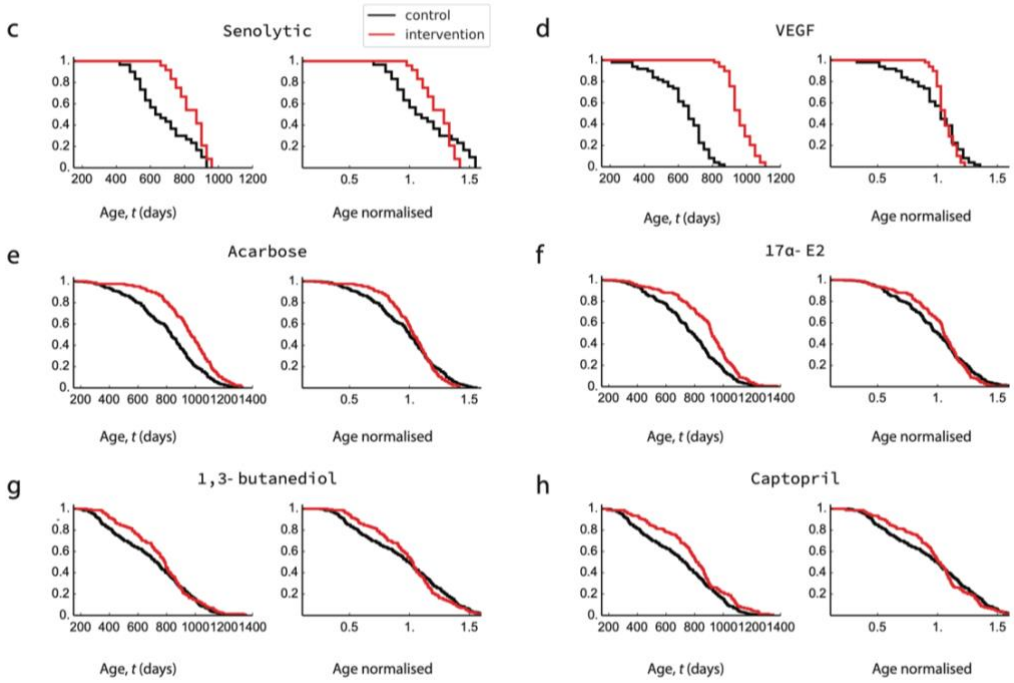


Fig 11.4 interventions in mice that steepen the survival curve and extend lifespan in the ITP and other sources. . Source Yang et al 2025

Sexual dimorphism Apart from caloric restriction and rapamycin, most interventions have strong sexual dimorphism. Generally the lifespan of male mice is easier to extend than female mice (which live longer and are more steep).

Human clinical trials on rapamycin

In an exciting recent advance, clinical trials for slowing aging have begun with drugs approved for other indications. The early awareness -raising work was done by Nir Barzilai suggesting metformin, a safe and common diabetes drug. The proposed TAME trial to measure the impact of metformin on a host of aging related phenotypes has not yet started but it got FDA approval and inspired many to try their own clinical trials on aging.

Advances have been published in 2024 on low dose rapamycin. The PEARL study used a cohort of about 115 individuals aged 60 on average to test placebo versus 5mg or 10mg weekly rapamycin on multiple health outcomes over 48 weeks. There were some significant improvements in bone mineral density in males and in lean mass in females. But the study is small. Additional studies indicate that similar doses of rapamycin improve immune function and vaccination effectiveness in the elderly.

There are also promising initial results in the VIBRANT trial on female fertility - low dose (5mg) Rapamycin was found to delay ovarian aging in humans. This trial has been expanded in 2025.

Some countries have approved clinical trials for aging outcomes and this research is expected to accelerate. It is fueled in part by a new medical specialization - **longevity medicine**- which aims to preserve and enhance physical and mental abilities in healthy middle aged and older individuals.

Combinations of steepening and scaling interventions have additive effects consistent with the SR model

One intensive area of research is the effect of combining interventions- maybe one can reap cumulative rewards?

Pair and share: which two drugs we discussed would you try to combine to get the most benefit?

Answer: drugs that affect different parameters such as rapamycin and acarbose are likely to add up, those affecting the same parameter might have diminishing returns.

The SR model can help predict the effect of intervention combinations. Intuitively, interventions that affect different pathways, such as damage production and damage removal, should act independently on survival. The SR model helps analyze such interventions - for example an intervention with scaling and an intervention with steepening are predicted to affect different pathways. Combining a perturbation that scales with one that steepens should therefore provide the best of both worlds - a steep survival curve in which lifespan is extended beyond either individual intervention.

This prediction is supported by ITP data on a combination of acarbose (steepening in males) and rapamycin (scaling) administered at 9 months. Longevity was enhanced compared to acarbose or rapamycin alone, and steepness was comparable to the acarbose mono-treatment (Fig. 11. 6). Thus the combination benefits from the sum of the longevity extensions of both interventions, together with the steepness benefits of acarbose.

Simulations of the SR model calibrated to these interventions corroborate this phenomenon .

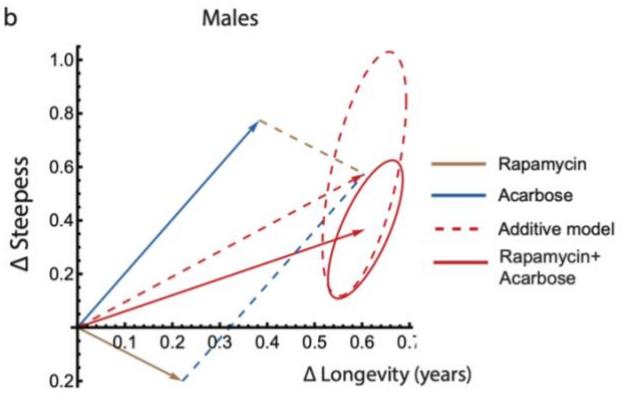


Fig 11.6 combination of a steepening drug acarbose and a scaling drug rapamycin in male mice gets best of both worlds- combined lifespan extension and steepness. Data from ITP. Source Yang et al 2025

Prioritizing FDA approved drugs for human healthspan clinical trials

Nir Barzilai in 2024 updated a list of drug candidates for clinical trials - these are safe drugs approved by the FDA for specific diseases and can be used off-label in clinical trials. He ranked them by their effect on multiple aging hallmarks, evidence in mice, epidemiological evidence in humans (e.g. a diabetes drug that also reduces risk of cancer). We can add another criterion to

this list - is the drug steepening? We would not want a drug that simply stretches out the sickspan. This might raise the ranking of SGLT2 inhibitors and Acarbose.

SGLT2 inhibitors work on the kidney and reduce glucose. The kidneys' job is to remove toxins from blood, but keep useful sugars and salts in the blood. One strategy would be to develop a pump for each toxin - but then what about toxins never seen before? So the kidney does something very clever- it first ejects everything smaller than a protein, and then only returns (reabsorbs) what is needed- mainly sugar and salts. SGLT2 is the pump that reabsorbs glucose, so inhibiting it lowers glucose.

But remarkably this drug seems to reduce other age related issues and even to be a senolytic. *"Sodium-glucose cotransporter-2 (SGLT2) inhibitors, primarily used to treat type 2 diabetes, show potential benefits for aging-related changes beyond glucose regulation. They have been found to promote the clearance of senescent cells (via reduction in checkpoint inhibitor on SnC), reduce inflammation and oxidative stress, improve vascular stiffness, and delay endothelial and vascular aging. Additionally, these drugs lower the risk of cardiovascular events and dementia, particularly in older adults, with studies indicating a 35% reduced risk of dementia among users. While these findings suggest a broader role for SGLT2 inhibitors in managing age-related conditions, further clinical trials are needed to confirm their efficacy and mechanisms in aging populations."*

Gerotherapeutic	Hallmarks of aging	Preclinical healthspan	Preclinical lifespan	Human healthspan	Human mortality	Score (out of 12)
SGLT2 inhibitors	2	2	2	3	3	12
Metformin	2	2	1	3	3	11*
Bisphosphonates	2	2	1	3	3	11
GLP1 receptor agonists	2	2	0	3	3	10*
Acarbose	2	2	2	3	0	9*
Rapamycin	2	2	2	3	0	9
Methylene blue	2	2	2	3	0	9
ACE inhibitors/ARBs	2	2	1	3	0	8
Dasatinib + (quercetin)	2	2	1	3	0	8
Aspirin	2	2	2	1	0	7
Beta blockers	1	2	1	0	3	7
N-acetyl cysteine	2	2	1	0	0	5*

Table 1 Ranking of FDA-approved drugs as potential gerotherapeutics based on scoring (out of 12) for preclinical and clinical evidence. Evidence suggesting COVID-19 mortality benefit is delineated by an asterisk in the total score column.

Aging clocks and their discontents

One current intense subfield is aging clocks- molecular measurements aimed to discover an individual's biological age.

If we had a good clock we could see rapidly whether an intervention is working in clinical Trials.

The first clock was discovered by chance. Steve Horvath wondered whether epigenetic information on the DNA - chemical

Modifications called methylations -
Carry information on sexual
Orientation. Steve tells that he has an identical twin broker who is gay and so he analyzed data on methylations. He found no signal
For sexual rotation. But as a control he compared to chronological age of the participants and Lund to his surprise that he could predict wa persons age form
The dna methylation.
The pioneering work by Hovarth in 2011 showed that DNA methylation (millions of sites in each genome, where each site can be methylated or not) can be distilled down to a few hundred sites that predict chronological age. The biological age is the average age that matches your biological measurement.
The mismatch between an individual's real
age and estimated biological age is considered their biological age acceleration (age difference actually) - and this seemed to correlate with things like smoking and morbidity.
This approach grew into a booming field with regression-based clocks using methylation (easy to measure), blood tests, transcriptomics and proteomics, and many other measures.
Generation 1 clocks use regression to chronological
age and poorly predict diseases, generation 2 clocks fit to mortality or disease data, and do a better job at predicting mortality and hazard ratios. Recently age per organ is measured.
The excitement is understandable: the big payoff of a real aging clock is a quick way to test potential anti-aging therapy in humans- instead of waiting for decades, we can see if the clocks are sped up in a short amount of time.

Several findings make me uneasy. First, an elegant study by Schumacher showed that if you simulate methylation by random walkers confined between zero and one, and repeat the clock regression method, you can choose a subset of walkers that will be linear in time with superb correlation (technical note: clocks regress on error squared, and random walkers go as sqrt time , so it works out to linear in time). Thus any stress that affects the random walk would look like biological aging.

This ties into another worry, that things like covid, surgery and pregnancy seem to make you older according to the clock. For example pregnancy registers at an older age during gestation and then young again according to current methylation clocks.
This means the clocks are not specific to aging. To understand this we did a detailed analysis of blood tests from 300,000 pregnancies and computed effective “lab test” age by comparing it to tests from 1.4 million people aged 20 to 80. The apparent age of the mother dropped by 8 years in the first trimester and then rose to 40 extra years at delivery, recovering over a year postpartum.
The rejuvenation seems plausible in some organs due to gestation induced physiology such as enhanced kidney filtration rate, cardiac output and insulin sensitivity (first trimester).
In contrast, the aging-like effects are only *superficially* like real aging. For example essential blood proteins (albumin) drop in both aging and pregnancy, but for very different reasons. In aging the drop is due to reduced production of these proteins in the liver. In pregnancy the liver actually makes *more* of the proteins to compensate for the 50% expansion of blood volume of

the mother. The compensation is not perfect resulting in a slight drop of the blood protein concentration.

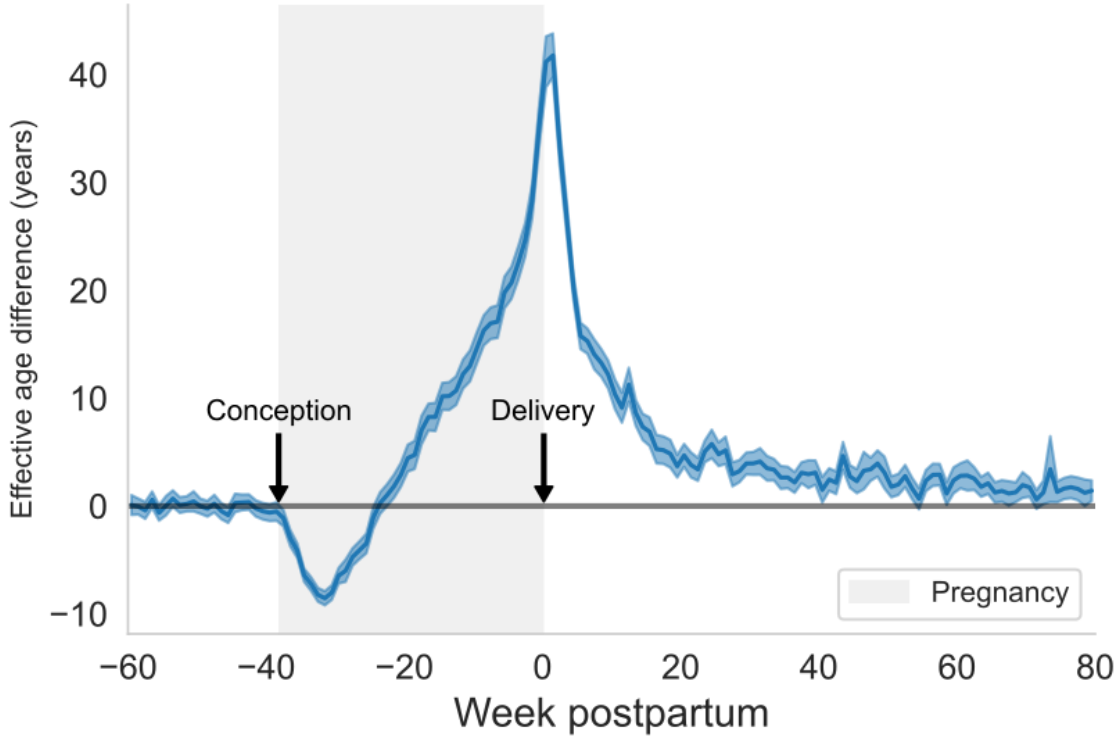


Fig 2. Mother's mean lab test age drops in trimester one, rises towards delivery and recovers postpartum. LabAge at each week of gestation and postpartum where age 0 is baseline clock age at 60 weeks before delivery. Gestation is in gray background; delivery is at t=0 (Moran 2025)

There is an argument In the field whether the methylation sites are causal for aging. It seems that the clock methylation sites are in genes and regions unrelated to aging, mainly in closed chromatin regions meaning they have slow stochastic changes, and since they are limited to between zero and one, it may be a Schumacher type effect. DNA methylation itself is unlikely to cause aging: yeast, worms and flies do not have DNA methylation - they rely on histone modification such as acetylation- and still they age.

I think the idea of a clock is important - if we can get a direct measurement of the garbage, houses and trucks relevant to the driver(s) of aging. Such a direct measurement of x will be specific to aging and will provide perhaps the closest molecular measure we can have of an individual's state of aging. One may hypothesise that measuring key histone acetylations in telomere regions, and lysosome deacidification/mitochondrial dysfunction might be closer to home.

To lower our biological age, let's take a nice deep sigh of relief.

Appendix In the SR model steady state solution we know how mean damage x rises with age, as we saw in lectures 3-4 (Karin 2019)

$$< x >= \frac{\eta k\ t\ + \epsilon}{\beta - \eta t}$$

The approximate time of death is when x crosses the death threshold X_c denoted t_C, and the onset of sickspan is when x crosses the disease threshold Xd, a time denoted t_d. Fig 11.2a Doing some algebra yields a relation between the sickspan as a fraction of lifespan and the sr model Parameters:

$$Relative\ sickspan = \frac{t_c - t_d}{t_c} = \frac{(X_c - X_d)(1 + X_c/k + \epsilon/\beta k)}{(k + X_d)(X_c/k - \epsilon/\beta k)}$$

For typical Human parameters $X_c = 17, X_d = 15, \kappa = 0.5, \epsilon/\beta\kappa = 3$ we obtain a relative sickspan of about 0.16, a bit high - it's more like 10-13% in the US where the lifespan is 77 and the mean sickspan is 8-9 years. But even if inaccurate in absolute terms, the dependence on parameters turns out to be quite accurate compared to full model simulations.

The formula shows that Relative sickspan does not depend on η**.** This parameter, the slope of damage production, shows a scaling of survival curves. Interventions that affect eta thus change median lifespan but not the shape of the survival curve - and also do not change relative sickspan. We conclude that - scaling interventions stretch sickspan and lifespan proportionally!

This makes sense since at steady-state eta stretches time like a rubber band. Since the damage x causes both death and disease, sickspan stretches by the same proportion as lifespan. This is a warning sign for scaling interventions such as caloric restriction and rapamycin, at least when not supplemented by additional interventions .
The sickspan formula does not include eta but it does include the rest of the parameters. Raising $removal\ rate\ \beta$ or decreasing noise ϵ - both steepening to the survival curve - compress the relative sickspan! Raising X_c and X_d by the same factor also compresses sickspan! See fig 11.2bcd. These interventions that steepen the survival curve also compress morbidity.