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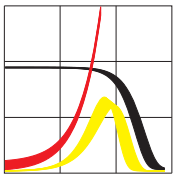

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How slowing senescence changes life expectancy

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HOW SLOWING SENESCENCE CHANGES LIFE EXPECTANCY

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ABSTRACT. Mortality decline has historically been a result of reductions in the *level* of mortality at all ages. The *slope* of mortality increase with age has been remarkably stable. A number of leading researchers on aging, however, suggest that the next revolution of longevity increase will be the result of slowing down the rate of aging, lessening the rate at which mortality increases as we get older. In this paper, we show mathematically how varying the pace of senescence influences life expectancy. We provide a formula that holds for any baseline hazard function. Our result is analogous to Keyfitz's "entropy" relationship for changing the level of mortality. Interestingly, the influence of the shape of the baseline schedule on the effect of senescence changes is the complement of that found for level changes. We also provide a generalized formulation that mixes level and slope effects.

1. INTRODUCTION

So far in human history, longevity gains have come largely from declining levels of mortality rather than slowing senescence. Recently, however, there have been a number of calls for taking the problem of

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aging head-on by reducing the rate at which people get old. In demographic terms, this means reducing the rate at which mortality rises with age. A prominent example by researchers in the *British Medical Journal* argues for medical research in aging to turn away from the disease specific model, and instead focus on slowing the aging process: "The most efficient approach to combating disease and disability is to pursue the means to modify the key risk factor that underlies them all – ageing itself" (Butler et al., 2008). Some observers such as De Grey and Rae (2007) in *Ending Aging* are optimistic about the possibility of slowing the aging process in the near future. In this article, we show formally how large the pay-off to slowing senescence would be. Our results complement the classic work of Keyfitz (1977) on the effect of changing the level of mortality on life expectancy.

Senescence is often defined as the increase of mortality risks that accompany the weakening of an organism with age (Medawar 1952).[1] Thus, one way to think about slowing senescence is as a reduction in the speed with which the risk of death increases with age. In the Gompertz case, when hazards are exponential, $\mu(a) = \alpha e^{\beta a}$, slowing senescence is equivalent to reducing β. More generally, for any pattern of increasing hazards, a slowdown in senescence can be modelled by

[1]It is worth quoting Medawar in full:

> It is a curious thing that there is no word in the English language that stands for the mere increase of years: that is, for ageing silenced of its overtones of increasing deterioration and decay. We obviously need a word for mere ageing, and I propose to use ageing itself for just that purpose. Ageing hereafter stands for mere ageing, and has no other innuendo. I shall use the word senescence to mean ageing accompanied by that decline of bodily faculties and sensibilities and energies which ageing colloquially entails.

letting the hazard at age a be equal to the hazard observed in a baseline schedule at age θa. For example, if $\theta = 1/2$, then an individual with slowed senescence is exposed at age 60 to the hazard observed in the baseline schedule at age 30, at age 80 to the original hazard at age 40, and so on.[2]

Increases in longevity that come from this kind of slowdown in senescence can be contrasted with increases that come from declines in the level of hazards (proportional hazards) and from increases that come from shifting the distribution of deaths (accelerated failure time). In this paper, we show how much of an impact slowing senescence has on life expectancy, clarifying the relationship between these different sources of mortality change. In particular, our results allow us to see why, in modern populations, reducing the pace of senescence by 1 percent, for example, will have a much larger effect than reducing mortality levels by 1 percent. As life table entropy falls, reducing mortality levels have a smaller and smaller effect on life expectancy, but reducing the pace of senescence has a larger and larger effect.

Our results here echo those of life table entropy (Keyfitz 1977, Mitra 1978, Goldman and Lord 1986, Vaupel 1986), except that we consider the case of changing the "slope" – the pace of aging – rather than the level of mortality.

[2]Although the mathematics of what follow applies to any baseline hazard, regardless of whether hazards increase or fall with age, the interpretation of θ can depend on the baseline schedule. When hazards are rising, then $\theta = 1/2$ slows senescence. If hazards were falling, e.g. during childhood, then $\theta = 1/2$ would increase the amount of time it would take for hazards to fall. Thus the model would delay "maturity" or slow "growth." (See Baudisch (2008)).

The model we call "senescence-slowing" has been recently introduced into the statistical literature by Chen and Wang (2000). They call it the *accelerated hazards* model, contrasting it with *proportional hazards* (Cox, 1972) and *accelerated failure time* (e.g., Kalbfleisch and Prentice 2002) models. Because the new literature on accelerated hazards models is primarily concerned with multivariate estimation, it appears that the simple result (1) relating to expected values has not been previously stated in an explicit way. We believe that relationship (2) in terms of entropy H is new.

Because it can be hard to keep straight which model is which, we refer to the accelerated hazards model as "senescence-slowing", and the accelerated failure time model as "death-delaying."

2. The effect of slowing senescence on life expectancy

We model a change in the rate of senescence by letting the hazard at age a be the hazard observed in the baseline schedule μ_0 at the age $a\theta$, so that

$$\mu^\star(a) = \mu_0(a\theta)$$

for $\theta \geq 0$.

Then, the new life expectancy at birth is

$$e^\star(0) = \frac{1}{\theta}\int_0^\infty l(a)^{1/\theta}\, da. \tag{1}$$

This result is general in the sense that no restrictions are made on the baseline lifetable.

Furthermore, if we write $\theta = 1 + \delta$, the relative change in life expectancy that results from accelerating senescence by δ is

$$\frac{\Delta e^{\star}(0)}{e(0)} \approx -(1 - H)\delta \tag{2}$$

where, as per Keyfitz, $H = -\int [\log l(a)] l(a)\, da/e(0)$.

Contrast this with the role of entropy H in

$$\frac{\Delta e^{*}(0)}{e(0)} \approx -H\delta$$

when mortality is changed proportionally via $\mu^{*}(a) = (1 + \delta)\mu_0(a)$.

Relationship (2) allows us to estimate the effect of slowing senescence. Current human life tables in low mortality countries have $H \approx 0.1 - 0.2$. As Keyfitz' analysis shows, a 10 percent decline in hazards at all ages would increase adult life expectancy by about 1 to 2 percent. But according to (2), a 10 percent slow-down in the pace of senescence would increase adult life expectancy by about 8 to 9 percent.

3. Derivations

Relationship (1) for life expectancy in terms of θ can be obtained via repeated substitution of the integral

$$e^{\star}(0) = \int_0^{\infty} \exp[-\int_0^{x} \mu_0(a\theta) da]\; dx.$$

First define a new variable $w = a\theta$ to get

$$e^{\star}(0) = \int_0^{\infty} \exp[-\frac{1}{\theta}\int_0^{x\theta} \mu_0(w) dw]\; dx$$

and then define $v = x\theta$ to get

$$e^\star(0) = \frac{1}{\theta}\int_0^\infty \exp[-\frac{1}{\theta}\int_0^v \mu_0(w)dw]\; dv = \frac{1}{\theta}\int_0^\infty l(a)^{1/\theta}\; da.$$

Values $\theta > 1$ correspond to accelerating senescence and values of $\theta < 1$ represent slowing senescence. Since

$$\frac{de^\star}{d\theta} = \int_0^\infty l(x)\left(-\int_0^x \mu'(a\theta)ada\right)\; dx, \tag{3}$$

we can describe the impact on life expectancy of changes in θ. If hazards are increasing, i.e. μ' is positive, then slowing senescence has the expected effect of increasing $e^\star$. Likewise, if hazards are decreasing, slowing senescence implies that it will take individuals longer to reach the lower mortality rates, and so longevity will be reduced.

Relationship (2) can be obtained by parallelling Keyfitz's analysis, approximating the effect of a small change in senescence on life expectancy as $\Delta e^\star(0)$ with $\delta \cdot \frac{de^\star}{d\delta}\big|_{\delta=0}$. Thus,

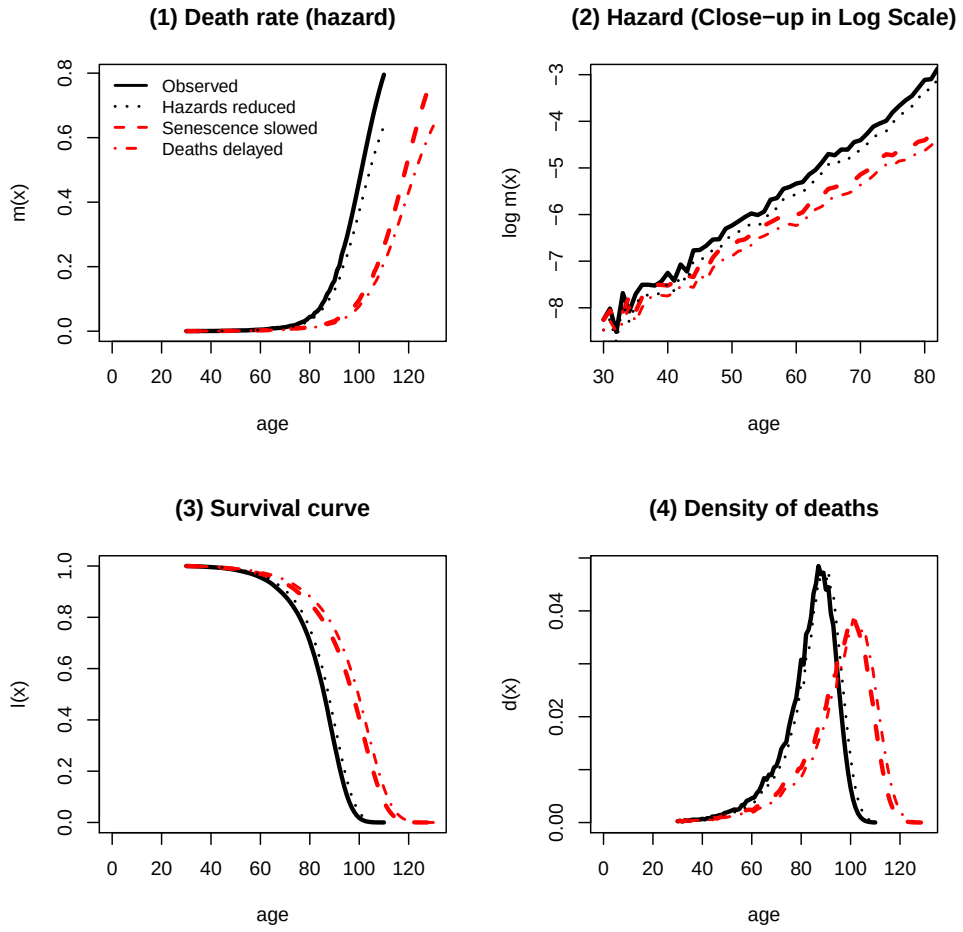
$$\frac{\Delta e^\star(0)}{e(0)} \approx \frac{\delta \cdot \frac{de^\star}{d\delta}\big|_{\delta=0}}{e(0)} = \frac{\delta \cdot \left[-\left(e(0) + \int \left[\log l(a)\,\right] l(a)\, da\right)\right]}{e(0)} = -(1-H)\delta,$$

where the last equality is found by substituting for H.

4. Applications

4.1. **Numerical illustration of reducing the pace of senescence for Swedish females.** We illustrate the consequences of reducing mortality via slowed senescence and other models using the 2007 period life table for Swedish females from the Human Mortality Database. In order to consider only the senescent portion of life, we focus on adult

FIGURE 1. **Illustrated mortality declines by various models.** The baseline is the 2007 period life table of Swedish females, aged 30 and over. Each model involves a 20 percent reduction, with the hazards reduced model being a 20 percent proportional reduction at all ages, senescense slowed model being a 20 percent decline in the rate of aging, and the deaths delayed model being a 20 percent decline both in the rate of aging and mortality level.



mortality, defined as ages 30 and above. This example shows us how the life table responds to different kinds of mortality change, and to compare and contrast these effects.

The first panel shows the observed age-pattern of death rates, along with three kinds of mortality reductions. The proportional hazards model, shown with the dotted line, reduces mortality rates by 20 percent at all ages. The effect is small compared with slowing senescence by 20 percent, shown with the heavy dashed line.[3] Finally, the effect of delaying deaths by 20 percent is shown with the lighter dot-dash line. We can see that delaying deaths is like applying the 20 percent reduction to the hazards that are obtained by slowing senescence. The space between the observed and proportional decline curves appears to be about the same as that between the slowed senescence curve and the deaths delayed curve.

The second panel shows a close-up view of the same mortality rates across a more limited range of ages and in the logarithmic scale. The near linearity of these logarithmic curves means that mortality is increasing approximately exponentially with age, as in the Gompertz model. The close-up view shows us that the senescence-slowing and death-delaying models are changing the slope of mortality increase with age, whereas the proportional decline model retains the slope of the original observations, but at a lower level. It is in this sense that senescence-slowing can be considered a slope change.

The third and fourth panels of the figure show us the impact of changing mortality rates on the survival curve and distribution of deaths. We see that the change in the survival curve is great for the senescence-slowing and delayed death models but small for the proportional decline

[3]This 20 percent slowdown in senescence was calculated by assigning to age $30 + a$ the mortality observed at age $30 + a/1.2$.

model. The distribution of deaths is moved to older ages as a result of the proportional change in deaths, a well-known result of applying proportional hazards to the Gompertz model (e.g., Vaupel 1986, Goldstein and Wachter 2006). In addition to a change in "location," the slowing of senescence also broadens the distribution of deaths somewhat.

The life expectancy at age 30 associated with the four curves are 53.5 for the observed lifetable, 55.4 for the proportional reduction, 64.3 for slowed-senescence, and 66.7 for delayed-deaths. The entropy value H is 0.16 for the observed life table. The application of linear estimate in relationship (2) gives an approximation for the life expectancy of the modified schedules but it not exact because of the large value of δ corresponding to a 20 percent change.

4.2. **A more formal comparison, along with a flexible hybrid model.** It is apparent that the three approaches to changing mortality – proportional reductions in hazards, senescence-slowing and death-delaying – can be subsumed in a more general hybrid model. Consider changing the baseline mortality schedule $\mu_0(a)$ with two parameters θ_1 and θ_2 to get

$$\mu(a) = \theta_1 \mu_0(\theta_2 a),$$

where the constant θ_1 provides a proportional change in mortality, and θ_2 changes the rate of senescence. Within this framework, the proportional hazards model is the case where $\theta_2 = 1$, the senescence-slowing model corresponds to $\theta_1 = 1$, and the death-delaying model refers to the particular circumstance with $\theta_1 = \theta_2$.

Table 1 provides a formal comparison of the models of mortality change we have considered, including the hybrid model.

TABLE 1. Models of Changing Mortality

Model	Hazard	Density	Life expectancy	$\frac{\Delta e}{e(0)}$
Baseline	$\mu(a)$	$\mu(a)l(a)$	$\int l(a)da$	0
Proportional hazards	$\theta\mu(a)$	$\theta\mu(a)l(a)^{\theta}$	$\int l(a)^{\theta}da$	$-H\delta$
Senescence-slowing	$\mu(\theta a)$	$\mu(\theta a)l(\theta a)^{1/\theta}$	$\frac{1}{\theta}\int l(\theta a)^{1/\theta}da$	$-(1-H)\delta$
Death-delaying	$\theta\mu(\theta a)$	$\theta\mu(\theta a)l(\theta a)$	$\frac{1}{\theta}\int l(a)da$	$-\delta$
Hybrid model	$\theta_1\mu(\theta_2 a)$	$\theta_1\mu(\theta_2 a)l(\theta_2 a)^{\theta_1/\theta_2}$	$\frac{1}{\theta_2}\int l(a)^{\theta_1/\theta_2}da$	$-H\delta_1-(1-H)\delta_2$

The first column gives the name of the model as used in this paper and the final column gives the proportional effect of a small change in θ on life expectancy, where $\theta = 1-\delta$ and so $\delta = \theta - 1$. For the hybrid model we use $\theta_1 = 1-\delta_1$ and $\theta_2 = 1-\delta_2$

In terms of the proportional effect of a change in the parameters on life expectancy, we see that death-delaying model is the combined effect of senescence-slowing and proportional hazards since

$$-H\delta + (-(1-H)\delta) = -\delta.$$

The effect of the mixed model is also the combination of these two models but with potentially different perturbations.

5. Discussion

The complementarity between the entropy H of the proportional hazards model and the effect of changing the rate of senescence $(1 - H)$ given in (2) means life tables with a large response to changing the level of hazards will have a small response when changing the rate of aging, and vice-versa. For example, when hazards are constant $H = 1$, so transforming age will have no effect at all. At the other extreme, when hazards are zero until some age at which they become infinite, all deaths will be concentrated at this age. In this case, $H = 0$ since proportional changes in zero and infinite hazards are without consequence. Any change in the age at which hazard become infinite, however, will be perfectly reflected in a change in life expectancy. Current human life tables in low mortality countries have $H \approx 0.1 - 0.2$. A 10 percent decline in hazards at all ages will increase life expectancy by 1 to 2 percent. A 10 percent slow-down in the pace of senescence would increase life expectancy by 8 to 9 percent.

Historically, entropy for adults has fallen over time, from about 0.3 in 19th century Sweden to about 0.1 in contemporary low-mortality populations. This decline in H means that the relatively greater impact of slope vs. level changes has itself increased over time. Whereas in the 19th century the benefit of slowing the aging process would have been perhaps 2-3 times the benefit of lowering the level of mortality, today the benefit is nearly 10 times as large. The mathematics of mortality

change thus provide one reason why researchers on aging are focused now, more than ever, on slowing aging itself. [4]

Finally, as H gets smaller, the distinction between the senescence-slowing model and the death-delaying model become less important. This is because the additional effect of changing the level of hazards has a smaller and smaller impact relative to the effect of changing the slope.

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[4]This comparison does not say anything about the relative difficulty of lowering the level of mortality and changing the rate of aging. It could well be that the same amount of effort or money spent on reducing mortality levels could have a bigger payoff than trying to slow aging.

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