Systems Medicine 2021 BE333 Lecture Notes
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Lecture 6
Basic facts of aging

Introduction:

Aging, aging, aging here and there
Aging x3 everywhere
Aging is a song that is universally sung
Aging is a thing you can ignore when you are young
But when you are older and begin to have dementia
You'll think back upon this course and wish you'd payed attentia
Aging, aging, aging here and there
Aging x3 everywhere

Welcome to part 3 of the course! Part 3 is devoted to the fascinating topic of aging.
In part 3, we use our three laws to develop a theory of aging, and test it against a wide range of experimental facts. This chapter will present some of the basic facts of aging. In the coming lectures, we will see fundamental principles that govern the rate of aging and set the pace of aging-related diseases.

-Gompertz
-exponential disease incidence
-linear decline
-frailty widening, but reducing heterogeneity
-lengthening timescales for healing
-scaling in some cases (is SES scaled?)
-rapid shifts in some cases
-evolution in mammals
-disposable soma

To understand aging, let's begin with a hypothetical organism that has no aging. Consider a group of these organisms that do not grow old. They are killed by predators at a constant rate, h_0. The parameter h_0 is called the **extrinsic mortality**. Over time there remain fewer and fewer organisms,

$$\frac{dN}{dt} = -h_0 N.$$

The solution is an exponential decay,

$$N(t) = N(0)e^{-h_0 t},$$

where $N(0)$ is their initial number.

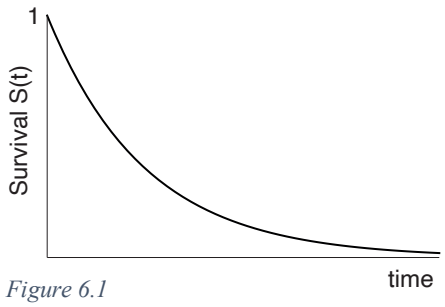

Figure 6.1

The **survival curve** for this population is defined as the number of organisms remaining at time t,

$$S(t) = N(t)/N(0).$$

Survival therefore decays exponentially, just like radioactive decay of particles (Fig 6.1). The probability of death per unit time, called the **hazard**, is the same regardless of the age of the organism, $h(t) = h_0$ (Fig 6.2). This is what no aging looks like, in terms of population dynamics.

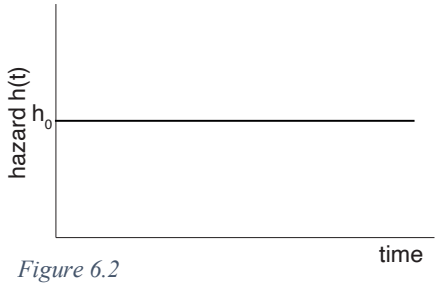

Figure 6.2

Let's now look at the human survival curve (Fig 6.3). It does not decay exponentially. Instead, death is delayed on average: the survival curve starts out nearly flat. Death is rare until the seventh decade, and then death becomes common.

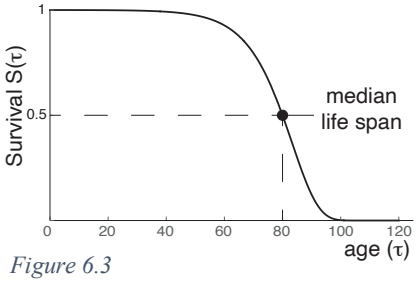

Figure 6.3

Ageing has nearly universal features

The risk of death per year allows us to see more details. This is the hazard curve, defined as the fraction that die in a given year of age out of all those that survive to that age. It has the following interesting shape when plotted versus age (Fig 6.4). This data is for Sweden in 2012, and similar graphs are found across the world. Risk of death is high in the first year: The human life cycle begins with rapid growth of the embryo and formation of the bodies' systems, with attendant diseases and errors (birth defects), as well as delivery risks (preterm and pregnancy complications). Examples of infant disease are mutations in the germline which cause

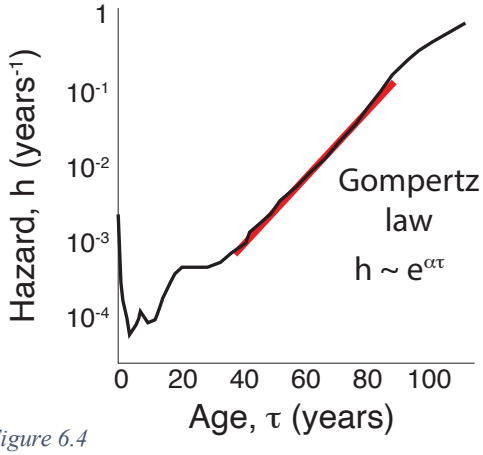

Figure 6.4

rare congenital diseases (over 6000 genetic disorders that together account for mortality on the order of 10^{-3} in the first year).

Then, risk of death drops to a minimum at childhood. In the teenage years, risk of death rises again, and plateaus in early adulthood. In this plateau, hazard is dominated by extrinsic mortality: accidents, suicides and homicide, at a rate of about 3 out of 10,000 /year. Then, starting at age 30-40, risk of death begins to rises. Risk doubles about every 8 years. This exponential rise in hazard is called the **Gompertz law**. If we denote age by τ, the Gompertz law is

$$h(\tau) \sim be^{\alpha\tau}.$$

The law was discovered by Benjamin Gompertz in 1825, a mathematician who found work computing life-expectancy tables for life-insurance. If we separate mortality into intrinsic and extrinsic components, we can see that the exponential rise in intrinsic hazard begins already at age 15-20, as seen for US mortality statistics (Fig 6.5). Different regions and historical periods differ mainly in their extrinsic mortality, and in the extent of childhood mortality (in past centuries and today in some regions about 20% childhood mortality and about 1% chance of mothers to die at childbirth). The Gompertz slope α is, however, much more constant across populations. Thus, hazard curves are often modeled by the **Gompertz-Makeham law** that adds extrinsic mortality

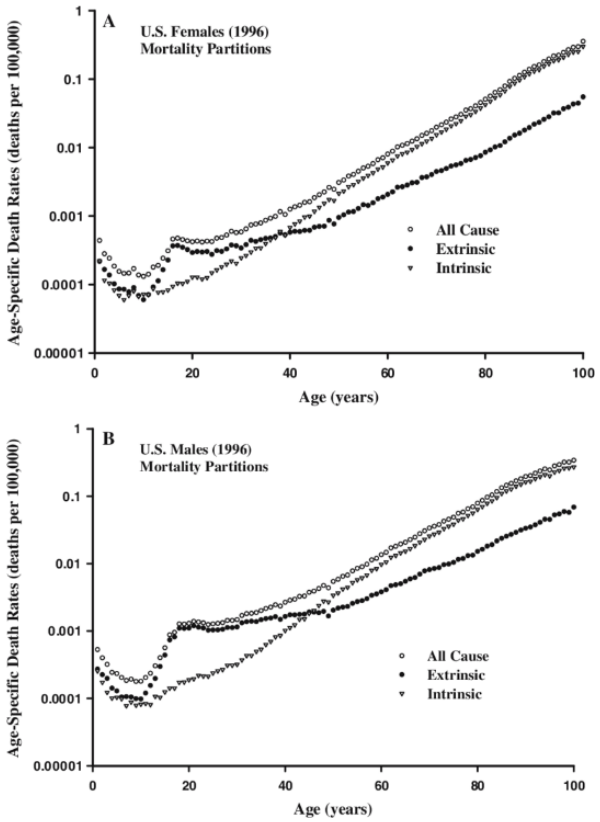

Figure 6.5

$$h(\tau) \sim be^{\alpha\tau} + h_0.$$

extrinsic mortality rises slightly with age as seen in Fig 6.5, perhaps because accidents are more lethal. It rises much more slowly than extrinsic mortality.

The Gompertz law is nearly universal. It is found in many organisms, including most mammals studied. It is found in the favorite model organisms of laboratory research: mice that live for about 2.5 years, *Drosophila* fruit flies that live for about 2 months, and *C. elegans* worms that live about 2 weeks. In 2019, Yifan Yang, Ariel Linder et al (Yang et al., 2019) found that the Gompertz law holds even in *E. coli* bacteria: when starved, their risk of death, measured by a dye that enters dead cells, shows the Gompertz law, with an average lifespan of about 100 hours. There are exceptions

to the rule, such as some trees in which hazard has been suggested to drop with age, and organisms that grow indefinitely or divide indefinitely.

Another universal feature is that the exponential Gompertz growth slows down at very old ages. In humans, around age 80 the exponential rise slows down. Above age 100 hazard is believed to plateau at about a 50% chance of death per year. This is sometimes described by the Gamma-Gompertz-Makeham law $h(\tau) = \frac{be^{\alpha\tau}}{1+ce^{\alpha\tau}} + h_0$.

Thus, aging means that there is something different about young and old organisms. The decade of 10-20 and the decade of 70-80 are different. Something accumulates in the body to make hazard rise sharply with age.

Indeed, most physiological and cognitive functions decline with age. This includes vision and hearing, and aspects of cognitive ability (Fig 6.6, 6.7). Similarly, heart and kidney functions decline with age. It is worth noting that organs have a large spare capacity: you can remove 90% of the pancreas or kidneys, and survive (although you lose resilience to extreme stress). That is why people can donate a kidney and remain healthy. Therefore, organs can take a lot of damage before they begin to lose function. Damage rises throughout life, but its pathological consequences are felt at old age when spare capacity is used up.

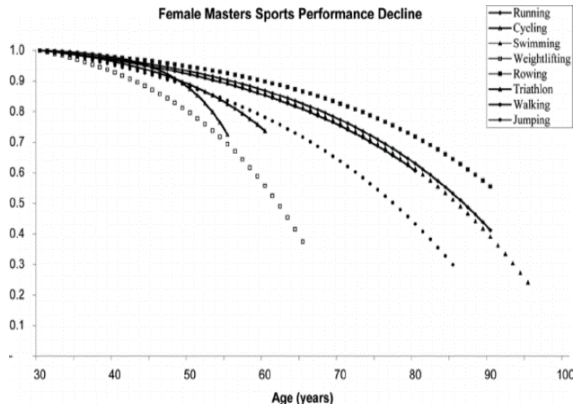

Figure 6.6

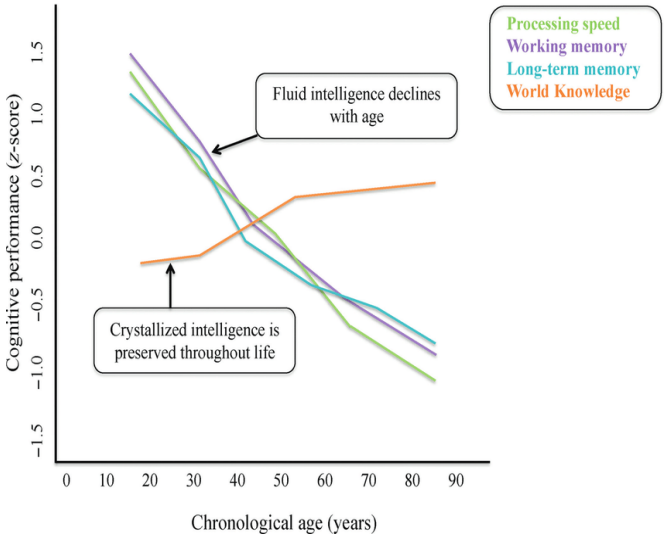

Figure 6.7

The incidence of many diseases, called **age-related diseases**, also rises exponentially with age (as we will discuss in an upcoming lecture). Major age-related diseases include type-2 diabetes, heart failure, Alzheimer's disease, osteoarthritis and most cancers. The incidence of many of these diseases rises with age with a similar slope of 6-8% per year.

Another universal feature of aging is that the *variation between individuals increases with age* in any physiological function measured. Young organisms are typically similarly healthy,

whereas old organisms can be healthy or sick to a wide range of degrees. The health of twenty year olds is like a mass-reproduced poster, whereas 80 year olds are each an individually crafted work of art.

One way to quantify this variability is the **frailty index**, studied by Rockwood et al (Mitnitski, Mogilner, MacKnight, & Rockwood, 2002). The frailty index is simply the fraction of deficits a person has out of a list of deficits, ranging from back pain and hearing loss to diabetes and cancer. The average frailty index increases exponentially with age (Fig 6.8). The standard deviation of frailty also grows exponentially with age, although a bit more slowly than the mean. Thus the relative heterogeneity, the coefficient of variation=std/mean, goes down with age. The distribution of frailty becomes wider and skewed to high values with age (Fig 6.9). One 80-year old can have the health of a typical 65-year-old whereas another has the health of a typical 95-year-old.

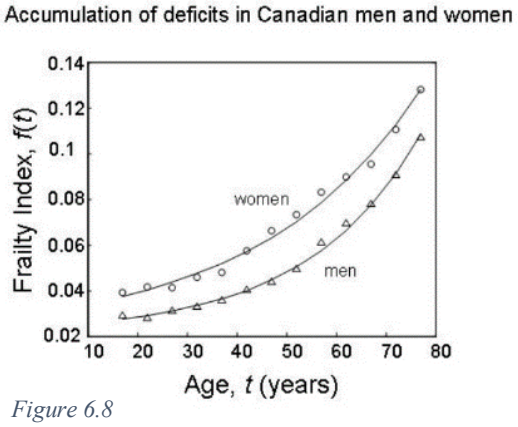

Figure 6.8

In this lecture we set the stage for the next lecture that will explore the organizing principles for such an accumulating and varying decline.

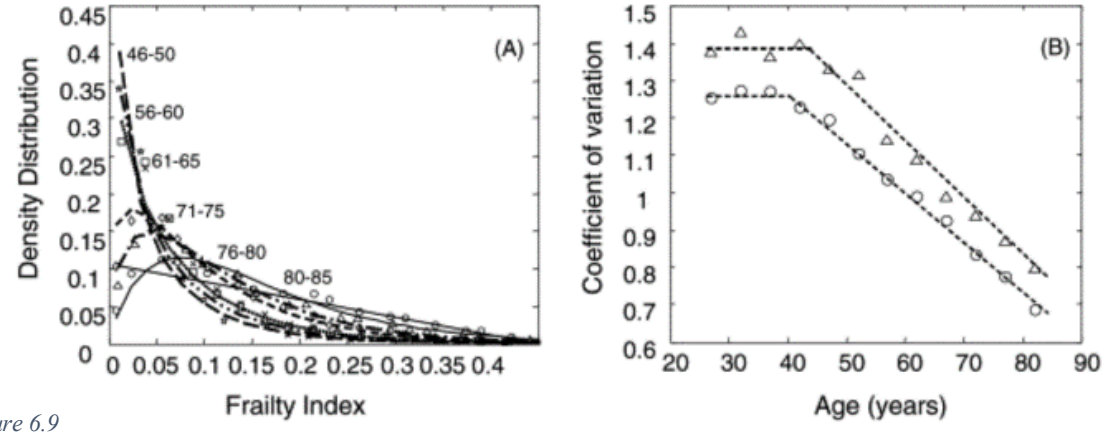

Figure 6.9

Genetically identical organisms die at different times

Genetically identical organisms grown in the same conditions, such as identical twin lab mice, die at different times. Their relative variation in lifespan is about 30%, which is similar to the variation in humans. Similar variation is found in every organism studied, including flies and worms.

In humans as well, which are of course not genetically identical except in the case of identical twins, the heritable component of the variation in lifespan is small. More than 80% of the variation in lifespan is non-heritable. What is more heritable is what people die of, as in genetic risks for

cancer or diabetes. Likewise, the environment affects human mortality. One important factor is low socioeconomic status, which goes with higher risk of disease and death in all regions. A decade of lifespan separates the lowest and highest income deciles in many countries. This disparity is found even when correcting for access to healthcare, and may in part be due to chronic stress accompanying low socio-economic status.

But beyond these genetic and environmental factors, the evidence from identical twin organisms suggests that the risk of death in all organisms *includes a large stochastic (random) component* (see the book “Chance, Development, and Aging").

Lifespan can be extended in model organisms

Work on model organisms shows that lifespan can be extended. Certain mutations extend lifespan in worms up to three-fold, and in mice by up to about 50%. A common factor for many such mutations in different organisms is that they lie in a pathway which controls the tradeoff between growth and maintenance, called the IGF1 pathway. The mutants activate a starvation program that increases repair processes at the expense of growth. The mutant organisms thus grow more slowly and live longer. In humans, a mutation that disrupts the same pathway causes Laron dwarfism, which is associated with increased lifespan and decreased risk of cancer and type-2 diabetes.

Nutrition can also affect longevity, in part by acting through the same IGF1 pathway: continuous caloric restriction that reduces 30-40% of normal calorie intake can extend lifespan in animals ranging from worms to monkeys. There are variations like restricting the time for feeding and restricting various components of diet that also seem to extend lifespan. In animals like flies and worms, lower temperature also increases lifespan.

The survival curves with these lifespan-changing perturbations shows an extended mean lifetime, as seen by their shifted half-way point (Fig 6.10). But when time is rescaled by the average lifespan, the survival curves for some (but not all) perturbations line up with each other, showing that they have the same shape (Fig 6.11). This **scaling** property, discovered in *C. elegans* by Strustourp, Fontana et al (Stroustrup et al., 2016), suggests that the stochastic processes in aging may have a single dominant timescale.

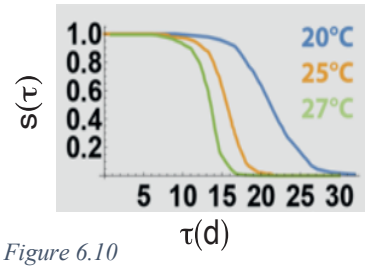

Figure 6.10

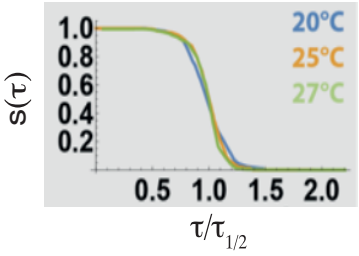

Figure 6.11

What if the intervention for life-span extension is done in mid-life? Interestingly, flies shifted from a normal diet to a lifespan extending diet show rapid shifts to the new Gompertz curve within days. This suggests that there is a rapid timescale to the stochastic process of aging (Fig 6.12). The same rapid shift also occurs the other way, when flies are shifted from life-span extending diet to normal diet. Other perturbations in flies, such as a temperature shift, show a change in Gompertz slope (Fig 6.13), but not a shift to another curve altogether. In the next lecture we will explain such dynamics.

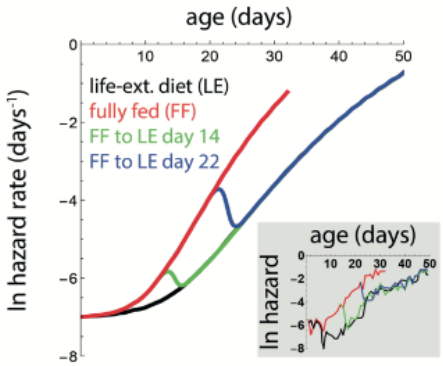

Figure 6.12

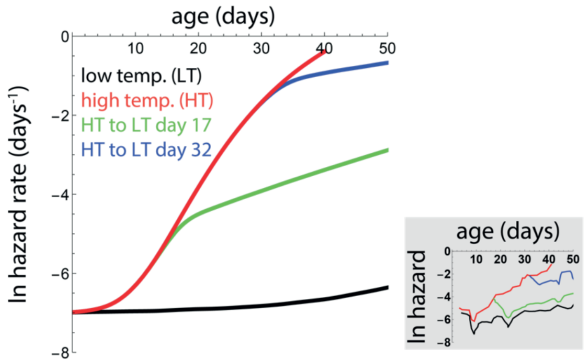

Figure 6.13

Lifespan is tuned in evolution according to different life strategies

Why does aging evolve? Early ideas were that aging is simply the second law of thermodynamics or increasing entropy. Other ideas suggested that ageing is programmed because death offers a selective advantage. Get rid of old professors to allow office space for new faculty. These theories don't generally seem to hold up in simulations.

Evolutionary theories of aging since the 1950s converged on a different idea called the **disposable soma theory**. This today dominates evolutionary thinking on aging. If an animal has high extrinsic mortality, like a mouse that is killed by predators in one year on average, it does not make sense to invest in repair processes that ensure a lifespan of 10 years. Instead, the mouse invests in growth and reproduction, making a lot of babies before extrinsic mortality finishes it off. In contrast, low extrinsic mortality as in elephants and whales selects for investment in repair, allowing a long lifespan.

Indeed, the lifespan of different mammals ranges from 2 year for shrews to 200 years for bowhead whales. A well-known relation connects mass to longevity: plotting longevity versus mass on a log-log plot shows that different mammals fall around a line in which longevity goes as the fourth root of mass, $L \sim M^{\frac{1}{4}}$. A 100-ton whale is 10^8 heavier than a 1g shrew, and thus should live 100 times longer, matching the 200 year versus 2-year lifespans (Fig 6.14).

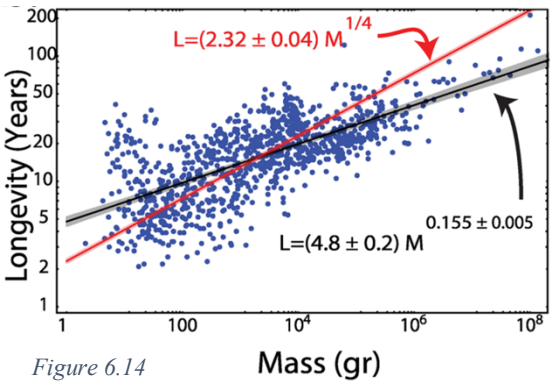

Figure 6.14

However, there are outliers. Bats weigh a few grams like a mouse, but live for 40 years, which is 20 times longer than a mouse; Similarly, naked mole rats weigh 10g and live for decades. For a long time these outliers were swept under the rug. Pablo Szekely, in his PhD with me, plotted longevity versus mass for all mammals and birds for which data was available ((Szekely, Korem, Moran, Mayo, & Alon, 2015)). Instead of a line, the data falls inside a triangle shape distribution, called the mass-longevity triangle (Fig 6.15).

At the vertices of the triangle are shrews, whales and bats. These three vertices represent three life strategies. Shrews and mice have a **live-fast-die-young** strategy, as described above. Whales and elephants, in contrast, have very low predation due to their enormous size. They have a **slow life-**

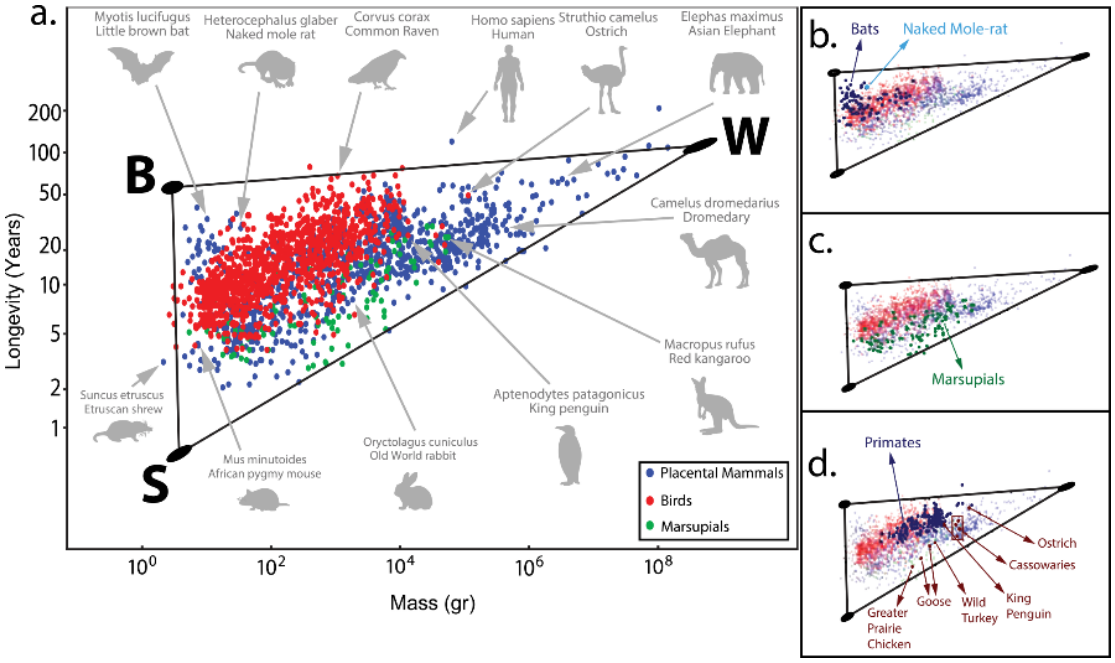

Figure 6.15

strategy of making a few offspring and caring for them for long times. Bats have a protected niche (flying, caves) and thus, despite their small size, they face very low predation. The **protected niche strategy** entails the longest childhood training of young relative to lifespan. Bats carry babies on their back to teach them, for example, where specific fruit trees are found.

In the triangle, near the bats are other animals with protected niches, such as tree-living squirrels, the naked mole rat that lives underground, primates with their cognitive niche, and flying (as opposed to flightless) birds. Flightless birds have shorter lifespan than equally-massed flying birds, and lie close to the bottom edge of the triangle

Why the triangle shape? Why are there no mammals below the triangle, namely large animals with short lives? It takes time to build a large mass, and thus such animals may be unfeasible. An additional answer is provided by the theory of multi-objective optimality in evolution. Tradeoff between three strategies, according to this theory, result in a triangle shape in trait space. The triangle is the set of all points that are closest to the three vertices, which represent archetypal strategies. Any point outside the triangle is farther from the vertices, and thus less optimal (Shoval et al., 2012; Szekely et al., 2015). Phylogenetic relatedness on its own does not explain this triangle shape, because species from very different families often lie close to each other (Adler et al, MBE 2021).

All in all, larger species tend to live longer. But above, we mentioned that within a species, some mutations that reduce growth increase lifespan. Indeed, dependence of longevity on mass *within* a species often goes against the trend seen *between* species. In dogs, for example, small Chihuahuas live 15-20 years whereas Great Danes live for 4-6 years. Some of the mutations that occurred during the breeding of these dog breeds are in the IGF1 pathway.

So far, we discussed the **population statistics** of aging. Such work requires counting organism deaths. What about the molecular causes of aging? Molecular causes of aging are intensely studied. However, the molecular study of aging and the population study of aging are two disciplines that are rarely connected. Our goal, in the next lecture, *will be to bridge between the molecular level and the population level laws of aging*. To do so, we need to first discuss the molecular causes of aging.

Molecular theories of aging focus on various forms of cellular damage

There are several ‘molecular theories of aging’ each focusing on a particular kind of damage to the cell and its components. Each theory arose because disrupting a specific repair mechanism that fixes a certain kind of damage causes accelerated aging. For example, disrupting DNA repair causes accelerated aging in model organisms, and also in humans in rare genetic diseases that cause

premature aging, called **progeria**. Likewise, accelerated aging is caused by disrupting the repair of damaged proteins.

The main types of damage include DNA damage, protein damage and damage to the cells membranes or their energy factories called mitochondria. An important cause of such damage is reactive oxygen species (ROS), leading to the ROS theory of aging. With age there are specific chemical modifications of DNA called epigenetic marks. Such marks can be used to 'measure' a person's chronological age, in what is known as an epigenetic clock. Another theory of aging is based on the fact that with each cell division, the ends of the DNA chromosomes called *telomeres* become shorter. When telomeres become too short, the cell can no longer divide. Thus, telomeres limit the number of cell divisions. Indeed, average telomere length drops approximately linearly with chronological age, and drops faster in some conditions of accelerated ageing.

None of these theories has been connected to the Gompertz law or the other basic facts of aging on the population level. To connect the population and molecular level, we need to explore what kind of damage can accumulate over decades.

Mutations in stem cells can accumulate for decades

To make progress, we now enter the frontier of research. We saw that ageing means that something in our body accumulates over decades leading to dysfunction. Let's ask what fundamental aspects are required for damage to accumulate with age. As we discussed in lectures 1-3, many tissues have cells that turn over within weeks to months. If one of these cells becomes damaged, it will be removed within months. That kind of damage doesn't accumulate over decades. In order to have accumulation over decades, the damage must remain in the body permanently.

Therefore, the damage that we care about should be in cells *that are not removed*. Since all organs age, these cells should be found throughout the body. The best candidate for such cells is **stem cells.** To understand stem cells, consider the skin. The top layer of the skin is made of dead cells that are removed within weeks. To make new skin cells, a deep skin layer called the basal layer of the epidermis houses skin stem cells, S (Fig 6.16). These stem cells can divide to make new stem cells, in a process called **stem cell renewal**. They can also **differentiate** into skin cells, D. These differentiated skin cells can divide a few times, a process called transient amplification. They rise in a column above the stem cells, until they reach the top layer of the skin, and are shed off. The stem cells continuously and slowly divide to replace the lost skin cells. They have enzymes that replenish their telomeres so they have

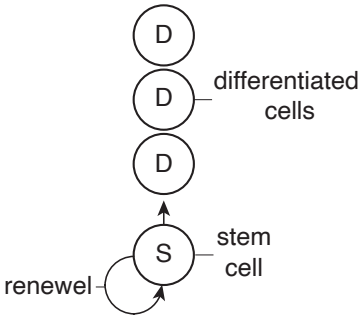

Figure 6.16

no limit to their divisions. Each stem cell division gives rise to many differentiated cells due to transient amplification by the divisions of the progeny cells.

Similarly, stem cells are found in the epithelial lining of the lungs, intestine and many other tissues. Stem cells in the bone marrow divide about once per month to produce the red and white blood cells.

Since stem cells divide through life, they run the risk of gaining mutations in their DNA. All cells mutate. There is on the order of one mutation per cell division, located somewhere in the genome. (because mutation rate is about 10^{-9}/bp/division and the genome has about 10^9 letters or base-pairs, denoted bp). Most of these mutations do nothing. A few are harmful to the stem cell, making it die or grow slower than its neighbor stem cells, and therefore such mutant stem cells are lost.

But some mutations lead to changes in genes that don't bother the stem cells, but affect proteins expressed in its progeny, the differentiated cells, D. These mutations produce malfunctioning proteins that cause cellular damage in the differentiated cells: for example, the malfunctioning protein might mis-fold and gum up the differentiated cell, or produce ROS, which damages the DNA and proteins of the differentiated cell.

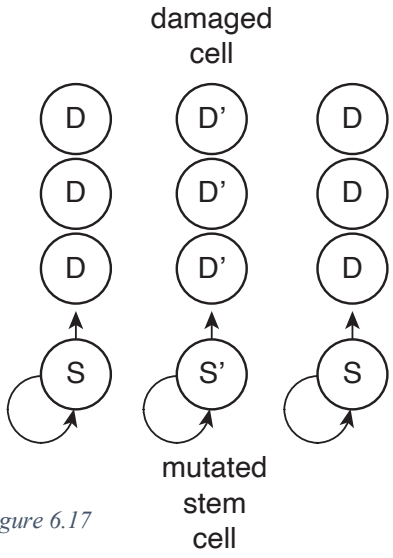

Figure 6.17

Thus, with age, there will be more and more mutant stem cells, S', that produce damaged differentiated cells, D' (Fig 6.17). There will be a column of damaged cells produced by each such mutant stem cell. The number of mutant stems cells S' increases with age. Since the number of divisions per unit time is roughly constant in adult life, the number of mutant stem cells should rise approximately linearly with age, S'~τ.

Indeed, measurements by Stratton and colleagues (Fig. 6.18) found that human stem cells have about 3000 point mutations on average at age 80. The

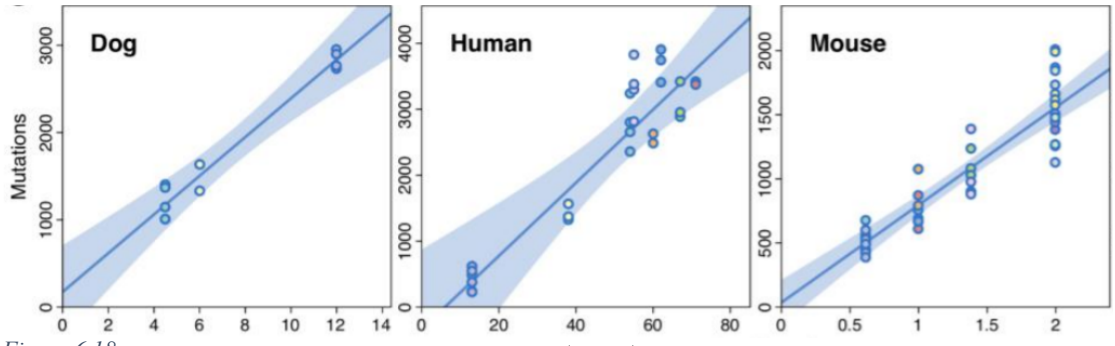

Figure 6.18

average number of mutations per cell rises approximately linearly with age. Interestingly, non-dividing neurons had a similar number of mutations, so mutation happens not only in cell division. The number of mutant cells measures chronoligcal time.

Strikingly, mice also reach about 2000 mutations but by age of 2 years. Dogs reach this by about 12 years. Different mammalian species have therefore an effective rate of mutation accumulation that scales as 1/lifespan (Cagan et al 2021): the shorter the lifespan the faster mutations accumulate.

Senescent cells bridge between molecular damage and tissue-level damage

What happens to the damaged cells, D'? As we saw in the previous lecture on wound healing, damaged cells send signals to call in the immune system, generating inflammation. One response of cells to damage is to commit **programmed cell death (apoptosis)**. The cells quickly and cleanly remove themselves. Damaged cells often take another route: they become zombie-like **senescent cells (SnCs)**. Here we focus on SnCs as a plausible accumulating factor that is causal for aging.

Senescent cells serve an essential purpose in young organisms: they guide the healing of injury. When organisms are injured, cells sense that they have been damaged, for example their DNA is damaged. If they keep dividing, they run the risk of becoming cancer cells. One solution is to commit programmed cell death, and thus to prevent cancer. However, if the injury is widespread and all cells kill themselves, the tissue will have a hole, which can be lethal.

Therefore, many cells at an injury site do something else: they enter a zombie-like state in which they permanently stop dividing, and thus maintain tissue integrity. These zombie cells are called **senescent cells (SnC).** They are large and metabolically active cells, and secrete important signal molecules called senescence-associated secretion profile, or **SASP** (Fig 6.19). The SASP includes signaling molecules that call in the immune system to clear the SnCs in an organized fashion. In other words, these signals cause inflammation. Indeed, certain cells of the innate immune system are charged with detecting and killing SnCs, such as macrophages and NK cells. The NK cells and macrophages also have other important jobs such as killing virus-infected cells and cancer cells.

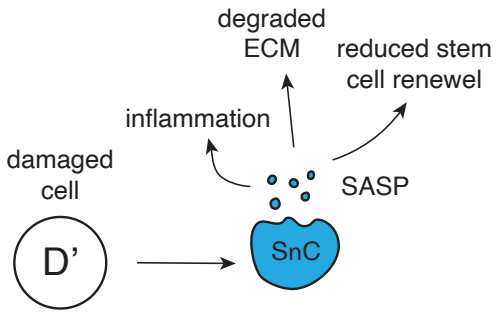

Figure 6.19

SASP also slows down the rate of stem-cell renewal around the SnC, in order to wait for the orderly clearance of the SnC by the immune system. Finally, SASP contains 'molecular scissors' that cut up the hard gel around the cells, called the extra-cellular matrix (ECM), to allow the immune system

to enter. Thus, after an injury, SnCs arise. They cause inflammation to call in the immune cells that remove the SnC in an orderly process over several days to allow healing.

However, SnC also have a dark side. This dark side arises because we are not designed to be old. As we age, mutations accumulate in stem cells. The mutant stem cells S' produce damaged cells D', which 'think' that there is an injury, and turn into SnC. The number of such 'garbage producing units' rises linearly with age as we saw. As a result, the production rate of SnC rises with age, $production \sim \eta\tau$. The amount of SnCs rises throughout the body with age. Then, according to our law 2, their removal processes eventually saturates. The accumulation of SnC then accelerates and is faster than linear with age – it is super-exponential with age. In the next chapter we will understand the cause for this accelerating rise, due to saturation of removal capacity.

Because the aging body becomes loaded with SnCs, their SASP causes chronic inflammation. This is a major symptom of aging, sometimes called **inflammaging**, which damages tissues over time. The SASP also slows stem cell renewal all over the body, and compromises the extracellular matrix. These effects increasingly lead to reduction in organ function. Accumulating levels of SnC have been shown to increase the risk of many age-related diseases including osteoarthritis, diabetes, Alzheimer's disease and heart disease.

Thus, SnCs sit at an interesting junction between the level of damage to cell components and the level of damage to tissues/organism (Fig 6.20). They unite all of the different molecular theories of aging, because virtually any form of cellular damage produces SnC, including ROS, DNA damage, shortened telomeres, epigenetic damage and so on. And they produce systemic effects that cause disease and physiological decline.

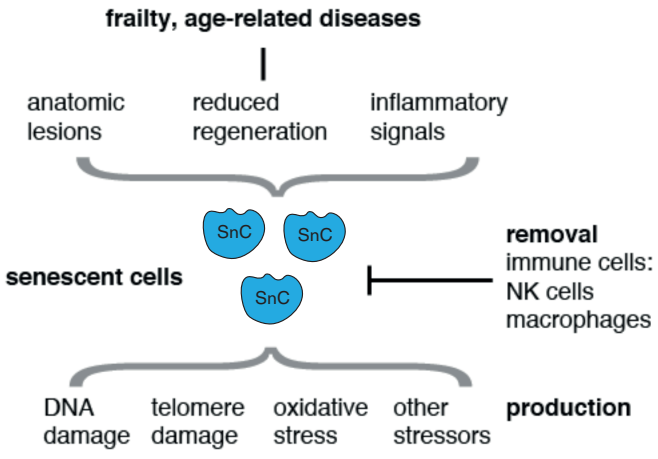

Figure 6.20

Removing SnCs in mice slows age-related diseases and increases average lifespan

In 2016 an experiment by van Duersen et al (Baker et al., 2016) galvanized the aging field. This experiment showed that accumulation of SnCs is causal for aging in mice: continuous targeted elimination of whole-body SnCs increases mean lifespan by 25%. Such removal also attenuates the age-related deterioration of heart, kidney, and fat. The original 2016 experiment has been repeated by many groups using different methods to remove SnCs. These methods include several families

of drugs called **senolytics** that selectively kill SnCs in mice. Some of these drugs are toxic for humans, but improved drugs are under development. Senolytics delay cancer development and cause improvement in age-related diseases including diabetes, osteoarthritis, Alzheimer's and heart disease.

For a sense of the effects of SnC removal, see the picture of twin mice at age 2 years from van Duersen's lab (Fig 6.21). One sibling had SnCs removed since the age of one year. It runs on the wheel, has shiny fur and overall better health. Its sibling, treated with mock injections, barely runs on the wheel and looks like a typical 2-year-old mouse with a hunchback, cataract and fur loss (Fig 6.21).

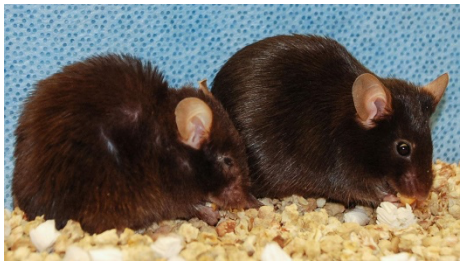

Figure 6.21

SnC are not the only cause of aging, as evidenced by the fact that these mice still age, get sick and die. But in the next lecture we will pretend that they are the only (or dominant) cause. We will also pretend that SnC are a single entity, even though they are heterogenous and tissue-specific. These simplifying assumptions will help us write a stochastic process that can explain many of the empirical obsrevations that we described in this lecture on the population features of aging.

In a nutshell, aging derives from our three laws:

- All cells come from cells (Stem cells produce differentiated cells)
- Cells mutate (Mutant stem cell number increases linearly with age, they produce damaged/senescent cells)
- Biological processes saturate (damged-cell removal processes eventually saturate eventually, and damaged/senescent cell levels rise sharply leading to inflammaging)

Dispolsable some theory fits here because damage removal capacity is selected for the young, not the old, and hence doesnot increase with age.

Excercises:

6.1 Survival and hazard: Survival $S(\tau)$ is the probability of dying after age tau. Hazard $h(\tau)$ is the probabiltiy per unit time to die.

(a) Show that $h(\tau) = -\frac{1}{S(\tau)}\frac{dS}{d\tau}$.

Solution: consider a cohort of No individual born at the same time. The number that survive untill at least age τ is $N(\tau) = N_o\, S(\tau)$. The number $D(\tau)$ that die in a small time interval δt around age τ is the number that survived till τ but not till $\tau + \delta t$: $D(\tau) = N_o S(\tau) - N_o S(\tau + \delta t)$. When δt is small, this equals $D(\tau) = -N_o \frac{dS}{d\tau}\delta t$. The hazard $h(\tau)$ is the probabiltiy per unit time to die for organisms at age τ, and thus

$h(\tau)\delta t = D(\tau)\delta t/N(\tau)$, providing $h(\tau) = -\frac{1}{S(\tau)}\frac{dS}{d\tau}$.

(b) Show that this means that

$$(P6.1)\; S(\tau) = e^{-\int_0^\tau h(\tau)d\tau}$$

6.2 Use equation P6.1 to solve and plot the survival curve in the following cases

(a) Constant hazard $h = h_0$

(b) Linearly rising hazrd: $h(\tau) = \alpha\,\tau$

(c) Gompertz law: $h(\tau) = b\, e^{\alpha\,\tau}$. In humans, empirical magnitude of the alpha-parameter is about 0.085 $year^{-1}$, implying a doubling of mortality every $log(2)/\alpha = 0.69/0.085 = 8$ years.

(d) Trees with hazard that drops with age as $h = a/(1 + b\,\tau)$.

(e) Gompertz-Makeham law, in which age-independent extrinsic mortality is added: $h(\tau) = be^{\alpha\tau} + h_0$. Estimate the parameters for human data based on Fig 6.4, Fig 6.5.

6.3 What is the median halflife in each of the cases of exe 6.2, defined as that age $\tau_{1/2}$ at which $S(\tau_{1/2}) = 0.5$?

6.4 Gompertz law with slowdown: one empirical relation that models the slowdown in hazard at old ages is calld the Gamma-Gompertz law: $h(\tau) = a\frac{exp(\alpha\,\tau)}{1+b\,exp(\alpha\,\tau)}$.

(a) What is the survival curve $S(\tau)$?

(b) What is the median lifespan?

(c) Estimate (roughly) the parameters a, b, and α that describe intrinsic mortaility of human data in Fig 6.4, 6.5. What is the estimated human median lifespan?

6.5 Lifespan distribution: What is the distribution of lifespanse given a hazrad curve $h(\tau)$?

6.6 Maximal lifespan: Consider a poluation of N individuals with a survival curve $S(\tau)$.

(a) Why can the maiximal lifespan be roughyl estimated as tha age τ when $S(\tau) = 1/N$?

(b) What is the estimated maximal lifespan for the case of the Gompertz law? How does it depend on population size?

(c) The worlds population is $N \sim 10^{10}$ people. Use the estimate of hazard from exe 6.4 to predict the maximal lifespan if there were 10^9 people, or 10^{11}, assuming that all pramaters remain the same. Note for reference that the oldest person is thought to be a woman who died at 122.

6.7 Disposable soma theory:

(a) Use evolutionary thinking to explain the phenomenon of menopause, which happens in very few species including humans and elephants.

(b) A gene has 'antagonistic pleiotropy', meaning that it provides reproductive advantage to a young reproductive organism but reduces survival at old age. How would natural selection affect the genes frequency in the population?

(c) Consider the case of senecent cells. What type of biological mechanism such as production or removal of senescent cells serve as a possible place to look for antagonistic pleiotropy?

6.8 Mass Longevity triangle: Consider the following graphs, that show various life-history features of animals, relative to the mean, as a function of their distance on the triangle from the three vertices. For example, panel a shows litter size (number of babys per birth), wit the animals closest t the S,B and W vertex at x=0. Stars indicate statstically signicnt incease or redcution in the animals closest to the vertx. Choose four fetaures and provide a brief explanation of these trends in terms of life strategies.

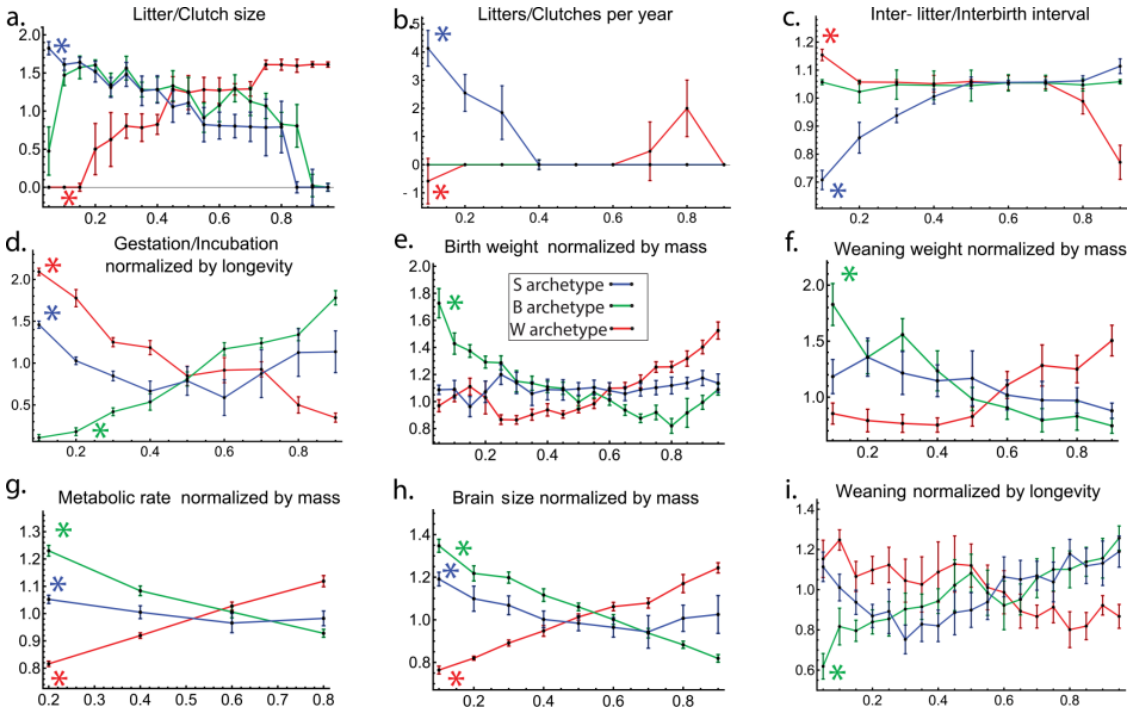

Figure 6.22

6.9 Estimated longevity: In the mass-longevity triangle, longevity is the maximal lifespan observed for each species, based on the Anage database. Discuss possible errors in this estimated maximal lifespan. How would such errors they affect the shape of the distribution of longevity versus mass?

6.10 Strehler-Mildvan correlation as an artifact

Read the following two papers and discuss a correlation in Gomparts Law parameters that may result from a fitting artifact: (Finkelstein, 2012; Tarkhov, Menshikov, & Fedichev, 2017)

6.11 Explain the difference in the impact of mutations in stem cells and in germ cells. Germ cells accumulate ~100 mutations between generations, but undergo strong quality control and negative selection that removes mutants of strong effect. Germs cells have most epigenetic marks removed, unlike somatic cells.

Further Reading

Baker, D. J., Childs, B. G., Durik, M., Wijers, M. E., Sieben, C. J., Zhong, J., … Van Deursen, J. M. (2016). Naturally occurring p16 Ink4a-positive cells shorten healthy lifespan. *Nature*. https://doi.org/10.1038/nature16932

Chance, Development, and Aging: 9780195133615: Medicine & Health Science Books @ Amazon.com. (n.d.). Retrieved June 24, 2020, from https://www.amazon.com/Chance-Development-Aging-Caleb-Finch/dp/0195133617

Finkelstein, M. (2012). Discussing the strehler-mildvan model of mortality. *Demographic Research*. https://doi.org/10.4054/DemRes.2012.26.9

Mitnitski, A. B., Mogilner, A. J., MacKnight, C., & Rockwood, K. (2002). The accumulation of deficits with age and possible invariants of aging. *TheScientificWorldJournal*. https://doi.org/10.1100/tsw.2002.861

Shoval, O., Sheftel, H., Shinar, G., Hart, Y., Ramote, O., Mayo, A., … Alon, U. (2012). Evolutionary trade-offs, pareto optimality, and the geometry of phenotype space. *Science*, *336*(6085). https://doi.org/10.1126/science.1217405

Stroustrup, N., Anthony, W. E., Nash, Z. M., Gowda, V., Gomez, A., López-Moyado, I. F., … Fontana, W. (2016). The temporal scaling of Caenorhabditis elegans ageing. *Nature*. https://doi.org/10.1038/nature16550

Szekely, P., Korem, Y., Moran, U., Mayo, A., & Alon, U. (2015). The Mass-Longevity Triangle: Pareto Optimality and the Geometry of Life-History Trait Space. *PLoS Computational Biology*, *11*(10). https://doi.org/10.1371/journal.pcbi.1004524

Tarkhov, A. E., Menshikov, L. I., & Fedichev, P. O. (2017). Strehler-Mildvan correlation is a degenerate manifold of Gompertz fit. *Journal of Theoretical Biology*. https://doi.org/10.1016/j.jtbi.2017.01.017

Yang, Y., Santos, A. L., Xu, L., Lotton, C., Taddei, F., & Lindner, A. B. (2019). Temporal scaling of aging as an adaptive strategy of Escherichia coli. *Science Advances*. https://doi.org/10.1126/sciadv.aaw2069