

# Chapter 6

## Basic facts of aging

Welcome to part 3! This part is devoted to the fascinating topic of aging. We will use our three laws to develop a theory of aging and test it against a wide range of experiments.

In this chapter I curated many quantitative patterns of aging. Such patterns are the basis for forming and testing theoretical understanding. In the coming chapters, we will use these basic patterns to develop fundamental principles for the causes and rates of aging and the origins of aging-related diseases.

### Aging is defined by risk of death and diseases that rise with age

To understand aging, and to introduce some of the basic concepts, let's begin with hypothetical organisms that do not age. Consider a group of these organisms that are killed by predators at a constant rate,  $h_0$ , regardless of age. The parameter  $h_0$  is called **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 the initial population.

The **survival curve** for this population, defined as the fraction of organisms that remain at time  $t$ , thus decays exponentially

$$S(t) = N(t)/N(0) = e^{-h_0 t}.$$

This decay is just like radioactive decay of particles (Fig 6.1). The probability of death per unit time, called the **hazard**, is independent on age,  $h(\tau) = h_0$  (Fig 6.2). This is what 'no aging' looks like, in terms of survival curves.

Let's now consider 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.

### Aging has nearly universal features

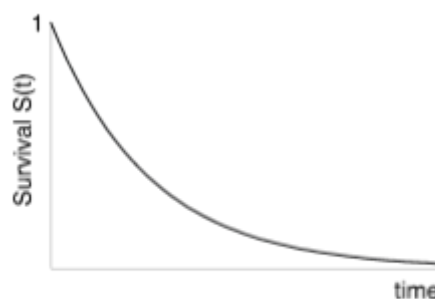


Figure 6.1: The survival curve - the fraction surviving to a given age - for organisms that do not age and have constant extrinsic mortality.



Figure 6.2: The hazard curve - probability of death per unit time - for the non-aging organisms of Fig 6.1 is independent on age.

The hazard curve allows us to see more details. It is defined as the fraction of individuals that die at a given age out of all those that survive to that age. Or mathematically,  $h = -\frac{1}{S} \frac{dS}{dt}$ . The human hazard curve has an interesting shape (Fig 6.4 (Barbieri et al. 2015)).

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 with accompanying diseases and delivery risks. Some infant diseases arise from mutations in the germline which cause rare congenital diseases; over 6000 known genetic disorders together account for a mortality rate on the order of  $10^{-3}$  in the first year.

The hazard curve drops to a minimum during childhood. In the teenage years, hazard rises again, and plateaus in early adulthood. In this plateau, hazard is dominated by extrinsic mortality: accidents, suicides and homicides at a rate of about 3 out of 10,000 per year. Then, starting at age 30, risk of death begins to rise sharply, and doubles about every 8 years. This exponential rise in hazard is called the **Gompertz law**. If we denote age by  $\tau$ , the Gompertz law is

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

where  $\alpha$  is the slope of log incidence called the Gompertz slope and  $b$  is the intercept. This law was discovered by Benjamin Gompertz in 1825, a mathematician who found work computing life-expectancy tables for an insurance company. If we separate mortality into intrinsic and extrinsic components, we can see that the exponential rise in intrinsic hazard begins already around age 15, as in Fig 6.5 (Carnes et al. 2006) showing US mortality statistics for males and females.

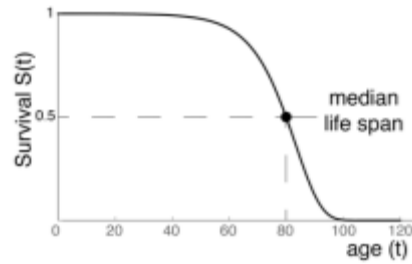


Figure 6.3: The human survival curve shows a death rate that increases with age.

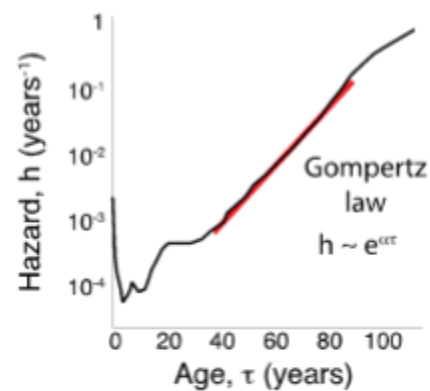
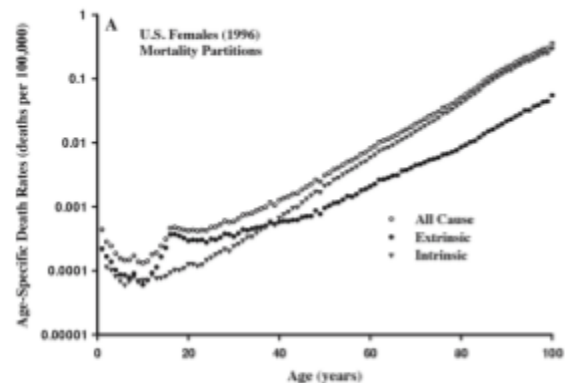


Figure 6.4: Human hazard curve shows an exponentially rising probability of death with age known as the Gompertz law, and a deceleration at very old ages (Adapted from Barbieri, M. et al. 2015).



Different regions and historical periods differ mainly in their extrinsic mortality and childhood mortality. In past centuries, and in some countries today, childhood mortality is about 20% and about 1% of mothers die at childbirth. The Gompertz slope  $\alpha$  is, however, more constant across populations. Thus, hazard curves are often modeled by the Gompertz-Makeham law that adds extrinsic mortality  $h_0$

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

Extrinsic mortality rises with age as seen in Fig 6.5, perhaps because accidents become more lethal. It rises more slowly than intrinsic mortality.

**The Gompertz law is nearly universal.** It is found in most animals studied. This includes 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 and Ariel Linder (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, rises exponentially with an average lifespan of about 100 hours.

There are exceptions to the rule, such as some trees in which hazard drops with age, and organisms that grow indefinitely such as hydra, or cells that divide indefinitely such as bacteria in rich medium.

Another universal feature is that the exponential Gompertz law slows down at very old ages, around age 80 in humans. The hazard curve begins to flatten out. Above age 100 hazard is believed to plateau at about a 50% chance of death per year.

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 or changes in the body to make the hazard curve rise sharply with age.

Indeed, most physiological and cognitive functions decline with age. This includes physical ability and organ function (Fig 6.6), male and female reproductive capacity, as well as vision, hearing and aspects of cognitive ability (Fig 6.7 (Zamroziewicz and Barbey 2018)). It is worth noting that organs have spare capacity: you can remove 90% of the pancreas or kidneys and survive (although you lose resilience to stress). That is why people can donate a kidney and remain healthy. Because organs compensate for damage before they

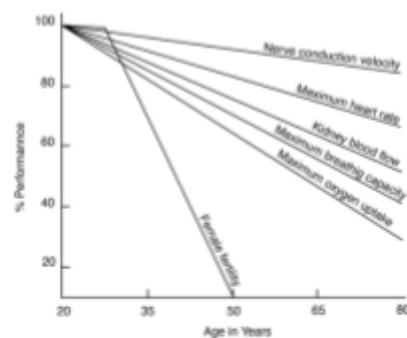


Figure 6.6: Most physiological functions decline with age (Adapted from Ginneken).



begin to lose function, the pathological consequences of the decline are felt only at old age when spare capacity is used up.

Other things improve with age like crystallized knowledge and, hopefully, wisdom. Life satisfaction and well-being also rise above age 60 on average.

The incidence of many diseases, called **age-related diseases**, also rises exponentially with age (as we will discuss in chapter 8). 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 most physiological functions. The young are typically similarly healthy, whereas the old can be healthy or sick to a wide range of degrees. The health of twenty year olds is like a mass-produced 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 et al. 2002). The frailty index is simple to define - the fraction of deficits a person has out of a list of deficits, ranging from back pain and hearing loss to diabetes and cancer. Thus the frailty index can range between zero – no deficits, and one – all deficits on the list.

The average frailty index increases in an accelerating way with age (Fig 6.8). The distribution of frailty becomes wider and skewed to high values with age (Fig 6.9A).

The standard deviation of frailty also grows with age. However, it grows more slowly than the mean. Therefore, the relative heterogeneity, the **coefficient of variation** defined as the standard deviation / mean, goes down with age (Fig 6.9b). We will return to this point in the next chapter- the variation between individuals in frailty rises in absolute terms, but drops in relative



Figure 6.8: Frailty index – the fraction of health deficits an individual has from a list of deficits – accelerates with age. Adapted from (Mitnitski et al. 2002a).

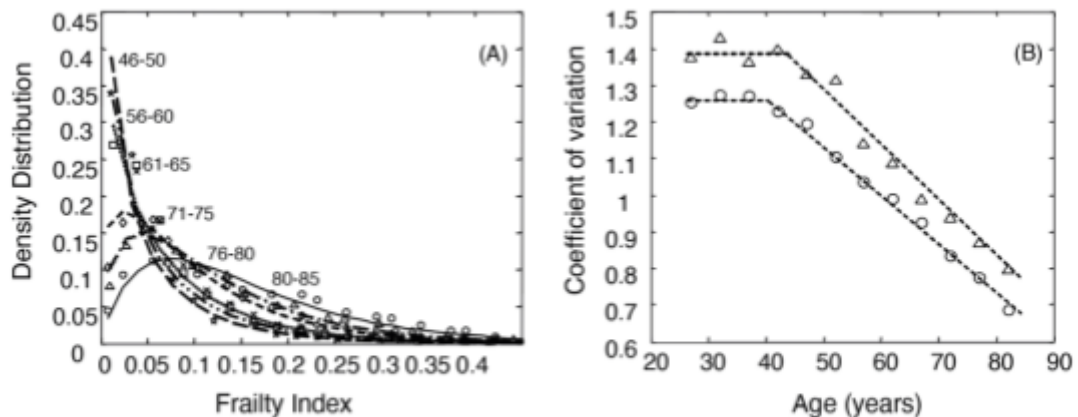


Figure 6.9: Distribution of frailty index is skewed to the right, and shows decreasing coefficient of variation with age. Adapted from (Rockwood, Mogilner, and Mitnitski 2004).

terms. There are differences in what deficits each person has, but in relative terms frailty becomes more similar between individuals with age.

This begins our survey of quantitative patterns of aging and aging-related decline- to set the stage for the next chapter that will explore theory and organizing principles to explain these patterns. This may be a good moment for a nice deep sigh of relief.

### **Genetically identical organisms die at different times**

Is the rate of decline due to the environment or genes? It turns out that the main effect is due to neither. Genetically identical organisms grown in the same conditions, such as identical twin lab mice, die at different times despite having the same genes and environment. Their relative variation in lifespan is about 30%, which is similar to the variation between unrelated mice. Such variation between genetically identical individuals is found in every organism studied, including flies and worms (Finch et al. 2000).

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 heritable is what people die of, as in genetic risks for cancer or diabetes.

The environment affects human mortality, of course. One important factor is low socioeconomic status that goes with higher risk of disease and death. A decade of lifespan separates the lowest and highest income deciles in many countries (Winkleby, Cubbin, and Ahn 2006). This disparity is found even when correcting for access to healthcare. It may in part be due to chronic stress accompanying low socioeconomic status.

Beyond these genetic and environmental factors, the evidence suggests that the risk of death in all organisms is dominated by *a large stochastic (random) component*.

### **Lifespan can be extended in model organisms**

At this point it is important to say that the goal of most (credible) researchers studying aging is not to unlock the secrets of immortality, or even greatly extend human lifespan, but instead to understand the biological process of aging in order to extend the health span and reduce the burden of age-related disease. Lifespan data is, however, informative and exciting, and can help us to understand the fundamental drivers of aging.

Research on model organisms shows that lifespan can be extended. Certain mutations and interventions extend lifespan in worms up to three-fold, and in mice by up to 50%. A common

factor for many such "longevity mutations" across different organisms is that they lie in pathways which control the tradeoff between growth and maintenance.

One such pathway is the IGF1 pathway. Mutants that inhibit this pathway turn on 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. Variations on this theme also extend lifespan, such as restricting the time for feeding and restricting certain components of diet. In animals like flies and worms, lower temperature also increases lifespan.

The survival curves with these lifespan-changing perturbations show an extended mean lifetime, as seen by their shifted half-way point (Fig 6.10). But when time is rescaled by the average

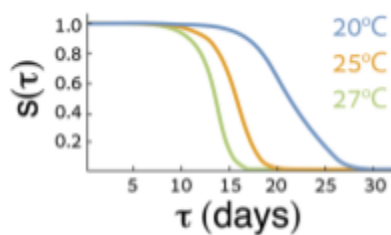


Figure 6.10: Survival curves for *C. elegans* show that median lifespan drops with temperature of growth. Adapted from (Stroustrup et al. 2016).

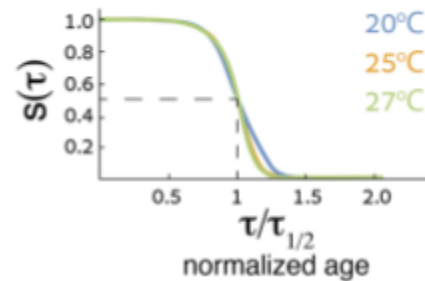


Figure 6.11: Survival curves for *C. elegans* fall on the same curve when age is normalized by the median lifespan. This property is known as survival curve scaling. Adapted from (Stroustrup et al. 2016).

lifespan, the survival curves for most (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 Stroustrup and Fontana (Stroustrup et al. 2016; Liu and Acar 2018) suggests that the stochastic processes of aging may have a single dominant timescale that determines longevity.

What if the intervention for lifespan extension begins 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 (Mair et al. 2003). This suggests that there is a second, more 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 complete shift to another curve altogether. In the next chapter we will explain such dynamics.

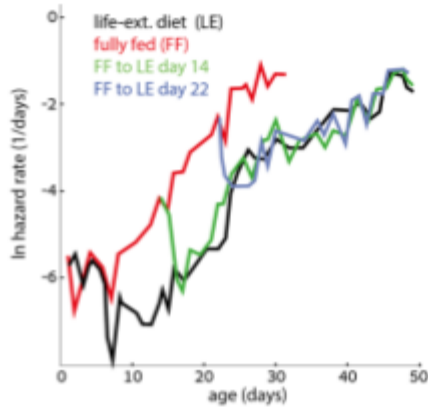


Figure 6.12: Fruit flies show rapid shifts to the better hazard curve upon a shift from normal to life-span extending diet. Adapted from (Mair et al, 2003)

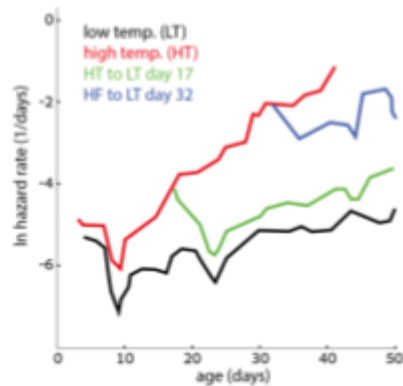


Figure 6.13: Fruit fly hazard curves change slope upon a shift in temperature. Adapted from (Mair et al, 2003)

### Lifespan is tuned in evolution according to different life strategies

In contrast to the modest extension of lifespan in laboratory experiments, natural selection can tune lifespan by a factor of 100 between mammals, ranging from 2 years for shrews to 200 years for whales.

Aging rates thus evolve. Why does aging evolve? Early ideas were that aging is programmed because death offers a selective advantage at the population level. Get rid of old professors to allow space for new faculty. However, these theories don't generally seem to hold up in simulations.

Evolutionary theories of aging since the 1950s converged on an idea called the **disposable soma theory**. This today dominates evolutionary thinking on aging. The theory notes that organisms wield a finite level of biological resources. They face a tradeoff between repairing their bodies (soma) and reproducing. When they are subject to high predation, it's better for them to invest those resources in rapid growth and reproduction.

Thus, if an animal has high extrinsic mortality, like a mouse that is killed by predators within 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 longer lifespan.

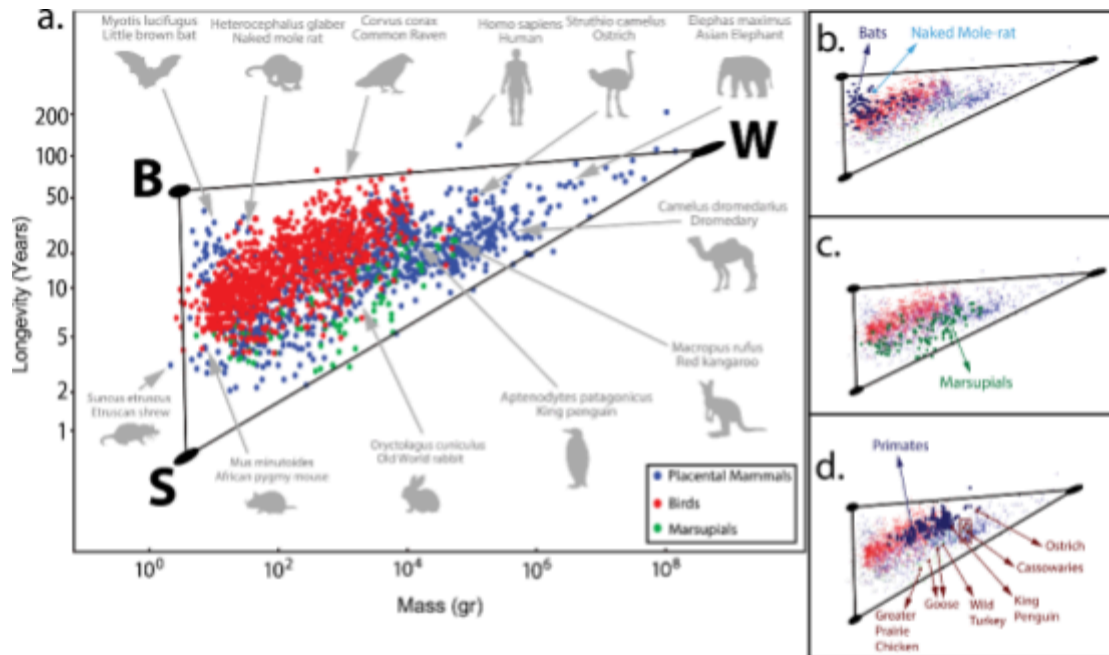


Figure 6.14: The mass-longevity triangle. Each dot is a mammalian or bird species. The vertices correspond to archetypal life-strategies denoted shrew (S), whale (W) and bat (B). Adapted from (Szekely et al. 2015).

Indeed, large animals face less predation than small animals and live longer. A well-known relation connects mass to longevity: on average, longevity follows 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 their 200 year versus 2-year lifespans.

However, there are exceptions. Bats weigh a few grams, like mice, but live for 40 years, which is 20 times longer than mice; similarly, naked mole rats weigh 10g and live for decades. Pablo Szekely, in his PhD with me, plotted longevity versus mass for all mammals and birds for which data was available (Szekely et al. 2015). Instead of a line, the data falls inside a triangle-shaped distribution, called the mass-longevity triangle (Fig 6.14).

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 strategy** of producing a single offspring at a time and caring for it for a long time. Bats have a protected niche (flying) and thus, despite their small size, they face low predation. The **protected niche strategy** entails the longest childhood training 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 flying birds of the same mass, and lie closer to the bottom edge of the triangle

Why the triangular 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, results in a triangle shape in trait space (Shoval et al. 2012). The triangle is the set of all points that are closest to the three vertices, which represent archetypal strategies. The closer a point is to a vertex, the better it performs the vertex strategy. For any point outside the triangle there is a point inside that is closer to all three vertices, and is thus more 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 on the triangle (Adler et al. 2022).

All in all, bigger species tend to live longer. But above we mentioned that within a species, there is an opposite trend - bigger individuals are shorter lived than smaller ones, such as the IGF1 mutants described above. Longevity and mass *within* a species often go against the trend seen *between* species. In dogs, for example, tiny Chihuahuas live 15-20 years whereas Great Danes live for 4-6 years. Some of the mutations that occurred during the breeding of these dogs are in the IGF1 pathway. Evidently, natural selection tunes longevity in different species by other means than adjusting their IGF1 pathway. Current evidence points rather to increased repair capacity in long-lived species.

So far, we discussed the **population statistics** of aging. Such work requires counting deaths. What about the molecular mechanisms 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 chapter, *will be to bridge 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 cellular damage**

There are several molecular theories of aging, each focusing on a particular kind of damage to the cell and its components. The main types of cellular damage include DNA damage, protein damage and damage to the cells' membranes or their energy factories called mitochondria (Miwa et al., n.d.). An important cause of such damage is reactive oxygen species (ROS), leading to the ROS theory of aging. Each molecular theory arose because disrupting a repair mechanism that fixes a specific kind of damage causes accelerated aging. For example, disrupting certain types of DNA repair causes accelerated aging both in model organisms and in humans in rare genetic

diseases that cause premature aging, such as Werner's syndrome. Likewise, disrupting repair processes that dispose of unfolded proteins or damaged mitochondria, called autophagy and mitophagy, cause premature aging.

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 with chronological age, and drops faster in some conditions of accelerated aging.

These theories have been collected into hallmarks of aging (Fig 6.15 , (López-Otín et al. 2023)). Each hallmark ideally satisfies three criteria: it rises with age, enhancing it speeds aging, and attenuating it slows aging in model organisms. Since the hallmarks interact with each other in complex ways, there is a need for simplifying concepts to make sense of aging. None of these hallmarks have been connected to the Gompertz law or the other quantitative patterns of aging discussed above. Making this connection is the goal of the next chapter. To prepare, we first need to explore what kind of damage can accumulate over decades.



Figure 6.15 Hallmarks of aging- factors that rise with age, whose enhancement speeds aging and whose attenuation slows it down. Adapted from López-Otín et al

### DNA alterations in stem cells can accumulate for decades

To make progress, we now enter the frontier of research. We saw that aging means that something in our body changes over decades leading to dysfunction. Let's ask what fundamental aspects are required for damage to accumulate with age. As we discussed in chapters 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 accumulate over decades, the source of damage must remain in the body permanently. Therefore, the source of 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.

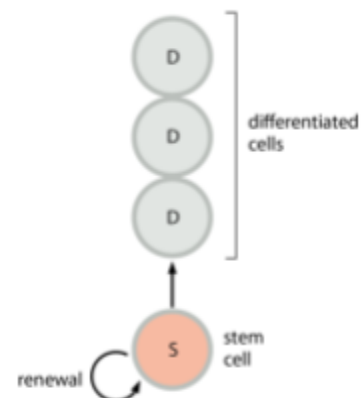


Figure 6.16: Stem cells S divide and differentiate into differentiated cells D. Stem cells often remain in the body for a lifetime, whereas differentiated cells in most tissues are removed in days to years.

A good candidate for such cells is **stem cells**. To understand stem cells, let's consider the skin as an example. 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).

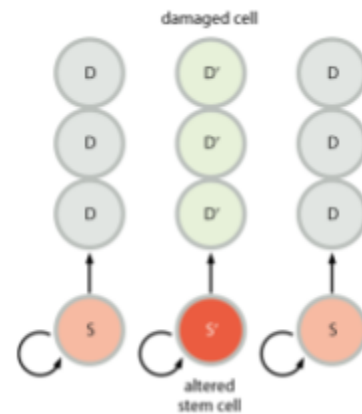
These stem cells divide to make new stem cells, in a process called **stem cell renewal**. They also **differentiate** into skin cells, D. These differentiated skin cells divide only a few times, a process called transit amplification. Each stem cell division gives rise to many differentiated cells due to transit amplification. The cells 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 no limit to their divisions.

Many tissues have their own dedicated stem cells. Stem cells are found for example in the epithelial lining of the intestine and skin. Stem cells in the bone marrow differentiate about once per month to produce the red and white blood cells.

Since stem cells stay in the body throughout life, and all cells mutate, they run the risk of gaining mutations and other changes in their DNA. Stem cells gain on the order of 50 mutations per year in humans due to passive chemical damage to their DNA. They gain a further few mutations with each division. 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 harm the stem cells, but affect proteins expressed in its progeny, the differentiated cells, D. These mutations encode for production of 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.

Thus, with age, there will be more and more mutant stem cells, denoted S', that produce damaged differentiated cells, D' (Fig 6.17). Since the mutations don't affect these stem cells, they are 'invisible' and the immune system can not remove them. Above each such mutant stem cell will be a column of damaged cells. The number of these 'damaged-cell factories' increases with age.



*Figure 6.17: Stem cells with certain epigenetic alterations or mutations can generate damaged differentiated cells, with no harm to the altered stem cell itself. Such altered stem cells remain indefinitely in the body and acts as damage producing units.*

Indeed, measurements by Stratton and colleagues (Fig. 6.18 (Cagan et al. 2022)) found that the number of mutations on average in each human stem cell rises linearly with age, reaching about 3000 point mutations by age 60. Therefore, the number of mutant stem cells  $S'$  that happen to

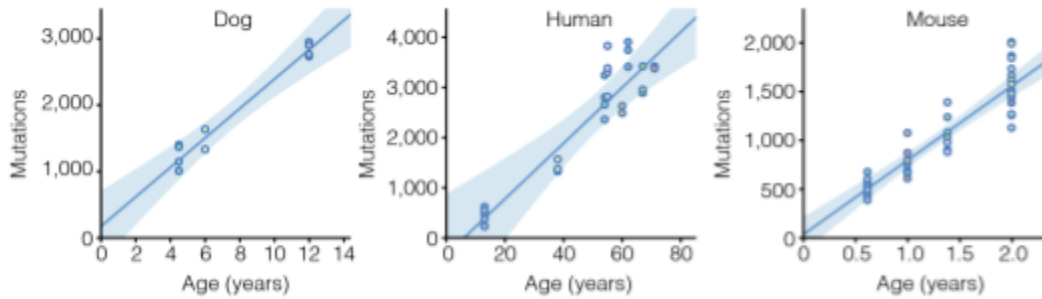


Figure 6.18: The number of mutations per crypt stem cell rises linearly with age in different species and reaches several thousand at old age. Adapted from (Cagan et al. 2022).

have a dangerous mutation for the differentiated cells, should also rise linearly with age,  $S' \sim \tau$ . In other words, the number of mutant cells tracks chronological time.

Interestingly, non-dividing neurons have a similar number of mutations, and may represent another repository of damage that stays in the body for a lifetime.

Strikingly, mice reach a similar number of mutations by the age of 2 years. Dogs reach this by about 12 years. Different mammalian species have an effective rate of mutation accumulation that scales as  $1/\text{lifespan}$  (Cagan et al. 2022) - the shorter the lifespan the faster mutations accumulate. Mutations alone, however, do not seem to account for aging. Humans and mice with enlarged mutation rates, such as those with defects in DNA polymerase or mismatch repair, often do not show premature aging (Robinson et al. 2021).

A more relevant DNA alteration that measures chronological age is epigenetic changes to the DNA. For example, some sites in the DNA become methylated or unmethylated, in a process that is stochastic and has a low rate. These methylations can alter gene expression. Other epigenetic changes include histone acetylation. They open up normally silenced regions such as telomeres, and cause aberrant transcription and even DNA damage due to structures in which RNA binds DNA improperly called r-loops. Many such epigenetic changes rise linearly with age during adulthood, giving rise to ‘aging clocks’ (Xia et al. 2021; Horvath and Raj 2018). Finally, the human genome contains numerous virus genomes called retrotransposons which can jump into new genomic regions and disrupt genes. The number of such jumps also rises with age (Andrenacci, Cavaliere, and Lattanzi 2020), and is another source of mutated stem cells.

We can treat stem cell mutations and epigenetic changes similarly for our purposes. We will call cells that produce damaged progeny without cost to themselves **altered stem cells**. The

main point is that the number of such altered stem cells rises approximately linearly with age during adulthood.

### **Damaged and senescent cells bridge between molecular damage and tissue-level damage**

What happens to the damaged cells, D'? As we saw in chapter 5 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, a process in which cells quickly and cleanly remove themselves. Damaged cells, however, often take another route: they become zombie-like **senescent cells (SnC)** (Fig 6.18).

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. If they keep dividing, they run the risk of becoming cancer cells. However, if all injured cells kill themselves, the tissue will have a hole. Therefore, turning into a senescent cell maintains tissue integrity without the risk of cancer.

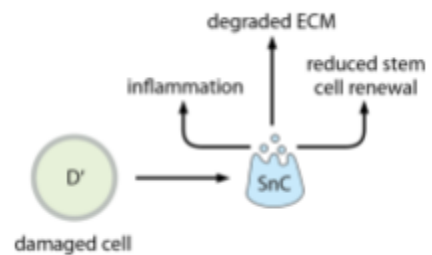
Here we focus on senescent cells as a plausible accumulating factor that drives aging.

Senescent cells are large and metabolically active cells which secrete signal molecules, collectively called the **senescence-associated secretory phenotype, or SASP** (Fig 6.19). The SASP includes signaling molecules that recruit the immune system to clear the senescent cells in an organized fashion. In other words, these signals cause inflammation. Certain cells of the immune system are tasked with detecting and removing senescent cells, such as macrophages and NK cells. The NK cells and macrophages also have other important jobs such as removing virus-infected cells and cancer cells.

SASP also slows down the rate of stem-cell renewal around the senescent cells, to wait for the orderly clearance of the senescent cells by the immune system. Finally, SASP contains 'molecular scissors' that alter the extracellular matrix (ECM) around the cells, to allow the immune system to enter.

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

However, senescent cells have a dark side. This dark side arises because we are not designed to be old. As we age, mutations and epigenetic changes accumulate in stem cells. The



*Figure 6.19: Damaged cells that are unable to repair themselves become senescent cells. Senescent cells secrete proteins called SASP that cause inflammation, degrade the extracellular matrix and reduce stem cell renewal.*

altered stem cells S' produce damaged cells D', which 'think' that there is an injury. Some of these damaged cells turn into senescent cells. The number of such altered stem cells, or 'damage producing units', rises linearly with age as we saw. As a result, the production rate of senescent cells rises with age,  $production \sim \eta\tau$  throughout the body. Eventually, according to our law 2, their removal processes saturate. When production exceeds removal, all bets are off and senescent cell abundance skyrockets. In the next chapter we will understand the ramifications of saturation of removal capacity.

Because the aging body becomes loaded with damaged and senescent cells, it is permeated with SASP. Even if, say, only 0.1% of the cells are damaged, their secreted inflammatory signals can affect the entire body, causing chronic inflammation. This is a hallmark of aging, sometimes called **inflammaging**. Inflammaging drives age-related diseases including osteoarthritis, diabetes, Alzheimer's disease and heart disease. The SASP also slows stem cell renewal all over the body and alters the extracellular matrix. These effects increasingly lead to reduction in organ function.

Thus, senescent cells sit at an interesting junction between the level of damage to cell components and the level of damage to organ systems (Fig 6.20). They unite the different molecular theories of aging, because virtually any form of cellular damage results in the cell turning senescent, including ROS, DNA damage, shortened telomeres, epigenetic damage and so on. And senescent cells in turn produce systemic effects that cause disease and physiological decline.

### Removing senescent cells 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. It showed that accumulation of senescent cells is causal for aging in mice: continuous targeted elimination of senescent cells increased mean lifespan by 25%. Such removal also attenuated the age-related deterioration of heart, kidney, and fat. The original 2016 results have been reproduced by many research groups using different methods to remove senescent cells. These methods include drugs called **senolytics** that selectively kill senescent cells in mice.

There are several classes of senolytic drugs. Senolytics delay cancer development and ameliorate

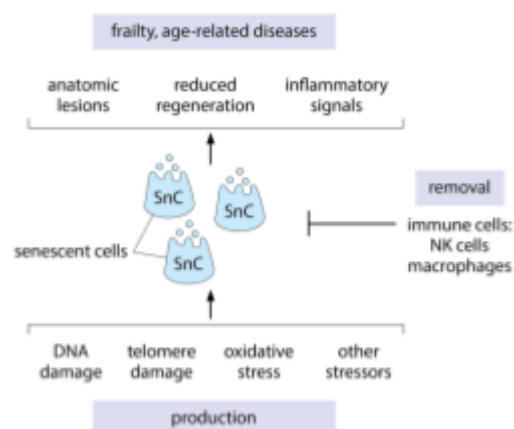
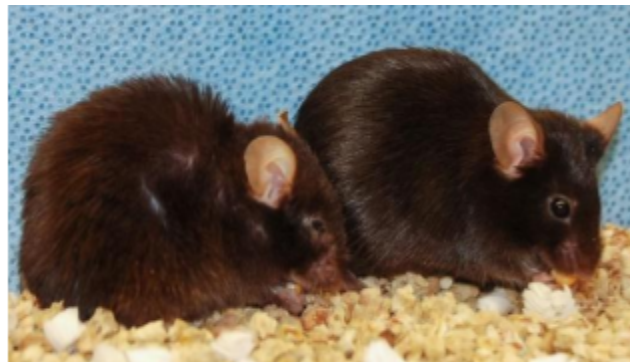


Figure 6.20: Almost all types of cellular damage can lead to senescent cells, which produce SASP proteins that lead to systemic effects that cause age-related diseases. Senescent cells are removed by immune cells including NK cells and macrophages.

age-related diseases including diabetes, osteoarthritis, Alzheimer's and heart disease in mice models.

For a sense of the effects of senescent cell removal, see the picture of twin mice at age 2 years (Fig 6.20), roughly equivalent to age 70 in humans. One sibling had senescent cells removed continually starting at the age of one year. It ran on the wheel, had shiny fur and overall better health. Its sibling, treated with mock injections, barely ran on the wheel and looked like a typical aged mouse with a hunched back, cataract and fur loss (Fig 6.21).

Accumulation of senescent cells is not the only cause of aging, as evidenced by the fact that these mice still age, get sick and die. But in the next chapter we will assume that they are the dominant cause. We will also make the simplifying assumption that senescent cells are a single entity, even though they are heterogeneous and tissue-specific. These simplifying assumptions will help us write a stochastic process that can explain many of the empirical observations that we described in this chapter on the features of aging.



*Figure 6.21: Rejuvenation of an old mouse genetically engineered to remove its senescent cells compared to its littermate in which senescent cells were not removed. Adapted from (Baker et al. 2016).*

### Exercises:

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

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

**Solution:** consider a cohort of  $N_o$  individual born at the same time. The number that survive until at least age  $\tau$  is  $N(\tau) = N_o S(\tau)$ . The number  $D(\tau)$  that die in a small time interval  $\delta t$  around age  $\tau$  is the number that survived till  $\tau$  but not till  $\tau + \delta t$ :  $D(\tau) = N_o S(\tau) - N_o S(\tau + \delta t)$ . When  $\delta t$  is small, this equals  $D(\tau) = -N_o \frac{dS}{d\tau} \delta t$ . The minus sign is due to the fact that survival  $S$  decreases, and thus has a negative slope. The hazard  $h(\tau)$  is the probability per unit time to die for organisms at age  $\tau$ , and thus

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

(b) Show that this means that

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

**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 hazard:  $h(\tau) = \alpha \tau$

(c) Gompertz law:  $h(\tau) = b e^{\alpha \tau}$ . In humans,  $\alpha$  is about  $0.085 \text{ year}^{-1}$ , 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:  $h(\tau) = b e^{\alpha \tau} + h_0$ . Estimate the parameters for human data based on Fig 6.4, Fig 6.5.

**6.3** What is the median half-life in each of the cases of exercise 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 called 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  $\alpha$  that describe intrinsic mortality 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 lifespans given a hazard curve  $h(\tau)$ ?

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

(a) Why can the maximal lifespan be roughly estimated as the age  $\tau$  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 world's population is about  $N \sim 10^{10}$  people. Use the estimate of hazard from exercise 6.4 to predict the maximal lifespan if there were  $10^9$  people, or  $10^{11}$ , if all parameters remain the same. Note for reference that the longest human lifespan is thought to be of 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 gene's frequency in the population?

(c) Consider the case of senescent 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 babies per birth), with the animals closest to the shrew (S), bat (B) or whale (W) vertex at  $x=0$ . Stars indicate statistically significant increase or decrease in the animals closest to the vertex. Choose four features and provide a brief explanation of these trends in terms of life strategies.

**6.9 Estimated longevity:** In the mass-longevity triangle, longevity is the maximal lifespan observed for each species, based on the AnAge database (Tacutu et al. 2018). Discuss possible

sources of error in this estimated maximal lifespan. How would such errors 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 Gompertz Law parameters that may result from a fitting artifact: (Finkelstein 2012; Tarkhov, Menshikov, and 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. Germ cells have most epigenetic marks removed, unlike somatic cells. What is the impact of these features on aging?

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