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 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 RISES 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 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 alive at time t, thus decays exponentially

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

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

DOI: 10.1201/9781003356929-12

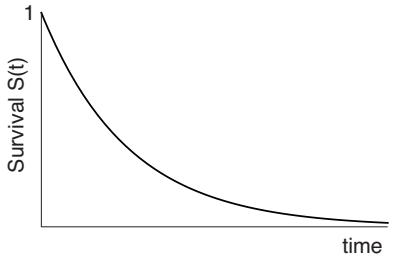

FIGURE 6.1 The survival curve – the fraction surviving to a given age – for organisms that do not age and have constant extrinsic mortality.

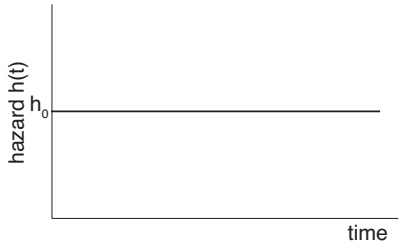

FIGURE 6.2 The hazard curve – probability of death per unit time – for the organisms of Figure 6.1 is independent on age.

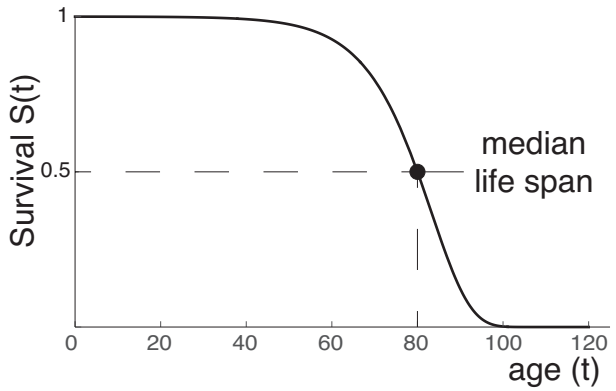

FIGURE 6.3 The human survival curve shows a death rate that increases with age.

Let's now consider the human survival curve (Figure 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. Risk of death is age dependent.

AGING HAS NEARLY UNIVERSAL FEATURES

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 (Figure 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 with accompanying diseases and delivery risks. Some infant diseases arise from mutations in the germline which cause rare congenital disorders; 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 τ, the Gompertz law is

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

where α 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 Figure 6.5 (Carnes et al. 2006) that shows US mortality statistics for males and females.

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 α is,

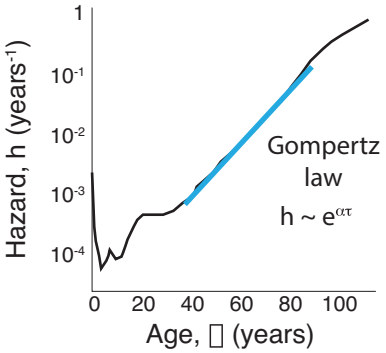

FIGURE 6.4 Human hazard curve shows an exponentially rising probability of death with age known as the Gompertz law, with deceleration at very old ages. Adapted from Barbieri et al. (2015).

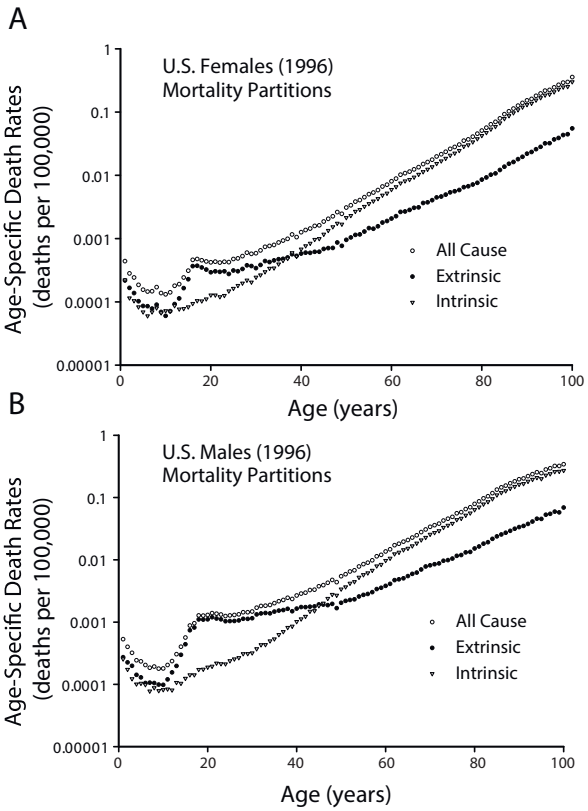

FIGURE 6.5 Hazard curves show that intrinsic mortality rises exponentially from teenage and on, and exceeds extrinsic mortality in adulthood and old age Adapted from Carnes et al. (2006).

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 Figure 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* roundworms that live about 2 weeks. In 2019, Yifan 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. Some organisms have very low intrinsic mortality, such as hydra that grows indefinitely, or cells that divide symmetrically such as bacteria in rich medium.

Another nearly 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. Age 20 and 70 is 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 (Figure 6.6), male and female reproductive capacity, as well as vision, hearing and aspects of cognitive ability (Figure 6.7). 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 begin to lose function, the pathological consequences of the decline are felt primarily at old age when spare capacity is used up.

Not everything declines; some 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 20-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** (Mitnitski 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. The frailty index can range between zero – no deficits, and one – all deficits on the list.

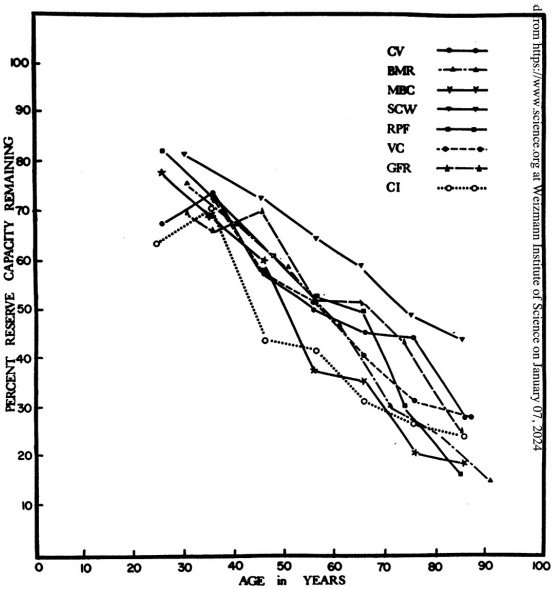

Figure 6.6 Percent of reserve capacity of a number of physiological functions, from cross-sectional data. Reserve capacities are normalized between maximum and basal level. Longitudinal data shows a linear decline and then curves down to an abrupt drop close to death. CV, nerve conduction velocity; BMR, basal metabolic rate; MBC, maximal breathing capacity; SCW, standard cell water; RPF, standard renal plasma flow (Diodrast); VC, vital capacity; GFR, standard glomerular filtration rate (inulin); CI, cargree- diac index.
Reproduced from Strehler & Mildvan (1960).

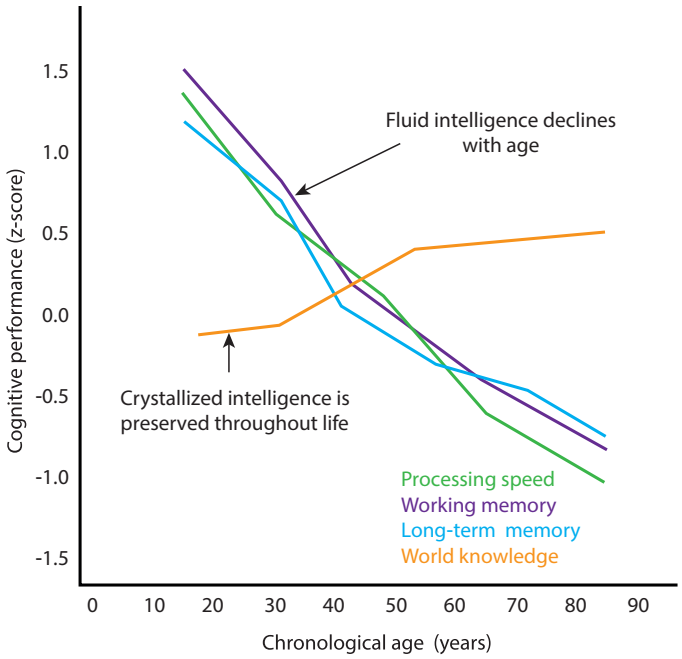

FIGURE 6.7 Most cognitive functions decline with age. Adapted from Zamroziewicz and Barbey (2018).

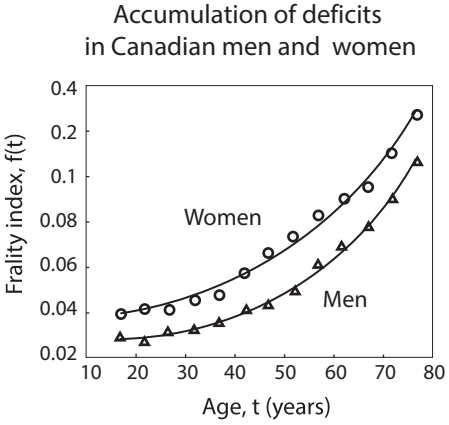

FIGURE 6.8 Frailty index – the fraction of health deficits an individual has from a list of deficits – accelerates with age. Adapted from Mitnitski et al. (2002).

The frailty index can help us understand in quantitative terms how health declines. The average frailty index increases in an accelerating way with age (Figure 6.8). The distribution of frailty becomes wider and skewed to high values with age (Figure 6.9A).

The standard deviation of frailty also grows with age. However, it grows more slowly than the mean. Therefore, the relative heterogeneity of frailty, the **coefficient of variation**

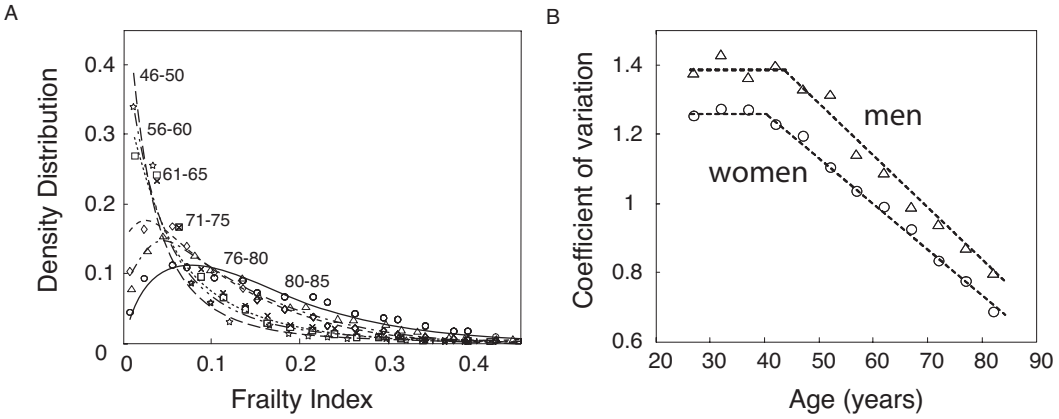

FIGURE 6.9 Distribution of frailty index is skewed to the right and shows decreasing coefficient of variation with age. Each curve is for a different age group. (A-B) described in text. Adapted from Rockwood, Mogilner, and Mitnitski (2004).

defined as the standard deviation/mean, goes down with age (Figure 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 terms. There are differences in which 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 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 roundworms 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 organisms ranging from yeast 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 roundworms, lower temperature also increases lifespan.

The survival curves with these lifespan-changing perturbations show an extended mean lifetime, as seen by their shifted halfway point (Figure 6.10). But when time is rescaled by the average lifespan, the survival curves for most (but not all) perturbations line up with each other, showing that they have the same shape (Figure 6.11). This **scaling** property, discovered in *C. elegans* by Stroustrup et al. (2016) (see also 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 better Gompertz curve within days (Mair et al. 2003). This suggests that there is a second, more rapid timescale to the stochastic process of aging (Figure 6.12). The same rapid shift also occurs the other way, when flies are shifted from life-span extending diet to normal diet.

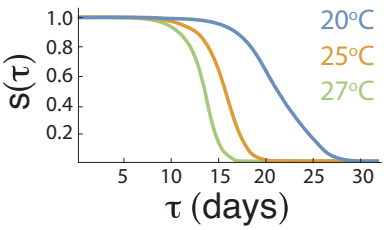

FIGURE 6.10 Survival curves for *C. elegans* show that median lifespan drops with temperature of growth. Adapted from Stroustrup et al. (2016).

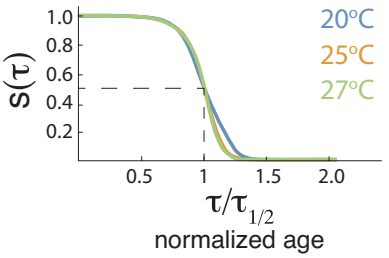

FIGURE 6.11 Survival curves for *C. elegans* fall on the same curve when age is normalized by the median lifespan. This property is known as survival curve scaling. Adapted from Stroustrup et al. (2016).

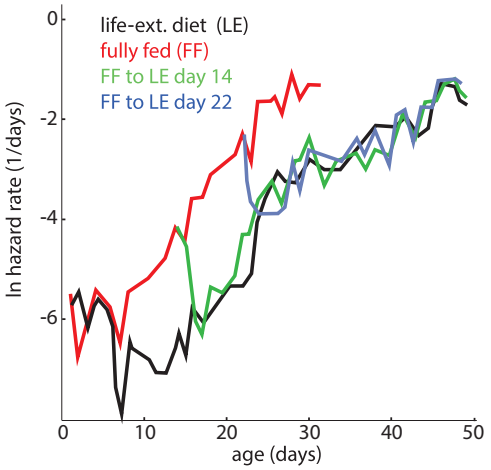

FIGURE 6.12 Fruit flies show rapid shifts to the better hazard curve upon a shift from normal to life-span extending diet. Adapted from Mair et al. (2003).

Other perturbations in flies, such as a temperature shift, show a change in Gompertz slope (Figure 6.13), but not a complete shift to a new curve altogether. In the next chapter, we will explain such dynamics.

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 have converged on an idea called the **disposable soma theory** (Kirkwood 1977). This today dominates evolutionary thinking on aging. The theory notes that organisms wield a finite level of biological resources. They face a tradeoff

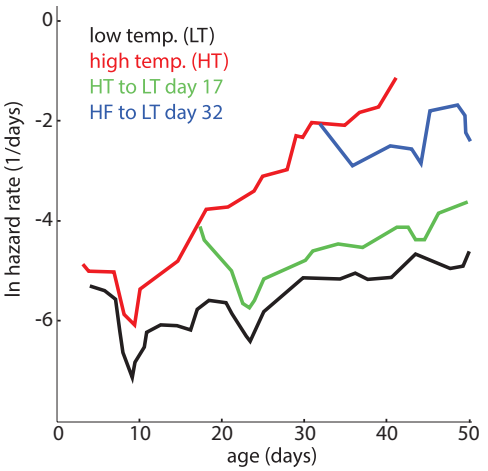

FIGURE 6.13 Fruit fly hazard curves change slope upon a shift in temperature. Adapted from Mair et al. (2003).

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 1 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.

Indeed, large animals generally 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 1 g 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 10 g 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 wedge-shaped distribution that we called the mass-longevity triangle (Figure 6.14).

At the vertices of the triangle are shrews, whales, and bats. These three vertices represent three archetypal 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 and the largest brain relative to body mass. Bats carry a baby on their back to teach it, 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.

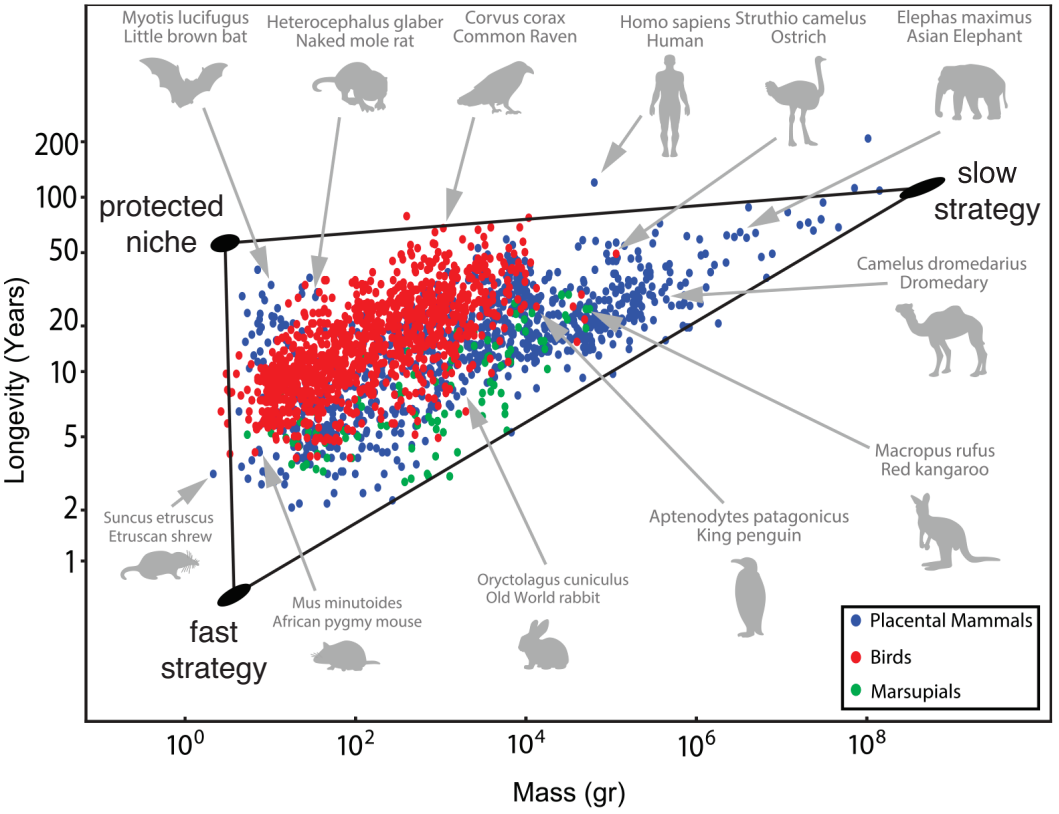

FIGURE 6.14 The mass-longevity triangle. Each dot is a mammalian or bird species. The vertices correspond to archetypal life-strategies denoted shrew (S), whale (W), and bat (B). Adapted from Szekely et al. (2015).

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 instead 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.