Systems medicine Lecture notes
Uri Alon (Spring 2019)

Lecture 5
Basic facts of aging

[Omer Karin, Itay Katzir, Avi Mayo, Yifan Yang, Amit Agrawal,

Valery Krizhanovsky, Uri Alon, 2019]

Introduction:

Welcome to part 2 of the course, devote to aging. We will explore fundamental principles that govern the rate of aging, and understand what timers set the pace of aging-related diseases.

To understand aging, let's begin with a system that has no aging. Consider a group of hypothetical organisms that do not reproduce and do not grow old. They are killed by predators at a constant rate, h_0. The parameter h_0 is called the **extrinsic mortality**. If we start with N(0) organisms, with time we will have fewer and fewer organisms left, $\frac{dN}{dt} = -h_0 N$. The solution is an exponential decay, $N(t) = N(0)e^{-h_0 t}$.

Figure 5.1

The **survival curve** for this population is defined as the number of organisms remaining to time t, $S(t) = N(t)/N(0)$. Survival therefore decays exponentially, just like radioactive decay of particles (Fig 5.1). 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 5.2). This is what no aging looks like, in terms of population dynamics.

Figure 5.2

Let's now look at the human survival curve. (Fig 5.3) 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 5.3

The risk of death per year allows us to see more details, and has the interesting shape shown in Fig 5.4 when plotted versus age.
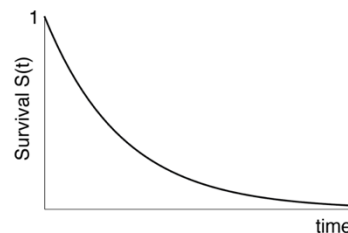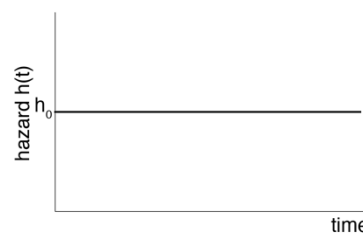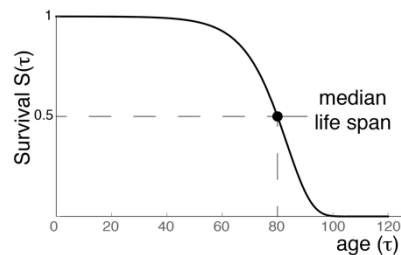
This data is for Sweden in 2012, and similar graphs are found across the world (Fig 5.4). Risk of death is high in the first year: The human life cycle begins with rapid growth of the embryo and formation of the bodies' systems, with attendant diseases and errors (birth defects), as well as delivery risks (preterm and pregnancy complications). Examples of early disease are mutations in the egg (congenital germline mutations), which cause rare diseases (prevalence $\sim 10^{-6}$).
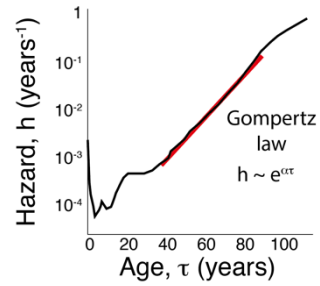

Figure 5.4

Then risk of death drops to a minimum. Growth slows down, with a spurt at puberty around age 12-14. With 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 about 3 out of 10,000 /year.

Then, starting at age 30-40, risk of death rises sharply. 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 $h(\tau) \sim e^{\alpha\tau}$. The law was discovered by Benjamin Gompertz in 1825, a mathematician who found work computing life expectancy tables for life-insurance. Adding extrinsic mortality results in the Gompertz-Makham law $h(\tau) = be^{\alpha\tau} + h_0$.

Around age 80 this exponential rise slows down, and above 100 is believed to plateau at about 50% chance of death per year.

Different regions and historical periods differ mainly in the extrinsic mortality, whereas the Gompertz slope is much more constant. If we separate mortality into intrinsic and extrinsic components, we can see that the exponential rise in hazard begins already at age 15-20 (Fig 5.5), as seen for US mortality statistics.
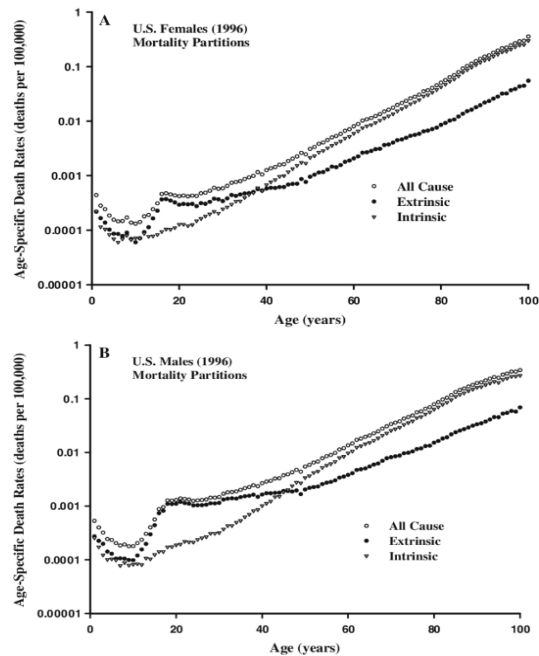

Figure 5.5

Thus, aging means that there is something different about young and old organisms. The decade of 20-30 and the decade of 70-80 are different. Something accumulates in the body to make hazard rise sharply. Indeed, many physiological and cognitive functions decline with age. This includes vision and hearing, and many aspects of cognitive ability (Fig 5.6,5.7). Similarly, organ functions, such as those of the heart and kidney, decline with age. It is worth noting that human organs have a large spare capacity: you can remove 90% of the pancreas or kidneys and survive (although you lose resilience to stress). Thus, organs can take a lot of damage before they begin to lose function. Finally, incidence of many diseases, called age-related diseases, rises exponentially with age (as we will discuss in a forthcoming lecture), including cancer, diabetes, heart failure, Alzheimer and osteoarthritis.
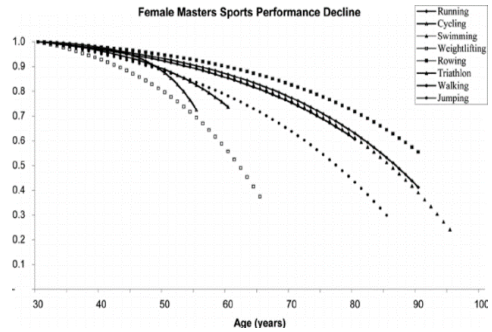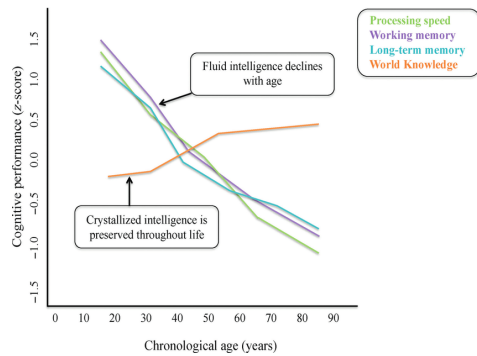

Figure 5.6

Figure 5.7

In this lecture we will explore what might be the fundamental principles for such accumulating decline.

The Gompertz law is nearly universal The Gompertz law of mortality is found in many organisms. This includes the favorite 'model organisms' for laboratory research: mice that live for about 2.5 years, *Drosophila* fruit flies that live for about a month, and *C. elegans* worms that live 2 weeks. In most mammals studied, the Gompertz law is found, to a good approximation. In 2019, Yifan Yang, Ariel Linder et al found that the Gompertz law holds even in *E coli* bacteria: when starved, their risk of death, measured by a die that enters the 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.

Genetically identical organisms die at different times Genetically identical organisms – such as identical twin lab mice- grown in the same conditions die at different times. Their relative variation in lifespan is about 30% of the mean lifespan, which is similar to the variation in humans. This goes for 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, less than 20%. What people die

of can be more heritable, as in genetic risks for cancer or diabetes. Likewise, the environment affects human mortality. An important factor is low socioeconomic status, which goes with higher risk of disease and death in all regions.

But beyond these genetic and environmental factors, risk of death in all organisms includes a large stochastic (random) component.

Lifespan can be extended in model organisms

Work on model organisms shows that lifespan can be extended. Certain mutations can 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. These mutants activate a starvation program that increases multiple 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 diabetes.

Nutrition can also affect longevity, and often through the same IGF1 pathway: caloric restriction can extend lifespan in animals ranging from worms to mice to monkeys. In animals like flies and worms, lower temperature also increases lifespan.

Figure 5.8

The survival curves with these lifespan-changing perturbations show an extended mean lifetime, as seen by their shifted half-way point (Fig 5.8). But when time is rescaled by the average lifespan, the survival curves for most perturbations line up with each other, showing that they have the same shape (Fig 5.9). This **scaling** property, discovered in *C elegans* by Strustourp, Fontana et al (2016), suggests that the stochastic processes in aging may have a single dominant timescale.
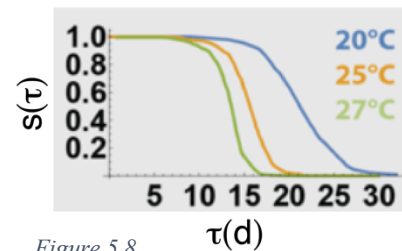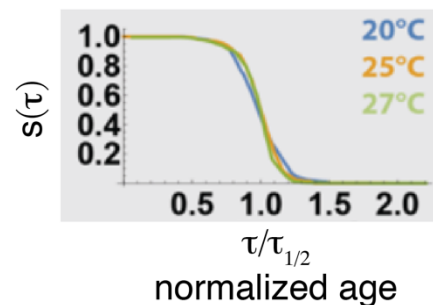

Figure 5.9

What if the 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 also a rapid timescale to the stochastic process of aging (Fig 5.10). Other perturbations, such as a temperature shift, show a change in Gompertz slope (Fig 5.11), but not a shift to another curve altogether. In the next lecture we will explain such dynamics.
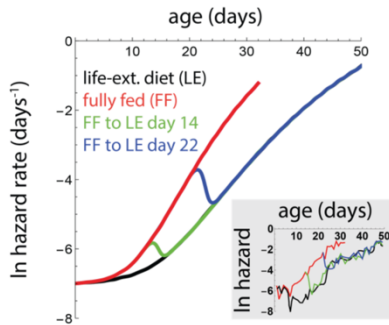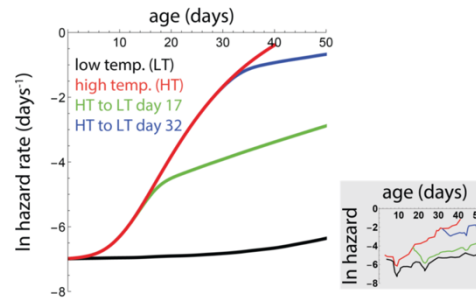

Figure 5.10

Figure 5.11

Lifespan is tuned in evolution according to different life strategies

Evolutionary theories of aging since the 1950s converged on an idea called **disposable soma theory**. If an animal has a 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. Instead, the mouse invests in growth and reproduction, making a lot of babies before extrinsic mortality finishes it off. In contrast, low extrinsic mortality selects for investment in repair, allowing a longer lifespan.

Indeed, the lifespan of different mammals ranges from 2 year for shrews to 200 years for bowheaded whales. A well-known relation connects mass to longevity: plotting longevity versus mass on a log-log plot shows that different mammals fall on a line: longevity goes as the fourth root of mass, $L \sim M^{\frac{1}{4}}$. Thus, 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.

However, there are outliers. Bats weigh a few grams and live for 40 years; 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. Instead of a line, the data falls inside a triangle shape distribution, called the mass-longevity triangle (Fig 5.12) (Szekely et al 2015).
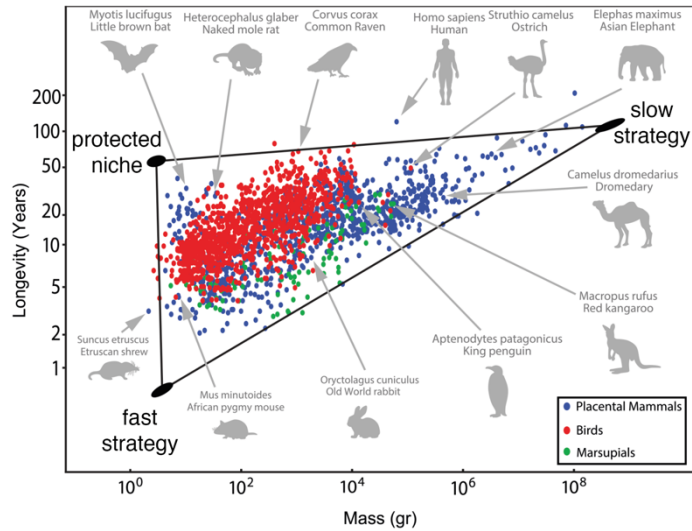

Figure 5.12

At the vertices of the triangle are shrews, whales and bats. These three vertices represent three life strategies. Shrews and mice follow a **live-fast-and-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 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 where, for example, fruit trees can be 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.

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 should 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, 2012, Sekely 2015).

All in all, larger species tend to live longer. But above we mentioned that within a species, 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 in their domestication 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 theories 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 repair mechanism against 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. Another theory of aging is based on the fact that with each cell division, the DNA ends called *telomeres* becomes shorter, limiting the number of cell divisions. Indeed, a decrease in telomere length is correlated with biological aging in some conditions. Finally, 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.

None of these theories has been connected to the Gompertz law.

To make progress, let's ask what fundamental aspects are required for damage to accumulate with age. As we discussed in lectures 1-4, 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 stay in the body.

Therefore, the damage that we care about should be in cells that are not removed. These cells are the **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, the deep skin layer called the epidermis houses the skin stem cells, S (Fig 5.13). These stem cells can divide to make new stem cells, in a process called stem cell renewal. They can also
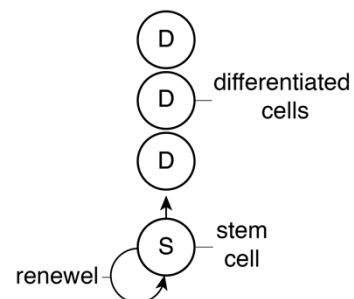
Figure 5.13

differentiate into skin cells, D. These differentiated skin cells can divide a few times. They rise in a column above the stem cells, until they make up the top layer of the skin, and are shed off. The stem cells continuously divide to replace the lost skin cells.

Similarly, stem cells are found in the epithelial lining of the lungs, intestine and many other tissues. Important stem cells in the bone marrow produce the red and white blood cells.

Since stem cells divide through life (they have enzymes that replenish their telomeres so they have no limit to their divisions), they run the risk of gaining mutations in their DNA. There is on average 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 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 thus the mutant cell is 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. These mutations produce malfunctioning proteins that cause cellular damage in the differentiated cells: they produce ROS for example, which damages the differentiated cells, or misfolded proteins that gum up the cell.

Thus, with age, there will be more and more mutant stem cells, S', that produce damaged differentiated cells, D' (5.14). There will be a column of damaged cells around each such mutant the 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 such mutant stem cells should rise linearly with age, S'~τ.
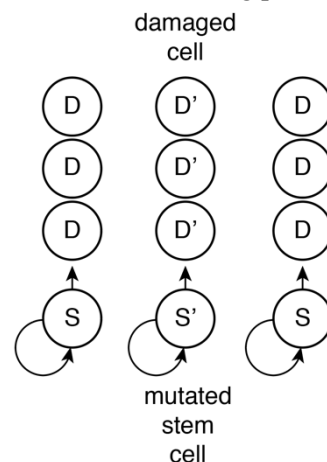

Figure 5.14

Senescent cells bridge between molecular damage and tissue-level damage

What happens to the damaged cells D'? One response of cells to damage is to commit **programmed cell death (apoptosis)**. The cells quickly and cleanly remove themselves.

However, damaged cells often take another route: they become zombie-like **senescent cells (SnCs)**. Here we focus on SnCs as a plausible candidate for an accumulating factor 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, the 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 **SASP** (senescence associated secretion profile) (Fig 5.15). The SASP includes signals
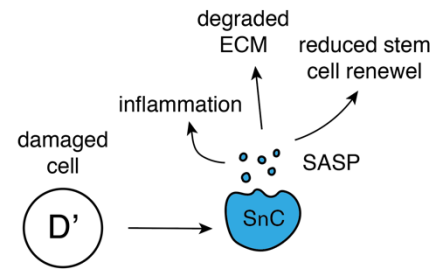

Figure 5.15

that call in the immune system to clear the SnCs in an organized fashion. In other words, these signals cause inflammation. Indeed, cells of the innate immune system are charged with detecting and killing SnC, such as macrophages and NK cells. The NK calls and macrophages also have other important jobs such as killing virus-infected cells, cancer cells and removing cellular debris.

SASP also slows down the rate of stem-cell renewal around the SnC, in order to wait for the orderly clearance 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, SnC arise and cause inflammation to call in the immune cells that remove the SnC in an orderly process over 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. As a result, the production rate of SnC rises with age, $\eta\tau$. The amount of SnCs rises throughout the body with age. The accumulation of SnC is much faster than linear with age – it is nearly exponential with age. In the next chapter we will understand the cause for this nearly exponential rise, due to saturation of removal capacity.

Because the aging body becomes loaded with SnC, 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 ECM. These effects increasingly lead to reduction in organ function. Accumulating levels of SnC have been shown to increase the risk of many age-related disease including osteoarthritis, diabetes, Alzheimer's and heart disease.

Thus, the SnC sit at an interesting junction between the level of damage to cell components and the level of damage to tissues/organism (Fig 5.16). They unite all of the different damage theories of aging,
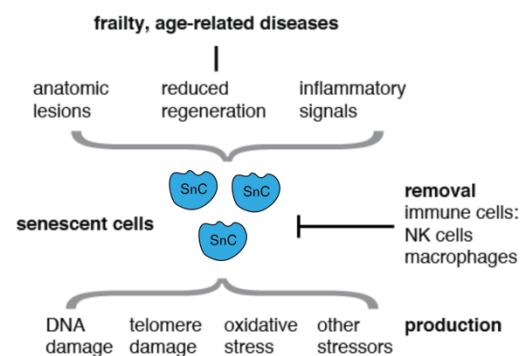

Figure 5.16

because virtually any form of cellular damage produces SnC, including ROS, DNA damage, shortened telomeres, epigenetic damage and so on. And SnC produce systemic effects that cause disease and physiological decline.

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

In 2016 an experiment by van Duersen et al galvanized the aging field in biology. 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 age-related deterioration of heart, kidney, and fat, delays cancer development[15] and causes improvement in age-related diseases. The original 2016 experiment has now been repeated by many groups using different methods. These methods include several families of drugs called **senolytics** that selectively kill SnC. Currently, these drugs are toxic for humans, but improved drugs are under development.

For a sense of the effects of SnC removal, see the picture of twin mice at age 2 years. One sibling had SnC 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 5.17).
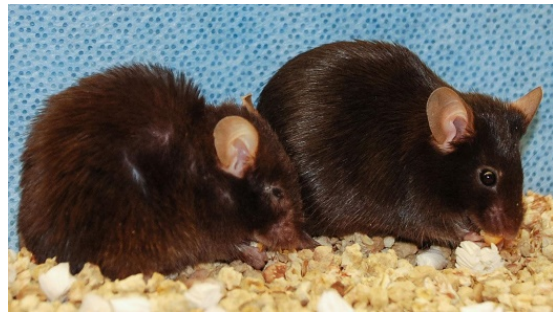

Figure 5.17

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, evn though they are heterogenous and tissue-specific. These simplifyign assumptions will help us write a stochastic process that can explain many of the empirical obsrevations we described in this lecture, on the population features of againg.