Systems Aging and Longevity
Chapter 1

Universal patterns of aging

I've curated for you some major quantitative patterns of aging . These are fascinating and also useful in order to develop a mechanistic theory of aging that will be the backbone of this book.

Risk of death rises exponentially with age

Death usually occurs at old age not at young. This is described by the hazard curve - the risk of dying at a given age. In the first year of life the chance of dying is one in a thousand due to birth and neonatal complications. Hazard then drops to a minimum at age 15- we are healthiest at childhood , then rises to a plateau until age 30- mostly of extrinsic deaths such as accidents, violence and, in the old days, infections such as typhus and cholera.

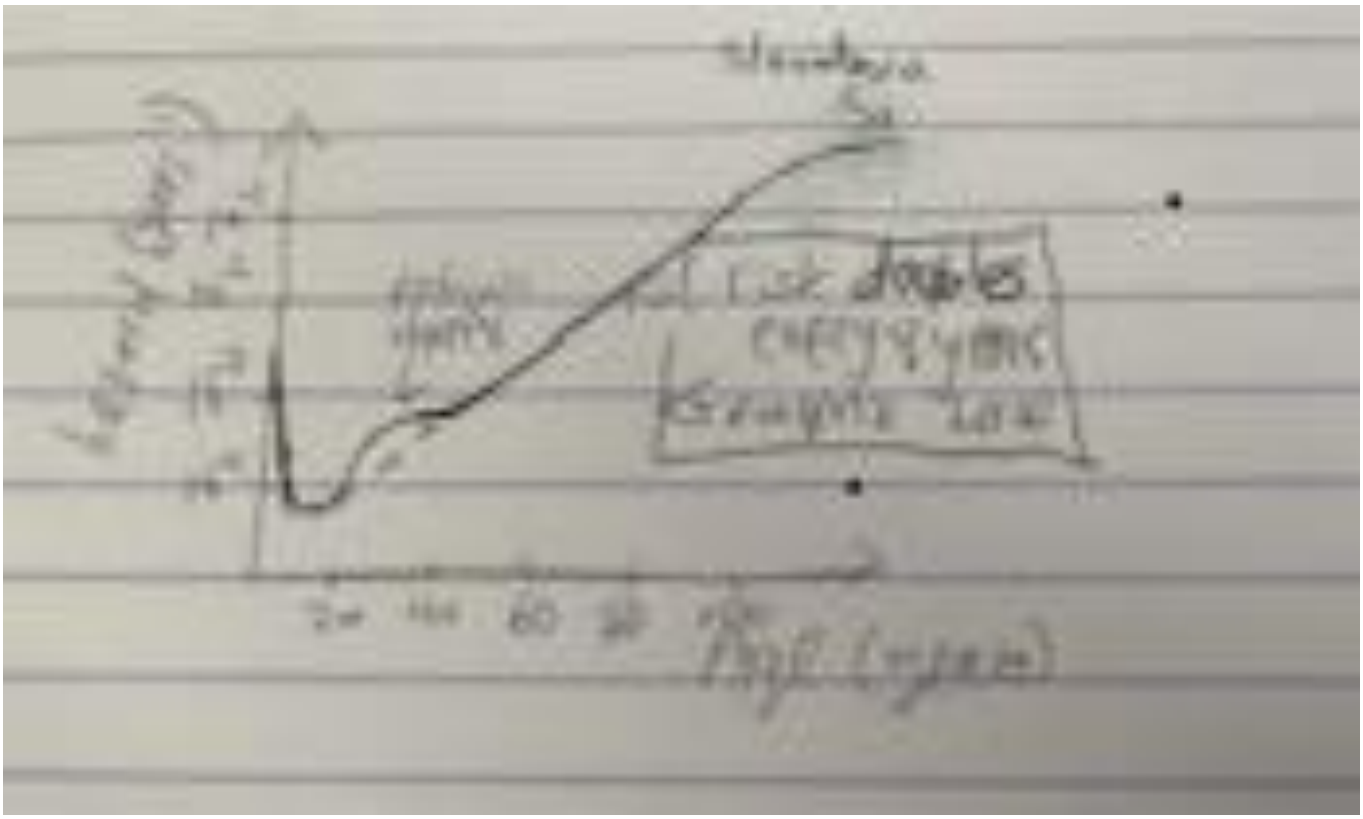
Then the risk of death skyrockets. An exponential rise seen as a straight line in this logarithmic plot . The risk of death doubles every eight years. The exponential rise is due to intrinsic deaths that arise for reasons within the body. If you exclude accidents and violence and look only at intrinsic deaths, you see that the exponential curve continues all the way down to age 15.

This skyrocketing slows down at 90. Above age 100 there is roughly a 50% chance to die each year , and this risk also mildly rises with age.

So what do you say to someone on their 120th birthday? Have a nice day.

This exponential rise over a few decades is our first universal pattern . It's called the **Gompertz law.** Named for its discoverer in the early 1800s, a British mathematician who found work computing life insurance tables.

The Gompertz law states that risk of death doubles every eight years. That number is useful to know- if you read that not exercising doubles your risk of death, it means that exercising makes you gain on average eight years of life!
By the way, that's accurate as we will see in our chapter on movement and exercise.



The Gompertz law is nearly universal- an exponential-like rise or at least a power law rise is found in yeast flies, worms and mice. These are the favourite experimental animals of aging researchers.

I say it's *nearly* universal Because there are exceptions that we will discuss later, including immortal organisms that don't seem to age.

The slowdown at very old ages is also seen in all experimental animals. It is also universal.

In the next chapters we will soon understand the origin of the Gompertz law and the slow down.

In different countries and in different periods some parts of this hazard curve change and some don't. The slope of the Gompertz law, doubling every eight years- is constant to within 10% between historical times and now. The main change is the extrinsic mortality and childhood mortality. Historically these were higher, and they are still high in some regions. in 1800 people had a one percent chance to die every year, mainly from infectious disease ; childhood was very dangerous.

extrinsic mortality went way down in the past two centuries due to sanitation,vaccination antibiotics and emergency medicine like getting IV fluids when you are sick. Now it's rare to die before age 60.

Since early deaths have gone way down, mean lifespan rose by 50 years over the past 200 years. The average lifespan steadily rises by about ¼ year with every year that passes. Today, the average lifespan in industrial countries is around 80. Females live longer, say 82 compared 80 years on average for males. The ten oldest living people are all female, many in Japan, with ages around 117-119 years.

Despite the fact that mean lifespan nearly doubled in the past two centuries, *maximal* lifespan hardly budged. The mean remaining life expectancy at age 90 rose by only 2 years. We will explore in later chapters why maximum human lifespan is hard to move, and what future interventions might affect it.

So we see that something changes in our body between age 20 and age 70 that increases the chance of dying. What this biological process might be will be the topic of chapter 3.

A Rising risk of death is sometimes
Used to define aging. But Death is only one of the three Ds of aging - death, disease and decline. Let's turn now to disease.
But first let's take a nice deep sigh of relief.

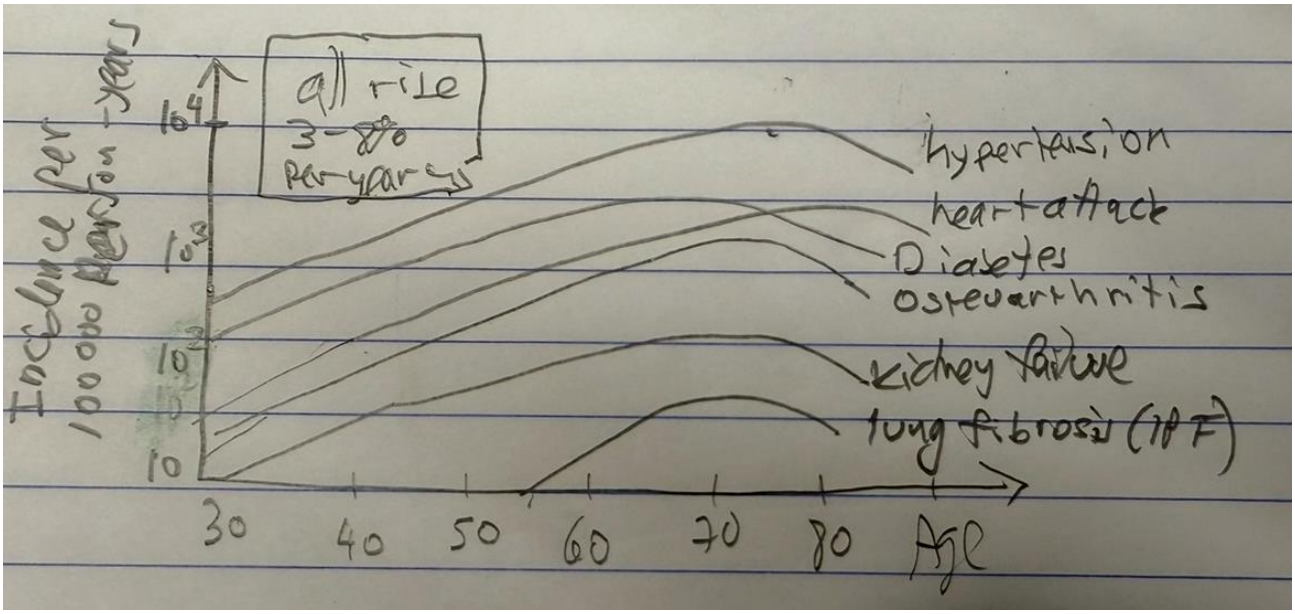
Disease incidence rises exponentially with age

Many diseases appear almost exclusively in old age . This includes the Top 4 killers in industrialized countries - cardiovascular disease which means heart attack and stroke , diabetes, cancer and neurodegeneration including Alzheimer's. We can add to the major killer list bone fractures (a 70 year old with hip fracture has a 50% chance of dying within a year). Another major killer is immune weakening that makes diseases like flu and Covid deadly at old age .

Age is THE biggest risk factor for over 1000 diseases. The chance of getting cancer at 70 is 4000% larger than at 20. It's a huge risk factor- smoking for example only increases cancer rate by factor of two. Despite this commonplace fact, biological research is still suffering a disconnect . Cancer biologists tend to study cancer in young mice. Integrating insights from aging research into mainstream biology is one of the goals of this book.

Disease incidence shows a universal pattern. Incidence is computed by asking how many people who don't have the disease will get the disease between age t and t+1, divided by the total number of people alive at age t.

Incidence of cancer rises exponentially and then drops at old age, so does incidence of diabetes, incidence of cardiovascular disease, incidence of cataract of hearing loss, osteoarthritis which is knee joint pain .



hundreds of diseases rose exponentially and drop at very old ages. The slopes are very similar about 3 to 8% per year

the similar slope are remarkable because these diseases are very different -cancer is caused by mutation on the background of inflammation, diabetes is caused by high glucose and insulin resistance and so on. the similarity of slope suggests that a common factor is at play. A common aging driver that impacts the onset of hundreds of diseases.

This leads to a central hypothesis called the GeroScience hypothesis

***I**f we can slow down the biological process of aging, we will delay all aging-related diseases in one fell swoop*

This is different from the way medicine works today which is largely by treating each disease once you get it. This reactive approach is expensive and sometimes ineffective since it is hard to treat advanced disease.

The GeroScience hypothesis suggests an elegant way forward - primary prevention of all age related disease by treating the core process of aging . our big challenge is to find what is the core process of aging and how to target it . This will be the subject of the coming chapters. I'll take you to the cutting edge

At old age people often suffer from multiple diseases which interact with each other. That's why gerontology is so fascinating. If the health of 20 year-olds is similar like reproductions of Andy Warhol prints, each eighty-year-old's health is a unique work of art. a unique syndrome of complication symptoms and diseases.

Pathologies interact. A 75 year-old has a hip fracture because with age as he got out of bed her baroreflex didn't adjust her blood pressure quickly enough her eyesight and low income made her save by turning off the cord light at night and she needed to go to the bathroom because of weekend bladder et cetera, et cetera she had no one no one was living with her to help her up, et cetera.

Death and disease are not the same thing; many deaths are not caused by major diseases like cancer or heart attacks. Sometimes a flu ends life that youth would easily ward off. The body's ability to repair, recover from injury and survive stress drops. This leads us to our third capital D which is a little different - decline of physiological function.

Physiological function drops linearly with age

Consider maximal heart rate- how many beats per minute when you're exercising to your full capacity, or carrying groceries up many flights of stairs. The familiar formula is 220 minus your age. maximum heartbeat therefore drops by one per year on average.

This gradual loss is unlike the exponential nature of death and disease which is much more explosive. heartbeat decays in a stately manner primarily due to the loss of pacemaker cells in the heart.

Many other functions behave similarly . for example, kidney filtration begins to drop after age 40 by by about 10 ml/min per decade. Here I'm talking about the cross-sectional average: take all people at 20 all people at age 30 et cetera plotted you get a linear decline.

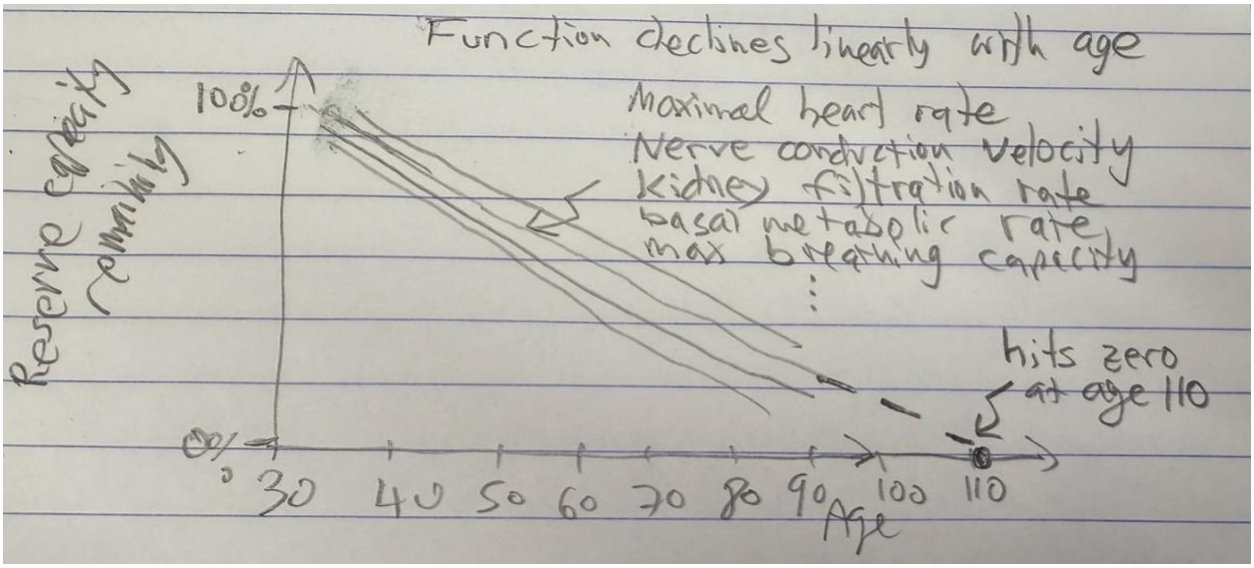
Kidney filtration is essential for purifying the blood. and it's ingenious- the kidney throws everything out of the blood and then takes back what the body needs, sugars and salt and amino acids . Everything else gets secreted into the urine. You even get rid of toxins never seen by evolution. Brilliant.

That's why a reduced kidney filtration rate when it goes below 20 mL per minute is incompatible with life. Many different physiological functions decline this way .

A universal pattern was found in 1960 by physicists Streller and Mildvan.
They plotted function at its maximum around age 30-40 as 100% and the minimum function ever measured in a living person is 0% . Many physiological declines collapsed on the same linear curve. The line hits Zero at around age 110. Give or take five years.

Nothing gets physicists more exciting than a good data collapse. It means that different processes might be coordinated by the same aging related core driver. This collapse includes nerve conduction velocity, basal
Metabolic rate, Maximum oxygen consumption VO2 max, considered by physiologists to be the most important measure of robustness and low VO2 max to be most correlated with death.

That's because before death people breathe in a lot in order to supply the oxygen for ATP to have energy for the final struggle.



All functions decay gradually, not all of them fall on the line. for example female reproduction drops more rapidly and ends at around age 50 . muscle function shows a curved decline rather than a linear one- strength is preserved longer and then has a kind of a concave drop ; as we will discuss in the chapter of movement and exercise.

A major objective of the next chapters is to explain how a single mechanism can cause exponential rise in death and disease and at the same time a linear decline in function. Stay tuned.

It's important to remember that these are cross-sectional means. A given individual can fluctuate, spell functions can be affected by lifestyle, and function can reduce sharply in disease and before death and fall away from the curve. That's why longitudinal measurements that track a person at several timepoints are important. Still, long before old age kicks in, function has declined enough that 50 year olds can feel it. Believe me.

Cognitive functions also decline with age in a gradual manner (in health, they decline faster in neurodegenerative disease). Cognitive functions are typically measured using tests and scored as a Z score - the number of standard deviations away from the mean of the population. The scores decline linearly with age for many aspects of cognition such as speed, short-term memory long-term memory.

Longevity interventions extend lifespan in animals

So far this might be a distressing reminder. Death, disease and decline are our future. So let's end this chapter on an optimistic note: lifespan and health can be extended, at least in animal models. and there are numerous ways to do so. Recently, clinical trials in humans have begun.

An experiment goes like this. You take animals in laboratory conditions and see how many survive to given age. That's called the *survival curve*. The age of 50% survival is called the lifespan. You now apply an intervention drug or a genetic intervention or a lifestyle intervention to another group of animals and look for an extension of lifespan, that shifts the curve to the right

lifespan can be tripled in worms that live two weeks, and extended by 50% in mice that live 2.5 years.

There are several classes of interventions that work in many species - yeast flies, worms and mice. We will discuss these in detail in the third part of the book. many of the interventions including caloric restriction, reduced insulin-pathway signaling and mTOR inhibitors use a natural knob to tune a crucial program in animals. This knob switches between growth and maintenance. When food is scarce you delay growth and reproduction and instead turn on repair and recycle mechanisms in order to survive to better times. These repair and recycle mechanisms extend lifespan.

Since the 50s evolutionary theory said it would not be psiible to find a single gene to extend lifespan. This was proven wrokng in mid 1990s by cynthai kenyon. Deleting the gene daf2 made worms live twice as long. They got a free lunch- they not only lived longer but seemed healhioer and on toital made almost as amny eggs as regular worms. They resisted stresses well too and moved rapidly to search for their bacterial food.
Whey dosent this mutation take over the worm nation- making super owmrs? In fact it dosent, regular worms have the option to switch form fast lives when food is plentiful to slow lives when starved. Teh daf2 mutants are stuck always int he slow mode, and the wild type (regular) worms outcompete them.
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Currently clinical trials in humans have begun on some of these drugs but we're not certain yet if they work. how strongly you can twerk human lifespan with the drugs that worked on mice is unclear especially given the fact that the longer the organism lives the less its lifespan can be extended.

One can ask what these lifespan extending do to the shape of the survival curve? A study on this question is what got me into aging research in 2016. I am a physicist that entered biology to seek elegant simplicity. As a fresh professor I found simplicity in gene regulation networks.
But I always thought that aging is messy, chaotic decay and thus no place for a physicist. The paper by Nick Strustrup changed my mind. he showed that many different interventions in worms that extend lifespan preserve the shape of the survival curve . You can see this if you divide age by the median lifespan - the curves collapse on top of each other.
a data collapse! This means that different interventions affect a single times scale, and proportionally extend median and maximal lifespan. We will explore this scaling property in upcoming chapters.

I would just like to say that certain interventions do change the shape of the survival curve, making it steeper, and these will turn out to be important.

do you need to intervene throughout the entire lifespan or can you start at old age? Are the sins of the past forgiven? An experiment on fruit flies tested midlife interventions. Fruit flies are great for measuring millions of deaths. Mayer et al compared a control group with a normal diet to a Group of flies were federal longevity extending diet. They both show the Gompertz law but the good diet has a lower hazard curve because they have a lower risk of death. Now the experimenters grew flies on the normal diet and shifted to the longevity diet in middle Age or old age . remarkably the sins of the past were forgotten. the flies transit to the hazard curve within a short time of a day or two.

This suggests aging has a process that acts on a rapid time scale, in addition to processes on the long timescale of the entire lifespan.
other types of interventions such as lowering temperature makes flies live longer but only changes the exponential slope. We will understand the difference between these behaviors in the next chapter.

Some people ask is it ethical to extend human lifespan? In my opinion the answer is yes if we also shrink the time people are sick. It is telling that no one asks this about curing cancer, even though lifespan is extended. My favorite way to think about this is to consider the functions that *improve* with age - the cognitive functions of crystallized knowledge, experience and wisdom. As a group, old people score higher on tests of wisdom. Wisdom includes emotional regulation- elders have more experience dealing with themselves . It also includes better decision-making - they have more experience in the world.

in my opinion a sizable part of the population with good health and wisdom is essential in order to tackle the challenges facing humanity.

From an economic point of view, compressing the time that a person is sick saves on healthcare costs. These savings are hefty, but they are dwarfed by the dividend of increased productivity. Each extra year of productivity is worth tens of trillions of dollars globally. And extending lifespan won't cause much of a population growth in the long-term because old people are post-reproductive.
We will address the social and humanistic aspects of aging in the last chapter

One last shared feature of aging I'd like to Mention is that

genetically identical organisms raised in the same conditions die at different times.

Identical twin worms or mice or humans raised in the same conditions die at different times, indicating that beyond genes and environment there is a random or stochastic aspect to aging.

Understanding this noise is one of the frontiers in aging research and we will address it in the upcoming chapter. Stay tuned.

That is not to say genes aren't important. Twin lifespans are more correlated than unrelated strangers. And some genes are the key to super long lifespans. We will see (chapter x) that human lifespan is more heritable than once believed, but noise and lifestyle still have a large effect.

Summary

Aging has nearly universal patterns. Animals age similarly- old dogs and old humans share many features like grey hair, rising risk of disease, cataract, slow motion, low energy. In many species the risk of death rises exponentially following the Gompertz law with slowdown at very old ages. The risk of diseases also rises exponentially with similar slopes, whereas functions decline more gradually, often linearly with age. The aging process has slow processes, fast processes and a stochastic component.

With these patterns in hand we now turn to develop a mechanistic theory of aging. The theory needs to explain all of these patterns. It will be the backbone of this book.