An Introduction to Evolutionary Biology

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Evolutionary Theories of Aging: Part 1

Hi, in our last discussion, we looked at the mechanistic theories of aging. In this discussion and the next, we will be looking at the evolutionary theories of aging. But before we go there, I need to remind you of the proximal-ultimate dichotomy that we talked about in the first week of our discussion. So, just to remind you, suppose there is a dead body lying there; then you can ask two kinds of questions in that context. One is, how did the person die? Was it due to a bullet wound, a knife wound, or something else? This is the kind of question that the forensic expert is going to ask. And the other thing is about, you know, what the reason for the person's death was.

What is the motive? This is the question that the investigating officer will ask. So, in biology, these two kinds of questions are known as the proximal and the ultimate kinds of questions. The evolutionary explanations are of the ultimate kind. So, this is pretty much what is happening in the context of the aging theories we are examining.

So, the mechanistic and evolutionary theories are not really antagonistic to each other. It is not that if one of them is true, the other has to be false. No, the mechanistic theories are essentially trying to figure out the proximate causes of aging. Whereas evolutionary theories try to figure out the ultimate cause of aging. In other words, the evolutionary theories primarily ask what the reason is for which we have, I mean organisms have not been able to get rid of aging, whereas the mechanistic theories are questioning. At the molecular level, which molecule is going up and which molecule is going down? Which molecule is causing, you know, some variation here because of which? We are experiencing the symptoms of aging and the negative effects of aging. So, this needs to be looked at explicitly in the context of the two sets of theories. The mechanistic and the evolutionary are not really antagonistic to one another. Now, as I told you, this particular question is why evolution has not been able to address aging over billions of years.

This has been around for a very long time. And the earliest evolutionary explanations for aging can actually be dated back to the Roman poet Lucretius, who said, I mean, I am not quoting him; this is just a paraphrase. He said that there might even be a benefit to aging and death. And the benefit is that they end up paving the way for upcoming generations. In other words, if the organisms die, only then will the resources be available for the younger generation.

So, this is something that was put into very nice words by Alfred Russell Wallace, the same as Darwin-Wallace. And what Wallace said is, "I am going to give you a quote: he said that for it is evident that when..." One or more individuals has provided a sufficient number of successors.

They themselves, as consumers of nourishment to an ever-increasing degree, are a burden to those successors. In other words, when the parents have produced enough babies, Then both the parents and the babies are using the resources. They are, in some sense, competing for resources, and in that case, the presence of the parents can be harmful to the babies. And therefore, natural selection therefore, weeds them out, them as in the parents and in many cases favors such races as die almost immediately after they have left successors. In other words, once your evolutionary job is done as you know by producing the babies, then it is better for the parents to die.

That is roughly what Wallace was talking about, and he thought that if there were a mechanism like that, Then, natural selection is going to favor that mechanism in a big way. That is what he means by saying that natural selection weeds them out. Now, this particular idea leads to the concept that death and aging, which lead to death, can be a programmed feature of organisms. And this idea was put forward most strongly by this gentleman, whom you met earlier, August Weismann. This is the person who was cutting off the tails of, you know, rats to show that acquired characters are not inherited.

So, he actually made multiple contributions to the field of biology; this is one of his more famous ones. So, he thought that perhaps organisms are programmed to die, and that this is an adaptation. which is favored by natural selection to eliminate the old and therefore, worn out members of a population. So, some people have joked that when Weisman was around, he was German. So, when Weisman was around in German academia, people had to wait for the professors to die.

Before their positions were taken by younger people. And some people have joked that maybe Weisman was actually, you know, thinking about that aspect of academia. When he wrote about this, it was just a joke; you knew nothing else. So, the mechanism that Weisman proposed was as follows: this is very interesting, you know. Look at it; this is the quotation.

Lifespan is connected to the number of somatic cell generations that follow one another in the course of an individual's life. So, he connects lifespan to how many somatic cell divisions are happening, and this number, The number of somatic cell divisions, like the lifespans of individual generations of cells, is already determined in the embryonic cell. In other words, he is explicitly saying that the number of divisions a cell in the body can undergo is limited; there is an upper limit to that. Now, please note that Weisman is writing this in the year 1882. At that point, and even after that, for a very long time, people actually thought that there was no end to how many times a cell could divide.

However, in 1959, H. Earle Swim actually ended up showing empirically that for many kinds of cells, There might be an upper limit to the number of times the cells can divide. And in 1961, this was again put forward by Leonard Hayflick, and today we know it. The Hayflick limit is the phenomenon that there is an upper limit to how many times most cells can divide. Now, of course, you know this guy Weisman was talking about this 70 years earlier, just based on theoretical observations.

So, that tells you what kind of mind Weisman had. So, anyway, now at face value, this looks like a very nice argument. However, if you think about it very closely, you will realize that there are issues with this argument. What kind of issues are we talking about? The primary issue is the so-called cheated argument.

Now, think about it. This entire argument is saying that those organisms that die earlier, and therefore leave space for their offspring, they are the ones who are going to be favored by natural selection, because the group is being favored. So, it is a group-selection argument. But suppose you have some mutation by which you get organisms that do not die early; what will happen? These organisms that are not dying early are living longer and are going to leave behind more babies. If they are going to leave behind more babies, then obviously their fitness is greater, natural selection is going to favor them. And therefore, by the logic of natural selection, after some time, the frequency of such individuals who do something that is bad will decrease.

For the group, it is good for them; these are the cheaters. The frequency of such individuals is what is going to increase in the population. In other words, you know, given equivalent reproductive output, the long-lived individuals. they are the ones who will be favored by natural selection. And therefore, there is no mechanism by which such a thing, such a programmed death, is going to be possible in any organism.

Now, that is what I am saying: there is no clarity on how such a mechanism will sustain itself. So, this is the theoretical argument against it. However, you know you can still ask, "That's fine; let us see if it works or not." And people actually searched for quite a long time, but they were not able to find any such mechanism. Then they looked at the data, and what they found was very, very interesting.

Now, before you think about it, we first have to understand what it is that needs to be observed. So, if there is indeed a death mechanism, then that death mechanism means that once an organism reaches a certain age, Which might be different for different organisms, that is fine; but once the organism reaches that age, changes will happen. In the body, because of which it will die, you will either know very soon or over a certain period of time; whatever the case, it will die. Now, if such a mechanism indeed exists, then under natural conditions, Organisms will most probably need to hit that value now and then, right? Now, why is this important? This is important because, under natural conditions, organisms die for all kinds of reasons. Sometimes they die due to predators, sometimes they die because they do not get enough food, and sometimes they die.

Because there is a flood or a massive storm, you know during which there is a thunder strike, etcetera, etcetera. So, there are all kinds of external reasons for which organisms can die. So, many organisms will probably die before this programmed death kills them; that is okay. But the point is that, at least in some cases, the organisms have to go up to their limit and be killed by programmed death because if that is not happening, then the organism will never require that and therefore, there will be no selective mechanism maintaining that. So, that is why you expect to know at least some of the organisms particularly those who are living slightly longer; at least they are dying because they have reached this particular limit. Now, if this is the case, then if you look at the lifespan of organisms under natural conditions, and you compare those lifespans with the same organisms when they are living under captive conditions, Because under captive conditions, they are provided with food, there are no predators, etc. So, those are benign conditions. If you compare these two things, lifespan in nature versus lifespan in captivity, You expect that these two will not be very different from one another. They will be slightly different, obviously, because under natural conditions the deaths are going to be, you know, There are many more ways in which you can die under natural conditions, but they should be somewhat different.

The difference between the two will not be very large. So, the way to observe this is to look at the lifespans of organisms under captive conditions. Look at their average lifespan under natural conditions and see what kind of difference you find there. And it turns out that you actually make a huge difference. In other words, under captive conditions, organisms live not only a little longer, but a lot longer.

Just to give you two examples, I mean these are just two; there are hundreds of examples of this kind. So, this is a bird called the chaffinch, and this bird, under natural conditions, The mean lifespan is about 1.5 years; in captivity, it can live up to 29 years. Similarly, if you look at the chimpanzee, the median lifespan in the wild is about 8 years. In captivity, the median lifespan is 23 years.

And if you look at the maximum lifespan in captivity, a chimpanzee can live up to 50 years. There are no known chimpanzees that have ever lived to be 50 years old under natural conditions, not even in protected parks. So, these kinds of examples straight away tell you that there is a huge difference. between both the mean and the maximum lifespan in captive conditions and in natural conditions, Which is completely against the prediction that you are receiving from the programmed cell death process. And that is why today the programmed theory of death is not really considered very seriously.

Now, this has very strong implications. What are the implications? Remember, I told you that one of the major, you know, lines of investigation is all over the world right now. This is how to increase the lifespan and health span of individuals, particularly humans. Now, if this programmed theory were correct and there were indeed a program, then it would have been very difficult. Change that because it is something that is, you know, part of the biology of the organism. But if you do not have a programmed, you know, death mechanism around, then that implies that it is perhaps possible to change the.

The lifespan of organisms, in this case, obviously, includes all the work that is being done all over the world that makes a lot of sense. So, in that context, proving that the programmed theory of death no longer works is very reassuring. Incidentally, Weisman himself changed his mind toward the latter part of his life, looking at various kinds of data. And toward the latter half of his life, he actually explicitly moved away from this particular programmed cell death theory. programmed death theory and was no longer subscribing to it.

Unfortunately, this change is not what people talk about. People only say that he propounded the programmed theory of death; they never said that he changed his mind. Anyway, from this, we now go to the more modern evolutionary theories of aging, and there are quite a few. We are going to look at just two of them, and these two are the most prominent. But before we understand the crux of these, you know, evolutionary theories, we need to revisit the definition of aging.

The evolutionary definition of aging that I talked about also requires us to consider three observations. So, if you remember, I defined aging from an evolutionary perspective as It is characterized demographically by increasing mortality and decreasing reproductive success with advancing age in adults. So, this is what you need to remember: for aging to happen, the rate of mortality has to go up, and the rate of reproduction has to go down. Why this is important will become clear in a few moments. The other three things that we need to keep in mind are the three absolute biological realities.

The first thing is that if you have an organism out there in nature, there is always a finite probability of death due to external reasons. It can be due to a predator, a pathogen, or any natural calamity, as I mentioned. It can be due to any reason: it can be due to an accident, it simply fell while running and broke its neck, or whatever. But there is always a finite probability of death, which means that you know that going from any Let us say from year 10 to year 11 or from year 15 to year 18; you can never say that it will definitely be able to make that transition. There will always be a small value; however small, there will always be a small probability of death.

The second thing is, this is very obvious, but you know that until people are told, they do not think about it. There is an asymmetric relationship between survivorship and reproduction. You can survive up to a certain age without reproducing. But if you want to reproduce at a particular age, you have to survive to that age first. In other words, suppose you know I am talking about how many babies I will have when I am 30 years old.

So, in order to reach that number of babies, I first have to survive until age 30; without that, I cannot have the babies. So, that is what I mean by saying that reproduction at a given age is contingent on surviving to that age. The third thing is that for any given reproductive effort, which basically means Let us say I decide to reproduce at the age of 30, or I decide to reproduce at the age of 31 or 32, whichever. For any given reproductive effort, there will always be a physiological upper limit to how many babies I can produce. Now, an organism can technically produce an infinite number of babies if it lives forever; that is fine.

But in a given reproductive effort in a particular year, there has to be an upper limit. And why am I saying that? That upper limit is going to be based on factors such as how much resource the organism can assimilate. You know, suppose we let us say I am talking about a human. It will be decided by how many babies can be accommodated inside the mothers' wombs. If I am talking about an insect, it will be determined by how many eggs the female can lay.

It can be a large number, but it can never be an infinite amount. This is a subtle point, but if you think about it closely, you will understand that for a given reproductive effort, There has to be an upper limit to how many babies can be produced. So, now that we have these three realities and that particular definition of aging, Now we are in a position to understand what exactly the crux of the evolutionary theories of aging is. And for this, what we will do is conduct a quick simulation. I will build the simulation for you from scratch, and we will do it in Excel.

So, let us assume that we have an organism, and let us first consider its ages. So, let us assume that we call the various age classes x, and let us say we are measuring age in years. It does not really matter; it can be in days, minutes, seconds, or whatever. So let us call the first age class 0. So, these are all the newborns, the babies, and then we have 1, 2, 3, and so on.

So, let us pull it to some arbitrary number, say 60, or whatever. Now, we assume that in this particular organism, the mortality rate from one age class to another stays constant. So, right at the beginning, it has to be 1 because everybody has, you know, this is the newborn class. But from the mortality rate going from 0 to 1, let us say it is 0.1, which is some value. Again, as you will see, the value I take does not really matter; the logic that we are building remains the same. So, let us assume that this is 0.1 for all age classes. Now, remember we said that, as per the definition, aging happens when the mortality rate goes up later in life.

But here, the mortality rate remains constant throughout life. So, from the mortality angle, this is not an aging population. Now, let us think in terms of numbers and, for the sake of calculation, Let us assume that we started our population with 100 individuals. So, for 100 individuals, the mortality rate of moving to the next age class is 10%. So, how many individuals will I have? Basically, this number is equal to this number minus 10% of this number. So, 100 - (10% * 100) = 90. So, what will happen in the next generation? 90 - (10% * 90) = 90 - 9 = 81, and we can click on this, and you can see it will continue. Now, obviously, in a real biological population, these numbers will not be in decimals, but we are conducting a simulation. So we will just let it be. The other thing to note is that since we are reducing the population size by 10% every generation, this will continue to happen indefinitely. The number will become smaller and smaller, never really reaching zero.

But for the sake of our simulation, we will assume that once it goes below 1, which is the case at this point, it will not recover. I will increase the size slightly; at this point, we will assume that the population size has reached 0. So, arbitrarily we will make the population size 0 at this point and we will delete everything else. Again, as you will see, this does not really affect our final outcome in any way.

This is just for the sake of calculation. So now we need to compute what the survivorship is for each age class. So, survivorship in technical language is also denoted by the letter l, and we call it lx, which means for that age class. So, here we have all of them surviving.

So, equal to this number is 100, which is 1. Here, 90 out of 100 are surviving. So, equal to this, I will just drag this. So, 90 out of 100 are surviving. So, this is 90 out of 100; 90/100 = 0.9; 81 out of 100 are surviving, which is 0.81, and so on and so forth. Now, look at the fact that this particular survivorship value, lx, is also telling us something else. What is that? It is also telling us what the probability is of any randomly picked individual from this group at the beginning. What is the probability that it will survive to that age class? So, for example, what this is saying is that the probability that a randomly picked individual will survive to age class 2 is 0.81. Now, many students find this very intuitive; they can understand it like this.

For many students, this transition, which affects survivorship probabilities, can be a little difficult. So, think about it this way: assume that these 100 individuals, these 100 newborns that we had right at the beginning. Let us assume that all the ones who are going to live to the next stage of the class; let us say we color all of them black. Let us assume that 10% of those who die are colored red. Now, we want to ask what the probability is of a randomly selected individual surviving to the next generation and to the next age class.

And so, this question can essentially be translated into asking if I put my hand in and select a random individual. From all the newborns at the beginning, what is the probability that I will pick a black individual? because black individuals are the ones that will survive. So, that probability is obviously 90 out of 100, which is 0.9, and in that way, this number also gives us.

The probability of a randomly picked individual surviving to that age class. Now, let us consider reproduction in age class x, which is technically typically denoted as mx. So, let us assume again for the sake of a simulation that right at the beginning of their lives, right when they are newborns, they are Able to produce babies, let us assume that they are producing at the rate of two babies throughout their lives at all age classes. Again, remember the definitions of aging: the evolutionary definition of aging suggests That the reproductive success of reproduction should decline towards a later part of life. But here we are explicitly assuming that it is the same throughout their lives, which means that Again, by the reproductive criteria as well, we assume that this is a non-aging population.

So, this is how many babies they are producing. Now, we come to the second postulate we made. What is the second postulate or second observation, which states that in order for an organism to reproduce, it must reach a certain age class? It will first need to survive to that age class. If it cannot survive, then it cannot reproduce. Therefore, if we are to understand, on average, how many babies an individual is expected to produce in a given age class, Then we need to multiply the number of babies produced in that age class by the probability of surviving to that age class, right? So, this is what is known as the reproductive success for x; I will just put it above the reproductive success for each class x.

And this is simply lx*mx = lx*mx, and we will click on this, and there we go. Now, note that because this mortality rate is present, there is a finite mortality rate in all age classes. Therefore, the overall survivorship across the age classes has to be a decreasing function. There is no age class at which this will be equal to zero; therefore, this will be monotonically declining. However, the same is not true for lx*mx. Why is that? In this particular case, we have assumed that all the values are the same, but we may encounter situations where, let us say, later in life an organism starts producing a greater number of offspring, and that happens all the time. I mean, take humans, for example; we do not produce any babies in the first 12 to 15 years of life. But then we start producing babies, and we can produce them at roughly a constant rate for a long time. If you look at Drosophila, for example, on the first day of its life, it cannot produce any babies; then it produces lots of eggs.

Then the reproduction comes down, and then it, you know, remains constant for some time. It slowly peters out over its entire lifetime. So, basically, different organisms will produce different numbers of babies at different points in their lives; and therefore, It is entirely possible that this reproductive success thing that we are computing, lx*mx, is. This need not necessarily be a monotonically declining function; it can have a peak somewhere in the middle. So, in the context of this non-aging population, it is going to be a monotonically declining phenomenon.

Now, think about what each one of these numbers is saying. Each one of them is telling what the expected number of babies are. That is what the organism will produce if it ends up surviving to that age class. So, now if I were to ask what the total number of babies that an organism is supposed to produce over its entire lifetime is, That is simply going to be the sum of all these values. So, let us do that sum: that sum is $\Sigma(lx*mx)$. So, this is the expected number of babies that the organism is expected to produce over its entire lifetime.

So, now we are going to quickly compute two other quantities: one is the cumulative reproductive success. What is that? That is simply how many babies it produces cumulatively as it goes over time. So, in order to compute this, at step 1 it is 2, and at step 2 this is equal to this plus this. So, 2 + 1.8 = 3.8. Similarly, at the next step, it will be 3.8 + 1.62 = 5.42. I click on this, and I get the entire accumulation. Not surprisingly, the last value here is this value. And now, this is just for the sake of plotting. We will also do this in terms of percentages. So, what is the percentage of its lifetime reproductive success? Does the organism achieve this by a certain age? So, in order to do that, what we will do is take this value.

And we will divide it by this sum over here, and this sum we need to put in two dollars to ensure that it is only dividing. You know the denominator is only this value and nothing more. So, that gives me the ratio, and now I multiply it by 100, and I get the cumulative percentage.

I click on this, and of course, it ends up being 100. Excellent. So, now that I have all the figures I want to look at, I am going to draw some plots. The first plot I will draw is that of survivorship, and as I go to insert it, I look at the charts, and there you go. As you can see, the survivorship is monotonically declining, but what you should also be able to see is That it is declining at a pace much faster than linear; it is actually declining exponentially. What is the second graph that I will draw? The second graph that I will draw will be this reproductive success thing; I will just call it lxmx over here: reproductive success lxmx. So, this is the reproductive success, but as I said, it is monotonic in this particular situation because of that fact that we have taken two individuals from all age classes. If you have higher reproduction in the middle, then this can have a peak. So, let me just show you. For example, let us say I make this value 20. You can see it has a bump over here. Suppose I make the next value 18; you can see that the bump is getting, you know, a nice bump is happening, and so on.

Anyway, this is the reproductive success lxmx, and the third one that we will look at is the cumulative percentage. And what is the cumulative percentage graph looking like? The cumulative percentage graph is going to look like this, right? But essentially, what this is saying is that even though, you know, in this particular case, my organism lives for 43 years, The value, reproductive success over its lifetime, comes very close to 100, much earlier than you know it is 43. So, in this particular case, for example, let us just look at it: you know, where does it hit about 90%? It hits 90% at about the age of 20, right? And for the remaining 24 years, it is just getting 10%. Now, let us reduce the size a bit more.

So, here are our three graphs, and with these three graphs, we are now in a position to understand them. What is the crux of the evolutionary theory of aging? So, let us go back to our PPT for that. So, yeah, these are the three graphs that we saw. Now, think about it. How does natural selection operate against, let us say, a mutation? Natural selection operates by reducing the fitness of organisms. In what form does it do so? In this particular case, it is going to be the number of babies, or it is going to be the lifetime reproductive success that we summed.

Now, if you look at that sum and how various ages are contributing to it, you see that There is a huge discrepancy between the contributions from earlier ages and the contributions from later ages. So, if you look at it here, you can see that the earlier ages are contributing much more. The later ages are contributing much less, which is also evident from this cumulative reproductive success. In the initial part, the cumulative reproductive success increases steeply, but in the later part of life, it becomes very flat. So, suppose you have a mutation, and that mutation, let us say, is causing some harm; it is causing a lack of fitness.

Now, that harm, let us assume, is being caused early in life. In other words, it slightly reduces reproduction early in life. In that case, the way it affects the organism's overall reproductive success is much greater. So, any reduction in survivorship or reproduction early in life is going to play a role in this part of the curve, which means. that natural selection is going to be very effective in favoring or weeding out if it is bad any mutation in the early part of life.

But suppose now you have a mutation that affects the organism only later in its life. So, even if the organism you know has that particular mutation, let us say it reduces reproduction to 0, or Even if it is killing off the organism and making your lx very, very low, the overall contribution to reproductive success remains. of that part is going to be very less because of which natural selection is hardly going to be of any major effect. So, that is what we mean by saying that the effect of natural selection goes down with age and late-life deleterious mutations.

They are typically much less affected by selection. This is what is technically known as selection shadow. So, I will just take you to this demonstration one more time to show you it. So, just to show this to you numerically, let me do one thing: let me calculate this cumulative reproductive success sorry, reproductive success; let me get this sum right here. This is the same 19.806 value that you saw. Now, let us assume that there is a mutation that is affecting individuals early in life, and because of that mutation, Let us assume that this reproductive success in the first two years is becoming zero. So, let us do that. What is happening? Just by affecting the reproductive success in the first two years, from 19.806 to 16.006, you have achieved quite a large reduction. But suppose now we do the same thing late in life; let us say we do it here, we make this 0, and we again make this 0.

From 19.806, you have gone to 19.76, just a 0.046 difference. So, this is what we mean by saying that the deleterious effect of a mutation that occurs earlier in life is much greater. In terms of overall reproductive success, it is more significant than the deleterious effect of a mutation that occurs much later in life. And because natural selection operates by, you know, making differences in overall reproductive success. Therefore, even if there is a slight change in, you know, this thing, natural selection will not be able to weed it out, or it will be much less effective in weeding it out if the deleterious effect is expressed later in life. As compared to if the deleterious effect is expressed earlier in life, this is the crux: not all mutations are the same. Early-acting mutations are worse in terms of affecting an individual's reproductive success. Overall reproductive success is compared to late-acting mutations. And this is what leads to the concept of selection shadow. Now, of course, one has to ask: does it really work? What does the data tell us about the effects of the selection shadow? How big is this effect? So, that is what we are going to look at in our next discussion. Thank you.