An Introduction to Evolutionary Biology

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Evolutionary Theories of Aging: Part 2

Hi, so in our last discussion, we saw that the force of natural selection decreases as an organism becomes older and older. And this happens because of the contribution to overall reproductive success. is much greater in the earlier age than in the later age. And that is why there is this concept of selection shadow, which says that somewhere during the later part of life, If there is a mutation that ends up having a detrimental effect on reproductive success, Then the overall effect of that mutation on fitness is going to be very minimal. In other words, the ability of natural selection to eliminate a detrimental mutation in the later part of its expression. Towards the later part of its life, it is much less compared to the same mutation if it expresses towards the earlier part of its life.

So, what does the data tell us? That is what we are going to discuss during this particular session. Now, the evolutionary theory suggests that the fundamental cause of aging. The fact that there is non-zero mortality during, you know, every phase of life. So, if that is the case, then that automatically leads to the prediction that if there is greater extrinsic mortality in a population, Then that population should age faster and have a lower lifespan.

Why is that? Because if most individuals are dying early in life, then all the mutations Those mutations are typically not even expressed, which are going to be expressed only later in their life. The carriers are dying even before those mutations you know play a role and therefore, in this way they will end up escaping selection. And when they escape

selection like this, if you bring them under benign conditions and let the organisms live, As long as they want to, these mutations will get a chance to express, and their deleterious effects will show up as aging. or show up as you know death at a earlier life. So, that is why we expect that high levels of extrinsic mortality is going to Lead to faster aging.

Now, do we have any reason to believe this? Turns out that if you simply look at the data, there is quite a bit of evidence that suggests that this is really the case. So, for example, flying is. We know that if an organism is able to fly, then the number of organisms that can predate on that organism is much less. In other words, flying reduces predation rates, and predation is one of the major sources of external mortality. Therefore, we expect that flying organisms, which you know, should in general live longer.

Now, it turns out that this is borne out in multiple cases. So, if you look at birds, they typically live longer than similarly sized non-flying mammals. Similarly, among mammals, the flying mammals are the bats; they typically end up living much longer than all other mammals. Similarly, if you look at insects, they typically have a high external source of mortality and therefore, they generally live short lives. The very nice exception to this rule is the queens of social insects like ants and termites, who actually have a very low source of mortality, because they are well protected by everybody else in the nest. They also get lots of food that is provided by the other people; therefore, their rate of external mortality is low. and therefore, their we normally see that their longevity is very high. So, this is very much in line with what we said. External mortality should lead to faster aging.

Do we have more concrete evidence, and more importantly, what we just looked at was across species, right? So, across species, so many other factors can be in operation. Do we have something under controlled conditions or under known conditions within a species? And it turns out that we do. So, this is one of the very famous examples. Sorry, before going to the example, let us look at what the predictions are. So, the prediction is that if there is reduced ecological mortality, which is external mortality, then, There is

going to be increased selection on late-acting deleterious mutations.

Why? That is because the organisms will be able to live longer, and therefore, all those mutations will be under selection and therefore, they will age slower. On the other hand, if you have increased external ecological mortality, most of the organisms will die young and The selection on late-acting mutations is going to be much less, which basically means organisms will end up aging faster. So, here is a pretty famous, you know, example of this. So, this is a study on Virginia opossums, commonly simply called opossums. These are marsupials, and they are found on the North American continent.

So, this organism has a peculiar tendency that if it feels really threatened, it actually plays dead. And this allows it to escape from many predators, particularly those that do not typically touch dead animals. Very interestingly, from a conservation point of view, this has actually played a negative role in their lives. Because what happens is, suppose you know that a lot of the stress they get is from vehicles on the roads. So, basically, when they see a vehicle approaching at a fast pace, they simply play dead and therefore, they end up becoming part of, you know, roadkill along highways. Anyway, this particular study was conducted by Stephen Austad, a big name in the field of gerontology. And here he used two populations of the Virginia opossum, one that was found on a mainland. and one that was found on an island called Sapelo Island nearby. So, it turns out that on the mainland, there were lots of predators, and therefore, there was a much higher rate of predation.

On the island, the rate of predation was much lower. But apart from this difference in predation, these two sites were actually extremely similar to each other. Austad spends a lot of the paper showing that temperature, precipitation, external parasite load, and availability of resources, etc. Everything is as similar as possible between these two sites and not significantly different.

Great. So, for this study what Austad does is he radio collared a large number of females shortly after their birth and followed them throughout their lives and essentially recorded

when they died. He had also recorded other kinds of data that I was going to discuss. Now, what was happening on these two islands because of the differences in the predation rates? So, it turns out that here we are showing you the survival proportion on the y-axis and the ages of the females on the x-axis. Now, note that we are putting this surviving proportion on a natural logarithmic scale, because of which I showed you. Typically, this falls negatively exponentially; survivorship on a normal arithmetic scale falls negatively exponential.

But if you do a log transformation, then they are going to fall linearly. And this, you know, is why these values -1, -2, -3 are in, you know, survivorship, which is going to be in decimals, right? So, that is why when you do a log transformation, they come out as negative numbers. In case you are wondering why we have a negative number on the y-axis, Now, you can clearly see that on the mainland, the survivorship is much lower than that on the island. So, for example, if you look at this around age 30 months or so. Almost all the individuals are dead on the mainland, whereas a large fraction of them are still alive on the island.

So, if you look at the values in terms of longevity, the mean longevity on the mainland is about 20 months. On the island, it was about 24.6 months; more importantly, the maximum lifespan found was 31 months on the mainland. On the island, it was 45 months; therefore, these are all statistically significant differences. So, this clearly shows that there is a huge difference between the survivorship on the mainland and that on the island.

So, now what is my prediction? Based on what I just told you in the previous slide, our prediction is that on the island, the Because ecological mortality is low, there will be increased selection on late-acting deleterious mutations. Which means that the island populations are expected to age more slowly. Was that really the case? So, what Austad did was look at two parameters to figure out the rate of aging. One parameter is a physiological parameter, and the other parameter is in terms of the growth rate of the litters. So, it turns out that these opossums, you know, give birth to their young over

multiple years.

Now, when you look at the rate at which the litter grows in the first year versus that of the second year, For the mainland populations, litter growth is much slower in the second year compared to the first year. On the other hand, if you look at the island's population, there is no difference. In both years, they are essentially growing at the same rate; the litter is growing at the same rate. So, this suggests that for the mainland population, the ability of the females to Provide nourishment for their kids; that ability decreases from the first year to the second year. Now, you could have said, "Hey, what if this is because of a difference in the availability of food?" But remember, I told you so.

Austad had explicitly shown that there is no difference in the amount of food available, which is the same in both places. So, this clearly suggests that this is related to how much the mother can provide for the babies. And that ability is going down for the mainland population, not for the island population, suggesting that. The mainland population is probably losing its physiological functions faster than the island population. Similarly, the other thing that Austad looked at was the brittleness of the connective tissues.

Now you know that when an organism, for example, even humans, is young, its connective tissues are very, very flexible. Now, as we grow older, certain connective tissues, collagen in this particular case, become much more brittle. Why does that happen? That happens because there are cross-linkages in the polymer that start to take place. Because aged organisms' connective tissues become less flexible, they tend to break more quickly. And what they ended up showing, Austad, was that if you looked at the rate at which the tissue was becoming brittle, This was happening much faster, significantly faster in the mainland populations compared to the island population.

This, again, is an indicator that the island population is aging more slowly. So, this was an experiment that aimed to show that ecological mortality could affect aging. A similar experiment was conducted on Drosophila populations. This is Stearns et al. PNAS 2000, where they took two sets of populations, you know, three populations each.

In one population, they externally imposed high levels of adult mortality; they call it the HAM population, or high adult mortality. And there was another set of populations where they did not expose it to high levels of mortality. They call it the low adult mortality (LAM) population. So, if the logic that I am showing you here is correct, Then the HAM populations were expected to evolve faster aging, and that is exactly what happened. They ended up showing that the ham populations were aging faster and that their mean longevity was also decreasing.

So, this is another direct test where people showed evolution. You know, high adult mortality early in life can lead to faster aging. So, now the question is how exactly a selection shadow will end up affecting aging. And it turns out that two major mechanisms have been proposed. One is known as mutation accumulation; the other is known as antagonistic pleiotropy.

The two are actually very close to each other, and I will show you quickly. what they imply through our Excel demonstration, the one that we had used earlier. So, this is what we did right, and if you remember this simulation, we showed the lifetime reproductive success. Is this value 19.80 in a population in which there is no aging and the density-independent mortality rate remains constant at 0.1? And the reproduction at every age class remains constant at two individuals. So, this is the sum of this, and what I will do is copy and paste it over here for reference. So, this is the reference value. This is when there is, I will just call it the reference value; that is all.

So, this value of 19.806 is the sum of reproductive success across all the edge classes. Now, suppose you have a mutation that only expresses its bad effects late in life. So, what kind of bad effect is it? Let us assume for a moment that this is something that ends up reducing, let us say, fecundity in later life. So, let us assume we have this, and let us say 1, 2, 3, 4, 5. Let us say that for these 5 cases, this fecundity basically becomes 0.

So, let us start from here. So, 0 0 0 0 0, right? So, here is a mutation that has caused the

organism to lose all known forms of reproduction. For the last five age classes, you can see that the overall effect on fitness has gone from 19.8 to 19.67. So, this is what I meant by saying that if there are late-acting mutations, then the effect of those mutations on the Overall reproductive success is going to be much lower, and therefore, selection's ability to weed out this mutation will be very low.

So, mutation accumulation theory simply says that deleterious mutations that express only late in life will tend To accumulate in the population, and when that happens, these bad effects will show up as aging. So, I showed you what happens if you have, let us say, a reproduction problem. Now, let us make it even better. We said that you know reproduction is contingent upon survivorship.

So now let us have a scenario where this occurs. This mortality becoming 1, as you can see, basically means that all individuals are dying. So, I have made mortality equal to 1 everywhere, and you can see that. Even if I have made it 1 for 5 cases from 19.8, it has gone down only to 19.63. Again, saying that it does not matter whether it affects survivorship or reproduction are late-acting mutations. They are typically going to have very little effect on fitness; therefore, they will tend to accumulate in the population. So, that is the mutation accumulation stuff.

Let us make this 0.1 again. The other thing is what is known as antagonistic pleiotropy: what is antagonistic pleiotropy? So, we know that when one mutation or one allele affects multiple traits, that is known as pleiotropy. Antagonistic pleiotropy is a special case of pleiotropy where a mutation has positive effects early in life but negative effects later in life. So, let us see what happens in this scenario. So, let us assume that we have a mutation that increases reproduction in the first age class by, let us say, 3 units, from 2 units to 3 units. But at the same time, it leads to death; let us say, it makes reproduction in the last five or six age classes equal to 0.

So, something like "sorry, something like this" is correct; look at what has happened. This reproduction has gone up by 1 unit; reproduction in 5 or 6 age classes has been

completely lost. Seven age classes have been completely lost; yet overall, the fitness has increased, and the lifetime fitness has gone up, right? It is clear why this is happening; right, I said that any change that occurs earlier in life. has a much greater effect on overall fitness than any changes that happen later in life. So, there is a small change here, a large change here, but overall, the effect is positive.

In other words, such a mutation is going to be selected. Now, if you have a scenario like this, what this is saying is that all mutations that have beneficial effects early in life are going. To be favored, even if it has bad effects later in life, as long as the overall effect on fitness is positive, is a case like this. So, such scenarios are known as antagonistic pleiotropic scenarios. With this, we will go back to our slideshow. So here are the definitions: mutation accumulation theory is typically the idea that this comes from the work of Ronald Fischer and Haldane are mentioned, but the person who really made it popular was Peter Medawar in 1952. So basically, the theory is that Late-expressing mutations will accumulate more readily in the population as the force of natural selection declines later in life. If these mutations are deleterious, their effects will show up as aging: antagonistic pleiotropy theory. Actually, the roots of this theory are also found in the works of Peter Medawar. But the person who makes it really popular and kind of shows it in more detail is G. C. Williams in a 1957 paper. And what he says is that genes or mutations can have an impact at multiple ages. All mutations that increase early fitness can be selected even if they negatively affect late-life fitness. If the overall reproductive success, as I showed you, is positive, then, therefore, he suggests that there is always a trade-off between early fertility and later fertility or survival. In other words, anything that increases your reproductive fitness early on is important. In general, it will be selected even if it has some negative effects later in life. So, just to compare these two things under the mutation-accumulation theory, There would not be any difference early in life, but in late life, fitness performance will go down. Under the antagonistic pleiotropy theory, performance in early life will be favored will go up, but the performance in later life is going to go down. Now, in practice, it is actually very difficult to differentiate between these two hypotheses. And, frankly speaking, they are not really mutually exclusive either. These two kinds of mutations or these two kinds of effects can

happen in the context of different traits. So, we will talk about some empirical support for both mutation accumulation and the antagonistic pleiotropy theory.

So, this is a selection experiment in which people took samples of housefly populations. and made them reproduce early in life; that is, 4 to 5 days after eclosion. So, if you are making them reproduce earlier and earlier in life, what do you expect? All the late acting mutations, those mutations are going to go out of the purview of selection. In other words, aging is going to happen faster, or its lifespan is going to decrease. What they did in this particular case is to reduce the selection for late-acting mutations leading to increased senescence.

So, what they did was conduct the selection, and every few generations, they actually allowed longevity to play out. You know the entire lifespan, and then you saw what the maximum lifespan looked like. And as you can see, within about 25 generations, both in males and females, the mean longevity in days went down. And it went down quite a bit, you know, from about 37 to, I don't know, 28 or so, about a 9-day reduction in females. From about 28 or 29 to about 25, there is a reduction of about 4 to 5 days in the males; that is a pretty large reduction.

Interestingly, although I am discussing this in the context of mutation accumulation, If you think about it closely, you will realize that antagonistic pleiotropy can lead to a similar effect as well. So, that is why I said that it is typically very difficult to distinguish. Between mutation accumulation and antagonistic pleiotropy, experimentally. What kind of support do we have for the antagonistic pleiotropy theory? Remember, it says that you know anything that is going to have a positive effect or positive value early in life. It will have a negative value later in life that is antagonistic pleiotropy.

For example, this is illustrated by a bird called the collared flycatcher. So, there are certain birds that start breeding at the age of one. Whereas some birds do not breed in the first year of their lives, they start breeding in their second year. So, Gustafsson and Part, what they ended up showing was that. If you start breeding earlier in life, then your

clutch size, although it increases, does not increase too much whereas, if you end up foregoing reproduction in the first year of life, there will be no reproduction. Then your clutch size starts much higher, actually goes up even higher, and stays much higher for your entire life. In other words, the early breeders pay a cost by having lower clutch sizes. Now, very interestingly, if you do the kind of analysis that we did for the survivorship multiplied by clutch size or mx, it yields interesting results.

So, clutch size is basically mx in our simulation. If you multiply their year-to-year survivorship by that mx and use this You compute the lifetime fecundity and the lifetime reproductive success; you find that despite having a lower value of mx, Throughout their lives, it is the early breeders who actually end up having greater lifetime reproductive success. But the main point we are trying to show here is that if you start breeding earlier in life, You pay a cost by not being able to increase your clutch size. Similarly, do you remember when we were talking about the experiments on Drosophila for an enhanced lifespan? There was another experiment that I talked about, which was that of Michael Rose in 1984 and was reported in the same year. So, this is a very famous line of work where they had two sets of populations, each containing five individuals. B populations, called the baseline populations, were the controls. The O populations, called old populations, are the ones that have been selected for increased lifespan. So, basically, every few generations, they collected the eggs later and later in life. So, in order for a population to be able to reproduce, it had to first survive to that age, and only then could it reproduce. So, this way, there was, you know, a selection for increased lifespan, and there was a massive response. The O populations had a much greater mean lifespan than the B populations. But more importantly, what was shown was that, I mean, the prediction here was that. There will be a trade-off between early-life and late-life fecundities. In other words, the O populations will be able to increase their lifespan only by sacrificing their early-life fecundity. That was the antagonistic pleiotropy thing that we were talking about, and that is pretty much what ended up happening. So, if you look at this, this is the age on the x-axis and what you have on the y-axis.

Is the net difference between the O and B mean fecundity? So, [mean fecundity of O -

mean fecundity of B], and what you can see is that in the early part of life, this is actually negative. Which basically means B's have greater fecundity than O's, but in the later part of life, it flips. Now the O's have greater fecundity than the B's, which essentially means that the B populations are declining. An antagonistic pleiotropy, it increases its fecundity early in life at the cost of reduced late-life fecundity. And the O population is increasing its longevity, but to do that, the early life fecundity it has must be considered.

That is going down, and because of that, all those genes that would have made them better in early life are affected. worse in late life those are being selected against. So, this is consistent with the antagonistic pleiotropy hypothesis. These two are not the only examples. This particular thing is that long-lived populations will have a trade-off between early-life and late-life fecundity.

This has been seen repeatedly. So, for example, if you remember, we talked about the Luckinbill et al. experiment from 1984, They had also selected for longer-lived Resophila populations; they reported a reduction in early life fecundity. Then there was a 2015 review by Lemaitre et al., which showed that These guys were looking at natural populations: 12 bird populations, 10 mammal populations, and 2 reptile populations. Out of these 26 cases, 21 ended up reporting a trade-off between performance in early life and late life.

In other words, those organisms that lived longer had a dip in their early-life performance. but an increase in their late life performance and vice versa. So, to conclude organisms according to evolutionary theories, Organisms age because selection largely overlooks those organisms that live to late life. Or because selection has favored individuals who seek early benefits, even at the expense of later costs. So, the first part is the accumulation of mutations that the mutation accumulation theory describes.

The second part of the selection has favored early benefits, even at the expense of later costs; that is the antagonistic pleiotropy theory. Here, I must mention a variant of the antagonistic biotrophy theory, also known as the disposable soma theory. So, antagonistic

pleiotropy says that if there is a mutation that has a positive effect early in life, then even if it has negative effects later in life it is going to be selected. Disposable soma theory also talks about a trade-off, But it discusses a trade-off between reproduction and long-term somatic maintenance. So, basically, this theory says that we should look for the fitness of an organism; reproduction is what is more important.

And once the reproduction has happened, even if the organism is not really, you know, maintaining or putting. Many resources for somatic maintenance later in life do not really affect its fitness too much. Therefore, any mutation that ends up benefiting reproductive output, particularly earlier in life, Even if it has negative consequences for somatic maintenance later on, it is still going to be selected. And this negative consequence for later life fitness is what shows up as aging. So, the disposable soma theory is also a well-known theory, but since it essentially talks about a trade-off, Many people have argued that this is nothing but a subset of the, you know, antagonistic pleiotropy theory, right? This looks pretty clean, and as I showed you, there is a lot of empirical evidence as well, but this leaves one, you know the nagging thing, one nagging doubt. What is it? It is in the context of immortal organisms. There are certain organisms that we apparently call "immortals." What about those? If this evolutionary theory is correct, then we should have no immortal organisms. So, where are immortal organisms coming from? I will just deal with one case study here. Perhaps the first thing that will come to anyone's mind when they talk about immortal organisms is That is an organism called a hydra.

So, those of you who, just in case you do not know what a hydra is, It is a very tiny organism; it is a cylindrate; it is a very, you know, early-evolving taxon. And it turns out that the press and all popular science just go bonkers over this particular organism. Because you know this is the name they gave it: the Immortal Hydra. Now, the first thing you have to realize is that there is a slight catch. When they talk about it in the popular press and when they use the word immortal, they seem to mean that this organism cannot die.

That obviously cannot be correct, can it? Because if that were indeed the case, the world

would have been full of hydras by now, and obviously, that is not happening. So, it turns out this is not immortal in the common sense of the word because it can and it does die due to all kinds of external reasons. It is not that they cannot die. Hydra is immortal in the technical evolutionary sense of the word because, essentially, What happens in them is that they have these stem cells, which can renew themselves indefinitely.

So, even stem cells remember that they cannot keep dividing forever. Most stem cells will stop dividing at some point, right? But the hydra stem cells are special in the sense that they can keep dividing indefinitely, and they actually show no signs of cellular aging. Now, it turns out that hydras reproduce asexually through budding. So, if you look at this particular picture right at the bottom, do you see that bulge on the left? That is essentially a bud; so, this is how most hydras will reproduce. At some point, they will create a bud, and then that bud will detach from the main organism to form a new hydra. Now, since they can reproduce by budding like this and since their stem cells will continue to divide forever, Therefore, they can continue to bud indefinitely, and it is in this sense that they have been called immortal.

That they can keep on dividing forever, not because they cannot die, needs to be kept in mind. Now, obviously, the question is what is happening over here: why is it that the stem cells of hydra can divide indefinitely? Now, this is a question that people have really looked at in great detail, among other things. One of the major properties, or one of the major regulators of this thing, is this gene called FOXO. So, it turns out that if you knock down this gene, as was done in the paper by Boehm et al., Then this property of continuous division actually gets halted.

Now, this is a bit exciting because FOXO is a very important gene that can actually be found across. Pretty much all organisms that are there, I mean up to human beings, you know, everyone has them. So, it looks like FOXO might be one of the keys; it is certainly not the only key; it might be one of the keys to aging. However, I mean that when you try to knock down or impact FOXO across many taxa, you see that aging is affected. But that does not mean that FOXO is the only factor that affects aging, right? Similarly, you have

insulin and insulin-related pathways; they are again very critical components in the metabolic pathways. Many organisms seem to be playing a big role in aging, but are they the only ones doing so? Absolutely not.

So, there is some promise that one day we will be able to find common genes that might affect aging. In multiple scenarios, it is also clear that they will not be the only ones determining aging in that particular organism. Their effects will be regulated by many other factors. So, again, I want to emphasize very critically that although I talked about the evolutionary theories of aging and The mechanistic theories of aging; these two theories actually operate at two different levels: proximate versus ultimate. And therefore, one is saying why aging happens at all; the other is saying. The mechanistic theories say that for a given organism, what are the factors and what are the molecules? that are causing the aging in that scenario under whatever environmental factors exist.

So, a proper study of aging requires you to take both the evolutionary and mechanistic aspects into account. Without that, not much will happen. I also appreciate that I told you correctly; 3 lakh papers were published in just 10 years. Many lakhs were published before that, and probably a few more lakhs will be published between 2023 and 2025. So, it is impossible for me to give you a very good, in-depth treatment in just a few lectures. But what I have done here is just give you an overview of the various lines of thinking about why organisms age.

But then there is a lot more to it; there is a lot more information, and maybe some of it. The papers that I have cited, you know, during these few discussions, will allow you to look into those details. So, we end our discussion of aging here and move on to the next pattern that we are going to talk about. There will be sex and sexual selection, but that is what is going to happen next week. See you then. Bye.