No Theory for Old Man

Evolution led to an Equal Contribution of Various Aging Mechanisms

Alexey Turchin
Open Longevity
alexeiturchin@gmail.com
December 2023

Does a single mechanism of aging exit? Most scientists have their own pet theories about what is aging, but the lack of generally accepted theory is mind-blowing in our age. Here we suggest an explanation: evolution works against unitary mechanism of aging because it equalizes 'warranty period' of different resilience systems. Therefore, we need life-extension methods that go beyond fighting specific aging mechanisms: such as using a combination of geroprotectors or repair-fixing bionanorobots controlled by AI.

Summary

This article states that natural selection has not produced a singular aging mechanism in living organisms, but rather multiple resilience or stability mechanisms, each with a similar "warranty period" before failure. Aging is thus the simultaneous expiration of all these resilience mechanisms. Secondary effects may arise, such as one resilience mechanism impacting others or partially compensating for another's failure.

This concept echoes antagonistic pleiotropy but diverges in key aspects: it centers on resilience mechanisms (as opposed to genes), their predetermined duration (rather than a gradual decline), and their collective contribution to observable aging.

The reason for the same “warranty period” for different resilience mechanisms is that if any resilience mechanism produces lower life expectancy than needed for successful reproduction, evolution works hard to increase the duration of this resilience mechanism. Equally, overly durable mechanisms accumulate detrimental mutations, leading to a convergence in the duration and impact of these mechanisms. This life expectancy varies significantly across species based on their reproductive strategies. This can also explain quick aging in salmon: the selection didn’t care about how exactly resilience will fail after expiration date, but it was eventually beneficial for salmon that they die quickly and could become food for youngsters.

This realization has significant implications for life extension research: no single treatment can dramatically increase lifespan.

Primary resilience mechanisms include mostly first-order repair systems like immunity, stem cells, and DNA repair, and also the mechanical resilience of the cellular matrix, which many consider a key aging mechanism.

Second-order repair systems that maintain these primary repair mechanisms are almost non-existent in nature. However, many proposed anti-aging therapies resemble such second-order repairs, like stem cell transplantation.

Human aging is unique due to recent evolutionary selection for longer lifespans, which has additionally balanced the effects of various resilience mechanisms on

aging. This complicates the application to human of anti-aging interventions successful in other species.

Also, human aging evolved into a special period of "old age" in personal life history, when a person is not directly participates in reproduction but continue to preserve cultural heritage (similar to grandmother effect but more than that).

To address the absence of a single aging mechanism in longevity research, we can:

- Bolster all major resilience mechanisms simultaneously with geroprotector's combinations, akin to the More-Dacca effect seen in antiretroviral therapy for AIDS.

- Eliminate aging accelerators such as smoking, metabolic syndrome, hypertension, and inactivity.

- Explore methods to decelerate the global biological clock, including hormonal and temperature adjustments and other meta-mechanisms.

- Adopt practices similar to second-order repairs, like adequate sleep and nutrition, which positively influence aging.

- Pursue organ replacement or damage repair (SENS approach).

- Implement complex individual management systems using bionanorobots and AI for comprehensive impact.

- Develop new intervention tools like bionanorobots, potentially modified human stem or immune cells directed by external controls, controlled by advance AI.

- Alternatively, bypass aging through body replacement, cyborgization, cryonics, and mind uploading.

Even minor deceleration of aging could help many people live to see groundbreaking life extension technologies and thus reach longevity escape velocity.

1. Introduction. Statement of the problem and current research

The world still does not have a universally accepted theory of aging which is mind-blowing fact. In the 20th century, many basic theories were formed, but they are mutually exclusive or fit together only mechanically, and none of them has been empirically confirmed through a significant increase in human lifespan. As a result, many scientists either refuse to search for a theory of aging altogether, moving on to statistical studies of molecular processes, or declare ways to combat aging that ignore aging mechanisms, for example through damage treatment (de Grey) or organ and even body transplantation.

At the same time, aging phenotypically arises in almost all living beings, and it is obvious that this is some kind of universal phenomenon that must have deep evolutionary roots. Thus, we are faced with a contradiction: on the one hand, aging must have an unambiguous cause, but on the other hand, no theory of aging has been more successful than any other. That is, there should be a theory of aging, but there is none.

In other words, our knowledge about aging looks like a black hole, especially in contrast to the successes of science in other areas. For example, infectious diseases have an unambiguous cause in the form of a pathogen; we know exactly which thermonuclear reactions lead to energy release in the depths of distant stars, etc. - but when it comes to the mechanisms of such a mundane thing as aging, science stalls. (On the other hand, there are several other such epistemological black holes: these are the problems of interpreting quantum mechanics, solving the Fermi paradox, or creating a reliable model of human psychology and values.)

In this article, we will propose a solution to the problem of theories of aging by deconstructing the very idea of "aging" itself. The object of observation has been incorrectly selected: we are studying the shadow, not the process itself, the hole from the donut, not the donut itself. Here we will consider the hypothesis that aging does not really exist, but there are processes that maintain stability (protection against cancer, DNA repair, replacement of dead cells). At the same time, natural selection leads to the fact that the contribution of each of these processes is equal and selected so as to "guarantee" approximately the same expected lifespan for a given species. This creates a trap for the scientific observer: he takes this correlation for the existence of a single "cause of aging". The multiplicity of observed stability mechanisms leads to a multiplicity of mismatching "theories of aging".

Since aging exists in almost all living things, it makes sense to try to find evolutionary reasons for its formation. There are two main points of view on the evolution of aging: (a) aging as an adaptation created by group selection and having a specific mechanism, and (b) aging as an artifact of evolution associated with the weakening of selection with age, or, as a special case, antagonistic pleiotropy. Here we will not describe theories about aging as a group adaptation, since this can only work for certain species (e.g. salmon) and only with selection for a shorter life.

Aging (in the sense of decrepitude and many human age-associated diseases such as cancer and Alzheimer's disease) is rarely observed in nature - it is found only in zoos, since most animals in nature do not live to old age at all (with the exception of higher predators, including humans), and therefore phenotypic aging itself is not a product of selection. Most animals are eaten by predators when aging reduces their mobility, and before complex forms of aging manifest themselves.

The article 'Senescence in natural populations of animals: Widespread evidence and its implications for bio-gerontology' https://www.pure.ed.ac.uk/ws/files/8520436/Senescence_in_natural_populations_of_animals.pdf claims that aging exists in nature. But this article describes two types of aging - frailty and mortality (increasing with age). And then it is said that frailty is rare, but an increase in mortality with age is common. That is, the beginning of the aging process exists, but there is no old age as a separate phenotype. And this is understandable: for example, if a deer started running 10 percent slower, the chances of it being caught by a predator would increase sharply. In humans, running speed decreases after age 30. Selection - in animals - acts primarily on the very beginning of aging - on slowing down the speed of running and reproduction. Human selection also acted on stretching out the old age stage due to the grandmother hypothesis - which is why people live for decades, running very slowly.

Another article report surprise: "Contrary to findings in captivity no observable symptoms of senescence were found in older wild mouse lemurs, i.e. over the age of five". https://helda.helsinki.fi/.../7e43ce47-0cc9-46d9.../content This could be explained that only some older lemurs survived who had needed agility to continue almost normal life.

We also can see phenotypical aging in elephants and tigers, which can be explained that they are on the top of food pyramid and not in the immediate risk from predators; and in some apes which explained mutual caring. But in general, we observe aged animals in the wild much less often when we observe humans with signs of aging on a street.

We will also talk about the weakening of selection with age, but formulate the same idea differently: as the action of selection on various stability mechanisms.

As written in the article "Evolution of Aging": "A more economical evolutionary explanation of aging requires an explanation based on individual fitness and selection, not group selection. This was realized in the 1940s and 1950s by three evolutionary biologists - JBS Haldane, Peter B. Medawar (Medawar, 1952) and George C. Williams, who showed that aging does not benefit the "species". Instead, in their opinion, aging develops because natural selection becomes ineffective in maintaining performance (and physical fitness) at an old age. Later their ideas were mathematically formalized by William D. Hamilton and Brian Charlesworth in the 1960s and 1970s, and today they find empirical support" (Fabian & Flatt, 2011).

Polina Loseva, referring to Gladyshev's ideas about the evolutionary equivalence of aging mechanisms, writes: "In the organism, accordingly, protection from other, not the most important causes of aging, will become weaker and weaker, until all mechanisms of

prolonging life do not start working equally poorly, and the causes of aging do not become equivalent. Thus, the task of "identifying the main cause of aging" is doomed to failure from the outset. If such a reason existed, then there would be only one way to stop the aging of organisms, and it would immediately prolong their lives many times over. Nevertheless, science does not yet know any highly effective methods, but there are many techniques that allow you to slightly (usually about 30-50% in mice, 2-10 times in invertebrates) prolong the existence of model animals" (Loseva, 2020).

In 2020, the article "What if there's no such thing as "aging?" was published (Cohen et al., 2020), which expresses similar ideas: that there is no single aging with a single mechanism. It cannot be said that aging has several mechanisms, since then these are not mechanisms. By saying "aging", we get into a linguistic trap in which many different phenomena are combined under one concept. If before they talked about the mechanism of aging, now they talk about hallmarks, and thus recognize the multifactual nature of the phenomenon, and therefore the fact that the same word denotes many different things. At the same time, aging is defined on the one hand through damage, and on the other hand through the mortality curve, but a Gompertz-like mortality curve can also arise due to phenomena unrelated to aging. They refer to Peto's article "There is no such thing as aging: Old age is associated with disease, but does not cause it (Peto & Doll, 1997)." In particular, they note that known signaling pathways (mTOR) regulate not aging, but repair or reproduction in a cell, and only indirectly affect what we call aging. Different metrics of aging may not correlate with each other.

The main difference between our article and this one is that we show the evolutionary mechanisms working against a unified theory of aging, and designate the role of stability maintenance and repair mechanisms as the main form of stability, and artificial interventions in their work are described as repairing the repair.

So, at the beginning, we explore the epistemology of aging: what and how we can know about it (Section 2). Then we will look at how selection affects different stability mechanisms and leads to equalizing their contribution to lifespan (Section 3). Section 4 is devoted to the analysis of stability mechanisms in humans and second-level repair systems. Section 5 will consider possible counterarguments against this theory. In Section 6, we will examine how aging can be slowed down and life prolonged, despite the fact that aging has no "essence". Section 7 will be devoted to the problem of "essential biomarkers" of aging. In section 8, we will look at how the lack of aging essence affects research strategies for aging.

2. Epistemology of Aging

The epistemology of aging is a theory about what and how we can learn about the nature of aging. The existence of many competing theories and the complexity of directly experimentally confirming them makes it difficult to establish the nature of aging. Moreover, the situation looks as if this nature does not exist at all, or rather, it exists, is confirmed in some experiments, but then slips through the fingers.

The relationship between the theory of aging, the evolutionary model of aging, and the proposed therapies for aging

A good theory of aging explains where aging came from, that is, its evolutionary causes, how exactly it is implemented in the organism, and what needs to be done to stop it.

The most striking example here is Skulachev's theory, which speaks of aging as an evolutionary program, proposes the release of reactive oxygen species by mitochondria as a molecular mechanism, and at the same time is already developing the drug: SkQ ion.

This is all very convincing until we encounter another scientist who has his own theory of the evolution of aging, his own molecular mechanism, and his own startup that produces the drug. A table with a list of different theories of aging is proposed in Appendix 1, in which we listed about 30 theories of aging.

Any "molecular mechanism of aging" suggests the existence of a target for medical intervention to stop aging, and on its basis - a candidate substance for an anti-aging drug that inhibits this target. This substance is then tested on model animals, first on yeast, then on mice, on which it usually gives less and less encouraging results, as the complexity and lifespan of model animals increases, and the cost of such experiments is constantly increasing. The presence of a target and molecule usually prompts the scientist to create a startup that promotes this molecule and attracts money for further research. But as a result, finding the truth turns out to be tied to the interests of investors, which leads to certain cognitive distortions. They are interested in a unambiguous and quick solution, and require a positive result.

At the same time, we always have different levels of description. You can describe everything at the molecular level, as in Ferber's aging scheme, but such a scheme resembles a giant tangle and is incomprehensible, but it can be useful for creating computer models of aging. Aging can be described at a higher level, speaking in general about evolution, homeostasis, accumulation of errors and life strategies. Such a description is more understandable, but it is difficult to extract from it the idea of which gene we need to affect.

Testing on mice and the limitations of confirming theories of aging

Most theories of aging can be confirmed to some extent in experiments on mice or other model animals - or by examples from nature, where there are always various special cases: non-aging animals, very short-lived animals with programmed aging.

Since the diversity of wildlife is very large, any theory of aging can find confirming examples - and a refuting example. This limits the value of such confirmations and refutations: we know in advance that such examples will exist. The same applies to experiments on simple model animals: at first experiments on Drosophila confirm, for example, the theory of antagonistic pleiotropy; but the very same experiments on guppies do not damage it.

Direct confirmation of theories of aging are experiments to prolong life. The simpler the animal, the greater the life extension achieved. Mice respond to life extension through many different interventions, but the extension is usually not radical, tens of percent. In humans, such experiments are more difficult to conduct, and the effect is smaller: for example, it is still unclear whether calorie restriction has a positive effect on human life expectancy.

One way to test a theory of aging is to derive the Gompertz law from it, which describes the mortality of most living things. The problem is that the Gompertz function is relatively simple, and can be derived from different models, and also, its rapid growth "hides" the details of the process, that is, different processes can be described by similar graphs. Different models leading to the same graphs again make aging "unknowable".

Three constraints on knowledge of the nature of aging: ethics, time and money

Since we are interested not in aging in general, but specifically in human aging, the ultimate truth will be experiments that prolong human life. However, experiments on humans in the field of aging are by their very nature extremely long: decades, and also require a lot of money and compliance with many ethical and legal restrictions. In fact, there are still very few such experiments, and they cannot be carried out instantly. It is also very difficult to get money for fundamental research on the nature of aging.

At the same time, there is no ready-made experiment design that would unambiguously prove the correct theory of aging (except perhaps checking theories about turning off the aging program). The same problem exists in nuclear physics: accelerators are getting more and more expensive, they are being built longer and longer, and the information return from them is decreasing. This means that a new experimental paradigm is needed.

The difference between the definition and mechanism of aging

Timofey Glinin has well shown that it is difficult to give a meaningful definition of aging without using hypotheses about its nature, and the only way to avoid this is to define aging non-biologically, through the mortality curve, the Gompertz function, in which the annual probability of death grows exponentially starting from a certain age. But this tells us almost nothing about the mechanism of aging.

3. Equilibrium contribution of stability mechanisms to life expectancy

The main hypothesis and its strong form

In this section, we will analyze our main hypothesis about the evolutionary pre-synchronization of aging mechanisms: natural selection leads to an equivalence in the contribution of all stability mechanisms to the aging process for species whose selection went towards increasing lifespan; at the same time, the main factors of stability are repair mechanisms. In other words, repair mechanisms age first of all, and their aging rate is synchronized by selection for a certain life expectancy.

Here we are actually repeating Medawar's original hypothesis about the "shadow of selection", but we apply it not just to alleles, but to stability maintenance mechanisms, the main ones of which turn out to be repair systems. Broadly speaking, repair systems include: mechanisms for repairing DNA damage, immunity, apoptosis and all anti-cancer protection, and regeneration, that is, the replacement of cells from a pool of stem cells.

In addition, we are talking primarily about organisms whose selection went towards increasing lifespan: naked mole rats, whales, elephants and of course humans; in the case when selection did not work in this direction, there may be one cause of death, as in mayflies and salmon.

In addition, Medawar's hypothesis is formulated as if we originally had absolutely perfect genes, and then harmful mutations began to accumulate in them, reducing lifespan, which is true only for selection towards reducing lifespan. When selection goes towards increasing lifespan, it must create new stability mechanisms (including second-order repair systems, that is, repairing repair mechanisms).

The strong form of this hypothesis is: all theories of aging have approximately equal predictive power. In this case, not only the contribution of individual molecular mechanisms is leveled, but also the predictive power of different high-level theories. We look for antagonistic pleiotropy - and find it; we look for an aging program - and it also works a little.

This hypothesis can be falsified if we find a single molecular mechanism of aging, and using it, can significantly increase human lifespan. Confirmation of it will be the derivation of all the main signs of aging from it, as well as the Gompertz curve.

Alignment of stability mechanisms during selection

The alignment of stability mechanisms leads to the fact that in humans, relatively unrelated groups of age-associated diseases appear at about the same age: cancer, heart disease, brain disease. Moreover, the main groups of these diseases have approximately equal probabilities of around 20-30 percent, that is, there is no single dominant manifestation of aging. This means that selection "planed" the stability mechanisms to approximately the same level. Humans do not have a single system that would have "too much stability," for example, could work 300 years; all systems age.

This can be illustrated with an example from industry: if a factory is going to make a car with a projected mileage of 100,000 kilometers, then it will purchase components with a projected service life of about 100,000 km (in reality a little more, for example, 120,000, since in order to provide a failure probability of less than X, it is necessary to multiply the probabilities of maintaining the stability of each of the parts, which are distributed normally: that is, the probability of machine failure is less than 0.1 requires a failure probability of 0.01 for each of the ten parts as a first approximation). It is important here that the plant has no point in purchasing some spare parts with a mileage of 300,000 km,

since they will be more expensive, but will never manifest themselves during the service life of the car. Just as the plant will not purchase parts with a mileage of 50,000 km, since they will inevitably break down before time. That is, selection for a certain life expectancy of the system implies selection for the life expectancy of the parts - not less, but not much more either.

Another example of the long work of selection to prolong life is the naked mole rat, which has several additional stability mechanisms. Natural selection in mole rats was so strong that they have negligible senescence. These stability mechanisms include enhanced cancer protection, a special form of hyaluronic acid, slowed metabolism.

On the contrary, in species with low life expectancy for external reasons, the cause of death from aging is often one: for example, neoplasms in mice or the death of the imago in short-lived butterflies. That is, one of the stability systems is "trimmed", and selection does nothing to fix it.

It can be assumed that evolution aligns different aging mechanisms, as a result of which weak stability systems are selected to the level of more durable ones, and more durable ones degrade towards weaker ones, and at the output different aging pathways turn out to be synchronized. An interesting thing happens. Imagine that there is some animal that atherosclerosis kills on average at 50, cancer at 70 (if it lives that long), and Alzheimer's disease at 80. And this species of animal finds itself in a situation where there is selection for increased longevity. First of all, selection will work against atherosclerosis, since few will live to cancer and even less to Alzheimer's.

At the same time, there will be no selection at all for Alzheimer's. As a result, the frequency of atherosclerosis will decrease, but the frequency of Alzheimer's will increase, since there is no selection against it at all (similar to how insects living in caves go blind - there is no selection that knocks out visual impairing mutations), and at the output we will have an animal in which atherosclerosis is 70 years old, cancer is 70 years old, but Alzheimer's is also 70 years old. That is, there will be an alignment of different aging mechanisms until they become equally probable and at the same age. As soon as one of the aging mechanisms tries to become the main one, the forces of selection will immediately work against it, like a plane against a knot, and again level it with all the others.

Moreover, the number of aging mechanisms increases with age for the same reasons: if there are only two or three main aging mechanisms, then selection for longevity is easy to fight against them, and it increases life expectancy until new and new stability maintenance mechanisms become "necessary".

The synchronization of aging mechanisms creates the illusion of the existence of some kind of single hidden aging mechanism and unfounded hopes of easily turning it off. This is written a lot about by Cohen et al. (Cohen et al., 2020).

An example of such alignment is the decrease in the probability of cancer (per unit body volume) with increasing body mass and life expectancy. An example of such work: an

elephant (which has a large body mass and thus a large number of cells and a higher risk of cancer) has 20x2 copies of the P53 gene in each cell, while a human has only 2 (one from each parent). This is a pro-apoptotic gene that protects the cell from turning cancerous.

Therefore, elephants get cancer much less frequently per unit body mass. In elephants, cells always choose the apoptotic pathway rather than DNA repair in the event of DNA damage, which also reduces the likelihood of cancer. Different large or long-lived animals have developed different mechanisms to combat cancer, resulting in a roughly equal probability of cancer for mice and humans. This is known as Peto's paradox: that larger animals with more cells have the same level of cancer incidence as smaller animals. At the same time, the number of cells within a species does affect the likelihood of getting cancer: taller individuals within a species get cancer more often. Peto's paradox is usually explained through evolutionary adaptation. To test it, a line of mice was bred with four copies of the P53 gene instead of two and an attempt was made to chemically induce cancer in them. In the control group, 11 out of 12 mice became ill, and among the "super mice" - only 4 out of 12.

Arguments in favor of the absence of a single aging mechanism

If aging were determined by only one single molecular mechanism, then failures in its operation would lead to much greater variability in lifespan, especially if it were an "aging program" leading to human "self-liquidation". From time to time, almost immortal people would be born. However, even in the "blue zones" of longevity, people live on average only 10-20 percent longer.

In addition, it has been noted that the root cause of aging cannot be a process that changes faster than aging itself. For example, blood immune cells are replaced in days and weeks, and therefore the depletion of these cells is not the cause of aging.

The peculiarity of human aging

In humans, natural selection worked to increase lifespan over the past few million years: it has doubled compared to chimpanzees, and apparently compared to the last common ancestor.

This happened because the pressure of selection from death from predators decreased in humans, and the benefit of longer survival appeared: the transfer of knowledge and caring for grandchildren required a longer lifespan. As a result, old men-sages, carriers of knowledge about culture, became necessary (this is still before writing, now they are not so necessary, and the evolutionarily fixed desire to "teach" and tell stories in old age remained) plus caring grandmothers involved in raising grandchildren. According to the book "The Secret of Our Success: How Culture Drove Human Evolution, Domesticated Our Species, and Made Us Smarter" (Henrich, 2015), individual preliterate tribal cultural traditions also evolved, accumulating "useful" mutations in the form of taboos and strange rules (such as pregnant women are not allowed to eat shark meat - later it turned out that it

contains a toxin). A long period of neoteny - a very long childhood in humans - was needed to learn the huge amount of new knowledge. But such training required experienced old teachers. Thus, humans are one of the few species in which the presence of old people is necessary (was) for survival. In the current era, when knowledge is becoming obsolete rapidly, the practical significance of the elderly is decreasing, which is reflected in the labor market bias towards the desire to hire young employees. The grandmother hypothesis speaks only of preserving the lives of women after menopause so that they can care for their grandchildren, but its natural generalization is the idea that the longer life of the elderly was necessary to preserve cultural information, since before the advent of writing, the human brain was its only carrier (Markov has a theory about brain size and the volume of culture preserved. https://www.youtube.com/watch?v=AERQrIyk7og)

In nature, chimpanzees live about 15 years, in captivity from 31 to 38 years and the official record is 63 years, that is, the life expectancy of our closest relatives is about half that of humans, which means that natural selection has worked to prolong it.

Moreover, it can be cautiously assumed that different ethnic groups of people also have different life expectancies, and that this may be related to the need to transmit the tradition of knowledge, as, for example, among Ashkenazi Jews, who lived in relatively caste-like conditions for about 1000 years and were engaged in jewelry, accounting and Talmudism. The average life expectancy of Jews in England is 5-6 years longer than the population. However, the increased life expectancy of Ashkenazi Jews came at a price in the form of a higher prevalence of short stature (due to lower IGF-1 gene activity). According to Nick Barzilai, this is due to three mutations: one leads to an increase in good cholesterol 2-3 times, another reduces thyroid activity, lowering metabolism, and the third alters the shape of the growth hormone, which protects against cancer and diabetes. I note that in general primates diverged from rodents about 90 million years ago, and apparently all this time they have been pumping up their sizes and life expectancy. On the other hand, in flies, selection for prolonging life occurs quite quickly in experiments: in several generations.

So, after the separation of rodents and primates about 90 million years ago, selection in primates went towards increasing lifespan (primates live longer than representatives of other orders of the same weight) (Judge & Carey, 2000).

Since selection worked to increase human lifespan, all simple solutions to increase lifespan have already been found by evolution, and what helps mice will not help us much. In addition, it is selection for increased lifespan that leads to equalization of the contribution of various stability mechanisms, and each individual "aging mechanism" can give only a small gain if canceled.

All this is very bad: trying turns out to be like a hydra: you cut off one, 7 grow. There is no single mechanism - there is no single cure. On the other hand, if the number of aging mechanisms is large but finite, then all of them can be blocked. In addition, it can be assumed that there are evolutionarily formed mechanisms of "anti-aging" lying in the field of immunity and regeneration, which can be used in some way to strengthen them.

But on the other hand, "old age" itself appeared - a long period of life when a person can neither reproduce, nor run, nor feed himself, but at the same time continues to retain the ability to process information. Medawar believed that aging does not have time to manifest itself in nature at all, but a recent study showed that there are a number of species where observable aging occurs. Still, aging in nature is much less frequently observed than in human society, primarily because of predators and the lack of animals caring for each other. This means that it is impossible to speak of the evolution of aging as the evolution of a trait, since it did not have time to manifest itself. Just as it is absurd to speak of the evolution of Alzheimer's disease, which no one lived to see before. But we can talk about the evolution of systems for clearing the brain of harmful protein aggregates.

Time as the essence of aging?

Aging has no single mechanism - everything falls apart at the same time and at all levels. However, the common denominator of all theories of damage, accumulation, dysregulation, increasing entropy, and execution of aging programs is time.

Time acts on the organism in such a way that it leads to aging. Accordingly, if we could affect time, we could slow down aging. Only flights at speeds close to the speed of light and falling into a black hole can slow down time itself - and this is not yet achievable.

But we can influence how the organism "senses" time. It can feel it directly, through the rate of damage, and through some kind of clock.

So, we need to either reduce the amount of damage per unit of time - or affect the clock. A number of ideas in the fight against aging are based on reducing the number of damages per unit of time: reducing oxidative stress and slowing down metabolism in general (as in the naked mole rat). Or even eliminating radioactive potassium from the diet. As well as avoiding stress, injury, toxins, etc. But all this does not lead to stopping aging, because time affects the organism in many ways.

Or we can influence the clocks of aging. There are several types of biological clocks:

1) Hormones. Certain hormones are secreted at different periods of life. Sex hormones lead to accelerated maturation and at the same time accelerated onset of aging. Therefore (probably) eunuchs live longer than ordinary men, according to data on Korean eunuchs.

2) Telomere shortening during cell division.

3) Epigenetic clocks within the cell that cause certain genes to be silenced by methylation. With age, the gene expression profile in the cell changes. However, the question arises here - is methylation just a biomarker of age, or a real clock, that is, a kind of clock generator that sets the order of stages of biological processes? Of course, we are interested in real clocks. The most famous are the Horvath epigenetic clocks, which measure the methylation of 353 sites in the genome from different tissues, and which can predict biological age (time left to death) quite accurately. It is unlikely that these 353 places where the level of

methylation is measured are directly related to the cause of aging, but rather their methylation reflects some general process. However, here we fall into the same statistical trap that all Alzheimer's disease research falls into: since everything deteriorates in the aging and diseased brain, whatever is measured correlates with Alzheimer's: heavy metals in the brain, bacteria, weakened immune system function. And if everything correlates with everything, then the very fact of correlation tells us very little about one main cause, if there is one at all.

4) Endocrine clocks within the hypothalamus. The hypothalamus produces hormones that control the production of other hormones, for example, in the thyroid gland. The hypothalamus also controls growth and puberty using gonadoliberin, which stimulates the secretion of gonadotropic hormones. The hypothalamus also secretes the hunger hormone orexin, which can increase lifespan.

5) Involution of the thymus as an aging regulator. The thymus is involved in training immune system cells, but begins to age early, from 16 years old, which ultimately leads to an increased likelihood of cancer, since the lymphocytes trained in it are involved in hunting down degenerate cells. Here is where Dr. Beloshveikin explained in detail how the five substances used by Gregory Fahy to rejuvenate the thymus are indeed long known as factors in its health (including zinc, vitamin D, and growth hormone, DHEA and metformin), but the growth of the thymus itself is not a measure of its health. In a sense, Fahy used the "more dakka" bombing principle, which is also used in the Bredesen protocol for Alzheimer's. Thymus transplantation research is underway (in mice).

The accumulation of damage is also a kind of clock in a sense, if it occurs at a more or less constant rate.

So, there are many clocks; they are all evolutionarily synchronized for each species according to its lifespan. The essence of aging once again slips through the fingers like an ancient bone, crumbling into dust. Maybe the essence of aging is decay itself? We are looking for an object, but in fact we need to look for decomposition.

Moreover, many processes that accelerate aging look like an acceleration of time (radiation). Atherosclerosis accelerates time, namely, the rate of division of bone marrow stem cells, which as a result age faster, since they experience clonal hematopoiesis, namely the numerical dominance of mutant cells (Heyde et al., 2021).

Reductionism, causality and the search for a single cause

The search for a single and sole, main mechanism of aging, its supercause, is a reflection of the general reductionism in modern science, that is, the desire to reduce a large whole to a set of simplest elements. See Ivanov-Petrov's post about how this leads to the emergence of absurd theories that explain the entire complexity of the historical process through some single phenomenon, as in Diamond's "Guns, Germs and Steel".

However, an alternative view is the denial of causality and the reduction of everything to statistics. Everything correlates with everything; everything deteriorates in an aging organism. Any pair of parameters can be taken and it can be shown that the deterioration of one leads to the deterioration of the other.

The third attempt to solve the problem: this is the construction of super complex schemes of interaction between molecular processes. But such a model, on the one hand, is never complete, and on the other hand, it is not accurate: there is backlash in its nodes.

In general, the very idea that a phenomenon can have a single cause is wrong. Even influenza has a cause not only in the virus, but also in weakened immunity.

References to complexity explain nothing. To say that something is complex is simple. There are general principles for describing complexity - synergetics, chaos theory, attractors.

So, neither "one cause", nor statistics, nor a model of molecular processes, nor a description of complexity as "complexity" work. One would like to suggest that successful models can work. Such a model is understandable on the one hand, and on the other hand, it well describes most of the observed complexity and allows it to be controlled. An example of such a model is the theory of the "natural layout" as the cause of the origin of primitive art (A.D. Stolyar, 1985).

The fractality of aging

Above we have shown that aging is evenly distributed across different stability mechanisms, which make an equal contribution and have an equal probability of death. However, the uniformity of the contribution goes further. As a result, aging becomes a fractal, that is, a self-similar process at different levels of organization.

The fractality of aging manifests itself in two circumstances: (a) aging occurs at all levels of organization, from large proteins to tissues and organisms, and (b) the complexity of aging does not decrease as we delve into the details of the process, just as the Mandelbrot set contains many details at any magnification level.

Alexey Moskalev formulated the fractal theory of aging in the article "Evolutionary Views on the Nature of Aging", 2010 (Moskalev, 2010), as follows: “In our opinion, the existing ideas and facts in modern gerontology are quite sufficient to try to build a consistent evolutionary theory of aging. The first thing to take as a basis is the multilevel and complex nature of the phenomenon of aging, then the echelonment of the stages of its appearance in evolution. It gives the impression that with the emergence of each new level of complexity of life, a type of aging corresponding to it appears. Thus, when modeling the process of evolution of aging, one should recall the self-similar (fractal) nature of the phenomenon of life as a whole. Despite the fact that the fractal-like nature of the phenomenon of life has been written about quite a lot, the fractal nature of aging (a

phenomenon generated by life and limiting it) has never been put forward by anyone before."

He then provides a table that links the sequential emergence of different levels of living system development, from self-replicating molecules to multicellular organisms, with corresponding aging mechanisms - and compensating anti-aging mechanisms. In this table, prelife is matched with such anti-aging mechanisms as repair and utilization of damaged molecules, at the cellular level apoptosis is added, and when eukaryotes appear, meiosis, antioxidant systems, autophagy, oocyte selection are added; then, at the level of organisms, all this is supplemented by regeneration from stem cells, as well as systemic compensation methods. That is, the complexity of the organism leads to new mechanisms of aging and new ways to protect against aging, for example, only multicellular organisms can get cancer, and only those with a nervous system suffer from Alzheimer's, and accordingly, new compensatory mechanisms are selected. As a result, aging occurs at all levels of organization, from protein to systemic.

At the same time, what is aging at one level becomes a mechanism for renewal or anti-aging at a higher level: the cell ages due to the Hayflick limit, but this protects the organism from cancer; likewise, the aging and death of individual organisms leads to the rejuvenation of society.

Decelerators and accelerators of aging are not a mechanism of aging

Aging can be accelerated in various ways (radiation, stress) and slowed down slightly in several ways (mTOR inhibition, calorie restriction). But these tools are not the mechanism of aging and do not act on it directly.

Example: if you load a car, it will go slower, and if you remove everything extra, it will go faster. But this tells us nothing about the nature of its engine. Moreover, some "aging decelerators" may simply be activation of organism modes that are already there, something like hibernation for protozoa, thanks to which they survive adverse environmental conditions.

Evolution as neural network training

Richard Watson suggested that genetic networks are trained like neural networks during evolution. An important property of neural networks is that knowledge in them is represented in a distributed, diffuse manner. The main result is reached by many paths (Not always so: there may be one neuron responsible for a certain property, but it itself relies on the output data of many previous neurons.)

The outcomes for the genetic network are the organism's properties in ontogenesis. But each of these properties is obtained by optimizing many parameters, including lifespan. Millions and billions of parameters are regulated until the desired result is achieved.

An example with catalase

People go gray because the gene encoding the catalase enzyme is destroyed in their follicles. This enzyme removes reactive oxygen species, namely hydrogen peroxide. It would seem that here it is, the universal mechanism of aging! But there are people with a congenital lack of catalase, and their only problem is mouth ulcers.

4. Stability mechanisms

Stability mechanisms and first and second order repair systems

In this chapter, we will describe "aging" through the disruption of stability mechanisms.

Stability is the ability to return to the original normal state after a certain deviation. In aging, stability decreases at all levels: to falls, to infections, to the emergence of precancerous cells. More broadly, stability is the ability to remain unchanged over time.

Similar ideas are proposed by Karnaukhov in his informational theory of aging: “The informational theory of aging suggests that the decrease in the functionality of the whole organism and its systems is the result of a decrease in the functionality of cell recovery mechanisms caused by the accumulation of genomic damage in cells” (Karnaukhov et al., 2017).

When stability exists, there is no aging, and the probability of death in response to external or internal events is negligible. Decreased stability means an increased likelihood of life-threatening illnesses. That is, decreased stability is a "pre-pre-disease," as Blagosklonny called aging.

Stability cannot be taken for granted. A clay doll will immediately collapse if a skeleton of sticks is not inserted into it. The stable existence of living things is ensured by many stability mechanisms. Stability mechanisms are not just individual alleles of genes associated with greater or lesser longevity, but complex adaptations whose operation is regulated by many genes. Here we are interested in stability mechanisms against internal damage that accumulates over time, that is, aging processes.

What are the stability mechanisms made up of? These are complex phenotypic traits encoded by groups of genes that express one or another form of stability. For example, the hardness of bones and its preservation with age. In other words, these are functions of the organism. Most functions must have a certain stability, no less necessary for the required lifespan. However, if they have excessive stability, it will be destroyed by random mutations, as required by Medawar's theory of selective shadow.

In addition, a living organism differs from a car in that it has many repair mechanisms:

1. immunity,
2. stem cells, growth and regeneration,
3. apoptosis of damaged cells,

4. clearance of cellular debris,
5. DNA repair
6. protection against cancer through the Hayflick limit, etc.

Most stability mechanisms cannot exist for long without repair systems: bones must grow, wounds must heal. There are many phenotypic signs of aging that seem unrelated to repair mechanisms, and there is simply mechanical aging - for example, tooth wear. However, in fact, humans have a mechanism for regenerating teeth - growing a second set of teeth after milk teeth fall out. And in geckos and some mammals, teeth are constantly renewed. However, constant tooth regeneration was not necessary for humans, since the existing teeth were enough for adult life.

That is, tooth aging (loss of stability) can be described as a lack of tooth regeneration (a problem with the repair system).

Aging of repair systems makes the main contribution to the rate of aging (it is mutations in genes associated with them that lead to the greatest variability in lifespan), and therefore in the future we will mean them in particular when talking about stability mechanisms. For example, one of the causes of progeria is impaired DNA repair due to a defective lamin A gene. There are significantly fewer of these repair mechanisms than there are functional systems in the organism, which is good news, since it means a finite number of possible points of intervention in the aging process.

But are we not deviating here from the idea that aging has "no essence" by proclaiming the disruption of repair mechanisms as the main mechanism of aging? It can be assumed that the evolutionary alignment of the contribution of different aging mechanisms primarily concerned the contribution of different repair systems. That is, the effect of different repair mechanisms is pre-synchronized in such a way as to provide the required lifespan, but no more. For example: the repair system is turned off in salmon, and it begins to "rot alive" when it goes to spawn. This is often cited as an example of a programmed aging program. But here the service life of its repair system is selected for its lifespan and no more.

The question arises whether there is a second order repair system, that is, repair of repair systems? In ordinary life we see many examples of repairing repair systems. For example, if a cleaning lady in a company is not coping, we fire her or hire an assistant for her. The preliminary assumption is that most living organisms do not have such a system, since this would mean the presence of a single aging control center and would manifest itself in the more frequent occurrence of "immortal" animals and people in whom this system is hyperactive. In the example of the enterprise, the dismissal of the cleaning lady is possible only if there is a director who is able to evaluate her, that is, a single control center for the process. And if the director does not cope with the selection of personnel, then he either needs to be replaced or improved.

However, we can try to create such a higher-order repair system, and then it would be a solution to the aging problem. For example, in the state as a social machine there is such a system - it is the internal security service of the police, as well as cross-control between

different law enforcement agencies, and finally the central government itself, which is able to reform law enforcement agencies if they become too corrupt.

It is possible that some rudiments of such a system of "management of management" also exist in a living organism. This may be a program for managing the development of an organism or correlations between different repair systems. All ideas about programmed aging look in this direction. It would be worth looking for such a system in species with negligible or negative aging (decrease in mortality rate with age).

If the hypothesis about the evolutionary pre-synchronization of aging mechanisms is incorrect, then there should be a conductor system for aging. Moreover, the unknowability of aging can lead to the fact that such a system both exists and does not exist - that is, the pre-synchronization of mechanisms extends to the second level repair system as well, and therefore its ability to regulate aging is limited.

So, we have proposed the following description of stability systems:

1) Mechanical stability systems: strength of DNA threads, hardness of bones, partly the intercellular matrix.

2) First order repair systems: DNA repair, stem cells, cancer protection systems, immunity, etc.

3) Second order repair systems - hypothetical: central regulation, growth, aging program (as an anti-second order repair system), interrelation of repair systems, and self-repair. Or artificial: replenishment of the stem cell stock.

Stability maintenance systems

All stability systems can be described through high-level repair systems. This is a convenient but at the same time simplified model, and there are other models (for example, aging as a continuation of Dilman's development program). Since selection acts on the result (prolonging life), not on specific aging mechanisms, its effects at the mechanism level are extremely scattered and correspond to different theories. In the same way, information in a trained artificial neural network is presented in a scattered form, and therefore it is difficult to say exactly what each specific neuron does or what the principle of information processing is.

Many of the breakdowns in repair systems are associated with the generally recognized signs (hallmarks) of aging proposed in the famous 2013 article. These hallmarks are: genome instability, telomere depletion, epigenetic changes, loss of proteostasis, dysregulation of nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication.

Table 1. First order repair systems, signs of aging and genes associated with longevity

Repair system	**Character of aging**	**Enhanced forms in some species**	**Interventions to improve**	**Hallmarks of aging associated with this system or its failure**	**Genes affecting lifespan**
Immunity (those aspects that are aimed at destroying cancer cells and repairing damage)	Involution of the thymus decrease in the number of naive immune cells, inflammaging		Regeneration of the thymus using 3 substances: metformin, growth hormone and DHEA Fighting inflammaging		
Cellular protection against cancer: Hayflick limit	Cessation of cell division		Telomerase gene therapy	Cellular senescence, telomere attrition	FOXO, Telomerase gene
Cellular protection against cancer: P53 apoptosis genes		An elephant has 20 copies of this gene	CRISPR?		P53
DNA repair in the cell	Progeria in case of violations			genomic instability	sirtuins
Regeneration and growth. Tissue renewal using stem cells;			Transplantation of own bone marrow stem cells	stem cell exhaustion	
Elimination of intracellular debris	Alzheimer's disease?				
Maintaining the stability of the intercellular matrix	The matrix regulates cell function through the niche. Fibroblasts are responsible for matrix restoration.	Special form of hyaluronic acid in the naked mole rat		altered intercellular communication??	
Antioxidant systems: reducing damage from reactive oxygen species		In the naked mole rat, the expression of genes protecting against oxidative stress is increased		mitochondrial dysfunction	FOXO?
Decreased metabolism and slowed development; neoteny		Lower body temperature in naked mole rats, periods of hibernation; decreased activity of insulin-like growth factor in		deregulated nutrient sensing	IGF-1

		some people			
****Chaperones**: restoring the correct shape to proteins damaged by heat shock.**					

Many animals that have well-developed regeneration systems also live very long, for example, koi carp, which live up to 200 years and are also very resistant to various kinds of damage. Axolotls live up to 15 years due to developed neoteny and ability to regenerate. As a result, if anti-aging means regeneration and error correction systems, then aging turns out to be the failure of regeneration systems, that is, the accumulation of errors not in the organism itself, but specifically in damage repair systems. In humans, these systems include the immune system, all stem cells, as well as intracellular damage repair systems: garbage disposal, apoptosis, DNA repair. In Rose's classic experiments in 1984 on selection for increased lifespan in fruit flies (which grew from 60 to 120 days), increased viability of flies and increased resistance to poisons (ether fumes) was also observed. Gladyshev showed that in longer-lived animals, DNA repair systems are more active (in the liver, where the load is greater) (MacRae et al., 2015).

Another example is hair follicle aging: stem cells constantly divide in it under normal conditions, then become hair material. However, with constant division, genetic errors accumulate in these cells, and more and more often they themselves undergo apoptosis, resulting in the death of the stem cell population in the follicle, the hair stops growing, and baldness occurs. That is, hair aging is caused by the accumulation of errors in the hair regeneration system, resulting in its self-liquidation so as not to become cancerous. Graying of hair is associated with a decrease in the level of the enzyme catalase, which decomposes hydrogen peroxide, essentially a reactive oxygen species.

Repair systems and deriving the Gompertz curve formula

Imagine we have a janitor who takes out the trash from an apartment. She can take out 100 units a day, and 50 units are generated in our apartment per day. Then we will have almost ideal cleanliness. Now suppose the janitor's capacity has dropped to 70 units, and the amount of garbage has risen to 80 units. Then 10 units accumulate every day, and the apartment will be filled with garbage in a finite amount of time.

A linear decrease in the quality of the repair system over time leads to an exponential decrease in the quality of the repaired system, and, accordingly, to a double exponential of the number of breakdowns over the entire elapsed time, that is, to a mathematical formulation of Gompertz's law.

In addition, repair systems have an inflection point: when the number of errors per unit of time is greater than they can correct. Only from this point in time does the number of errors begin to accumulate, until it leads to an irreversible catastrophe. It can be assumed that for humans this is about 10 years old, when the probability of death begins to increase with age.

Natural second order repair systems

Is there in living organisms a second order repair system, or is it limited to just the usual repair systems that then fail and lead to aging?

There does not seem to be a specialized system that deals only with repairing repair systems. However, living organisms have systems that control the repair process, and therefore are closer to second level repair. The higher the level of the repair system, the more its centralization and universalization, since it manages other error correction systems from this center.

An example of such a central system is the mTOR protein system, which at the cellular level determines whether the cell will grow or engage in self-repair, and the main candidate geroprotectors regulate this system: calorie restriction, metformin, resveratrol and rapamycin, but act at different points in the mTOR-related molecular pathway.

Sleep. At the level of the whole organism, sleep resembles a second order repair system. In sleep - in a way that is still not very clear to us - simultaneous repair and garbage disposal of cells occurs both in the brain and in the intestines (free radicals kill cells there if there is no sleep). The same can be said about rest in the broad sense: a trip south allows you to get the right amount of sunlight, etc.

Hormesis - a stress response and transition to repair mode - can also be considered a repair management system.

Physical activity also initiates repair at all levels. That is, a person runs not to get somewhere, but to turn on repair systems that increase muscle size, etc. and which are activated in response to microdamage to muscles during exercise. If it were not for this compensatory response, sports would be completely harmful.

Intelligence as the essence of anti-aging

Imagine we have a repairman who repairs some complex device. Obviously, he must understand how this device is constructed, then understand how it can break, and then solve the riddle of how to diagnose the nature of the breakdown based on observable indicators. To be fully able to do this, the repairman's intellect must be equal to or even superior to the intellect of the device's creator. Since he has to solve many inverse problems: based on observable symptoms, calculate the essence of breakdowns. Thus, intellect is the essence of repair.

However, intellect is very expensive. Evolution, when it created repair systems in the body, could hardly have led to the creation of very smart systems. Although, for example, the immune system is very complex and interesting. The system of generating the right antibodies and then delivering them with killer cells has a high level of optimization. Here we can recall Yudkowsky and his idea that intelligence can be measured as the force of optimization, that is, a measure of anti-entropy.

To avoid the complexity of repair, evolution has come up with several "life hacks".

The first is the complete replacement of a faulty system: it broke, throw it away, buy a new one. For example, apoptosis of cells and their replacement with new stem cells.

The second is the search for typical errors according to predefined templates. This is how the DNA repair system looks for and fixes single nucleotide substitutions and splices DNA breaks. And if it fails, it triggers apoptosis. This is how most people repairmen work: they look for typical errors according to a template and then replace the faulty unit as a whole.

These life hacks are enough to make repairs as long as the damage level is low - and then it is more profitable (for evolution) to replace the entire organism, that is, death and new generations

In other words, the limitation of human repair systems is related to the limitation of the intellect of repair systems. And this limitation means the inevitability of aging. We amplify these repair systems by adding our intellect: this is medicine. In the future, we will amplify them even more using big data, personalized medicine and AI (Batin et al., 2018).

Alternatively, this can be stated: aging is the increase in the complexity of damage at all levels of organization (fractality according to Moskalev). Aging has no single simple mechanism. Therefore, no simple tool can completely stop aging. The ideal tool for stopping aging must have infinite complexity (like, for example, a robot that can reassemble a shattered cup - more complex than making the cup). At the same time, any repair tool itself tends to break down, accumulate errors and make mistakes, like Maxwell's demon (as described by Feynman).

Of course, cells may turn out to be much smarter than they seem (see video of a lymphocyte attacking a microbe): but then we need to study what exactly controls their complex behavior, where the "brain" of the cell is located, and we cannot get away with separate chemical pathways to explain aging. And still, the cell has a limit to the complexity of tasks it can solve as a repairman.

Since the cell does not have the intellect of Dr. House, the complexity of repair tasks it can solve is limited. This means the inevitability of aging when the complexity of damage exceeds a certain threshold.

Interaction of repair mechanisms

Above, we hypothesized that the stability mechanisms represented in humans by repair mechanisms are selected by evolution for the same lifespan. And, accordingly, we assumed that they act independently, but this is true only as a first approximation.

If we have a house standing on five pillars, and one broke off, then the load on the remaining four will increase, and they will wear out faster. The same with atherosclerosis accelerating aging of the hematopoietic system (Heyde et al., 2021).

The company Gero applied the developments of synergetics to analyze the causes of aging. They used a self-organized criticality model. An example of this: when the slope of a sand pile reaches a critical level, everything collapses literally. From their point of view, aging is caused by organized criticality in the accumulation of errors in the genome, which begin to grow exponentially after reaching a certain critical level. This is especially noticeable in the genesis of cancer: according to one theory, the cell first loses stability and begins to experience many more mutations, and only then do 5-6 critical mutations occur in it that lead to a tumor.

That is, chaos leads to increased chaos, and we have all seen this in the form of increasing chaos in bureaucratic organizations. So the essence of aging turns out to be self-amplifying chaos. This is not just a "hole from a donut": it is the next degree of non-existence of order. Hence the fractality.

The reverse - good - side of this is that stability systems can, within certain limits, help each other and exchange the results of their optimization. If cellular protection against cancer fails, immunity may help.

Moskalev writes: “In our opinion, the deviation of the distribution of life expectancy from the normal one testifies not so much to the aging program as to the “buffer capacity” of protective mechanisms that delay and compensate for the accumulation of random errors and suppression of the body's functional capabilities” (Moskalev , 2010).

Positive feedback between aging mechanisms and central regulation

Evolution makes the "warranty period" of all stability mechanisms approximately the same. However, in humans, the lifespan of functions is not just the same: aging of all of them occurs simultaneously, as if there were a central regulator.

Such synchronization without a regulator can be explained by positive feedback between different aging mechanisms, which leads to their additional synchronization. For example, a person began to gain more weight, it became more difficult for him to play sports, and as a result he began to gain even more weight. But the strength of these positive feedbacks is suppressed by selection, so that the system does not immediately go into overdrive.

In addition, central regulation has not gone anywhere, primarily through hormones and regulation of the development program. Just the scale of its contribution is limited by the same evolutionary forces: you cannot issue a command for a longer lifespan without

collecting the entire system from longer-lived elements. That is, there is some regulation of the rate of aging, but it cannot significantly slow down aging with its help. The theory is both true and false at the same time.

The article Aging in complex interdependency networks (Vural et al., 2014) states that the "shadow of selection" should predict a monotonic increase in mortality, not the Gompertz curve, and that not all mutations harmful in old age promote early reproduction, and introduces the assumption that the object of selection was a network of interconnected but error-prone processes. Mathematical modeling showed that the probability of disintegration of such a network is described by the Gompertz function, that is, a double exponential and, therefore, aging should be structured in the same way. We can assume that these processes (connected in a network) are primarily not the functions of the organism, but the stability systems.

Interaction of stability maintenance systems

So far we have considered the problem of aging at a highly theoretical level and created one of the possible models, certainly not complete, but interesting. It introduces the idea that lifespan depends on several independent stability maintenance systems pre-synchronized by natural selection. It is clear that in reality these systems are interrelated, and if something flies off, the other will crumble. And the allocation of individual stability systems may also be arbitrary.

If you look closely, there is also a hierarchy between damage repair systems (see the hierarchy of aging mechanisms from Moskalev above). For example, if the internal cell repair systems fail, it undergoes apoptosis or is killed by leukocytes, and then a new stem cell comes in its place. As a result, there is a hierarchy of repair systems: stem cells at the top - below immunity - below DNA repair. Stem cells, in turn, can be regulated by the niche in the intercellular matrix. But the matrix can also be repaired by the work of fibroblasts (but not completely - some types of crosslinks cannot be destroyed, according to Moskalev and Fedintsev).

The interaction of repair systems with each other is not quite the same as repairing the repair. This is more like level 1.5.

An example of how the aging of an error correction system itself turns out to be the cause of aging is inflammaging. Inflammation is a natural immune response to damage, that is, it is the work of the repair system. But in old age it goes wild and begins to attack healthy tissue. Fixing this repair system is one of the strategies to combat aging.

The same with sirtuins (proteins that, among other things, are activated by resveratrol): at first, they are involved in epigenetic regulation and error correction, and then they fail to cope with epiregulation and unwanted gene expression begins.

Social organisms also age, and a dysfunctional Nash equilibrium of individual strategies arises in them, for example, when corruption permeates all layers of society, but no

participant can refuse it, since he immediately finds himself in a less advantageous position. Social organisms fight this through "rebooting" through elections or revolutions. Cells and processes in the body also compete with each other for resources. For example, the need to store energy conflicts with the need for mobility: obesity overloads the heart, its walls thicken, and the quality of its work decreases.

No Repair Without Damage

Another published theory explains aging this way: DNA repair cycles lead to changes in their epigenetics. (DNA Break-Induced Epigenetic Drift as a Cause of Mammalian Aging.) Lysosome malfunctions lead to the accumulation of lipofuscin. All this can be explained by the general principle: there is no repair without damage.

Many Approaches to Combating Aging Can Be Described as Activation of Repair

What works, even slightly, on model animals is most often related to the activation of repair, for example, by influencing the mTOR pathway through fasting or rapamycin; or by activating repair through the activation of heat shock proteins, chaperones. This includes fighting thymus involution.

The mTOR complex, to put it very briefly, stimulates cell growth, and its suppression activates cell repair and survival. Artificial suppression of mTOR, for example, with rapamycin, is the activation of repair in all body cells and slowing down their division, which reduces the chances of cancer. And this leads to a measurable extension of the lifespan of model animals.

But here too, the law of diminishing life extension effects applies as we move to more complex and long-lived animals, which have already used all the life extension tools through evolution and for which selection has favored lifespan extension. For larger animals, all this works less effectively, and whether it works for humans at all is unknown, and cannot be ascertained without expensive, lengthy, and ethically questionable experiments, which, essentially, make the cure for aging "unknowable."

Mobility as an integral measure of aging and Friston's free energy principle

When an animal's mobility decreases, it becomes easy prey for predators - or can no longer hunt effectively itself. Thus, decreased mobility is the main deadly manifestation of aging for many animals. Human mobility decreases with age and can be used as an integral marker of aging. The company Gero measured aging using a mobility tracking program.

In a broader sense, one can talk about "available energy". For example, if I have a lot of money (social energy), but I don't have the strength to clean my room, I can hire a cleaning lady. If I get sick, money, to a certain extent, will replace my youth for me: I can use a car with a driver, hire doctors, take supplements. It can be assumed that inside the human body there is also some kind of "currency" that could be directed to solve certain problems. But there is no direct analog of such a currency: it is not ATP, not glucose, not attention, not blood. Rather, this could be called something like "the degree of freedom of regulatory functions", that is, stability mechanisms again.

Here we can recall Friston's free energy principle, which states that a living being seeks to reduce its state of uncertainty either by changing its model of the world, or by acting on the observable world. The accumulation of damage during aging is equivalent to an increase in uncertainty, and the ability to do something about it (that is, the state of repair systems) is its reduction. High uncertainty about the future means high risks of catastrophes and death.

Stem cells and second order repair system

Paradoxically, the aging of most cells in the human body (except for stem and germ cells) is unimportant for the aging process, since these cells undergo apoptosis or are destroyed by immune cells, with a period from days to years. Therefore, the breakdown of repair systems in them is also not so important for aging (unless it leads to cancer). These transient cells are replaced by the differentiation of stem cells, either hematopoietic from bone marrow, or organ specific.

That is, stem cells essentially act as a high-level repair mechanism that replaces other repair processes. However, with age there is depletion of the stem cell pool, accumulation of mutations in them, and accumulation of "selfish clones" of stem cells that divide less frequently and/or reluctantly differentiate.

At the same time, the stem cell system is in principle capable of self-repair during symmetrical stem cell division, that is, they could restore their number. However, this self-repair of stem cells also gradually fails, since frequent division enhances the accumulation of mutations in stem cells and leads to the spread of selfish clones that differentiate less efficiently. (More on stem cell aging - here When stem cells grow old: phenotypes and mechanisms of stem cell aging. (Schultz & Sinclair, 2016).)

In the early 21st century, there was a boom in stem cell research and regenerative medicine, and it seemed that if you "inject stem cells", you can trigger regeneration from within. But the level of results was not as high as expected, and in addition, there were frequent cases of cancers caused by improper differentiation of stem cells: teratomas.

It became clear that not so much the stem cell itself is important, but the control over it. Just as society is renewed through the birth of children, but you cannot effectively "regenerate" society if we leave children in the woods; children must receive a proper education to become new members of society.

Stem cells are controlled in the stem cell niche by various signaling substances and form factors. But the niche is damaged during aging due to chronic inflammation and accumulation of damage to the extracellular matrix. As a result, the circle closes: a properly functioning niche could be a second-level repair system, producing many necessary stem cells, but its damage occurs due to the lowest-level mechanisms of mechanical wear of the matrix and its damage by such processes as glycation of matrix proteins.

Michael Levin has an interesting idea that regeneration and anatomy are controlled through electrical connections between cells https://www.youtube.com/watch?v=HKWyB9qLP_s.

It follows from the above that, although a second-level regeneration system is present in humans to some extent, it cannot be reduced to any single simple switch that could then be turned on with a miracle molecule. With its help, aging can be slowed down a little, maybe by 10-20 percent, but this is not a solution to the problem of aging.

Apoptosis in humans? Stress, loneliness, accelerated aging and suicide

The pattern is clear: stress, increased pressure, heart attack, death. When the dispossession of creative unions began in 1931, my great-grandfather was worked over so hard there that he came home and died. But he was able, by force of will - as the family legend has it - to delay death and wait for my grandfather to come from school. According to another legend, a museum director could yell at someone so much that the person would be taken away with a heart attack.

Rats that lose a fight for status die within two weeks. Abandoned dogs can die of loneliness, and loneliness also shortens a person's life. But still, if aging is a program, can it be launched? Why do people go gray from stress? Cortisol?

Retirement is the main factor in premature death; many creative people who continued to work all their lives lived long lives. People who have something to care about also live long lives.

Such "human apoptosis" is one of the factors that affects life expectancy, but only within certain limits that do not exceed the biologically available life expectancy. Someone will live 50, someone 90.

5. Arguments and counterarguments

Overview of main objections

A recent review "Horizons in the evolution of aging" (Flatt & Partridge, 2018) shows that not everything is so unambiguous with evolutionary theories of aging: "In the 1930s-1950s evolutionary biologists developed a successful theory of organismal aging, firmly rooted in population genetic principles. By the 1980s the evolution of aging had a sound empirical footing. Because the force of selection declines with age, aging evolves from the accumulation of mutations or trade-offs with early-life fitness. Here we review major insights and challenges that emerged over the past 35 years: selection need not always decline with age; higher extrinsic (i.e. ecological) mortality need not always accelerate aging; conserved pathways of aging control prove more diverse than assumed earlier; aging need not be universal; life-history trade-offs linked to aging can be ‘broken’; aging can be decelerated by pharmacological intervention; and the challenge persists to ameliorate late-life morbidity, despite increases in average lifespan."

The idea that evolution works towards synchronizing different stability mechanisms, and that aging is the simultaneous failure of all these mechanisms, can be criticized using various counterarguments:

Counterargument: Analogies with animal life extension suggest that life extension is simple.

Analysis: Impacting just one gene (insulin-like growth factor) led to a significant increase in the lifespan of nematodes and mice. People with defects in this gene also live longer, but the increase is much smaller in percentage than in mice. In addition, low growth associated with a deficiency in this factor would have been an obstacle to long life in other historical periods, in conditions of war and hunting: that is, some traits prolong life only under certain conditions. However, humans have already undergone a very powerful selection for prolonged life, and therefore all the “low-hanging fruit” has already been used.

Counterargument: Short-lived and long-lived species differ in the operation of just a few genes. However, these genes are often associated with repair systems.

Counterargument: Long-lived people. Women in Mediterranean countries very often live to be 90-100 years old. This means there is some potential to increase life expectancy. However, an increase of 10-20 percent is not an increase in multiples, and therefore not a fundamental solution to the problem of aging.

Counterargument: The growth and development of the child is centrally controlled by hormones, and therefore subsequent degradation must also have a single control center. This is not necessarily true: for example, a car is produced centrally, but rusts in a decentralized manner.

Counterargument: The lifespan of neurons and stem cells is greater than that of the organism. Fedintsev: "It is important that the mechanisms for eliminating intracellular damage must be present in all cells, and experiments show that they work perfectly - neurons and stem cells live much longer than the maximum lifespan of the species. SC, for example, at least three times longer." There is no contradiction: in order for the brain to function, most neurons in it must survive, say up to 70 years old, and therefore the average life expectancy of each neuron must be greater. For example, if the "half-life of a neuron" is 210 years, then by age 70, seven-eighths of neurons will survive.

Counterargument: Aging can be accelerated by various factors: radiation, stress, progeria, and therefore there is a center controlling it. However, synchronization of repair processes is still not tantamount to the presence of a full-fledged meta-repair system. In addition, breaking is not building. If you turn off one of the repair systems, you will get something very similar to aging, but that does not mean it will be aging entirely.

Aging is programmed into genes, but it is not a program

The rate of aging varies greatly between different species, even between similar species, and therefore it is encoded in genes. But this is not tantamount to the statement "we have an aging program". The latter statement implies the existence of a separate system that explicitly describes the aging phenotype and implements it.

Imagine we have a computer running 100 programs, each printing one dot on a printer. The output will be 100 dots. But if you say "we have a program to print a hundred dots," that would be wrong. 100 dots appear as the joint effect of various programs, but not one aging program appended to the side. If you turn off one of the programs, only one dot will disappear.

Blagosklonny described aging as a "pseudo-program", that is, as the shadow of the developmental program (Blagosklonny, 2013).

6. Ways to prolong life in the absence of a single mechanism of aging

If aging has no single mechanism, it is disappointing: how to fight it? However, one can try to turn this disadvantage into an advantage.

SENS and the repair problem

Aubrey de Grey was one of the first to realize that researching the "nature of aging" is a trap. There is no single fundamental mechanism of aging that we could break. Moreover, for most people in the second half of life, the aging stage as a pre-disease has already passed, and there is already significant damage at all levels caused by aging. To avoid this trap, he proposed SENS, the essence of which is to repair the damage that has already occurred. That is, we hit the point where aging has already turned into visible damage, but has not yet caused fatal diseases. At the same time, the original list of what de Grey originally included in SENS probably needs to be adjusted, since the list is 20 years old and much has been discovered about the nature of aging since then. I will remind you that originally SENS consisted of 7 areas:

- eliminating genes from cells that lead to cancer

- preventing damage by free radicals to cells by transferring mitochondrial genes to the nucleus

- fighting cellular garbage (eliminating atherosclerosis)

- fighting extracellular garbage (eliminating Alzheimer's disease)

- replacing lost cells (eliminating Parkinson's disease)

- removing dysfunctional cells (senolytics)

- removing intercellular polymeric bonds (correcting matrix damage)

However, in general, repair requires tools that are commensurate in complexity with the object being repaired. To fix a soldering iron you need another soldering iron, and to tow a ship you need another ship. That is, the problem of treating aging by repair is the problem of creating a tool more complex than aging itself, for example, a system of nanobots controlled by AI. We will not be able to cure all damage with one or even several "miracle molecules".

SENS also does not take into account the importance of improving the functioning of biological repair systems. Many precancerous cells are successfully destroyed by the immune system throughout life, but the weakening of the immune system with age leads to an increase in the incidence of cancer.

More Dakka, the multilayer nature of aging, and combinations of geroprotectors

Sarah Constantin works on fighting aging at the intersection of rationality and effective altruism. She created the Longevity Research Institute Foundation. The main idea is to test various (6000 pieces) already existing and safe drugs on worms, choose those that prolong life the most, then test their combinations on mice and then on humans. She expects to get a working combination by 2030, but needs half a million dollars to start the experiments. (Another similar project https://www.morelife.tech/ by Shrey Amin.)

And this makes a lot of sense. If aging is caused by many reasons, then the best means to influence it should consist of many drugs. That is, a combination of geroprotectors is needed. However, one must take into account the possibility that some geroprotectors will interfere with each other. This can be discovered by conducting n - 1 combination tests for all n. If one of these combinations prolongs life more than the sum of all geroprotectors, it means that one of them interferes with all the others. You can also come up with other ways to mathematically predict which specific combinations of geroprotectors will fail. We consider some of them in the article "Artificial Intelligence in Life Extension" (Batin et al., 2018).

More Dakka is the principle of enhancing the positive effect, named after the classic TV trope, the essence of which is solving problems by cramming as many combat rounds into them as possible. Yudkowsky describes it in his book Inadequate Equilibrium: it turned out that increasing light improves the mood of people with seasonal depression, and the more light, the better their mood. To solve his depression problem, he bought an insanely huge unreal amount of high-power LED lamps and made them into a light wall. After that, the depression went away, but interestingly, in studies of light therapy, no one had ever tried using really powerful light sources. Researchers saw that "more light" improves results, but never tried to find the limit of improvements. The same principle works for many medical interventions, as Sarah Constantin's post states:

"Chemotherapy didn't work against cancer until doctors made drug cocktails, ramped the dosage up as high as patients could stand, then mitigated side effects with prednisone and intermittent dosing. If they'd just used a safe daily dose of one chemo drug, they would have concluded chemo doesn't work... Same for HIV. The virus has a replication rate and a clearance rate; the replication rate is also its mutation rate; an antiviral can drive the clearance rate above the replication rate, which will cause an exponential decline in the virus's numbers, but if there's only one drug, the virus gets a chance to develop resistance before the population drops enough it can't be detected. This is a simple distinction you can calculate mathematically years before you know what the drugs ought to be. One drug: death. Two drugs: death. Three or more drugs: life."

Aging cannot have an infinitely large number of mechanisms, otherwise we would have had an infinitely large number of different diseases and different types of individual aging. It can be assumed that there are from 10 to 100 major stability mechanisms selected by selection and synchronized. And if we find 10 (or 100?) geroprotectors acting on different molecular pathways (one on the matrix, the other on insulin-like growth factor, the third on epigenetic clocks, etc.), then suddenly aging will slow down sharply.

The most interesting Singaporean experiment on combining geroprotectors in nematodes is set up quite complexly (Dessale et al., 2017). At the beginning, 5 different genetic pathways associated with aging were selected, that is, molecular mechanisms - and 11 substances that are safe for humans that could in principle affect them. Then the activity of each was measured in prolonging life, which turned out to be less than promised by the scientists who had previously studied them (this is a known phenomenon of fading results over time, associated with the influence of various cognitive biases and fakes on statistics, such as regression to the mean, hiding negative results, placebo, etc.), and only 5 out of 11 substances had any statistically significant effect on nematodes in prolonging life (rapamycin, rifampicin, allantoin, metformin, PSORA-4).

The flies were then tested for individual substances as well as the effective combinations discovered, and it was found out that the combination of rapamycin, rifampicin and allantoin prolongs the life of fruit flies, and synergistically (that is, the effect of the sum is greater than the effect of the addends) from 23 to 42 days.

It can be posited that the combination of several safe and long-established individually tested agents in humans has the potential to extend life expectancy by a few percentage points. The inherent safety of these interventions would facilitate their rapid implementation. Such agents might include metformin, green tea, and vitamin D. Extending lifespan by a few percentage points does not solve the problem of aging per se, but it represents a significant societal benefit; moreover, it could allow many individuals to survive long enough to benefit from forthcoming life-extending technologies, thus gaining a chance to achieve longevity escape velocity (Turchin et al., 2017).

Polina Loseva has described the ideal geroprotector as follows:
"Even today, we can conceptualize the makeup of a multicomponent elixir of immortality and outline its tentative formulation. Instead of alcohol and opium, which were the choices

of Prague alchemists, its foundation will be some agent capable of halting the quasi-program: rapamycin, metformin, or another mTOR cascade blocker, perhaps not just one.

The second layer – instead of 77 herbs – will consist of agents targeting the direct causes of aging. Among these will likely be a telomerase activator, which will enable cells to divide longer, and some form of agent capable of reprogramming cells, that is, returning them closer to a stem cell state. Gene therapy also falls into this category. However, turning 'aging genes' on or off will need to be done in adulthood, as many of these genes are necessary for growth and development in childhood.

The third layer is aging prevention. This may involve hormetins, either already known or new, synthetic ones. Which one of these will be the most effective – exercise, fasting, temperature variations, or toxins – is something we still need to determine.

Finally, some signs of aging will need to be combatted post facto – this is the very repair process that Aubrey de Grey urges us to focus on. As the fourth layer here, we will require senolytics to purge the body of senescent cells and possibly other agents, for example, to break down cross-links in the molecules of the extracellular matrix or dissolve protein aggregates in tissues."

Identifying and Halting Age Accelerators

Given the absence of a unified mechanism of resilience, the majority of factors that expedite aging must concurrently influence numerous resilience mechanisms. However, an evident exception exists: progeria, which is induced by the damage to a single gene, lamin A. In other words, since aging lacks a singular essence, our combat must be directed against elements that disrupt stability, not against the "nature of aging" per se.

Throughout a human's life, a multitude of factors act to accelerate aging, and if we can counteract many of these, we will gain an advantage in extending life span. While not a radical extension, since aging itself is not abolished, it would be substantial enough to allow more individuals to reach an age where more effective life-extending technologies are available.

Internal Accelerators:
1) Reactive oxygen species within cells
2) Obesity and metabolic syndrome
3) Hypertension
4) Chronic inflammation
5) Lipofuscin and other cellular debris

Infections:
1) HIV
2) Chronic viral infections (there's even a viral theory of aging)
3) Corresponding chronic inflammation
4) COVID-19

Dependencies:
1) Alcohol
2) Smoking
3) Overeating
4) Hard drugs (cocaine induces accelerated aging of the brain)

External Damaging Influences:
1) Excessive ultraviolet sunlight exposure to the skin
2) Radiation (including internal exposure from the isotope potassium-40)
3) Toxic burden (poor diet, air pollution with fine particulate matter, toxins from mold, etc.)
4) Galactose – induces matrix cross-linking, formed from lactose in milk

Lifestyle:
1) Sedentary behavior (including internet dependency)
2) Wear and tear, and injuries, physically demanding lifestyles, like that of a miner
3) Stress, cortisol
4) Sleep disturbances

In small doses or when occurring sporadically, most of the aforementioned factors can be beneficial, as they induce hormesis, i.e., enhanced repair mechanisms.

The number of aging outcomes is finite, and these are pre-diseases

M. Blagosklonny defined aging as a pre-pre-disease, but aging has countless interrelated mechanisms, so it is not clear where to strike. However, the outcomes of aging are pre-disease states, which are well known, and acting on which reliably leads to prolonging people's lives. For example, hypertension, atherosclerosis, obesity, chronic inflammation, neoplasms, thymus involution.

As far as I understand, D. Veremeenko's theranostics is based on an attempt to measure indicators associated with pre-diseases and recommend (together with a doctor) actions that have proven to improve these indicators and are associated with increasing human life expectancy. That is, to attack not aging itself, but the pre-diseases that arise from it. SENS also hits somewhere nearby, as it tries to correct damage. But SENS acts at the cellular level, and theranostics - at the level of the organism.

Impact on pre-diseases is essentially prevention. It can be simple, like diet, and complex, like cell transplantation to treat emerging Parkinson's disease.

Organ replacement

In general, in terms of the body's functioning, we are interested not in the organs themselves, but in their functions. The ideal solution to the problem of aging teeth is artificial teeth. They do not hurt and do not deteriorate if made well. It would be ideal to replace aging body parts or even the body itself with mechanical or bionic analogues with

much greater strength margins than normal organs - and then with the ability to self-repair. Here I will just outline this complex topic, which includes regeneration control, cyborgization and therapeutic cloning, and growing organs inside GMO animals.

An interesting project: growing new organs within a person's own lymphatic system is being developed by [ref].

Skin as an anti-aging system tester and deployment accelerator

Alantoin, which is included in the list of the best combination of geroprotectors from the Singaporean study, causes skin rejuvenation and is often used in various cosmetic preparations. In general, the skin can serve as a bridgehead for testing anti-aging drugs: on the one hand, the result is quickly apparent, and there is paying demand, and on the other hand, drugs do not penetrate deep and are therefore relatively safe. In this sense, the skin regenerator panthenol (a vitamin B5 metabolite) is interesting, which accelerates its healing 2-3 times: but can it be applied not only to the skin?

Comprehensive impact based on big data

As we wrote in the article "Artificial Intelligence in Life Extension" (Batin et al., 2018), at the molecular level, aging is a very complex process, individual and evolving over time, and to compensate for it, you need to obtain large data on the state of the organism, and then based on them calculate the compensating effect. This compensating effect must also be complex, not just one pill, but constantly changing therapy for different organs and tissues. The ideal rejuvenation system based on SENS also needs to work like the rejuvenator robot from the Elysium movie.

Mood - hormones - stress - aging

If the mechanism of central regulation of the aging rate exists, then it must be connected with the brain and most likely with hormones. For example, the hypothalamus controls the release of other hormones through release factors, including cortisol. However, the emotional state of a person influences the hypothalamus itself, and thoughts influence emotions. Emotional state, in turn, is controlled by attention and control systems: a person with a higher level of "self-control" will be less prone to emotional outbursts, and therefore stress and compensatory addictions (such as alcohol and smoking) - and all this is a factor in accelerated aging, except in the case of small doses that, on the contrary, cause a hormetic effect. There is a study that people who control themselves better live longer.
A person who is in the right frame of mind ("immortality warrior") will, in general, have better chances of survival and a lower aging rate.

Super-technologies: Nanomedicine and Mind Uploading

The fight against aging is, in a sense, a tool problem. As soon as a new tool appears, we look at whether it can be applied to combat aging: pills, CRISPR, genetic vectors - everything is used. Existing tools are simple and undifferentiated: diets, sports, pills, and they simply cannot compete with the complexity of aging. There is some hope that aging has weak spots that can be hit after a long trial and error. But evolution has already found almost all these weak spots by prolonging human life. Therefore, the effect on humans from simple interventions is small, unlike in mice.

An alternative viewpoint is that we need to move to a meta-level and create a tool more complex than aging itself. There are several ideas of what this could be: medical AI, Drexlerian nanorobots, bionanorobots, or uploading consciousness into a computer.

Hypothetical Hyper-regeneration Regime

Apocryphal stories tell of a man who returned from war, lay in an anthill for three days, allowed the ants to bite him, and after three days all his wounds healed; in another story, grandmothers were forced to carry bags of cement, which resolved their back problems. Mice that had half their blood drained and replaced with saline also rejuvenated in real experiments, reminiscent of the ancient tradition of bloodletting; the explanation here may be that blood loss triggered natural regeneration processes. While the credibility of such stories is close to zero (except for the experiments with mice), they describe what an ideal hyper-regeneration regime might look like, i.e., activating all damage repair systems at maximum speed, which would not only destroy incoming harmful effects but also correct many accumulated damages up to that point. It's like a major cleanup.

In our model, where aging mainly occurs at the level of repair systems, rejuvenation is theoretically possible if damage elimination occurs faster than its accumulation. Alas, not all real aging processes can be reduced to this model: for example, the thickness of the lens of the eye grows constantly throughout life, leading to farsightedness, but there is no repair system for its thickness.

There is an article with the wonderful title "Reversibility of Irreversible Aging" by Gladyshev (Galkin et al., 2019), which discusses whether aging can be reversed considering that nature does not envisage the repair of some parts of the body (neurons, skeleton). The article says that different organs and systems age at different rates, and cell reprogramming plays a big role in this. The link between the aging of the organism and the aging of its parts is not straightforward. He points to two main potential mechanisms of rejuvenation that work in experiments: parabiosis and epigenetic regulation. Also, brain plasticity induced by exercises and caloric reduction can be considered a form of rejuvenation.

In humans, almost all cells are replaced every 10 years (except for neurons, cardiomyocytes, and visual cells in the eye), so the aging of differentiated cells cannot be the main mechanism of aging, and thus the length of telomeres in them is not very informative since it essentially tells about the number of divisions of stem cells needed to create a given cell (or about the aging of the stem cells themselves). Moreover, senescent

cells do not live the whole life of a person, but are constantly in turnover: some arise, others are destroyed, and their concentration reflects the rate of turnover: just as the proportion of elderly people in society is maintained, although individual people change.

It would be interesting to find out whether there are cases of spontaneous slowing down or even reversal of aging sometimes. Some people claim that they have managed to cure something by the power of self-suggestion. Or is it a placebo effect? And there are cases of creating illnesses by the same power of self-suggestion, for example, stigmata.

What should the ideal solution to the problem of aging look like?

The ideal solution to the problem of aging, as understood in the Theory of Inventive Problem Solving (TRIZ), would be to wake up in a fully young body at the peak of its abilities, for instance, at the age of 16 (by 18, I began to bald, gain weight, and couldn't jump from a four-meter ladder). However, body transplantation is a risky operation, and it's still unclear what to do about brain aging. An old brain in a young body would still be at risk of diseases such as Alzheimer's, cancer, stroke, dementia; and a body transplant would only extend such a brain's life by about 10-20 years.

Another ideal solution is internal body regeneration, where the body would repair damages at the same rate they occur, or even faster, thus rejuvenating itself. However, aging is complex, and this complexity must be matched by the complexity of the counteraction.
Imagine we had a "bionanorobot": a genetically modified human stem cell capable of penetrating all areas of the body to treat any damages or transform into any needed tissue type. On one hand, it's a regular human cell; on the other, it contains an additional chromosome coding something akin to a computer, capable within certain limits of analyzing the situation, executing programs, transmitting data, and synthesizing various mechanisms, perhaps using DNA origami.

The first step in this direction involves one's own immune cells, invasive macrophages, which are taken from the body, trained to attack tumors, and then returned to the body. Another direction involves special stem cells that have not yet lost the "immortality" inherent in embryonic stem cells and can transform into any tissue. AGEX Therapeutics is developing such cells. A critical task is to protect pluripotent cells from cancer or transformation into teratomas (uncontrolled differentiation). To this end, they could be fitted with something like a "cancer vaccine"—a set of genes protecting against cancer, such as additional copies of P53, as well as some kind of switch (or switches) that can destroy the new cells if something goes wrong inside the body.

There are also clones of specialized immune cells taken from highly efficient organisms. For example, a group of special anticancer T-killers has recently been discovered... [ref]

Transplanting one's own bone marrow, frozen in youth, may lead to the regeneration of the hematopoietic system and, along with it, immunity. This project is being developed by Timofey Glinin. [ref]

The "Symbiont" project and natural symbionts

Another idea, proposed by Mikhail Batin, is to use the same evolutionary forces that spawned aging to defeat it. Since aging has no entity, it is "smeared" across the genome, and you need to act on many molecular mechanisms in a complex way to slow it down. A cancerous tumor can evolve to avoid immunity and remain immortal, but how can this same power be directed towards life extension? The idea is to set up an experiment on the co-evolution of model animals and an organism-symbiont, in which the selection of the symbiont over many generations will go towards extending the life of the model organism. However, for humans, such an experiment would require millennia.

Luckily, de facto a similar experiment was carried out long ago during the domestication of various agricultural crops and animals: those crops that succeeded in domestication survived better, and the survival of human culture requires a long historical memory, that is, the preservation of the elderly. Domestication began in the Neolithic era 10-15 thousand years ago, even before the advent of writing 5 thousand years ago, and it was then, possibly, that cultural plants and animals conducive to prolonging human life were selected.

People began to live in "symbiosis" with various agricultural plants (and animals), and these plants were "interested" in the success of those human communities in which they were cultivated. Among such ancient cultivated plants whose consumption is associated with prolonging life: olive oil, grapes and green tea.

Different plants helped different cultures: olive oil and wine - the Mediterranean culture, and green tea - the Far Eastern (and tobacco - the American one; it is quite possible that pure nicotine, free from resins, can also have a positive effect on thinking and longevity).

Potential candidates for life-prolonging symbionts and associated longevity regions:

- Fermented dairy products: Bulgarian kefir grains and long-lived highlanders.

- Grapes - require long-term care within a resilient family. Wine is associated with greater life expectancy in Mediterranean culture, possibly due to resveratrol; people in this region also better metabolize alcohol in the body, that is, genome changes clearly occur to adapt to winemaking.

- Olive oil - Mediterranean culture. The olives themselves live very long, and countries with high olive oil consumption have some of the highest life expectancy rates, despite widespread smoking among the population (e.g. Greece and especially the island of Crete).

- Coffee - has a shorter history and is associated with Sufi Islamic monasteries.

- Green tea - improves brain function and prolongs life. Longevity culture in China.

- Blueberry - in the north there are few animals, and blueberries reproduce by transferring seeds in the stomach of animals that have eaten them. Therefore, it was the northern blueberry that was interested in increasing the number of those eating it, and possibly their longevity as well. By the way, the effect of improving vision from blueberries is actually related to improving brain function, not eyes.

- Cats and dogs - people with pets live longer.

- Spices and medicinal plants that were cultivated. Possibly brewer's yeast, and even rice and wheat.

So, the most promising natural life-prolonging symbionts are green tea, coffee, grapes, olive oil, blueberries, kefir. But many of them existed in different cultures, and now we can buy them all in a nearby store. This should have the overall effect of a "combination of geroprotectors" and may partly explain the increase in life expectancy in the 20th-21st centuries.

Anti-aging vaccine

Editing the genomes of embryos can be used to slow aging and prevent many future diseases. This includes both removing dangerous gene alleles and introducing known alleles associated with the absence of certain diseases: proper cholesterol metabolism - or associated with longevity in general (lower IGF-1 activity). In addition, individual solutions that work in other animals can be applied, for example, multiple copies of the P53 gene (as in elephants) or something taken from naked mole rats. Unfortunately, how all this works together we will find out only after decades. Evolution could test combinations of genes by killing billions of creatures, but we cannot. And ethics committees will not allow this. Only if we have the ability to launch full-fledged simulations of the entire living organism on a computer and study the effects there.

For currently living people, such a vaccine is useless: even CRISPR will not allow editing all cells in the body - and not create a lot of new critical errors in the process. Of course, we can modify stem cells, and then, with their help, replace most of the cells in the body with corrected ones - but how exactly this will work is still hard to imagine.

It is also possible, of course, to clone people who have high life expectancy or use their germ cells for reproduction, but all this takes a long time and is unethical. During this time, something else will be invented.

A vaccine against aging for the currently living: transplantation of specially trained immune cells
Another idea is something akin to training one's own immune cells in such a way that they perform all tasks related to repairing the body from age-related damage. The first step in this direction is the use of trained autologous lymphocytes to attack tumors (CAR-T technology is already in use).

The trained autologous cell would be something like a nanorobot with dozens of programmed functions, or something like a "SENS machine," that is, a terminator of damage. Among its functions:

1) Restoration of the stem cell pool (perhaps it will transform into them).
2) Removal of senescent cells
3) Hunting for cancer cells
4) Removal of atherosclerotic plaques
5) Destruction of protein aggregates associated with Alzheimer's
6) Restoration of the extracellular matrix.

Such an approach could be commercialized in stages, as new functions are added, and tested on older people. Such a device – or something similar, because if we knew exactly what to do, we would already be doing it – can be expected from George Church, head of "Human Longevity."

The main thing is that this project does not suffer from the need for overly lengthy experiments since it is aimed at treating aging that has already occurred, not its inception in relatively young people. Therefore, it can be useful for currently living people and help with individual age-related diseases.

The flip side of such a bionanorobot is the humoral interface, that is, the connection of the human immune system and a computer from the outside, to accelerate diagnosis and regulation.

The power of prevention – catching diseases before they begin

Hygiene, vaccination, regular screening – these are simple methods of prevention that prevent diseases from developing. They are responsible for the increase in life expectancy in developed countries.

In terms of combating aging – this is the moment of capturing when molecular damage to cells begins to turn into a specific disease: diabetes, hypertension, plaques, tumors. And then treatment at an early stage.

7. Essential biomarkers of aging

The problem of correlational biomarkers

Biomarkers of aging are used to diagnose aging and are needed to accelerate experiments to combat aging. If aging had one specific mechanism, then there would be no big problem with biomarkers: the cause of aging would be the genuine biomarker, just as the presence of a virus in the blood is a genuine biomarker of an infectious disease.

Most proposed biomarkers of aging are correlational, not essential. For example, we can estimate a person's age by their graying hair. But if such a person dyes their hair, it does not mean that they will become younger. Known biomarkers are Horvath's epigenetic

clocks. However, even here we cannot claim that epigenetic changes are the sole cause of aging, and therefore, reversing such changes will unequivocally correlate with slowing aging.

From the point of view of the hypothesis of evolutionarily presynchronized repair mechanisms as a mechanism of aging, biomarkers of aging will actually be the states of these repair mechanisms, and to a lesser extent – the state of the systems they repair. That is, it will be a matrix of numbers, not one "biological age."

As we have agreed above, aging is an absolutely inevitable process that happens to everyone with age. This means that in principle, a person's chronological age should tell us how old they are biologically. However, since there is accelerated aging, in some cases we can say that a person is older or, conversely, younger than they should be at a given age.

Thus, biomarkers of aging can tell us that a person is aging faster than they should – and something needs to be done about it; or that they have preserved themselves better, and it is possible to find out thanks to what. Since age is the main predictor of the onset of diseases, personal biomarkers of aging can act as an improved form of such a predictor.

Biomarkers are needed for experiments

However, the main benefit of biomarkers of aging is not personal but global. The fact is that if we test drugs against aging in the traditional way, it will take 500 years. Suppose we extended a person's life to 100 years. This means that the first phase of clinical trials will take 100 years, the second another 100 years, then something will go wrong, and the whole process will need to be restarted – that's how you get 500 years. And in 500 years, we will all die, all our children and grandchildren will die, there may be a global catastrophe, or they will find a way to extend life with nanorobots. In general, testing drugs against aging is like flying to Alpha Centauri on a chemical rocket: long, expensive, and in the end, starships on photon traction will overtake.

But if we have reliable biomarkers of aging, then we can conduct these experiments much faster. For instance, in five years, we could observe an improvement in a certain biomarker, and then we wouldn't need to wait for everyone in the experiment to die to say with high confidence that a particular intervention slows down or even reverses the aging process, and is also safe enough to be given to healthy individuals as a preventive medicine.

However, to obtain such a biomarker, it must be thoroughly calibrated in experiments and underpinned by a solid theoretical basis. After all, we do not want to end up in a situation where initially, a substance acts well and improves the quality of life, but after 10 years, all those who took it start developing cancer. This is especially important because anti-aging drugs should be given to healthy people in whom aging has only just begun to emerge, for example, starting at 30 years old. Here, a very high level of safety is needed - higher than for drugs given to already sick people, where there is already a high risk of death, and the pros and cons are weighed differently. For example, chemotherapy for cancer is very toxic, but it increases survival on average, so it is worth giving to sick people;

similarly, many antibiotics have dangerous side effects in one case per thousand, but gangrene is even more dangerous.

Since drugs that slow down aging are expected to have effects that fully manifest decades after starting them, it is very important to track the long-term consequences of their use. But we don't have these decades because we want results sooner.

There is a workaround – using drugs and substances whose safety has already been proven because they have been in people's diets or used by medicine for decades, and their safety profile is well-studied. For example, metformin has been used for decades, and it is known what complications – very rare ones – it can cause, as well as their signs and precursors.

Many biomarkers of aging have a statistical character: as we age, everything deteriorates, and everything correlates with everything else. However, if we choose one correlate, we can fall into the trap of Goodhart's law: as soon as a certain parameter is taken as a measure of success, it ceases to be a good measure of success. For example, if we measure the productivity of employees by the amount of time spent, they will start to stay at work deliberately longer to create the appearance of greater efficiency. Aging, fortunately, is not sentient, but as soon as we start changing one parameter, it will immediately begin to disassociate from the holistic process of aging.

Mortality as the main biomarker of aging

Since ultimately, we are not interested in aging itself, but its endpoint, death, another way to measure the speed of aging is to measure the number of deaths within a large group of subjects. Here we should be concerned not with the number itself, but with the rate of its change. In principle, in any group, mortality should increase according to the Gompertz curve, but if we successfully apply some therapeutic intervention against aging, then the rate of this increase will be slower. To see this second derivative, we need experiments (or rather, observations) with a large number of people, but such experiments can be relatively fast (a few years). For example, there is data that the famine in Copenhagen during the years of World War I led to a sort of "caloric reduction" analogue, and this led to a reduction in mortality. Then one can follow the fates of these people.

Such experiments on the past are only possible with the presence of big data on the life histories of people - and there needs to be much more data than just the number of deceased to take into account various confounders.

Here we come to the point that good biomarkers can be calculated if we use big data and some form of AI. For example, we can train a neural network to predict life expectancy based on a large array of data about a person. Such a prediction will be more accurate but less "biological," as it's not clear what needs to be changed. Another way is to use AI to find certain invariants in the data about the body, which would correlate with the expected life expectancy, but would also imply recommendations for what can be changed to improve them. Moreover, big data would allow individualizing biomarkers of aging, for example, by linking them to the expected life expectancy based on genes.

Biomarkers from AI

Biomarkers from AI

In 2019, AI based on deep learning was more accurate than any other method in predicting human death, using data from the UK BioBank, an open medical database with information on 500,000 patients. The AI not only predicted who died but also identified which factors were most influential in the predictions; in this case, they were hazardous work, air pollution, and alcohol consumption, but not weight or diet.

Now, human data has become the new oil, and everyone is collecting it, but these data are divided among various firms and commercial organizations, and they are anonymized to such an extent that some useful information is lost. Ideally, all data about all people (genomes, medical records, dietary habits, various omics, and fitness trackers) should be consolidated into a single database, accessible to all scientific organizations for research. Vast amounts of data could make many experiments unnecessary. Billions of people take all possible bio-additives every day, post photos, undergo tests – and all these data should be combined into an open, non-commercial database. It should be non-commercial because it will reduce research costs, eliminate commercial deception, and remove obstacles between different databases.

Currently, there are many different aging biomarkers: Moskalev wrote a book about this. Moskalev notes that there are about 600 different aging biomarkers, including changes in DNA methylation, changes in skin fluorescence due to the accumulation of protein cross-links, accumulation of 8-oxoguanine as a marker of DNA damage.

Aging Clocks as Biomarkers

What is known as aging clocks, for example, Horvath's epigenetic clocks, are essentially biomarkers of aging, not real controlling clocks – or more precisely, more biomarkers than clocks. "Biological age" is an integral assessment based on multiple biomarkers. However, "aging can occur at different rates in different tissues and systems, for example, old transplanted blood cells remain old; moreover, the assessment of biological age is population-dependent" (Kishkun A. "Biological Age and Aging: Opportunities for Determination and Ways of Correction," a guide for physicians, 2008).

This raises the question of whether aging is synchronized between different tissues. For instance, the effects of parabiosis suggest the possibility of such synchronization, where young blood rejuvenates. But synchronization requires that aging has one mechanism that is transmitted, like a control signal or poison, or an elixir of youth, between different tissues.

Diseases as Biomarkers

Another type of biomarker is diseases associated with aging. For example, osteochondrosis. The disease is not fatal, relatively easy to measure, and most importantly, does not require special permits for experiments in which aging will be recognized as a disease. Unity Biotechnology is testing its anti-aging drug on osteochondrosis; Skulachev is testing his ion – on cataracts.

If an anti-aging drug works, it will help with the disease being studied, and at the same time, data can be collected on many other biomarkers. Of course, it may only help with this disease but not with others, for example, it may even increase their risks and as a result not increase lifespan. Finally, testing an anti-aging drug on diseases accelerates the path to its commercialization, as it breaks down a complex problem into many small steps, each of which provides resources to continue moving (as Elon Musk develops his business).

Types of Biomarkers

In general, there are several types of biomarkers:

1) Causes of aging. If we directly influence them, then aging as a whole, throughout the organism, will decrease. So far, such are generally unknown to us, although we can improve individual subsystems: regenerate the thymus a little, reduce pressure. Moreover, since there is not one single cause of aging, as there is no single mechanism of aging, there is also not one definite "causal" biomarker.

2) Correlates of aging. These are parameters that correlate unequivocally with aging but are not its cause. Therefore, acting on the parameter itself is rather pointless, but if we manage to act on aging itself, then the parameter will change. However, because everything is tightly connected, often it is enough to act on a correlate to have an effect on aging (the longevity of the organism as a whole). For example, the mobility of the organism is a correlate of aging, but if you start moving more, then the lifespan will increase.

3) Consequences of aging. For example, already gray hair. They can be used to determine chronological age, but if we change them, nothing will happen with aging, and if we rejuvenate the organism, the consequences of this type will not disappear. In general, this is the most useless type of biomarkers, suitable perhaps only for cosmetics.

4) Rejuvenation as one of the most potent biomarkers: if we could not just slow down the aging process but actually rejuvenate the organism, it would indicate that we are affecting the true causes of aging.

Correlates or Confounders

Correlates are often mistaken for causes, but in reality, they are the effects of confounders. For example, one study found that the Mediterranean diet only benefited the wealthy; meaning in reality, the wealthy lived longer and could afford a more expensive diet with wine, olive oil, and fish, and the fact that someone ate a Mediterranean diet simply reflected their income level. But even income level may not be the direct cause, it might just reflect access to better healthcare, good genetics, or something else.

Safety Biomarkers of Anti-Aging Therapies

We need not only biomarkers for the effectiveness of anti-aging therapies but also biomarkers for their safety. Several Russian actresses developed brain cancer (Zhanna Friske, Anastasia Zavorotnyuk, the wife of Konstantin Khabensky), possibly after stem cell therapy "for rejuvenation" 15 years ago. Whether they actually received stem cell injections, and which ones, is now impossible to determine, but the possibility exists. Since

most anti-aging therapies rejuvenate and/or stimulate cells (hormones, rejuvenation factors, stem cell injections, niche management, gene therapy), they could hypothetically increase the likelihood of cancer.

However, cancer may manifest decades later (still earlier than the expected time of its occurrence in the course of natural aging). Thus, the first stage of trials for a strong anti-aging drug must be very long to prove its safety, likely decades. But in that time, billions of people, including ourselves, will die. This means we must either use well-known and therefore inherently weak interventions (green tea, metformin) with a known safety profile – or look for negative biomarkers of aging, i.e., ways to predict an increase in the likelihood of cancer before it begins.

But it's hard to find a few transformed cells inside the body until cancer has started. Testing for safety becomes even more important if we want to offer such therapies to relatively young people (about 30 years old). If, however, we test aging therapies on 70-year-olds, then the results will be visible faster, and the risks are lower for the elderly: for example, there are no risks regarding genetic damage in offspring.

In addition to calibrating an aging biomarker, i.e., proving its correlation with the likelihood of future age-dependent diseases, it must also be proven to remain relevant after we add some kind of anti-aging therapy. An exaggerated example: weight is a good biomarker of obesity, but if a person's legs are amputated, the drop in weight will not signify a decrease in obesity.

8. Conclusion

Strategies for Combating Aging

There are a multitude of theories on aging and ideas for treating it. However, when we add the requirement that the strategy for implementing research must be fast enough for us to benefit from the results in our lifetime, only a few main paths remain:

1. A quick path with modest results using combinations of simple and safe molecules. Combinations of geroprotectors whose safety has already been proven. It is unlikely that we can achieve much here; Sarah Constantin estimates a gain of plus 10 years in average life expectancy, which I think is hyper-optimistic, as the Gompertz curve is very steep, and even defeating cancer will only add three years of life. However, such research can be conducted relatively quickly. Moreover, different combinations of geroprotectors can be consumed even before they are conclusively proven: drink green tea with olive oil and metformin, or take PolyPill (a combination of aspirin, statin, and two blood pressure-lowering substances, which together reduce the risk of heart attacks by half).

2. Complete control of both aging and the damage it causes using bionanorobots, GMO-modified stem cells, or other complex AI therapies. This technology will yield faster results in older individuals and can act more definitively, not probabilistically; furthermore, it can also remove its own negative and unforeseen consequences. Thus, it can be tested and

implemented much faster. The therapy described here is similar to SENS: we treat not aging itself, but the damages it has caused (the list may be longer than the original SENS list, but that is not important). The main thing that distinguishes this project from SENS is the creation of the main tool of change, which is the bionanorobot, or rather, a modified human cell itself that performs all the work. This project differs from Freitas's nanomedicine, where most of the work inside the organism is done by completely artificial nanomechanisms. Such nanorobots are possible, but they must solve all the same tasks as a living cell, such as: reproduction, maintaining homeostasis, nutrition, so designing such a robot will be an unnecessary additional task that we do not need at the stage of biomedicine.

3. Other ideas have lower a priori chances of success because they have not yet been experimentally confirmed, such as the idea of launching a hyper-regeneration mode or activating second-order repair systems. On the other hand, rejuvenation of a cell after epigenetic changes under the influence of Yamanaka factors cannot be explained other than by the launch of this hyper-regeneration, which eliminates most of the accumulated changes. Obviously, launching hyper-regeneration in a young person is risky due to cancer risk, meaning again, long tests are needed.
However, if we find a way to hyper-regenerate, it will be relatively easy to clinically prove: slowing down aging happens slowly, but rejuvenation could be seen immediately. Implementing it will also be easier, as it will immediately provide a reduction in the likelihood of various diseases and/or recovery from them, especially chronic ones, as well as a reduction in pre-disease factors such as hypertension and atherosclerosis, which have already branched off from the main trunk of aging but have not yet become diseases.

4. Bypassing the problem of aging through head and body transplants, cyborgization, cryonics, and mind uploading.
And that's essentially it: either something simple and fast, or super complex and smart. The middle ground does not work. Many other therapies, such as gene therapy, require very long research, primarily to verify long-term safety. Such research can easily take 50 years if we start giving the drug to 30-year-olds to prevent aging, and we will check their life span at 80+. For example, gene therapy, stem cell therapy, or any new drugs, like senolytics.

In other words, we need something very simple and very safe that can be started right now on young people, or something super complex and risky that can be applied to old people who have nothing to lose and are willing to take the risk in exchange for a big gain. Everything in between, complex and new-dangerous, requires too long and extensive research.

Conclusion. Strategies for Combating Aging

The most important question is not whether aging can be defeated in general, but whether it can be defeated within our lifetime. However, authors and readers vary in age. Some are 60 years old, while others have another 50 years of expected remaining life.

Short answer: aging can be defeated if breakthrough super-technologies, like a bionanorobot, are quickly implemented. To survive until then, one can use weak and not very proven interventions, hoping that they will work. Here the gain is much greater than the loss: a slight extension of life gives a greater chance of living to see immortality, while a slight reduction means less loss, as the probability of creating super-technologies is distributed in time not linearly, but exponentially.

Literature:

Batin, M., Turchin, A., Markov, S., Zhila, A., & Denkenberger, D. (2018). Artificial Intelligence in Life Extension: From Deep Learning to Superintelligence. *Informatica (Slovenia)*, *41*, 401.

Blagosklonny, M. V. (2013). Aging is not programmed: Genetic pseudo-program is a shadow of developmental growth. *Cell Cycle*, *12*(24), 3736. https://doi.org/10.4161/cc.27188

Cohen, A. A., Legault, V., & Fülöp, T. (2020). What if there's no such thing as "aging"? *Mechanisms of Ageing and Development*, *192*, 111344. https://doi.org/10.1016/j.mad.2020.111344

Dessale, T., Batchu, K. C., Barardo, D., Ng, L. F., Lam, V. Y. M., Wenk, M. R., Tolwinski, N. S., & Gruber, J. (2017). Slowing ageing using drug synergy in C. elegans. *BioRxiv*, 153205.

Fabian, D., & Flatt, T. (2011). The evolution of aging. *Nature Education Knowledge*, *3*(3), 1–10.

Flatt, T., & Partridge, L. (2018). Horizons in the evolution of aging. *BMC Biology*, *16*(1), 93. https://doi.org/10.1186/s12915-018-0562-z

Galkin, F., Zhang, B., Dmitriev, S. E., & Gladyshev, V. N. (2019). Reversibility of irreversible aging. *Ageing Research Reviews*, *49*, 104–114. https://doi.org/10.1016/j.arr.2018.11.008

Harshman, L. G. (2003). Life Span Extension of Drosophila melanogaster: Genetic and Population Studies. *Population and Development Review*, *29*, 99–126. https://www.jstor.org/stable/3401348

Henrich, J. (2015). *The secret of our success*. princeton University press.

Heyde, A., Rohde, D., McAlpine, C. S., Zhang, S., Hoyer, F. F., Gerold, J. M., Cheek, D., Iwamoto, Y., Schloss, M. J., & Vandoorne, K. (2021). Increased stem cell proliferation in atherosclerosis accelerates clonal hematopoiesis. *Cell*.

Judge, D. S., & Carey, J. R. (2000). Postreproductive Life Predicted by Primate Patterns. *The Journals of Gerontology: Series A*, *55*(4), B201–B209. https://doi.org/10.1093/gerona/55.4.B201

Karnaukhov, A. V., Karnaukhova, E. V., Sergievich, L. A., Karnaukhova, N. A., Bogdanenko, E. V., Manokhina, I. A., & Karnaukhov, V. N. (2017). The information theory of aging: The major factors that determine lifespan. *Biophysics*, *62*(5), 829–835. https://doi.org/10.1134/S0006350917050098

Ke, Z., Mallik, P., Johnson, A. B., Luna, F., Nevo, E., Zhang, Z. D., Gladyshev, V. N., Seluanov, A., & Gorbunova, V. (2017). Translation fidelity coevolves with longevity. *Aging Cell*, *16*(5), 988–993.

Loseva, P. (2020). *Against clockwork. What is aging and how to fight it.* Alpina non-fiction.

MacRae, S. L., Croken, M. M., Calder, R. B., Aliper, A., Milholland, B., White, R. R., Zhavoronkov, A., Gladyshev, V. N., Seluanov, A., Gorbunova, V., Zhang, Z. D., & Vijg, J. (2015). DNA repair in species with extreme lifespan differences. *Aging (Albany NY)*, *7*(12), 1171–1182. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4712340/

Medawar, P. B. (1952). *An unsolved problem of biology*.

Peto, R., & Doll, R. (1997). *There is no such thing as aging: Old age is associated with disease, but does not cause it*. British Medical Journal Publishing Group.

Schultz, M. B., & Sinclair, D. A. (2016). When stem cells grow old: Phenotypes and mechanisms of stem cell aging. *Development (Cambridge, England)*, *143*(1), 3–14. https://doi.org/10.1242/dev.130633

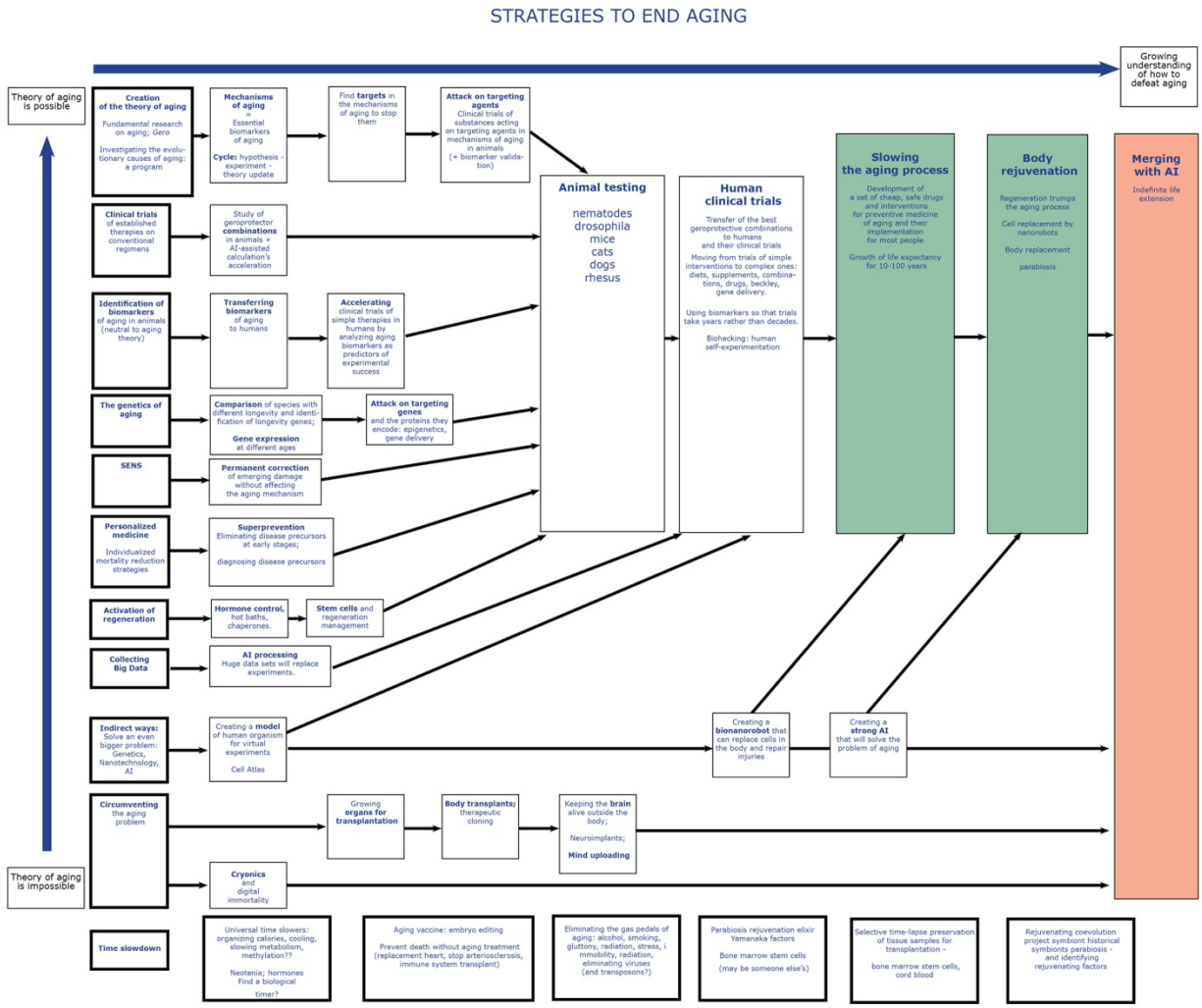
Turchin, A., Denkenberger, D., Milova, E., Egorova, A., & Batin, M. (2017). *Fighting aging as an effective altruism case: The model of impact*.

Vural, D. C., Morrison, G., & Mahadevan, L. (2014). Aging in complex interdependency networks. *Physical Review. E, Statistical, Nonlinear, and Soft Matter Physics*, *89*(2), 022811. https://doi.org/10.1103/PhysRevE.89.022811

Weinert, B. T., & Timiras, P. S. (2003). Invited review: Theories of aging. *Journal of Applied Physiology*, *95*(4), 1706–1716.

Москалёв, А. А. (2010). Эволюционные представления о природе старения. *Успехи Геронтологии*, *23*(1), 9–20.

Appendix 1. Social Strategies for Combating Aging



Picture 1. In the chart above all possible strategies to fight aging are presented.

From the theory of the evolution of aging – to the strategy of combating aging

In this section, I want to bridge our basic understanding of the evolution of aging - and our strategy for defeating aging in our lifetime. That is, the strategy for defeating aging is the

evolution of aging in reverse: we must produce the changes that the evolution of aging made in reverse order.

If aging were an evolutionary program with a single mechanism, then the strategy for attracting funding would consist of demonstrating a single artificial non-aging animal in which such a program is turned off. Whoever did this could receive an unlimited budget for further research and implementation. However, aging is not a program with a clear molecular mechanism.

The strategy for defeating aging itself consists of three main parts: a strategy for attracting funding for scientific research, a plan for experiments, and then a strategy for implementing the technology created, i.e., obtaining the necessary permits and distributing it to the maximum number of people. In other words, we have a what-strategy that describes the plan of action (for example, researching head transplantation in primates) and a how-strategy (where we will get the money, permits, scientists to implement the project) and how we will make it widely accessible.

From the point of view of effective altruism, a strategy for defeating aging that only a few can use is not a true victory: however, a strategy available to a few is essentially an icebreaker and paves the way for millions.

The connection between aging theory and methods of combating it: an overview of possible strategies

Each theory about the nature of aging corresponds to a certain method of combating it, and to implement this method, a specific series of scientific research is needed. The problem is that aging does not have one simple mechanism that can be blocked. As a result, the idea of trying to defeat aging, ignoring its "nature" in one way or another, arises. Most of the ideas in the list below are about how to bypass the unknowability of the aging problem.

Table 3 (link to pdf) provides an overview of what-strategies for defeating aging. Below is a list of these main approaches:

1. Create a theory of aging. The first of these strategies suggests attacking the problem head-on. First, create a general theoretical model of aging, for example, the accumulation of errors, programmed aging, or oxidative stress. Then identify "essential biomarkers of aging" that follow from this theory, i.e., those pathological changes that are the direct cause of aging (not just a correlation, like gray hair; but an actual cause, like the flu virus is the cause of the flu.) Searching for such biomarkers will allow both testing the theory and accelerating future experiments to stop aging. Biomarkers translate pure theory into the language of molecular mechanisms. Then these essential biomarkers need to be interpreted as targets and find ways to influence them: antibodies, inhibitors, and so on. Next is testing on mice: can their lifespan be extended? And if so, then on larger animals and then on humans.

2. Find a life-extending substance without a theory. An alternative view is that we do not actually need a theory of aging: we can find life-extending substances without understanding exactly how they work, simply by experimental trial and error and combining combinations of geroprotectors. The "screening" experiment, which was conceived by Batin and conducted by Chikunov, but whose results have not been published, was supposed to test about 1,000 known and safe substances on mice for life extension. However, the problem with such large-scale screening is that it will randomly have a high level of noise: that is, purely by chance, there will be results around the order of p=0.001.

3. Create aging biomarkers and base therapy on them. Alternatively, one can find biomarkers of aging without creating the actual theory of aging, simply by identifying a large number of parameters that correlate with lifespan. Then, look for substances that affect these biomarkers directly in humans. For example, if a certain therapy reduces weight, improves vascular health, strengthens muscle mass, we can assume with high probability that it extends life and slows down aging. This idea is largely the basis for the Open Longevity approach to the panel of aging biomarkers.

4. Comparative genetics of aging. The next approach is based on the comparative genetics of aging: that is, identifying genes that differ in similar species with different lifespans. If such genes are known, one can influence the results of their work – or even introduce additional copies of these genes into the organism. The introduction of myostatin and telomerase genes extended the lifespan of mice, and Liz Parrish, according to her words, tried this therapy on herself. While we cannot change the genes in all cells of an adult organism, which number about 30 trillion, for some interventions it is sufficient to change genes only in some cells. Of course, knowing which genes are associated with aging (and cancer) could make an "aging vaccine" that would treat human embryos at early stages, similar to how children's genomes were recently modified in China to make them resistant to HIV, but the risks here are unclear, and most importantly, it would do almost nothing for the currently living people.

5. The treatment targets not aging itself but the damages caused by aging. Aubrey de Grey's SENS proposes to shift the focus away from "theories of aging" and their causes and instead repair the damages that aging brings, as there is much less disagreement about these damages and they are more evident. "Personalized medicine" also implies treating not aging itself, but all diseases that arise due to it through early-stage diagnostics.

6. Computer modeling of the organism and big data collection. Another way to "avoid" creating a theory of aging is to directly address the issue at the level of molecular pathways and their computer modeling. This approach is based on the collection of large amounts of data about the organism and then creating a complete model of the processes occurring within. An example is the Cell Atlas being developed by Zuckerberg, aimed at "curing all diseases."

7. Activation of regeneration – here we assume that the body fundamentally knows how to heal itself, but needs help. For example, visiting a sauna activates heat shock proteins,

chaperones, which also clean the cells from debris. Periodic use of a diluted cocktail of Yamanaka factors (a group of four substances that create induced pluripotent stem cells) is also in this category. Small doses do not cause cancer in mice but (possibly) lead to their rejuvenation.

8. Solve an even bigger task, in which victory over aging is a special case. This could be the creation of one of the super-technologies: strong AI, advanced nanotech with nanorobots, or a fully controllable living cell (bionanorobot).

9. Circumventing the aging problem: cryonics, digital immortality, head transplantation onto a clone's body.

10. Slowing down time. In a sense, time is the essence of aging, as it is associated with it. But it's not the pure time of atomic clocks, but biological time, determined by the sequence of changes that occur. In a computer, time is set centrally by clocks that issue commands to change cycles. If we could find such a timer in humans, we could slow down time. The timer could either be some kind of upper regulating system, likely related to hormones, or, conversely, lie at the very bottom of all processes and be linked to temperature since all chemical processes slow down with temperature and animals with lower body temperatures live longer.

11. Aging vaccine: editing embryos, for example, by introducing copies of the P53 gene, which protects against cancer. However, testing its safety is very difficult: some mice with additional copies aged faster.

12. Preventing death without treating aging (spare heart, stopping atherosclerosis, immune system transplant). This is similar to SENS, as here we fight not with the mechanisms of aging, but with its consequences, and not at the cellular level, but at the level of diseases. Broadly speaking, all modern medicine is about this. It can be called "function replacement": we replace a tooth with an implant, but the function is preserved.

13. Elimination of aging accelerators: alcohol, smoking, gluttony, radiation, stress, sedentary lifestyle, radiation, destroying viruses (retrotransposons and transposons?).

14. "Elixir" of rejuvenation. Possibly, there are modes in the body when it performs its own rejuvenation, for example, dedifferentiation of stem cells, and this mechanism can be triggered. Examples of such approaches: parabiosis, Yamanaka factors, bone marrow stem cell transplantation (perhaps from others or one's own, frozen from youth).

15. Selective slowing of time. Preservation of tissue samples for transplantation: bone marrow stem cells, umbilical cord blood.

16. Rejuvenating co-evolution. Searching for human symbionts that lead to rejuvenation or artificially cultivating them. Many cultural plants received evolutionary benefits because their hosts survived better, meaning selection for these effects has already occurred, and we can combine life-extending cultural plants from different cultures to get a synergistic

effect. There are several suitable candidate cultural plants: grapes and olives in Mediterranean culture, green tea in East Asian. Bacteria can also be selected for human life extension, for example, Bulgarian yogurt and brewer's yeast, and perhaps some animals that we consume as food (cows?), consume dairy products, or simply use as companions (people with pets, cats and dogs, live longer).

17. Regeneration of regeneration. The idea here is to influence resilience systems that control other resilience systems.

I assume this list is complete, meaning it includes all the "what-strategies" (what we do) for fighting aging that have been proposed before. How-strategies tell us how to get funding to implement what-strategies.

Public Strategies: How to Organize Research (Where to Get Funding)

How wonderful it was in Montenegro! Our longevity school was held in Yugociani - an abandoned naval ministry on the shores of the Bay of Kotor, transformed by Marat Gelman into a residence for artists. Lists of some steamships, someone's paintings were scattered everywhere, and from the window of the toilet, there was a view of the expanse of the bay. Downstairs was a bar, with which we agreed that they would make us a life-prolonging menu. Every day there were salads with pomegranate seeds, greens, olives - and those who wanted to break the diet went to the meat shop, where I ate the most delicious meat in my life: pieces soaked in olive oil were grilled right in front of you, amply supplied with vegetables and carried out to the shady courtyard.

The day began with lectures by Veremeenko (but before that there was yoga for those who wished), then a lecture by Batin, then scientists: Timofey Glinin, Alexander Kolyada, Pyotr Fedichev. I printed and hung huge maps on the walls. In front of Yugociani was an abandoned courtyard, and we carried out tables and set them on the decking right by the water, with huge ships entering the bay as our backdrop. Here began the disputes, which then continued at night in the narrow streets of Kotor. And at the same time, it was scientific research: everyone took tests before the trip and after, and we observed changes in biomarkers.

It's great to do the most important thing in the world together with friends in a magical place. And the idea arises: let's scale this up, let's attract more people, hold meetings more often and for longer. Alas, I write these lines while on quarantine in 2020, when another school in Montenegro was canceled and no one knows what will happen next, whether air communication will be opened or parties will be allowed. The strategy constantly changes, but the goal remains the same.

One part of the Open Longevity strategy is the study of what strategies different organizations have to solve the problem of aging. A large excel file with such an analysis was made on the website http://openlongevitystrategy.org/ (not to be confused with the site http://openlongevity.org/, which describes the strategy of Open Longevity itself). In this excel file, you need to scroll to the right, and in the invisible part of it, a column with

program statements of different companies will open. In this right column are descriptions of companies' strategies:

"The main idea of Juvenescence is that multiple, well-differentiated approaches that are adapted to key pathologies and tissue-specific features of aging will be required to treat aging. We believe that people may need different therapeutic agents or combinations of therapeutic agents at different points in their development. To this end, Juvenescence is building a diversified portfolio of companies focused on various aspects of aging, weaknesses, and aging."

"The Coalition for Radical Life Extension unites like-minded people who come together to fight for radical life extension and physical immortality. Supported by People Unlimited, the coalition is a non-profit organization that works with groups and individuals who are already interested in radical life extension and physical immortality, with the aim of stimulating and focusing our energy in a broad movement that is self-sustaining and expansive. This group of early adopters, numbering in the thousands, forms a platform to influence a much broader audience and, ultimately, the mainstream."

The jargon-laden descriptions of startup missions are challenging to comprehend, and the fact that they are not featured prominently on the company's homepage or articulated in a single understandable language makes the analysis of company strategies practically inaccessible. Moreover, these missions often seem to be written more to dazzle investors than to guide action, resembling "how-strategies" — narratives about how to attract funding (through crowdfunding, investment portfolios, etc.) rather than concrete action plans. An empirical approach to analyzing the strategies of individual companies often becomes overwhelmingly complex.

In the field of anti-aging, the how-strategy generally answers the question of how to raise funds and conduct research. In contrast, the what-strategy specifies which research should be conducted. In nuclear weapons manufacturing, fundraising is not an issue since the state allocates funds and demands project execution. To find the right how-strategy, we look from the top-down, from the perspective of all possible theoretical projects, almost each of which has some organization working on it.

Table 4 (see below) lists all possible ways to raise funds for life extension research, classified by funding sources, and each method has been tried by someone. For instance, I once attended Aubrey de Grey's Ending Aging conference in Santa Clara, where a very imposing figure rumored to be a billionaire appeared. This Canadian billionaire, Nygard, had changed Bahamian legislation to experiment with stem cells there, though he was later arrested for sexual crimes.

Thus, the struggle for life extension boils down to funding. While there are plenty of good ideas and experiments to be conducted, funds, scientists, and interest in not dying are not lacking in the world; they just don't connect. From an investor's perspective, the situation might look different: the funds are there, but not the teams capable of utilizing them effectively. Even money misspent on immortality is better than funds buried in a cemetery.

So, where to get the money? The first thought for a person with an idea but no funds is to conduct the necessary research for free, through online collaboration, self-experimentation as a biohacker, or by assembling a group of enthusiastic volunteers, essentially creating a patient organization. The well-known biohacker Gwern conducted double-blind self-experiments with nootropics, taking unlabeled pills and recording the outcomes, though most did not work. Biohacking forums like Longecity are filled with self-reports of various self-experiments. However, research can never be entirely free—volunteers need to eat, and reagents must be purchased. Free projects are hard to scale and often stall.

Another idea is the commercial approach: if we create a valuable product, it should sell. But payment only comes in the future and only if successful. This requires transferring money from the future to the present, getting an advance. Banks won't provide this, so the classic startup form helps. A startup sells promises. Another concept is selling shares in a future anti-aging drug as an option to acquire it upon development. Or one could start selling something immediately, like supplements, tests, webinars, or merchandise. Ultimately, the pharmaceutical industry has funds—it's about engaging them to conduct the necessary research. If it's all about faith, why not create a new religion? But none of these methods seem to work. Earning money is hard, and it's even harder to extract funds from that process for another cause. Moreover, an anti-aging drug is a public good requiring long-term research, hence it's not a business project but a governmental one. The money must come from the state. How? One can work in a government institution, as most scientists do. But now, funding is needed again, and grants, issued by both states and private foundations, become the source. There are many problems with grants, but one can also attempt to indirectly influence government policy through political parties in democratic countries or bureaucratic lobbying. Finally, there's the "Bolshevism" idea—coming to power in a particular country.

However, the state only reallocates funds. The source of money is the people. Perhaps we should take money directly from the people? For instance, through membership fees or crowdfunding, selling them dietary supplements, or donations, or ICOs. But these are all voluntary contributions. The main source of money is the demand for anti-aging, which mainly goes to fraudsters: 300 billion dollars a year. How can we direct these funds to research?

On the other hand, most people live from paycheck to paycheck. They can't afford to donate; they've already given everything and are living in debt. But there are natural points of money concentration: billionaires. Having sold goods at inflated prices, they have collected the cream of the crop from the people, and now they could spend it on something useful. Many billionaires have signed the "Giving Pledge" – to donate half of their wealth to charity. Moreover, it would be in their own interest to live longer! The capitalization of a deceased investor is zero. But billionaires are continuously targeted by all sorts of projectors, and if they easily gave away money, they would quickly go bankrupt. How to influence a billionaire? It's difficult, as they are used to influencing others. And they know how to attract money, not give it away. Writing letters, elevator pitches? Or write a book, like this one? Or try to become a billionaire yourself?

But aside from billionaires, there are also institutions. For example, insurance companies – they would generally benefit from people getting sick less. Pension funds, on the other hand, may be legally obliged to care not only about money but also about investing in life extension. Investment funds, like Soft Bank, purportedly aim for the singularity. The military, who need super soldiers and protection against radiation, which is very similar to aging in effect. This also applies to manned spaceflight research. And what about aging dictators, who are like billionaires but even more powerful. Finally, many tech giants have already expressed interest in fighting aging and all diseases: Google, Facebook. And the WHO could finally recognize aging as a disease. Lastly, the aging population is becoming a primary concern for entire states: China, Japan, South Korea, Singapore.

But the truth is, it's very hard for a small organization to access big money. Therefore, one must and should take an indirect path. For example, by increasing the societal value of life extension, spreading rationality, sowing ideas, translating books and articles, and increasing the number of convinced supporters.

Table 4. Where to Get Money?

№	Main Source of Money	Main Varieties	Cases	Evaluation of Prospects
1	Conduct research without money.	Online Institute, Longecity – forum, Indian TB project	Lots of noise without a controlling authority	Biohackers, Gwern: Low value of the obtained data. Patient organizations: Effective for gays but require a cohesive community.
2	Commercial approach.	Start-ups (Gero, Insilico, Unity), Future shares (IVAO), Big Pharma	Selling ancillary services, Creating a new religion (Terasem)	

№	Main Source of Money	Main Varieties	Cases	Evaluation of Prospects
3	The state as a source of money.	Working within an existing medical institution or university, Obtaining grants for research (NIH); donors	Parties: increasing work in parliament, Lobbying, Seizing power in a particular country (Bolshevism)	
4	People as a source of money.	Selling supplements (Life Extension Foundation), Crowdfunding, Donations (effective altruism, SENS), ICO, Membership fees, Souvenir products	Using fundraising ideas for a non-profit fund, Redirecting demand from fraudulent anti-aging services to scientific research	
5	Billionaires.	Writing letters to billionaires, Convincing them with books, Organizing meetings with them and personal persuasion	Becoming rich oneself	
6	Major players with other, but similar goals.	Pension funds, Investment Funds (Soft bank), Military, Space research, Insurance companies, Aging dictators, Technology giants (e.g., Google with Calico), The Pope, WHO	Countries with strong population aging (China, Singapore, Japan)	
7	Indirect methods.	Spreading the value of life extension, Spreading rationality, Sowing ideas, Preparing convincing strategies, Creating a superintelligent AI		

№	Main Source of Money	Main Varieties	Cases	Evaluation of Prospects
		Increasing the number of supporters, Creating a large organization that generates money in various ways, Making fraud in life extension unprofitable, PR of star scientists (e.g., Church, Venter)		

One can also add a meta-strategy—that is, a strategy for developing a strategy. On the one hand, all possible and impossible ways of attracting money have already been tested by various organizations unrelated to aging, and there are different lists like "200 ideas for fundraising."

Of course, the problem of aging is very complex. But by calling problems "systemic" and "complex," we don't learn anything new. All problems are systemic and complex. However, what's interesting is that there are two types of complexity: one is the complexity we are familiar with, such as the weights of a neural network or the management of an army by its headquarters. That is, we have a complex system for which we know the location of all its screws.

The second complexity is the black box complexity, which is filled with unknowns. This is the complexity of aging, the external world, the psyche. Danila Medvedev suggests managing known complexity with a super-complex plan, based on the principle that the control system is more complex than the controlled system. But the complexity of the future is unknown. Therefore, here we need a simple plan for catching fish in muddy water, that is, a way to utilize this unknown complexity for our intended purpose. In situations of hypercomplexity, only very simple models work, but they utilize the diversity of the environment implied by hypercomplexity: for example, one such model is "just throw the hook many times," and the second is "throw the hook in different places." If we produce too complex a model without having access to the object being controlled—that is, the front of scientific development—then by the time we tinker with it for five years, everything will have already changed.

The uniqueness of the strategy is important

Jack Ma, the founder of Alibaba, wrote that if an idea comes to mind to the majority of meeting participants, then it is bad because the same idea is obvious to competitors. Unique ideas are needed.

Batin says that since settlements for life extension will inevitably arise in the future, it means we must make them. I objected that some things arise on their own, but there is no need to make them. But he said that it should grow out of the school of longevity, which can occur in different places, that is, we are not necessarily talking about a physical settlement.

But I also thought that here an important part of the discourse is "what exactly can WE do." There are many good and important things that we cannot do because we do not have the necessary competencies and resources. But there are a number of things that only we can do because we have unique skills that are unique in the world. Essentially, our strategy is a choice between such unique things that only we could do, because what others can do well, let them do.

Also, strategy is not a list; you cannot say, "we will do both A and B." Strategy is a choice of priority over the list, that is, first A, then B—or vice versa.

At the same time, our strategy must answer the question of how to direct 100 billion a year on a global scale to aging research over the next 5-10 years. If it cannot scale to such a scale or at such a speed, then it is not suitable for us, even if it works a little.
So, what we choose between:

- Longevity schools, turning into a university of longevity (with settlements, research institutes, diagnostics)
- A patient organization (scaling research at the expense of patients)
- A global party of life extension (activism, attracting attention, participating in parliament and receiving government money)
- Write a book that will turn the world upside down ("Immortality" A new bible?)
- Scientific articles in English proving the importance of different strategic decisions
- Writing a detailed research plan, what-strategy.
- Hanging out with billionaires.

Here we need to ask, what is the best immediate alternative to his project? If not A, then what is B? That is, what good are we giving up?

And since we need a fundamental solution, we need long-term money directed at long-term experiments with a high probability of failure. This means that it is not the money of private investors in startups, but government money directed to universities, and not only Russian ones, but also American or other major players.

How much funding is necessary for fundamental research in the field of aging?

There are two interrelated issues: the required amount of funding and the extent to which progress can be accelerated. For instance, no amount of investment in the 19th century could have led to the creation of the atomic bomb, as the direction for research was unclear until the discovery that uranium salts fog photographic film. Similarly, it may be impossible to develop an anti-aging drug without a discovery akin to CRISPR. Conversely, without any effort, an anti-aging drug might eventually be invented by someone.

So, how much money is needed to expedite progress in creating an anti-aging drug? We can look at reverse examples: for decades, cryonics, combinations of geroprotectors, and head transplants could have been studied but weren't, due to various social reasons (ethics, misunderstanding). Thus, it's conceivable that progress can be accelerated—or delayed by decades, but not centuries (barring a global catastrophe). Aging will eventually be halted; for humanity, it's a resolved issue. But for us living now, decades are the critical difference between life and death.

How much money is needed to accelerate progress in life extension? Indeed, large sums have sometimes attracted fraudsters and destroyed entire knowledge fields due to excessive funding, as with nanotechnology, which failed to produce nanorobots and instead redefined various thin films. There's also a limit to the meaningful expenditure at each stage: too much money might end up with the wrong people, leading to a majority of inefficiency, decreased quality, and shifted focus.

Currently, there aren't enough scientists with ready experiments in life extension to justify immediate tens of billions in funding. In contrast, global defense spending is around a trillion a year, arguably the upper spending limit worth considering. According to WHO, global healthcare research expenditures amount to hundreds of billions annually, but are extremely unevenly distributed among different mortality causes (e.g., malaria and tuberculosis are underfunded, receiving only 1% despite contributing 12% to the overall "disease burden"). Meanwhile, individuals spend 200-300 billion on unproven aging therapies annually, indicating the size of the paying demand.

A yearly sum of approximately 100 billion dollars for combating aging seems realistic: it wouldn't overload or distort the existing scientific research system. The situation might change in decades, with new generations of scientists and robotic research systems able to handle larger investments, but for now, 100 billion seems a reasonable limit—albeit unlikely to be reached. Actual spending, considering budgets of national aging institutes, Calico, and various startups, is closer to 1 billion a year, and not always maximally effective.

Thus, it would be beneficial to increase funding for anti-aging by 100-fold in the 2020s. Ideally, the world would adopt an emergency "war" mode, acknowledging that people are dying, and create an infrastructure capable of efficiently investing a trillion in life extension research technologies. However, this isn't even happening with green energy, despite all the hype and figures like Greta Thunberg. Yet, when the COVID-19 pandemic struck, it became apparent that medicine is more important to us than tanks, flags, and territories,

and many scientists shifted focus to COVID-related projects. Moreover, COVID-19's mortality curve is similar to the Gompertz curve for aging, making aging the primary mortality factor for COVID-19, and thus the main cause of death from the virus.

How can billions be mobilized with minimal effort? How can the potential demand from wealthy retirees, dictators, billionaires, and states with aging populations be connected to the island of scientists capable of conducting the right experiments? The main idea is to lay a thin steel thread that will carry the electrical charge connecting positive and negative poles.

One might think it sufficient to explain to all stakeholders that it would be rational to direct money towards honest fundamental aging research, from which everyone ultimately benefits. Perhaps just one explanation, or even one book—this book, "Immortality"—would suffice? Another idea is to demonstrate the benefits of such a rational approach. For example, insurance companies could profit if people were healthier; billionaires could hold onto their wealth longer, and so on. But even this simple thought must be communicated. Generally, there is a chain of events through which an idea penetrates the masses: from a random thought in discussions on a closed internet forum to a scientific article, then a book by a popular philosopher like Bostrom or Harari, followed finally by a tweet from Musk and a half-page discussion on CNN. Then, it becomes a topic discussed everywhere. Ideas about dangerous AI or Roko's Basilisk developed similarly.

The strategy to combat aging should be a SMART goal: specific, measurable, achievable, relevant, and time-bound. When it comes to attracting funds for research, this is measurable: we need to increase funding to 100 billion dollars a year over 10 years.

Collaboration with one's copies and collective strategy

It seems pointless to vote in elections: there are millions of people, and my single vote will not make a difference. However, if everyone reasons this way, our candidate will lose. If I decide not to vote, then many other people who think like me will also not vote. Thus, in some acausal, non-causal way, my decision not to vote influences the decisions of others. Does it sound absurd? But this is what the functional decision theory, developed at MIRI, suggests.

This is easiest to understand using the example of copies. Suppose there are 1000 copies of me, and each contributes one dollar to the crowdfunding of aging therapy. Bam – we have 1000 dollars. However, if I, one of the copies, decide not to contribute, it won't causally affect the other copies: they won't know about it. But each of them, being an exact copy of me, will reason in the same way as I do. As a result, none will contribute, and not a penny will be raised.

Okay, but what if the copies are not exactly the same? One copy holds a paper with the number "1" on it, another "2", and so on. And here I am, the first of the copies with "1" in my hands, deciding not to contribute to the crowdfunding. But I'm just being stingy, and the number in my hands didn't explicitly influence my thoughts, except perhaps as a source of randomness. Then all the other copies will also reason the same, even being slightly

different. And, continuing this line of thought, one can move away from the concept of copies altogether, leaving only identical lines of reasoning.

As a result, by making a certain decision, I decide not only for myself but for all who reason exactly as I do, which greatly amplifies our collective power.

Radiation Damage and the Szilard Theory

Radiation damage is similar to aging. For example, prolonged exposure to the sun causes skin aging. But could aging itself be caused by the weak radioactive background in which we live? From this background, the most important is the internal irradiation from the natural isotope potassium-40, which, like uranium, has a half-life of several billion years. It cannot be eliminated because potassium is vitally necessary. The dose from potassium-40 is 0.16 mGy per year = 16 millirads per year, and this needs to be multiplied by the internal absorption coefficient, which is on the order of 40-100. This is roughly equivalent to 1 roentgen per year, or 80 roentgens over a lifetime. The overall dose is not small.

Interestingly, Leo Szilard, the discoverer of the principle of the nuclear bomb, created his aging theory in 1959, based on the idea that the number of cells in the body decreases with age due to various random processes, which he called "hits of aging" (he did not yet know about the existence of stem cells, but if his theory is applied to the reduction of the stem cell population, it already resembles part of the truth.) In 2009, his theory was revisited with new data, and instead of chromosomal destruction, they began to consider the deactivation of individual genes. Overall, his theory predicts the observed mortality curve well (which, however, other theories do too).