

Altruism and Phenoptosis as Programs Supported by Evolution

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Abstract—Phenoptosis is a programmed death that has emerged in the process of evolution, sometimes taking the form of an altruistic program. In particular, it is believed to be a weapon against the spread of pandemics in the past and an obstacle in fighting pandemics in the present (COVID). However, on the evolutionary scale, deterministic death is not associated with random relationships (for example, bacteria with a particular mutation), but is a product of higher nervous activity or a consequence of established hierarchy that reaches its maximal expression in eusocial communities of Hymenoptera and highly social communities of mammals. Unlike a simple association of individuals, eusociality is characterized by the appearance of non-reproductive individuals as the highest form of altruism. In contrast to primitive programs for unicellular organisms, higher multicellular organisms are characterized by the development of behavior-based phenoptotic programs, especially in the case of reproduction-associated limitation of lifespan. Therefore, we can say that the development of altruism in the course of evolution of sociality leads in its extreme manifestation to phenoptosis. Development of mathematical models for the emergence of altruism and programmed death contributes to our understanding of mechanisms underlying these paradoxical counterproductive (harmful) programs. In theory, this model can be applied not only to insects, but also to other social animals and even to the human society. Adaptive death is an extreme form of altruism. We consider altruism and programmed death as programmed processes in the mechanistic and adaptive sense, respectively. Mechanistically, this is a program existing as a predetermined chain of certain responses, regardless of its adaptive value. As to its adaptive value (regardless of the degree of “phenoptoticity”), this is a characteristic of organisms that demonstrate high levels of kinship, social organization, and physical association typical for higher-order individuals, e.g., unicellular organisms forming colonies with some characteristics of multicellular animals or colonies of multicellular animals displaying features of supraorganisms.

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I once asked my old friend, the famous philologist and metrician M. L. Gasparov: “Mikhail Leonovich! How would you call the programmed death of an organism if a similar type of phenomenon with respect to a single cell is called “apoptosis”? “Phenoptosis!” – answered the academician without any hesitation.

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INTRODUCTION

The problem whether biological evolution could naturally lead to the development of counterproductive (harmful to an individual) programs has been debated for more than 50 years. The opponents of this idea claim (see

the history of this issue in [1, 2]) that the development of such programs as aging and lifespan limitation under the pressure of selection is impossible, because individuals in which these programs are disrupted (e.g., due to random mutations) receive reproductive advantage and will displace the carriers of the counterproductive programs. However, the study demonstrating that mutation in the insulin receptor gene *daf-2/IGF-1* could more than double the lifespan (LS) of the nematode *Caenorhabditis ele-*

Abbreviations: LS, life span.

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gans [3] has rekindled the discussion on possible adaptive advantages of aging. It has been suggested that the wild type *daf-2* allele could provide selective advantage through the increased genetic diversity or decreased competition between parents and offspring in the species with short LS [3]. The adaptivity of aging and death programs predicted long ago by Weismann [4] has been recently confirmed, first, through mathematical modeling [5], and next, in the studies by the D. Gems group [6-8]. This has shifted the discussion on the emergence of counterproductive programs in the course of evolution from the philosophical to the scientific one.

Under certain circumstances, programs that had initially developed as protective ones could become counterproductive. These include inflammation, which is not a disease *per se*, but rather a response of an organism to pathology at a certain location. However, if no cure is provided and the disease becomes chronic, inflammation could bring even more suffering than the disease itself, and could facilitate inflammaging [9]. Wang and Medzhitov [10] postulated the existence of correlation between thermoregulation, metabolism, and host response to infection. According to the authors, immune system utilizes body temperature regulation as a strategy to control the rate of metabolism, which, in turn, promotes the resistance to the inflammation-associated damage. Let's look at the pain syndromes as an example. Pain is definitely useful as it informs an organism on injury or unacceptable parameters of external or internal medium (temperature, etc.). However, chronic pain could make an individual to suffer, so that the only thought would be on how to switch off this system, which is actually most useful from the evolutionary point of view. At present, pharmaceutical companies spend a lot of money on the development of anti-inflammatory and anti-allergic preparations, as well as on painkillers.

The mechanism of pathology development has been explained by Ye and Medzhitov [11], who imagined the homeostatic state as a ball inside a parabolic-shape hole of the norm. When some factors attempt to throw the system off-balance, homeostasis-regulating factors will try to bring the system back, similarly to the ball rolling back to the bottom of the hole under the force of gravity. However, excessive acceleration of the ball (even for the fast stabilization at the hole bottom) could bring it outside of the hole without the possibility to come back, and in this case, the system cannot return to the normal state. The inflammatory response is required to restore the equilibrium, but in the case of severe pathology, this response could push the system further away from the norm, which could result in its stabilization in the state of chronic pathology.

In particular, inflammation could develop in response to allergens and poisons, tissue damage, stress conditions (environmental factors, unhealthy life style), and, obviously, infection. In all these cases, such response

is evolutionary and physiologically justified, as it protects the organism by removing harmful agents, conditions, and "invaders", and restores the damage. However, excessive response could cause problems, e.g., development of allergy due to the excessive hostility towards foreign (even harmless) compounds. Continuous fight against infection could lead to the emergence of autoimmune response and even sepsis. Pathological tissue healing could cause fibrosis and cancer. Severe allergic reaction can lead to rapid health deterioration, shock, or death, even if the original allergen itself is relatively harmless. The failure of the body defense systems could be the reason for autoimmune diseases, which are, however, caused by the highly programmed immune response. It is commonly recognized now that the immune response is stimulated by different damage-associated molecular pattern molecules, DAMPs, and pathogen-associated molecular patterns, PAMPs. These molecules are quite diverse structurally and could be both of protein (endogenous heat shock proteins S100 or HMGB1) and non-protein nature (uric acid, heparin sulfate, mono- and polysaccharides). The same effect is observed when DNA is present anywhere other than the nucleus and mitochondria, as well as when nucleotides (ATP) and nucleosides (adenosine) are found at high concentrations outside the cell [12, 13].

However, the most known counterproductive programs that could emerge (and emerged) in the course of biological evolution are phenoptosis and altruism.

The term "phenoptosis" was first introduced in the literature by Professor V. P. Skulachev in 1997 [14] (see also [15-18]). According to the definition, phenoptosis is the most counterproductive program among all mentioned above, as it leads to death.

The issue of the programmed nature of slow (chronic) phenoptosis (aging) is complicated by the ambiguity of the term "programmed aging" [19, 20], which could lead in logical confusion [6] and should be eliminated to avoid conceptual errors.

The word "aging" in the term "programmed aging" should not be referred to all changes occurring with age (including favorable changes associated with maturation), but rather to the age-related changes associated with the organism deterioration (or *biological aging*) [7], implying that such program has developed under the selection pressure to increase adaptability.

Cell cycle program can decrease the organism adaptability, as in the case of cell proliferation in malignant tumors [7]. Blagosklonny [21] suggested the term "quasi-program". In this case, aging (similar to continuing growth during the development) would be due to an inadequately intense cell functioning. The theory of hyperfunctioning quasi-programmed aging explains inflammation and immune aging, hyperinflammation, hyperthrombosis, hypothrombosis, and cytokine storm associated with the age-related increase in the organism

susceptibility to COVID-19. Hence, programmed aging was divided into adaptive and non-adaptive (or programmed and quasi-programmed). On the other hand, to protect from this type of death, mammals in the process of their evolution have lost necroptosis several times: either via the absence of central components of necroptosis, such as RIPK3 (receptor-interacting protein kinase 3) and MLKL (mixed lineage kinase domain-like protein) important in etiology and development of many disease with the increased risk of death (ischemic damage and sepsis) or due to inactivating mutations in these proteins (frameshifts mutations or premature stop codons) [22].

Increased diversity and complexity of counterproductive programs is a consequence of the emergence of organized communities (societies, herds, flocks, etc.) consisting of *multiple individual* organisms. These communities are capable of performing coordinated actions similarly to how individual cells in a multicell organism behave. However, cell functioning in a multicellular organism is coordinated by special centralized regulatory systems (e.g., nervous system), which are lacking in the groups of individual organisms. Hence, the actions of such individual organisms are coordinated by other mechanisms, including *quorum sensing*. The key signal triggering the mechanism of community formation is often crowding. When the concentration of signaling molecules exceeds a certain threshold, global gene expression patterns change due to quorum sensing [23]. For example, *Vibrio fischeri* bacteria start to emit light only when a certain cell density is reached [24]. The differences in the composition of human gut microbiota are associated with pathologies, e.g., inflammatory diseases. Bacteria communicate with each other with the help of extracellular molecules (autoinducers) in the process termed quorum probing [25, 26]. It is assumed that bacteria communicate with each other and with their host, and the information on these interactions affects the population density and species composition of commensal bacteria, as well as the physiology of the host cells [25, 26].

Altruism is commonly considered to involve behavioral strategies and actions that are unfavorable for an individual, but provide advantage to other members of the community (with respect to reproduction and adaptation). In a biological sense, altruism is a type of behavior resulting in the increase of adaptability (and, as a result, reproductive success) of other community members at the expense of the chance of successful reproduction of the altruistic individual.

In this article, we discuss the mechanisms behind the evolutionary emergence and modifications of such counterproductive program as altruism, one of the high-level manifestations of which is phenoptosis (i.e., when an individual helps others at the expense of its own reproduction and life).

ALTRUISM

Altruism could be divided into two distinct types. In the first case, an individual becomes an altruist *passively* under the effects of the environment, without any internal changes. These environmental factors could be changes in other individuals (e.g., cheaters), or when an individual is forced to become an altruist in the communities with strong hierarchy. In the second case, an individual becomes an altruist *actively* due to the changes in its own organism. At the first glance, emergence of the latter type of altruism in the evolution, the driving force of which is absolutely egoistic natural selection, seems paradoxical.

However, natural selection implies automatic and unbiased evaluation of all favorable and unfavorable effects on all allele copies in the population – if advantages outweigh disadvantages, this allele propagates. Hence, from the “altruistic allele” point of view, this situation is not altruistic at all, but pure egoism. This allele forces all its carriers to perform altruistic acts and to sacrifice several of its copies in order to bring advantage to its other copies. The moving force of evolution is natural selection of random hereditary changes [27]. If organisms pass down their individual features to the offspring, if these features change randomly sometimes, and finally, if at least some of these changes increase the probability of reproduction, then the future generations of these species must become more perfect without any external intervention. In this case, perfection is understood as adaptability manifested as the reproduction efficiency [28].

Altruistic sacrifice of one’s reproduction could be either partial or complete. In the latter case, it is in essence phenoptosis (*phenoptotic altruism*) with the difference that it is the offspring and not the individual that gets eliminated.

The mechanisms of altruism emergence. There are multiple ways for the altruism to emerge in the evolution. In particular, it can appear as a result of kin selection. The Hamilton rule asserts that an altruistic gene (more precisely, allele facilitating altruistic behavior) will be favored by selection and will propagate in the population, thus eliminating the competing “selfish allele” from the gene pool. If $nrB > C$, where r is the genetic relatedness of the altruist to the beneficiary; B is the reproductive benefit gained by the recipient of the altruistic act; C is the reproductive cost to the individual performing the act, and n , number of recipients of the altruistic act. If $nrB > C$, the altruistic allele will automatically and inevitably increase its frequency in the population gene pool.

Other mechanisms of the evolution of altruism are not directly associated with the relatedness between the altruists and beneficiaries. For example, the Simpson’s paradox describes a situation when a total fraction of altruists increases in the entire population even if in each local group, altruists lose to egoists in competition and

their fraction decreases. This phenomenon was experimentally demonstrated for two modified laboratory strains of *Escherichia coli* [29]. The essence lies in the fact that if the number of founders of a new group is low, which happens when the population is dispersed, this group can randomly contain an increased percent of altruists. Due to initial abundance of altruists, the number of individuals in this group will increase fast, while groups including a higher proportion of egoists will grow slower. As a result, the Simpson's paradox will ensure the total growth of the fraction of altruists in the entire population. Population bottlenecks (i.e., periods of significant decline in the population size followed by its restoration) can serve as analogy of fractionation (partition of cells between test tubes) in nature. This occurs, for example, when new substrates are seeded with very low numbers of microbial "progenitors".

Egoistic evolution of individual symbionts within a cooperating system is impossible in the case of their genetic homogeneity, i.e., in the absence of variability, which is one of the main components of Darwin's evolution.

The mechanism for the maintenance of genetic homogeneity in symbionts of termites of the Macrotermitinae subfamily is very interesting. The termites collect spores of *Termitomyces* fungi in the vicinity of the nest to create fugal gardens. The initial seeding material is genetically diverse; however, each host colony is associated with a single fungal symbiont [30]. It was found that genetically identical *Termitomyces* mycelia help each other (but not other mycelia) to generate conidia [30], which eventually results in the formation of monoculture.

When the evolution could not ensure the identity of cooperators, the hosts have to fight against egoists using different methods or to rely on the mechanisms ensuring the balance between the number of egoists and noble cooperators (Simpson's paradox, or balancing selection).

The discussed examples suggest that if it were not for the problem of cheaters emerging due to the lack of evolutionary preference for the benefit of species (and not the gene) and the absence of evolutionary foresight, cooperation and altruism could have become the dominating forms of relationships between the organisms on our planet. But evolution is blind and, hence, cooperation develops only when a certain set of circumstances either curb the number of cheaters or prevent their emergence.

It could be stated in conclusion that natural selection could ensure altruism development under certain circumstances, even if it favors egoists in each separate group (community), condemning altruists to gradual extinction. The spectrum of conditions that facilitate the Simpson's paradox is quite narrow; that is why its role in nature is likely insignificant.

Genetic basis of altruism in humans. When speaking about altruism evolution in primates, especially in

humans (regular biological evolution based on gene selection), one must also consider social and cultural evolution that implies selection of ideas and memes (such as moral and ethical standards, rules of conduct in the society, etc.), as well as the intergroup competition [31, 32].

Twin studies revealed that the inclination to kindness, trustfulness, and thankfulness is of genetic nature. These features are partly hereditary and at least by 10-20% are determined by the genes [33]. This means that biological evolution of altruism in humans has not finished. Human population is still characterized by genetic polymorphism that determines higher or lower inclination for cooperative behavior and mutual trust. Depending on the environmental, social, and economic conditions, natural selection might favor either trustful cooperators or wary egoists, and the variability of these conditions maintains the existing diversity. This could also be explained by the frequency-dependent balancing selection: the more trustful altruists are around you, the more profitable it becomes to nonreciprocally benefit from other's kindness. However, if the number of such parasites is high, their strategy becomes less profitable; the society starts to perceive them as a real threat and implements measures to curb egoism. Several genes have been identified that affect human personality, including moral qualities [34]. For example, intranasal administration of oxytocin in humans increases their inclination to express selfless altruism [35]. Similar effects have been found for the allele variants of the AVPR1a vasopressin receptor gene and oxytocin receptor gene (OXTR) [36].

Altruism and society. Some authors state that real selfless altruism toward non-kin is very rare in nature [37]. At the same time, parochial altruism (benefit to the in-group) is common for humans, and such in-group does not have to include blood relatives only. Indeed, observing human society reveals that many people selflessly help and support non-relatives over relatives. In this case, the preference is to the "kindred spirits". Very often this involves supporting people with attractive (and new before their first expression) ideas. In developed countries, help is provided mainly in a form of money; in poor countries, other forms of support are more common. At the same time, people do not support those they do not like (even if they are blood relatives). The closest relatives are often an exception, since it is customary to help them in any situation (this refers primarily to the Western industrial societies, while in the traditional societies, social institutes based on kinship are more developed [37]).

In reciprocal altruism, individuals behave altruistically to each other, but only in the case when they expect reciprocal sacrifice [38]. This can be observed in animals that are sufficiently intelligent to select reliable partners, monitor their reputation, and punish cheaters.

In the within-group tug-of-war model [39], each individual selfishly expends some fraction of the total

group output (“communal pie”) to increase its share of that output. This selfish fraction expended for the within-group competition is called the “selfish effort.” An individual’s share in the tug-of-war (“slice of communal pie”) depends on the individual’s selfish effort in the tug-of-war relative to the summed selfish efforts of other group members. The model of the between-group tug-of-war relationships is based on the same principles, which creates a two-tiered, nested tug-of-war competition. The more energy is expended by individuals in the within-group competition, the less energy remains for the between-group tug-of-war, and the less is the size of the “communal pie”. Studying this model using the game theory confirmed that the between-group competition (manifested in this case as the decrease in the individual selfish efforts) should increase with the increase in the degree of the within-group kinship (which is in complete agreement with the theory of kin selection). However, the model demonstrated that if the competition between the groups is intense, cooperation could exist even in the case of very low degree of kinship between the group members.

Intergroup competition is one of the main factors stimulating development of cooperation and altruism in social organisms [39]. Darwin was the first to suggest an association between the evolution of altruism and intergroup competition [40]. Later, this theory was applied to social insects. Nothing brings community closer together than joint confrontation with other communities; this is a very reliable strategy for building an altruistic “anthill” [39].

Mathematical modeling supported the idea that in humans, altruism towards members of one’s own group could develop only in combination with the development of parochialism (hostility to strangers) [41, 42], as it has occurred in multiple intergroup conflicts. According to Bowles [42], tribes of our ancestors feuded between themselves and had strong kinship within the tribes, which could facilitate the development of altruism in the groups due to natural selection. Bowles demonstrated that the level of altruism development depends on four parameters: (i) intensity of intergroup conflicts, which can be evaluated based on the number of war-related deaths; (ii) effect of the increase in the fraction of altruists (for example, soldiers ready to die for their tribe) on the probability of winning in the intergroup conflict; (iii) how much higher is the degree of kinship within the group than the kinship between the groups; and (iv) group size. According to the calculations, selection in the society of primitive hunter–gatherers should favor intragroup altruism at a high level with the corresponding decrease in the individual adaptation of altruists by 2–3%. In other words, an altruistic gene could spread in the population even if the chance to survive and reproduce of the carriers of this gene was 2–3% lower than for the egoistic tribesmen. Bowles presented two following calculations. If the initial allele frequency in the population is 90%, and the repro-

ductive success of the carrier of this allele is by 3% lower than of the carriers of other alleles, the frequency of the “harmful” allele will decrease from 90 to 10% already after 150 generations. Hence, from the natural selection point of view, reduction in adaptability by 3% is critical. If the same value (3%) will be considered from the “military” point of view, then in order to keep the degree of altruism at the level of 0.03, the death toll in military conflicts must be more than 20% (taking into account the frequency and severity of Paleo wars). This means that in the case of serious war conflicts, every fifth altruist must sacrifice his life for the common victory [42].

Hence, it is likely that such opposite human qualities as kindness and aggressiveness have developed simultaneously [43]. It was established that among 3 to 6-year-old children, only 5% are selfless altruists. This value grows with age, holding back the development of social parasitism [43]. These features of child psychology are products of both biological (genes) and social (upbringing) evolution. For example, a new behavioral attribute could initially be passed from generation to generation through education and imitation (similarly to the process occurring in ants and many other animals) and then will be gradually be incorporated into the genes (Baldwin effect) [44].

Natural selection in the evolution of social animals results in the development of various predominant forms of social and reproductive behavior. For example, rodents can live in small and large groups, be more acceptive or aggressive toward their relatives (including newborns), and either form or not form relationship with other member of the group (including breeding partners). Any of these behavioral adaptations could promote adaptation to certain environmental conditions, but could also require compromises, such as communal use of resources, higher parental investment, increased risk to become a victim of a predator, and others [45]. Any communities – primitive anonymous communities or highly developed personalized communities *in which all members know each other from personal experience* – can facilitate adaptation and be supported by selection. The lifespan of social animals is usually longer than of their single counterparts. The pinnacle of sociality evolution is eusociality. Most researchers [46–49] define eusociality as an adaptation to communal living in the same nest inhabited by adult individuals when (i) they are represented by at least two generations, (ii) they cooperate in performing various tasks, and (iii) have particular reproductive functions (existence of casts). Eusociality is widespread among Hymenoptera (ants, bees, Vespidae and Sphecidae wasps) and termites. In each of these groups, social life has emerged independently. Communities of these insects are personalized. For example, northern paper wasps (*Polistes fusca-tus*) recognize each other by facial patterns [50, 51].

It has been assumed previously [52] that eusociality in insects could develop as either a parasocial phenome-

non (voluntary association of individuals into community that develops more complex care of the offspring), or sub-social phenomenon (development and increase of complexity of parental behavior). In reality, the parasocial pathway is unlikely to exist, because firstly, there are no known species whose colonies end their development without transitioning to the mother–daughter relationship [53]. At the same time, *eusociality* development through the subsocial pathway has been demonstrated for all studied bee and wasp species. The emergence of non-productive cast in the mother–daughter societies only is also postulated by the haplodiploidy hypothesis. According to this theory, due to the haplodiploid sex determination in Hymenoptera, sisters become more close relatives than mothers and daughters, and, hence, according to the Hamilton's rule, it is more profitable for an individual to take care of sisters than to produce its own daughters. Moreover, it has been shown that even a high degree of genetic relationship between the workers in the nest is often insufficient for “reasonable selfishness”, i.e., voluntary refusal of workers to lay their own eggs. It is likely that this mechanism is maintained more efficiently, when strict “police measures” are implemented (such as destruction of “illegal” eggs by other workers) [53].

Mechanisms for the maintenance (regulation) of altruism. After altruism has emerged, it should be maintained, which is hindered by cheaters. In order to survive, species with a high proportion of altruists should protect themselves from “free riders” (cheaters). The presence of egoists makes the emergence of mutations providing protection from them very likely. In the social amoeba *Dictyostelium*, this results in the evolutionary arm race between the cheaters and “noble” amoebas [54]. Experiments in genetics and selection have allowed to produce mutant amoebas that were securely protected from the cheaters due to the emerged protective mutation (although not from all cheaters, but only from those they competed with in the experiment). Moreover, the mutants protected both from cheaters themselves and other noble amoebas if the latter were present. These experiments were repeated many times, and every time, one or another strain of amoebas developed mutations responsible for the emerging resistance, although these mutations were in different genes and determined different resistance mechanisms in each case. In the process, some cheater-resistant strains became cheaters themselves towards the “wild” amoebas, while the other remained noble [54].

A single mutation in the *Mixococcus* bacteria in one of the regulatory genes affecting bacteria behavior transformed cheaters into cheater-resistant altruists [55].

In yeast, “peaceful co-existence” of altruists (producers of commonly beneficial product invertase, an enzyme cleaving sucrose into glucose and fructose) with cheaters (yeast cells that do not synthesize invertase, but consume glucose produced by other community mem-

bers) is ensured by a small advantage received by the altruists in the presence of very low glucose concentrations in the medium, as well as by the special non-linear dependence of yeast proliferation on the amount of available nutrients. Around 1% of the monosaccharides produced by altruists are consumed by altruists themselves; hence, if the content of altruists in the mixed population is very low, it becomes more beneficial to produce invertase than not to do this [56].

It is likely that the evolution of social bacteria and Protozoa has shifted many times towards the formation of multicellular organism. However, no real multicellular organisms had formed in the course of evolution from social bacteria or Protozoa (only plasmodia and fruiting bodies). One of the reasons for the evolutionary futility of the multicellular organism formation from associations of single-cell individuals is the fact that such associations provide ideal conditions for the development of social parasitism. Any mutation that provides a single-cell individual with the ability to use advantages of living in a multicellular community without contributing to it in return has the chance for spreading despite its disastrous consequences for the community.

The mechanism of altruism maintenance through improving the reputation of an altruist (“indirect reciprocity”) is realized in humans through verbal communication – the most ancient way of spreading compromising information about the unreliable members of the community, which facilitates team building and punishment of egoists [57]. Interestingly, Arabian babblers (*Turdoides squamiceps*) compete for the possibility to perform “good deeds” (acting as sentinels, helping to take care of chicks, feeding other adult birds), because it improves their social status. In other words, these birds have an institution similar to human reputation [58].

Possible mechanisms of phenoptosis development. In a wider sense, phenoptosis is a programmed death that often develops as an adaptive (benefiting descendants) death [7, 59, 60]. Based on the latest data [6-8], we can say with confidence that adaptive death exists in many groups of organisms, from unicellular ones to vertebrates. The question remains open whether phenoptosis could have developed in the course of evolution if it does not provide any benefits to the community. Adaptive death increases combined (inclusive) adaptation, i.e., the efficiency of the individual's gene transfer to the next generation independently on the carrier of gene copies (individual's offspring or relatives) [6].

Colonial unicellular organisms (*Saccharomyces cerevisiae* yeast), demonstrate the type of adaptive death of named “biomass sacrifice” [6]. As the availability of nutrients in the aging yeast colonies decreases, some cells in the colony center undergo programmed death [60-62].

Another variant of adaptive death recognized by Galimov and Gems [8] as *consumer sacrifice* was described in detail for a number of bacteria in [63, 64].

For example, individual cells of *Myxococcus xanthus* die in order to stop to consume nutrients, which increases the availability of these nutrients for the relatives [65]. Some cells in *Bacillus subtilis* biofilms form spores and continue to grow using alternative metabolites [66]. Sporulating cells produce cannibalistic toxins, which kill their non-sporulating relatives. *Streptococcus pneumoniae* bacteria acquire ability (competence) to absorb exogenous DNA and produce bacteriocins that selectively kill non-competent cells [64, 66, 67]. The mechanisms of adaptive death have been investigated by Galimov and Gems [8] in the free-living nematode *Caenorhabditis elegans* [6, 68]. Adult *C. elegans* are hermaphrodites that first produce spermatozoa and then oocytes. The resulting limitation of the number of spermatozoa results in the cessation of reproduction already 2–3 days after the worm reaches its reproductive maturity, which potentially facilitates evolution of adaptive death [6]. Furthermore, significant age-related reduction in the consumption rate in *C. elegans* increases the availability of food for the relatives [69]. Galimov and Gems [8] used modeling to demonstrate that in the case of high reproductivity, shorter reproductive period and shorter lifespan increase the colony adaptivity by decreasing nonproductive food consumption in the population.

In general, adaptive *death* develops easier in the organisms subjected to reproductive *death*: early termination or slowdown of reproduction (for any reason) create premises for the evolution of phenoptosis [6, 70]. One of the known examples of reproduction-associated altruistic behavior is observed in the representatives of Mantises order (for example, in *Miomantis caffra*). In this case, self-sacrifice of males is probably the best strategy. Males that are ready to sacrifice their life have received the advantage in the course of natural selection. Mantis male is an ideal food for the fertilized female, which can provide sufficient amount of protein for the entire pregnancy, thus improving the chances for procreation. It was found that the amount of nutrients in the eggs from females that ate their males was 3-fold higher than when the male partner remained alive. Therefore, mantises devour their males for the sake of providing future progeny with protein. However, this behavioral response is not absolutely determined and allows variations – in half of the cases male mantises manage to avoid death [71].

Some spider males really “want” to be eaten and plunge themselves into female chelicera. This is observed for spider species (for example, *Argiope bruennichi*) in which the number of small males is significantly higher than the number of large females, i.e., an individual male has virtually no chance for repeated mating even if it remains alive [72].

The synthesis of catecholamines and neuropeptides responsible for feeding behavior drops drastically in the tissues of optic glands of the California two-spot octopus (*Octopus bimaculoides*) females in the course of reproduc-

tive cycle (when females care for eggs). Simultaneously, the synthesis of steroids involved in the metabolism of cholesterol and insulin increases in the optic gland [48]. These results contradict the hypothesis of a single “self-destruct hormone” implying that the programmed death of female octopus is associated with complex changes of its hormonal status (i.e., operation of Master Biological Clock, in fact) [48]. Similar phenomenon has been observed in mammals. Male pouched mice (*Antechinus*) experience severe hormonal disbalance during the mating period that results in their death at the end of mating period [73].

It was supposed [5] that adaptive aging (and adaptive death) could develop in the colonial viscous (non-dispersed) populations under two conditions: (i) high viscosity (low intermixing), which guarantees a high probability that resources freed by the death of an individual will be inherited by the offspring and relatives; (ii) relatively early and fast reduction of reproduction (as in *C. elegans*). Pacific salmon (*Oncorhynchus nerka*) is known by its ability to return in large numbers (from 73 to 98%) to the creeks of its birthplace. Moreover, local salmon populations are not panmictic, but exist as metapopulations with a hierarchic structure [74]. This means that Pacific salmon that return to the creeks to spawn have a high degree of kinship, which likely guarantees that all benefits of paternal biomass sacrifice would be available to the relatives. A similar pattern of death after spawning has been described for the lampreys [75]. Adaptive *death* is a form of extreme altruism, which is likely limited to the organisms demonstrating such a high degree of kinship, social structure, and physical association that they acquire the features typical for a higher order of organization (e.g., formation of colonies of unicellular organisms that share some features with multicellular organisms or colonies of multicellular animals with some supra-organism features). This is a part of a wider phenomenon, when adaptation at the colony level increases at the expense of adaptation loss at the individual level.

Another mechanism of the emergence of phenoptosis is associated with the limits of brain hyperdevelopment and behavioral models in humans. In human society, biological evolution has turned its back to the cultural evolution. As discussed in the recent review [32], genetic-cultural evolution in humans can not only limit brain development, but can also facilitate counterproductive process – support brain degradation (intellectual stagnation or decrease in IQ). This occurs when reproductive success of an individual becomes independent on the advantage of this individual in the competition for resources (or when at a certain stage of cultural and social development, individuals with lower cognitive abilities become more competitive). And if the success in life is not converted into the reproductive success, the cultural drive cease to work (or works in the opposite direction: the worse, the better) [32].

Effect of type of selection on the adaptive death and aging. The existence of *adaptive death* in clonal populations could be explained by kin selection (aiming at the preservation of features that favor survival of close relatives), because clonal colonies could be considered as “super-organisms”. As mentioned above, according to the Hamilton’s rule, natural selection can promote altruistic behavior when $nrB > C$, where r is relatedness; B is the benefit of the recipient; n is the number of recipients, and C is the cost for the altruist [76]. If the coefficient of relatedness $r = 1$, the Hamilton’s rule $nrB > C$ is simplified to $nB > C$, and it becomes easier to meet its requirements. The cost (C) of *death* of an individual is outweighed by the benefits (B) for multiple relatives. Travis [70] used computer modeling to demonstrate that it could also be true for spatially structured populations with a high proportion of older individuals. The main requirement for the kin selection to work in the Travis model is low dispersal as a condition for the “inheritance of resources” (transfer of resources from dying individuals to their relatives) [8]. This requirement is met in the colonies of bacteria and even *C. elegans*. Similar results have been reported by Markov [5].

Adaptive death develops easier in the organisms subjected to *reproductive death* [6, 70]. Similar to salmon, hermaphroditic *C. elegans* nematodes experience reproductive death [6, 8]. This could reflect the co-evolution of two features predicted by the Hamilton’s rule. Individual adaptation of semelparous organisms (organisms that reproduce only once in life) becomes negligibly low after the reproduction episode. This means that the adaptive *death* either causes an insignificant decrease in the individual adaptation (C) or does not decrease it at all, while potential benefits for other individuals (B) remain. Similar notions have been used recently for explaining the evolution of mass suicide of *Escherichia coli* cells [6, 77]. Hence, *adaptive death* is plausible in organisms that are not clonal or colonial.

The majority of biological populations are arranged into classes (according to sex, age, cast, etc.); hence, adaptation of a social group could change due to the rearrangement of classes, i.e., not be directly associated with genes and natural selection [8, 78–81].

As mentioned above, evolutionary benefits of adaptive *death* would be more pronounced if a significant portion of the population is old [82]. Stress conditions could accelerate aging (one of the aging programs is induced by the mitochondrial reactive oxygen species, ROS) by reducing the reproductive function and, hence, increasing the benefits of the *adaptive death* [83].

Aging has also been investigated from the point of view of multilevel selection [5, 70, 84]. The effect of the decrease in the force of natural selection with the individual’s age on the evolution of aging was described mathematically for idealized (i.e., dispersed and interconnected) Wright–Fisher populations without taking into

account social and ecological factors, such as spatial structure, availability of resources, or dispersion [85, 86]. Lohr et al. [6] demonstrated how the death of an organism in the course of cell aging could evolve as an adaptive group feature in species existing as populations with a high degree of kinship (especially for the populations of clones) and low level of dispersion.

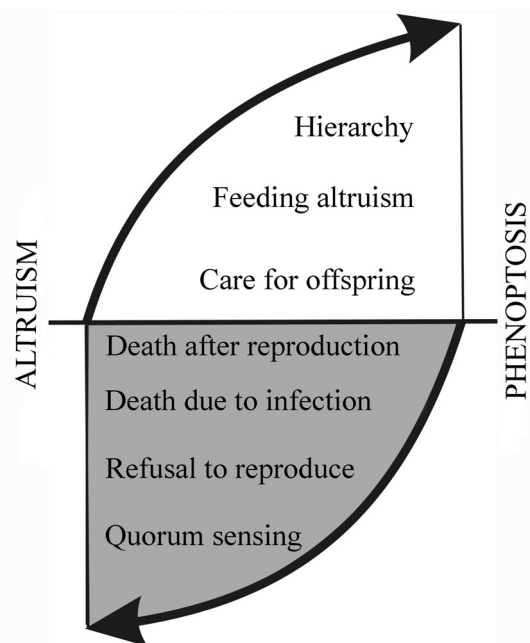
Each particular species has the maximal recorded LS value. It is still unclear whether the LS limit is supported by selection directly (i.e., if it is an adaptation) or this is a side effect of selection based on other features that increase adaptability. Identification of LS-increasing mutations implies that aging is under control of genes, while evolutionary forces limiting LS have not been elucidated yet.

The model developed by Lidsky and Andino [87] demonstrated that limitations of LS are beneficial for the fight against epidemics and provided possible explanation for the selection of particular LS values and the absence of immortal mutants. Their hypothesis states that selection for the LS control prevents in part and limits the outbreaks of chronic infections. Populations migrate often to colonize new habitats or just encounter factors that can significantly decrease the population density. The authors investigated the correlation between the pre-determined LS and pathogen load in the case of host migration to another habitat, including reduction of the population size, or population “bottleneck”. In particular, they demonstrated that the infected founders in the populations with a shorter LS would die before the population density reaches the level facilitating fast pathogen transmission. Respectively, shorter LS limits the spread of infection and accelerates elimination of pathogens in comparison with the populations with a longer LS [87]. Limitation of LS is especially beneficial in the context of transmission of zoonotic pathogens, which requires their adaptation to a new host. We believe that infection outbreaks can promote control of the evolutionary determined LS values for species.

CONCLUSIONS

In many cases, altruism provides certain benefits for adaptation, which is undoubtedly proven by the variety of mechanisms of its emergence (figure).

There are at least two global mechanisms of altruism emergence. In the first one (induced), an individual becomes altruistic when affected by environmental factors without undergoing any internal changes, i.e., passively. Such factors could originate from changes occurring in other individuals (for example, cheaters). In the second mechanism, an individual become altruistic due to changes in its own behavior. For example, the right for reproduction in a community is preferentially given to the highly-ranked individuals, while the low-rank individuals



Diversity of altruistic programs. The upper part of the figure shows examples of altruistic behavior, which when developed or promoted (arrow), can result in the organism death and/or cessation of reproduction and elimination of the possibility to pass genes to the next generation (i.e., to phenoptosis in one of its manifestations) (see examples in the figure). The lower part of the figure (on a darker background) shows examples of phenoptotic programs that while causing the death of animals, also can have an altruistic component (i.e., resulting in the altruistic behavior; shown with arrow), thus facilitating adaptation (e.g., due to the termination of infection spread, improvement of living conditions of the population, or survival of offspring).

are assigned an altruistic role of “service personnel”. In the majority of highly organized communities, altruists do not appear randomly, but are rather appointed. In the limiting cases (eusocial communities), the inequality is established genetically. The emergence of such inequality in the course of evolution could be seen in ants: gamergates (working ants capable of reproduction) exist in more primitive ant species, but not in more evolutionary developed ones [88]. Another example of the second mechanism of altruism emergence as a result of group selection and Simpson’s paradox is *adaptive death* (usually, acute phenoptosis) as a form of acute altruism (see discussion in this article).

Phenoptosis as an altruistic program. At first glance, emergence of phenoptosis in the course of evolution seems paradoxical. Longevity *per se* is not the primary evolutionary goal of living organisms. From the evolutionary point of view, the priority is adaptation to environmental conditions linked to the need for survival, food supply, and reproduction. Regulation of homeostasis and organism repair comprise a complex network of interconnected reactions, the efficiency of which decreases with

age. Both known types of phenoptosis (chronic and acute) have adaptive significance [89], while acute phenoptosis is primarily associated with the (excessive) response to abrupt action of external factors (such as infection). On the other hand, chronic phenoptosis is associated with the action of internal factors, with optimization of LS as a species trait (such as height, size, mass, etc.).

Hence, we can see a broad diversity of types of programmed death in nature, especially if it is associated with reproduction. At the same time, such death is not always altruistic.

When environmental conditions change abruptly, species with the highest plasticity of phenotypic (including behavioral) features, which are capable to alter as fast as the environment, have an advantage over species most adapted to the external conditions. As mentioned above, this is the main characteristic of counterproductive programs (ability to respond to the cue very fast independently on its harmfulness). It is likely that on the evolutionary timescale, such feature helps its carriers rather than interferes with their existence. In particular, it would be useful for passing through the evolutionary bottlenecks (sharp reductions in the population size due to natural disasters or epidemics). Even in the history of humans, who are famous for their adaptability, there had been at least three bottlenecks, when the size of human population decreased to several tens of thousands of people [90]. Exposure to infectious agents (such as malaria agent) reveals a wide spectrum of genetic diversity, which underlies the variability in the susceptibility to infectious diseases and their complications [91]. Moreover, the adaptive value of a feature could change due to the changes in lifestyle. Therefore, the capacity for the super-strong response, which had been beneficial for Stone Age humans, likely became less adaptive recently. In particular, the immune system of the first farmers had become weaker during transition from the hunter–gatherer lifestyle to agriculture in order to prevent induction of the cytokine storm that could kill the infected individuals [92].

Deaths caused by the COVID-19 pandemic as phenoptosis with altruistic goals. At the early stages of human evolution, when human populations were scattered to the same extent as present population of other large animals, programmed death helped to overcome diseases (and prevent their spread over large areas) via rapid death of disease carriers (e.g., sepsis or diseases, such as plague, cholera, etc.). Infected individuals died because of the induced internal program, as well as due to the exclusion from the society (as communities tried to steer clear from sick people). One of the new recent examples are minks in Denmark. When the COVID-19 virus was discovered in a small population of minks, it was suggested to kill them all, which solves the problem from the evolutionary point of view. According to the data on

23 large pandemics and epidemics, COVID-19 is not in the top ten of most deadly epidemics (for this, the number of victims should reach 38.5 million people, and to be in the first five – up to 210 million). The deadliest disease in the human history was plague that took the life of 200 million people in 1347-1351 A.D. (~42% of the world population at that time). The number of deaths during the plague epidemics in 541-542 A.D. was 60 million people (28.5% of the world population) [93, 94].

The deadliest infectious disease is currently HIV/AIDS. Infection with human immunodeficiency virus has caused the death of 30 million people since the discovery of this disease in 1981. The outbreaks of severe acute respiratory syndrome (SARS), Middle East respiratory syndrome, and influenza virus H1N1 had happened in the early 2000s. In most recent pandemics, the virus was transmitted to humans from animals. All coronaviruses – SARS, MERS, and COVID-19 – had been transmitted to humans from bats [95].

A serious question remains unanswered on whether SARS-CoV-2 will continue to circulate in the human population or could it be eradicated by vaccinations and anti-epidemic measures. According to the optimistic forecasts, the pandemics should end after a year of massive and effective vaccination. However, it has become clear that vaccination of 75% of population is impossible due to social issues. Even more so is vaccination of 90% of population, which seems unachievable. The situation is complicated by the fast-emerging new mutant variants.

According to Wenzel [96], the outbreaks of viral infections are natural life events. Although the time of disease outbreak and the severity of viral infection are unpredictable, the spread of the disease will eventually come down. In our opinion, it is important to search for the ways to reduce the intensity of organism's excessive and potentially lethal response. Such hyper-response is a powerful evolutionary acquisition that allows the body to adapt to acute changes in living conditions. In essence, one of the most ancient prototypes of such lethality is the well-known phenomenon of quorum sensing, when triggering a process that significantly affects the fate of the entire population is beyond the capacities of a single individual, but becomes possible, when the size of population reaches a certain threshold. Based on the data presented in this work, if death of a fraction of the population prevents further spread of infection, it is an altruistic event. In some cases, aging can also have adaptive significance. Sometimes, phenoptosis is a continuation of the development programs, as for instance, the mechanism of Nrf2 inhibition by glycogen synthase kinase GSK3 β , including via induction of inflammaging [97, 98]. Some of the promising agents are antioxidant preparations targeting different metabolic processes, e.g., those preventing cytokine storm [99], both traditional (plant extracts [100] and active components of blood serum [101]) and derived, for example, from insects [102]. The most prom-

ising at the moment are the main antioxidant of the body, glutathione [103], and, in addition, artificially synthesized antioxidants [103], such as the mitochondria-directed SkQ-ions [104]. It was shown recently that the death of mice caused by administration of lipopolysaccharides, intravenous administration of mitochondria, and exposure to cold or toxic shock could be prevented by application of Skulachev ions (SkQ) [104]. Another important direction is identification of effector molecules and markers of phenoptosis in metabolomics studies [105].

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