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OPINION ARTICLE

Keeping up with the Red Queen: the pace of aging as an adaptation

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Abstract For decades, a vast majority of biogerontologists assumed that aging is not and cannot be an adaptation. In recent years, however, several authors opposed this predominant view and repeatedly suggested that not only is aging an adaptation but that it is the result of a specific aging program. This issue almost instantaneously became somewhat controversial and many important authors produced substantial works refuting the notion of the aging program. In this article we review the current state of the debate and list the most important arguments proposed by both sides. Furthermore, although classical interpretations of the evolution of aging are in sharp contrast with the idea of programmed aging, we suggest that the truth might in fact very well lie somewhere in between. We also propose our own interpretation which states that although aging is in essence inevitable and results from damage accumulation rather than from a specific program, the actual rate of aging in nature may still be adaptive to some extent.

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Introduction

Aging may be characterized as the progressive worsening of organismal function leading to increasing age-specific mortality (Kirkwood and Austad 2000); therefore, the final average lifespan of a given species is determined not only by how fast it ages but also by its baseline mortality, which is the result of the combined effects of different life determinants. Aging is a widespread but not universal (Martínez 1998; Guerin 2004; Finch 2009; Jones et al. 2014; Petralia et al. 2014; Munné-Bosch 2015; Schaible et al. 2015) biological phenomenon which has captured the thoughts of scientists for generations. However, even after centuries of research there is little scientific consensus regarding the fundamental question which is best summed up as simply "Why do we age?". A great number of theories have tried to provide an answer to this question by examining it from a mechanistic point of view, proposing various sources and many different forms of cumulative damage as the trigger of aging (Medvedev 1990; Holliday 2004; Moskalev et al. 2013; Lenart and Krejci 2016; White and Vijg 2016). The above mentioned question may also be approached from an evolutionary angle, one

which leads to a different set of theories which argue whether aging is programmed (Longo et al. 2005) or not (Kirkwood 2005; Kirkwood and Melov 2011), whether it constitutes a byproduct of developmental programs (Blagosklonny 2012, 2013) or whether it is purely stochastic (Hayflick 2007) in nature. Nevertheless, for the purpose of this article, we will merge these categories together and focus purely on whether aging is programmed/adaptive in nature.

The first inquiries into the evolution of aging are commonly attributed to August Weismann who (Weismann et al. 1891) argued at the end of 19th century that aging evolved to benefit a species rather than individuals. However, his opinions changed over time and he subsequently began to consider aging a neutral rather than a beneficial phenomenon, arguing that it is caused by the "perishable and vulnerable nature of soma" (Gavrilov and Gavrilova 2002).

A very important milestone in the ongoing discussion regarding the evolution of aging was reached in 1951 when Medewar postulated that the force of natural selection declines with age (Medawar 1952). After all, every organism dies eventually, be it from predation, disease or accident, and genes which are beneficial in early life therefore have a higher selection advantage compared to those which are beneficial later in life. Therefore, selection does not have enough power to eliminate late acting deleterious mutations. This should lead to their accumulation, which could subsequently result in aging. This reasoning has become known as the mutation accumulation theory of aging (Gavrilov and Gavrilova 2002). If we follow reasoning about the declining force of natural selection, it is not difficult to imagine that some selected genes may be beneficial early in life but deleterious later on; the existence of such genes—postulated as the cause of aging by Williams in 1957—is now known as the hypothesis of antagonistic pleiotropy (Williams 1957). These almost obvious but very powerful notions are probably among the first one needs to consider before investigating any new aspects of the evolutionary theory of aging.

A second key evolutionary theory of aging is the disposable soma theory formulated by Kirkwood in the second half of the 1970s (Kirkwood 1977; Kirkwood and Holliday 1979). This theory suggests that aging results from limited selective pressure to invest in mechanisms of somatic maintenance. While high levels of repair and maintenance are required in germs cells to prevent generation-to-generation deterioration, somatic cells need to be repaired only in order to prevent overly rapid decline (Kirkwood and Melov 2011).

Programmed aging was out of the question during a great part of the 20th century as aging in most species was believed to be effectively out of reach of natural selection and therefore any kind of aging program was simply thought to be impossible to evolve (Williams 1957; Rose and Graves 1989). However, with the beginning of the new millennium, new theoretical standpoints and discoveries convinced several authors that programmed aging is indeed a valid concept (Libertini 1988; Bowles 1998; Mitteldorf 2004; Bredesen 2004; Prinzinger 2005; Longo et al. 2005; Mitteldorf 2006; Milewski 2010; Goldsmith 2013; Skulachev and Skulachev 2014). As a consequence of the stark contrast between the opinions of these authors and the employed viewpoints—derived from classical theories of aging—the current discussion regarding the evolution of aging seems to be very black and white. Most authors seem to be either strongly against the potential existence of an aging program or strongly in its favor. We think that this may have led to their ignoring important points, one of which is that asking whether an aging program may evolve under specific conditions is not the same as asking whether an aging program actually has evolved. For example, even though natural selection is generally considered to work on the level of individuals and not groups, it may well be that it in some specific cases works on the population level as well, e.g. in the case of sufficiently low gene flow between groups or in case a population is divided into smaller populations which arise and go extinct over time (Alexander and Bargia 1978; Shanahan 1998). However, such circumstances are almost certainly not met by all aging species. Therefore, theories arguing in favor of the adaptive role of aging should focus not only on whether aging could have developed as an adaptation but also on whether the conditions they describe are common enough to explain why aging is such a widespread phenomenon.

This article thus reviews the current state of the programmed/non-programmed aging debate and lists the strongest arguments proposed by both camps. Furthermore, although classical interpretations of the evolution of aging are in sharp contrast with the idea of

programmed aging, we suggest that the truth might in fact very well lie somewhere in between.

Arguments in favor of the notion of programmed/adaptive aging

Programmed aging is most appropriately considered in the context of adaptive theories of aging, which favor the direct selection of life termination. This is essential, because had aging evolved in a non-adaptive way, it would have been impossible to provide justification for any well-defined program (Kirkwood and Melov 2011). Since aging is a widespread biological phenomenon, this implies that aging provides great selective benefits; however, it is not clear what exactly these benefits are and how they could outweigh the obvious side-effects of aging for individuals. Several authors have proposed different mechanisms in order to explain how aging could be favored by natural selection. Surely the most common proposition is that aging can be selected through group selection. Some authors have supported this notion by arguments based on empirical observations that aging appears to be programmed (Longo et al. 2005). Others have proposed mathematical models illustrating how programmed aging could be selected by group selection. One mathematical model has shown that if we assume pre-existing decreasing fecundity, programmed death can evolve as an adaptation in spatially structured populations (Travis 2004). However, this model does not adequately explain why fecundity should decrease with age were aging absent. Another study presents a model which supports the notion that senescence may be an important adaptation limiting the spread of diseases and may be selected for if we consider it within the context of the Red Queen hypothesis (Mitteldorf and Pepper 2009), a theory best known in connection with the evolution of sexual reproduction. Yet another study has shown that aging can be beneficial for the lineage by accelerating the rate of adaptation to changing conditions and can therefore be selected under certain conditions (Martins 2011); however, this model assumes the pre-existing decrease of competitive fitness which could be considered by some as circular reasoning, i.e. in a certain sense it may be seen as stating that we age because we age. Nevertheless, a more recent study demonstrates that aging could be selected in spatial systems even without similar assumptions (Werfel et al. 2015). Even though altogether these mathematical models may seem very convincing, their methodology, the assumptions or conclusions of each one of them were recently challenged in great detail by (Kowald and Kirkwood 2016). Generally, while thought provoking and enriching with respect to the debate about the evolution of aging, these models are still too simple and approximate to provide any answers about the evolution of aging in the real world. Furthermore, even the notion of programmed aging itself has met with significant opposition (Kirkwood and Melov 2011; de Grey 2015) which has very strong positions partially thanks to the wide-spread notion that group selection is too weak to outperform individual selection.

During the past decade, some additional remarkable evidence was suggested as possible support for the aging program. An influential paper written by Kirkwood and Melow states that: "Yet among the many gene mutations that have been discovered that affect life span, often increasing it significantly, none has yet been found that abolishes ageing altogether" (Kirkwood and Melov 2011). However, it was suggested by Skulachev that such a mutation has indeed been found in plants (Skulachev 2011). According to Skulachev's interpretation, a 2008 study published in Nature Genetics which found that *Arabidopsis Thaliana* with a mutation in two genes (*soc1* and *full*) switches from sexual to vegetative reproduction and does not die from seed induced senescence (Melzer et al. 2008) can serve as an example of precisely this kind of mutation, since the lifespan of mutant plants increased from 80 to 90 days to practically infinity. Another interesting point is that although aging surely has a negative impact on the fitness of individuals, this negative impact is not as pronounced as in the case of sexual reproduction—and there is no doubt that sexual reproduction constitutes an adaptation (Mitteldorf and Martins 2014). Highly interesting perspectives were also proposed by Mitteldorf in a series of papers (Mitteldorf 2006, 2012; Mitteldorf and Goodnight 2012). Their common idea, i.e. that aging has evolved in order to stabilize population dynamics, can be branded as the Demographic theory of aging as proposed by Mitteldorf himself (Mitteldorf 2006, 2012). In his original work from 2006 Mitteldorf suggests that individual selection has the tendency to push birth rates higher and higher until the growth of a population outpaces the

rate at which an underlying ecosystem can recover, which can in turn push the entire system into a chaotic state in which the entire population may quickly go extinct. Mitteldorf then argues that demographic stability has been an important target of natural selection and supports this argument by providing convincing evidence from several authors showing that it seems easy to breed animals with higher individual reproductive values (Leroi et al. 1994; Reznick et al. 2000; Guarente and Kenyon 2000; Reznick et al. 2004), thus illustrating that the maximization of fertility and lifespan is suppressed in nature. The conclusion derived from this point of view is simply that senescence has evolved as a mechanisms which helps to achieve higher population stability (Mitteldorf 2006). Mitteldorf's later work from 2012 further suggests that this framework of demographic stability may also be used to explain the unexpectedly high occurrence of the post-reproductive life span in nature and provides results of evolutionary simulations showing that under certain conditions organisms exhibiting reproductive senescence, post–reproductive life span and vitality senescence are favored in comparison with organisms with no senescence. (Mitteldorf and Goodnight 2012).

Key arguments supporting the notion of adaptive aging or directly contradicting predictions of non-adaptive evolutionary theories of aging are listed below:

1. The life span can be significantly extended as a result of single gene manipulations; the effect of such manipulations is often conserved even in evolutionary distant species (Kenyon 2010b; López-Otín et al. 2013).
2. In addition to single genes, even entire pathways modulate the life span; these pathways (Bredesen 2004) are also often conserved.
3. Several species including e.g. *Hydra magnipapillata* (Hydra), *Rana aurora* (red-legged frog) are known for not exhibiting any measurable aging (Martínez 1998; Jones et al. 2014; Schaible et al. 2015); this means that aging as we know it does not constitute an unavoidable consequence of physical laws but rather one of at least two options. Interestingly enough, even though species with negligible senescence exist, they seem to be relatively rare—which is surprising if we consider that according to the most common interpretation of evolutionary theory, negligible senescence should be in opposition to aging, beneficial to fitness and therefore favored by natural selection in almost all species.
4. Mortality in some species, including e.g. *Gopherus agassizii* (desert tortoise), *Avicennia marina* (white mangrove), actually decreases with age (Jones et al. 2014); if we consider aging as an increase in mortality rate over time, it could actually be argued that individuals of the above mentioned species are getting "younger" with age. However, while this interpretation is probably just a wild exaggeration, this mortality trend further supports the notion that observed aging is not the unavoidable outcome of physical laws.
5. Experimental evolution can lead to changes in the life span and aging (Archer et al. 2015). In addition, there are also great differences in median and maximal life span even between highly related taxa (de Magalhães et al. 2007) which hints at the rapid evolution of the aging phenotype. Interestingly, water-fleas have been shown to modulate their life span after sensing the olfactory factors of predators (Pietrzak et al. 2015).
6. Contrary to long-standing beliefs, recent studies have shown that aging is common in wild populations (Promislow 1991; Nussey et al. 2013; Kowald and Kirkwood 2015) and could therefore be selected for or against. Interestingly, senescence has been observed even in wild populations of the short-lived antler fly insect (*Protopiophila litigata*) with a median lifespan of 6 days. The authors of a study which has identified senescence in the antler fly have also argued that since the fitness cost of senescence in this species is about 20%, senescence is actually under strong selection in wild animals (Bonduriansky and Brassil 2002). However, supporters of the position that aging cannot be manifested in a natural population can make at least one counter argument. It may be argued that the occurrence of senesce in wild populations is a result of human activity which has disturbed natural ecosystems, e.g. by reducing the number of predators which would otherwise effectively

eliminate older individuals. Nevertheless, it may be particularly tricky to determine whether and to what extent human activities play a role in the occurrence of senescence in wild populations.

7. A relatively common argument in favor of adaptive aging is the existence of programmed death in single cell organisms (Fabrizio et al. 2004; Longo et al. 2005; Mitteldorf and Martins 2014); however, it should be noted that in such species entire populations could be and often are made up of clones, i.e. no relevant distinction may be made between individual cells from an evolutionary point of view. In other words, while a cell may die, its genome survives untouched in other clones, a situation which is vastly different from that encountered in the case of multicellular organisms. However, programmed death also exists in some multicellular organisms. This phenomenon, known as semelparity, represents a life strategy in which reproduction is almost immediately followed by death. A notorious example is the pacific salmon, whose death—which takes place immediately after spawning—is considered programmed not only by those specifically proposing programmed aging (Skulachev 2012) but also by authors who are in favor of the non-adaptive nature of aging (Vijg and Kennedy 2016). While both positions agree that the semelparous life cycle is an example of programmed death, their positions on its connection with aging in iteroparous species such as humans differ dramatically. On the one hand authors in favor of programmed aging see it only as a more extreme case of aging and use it to argue that since programmed death can clearly evolve there is no reason why this should be different for programmed aging. On the other hand authors skeptical of programmed aging interpret programmed death in semelparous species only as a specific life strategy which is clearly distinct from aging in iteroparous species such as humans because it lacks a slow progressive decline of function. Furthermore, they consider this gradual decline of function as an "unclear solution" which serves no purpose (Vijg and Kennedy 2016).
8. A majority of genes and microRNA (miRNA) differentially expressed during aging are also differentially expressed during development (Somel et al. 2010) and many age-dependent gene expression changes and epigenetic changes originate in developmental programs (Lui et al. 2010; Takasugi 2011). This suggests that changes in gene expression during aging are prearranged by a developmental program rather than being merely the result of random damage accumulation. However, this could also be explained without the need to suggest the adaptive role of aging (de Magalhães 2012; Blagosklonny 2013).
9. Contrary to a long-standing dominant opinion, the power of natural selection does not necessarily have to decline with age (Baudisch 2005). Simply by employing different—but still reasonable—mathematical indicators of the strength of natural selection than those used originally by Hamilton (Hamilton 1966), it may be shown that the power of natural selection may indeed decrease or increase throughout the life span (Baudisch 2005).
10. Hormesis is a phenomenon whereby small doses of otherwise harmful stimuli result in beneficial effects (Rattan 2005). In the case of aging this means that several stressors such as irradiation, heat shock, food limitation, reactive oxygen species and other radicals supplied in small doses actually exert an anti-aging effect (Rattan 2008). This hormetic effect is commonly explained by the stimulation of maintenance and protective mechanisms of cells. However, some have argued that this explanation is not satisfactory and paradoxically suggests that damage prevents damage (Blagosklonny 2011). From the point of view of programmed aging theories, hormetic response is interesting for several reasons. First, it shows that organisms have latent potential to age slower and live longer. Second, within the programmed aging framework, hormesis makes a lot of sense since it represents a mechanism by means of which the life span of organisms is extended in harsh conditions in order to increase the chance of producing progeny. The third reason is rather specific since it points to a discrepancy in the

disposable soma theory which suggests that repair is limited by insufficient resources (food) which means that more food should enable better repair. However, contrary to this prediction, overeating has been found to lead to a shorter life span while caloric restriction (30–40% reduction in caloric intake without malnutrition) extends the life span in a great variety of model organisms (Blagosklonny 2007).

11. The disposable soma theory (Kirkwood and Holliday 1979) and the theory of antagonistic pleiotropy (Williams 1957) both predict that life span and reproduction are involved in a trade-off relationships which makes it impossible for them to increase simultaneously. Nevertheless, the results of several studies suggest that this prediction is probably not generally true. A study focusing on the relationship between the number of produced offspring and the life span in a captive zoo population examined 18 species of mammals and 12 species of birds and found no evidence that the number of offspring influences the age of death (Ricklefs and Cadena 2007). Neither does the number of offspring influence the lifespan of individual mice and there is no significant difference between the lifespan of virgin and mated mice (Tarín et al. 2014). In reaction to these and other contradictory results, some studies have suggested that reproduction has a negative effect on the life span only in a stressful environment (Beaulieu et al. 2015). However, this suggestion seems to be contradicted by a study which found that the health cost of reproduction in humans is minimal even in societies with high fertility, high mortality and minimal healthcare (Gurven et al. 2016). While the above mentioned studies seem to indicate that there is simply no connection between reproduction and aging, some model organisms provide substantial evidence of manipulations of the reproductive tract leading to modulations in the life span (Kenyon 2010b). Removing germs cells (but not the somatic cell tissue) extends the life span of *Caenorhabditis elegans* by 60% (Hsin and Kenyon 1999; Kenyon 2010a); however, it is interesting to note that removing the entire reproductive system does not extend the life span, which thus constitutes an argument against a simple reproductive trade-off (Hsin and Kenyon 1999; Kenyon 2010a, b). Furthermore, transplanting ovaries from young donors to old recipients in mice leads to an increased life span in the transplant recipients (Mason et al. 2009), i.e. a situation reminiscent of a finding likewise established in the case of mice, namely that the blood of a young donor can rejuvenate an old recipient (Conboy et al. 2005). The relationship between the state of the reproductive tract and the life span thus seems to be more about communication within the body than about resource allocation between reproduction and somatic tissue maintenance.
12. There is little evidence of antagonistic pleiotropy of known aging genes (Kirkwood 2005; Leroi et al. 2005; Blagosklonny 2010) and even though some works have shown pleiotropic genes influencing the life span (Paaby et al. 2014), it has been shown that recombination can generate genotypes which are positively correlated with both life span and reproduction (Khazaeli and Curtsinger 2013), thereby further questioning the notion of a trade-off between reproduction and life span predicted by the disposable soma theory.
13. While life expectancy in humans has risen dramatically during the course of the past century, maximum life span remains relatively unchanged. However, if aging is purely the result of long-term damage accumulation, reducing damage intake should prolong not only median life span but also maximum life span. The fact that reducing extrinsic causes of mortality does not increase the maximum life span seems to indicate that aging does have an intrinsic source after all, though this of course could also be explained by mechanisms which do not require an aging program.

Though many aspects of aging may hint at the existence of a program, alternative explanations are in fact just as likely. We believe that the problem facing most theories of programmed aging is their excessive focus on individual hints of such a program, on specific inconsistencies vis-à-vis classical theories of

aging or on very specific mathematical models and simulations while simultaneously offering very few testable predictions. Therefore, they cannot generate the hard evidence essential for discounting classical evolutionary theories of aging as fully obsolete.

Arguments in favor of the non-adaptive nature of aging

Even though programmed (i.e. adaptive) theories of aging have gained some popularity in the past fifteen years, a majority of researchers still consider the adaptive nature of aging to be highly unlikely (Austad 2004; Kirkwood and Melov 2011; Blagosklonny 2013; Pitt and Kaeberlein 2015). While this opposition to the adaptive nature of aging has been well-established for a long time and its basic arguments all articulated in the previous century (Medawar 1952; Kirkwood 1977), new perspectives are being generated even today (Blagosklonny 2013). However, by the very nature of this conversation, most recent papers supporting this prevalent opinion of the unlikelihood of programmed aging focus more on rebutting the arguments of the proponents of programmed aging than on developing new arguments for this well-established position (Vijg and Kennedy 2016; Kowald and Kirkwood 2016).

The most common and most important arguments in favor of the non-adaptive role of aging are listed below:

1. Genetically identical animals living in the same environment have different life spans (Turturro et al. 2002; da Costa et al. 2016); this applies even to identical human twins (Herskind et al. 1996; Ljungquist et al. 1998; Finch and Kirkwood 2000; Skytthe et al. 2003). This finding is in sharp contrast with behavior which could be expected of any "normal" program. However, a study which has considered the relative variability of age of death in humans found that this variability is only two times higher than the relative variability of age of menarche. Furthermore, the relative variability of the age of menopause, which can be considered as reproductive aging, is basically the same as the relative variability of menarche (Gavrilova et al. 2012). The authors used these findings to conclude that aging is in fact not much more variable then programmed developmental process menarche.
2. It is widely accepted that the power of natural selection declines with age (Medawar 1952; Hamilton 1966). However, it has been shown that this is not true under all circumstances: when different mathematical indicators of the strength of natural selection are employed than those used originally by Hamilton (Hamilton 1966), the power of natural selection may even increase with age (Baudisch 2005). For example, if we calculate the force of selection using change in fitness, probability of death and probability of survival, i.e. instead of only using change in fitness and probability of survival, the force of selection can both increase and decrease with time.
3. Aging decreases the fitness of individuals, i.e. the potential benefits of aging are purely hypothetical, not commonly accepted and difficult to test. Furthermore, group selection—required by most theories of programmed aging—has long been considered to be much weaker than individual selection (Smith 1976).
4. Kirkwood suggested that if an aging program does in fact exist it should be prone to mutations and we should therefore be able to identify non-aging mutants (Kirkwood and Melov 2011). It is generally believed that no such mutant has ever been identified, though some argue otherwise (Skulachev 2011).

It should be noted that for decades aging had not been considered a significant cause of death for animals in the wild because it was thought that they generally die from other causes (Kirkwood and Melov 2011); this fact was therefore considered an important argument against programmed aging. However, recent studies have shown that aging is more common in the wild than previously thought (Promislow 1991; Nussey et al. 2013; Kowald and Kirkwood 2015). A meta-analysis published in 2013 by Nussey et al. states that based on 340 long-term studies, there is irrefutable evidence that senescence can be commonly detected in at least 175 different animal species including mammals, birds, other vertebrates and even insects (Nussey et al. 2013). In the light of these recent findings, any argument pointing out the scarcity of aging in the wild is simply no longer valid.

Nevertheless, there is at least one possible way to express doubts about these findings. It may be argued that the existence of senescence in wild populations is possible only because human activities have greatly affected natural ecosystems which have enabled some individuals to live until old age, e.g. thanks to a reduced number of predators. However, even though this line of argumentation may seem plausible, the current amount of data showing the occurrence of senescence in the wild is staggering and thus—without solid experimental evidence that senescence in wild populations is "man-made"—any conclusion for now seems to be simply that senescence in wild populations is common.

Though arguments in favor of the non-adaptive nature of aging appear to be fewer in number, this is solely due to their more general nature and the fact that it is always easier to pick out individual discrepancies in an existing theory than generate a valid general statement. However, although these arguments are persuasive and have thus convinced a majority of biogerontologists, they are no longer bulletproof. All of the above mentioned statements have been challenged by various interpretations and only time will tell how successful these "challengers" will be.

In search of a middle ground

We believe that—given the current state of knowledge—it is no longer rational to simply dismiss the possibility of programmed aging as entirely improbable. Accumulating evidence does seem to point in the direction of adaptive aging, and even though the possibility of programmed aging may still be dismissed in the end, we believe that the amount of evidence amassed in its favor should still warrant a certain amount of attention and generate a greater degree of interest among the scientific community. In short, while we believe that aging is more likely to be non-programmed than programmed, it is no longer the only available option.

Life is complex and it should thus be no surprise that history has repeatedly shown us that in biology even two seemingly contradictory interpretations can both be partially correct. For example, the question of whether traits acquired during life can be passed on to succeeding generations was seemingly answered by classical genetics as a clear "no" while later findings established by epigenetics have shown us that the answer is in fact "in some cases yes" (Heard and Martienssen 2014). Accordingly, the evolution of aging may be viewed as one such complex question, i.e. one where neither of the two opposing viewpoints is entirely wrong or entirely correct. We thus propose that aging is programmed to some extent in most species but that this program only accelerates processes which would eventually occur anyway. In other words, in our view the "aging program" is neither the ultimate cause of aging nor a true program in its own right; however, we do believe that it is responsible for a substantial part of the observed phenotype.

Nothing is perfect. This is true of all matters—and especially of biology. No matter how well-tuned a biological process is, it is still prone to making mistakes from time to time. Even DNA replication, i.e. probably the most fundamental biological process, is still far from perfect: even the most high-fidelity polymerase makes mistakes. These mistakes are of course necessary since without them there would be no new mutations (or far fewer of them) and organisms with "perfect replication" would certainly succumb to other organisms which—thanks to new mutations—would be able to better and more rapidly adapt to a changing environment and to competing species. Likewise, all other cellular mechanisms, including DNA repair, apoptosis, mitosis, meiosis, cell cycle control, etc. are also imperfect: they sometimes function improperly and may even cause a substantial amount of collateral damage (e.g. gross chromosomal rearrangements as a result of recombination). Due to inherent imperfections present in all biological systems, time-dependent deterioration is simply inevitable and the only remaining question is the issue of how rapidly it progresses. The conclusion that aging is in essence inevitable may be further supported by the general tendency of entropy to increase and by the fact that organisms accumulate irreparable damage caused by biochemical side-reactions (Yin and Chen 2005) as well as DNA damage (Moskalev et al. 2013; Lenart and Krejci 2016).

To underline the inevitability of aging from another perspective, it may be also useful to undertake a short excursion into the realm of physics, namely thermodynamics. Aging, in its most vague and general definition, could in fact be applied to both living organisms and abiotic mass. The second law of thermodynamics tells us that the total entropy of an

isolated system always increases over time or remains constant in ideal cases where the system is in a steady state or undergoing a reversible process. For several reasons, this is, however, not universally true of living organisms. First, living organisms are thermodynamically open systems. Second, the statement does not reflect the fact that there are many systems in nature which are in a metastable state only, i.e. they do not achieve equilibrium but retain their state (they do not necessarily increase their entropy) unless influenced from outside, which may induce a phase transition in order to achieve another metastable state. This does not necessarily contradicts Schrödinger who states that "a living organism continuously increases its entropy (Schrödinger 1992)", although the relationship between entropy accumulation and aging might not be so mechanistic as Schrödinger presumed.

With respect to entropy production and accumulation by living organisms, it has been suggested that aging is related to entropy accumulation in living mass as well as in regulatory circuits (Aoki 1991). The interpretation of the evolutionary consequences of entropy accumulation is somewhat tricky, as on one hand evolutionary forces seem to go against the second law of thermodynamics in that they induce a state of higher local order, while on the other hand it provides a constant fitness measure in the sense that for survival and reproduction it is necessary to maintain a highly ordered internal environment. In silico evolution recently provided us with a quantitative demonstration that continuous positive selection is capable of generating complex phenotypes from simple components by incremental evolution, in line with what Darwin proposed (François and Siggia 2010).

However, restricted physical approach basically tells us very little about what the actual rate of aging should be in order to maximize one's species' chances of survival and reproduction or the other way around, i.e. why very similar and highly related species age at such different rates. Another example of what makes entropy accumulation in individuals organisms or populations a highly biological problem is that all currently living organisms share a last universal common ancestor, meaning that all living organisms are derived from continuously produced germ cells whose replication has successfully continued for billions of years, making the germ line immortal from this point of view. One might ask whether—if uninterrupted replication continues for eons—even unicellular organism such as budding yeast would have replication senescence? In this respect, physics does not currently offer satisfactory explanations, while biology may provide us with more plausible hypotheses.

While it may not be possible to answer the question of how fast "inevitable" aging should progress with the help of current entropy-based thermodynamic theories which attempt to tackle this problem from the perspective of physics (Rahman 2007; Hayflick 2007; Silva and Annamalai 2008; Silva et al. 2009; Lenart and Bienertová-Vašků 2016), it is likely much less controversial and somewhat more illustrative to simply consider the case of species which do not seem to age. Though there are other candidates (Jones et al. 2014), a classic example of a species which does not seem to age is Hydra (Schaible et al. 2015). Interestingly, Hydra's extreme longevity seems to be regulated to some degree by the transcription factor forkhead box O (FoxO) (Boehm et al. 2012) which also seems to be connected to human longevity (Willcox et al. 2008; Morris et al. 2015). It was calculated that under proper conditions 5% of hydras should be able to survive up to 1400 years (Jones et al. 2014). Though this seems astonishingly long, it is only a fraction of the age of the longest living tree, currently estimated to be 5062 years old (Brutovská et al. 2013). Furthermore, in some organisms such as *Gopherus agassizii* (Jones et al. 2014), mortality has been found to decrease with age. All in all, what does this tell us about how fast the "inevitable" process of aging really is? Not much in fact. However, while it is impossible to formulate a precise answer given the current state of knowledge, one thing seems almost certain: "inevitable aging" is a much slower process than the one commonly observed in nature. Furthermore, it could be expected that the accumulation of somatic mutations should eventually lead to the disruption of proper organismal function and thus to increased mortality, i.e. the accumulation of mutations should result in aging. However, based on the fact that neither transgenic mice nor yeast with an increased rate of mutation accumulation exhibit any symptoms of accelerated aging (Narayanan et al. 1997; Busuttil et al. 2005; Kaya et al. 2015; Lenart and Krejci 2016), we may conclude that the accumulation of mutations does not have a causal role in aging as observed in nature. Nevertheless it is almost certain that with a

long enough life and sufficient capability to escape cancer, the accumulation of mutations in tissues would eventually be detrimental by itself, though in the case of most organisms aging simply happens too quickly for this to manifest.

How can we explain that aging in nature happens much more rapidly than it has to? There are at least two possible explanations. The first is that most organisms are simply not "tuned" well-enough due to a lack of evolutionary pressure on extending their life span. However, given the fact that senescence is commonly detected in nature (Nussey et al. 2013) and that some species have not been observed to age (Jones et al. 2014), arguing that there is no evolutionary pressure to select against aging is basically arguing that aging impacts fitness either not at all or merely to a negligible extent. We find this to be highly unlikely and therefore propose a second option, i.e. that aging indeed has a strong negative effect on the fitness of an individual but that it also confers benefits which outweigh this—in other words that aging as observed in nature is adaptive.

While the precise mechanisms of the potentially adaptive nature of aging are perhaps difficult to comprehend, some inspiration may be gleaned from another well-known biological phenomenon which has puzzled evolutionary biologist for decades: sexual reproduction. Sexual reproduction reduces fitness more than aging but it is assuredly adaptive. One possible explanation of how sexual reproduction could have evolved is the Red Queen hypothesis, which suggests that organisms have to adapt not only to an abiotic environment but also to other organisms, i.e. that prey must evolve in order to escape a predator and a predator must evolve in order to catch prey. As a result, evolution is basically a never-ending arms race between organisms. This arms race between host and pathogens has also been suggested as the driving force behind sexual reproduction since it enables higher organisms to retain higher variability and therefore keep up with otherwise much faster parasites (Morran et al. 2011). We believe that a similar argumentation scheme is also applicable to aging.

Let us assume a population which consists of aging and (relatively) non-aging individuals. Aging in this thought-experiment would constitute real aging, i.e. an age-dependent decrease in function and increase in mortality, not just programmed death. This would mean that under favorable conditions, a gradual decline in function would facilitate a relatively long life span which would reduce the fitness cost of aging; however, under unfavorable conditions older individuals would die much faster than younger ones. The ability not to age is genetically determined and requires the cooperation of several genes which are mostly—but not exclusively—recessive when compared to alleles responsible for the aging phenotype. As a result of this setup, most crosses between aging and non-aging individuals would produce aging offspring. Though background mortality would be very low, the model population outlined above also suffers from a deadly pathogen which would kill or cripple most of its hosts. To be more specific, this unicellular parasite would interact with its host trough a specific cellular receptor and since there is a natural genetic variability in the forms of this receptor in the host population, these different receptor forms would confer variable levels of immunity against the pathogen. This is a scenario of what would happen over time:

- At the beginning of our model situation the number of aging and non-aging individuals is more or less the same. All of them are relatively immune to the pathogen since they are all offspring of the survivors of the last epidemic. For some time, there is no disease outbreak which leads to the rapid expansion of population.
- Several generations later (in this scenario the aging part of the population has discrete generations) non-aging individuals and their offspring account for a great majority of the population; however, while the aging part of the population has exchanged their repertoire of receptors several times, non-aging individuals and their offspring are generations behind since the original non-aging part of the population still contributes to the original alleles.
- After some time, the pathogen finally adapts to most common receptor forms and begins to rapidly spread throughout the population. This has a much worse influence on non-aging individuals since they are less variable and the pathogen has adapted mainly to receptors common in this group (since there are a majority of them). Following the deadly outbreak, non-aging individuals are radically reduced in number and no longer account for a majority of the population.

- Most non-aging individuals are the result of crosses between two non-aging parents since mating between aging and non-aging individuals produces predominantly aging offspring and also because the chances of aging parents producing non-aging offspring is relatively small as this trait is determined by multiple genes. As a direct result of this process, non-aging individuals suffer from much higher rates of inbreeding then aging individuals—even when mating is completely random. This is caused by the high likelihood of an event equivalent to having children with the daughter of your great–grandfather and your grandmother. This higher incidence of inbreeding further reduces genetic variability in non-aging individuals and thus reduces their fitness. Furthermore, populations with overlapping generations are also known to exhibit considerably larger allele shifts (resulting from genetic drift) than populations with discrete generations of the same effective size (Ryman 1997). Because in this scenario (though not necessarily in others) "non-aging" would result in the most extreme case of overlapping generations imaginable, these large allele shifts would also lead to the random fixation of alleles in the non-aging part of population, resulting in even more decreased variability.
- Even with decreased variability and fitness, the non-aging part of the population will—thanks to its non-aging advantage—slowly outnumber its aging counterparts. However, because of their reduced variability and smaller tolerance to environmental attacks, any future epidemic would be even more devastating.
- This would lead to several cycles of the spreading and declining of the non-aging phenotype, resulting in ever-decreasing variability and fitness of the non-aging individuals. Decline in fitness and variability could be temporarily stalled by the rare occurrence of non-aging offspring being born to aging parents, but this will likely not change the general trend. Over time aging individuals will accumulate mutations in genes originally responsible for non-aging and the chance of them having non-aging offspring will decrease as a result.
- In the end, low genetic variability and high inbreeding among non-aging individuals will lead to their extinction. While a rare non-aging individual may still be born to aging parents, there will be no mate with which it could produce non-aging offspring. After a certain amount of time it will die of causes unrelated to age while the aging population continues to accumulate mutations in non-aging genes resulting, ever decreasing the likelihood of non-aging individuals to be born.

It is important to highlight that even though the host–pathogen relationship may play an important role in the evolution of aging rate as described above, it is hardly the only relevant factor. We believe that all other dynamic processes should favor aging individuals due to their ability to react faster to changing conditions. For example, coevolution of predator and prey should essentially affect aging in the same way that coevolution with a pathogen does. Non-aging individuals would conserve older genotypes which predator or prey or both would adapt to much more easily. The aging—and more rapidly adapting—part of a population would therefore be better at escaping predators and catching prey. Interestingly, this effect could function in an additive fashion along with the effects of pathogens, since even a pathogen which is not deadly by itself could turn its host either into easier to catch prey or into a worse hunter. For the same reasons, changing environmental conditions would also work against non-aging individuals and their offspring. Radical changes in the environment could present a significant issue to older and less variable genotypes adapted to previous conditions. In the end, every change which requires a new adaptation should favor aging over non-aging and various factors would most likely add up to greater overall pressure on greater variability and newer genotypes. In other words, non-aging would constitute a great evolutionary benefit in stable conditions and under low pressure from predators and pathogens, but not so much in the real world. In the real world most organisms simply need to evolve fast enough to keep up with the Red Queen—even if this requires a sacrifice in the form of aging.

The main prediction to be derived from our model is clear: aging individuals should outcompete non-aging individuals due to pressure from pathogens and environmental stress. This could be experimentally tested. For example, it should be possible to derive an aging mutant of the *Hydra* genus and test whether this mutant would outcompete its non-aging counterparts in a mixed population of aging and non-aging

individuals. To the best of our knowledge this crucial experiment has yet to be performed.

Furthermore, we wish to emphasize that this "thought experiment" is only an illustration of an extreme case of potential competition between aging and non-ageing species, i.e. that this precise formulation is only applicable to a minority of species. In most species negligible senescence and extreme longevity have never evolved to be selected against, in first place. We propose that in these species their actual lifespan and rate of aging have evolved as a trade-off between the production of offspring and evolvability, the capacity of the system for adaptive evolution (Pigliucci 2008) which should enable organisms to cope with the negative effects of pathogens, predation or changing environmental conditions. Therefore, another prediction which can be derived from our interpretation is that aging should essentially be faster in a more "dynamic" environment. In other words, increased predation, parasite pressure or other changing environmental conditions should lead to faster aging. Although this prediction may seem to be the same as predictions made by classical evolutionary theories of aging, there is a small but notable distinction. From our point of view, the rate of aging is an adaptation and not the result of a passive mutation accumulation, pleiotropy, etc. Therefore, if mortality is too high, resulting in almost all members of a population dying young, evolutionary pressure for faster aging should be relatively weak and more focused on the deterioration of traits which can directly affect survival even before reaching "old" age. On the other hand, if high mortality is only short-term and possibly cyclical, caused by e.g. food shortage due to local overpopulation or change of season, pressure for faster aging should be high. This interpretation is thus compatible even with a study which has shown that guppies from highly predatory sites (20–30 $\times$ lower probability of 6-month survival) seem to age slower in some respects than those from less predatory sites when raised in captivity, but their neuromuscular performance, which can directly influence the ability to escape from predators, deteriorates significantly more rapidly than in the case of guppies from low predatory sites (Reznick et al. 2004). In our framework, the interpretation of this phenomenon would simply be that selection for faster aging was focused on those traits which can directly influence survival.

We also suggest that the gradual decline of organism function may not be merely a feature of aging but could also serve a specific purpose. Under favorable conditions, the gradual decline of function should still enable a relatively long life span which reduces the fitness cost of aging. On the contrary, the greater vulnerability of older organisms to unfavorable conditions should help to remove old and least adapted genotypes when necessary.

We also propose that epigenetic transgenerational inheritance, which has recently been established in different organisms (Daxinger and Whitelaw 2010; Heard and Martienssen 2014; Triantaphyllopoulos et al. 2016; Bunkar et al. 2016), can at least hypothetically play a role in the evolution of aging. If, due to changes in external conditions, an organism changes one of its traits during its life span (e.g. a change in behavior) this can surely influence its reproductive success. If these changes are inherited by its offspring by any means, it can subsequently affect their reproductive success. Since it may be expected that the lifestyle of most organisms is relatively well adapted to the conditions they live in and that epigenetics is influenced by a number of relatively random factors such as DNA damage (Dabin et al. 2016), we suggest that there may be a higher probability that the influence of epigenetically acquired changes in traits over the course of an extremely long life span on fitness is negative rather than positive. Long-living non-aging individuals would thus accumulate more "negative" than "positive" epigenetic changes throughout their life span simply due to a balance of probability; this would in turn reduce the fitness of their offspring and at least slightly reduce the benefit of their prolonged reproduction. This proposal is also testable since it predicts that even species with currently chronologically immeasurable aging, old individuals should produce on average less fit offspring than younger ones.

In order to establish our proposal within the context of previously published models, it is interesting to note that Bowles in 1998 published a hypothesis which similarly to ours proposes that aging can be beneficial as a tool enabling adaptation to predation (Bowles 1998). However, while this hypothesis provides some similar conclusions, there is a great difference in the mechanisms invoked. We propose that aging provides the benefit of higher variability and enables quicker evolution, a great benefit in a highly dynamic

Table 1 Key proposals regarding the evolutionary nature of aging

1. Aging is in essence inevitable, but the rate at which it occurs in nature is much faster than necessary
2. The actual rate of aging is adaptive since it allows for a faster adaptation to changing conditions, especially in order to keep pace with the evolution of pathogens, predators and prey
3. Even though the actual rate of aging is adaptive, it does not require any specific program: its speed is tuned simply by changes in the efficiency of systems responsible for repairing damage to DNA or proteins or in systems responsible for preventing this damage
4. We interpret the gradual decline of function as an adaptive feature of aging. While under favorable conditions this facilitates a relatively long life span which reduces the fitness cost of aging, troublesome conditions result in older individuals dying first, thereby removing older genotypes from the gene pool and producing generations of new genotypes in a more rapid manner
5. In the long run, excessively slow aging is disadvantageous for the fitness of individuals because it endangers the survival of the entire genealogical line derived from that individual by gradually increasing the probability of equipping succeeding members of the genealogical line with outdated genotypes. This interpretation is based on the premise that even if such an individual has had more offspring than the average member of its population after a number of generations, it would still be possible for the entire genealogical line derived from this individual to die out after several additional generations. As a result of this process, the real fitness of that individual would in the end be zero
6. We also propose that the prolonged accumulation of epigenetic changes could reduce the fitness of hypothetical non-aging individuals and may even negatively influence their offspring, which could to some extend reduce the benefit of non-aging

evolutionary arms-race with no permanent solutions. On the other hand, Bowles described a very specific scenario where aging is selected mainly because it increases genetic drift and thus increases the chances of an ultimate beneficial form of a given trait being fixed. In other words, the main difference between these models is that while Bowles considers the static evolution of "fast/slow rabbit", we consider a dynamic evolution scenario where the "fast rabbit" could always be a little bit faster or better at hiding—and so could "the fox". The interpretation of the evolution of aging with regard to the Red Queen theory has been previously attempted by (Mitteldorf and Pepper 2009). Furthermore, Mitteldorf and Martin subsequently proposed that the evolution of aging is driven by pressure to attain higher evolvability (Mitteldorf and Martins 2014). However, our interpretation and proposals (Table 1) differs in several important aspects. Firstly, we do not propose extinctions of entire populations as primary selection mechanisms. Secondly, senescence, as presented in a model by Mitteldorf and Pepper in the form of maximum life span, is more similar to programmed death then to actual aging. Most importantly, contrary to the above mentioned models, we do not propose the existence of a specific aging program though we do propose the adaptive role of aging. Therefore, our proposal is also fully compatible with the view that no simple "silver bullet" approach can stop aging. Furthermore, our interpretation is capable of explaining why aging is a gradual process instead of sudden programmed death. Also, our model can benefit from the idea of essential life span, i.e. the time window in life during which reproduction must occur (Carnes 2011; Carnes and Witten 2014). This essential life span limits the maximum possible rate of aging in a given species as aging which would lead to death before reproduction would ultimately lead to the extinction of given species.

Conclusion

It is difficult to say how our model might be accepted in the light of future discoveries; however, we hope that it will stimulate further discussion which we believe is the best way to improve our understanding and come closer to the truth. Although the discussion about the evolution of aging is certainly one of the more controversial ones in the biology of aging, this does not mean that it is not an important one—quite the contrary, it is extremely important since it can provide an answer to one of the most fundamental questions in biogerontology: how much can we regulate aging? And even though the evolution of aging is still an open question, the good news is that in contrast with e.g. the discussion on whether aging is a disease (Bulterijs et al. 2015) or not (Rattan 2014), we may at least be certain that an objectively correct answer does in fact exist.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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