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# Senescence in the Wild: Theory and Physiology

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## Senescence and Longevity in the Wild

Senescence is defined as a decline in survival (i.e. actuarial senescence) and reproduction (i.e. reproductive senescence) with increasing age (Partridge and Barton, 1993). From an evolutionary perspective, assessing and understanding such declines in demographic parameters is crucial because they directly impact fitness (i.e. the individual's contribution to the gene pool of the next generation) and population dynamics. By extension, any decline in traits that are known to be positively associated with fitness can be considered as evidence of senescence. For instance, adult body mass is a strong determinant of longevity in large mammalian herbivores, and any progressive loss of body mass with increasing age can be interpreted as senescence (Gaillard et al., 2017). The same logic applies for any phenotypic trait or physiological function that is tightly linked with reproductive success and/or survivorship.

While the process of senescence has been studied in standard laboratory models for a long time, the study of senescence within and across populations of wild animals and plants is much more recent (Shefferson et al., 2017). To some extent, this bias toward laboratory-based approach takes its roots in the misbelief that senescence should not occur in the wild. Indeed, during most of the 20th century, the predominant thought was that individuals never experience senescence in the wild because they die from various causes (e.g. infectious diseases, predation) prior to the occurrence of any decline in survival or reproductive probabilities. The emergence of long-term longitudinal studies of wild animal populations in the 1970s has allowed revisiting this fallacy (Nussey et al., 2013). Basically, in longitudinal research programs individuals are monitored from birth to death, which thus provide accurate estimation of age-specific demographic parameters (e.g. survival) in a given population and across years based on Capture-Recapture methods. Such analyses of long-term datasets have repeatedly documented senescence through declines in both age-specific survival and fecundity. One of the last syntheses of published literature reporting evidence of senescence (Nussey et al., 2013) has compiled 340 different studies of 175 different species that reported statistical evidence for senescence in the wild. The great majority of the compiled studies were performed on vertebrates, especially birds and mammals, likely because most long-term studies of animal populations in the wild have so far focused on these taxa. However, senescence has also been reported in a taxonomically diversified range of species including insects or plants (see Shefferson et al., 2017 for reviews). Until very recently, most studies have reported actuarial senescence and/or senescence in female reproductive traits. There is, however, an increasing number of reports of senescence in traits as diverse as body mass, level of immune parameters, or size of male secondary sexual traits in wild animal populations (Nussey et al., 2013; Lemaître and Gaillard, 2017). Taken together, these results suggest that senescence is the rule rather than the exception in the living world and the universality of the senescence process is accordingly now rarely questioned, at least in vertebrates. When it is, as in some long-lived animals such as bats or turtles, a too short duration of the monitoring relative to longevity, rather than the occurrence of a negative senescence (*sensu* Vaupel et al., 2004) is likely to account for the lack of observed senescence (see e.g. Warner et al., 2016).

Importantly, the almost ubiquitous nature of senescence does not preclude the evolution of extreme longevity in some species. Across species, longevity is tightly linked with body size following an allometric relationship and species with extreme longevity classically break this allometric relationship (i.e.  $\text{Ln}(\text{Longevity}) = \text{Ln}(\alpha) + \beta \text{Ln}(\text{Body Size})$ , with  $\text{Ln}(\alpha)$  and  $\beta$  being the allometric intercept and allometric slope, respectively; when body mass is used as a measure of body size,  $\beta$  is generally close to 0.25) by living an exceptionally long life for their size (Peters, 1983). This is notably the case for cave organisms such as olm (e.g. *Proteus anguinus*) compared to other similar-size amphibians, some colonial rodents (e.g. naked mole rats, *Heterocephalus glaber*; blind mole rats, *Nannospalax ehrenbergi*) and many species of bats (Austad, 2010) compared to other similar-sized mammals. However, such exceptional longevity does not imply that age-specific survival and reproductive traits stay constant with age. This is well illustrated in painted turtles (*Chrysemys picta*) that undoubtedly show a decrease in age-specific fitness components even if some individuals can live for more than 50 years (Warner et al., 2016).

Many comparative studies performed so far have been successful at identifying ecological and biological factors underlying the observed interspecific differences in longevity (e.g. Healy et al., 2014). While biologically informative, these studies often used the

metric of maximum lifespan to measure species longevity and did not embrace the full age-specific dimension of mortality and reproductive patterns. Maximum lifespan of a given species increases with sample size and is not an appropriate metric of the duration of life to compare across species (see Tidière et al., 2016 for a discussion). Quantifying the variation in senescence patterns across species from the full survival and reproduction trajectories and identifying the evolutionary roots of this diversity constitute central objectives of various scientific fields such as evolutionary ecology, biogerontology and demography.

## The Variability of Senescence Patterns in the Wild

Comparative analyses of age-specific demographic parameters performed so far have revealed that actuarial senescence patterns can be highly variable across species (Ricklefs, 2010). Among vertebrates, interspecific differences in the timing and the intensity of actuarial senescence are mostly accounted for by body size (Ricklefs, 2010) and the species position along the slow-fast continuum of life histories (Jones et al., 2008) (Fig. 1). Fast species, which typically show short biological times (e.g. early age at first reproduction, high reproductive rate, and short lifespan leading to a short generation time) suffer from a steeper rate of senescence (i.e. that measures the increase of mortality with age) than slow species that typically show long biological times (e.g. late age at first reproduction, low reproductive rate, and long lifespan leading to a long generation time) (Gaillard et al., 2016). Patterns of actuarial senescence do not only include the rate of senescence, but also include the age at the onset of senescence when mortality starts to increase (Fig. 1). For a long time, it has been assumed that the age at the onset of senescence was immutably set at the age of first reproduction (Hamilton, 1966). However, accumulated empirical evidence has revealed that the age at the onset of senescence does not consistently match the age of first reproduction and can in fact vary a lot across species (Gaillard and Lemaître, 2017). Similar to what is observed for the rate of actuarial senescence, variation in the age at the onset of actuarial senescence is also partly determined by the species position along the slow-fast continuum (with slow species typically displaying a late age at the onset of senescence, Fig. 1) (Gaillard and Lemaître, 2017). A next step would now be to look beyond the slow-fast continuum and to investigate whether genetic, physiological, lifestyle or ecological variables can explain among-species variation observed in actuarial senescence. While some studies have revealed that avian senescence patterns could be influenced by both latitude and migration distance (Møller, 2006), this research area is still in its infancy and factors modulating senescence patterns at a fine-scale are yet to be discovered. Moreover, most comparative studies performed so far have focused on actuarial senescence and little is known on variation in reproductive senescence across species, even if studies performed within primates and large herbivores suggest that reproductive senescence displays quite strong among-species variation as actuarial senescence does, but does not start with actuarial senescence. This is illustrated by an analysis performed on a sample of seven species of large herbivores where the onset of reproductive senescence was consistently later than the onset of actuarial senescence (Gaillard et al., 2017).

In addition to the above mentioned among-species differences in actuarial and reproductive senescence, a few studies have revealed that senescence patterns can also vary across populations of a given species. These observations are particularly valuable as they can shed light on the role played by environmental conditions in shaping senescence patterns. Unfortunately, studies embracing this direction remain rare because they require long-term data to be collected in at least two populations of the same species in the wild. However, the few studies published so far in that context indicate that local conditions markedly influence actuarial senescence. For instance, when comparing two populations of elk (*Cervus elaphus canadensis*) in the Yellowstone National Park, Garrott and colleagues (Garrott et al., 2002) found that the onset of actuarial senescence was about 5 years earlier for the elk population living in an ecosystem where geothermal water, soil and plants are naturally enriched in silica and fluoride compared to another population further north where female elk did not experience geothermic activity. In this particular case, excessive fluoride concentrations in the diet produced a rapid tooth wear (Garrott et al., 2002). As tooth wear directly impacts actuarial senescence in

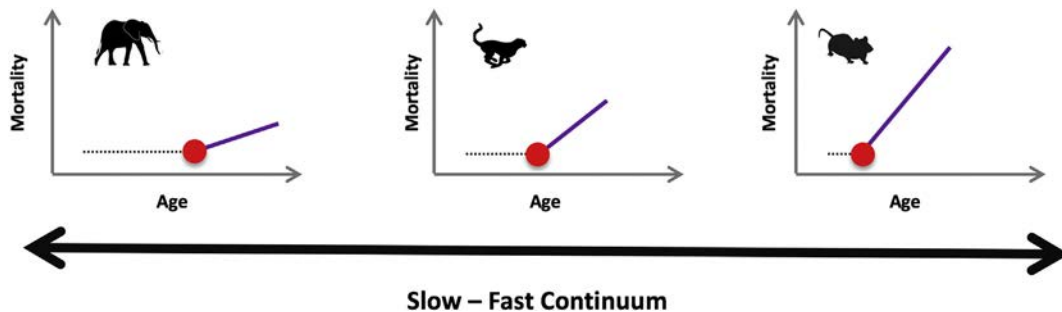


Fig. 1 Actuarial senescence patterns in three species occupying different positions along the slow-fast continuum. Elephants are located at the slow end of the continuum and typically show a late onset of senescence (identified by the red dot) and a slow rate of senescence (slow increase in age-specific mortality, highlighted in purple). Conversely, small rodents such as house mice display an early onset of senescence and a fast increase in age-specific mortality. Large carnivores such as cheetah that occupy an intermediate position on the slow-fast continuum of life histories show an intermediate timing and intensity of senescence. Note that current empirical knowledge strongly supports the association between life history strategies and timing of senescence but is much weaker about the association between life history strategies and rate of senescence.

mammals (Gaillard et al., 2015), this study provides an illustrative example on how environmental conditions can shape actuarial senescence at a small geographic scale. One alternative approach, albeit extreme, is to compare populations living in wild and captive conditions.

Zoological gardens are expected to confer patent survival benefits to individuals as they provide food, veterinary care and offer protection against predators. Unsurprisingly, longevity records are generally found in zoos (Tidière et al., 2016), but do captive populations consistently show a delayed onset of senescence and/or a slower rate of senescence compared to their wild counterparts? A first answer to this question was brought by Ricklefs and Scheuerlein (2001) who found across 12 mammalian species that the rate of actuarial senescence is generally slower in captive populations. However, in this study, the survival benefit of captivity was highly variable and, in some cases, survival was even higher in the wild population. Subsequent comparisons of senescence patterns across wild and captive mammalian populations have since provided insights on the ecological and biological factors that mediate the direction and the magnitude of the survival benefits. For instance, a comparison across 22 species of large mammalian herbivores revealed that although captive populations generally display a slower rate of actuarial senescence, the magnitude of the difference in senescence rate between captive and wild populations was influenced by the proportion of grass in the natural diet. More specifically, senescence was much less reduced by captivity in species with a diet containing only a small fraction of grass, as it is typical for roe deer (*Capreolus capreolus*) or Greater kudu (*Tragelaphus strepsiceros*). More recently it has been found that the gain in longevity for captive mammalian populations was clearly impacted by the species position along the slow-fast continuum, with fast species such as the North American beaver (*Castor canadensis*) or the European rabbit (*Oryctolagus cuniculus*) enjoying longer life in captivity than in natural conditions (Tidière et al., 2016). This longevity gain was primarily due to a delayed age at the onset of senescence and a tendency for the rate of senescence to be slower in captive populations of species close to the fast end of the slow-fast continuum (Tidière et al., 2016). On the other hand, little or no advantage of living in captivity occurred in slow species, and in some cases such as elephant (*Loxodonta africana*), the pattern was reversed. Species close to the slow end of the slow-fast continuum better survived in the wild than in zoos (Tidière et al., 2016).

Despite being highly variable among populations, senescence appears to be widespread across the tree of life, being observed in almost all species studied so far and in populations facing a large range of environmental conditions. Yet, this process constitutes a paradox in evolutionary biology because natural selection should remove any mutation with detrimental effects on fitness from a given population. Theoretical advances in the second half of the 20th century have enabled to reconcile empirical evidence of senescence in the wild with Darwin's theory of evolution by natural selection.

## Evolutionary Theories of Senescence

Almost 70 years ago, Sir Peter Medawar (1952) was the first to propose an evolutionary explanation (i.e. mutation accumulation theory, Medawar, 1952) to solve the paradox of the existence of senescence. He proposed that deleterious mutations should accumulate in the genome as a direct consequence of the declining forces of natural selection with increasing age. Since there are fewer individuals in the late-life age classes and because these individuals contribute much less to reproduction, any mutation associated with late-life deleterious effect will have less chance to be purged by natural selection. The accumulation of deleterious mutations in the genomes could thus be responsible for the evolution of senescence (Medawar, 1952). It is important to note that under the theory of mutation accumulation natural selection does not select for senescence, but senescence is rather simply a by-product of the declining force of natural selection with increasing age. The relevance of the declining strength of natural selection with age in the evolution of senescence in age-structured populations was mathematically formalized by William Hamilton (Hamilton, 1966) and constitutes a pillar of one of the most influential contributions to the evolutionary biology of aging: the *antagonistic pleiotropy theory of aging* proposed by George C. Williams (Williams, 1957). In 1957, Williams built on Medawar's process involving a declining force of natural selection with increasing age to elaborate an evolutionary theory of aging framed into population genetic concepts. Williams' theory relies on the existence of allele(s) that would be selected by natural selection through a positive effect on individual fitness during early life even if such allele(s) is(are) responsible for an increased senescence in late life (and more generally for a reduced longevity) (Gaillard and Lemaître, 2017; Williams, 1957). When Williams proposed the antagonistic pleiotropy of aging, no such alleles were yet identified. However, this seminal paper has stimulated an important body of research in laboratory models that allowed identifying such long-lived mutants in worms, fruit flies or house mice. In many cases, these alleles have been found to increase lifespan at the expense of early-life reproduction (Nussey et al., 2013). For instance, compared to wild-type worms, long-lived *Caenorhabditis elegans* mutants carrying the age-1 (*hx546*) allele suffer from a lower egg-laying rate during their first 3 days of life but have a higher reproductive performance in late life (Maklakov et al., 2017). In the wild, the identification of such alleles is challenging and the still rare tests of the theory have used a quantitative genetic approach. Under the antagonistic pleiotropy theory, a genetic covariation between early- and late-life fitness contributions is expected to show up. In support, using detailed pedigree of red deer (*Cervus elaphus*) in a population living on the Isle of Rum and an 'animal model' statistical approach, Nussey and colleagues found a genetic negative covariation between a measure of early life fecundity (i.e. number of offspring produced by a female before reaching 9 years of age) and the rate of senescence in offspring birth mass (Nussey et al., 2008a).

The third important conceptual component of our current evolutionary understanding of aging is the disposable soma theory proposed and developed by Thomas B. L. Kirkwood in a series of articles starting in the late 1970s. This theory takes its origin in a work focusing on the maintenance of molecular and cellular integrity (Kirkwood, 1977). At that time, the theory was primarily focused on fine-scale mechanisms regulating cellular aging but the evolutionary implications of this theory were progressively put

forward in several contributions (see Kirkwood, 2017 for the most updated synthesis). In its current form the disposable soma theory shares lots of assumptions and predictions with the life history evolution theory by providing the key role to the principle of allocation (Cody, 1966). This principle states that individuals have to share between different functions the finite pool of resources they can extract from their environment and thus predicts that a negative covariation should occur between any measure of reproductive effort (e.g. age at first reproduction, litter/clutch size) and survival. The disposable soma theory explicitly involves the concept of 'somatic maintenance' (Kirkwood, 2017) based on the evidence that organisms rely on energetically costly dedicated mechanisms (e.g. enzymatic complex) to insure the fidelity of DNA replication and maximize the accuracy of protein synthesis (Kirkwood, 2017). Since all these survival insurance mechanisms are energetically demanding, resources devoted to growth and reproduction cannot be simultaneously used for somatic maintenance, which might compromise cellular integrity and, on the long-run, be responsible for a premature and/or accelerated senescence (Kirkwood and Rose, 1991). Natural selection is thus expected to shape the optimal resource allocation strategy that will maximize fitness payoffs in a given environment (Kirkwood, 2017). The life-history component of the theory might explain why the disposable soma theory has become increasingly popular in the field of evolutionary ecology.

The cardinal prediction from the current version of the disposable soma theory is that a substantial allocation of resources to growth and/or reproduction during early adulthood should be associated with an earlier and/or more pronounced senescence. One of the first support to this theory has been reported in collared flycatcher, *Ficedula albicollis* in a reproductive senescence context (Gustafsson and Pärt, 1990). In this passerine, females with an experimentally enlarged clutch size at 1 year of age laid much smaller clutch size in the following years than females with nonmanipulated broods. Since the 1990s, this prediction has been tested many times in wild populations. A review paper published in 2015 identified 26 studies (encompassing 24 species, mostly birds and mammals) testing for such trade-offs between allocation to reproduction during early life and senescence in late life (Lemaître et al., 2015). Among them, 21 studies supported the existence of a late-life cost of early allocation to reproduction. The probability to find a support for an early- vs. late-life trade-off increased when studies controlled for age-specific changes in the demographic structure of the population, thus corroborating the importance of controlling for processes such as selective disappearance when studying senescence in the wild (Nussey et al., 2008b).

Strikingly, the compiled studies stressed the occurrence of an early- vs. late-life trade-off through the use of multiple traits. For instance, litter size, age at first reproduction and breeding success have all been used to assess the allocation to reproduction during early life and an even higher number of traits have been used to measure individual performance in late life, including notably metrics that do not fully account for the age-specific decrease in fitness-related traits such as individual lifespan. Moreover, it is important to stress that the support for the disposable soma theory per se currently available remains somewhat indirect. All the compiled studies were correlative and none of them actually investigated whether the negative relationship between a high reproductive allocation early in life and an increased senescence in the focal trait was underpinned by an impaired maintenance of the cellular machinery. They thus support more broadly the principle of allocation (Cody, 1966). Moreover, despite the absence of antagonistic pleiotropic alleles clearly identified in such studies, these negative relationships might also provide an indirect support for the antagonistic pleiotropy of aging (Gaillard and Lemaître, 2017).

In the context of allocation trade-offs between early-life performance and senescence almost all studies have used a proxy of reproductive effort to depict allocation to fitness-related traits during early life. Indeed, although growth is also an energetically demanding process (see Metcalfe and Monaghan, 2003 for a review), the long-term consequences of growing fast have been seldom analyzed. However, a recent analysis of long-term age-specific data on body mass collected in two roe deer (*Capreolus capreolus*) populations revealed that growing fast was associated with a steeper decrease of body mass in late life (Douhard et al., 2017). Whether senescence in body condition mediates a possible relationship between growth and both reproductive and actuarial senescence in the wild remains unknown but is worth to investigate because long-term survival costs of growing fast have already been observed in the laboratory (see Lee et al., 2013 in three-spined sticklebacks, *Gasterosteus aculeatus*).

In addition, most studies published so far focused on females, which can reasonably be explained by the fact that demographic studies traditionally focused on females and that an accurate assessment of male reproductive success in the wild is more strenuous because it requires molecular tools in most cases. In males, the allocation to reproduction takes a very different form as males have to allocate energy extracted from the resources available in the environment to growth, maintenance of secondary sexual traits, and conspicuous sexual behavior especially in species subjected to intense sexual selection (i.e. species where males face an intense competition to gain mating opportunities with females). The allocation of resources to reproductive expenditures might strongly limit the quantity of resources available for the set of 'survival insurance mechanisms' and accelerate thereby male senescence on the long-run. For instance, in the red deer population from the Isle of Rum, males that allocate substantially in sexual competition between 4 and 9 years of age (as assessed through the number of days spent rutting or through harem size) suffered from a steeper decline in the same traits from 9 years of age onwards than males allocating much less to sexual competition during early life (Lemaître et al., 2014). As male red deer can lose up to 40% of their body mass during the rutting season, males allocating a large amount of resources to control mating opportunities during early adulthood are likely to suffer later in life from a steeper rate of senescence in competitive abilities caused by an impaired body condition. Such support for early- vs. late-life trade-offs in males has also been reported in badgers (*Meles meles*) where males that face an intense level of sexual competition during early life (assessed through population density) suffer from a pronounced senescence in body mass (Beirne et al., 2015).

Overall trade-offs between allocation to growth/reproduction and senescence are pervasive in natural populations of birds and mammals. In parallel to the increasing number of studies revealing such trade-offs, many studies are currently exploring the physiological pathways that mediate these trade-offs. As discussed below several physiological traits and functions are currently under

the spotlight of evolutionary ecology. It is beyond the scope of this article to review thoroughly the abundant literature relative to each of these physiological traits and to provide the fine-scale mechanisms linking them. Instead, we will focus on the rationale for considering these traits as possible mediators of trade-offs between performance in early life and performance in late life, which we will illustrate with selected examples from the ecological literature.

## An Overview of the Physiological Basis of Senescence in the Wild

Identifying the precise genetic, cellular and physiological pathways underlying senescence is the main objective of medical research in biogerontology with the ultimate goal to prolong healthspan and lifespan. In the past recent years, this research has led to tremendous advances in our understanding of conserved mechanisms underlying the age-related deterioration of organisms and ultimately longevity. In the field, studies looking for identifying the physiological basis of senescence are generally driven by the theoretical background offered by the evolutionary theories of aging (Fig. 2). As detailed above, the current view gives to the amount of resources that individuals are able to acquire and allocate a central role in shaping life history trade-offs. Classically, the disposable soma theory posits that resources allocated either to growth or reproduction cannot be used for longevity insurance mechanisms that are also energetically costly to develop and maintain (Lemaître et al., 2015). In that context, the role of immunity has been heavily discussed, probably because infectious diseases are a major cause of death in the wild (Pedersen et al., 2007).

The immune response is a physiological mechanism involved in the organism’s defense against pathogens. There is now widespread evidence that maintaining basal immunity and mounting an immune response is associated with metabolic cost and largely depends on the available amount of resources available (see Demas et al., 2012 for a review). Following our current understanding of the evolution of senescence in the wild, the allocation of resources towards costly biological processes such as growth or reproduction should thus be associated with a decrease in the efficiency of the immune system, in line with the predictions of the disposable soma theory (Kirkwood, 2017). Long-term longitudinal analyses of populations of vertebrates have revealed that immune performance indeed decreases with increasing age (the so-called *immunosenescence* process) as notably evidenced in greater sac-winged bat, *Saccopteryx bilineata* (Schneeberger et al., 2014). It is important to note that patterns of age-specific decline might differ among populations, between sexes, and among markers of the immune system (e.g. neutrophil vs. lymphocyte counts, Cheynel et al., 2017), which emphasizes the complexity of this process and suggests that possible age-dependent allocation trade-offs occur between the different components of immunity (Cheynel et al., 2017). The decrease in immune performance with increasing age is considered as one of the key physiological mechanism underlying aging (Gruver et al., 2007). In the wild, survival can be predicted by the level of some immune parameters (e.g. white blood cell counts in greater sac-winged bat, Schneeberger et al., 2014). However, to what extent the timing and intensity of the decline in immune traits with increasing age can have direct consequences in terms of demographic senescence per se remains largely unknown.

So far, the importance of immunity as a potential mediator of early- vs. late-life trade-offs has been mainly assessed through experimental manipulations of brood size in birds (see Demas et al., 2012 for a review). As a trade-off between growth and late-life performance has been documented (e.g. Lee et al., 2013), a strong allocation to growth should also be associated with impaired immune performance, which might be even reinforced by the cost of developing immunity when young. Rather than directly testing whether growing fast impairs the immune functions, most of previous studies took the opposite direction by experimentally challenging and stimulating the immune system of young birds (Demas et al., 2012). Overall, the results of these studies validate the hypothesis that mounting an immune response limits the growth rate as a direct consequence of resources allocation biased towards the immune functions rather than towards body growth (e.g. Soler et al., 2003 in magpies, *Pica pica*).

Overall, physiological costs following a substantial allocation to growth or reproduction are good candidates for mediating early- vs. late-life trade-offs (Fig. 2). It is thus not surprising that research in ecology has somewhat been dominated by the possible

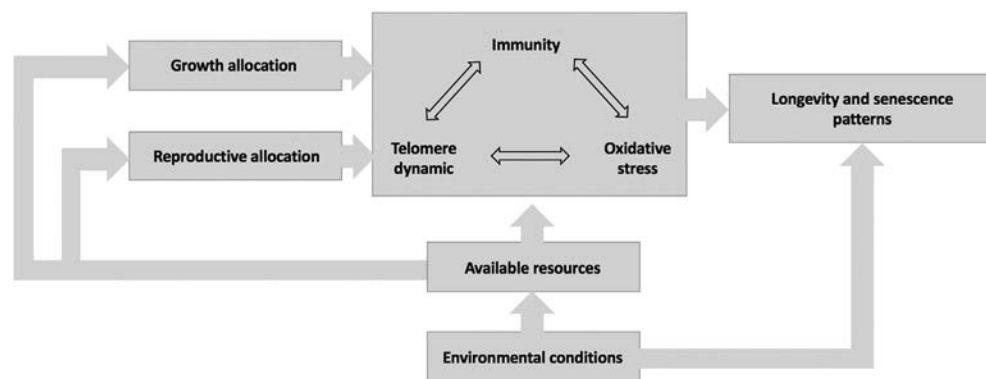


Fig. 2 Conceptual diagram synthesizing our current views of the functional relationships linking growth and reproduction to senescence in wild populations of animals.

pivotal role played by the oxidative balance. Basically, oxidative stress refers to the detrimental accumulation of oxidized molecules in tissues, which in turn is associated with cell disorders, the etiology of numerous degenerative diseases and possible accelerated senescence (Finkel and Holbrook, 2000). Typically, oxidative stress occurs when the rate of reactive oxygen species (ROS) generated during normal oxygen metabolism within mitochondria overcomes the efficiency of the antioxidant machinery causing damage to cell structures. A widespread assertion in evolutionary ecology is that high allocation in reproduction may increase ROS generation, which in turn contributes to oxidative stress. If the cellular damage induced by ROS are not compensated by increased allocation to antioxidant defenses or repair mechanisms (that are themselves energetically costly), senescence might be accelerated (Selman et al., 2012). This accumulation of damage in somatic tissues should thus be logically responsible for both increased actuarial and reproductive senescence. However, evidence accumulated so far that high reproductive expenditure leads to oxidative costs or that increased oxidative stress accelerates senescence in either wild or laboratory conditions is rather mixed (Selman et al., 2012). Whether oxidative stress is a reliable indicator of demographic senescence and mediates early-late life trade-offs in the wild remains an open question that requires repeated measures of life-history traits combined with a large array of physiological and/or molecular markers to be answered. Interestingly, oxidative stress could also influence senescence through an increased telomere loss (Fig. 2), as recently revealed by in vivo studies in which the level of antioxidant defense was experimentally altered (Reichert and Stier, 2017).

Among the set of genetic and physiological mechanisms that have been proposed to mediate life-history trade-offs in animals, the role of telomere dynamic is currently attracting lots of attention (Monaghan and Haussmann, 2006). Telomeres are non-coding repetitive DNA sequences (e.g. TTAGGG in vertebrates) that are found at the ends of linear chromosomes in eukaryotes. They play a critical role in maintaining the genomic integrity of the chromosomes. However, telomere sequences generally shorten over time through the cumulative effects of both incomplete replication of chromosome ends during cell division and oxidative stress even if the telomerase (i.e. an enzyme involved in telomere replication) can, in some specific species and tissues, repair and elongate telomere sequences (Monaghan and Haussmann, 2006). Based on inputs from cellular biology and comparative physiology, an inevitable decline in telomere length with increasing age is thus expected. As telomere shortening with age is functionally linked to apoptosis and cellular instability, many efforts have been devoted to link telomere length to individual's survivorship. Relationships between telomere length and lifespan have been repeatedly looked for in wild populations of animals and a recent meta-analysis based on 27 vertebrate populations in the wild revealed that birds with short telomeres indeed suffer from an elevated mortality risk (Wilbourn et al., 2018). One mandatory assumption of studies giving to telomere dynamic a pivotal role in life history trade-offs is that allocation to growth (though increased cell division rate) or to reproduction (through increased level of oxidative stress) accelerates telomere loss (Young, 2018) (Fig. 2).

A few studies performed on a wide range of organisms have now tested these predictions. If we take the example of telomere studies seeking to identify physiological costs of reproduction, support have been provided in blue tit (*Cyanistes caeruleus*), where individuals caring for enlarged broods suffered from a steeper telomere loss than control individuals (Sudyka et al., 2014). On the contrary, in Magellanic penguins (*Spheniscus magellanicus*), the number of chicks fledged was not associated with telomere loss (Cerciara et al., 2017). So far, life history studies performed in the context of telomere loss have analyzed the contribution of growth and reproduction separately. The association between reproductive costs and telomere loss reported in some correlative studies might in fact only reflect long-term costs of growing fast because fast growth allows an early access to reproduction. Deciphering the relative role of growth and reproduction in telomere dynamics now constitutes an important step in the study of senescence in wild populations.

Research on immunity, oxidative stress and telomere dynamics constitutes nowadays the vast majority of studies focusing on the physiological basis of senescence in the wild. We have mentioned above the functional links that exist between oxidative stress and telomere dynamics but the relationships between these processes and the immune function are also close, which emphasizes important limits in our current understanding of the physiological basis of senescence in the wild (Fig. 2). For instance, blood is the easiest biological tissue to collect in the field, especially in longitudinal studies. With mammalian blood, telomeres can only be measured in white blood cells, which leads telomere length to represent most of the time average measurements across different types of leukocytes. However, the different types of leukocytes might show markedly different patterns with increasing age and age-specific changes of telomere length can potentially be affected by changes in the relative concentration of each cell type.

## Concluding Remarks

This review emphasizes how the study of senescence through the lens of evolutionary biology can provide important insights to understand not only the evolutionary roots of this nearly ubiquitous biological process, but also the genetic and physiological mechanisms underlying its variability at the species, population and individual levels. In that context, the full integration of senescence within the life history framework has been particularly successful, by notably highlighting that both age-specific decreases in survival and reproductive probabilities observed in late adulthood across animals can be explained by the selection for a substantial resource allocation to growth and reproduction during early life. In return, this eco-evolutionary framework has leveraged eco-physiology studies trying to decipher the complex and tangled physiological pathways linking growth, reproduction and survival in natural environments where the availability in resources vary both spatially and temporally.

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