Why organisms age: Evolution of senescence under positive pleiotropy?

Alexei A. Maklakov[1]*, Locke Rowe[2] and Urban Friberg[3,4]

Two classic theories maintain that aging evolves either because of alleles whose deleterious effects are confined to late life or because of alleles with broad pleiotropic effects that increase early-life fitness at the expense of late-life fitness. However, empirical studies often reveal positive pleiotropy for fitness across age classes, and recent evidence suggests that selection on early-life fitness can decelerate aging and increase lifespan, thereby casting doubt on the current consensus. Here, we briefly review these data and promote the simple argument that aging can evolve under positive pleiotropy between early- and late-life fitness when the deleterious effect of mutations increases with age. We argue that this hypothesis makes testable predictions and is supported by existing evidence.

[1] Department of Animal Ecology, Evolutionary Biology Centre, Ageing Research Group, Uppsala University, Uppsala, Sweden
[2] Department of Ecology and Evolutionary Biology, University of Toronto, Toronto, ON, Canada
[3] Department of Evolutionary Biology, Evolutionary Biology Centre, Ageing Research Group, Uppsala University, Uppsala, Sweden
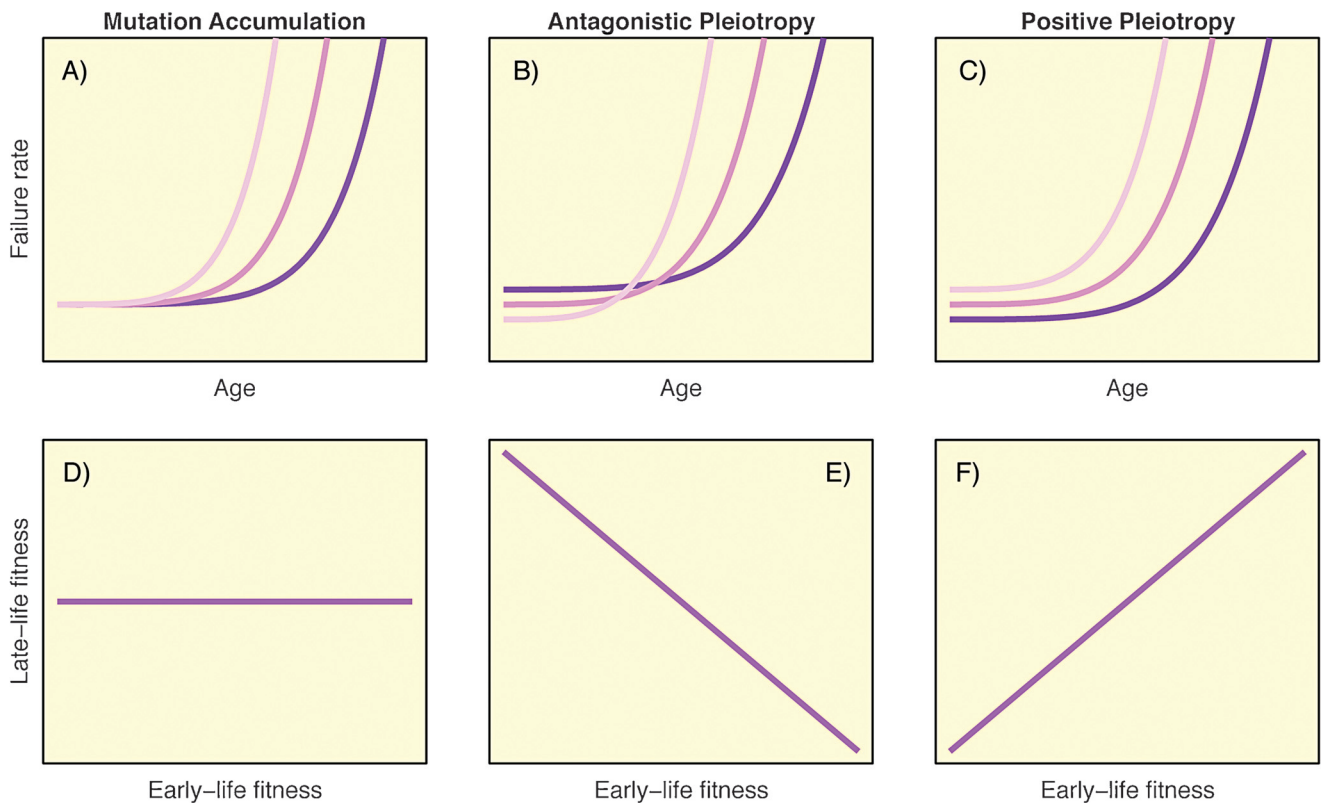[4] IFM Biology, AVIAN Behavioural Genomics and Physiology Group, Linköping University, Linköping, Sweden

Corresponding author:
Alexei A. Maklakov
E-mail: alexei.maklakov@ebc.uu.se

Abbreviations:
AP, antagonistic pleiotropy; **MA,** mutation accumulation.

Introduction

Aging, or senescence, is a physiological deterioration of the organism, resulting in reduced reproduction and increased probability of death with advancing age. Aging is deleterious for Darwinian fitness, yet is a pervasive feature of most living beings. Given the large number of known repair mechanisms, it is not clear why organisms should senesce. This apparent paradox is resolved by the evolutionary theory of aging, which relies on the fundamental principle that the strength of natural selection declines with age, because of extrinsic (non-aging-related) mortality resulting from the cumulative effects of a variety of biotic and abiotic factors [1–8]. Hence, the intrinsic organismal repair mechanisms are imperfect, because even if they perfectly repaired all damage, their benefit would gradually be nullified by the increasing risk that the organism will die from other cause anyway. This decline in the strength of selection, which stems from the reduction of the residual reproductive value with age, forms the basis of the two theories for the evolution of aging: mutation accumulation (MA) [1] and antagonistic pleiotropy (AP) [2]. These two leading theories rely on mutations with very different properties and, therefore, have distinct sets of predictions.

The mutation accumulation theory

MA relies on mutations with age-specific effects on fitness [4, 6, 8, 9] (see Fig. 1A and D), whereas AP relies on mutations that affect fitness across a broad range of age classes [5, 6] (see Fig. 1B and E). Under MA, mutations whose deleterious effects are confined to late life can accumulate in a population because selection is too weak to weed them out. An MA allele that causes a life-threatening condition in late life is invisible to selection in early ages when most fitness is accrued, whereas few individuals will survive long enough to experience its deleterious effects in late life. Thus, under MA aging is maladaptive, because it reduces fitness of organisms carrying these mutations. An important inference of this theory is that it does not predict a correlation between early-life fitness and the rate of aging, because those

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Figure 1. The relationship between failure rate (deleterious effect on fitness) and age (panels **A**, **B**, and **C**) for three different genotypes under classic mutation accumulation (MA), antagonistic pleiotropy (AP), and positive pleiotropy with age-specific increase in deleterious mutational effect (modified mutation accumulation, MMA), respectively. MA mutations only affect fitness late in life (**A**), while AP (**B**), and MMA (**C**) mutations affect fitness across all ages. MA predicts no correlation (**D**), AP predicts negative genetic correlation (**E**), and MMA predicts positive genetic correlation (**F**) between early-life and late-life fitness.

mutations causing senescence have no impact early in life (e.g. [10], see also Fig. 1A and D). Early treatments of MA suggested narrow "windows" of age specificity of mutational effects and predicted a "wall-of-death" after the end of reproduction. However, more recent modifications of this theory [8] suggest that age-specific mutations can affect several adjacent age classes, or even all age classes after a given age, thus allowing for post-reproductive lifespan and a decline in mortality rates at very late ages [11]. This modified MA theory allows for the widest "windows" of mutational effects and predicts positive genetic correlations across a relatively broad range of ages. This model assumes that deleterious mutations affect the organism from certain point in time and onwards, resulting in positive genetic correlations for fitness across later, post onset, ages.

The antagonistic pleiotropy theory

Contrary to MA, AP contemplates mutations with a window of effects that span early and late life, and instead focusses on

the sign of age-specific effects. Here, relevant mutations are assumed to have positive effects early in life and negative effects late in life. Indeed, if detrimental mutations with late-acting deleterious effects can accumulate under MA, it is easy to see that mutations that increase fitness early in life at the cost of reduced fitness late in life will be favored. A physiological account of aging as an adaptation is the "disposable soma" theory, which emphasises the trade-off between reproduction and survival [6, 7, 12]. This theory suggests that organisms allocate limited resources to current reproduction and somatic maintenance, which improves survival and future reproduction. Given that selection is weaker later in life, optimal allocation of resources will result in suboptimal somatic maintenance and aging. Thus, AP and "disposable soma" theories both predict a positive genetic correlation between early-life fitness and rate of aging, and a negative genetic correlation between early- and late-life fitness.

Although MA and AP are not mutually exclusive, considerable research effort has been put into quantifying their relative contribution to the evolution of aging [11]. A classic approach has been to estimate the genetic correlation between early and late-life fitness (or aging), because here the two theories produce contrasting predictions. Surprisingly, several studies produced rather unexpected results – a positive genetic correlation between early- and late-life fitness, often resulting in a negative genetic correlation between early-life fitness and the rate of aging, i.e. that genetic factors that are beneficial for early-life fitness also correlate with relatively slower rates of aging. These results are not easily understood within the existing theoretical framework.

How common is positive pleiotropy between early- and late-life fitness?

The question of whether there is a positive genetic correlation between early- and late-life fitness and aging is an old one. Rose [5] devoted a special section to this discussion because he felt that its resolution is vital for the evolutionary theory of aging. At the time, there was already substantial evidence in the literature for positive correlations between early and late fecundity; between rate of reproduction and longevity; and between early reproduction and longevity (reviewed in [5]). However, most of these studies could be criticized on a variety of methodological grounds [5]. Some failed to separate between phenotypic and genetic correlations; others used inbred lines that could differ in degree of inbreeding (health), which could result in overwhelmingly positive genetic correlations; yet other studies involved recently established laboratory populations, which could lead to spurious results because of genotype-by-environment interactions. However, more recent studies that have attempted to quantify genetic correlations across age classes while avoiding some of these pitfalls, also tend to find positive genetic correlations, as discussed below.

These empirical studies can be broadly divided into those focusing on (i) segregating genetic variation; (ii) the effects of spontaneous mutations; and (iii) experimental evolution studies, which rely largely on segregating genetic variation, but can incorporate novel mutations if conducted over a sufficiently long period of time. Early work by Rose, Luckinbill, and others [13, 14] made a strong case for antagonistic pleiotropy by identifying negative genetic correlations between early and late-life fitness in fruit flies selected for early or late age at reproduction. However, follow-up studies in *Drosophila* and other taxa revealed a more complex pattern of responses [15–21], suggesting that the relationship between early fecundity and longevity described in earlier studies may not be causal [22, 23]. In particular, Khazaeli and Curtsinger [23] created recombinant inbred lines from Luckinbill et al. [13] selection experiment and showed that antagonistic pleiotropy disappears in recombinant genotypes, hence, arguing against the importance of AP in generating previously observed correlated responses to selection on age at reproduction. Other studies that used different quantitative genetic approaches to study segregating genetic variation found negative genetic correlations between age-specific mortality and fitness [24–26].

It has been noted several times that analyses of segregating genetic variation can be biased against detecting fitness variance arising from AP alleles, because these alleles are adaptive and would quickly go to fixation (e.g. [6]). It has been argued that a more fruitful approach would be to estimate pleiotropy and age specificity of spontaneous mutations. Unfortunately, this approach has rarely been used, and nearly all relevant studies are limited to *Drosophila* (but see [27]). Nonetheless, at least four independent studies of the effects of spontaneous mutation found that genetic correlations between age-specific fitness components, such as mortality or fecundity, are mostly either positive or zero [11, 28–30] with only two of these studies [11, 29] providing clear

evidence for mutations with age-limited effects required by the MA theory. Moreover, in *Caenorhabditis elegans*, there was a positive genetic correlation between early- and late-life fitness [27]. Nevertheless, it should be stressed that AP alleles can be very rare and the absence of such alleles in the mutation accumulation experiments does not necessarily contradict AP theory [28]. It is therefore particularly interesting to look at long-term selection studies that apply selection for early-life fitness.

Two recent studies using *D. melanogaster* found positive genetic correlations between fitness and longevity and negative genetic correlation between fitness and rate of aging both for cytoplasmic [25] and nuclear [30] parts of the genome. The latter study is particularly interesting because it showed that *Drosophila* lifespan remained unchanged in both sexes following several hundred generations of selection for early reproduction. The follow-up mutation accumulation experiment showed that mutations reducing "post-reproductive" longevity were the same mutations that reduced reproductive performance early in life, thereby maintaining the remarkable ability of flies to survive eight times longer than necessary [30]. In other words, the same alleles that confer high fitness during the fifth day of the adulthood of a fly increase its chances of survival when it is a senescent 40-day-old insect.

Early work by Houle et al. [28] suggests that these results are generalizable across traits as well as ages. Looking at the age- and trait-specific distribution of novel mutations, the authors found that mutational correlations across all traits and ages were positive. They argued that their results were incompatible with narrow-sense MA models of senescence, and suggested that average effect of alleles could increase with age. This explanation fits well with the recent studies of standing and novel genetic variation cited above, as well as with studies suggesting that increased selection early in life results in the evolution of increased intrinsic longevity [21, 31]. What we can conclude from these mutation accumulation studies is that mutations tend to have an extremely wide window of negative effects, leading to positive pleiotropy across all life history stages (e.g. [21, 25–28, 30]).

Aging can evolve when deleterious mutations have small effect early in life

How do we reconcile the accumulating evidence for positive pleiotropy with the traditional evolutionary theories of aging? As noted above, MA centers on mutations with narrow windows of effect, whereas AP focuses on the shape of mutational effects across the life history. Positive pleiotropy suggests that we need to consider a third class of alleles: one with negative effects across all ages, but tilting toward late life (Fig. 1C). Such mutations reduce fitness and increase the probability of failure at any point of an organism's life, but their negative effect on age-specific fitness relative to non-mutant wild type increases with age. It is easy to imagine the accumulation of two alternative alleles with similar net negative effects (when expressed); first, an AP allele with minor early-life positive effects and severe late-life negative; or second, an allele with minor negative effects

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early in life and moderate negative late-life effects. The data reviewed above suggest that it is the latter class that is perhaps more common. In theory, the greater the tilt of these positively pleiotropic alleles toward late life, the less likely it is that they will be selected against, and the more likely that they will contribute to the evolution of aging.

It is common to think of MA theory in terms of alleles with age-specific effects, the classic example being Huntington's disease in humans, which is caused by a dominant allele with late age of onset [4, 32]. Alternatively, alleles with pleiotropic effects across age classes are usually considered within the framework of AP theory [5, 32]. However, several studies have suggested ways to extend and generalize the classic theory in recent years [8, 33–36]. In particular, recent demographic modeling work by Wachter et al. [35, 36], suggests that the assumption that late-acting deleterious mutations have small but appreciable effects on fitness in early life is crucial for MA theory, which otherwise would generally predict the evolution of unrealistic "walls of death" in late-life and loss of equilibria under mutation-selection balance. Following Houle et al. [28] and Wachter et al. [35, 36], we suggest that deleterious mutations whose effect on fitness increases with age are particularly important in shaping evolution of longevity and aging (Fig. 1C and F). Such mutations would have small effects on fitness early in life and, therefore, can be maintained at appreciable frequencies in a population under mutation-selection balance. The key assumption necessary for the evolution of aging under such scenario is the relative increase in deleterious effect of mutation on performance (e.g. intrinsic mortality) with age (Figure 1C). Assuming an age related increase in the effect of mutations on intrinsic mortality and in the variance of this effect, aging evolves according to classic Medawar–Williams predictions when extrinsic mortality is random, that is, increased extrinsic mortality results in the evolution of rapid aging (Fig. 2A and B). However, when extrinsic mortality is non-random and preferentially removes low-fitness genotypes from the population, increased extrinsic mortality will result in the evolution of slower aging Fig. 2C (see also [37, 38]).

When extrinsic mortality is reduced, for example, when animals are maintained in a safe laboratory environment, a much larger fraction of individuals would reach late-age, resulting in extended realized longevity. Under these conditions, selection against genotypes with faster aging and shorter intrinsic longevities would increase as the relative difference in fitness between genotypes becomes larger (Fig. 2). By contrast, if animals are subjected to increased rates of random mortality, the relative difference in fitness between genotypes becomes smaller, resulting in reduced selection against fast-aging genotypes, thereby increasing their proportion in the population and reducing longevity. However, if mortality is non-random and increased mortality increases selection against low-fitness genotypes early in life, such a regimen can paradoxically result in the evolution of increased intrinsic longevity under increased extrinsic mortality, as has recently been found in *Caenorhabditis remanei* nematodes [21]. Thus, this hypothesis enables us not only to predict the evolutionary response of aging under differential mortality rates, but also to make specific predictions regarding
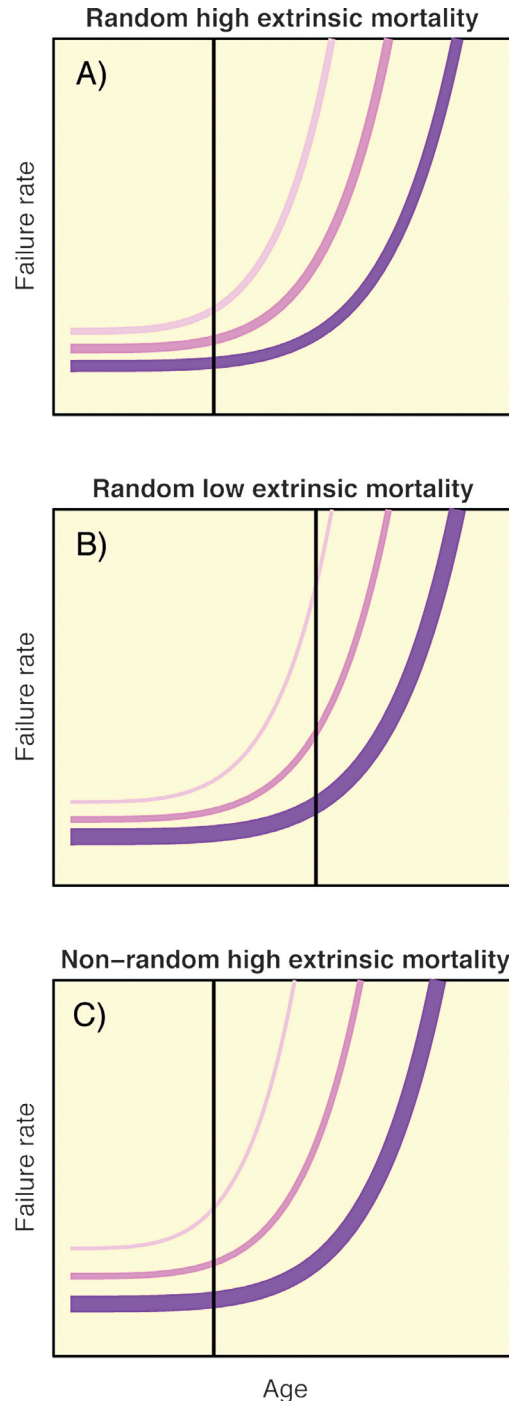
Figure 2. The effect of extrinsic mortality on aging under positive pleiotropy for fitness across all age classes, with an age-specific relative increase in deleterious mutational effect. The vertical lines show expected lifespan resulting from extrinsic factors in a random high-mortality environment (**A**) and a random low-mortality environment (**B**). The thickness of the curves reflects the frequency of the three genotypes under mutation selection balance in the two environments. Fast-aging genotypes increase in relative frequency under random high-mortality (cf. **A** and **B**). However, when high mortality is non-random and low-fitness genotypes have higher risk of death early in life, increased extrinsic mortality will result in the evolution of increased longevity, because high-fitness low-aging genotypes will increase in frequency (**C**).

the direction of the response depending on whether extrinsic mortality is random with respect to fitness.

Age-specific increase in mutational effect is also compatible with the quantitative genetic studies described above that find null or positive genetic correlations across age classes. While this hypothesis predicts positive genetic correlations, the power to detect such correlations declines with increasing age "window" and might require a very large sample size, especially when very early ages are concerned.

Should we assume that mutational effect increases with age?

Is age-specific increase in mutational effect an assumption that is likely to be true? In essence, this hypothesis is an extension of the classic MA, with the important caveat that mutations that cause substantial problems late in life also negatively affect fitness early in life, but to a lesser extent. One additional prediction of this hypothesis is that genetic variance in fitness components should increase with age, which coincides with the prediction for MA theory. This prediction has been tested and supported multiple times in different taxa ([11, 39–42], reviewed in [43, 44]). It is particularly interesting that generally positive or null genetic correlations together with age-specific increase in additive genetic variance were reported in two wild populations of mammals [44], suggesting that these patterns extend beyond what is found in laboratory experiments.

Some mutation accumulation studies suggested that spontaneous mutations preferentially affected early-life fitness [29, 45], although this effect disappeared with increasing number of generations. It is not entirely clear whether these results indeed reflect the prevalence of age-specific effects early in life at the initial steps of mutation accumulation or simply result from hidden environmental heterogeneity within the cohorts [46] leading to rapid selective disappearance of sick individuals early in life. This is because environmental heterogeneity within isogenic lines can directly affect the penetrance of deleterious mutations and lifespan [47]. In other words, because deleterious mutations can be buffered more in some individuals than others, late-life cohorts can be more similar to wild type and to each other than early-life cohorts. However, even if these results do reflect the underlying distribution of mutations [34], they do not necessarily disagree with the hypothesis that we discuss here. De-novo deleterious mutations with age-specific increases in mutational effect do not have to be the most common; it is merely the case that they are expected to exist. Alleles whose strong negative effects are confined to early life will be under strong natural selection and thus are expected to be present in the populations in lower proportion than alleles with small early-life effects even if the latter are rarer.

Conclusions and outlook

Aging is a multi-faceted phenomenon that is likely to result from several evolutionary processes. Here we suggest that a very simple assumption (an age-specific increase in the deleterious effects of mutations that affect all ages) can account for both so-called classical and non-classical evolutionary responses in age-specific life histories to selection under differential risk of death. This approach, first suggested by Houle et al. in 1994 [28] and lately developed by Wachter et al. [35, 36], reconciles the idea that aging evolves because of declining strength of natural selection with age with empirical observations that genetic variation for fitness is positive across age classes and that selection on early-life fitness can result in increased longevity and decelerated rate of aging (see also [37, 38]). Most importantly, this modified mutation accumulation (MMA) hypothesis makes testable predictions regarding the evolutionary response in longevity and aging to a change in extrinsic mortality rate depending on whether mortality is random or condition dependent (i.e. when low-condition individuals suffer higher or lower rates of mortality). Although it is likely that many classic MA and AP alleles are segregating in populations, the data suggest that these could be overwhelmed by alleles that have positively pleiotropic fitness effects across all ages. We suggest that this observation is congruent with the evolutionary force underlying aging (a decline in the efficacy of selection with age) if one considers deleterious alleles whose effects increase with age. Including these alleles also leads to testable hypotheses.

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