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The handle http://hdl.handle.net/1887/31591 holds various files of this Leiden University dissertation

Author: Wensink, Maarten Jan
Title: The evolution of ageing : concepts, causation and calculus
Issue Date: 2015-01-27

Chapter 5

No senescence despite declining selection pressure: Hamilton's result in broader perspective

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Abstract

Theory predicts that senescence should inevitably evolve because selection pressure declines with age. Yet, data show that senescence is not a universal phenomenon. How can these observations peacefully coexist? Evolution of any trait hinges on its impact on fitness. A complete mathematical description of change in fitness, the total fitness differential, involves selection pressure along with a perturbation function that describes how the vital rates, mortality and fecundity, are affected across ages. We propose that the perturbation function can be used to model trade-offs when vital rates are perturbed in different directions and magnitude at different ages. We find that for every trade-off we can identify parameter values for which senescence does evolve and others for which it does not. We argue that this reconciles the apparent contradiction between data and theory. The total fitness differential is also instrumental in deriving mathematical relationships between alternative indicators of selection pressure. We show examples and highlight that any indicator combined with the right perturbation function can be used to parameterize a specific biological change. Biological considerations should motivate what perturbation functions are used. We interpret the relevance of Hamilton's finding that selection pressure declines for the evolution of senescence: declining selection pressure is a necessary but not a sufficient condition.

Introduction

Higher ages are of less evolutionary importance than younger ages. As organisms go through their life course, more and more offspring are born, so more and more of the organism's contributions to the gene pool come to lie in the past. Since earlier contributions cannot be affected by later events, death of older individuals incurs less of a penalty to evolutionary fitness than death of younger individuals. In a nutshell, this declining selection pressure is the basis of evolutionary explanations of senescence, the deterioration of an organism's vital rates due to changes in its state as the organism gets chronologically older [1-3]. Selection pressure declines for any pattern of fecundity and survival [3], even for organisms that initially exhibit 'sustenance', unchanging rates of reproduction and survival with age (sensu [4]), or organisms that show 'negative senescence', defined by rising rates of reproduction declining rates of mortality with age (sensu [5]).

If declining selection pressure were a sufficient condition for the evolution of senescence, then evolution should mold any life course, even those that initially exhibit no or negative senescence, to the senescent phenotype after sufficient evolutionary time. Yet, patterns of sustenance and negative senescence can be observed in nature [5,6]. Therefore declining selection pressure alone cannot be the decisive argument, and something else must be at play [6].

Selection pressure expresses the sensitivity of fitness to some standard unit of change in a vital rate, mortality and fecundity, at a specific age. To know how fitness changes as a result of some real biological perturbation, it is necessary to know which vital rate(s) are affected, at which ages, and how strongly. These changes can be captured in a perturbation function, which describes the effects on mortality and fecundity as a function of age. The perturbation function completes the total fitness differential, which is the full and general analytical description of how fitness changes if mortality and/or fecundity change(s) [7,8]. Any effect on fitness can only be known if the total fitness differential is considered.

To find an appropriate perturbation function, one has to consider the underlying biology: if mortality is perturbed at one age, what would happen biologically at other ages, and what does that mean for the perturbation function? The complex causal pathways leading to changed gene expression, the accumulation of damage, loss of physiological control, but also growth and learning (all of which affect mortality and fecundity patterns), are likely to be tied in some more or less continuous trajectory of change. These cannot be reduced to independent age-specific changes [9,10]. Here, the perturbation function is helpful, since it describes such age-patterns.

The combination of selection pressure and perturbation is commonly studied in age-structured models [11,12], matrix population models [13, §9.1.6 of 14], and quantitative genetics [15]. Yet, studies of senescence typically invoke standard-unit changes at particular ages (or age-ranges), drawing conclusions from verbal comparison of 'early' (low ages) versus 'late' (high ages) [e.g. 1-3,16-18]. In the same vein, conclusions about the evolution of senescence are frequently drawn directly from patterns of selection pressure [e.g 19-24]. We exemplify biologically realistic perturbation functions and use those in combi-

nation with the associated selection pressure, thus completing the evolutionary analysis. This leads to results that are not evident from models based on selection pressure alone. Mathematical relationships between alternative indicators of selection pressure are clarified using the perturbation function. We conclude with showing that Hamilton's finding is a necessary but not a sufficient cause for the evolution of senescence.

Fitness consequences of changes in vital rates

Hamilton [3] used the intrinsic rate of increase $'r'$ as a measure of fitness, defined as the unique real root of the Euler-Lotka equation, within the framework of stable population theory [11,14,25]:

$$\int_0^\infty e^{-rx}\ell(x)m(x)dx = 1 \tag{5.1}$$

In this equation $\ell(x)$ denotes survival up to age x, and $m(x)$ denotes age-specific fecundity. Survival is related to the instantaneous mortality rate $\mu(x)$:

$$\ell(x) = e^{-\int_0^x \mu(t)dt} \tag{5.2}$$

By implicit differentiation of r with respect to an additive perturbation of mortality and fecundity respectively, Hamilton [3] derived indicators of selection pressure on age-specific additive perturbations of mortality and fecundity. These indicators are:

$$\frac{dr}{dF_a} = \frac{e^{-ra}\ell(a)}{T} \tag{5.3}$$

$$\frac{dr}{d\Delta_a} = -\frac{\int_a^\infty e^{-rx}\ell(x)m(x)dx}{T} \tag{5.4}$$

where

$$T = \int_0^\infty xe^{-rx}\ell(x)m(x)\,dx \tag{5.5}$$

which is the average age at reproduction in a population, i.e. generation time [11]. Furthermore, $d\Delta_a = d\mu(a)da$, an infinitesimal additive change in mortality multiplied by an infinitesimal neighborhood of the age at which this change takes place, and $dF_a = dm(a)da$, an infinitesimal additive change in fecundity multiplied by an infinitesimal neighborhood of the age at which this change takes place.

Using functional calculus, Arthur [7] derived a general analytical expression for the sensitivity of r to changes in the patterns (rather than age-specific values) of fecundity and survival, writing r in its differential form:

$$dr = \frac{1}{T}\left[\int_0^\infty e^{-ra}d\ell(a)m(a)da + \int_0^\infty e^{-ra}\ell(a)dm(a)da\right] \tag{5.6}$$

If the perturbation of survival is considered at the mortality level, the two being related through equation (5.2), applying the product rule to $d\ell(a)$ and integrating by parts, this

expression can be rewritten as:

$$\frac{dr}{d\varepsilon} = \int_0^\infty \left[\frac{e^{-ra}\ell(a)}{T} \frac{dm}{d\varepsilon}(a,\cdot) - \frac{\int_a^\infty e^{-rx}\ell(x)m(x)dx}{T} \frac{d\mu}{d\varepsilon}(a,\cdot) \right] da \qquad (5.7)$$

Perturbation parameter ε captures small perturbations in fecundity ($dm/d\varepsilon(a,\cdot)$) and mortality ($d\mu/d\varepsilon(a,\cdot)$). These perturbations can be functions of age, and possibly other parameters, indicated by the dot. The two other elements can be recognized as Hamilton's indicators of selection pressure, equations (5.3) and (5.4). Writing H^* and $H^\dagger$ for Hamilton's indicators of selection pressure on additive changes in fecundity and mortality rate respectively, the general equation for change in r is:

$$\frac{dr}{d\varepsilon} = \int_0^\infty \left[H^*(a) \frac{dm}{d\varepsilon}(a,\cdot) + H^\dagger(a) \frac{d\mu}{d\varepsilon}(a,\cdot) \right] da \qquad (5.8)$$

At every age, the effect of change in mortality and fertility on fitness is given by the product of fitness sensitivity (H^* or $H^\dagger$) and the perturbation in the vital rate ($dm/d\varepsilon$ and $d\mu/d\varepsilon$). Integration over all ages then yields the full fitness consequences. As an example of a perturbation function, mortality μ could equal some constant c in the baseline scenario, while perturbed mortality could be given by

$$\mu(a,\varepsilon) = c + \varepsilon(a - p)s \qquad (5.9)$$

where age p is the one age at which the perturbed mortality function crosses the baseline (constant) mortality, $\varepsilon \geq 0$ is a perturbation parameter, while parameter $s > 0$ models the strength of the trade-off. Both s and ε are given in units of time^{-1}. Except for its dimensionality, parameter s is redundant in this case, but not in other perturbations (see below), and is included here for consistency. The perturbation function expresses how strongly mortality gets to deviate from the baseline scenario, which in the case of equation (5.9) is

$$\frac{d\mu}{d\varepsilon} = (a - p)s \qquad (5.10)$$

Notice that this perturbation function involves changes at all ages.

Invasion study

Expression (5.8) can be analyzed for any perturbation functions $dm/d\varepsilon(a,\cdot)$ and $d\mu/d\varepsilon(a,\cdot)$ of interest, in the context of the life histories of a resident phenotype, which determine H^* and $H^\dagger$. Notice that selection pressure is "situational" (pg 34 of [26]): as soon as vital rates actually do change, selection pressure changes with them. As a result, the fitness differential can be used to indicate an initial direction of change, but for real-life, non-infinitesimal changes, it provides only a linear approximation (see [27-29] for methods to improve on this limitation). We need therefore to choose a phenotype for the resident population to be able to derive exact expressions for selection pressure.

We choose a *sustenant* resident phenotype. Although it is not evident that early organisms were sustenant, this assumption avoids presuming that senescence has evolved before explaining that very phenomenon, and has therefore often been taking as a starting point in previous approaches [e.g. 1,2,12,13,30].

The perturbation function, we propose, can be used to mimic trade-offs, since this function can express different direction and magnitude of perturbation of vital rates at each age, which is what happens under a trade-off. The perturbation functions are assumed to pertain to all organisms in a population. The environment is assumed to be constant.

Having thus obtained the ingredients for the fitness differential, the latter can be evaluated to determine whether invasion is possible. If and only if a positive fitness differential exists, i.e. $dr/d\varepsilon > 0$, improvement is possible locally, so that invasion will take place if the necessary variation exists. If $dr/d\varepsilon = 0$, there is no advantage of one phenotype over the other (neutral change can occur), while if $dr/d\varepsilon < 0$, improvement is not possible.

For a sustenant phenotype the life history is characterized by constant fecundity (m_0) and constant mortality (c). Solving equation (5.1) with $m(x) = m_0$ and $\mu(x) = c$ yields $r = m_0 - c$. Substitution of this result in equations (5.3) and (5.4), accounting for equation (5.2), and integrating by parts gives the following results:

$$H^* = m_0 e^{-m_0 a} \tag{5.11}$$
$$H^\dagger = -m_0 e^{-m_0 a} \tag{5.12}$$

In a sustenant phenotype, selection pressure is an exponentially declining function of age. These are the indicators of the force of selection on an age-specific additive change of mortality and fecundity respectively that determine whether a mutant phenotype can invade a resident sustenant phenotype under the trade-off of interest (similar to equation (6) in [12]).

Substitution of the results in equations (5.11) and (5.12) in equation (5.8) yields:

$$\frac{dr}{d\varepsilon} = m_0 \int_0^\infty e^{-m_0 a} \left(\frac{dm}{d\varepsilon}(a, \cdot) - \frac{d\mu}{d\varepsilon}(a, \cdot) \right) da \tag{5.13}$$

This equation can be evaluated for alternative perturbation functions. First, to demonstrate the principle, we consider a linear trade-off within the mortality function, such that the mortality rate is initially reduced, but increases linearly with age. Second, because this trade-off has received considerable attention, we evaluate a trade-off that involves both mortality and fecundity. In the disposable soma theory [30,31], fecundity is increased at a cost to repair. The perturbation function associated with this trade-off could be such that mortality increases linearly with age while reproductive rate is increased by a constant at all ages. Third, illustrating a case when negative senescence can evolve, we evaluate an exponential trade-off within mortality, such that the mortality rate is reduced at low ages but increases exponentially with age or vice versa.

Linear trade-off within mortality

This trade-off is characterized by perturbation function (5.10). Substitution in equation (5.13) yields:

$$\frac{dr}{d\varepsilon} = -m_0 s \int_0^\infty (a - p)e^{-m_0 a} da \qquad (5.14)$$

Rearranging and integrating by parts gives:

$$\frac{dr}{d\varepsilon} = -m_0 s \left(\frac{1}{m_0^2} - \frac{p}{m_0} \right) = s \left(p - \frac{1}{m_0} \right) \qquad (5.15)$$

Whether the derivative in equation (5.15) is greater than zero, so that the senescent phenotype can invade, depends on parameter p: the higher age p, the longer the mortality rate stays below its original constant level. Thus, high values of p should promote the evolution of senescence, while low values should not. Age p_0 marks the boundary between trade-offs that do (greater p) or do not (smaller p) favor the evolution of senescence. Substituting p_0 for p in equation (5.15), setting $dr/d\varepsilon = 0$, and solving for p_0 yields:

$$p_0 = \frac{1}{m_0} \qquad (5.16)$$

Interestingly, $p_0 = 1/m_0 = T$. Thus, for all p greater than generation time T the senescent phenotype can invade, while for smaller values it cannot. Notice that this result holds only in a specific resident life history under a specific perturbation function.

Linear trade-off involving both mortality and fecundity

Another possibility is that a trade-off results in a linear increase in mortality and a higher constant reproductive rate. Mortality and fecundity then become:

$$\mu(a, \varepsilon) = c + \varepsilon a s \qquad (5.17)$$
$$m(\varepsilon) = m_0 + \varepsilon \qquad (5.18)$$

For mortality this is the same perturbation as in section 3.1 with $p = 0$. Whether the senescent phenotype can invade or not is now not a function of p (since $p \equiv 0$ from the nature of the trade-off), but of the rate at which mortality increases with some increase in reproductive rate, modeled by parameter s. Substituting $d\mu/d\varepsilon = as$ and $dm/d\varepsilon = 1$ (from equations (5.17) and (5.18) respectively) in equation (5.13) gives:

$$\frac{dr}{d\varepsilon} = m_0 \int_0^\infty e^{-m_0 a} da - m_0 s \int_0^\infty a e^{-m_0 a} da = 1 - s/m_0 \qquad (5.19)$$

If $dr/d\varepsilon > 0$ the senescent phenotype can invade, which is the case if $s < m_0$. For greater values of s (when mortality increases faster for the same m) the senescent phenotype cannot invade.

Exponential trade-off within mortality

In the previous paragraph we evaluated whether a senescence phenotype could invade. Of equal interest is the question whether a negatively senescent phenotype, with improving vital rates over its adult lifespan, can invade the sustenant resident phenotype. The study of negative senescence versus sustenance requires care, since many functional forms of the perturbation function are biologically intractable. For instance, a continuous additive decline in mortality or fecundity would lead to negative mortality and fecundity at high ages, which is not biologically possible. There are two conceivable solutions to this problem. The first is to calculate $dr/d\varepsilon$ on some interval on which mortality and fecundity take strictly positive values. If the vital rates on that interval are biologically plausible, and $dr/d\varepsilon$ takes a negative value on that interval, it could well be argued that the negatively senescent, 'negasent', phenotype could invade. However, in this method implicit assumptions about vital rates after the interval of investigation are made, so that the vital rates remain strictly non-negative. A more elegant method is to limit the study of negative senescence to perturbations that do not lead to negative mortality and fecundity on the entire positive real domain, as in the following case.

Consider an exponential perturbation of the mortality function:

$$\mu(a,\varepsilon) = c + \varepsilon(e^{s(a-p)} - 1) \tag{5.20}$$

This gives $d\mu/d\varepsilon = e^{s(a-p)} - 1$. As before, p is the age at which there is no perturbation of mortality, while the farther away from p, the greater the perturbation is, but now in an exponential fashion. The strength of exponential increase is modeled by s. The greater s is, the more the mortality rate is reduced before age p, and the more it is increased after age p. Substitution of $d\mu/d\varepsilon$ from equation (5.20) in expression (5.13) yields:

$$\frac{dr}{d\varepsilon} = -m_0 \int_0^\infty \left(e^{s(a-p)} - 1\right) e^{-m_0 a} da \tag{5.21}$$

$$= -m_0 \left[\int_0^\infty e^{s(a-p)-m_0 a} da - \frac{1}{m_0}\right] \tag{5.22}$$

Since it is required that $dr/d\varepsilon > 0$ for the senescent phenotype to be able to invade, it is also required that:

$$\int_0^\infty e^{(s-m_0)a} da < \frac{e^{sp}}{m_0} \tag{5.23}$$

The integral in inequality (5.23) does not converge if $s \geq m_0$, irrespective of p, so that the inequality does not hold. The interpretation of this is that if, as the result of the trade-off, mortality increases faster than selection pressure declines, there is a growing, negative effect at higher ages, and the net effect on fitness will be deleterious. If $s < m_0$, the integral does converge and takes the value $\frac{1}{m_0 - s}$. Just as in the linear case, it is possible to find a $p_0(s)$, so that for $p > p_0$ the senescent phenotype can invade, while for $p < p_0$ it cannot.

This is done by substituting p_0 for p in equation (5.23), setting $dr/d\varepsilon = 0$, and solving for p_0:

$$p_0 = \frac{ln(\frac{m_0}{m_0 - s})}{s} \tag{5.24}$$

The exponential trade-off also facilitates an exponential decline in mortality from a higher initial level, while mortality takes strictly positive values, in which case we allow $i < 0$. The negasent phenotype can invade if $p < p_0$, with p_0 as in equation (5.24).

Alternative indicators of selection pressure

The perturbation function given by equation (5.7) can be used to show relationships between alternative indicators of selection pressure. Baudisch [32] derived several alternative indicators of selection pressure, for instance the sensitivity of fitness to an age-specific *proportional* perturbation of mortality. All these indicators [32,p.8264] consist of one of Hamilton's elementary indicators, expressions (5.4) and (5.3), scaled by some factor that depends on the actual value of mortality or fecundity. Considering Baudisch's alternative indicators, the same result can be derived by using Hamilton's elementary indicators, while scaling the perturbation function by the same mortality- or fecundity-dependent factor that is used to obtain the alternative indicator.

Hamilton [3] also derived the sensitivity of fitness to an additive perturbation of mortality from some age onwards (as opposed to *at* some age):

$$\frac{dr}{d\Delta_{a\ldots\infty}} = -\frac{\int_a^\infty (x-a)e^{-rx}\ell(x)m(x)dx}{T} \tag{5.25}$$

In a thorough discussion on the difference between $dr/d\Delta_a$ and $dr/d\Delta_{a\ldots\infty}$, Abrams [33] argued that a senescent change is best characterized by $dr/d\Delta_{a\ldots\infty}$, because an intrinsic deterioration (senescence) at age a will last throughout life, and will thus continue to affect mortality and fecundity.

If senescence is characterized as Abrams [33] argued, so that at some age mortality is increased for the rest of the lifespan of an organism, then the corresponding perturbation for $dr/d\Delta_a$ is:

$$\frac{d\mu}{d\varepsilon}(x) = \begin{cases} 0 & \text{if } x < a \\ 1 & \text{if } x \geq a \end{cases} \tag{5.26}$$

Substitution of this perturbation in equation (5.7) gives

$$\frac{dr}{d\varepsilon} = -\frac{1}{T} \int_a^\infty \int_z^\infty e^{-rx}\ell(x)m(x)dxdz \tag{5.27}$$

Using differentiation by parts, it can be shown that expression (5.27) equals $dr/d\Delta_{a\ldots\infty}$ (equation (5.25)).

A biological change has a unique fitness effect. The biological change is expressed in the *combination* of perturbation function and indicator of selection pressure, i.e. the

parameterization of the fitness differential. If the same perturbation function is combined with a different indicator of selection pressure, a different biological change is expressed. Any two parameterizations that express the same biological change always give the same result.

Discussion

If it is argued verbally that fitness increases under some trade-off given a (declining) pattern of selection pressure [e.g. 2,3,16,17], this is equivalent to the mathematical statement that under the trade-off there exists a positive fitness differential, i.e. $dr > 0$. Going beyond the verbal argument, we formally evaluate this fitness differential. The fitness differential depends on the indicators of selection pressure, defined by the life history of a resident phenotype, and on the perturbation function, defined by physiological mechanisms. So what are biologically realistic perturbation functions? Abrams [33] considered a stepwise perturbation that remains over the rest of the lifespan. He motivated this perturbation by considering a trade-off that results in increased fecundity at age a, at the cost of unrepaired molecular damage originating at age a. The resulting deteriorated state of the organism will remain, and will continue to affect mortality throughout the organism's lifespan. On the other hand, Wensink et al. [34] discuss the possibility that it may be evolutionary beneficial for an organism to grow to a state that is simply unmaintainable with the resources that it has at its disposal. In that case, other than in the case of resource allocation taking place at each age, attaining such a state at some age puts the organism on a trajectory of deterioration for the rest of its life. Thus, an initial improvement of vital rates results in further deterioration of these vital rates at all subsequent ages. A similar trajectory of accelerating deterioration rather than a stepwise increase may be expected if senescence is the result of dysregulation with age, or of loss of robustness [35]. There is evidence that suggests that the accumulation of damage with senescence may sometimes be a matter of correlation without causation [36,37], although damage accumulation will no doubt play a role. In both examples above, one inside and one outside the paradigm of senescence being caused by damage accumulation, the senescent change is not a one-time increase, but rather a continuous deterioration.

 For the evolution of negative senescence, Vaupel et al. [5] hypothesize that organisms that do not stop growing upon reaching maturity may exhibit negative senescence, since for many species (for instance fish), growth results in higher fertility and lower mortality. If growth or learning are considered decisions taken at every age (whether to grow or not, whether to learn or not), they could be characterized by a perturbation that models a one-time improvement from some age onwards. If, on the other hand, negative senescence is characterized by continuous improvement (growth and learning is a character that is either part of the phenotype across ages, or not), there is a trajectory of improvement rather than a one-time increase, parameterized by a perturbation function such that mortality decreases monotonously and fecundity increases monotonously.

 As briefly mentioned in the introduction to section 3, indicators of selection pressure are situational. Results obtained from indicators of selection pressure, i.e. the fitness

differential, indicate the initial direction of evolution, which is bound to change as the resident phenotype evolves. Hence, the results apply only locally; a global optimum is not demonstrated. This is a general limitation of such approaches [e.g. 16-24]. Still our point remains valid that perturbation functions can always be found which for some range of parameters lead to senescence and for another lead to negative senescence, which clarifies the relation between direct optimization models and models of selection pressure. Direct optimization models maximize fitness under a set of constraints defined at all ages. These models do not contain Hamilton's indicators of selection pressure explicitly, and can predict absence of senescence or even negative senescence to evolve [4,5,38-40]. Models of selection pressure calculate fitness sensitivities to changes in vital rates at specific ages and explore how the pattern of decline of selection pressure is affected by varying model parameters. No formal equation automatically ties together changes at particular ages, and the (pattern of) decline is often taken to directly predict the outcome of evolution [2,3,16-24]. Evaluating the fitness differential, this deficiency is fixed. Changes at particular ages are tied together by the perturbation function, and it turns out that the finding of sustenance or negative senescence as possible outcomes of evolution is not a peculiarity of optimization models: this result can equally well be derived from the calculus of selection pressure when the full fitness differential is considered, in line with the result of Charlesworth that quantitative genetics and optimization models should in principle lead to similar results [41].

The view that trade-offs only determine specifics of the pattern of senescence, while the evolution of senescence itself is inevitable because of declining selection pressure, needs to be adjusted. Trade-offs do more than just determine the details of senescence: they co-determine whether senescence evolves at all. If trade-off perturbation functions that promote sustenance or negative senescence capture biologically realistic conditions, then it follows that the evolution of senescence is not inevitable.

Why is it that some biological mechanisms (perturbation functions) defy the inevitability of senescence, and how does this work out mathematically? At high ages selection pressure may be low, but perturbations that grow over ages may have become large. An organism will have had a lot of time to learn and grow, so that improvement (higher fecundity, lower mortality) may be considerable. There exists no mathematical reason why improvement of vital rates would have a limit: mortality can continue to decline asymptotically to zero, while fecundity can continue to go up. In addition, the benefits of sustenance or even negative senescence remain over a potentially unlimited range of ages: there is no age beyond which survival is impossible *a priori*, and with dropping mortality, very high ages may be attained. As a result, possible loss of fitness by senescence is limited by fitness itself, but the possible gain in fitness by negative senescence has no mathematical limit.

In contrast to trade-off perturbations, the theory of mutation accumulation invokes perturbations with very small effects that are only deleterious. In the mutation accumulation theory, mutations with a late-acting deleterious effect on fitness are not removed by natural selection because their overall effect on fitness is small. As a result, such mutations accumulate over evolutionary time. The later the age at which they act, the less likely

they will be removed [1,3,11]. As trade-offs and mutation accumulation are not mutually exclusive, would it not be true that even if trade-offs lead to negative senescence, senescence still evolves because selection pressure declines, giving way to 'loss-only' processes under the mutation accumulation theory?

We do not think so. First, existing life histories will be a combination of both types of perturbations. The question would then be which process dominates, mutation accumulation or trade-offs [42]. If trade-offs lead to significant negative senescence, this could offset deterioration by mutation accumulation. Which process dominates the demographics is not necessarily the same at all ages. Perhaps the two effects together could explain why organisms that show protracted negative senescence throughout their lifespan could still show a little upswing in their mortality function at very high ages [5]. Second, since the mechanisms of senescence are likely to lead to sustained or increasing deterioration rather than age-specific effects, the costs of senescence are much higher than Hamilton's age-specific indicators may suggest (see also [9,33]). Consequently the evolution of senescence by mutation accumulation may be rare. In any event, the empirical finding of protracted improvement during adult lifespan is strongly suggestive of trade-offs playing an important if not decisive role in the evolution of senescence[6].

Then what, if not the inevitability of senescence, does Hamilton's finding that selection pressure universally declines really mean? If selection pressure did not decline, any cost of senescence would be infinite, i.e. equation (5.8) would not converge, so that senescence could not possibly evolve. We propose that declining selection pressure is a necessary but not a sufficient condition for the evolution of senescence.

Conclusion

To study selection pressure alone does not suffice for drawing conclusions about the evolution of senescence; the actual perturbation needs to be considered as well. This completes the total fitness differential, which is the full description of change in fitness. Different combinations of alternative indicators of selection pressure and perturbation functions (parameterizations of the total fitness differential) can capture the same pattern of change in vital rates, predicting the exact same effect on fitness. At high ages selection pressure may be low, but perturbations that grow over ages may have become large, defying the inevitability of the evolution of senescence. For a complete understanding of aging, we recommend including the total fitness differential in discussions of senescence, rather than Hamilton's indicators of selection pressure alone.

Acknowledgments and Author Contributions

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