Programmed Life Span in the Context of Evolvability

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abstract: Population turnover is necessary for progressive evolution. In the context of a niche with fixed carrying capacity, aging contributes to the rate of population turnover. Theoretically, a population in which death is programmed on a fixed schedule can evolve more rapidly than one in which population turnover is left to a random death rate. Could aging evolve on this basis? Quantitative realization of this idea is problematic, since the short-term individual fitness cost is likely to eliminate any hypothetical gene for programmed death before the long-term benefit can be realized. In 2011, one of us proposed the first quantitative model based on this mechanism that robustly evolves a finite, programmed life span. That model was based on a viscous population in a rapidly changing environment. Here, we strip this model to its essence and eliminate the assumption of environmental change. We conclude that there is no obvious way in which this model is unrealistic, and that it may indeed capture an important principle of nature's workings. We suggest aging may be understood within the context of the emerging science of evolvability.

Keywords: evolution, senescence, aging, individual-based model (IBM), adaptation, evolvability, group selection, multilevel selection (MLS).

Introduction

The modern history of evolutionary theories of aging began with a realization that the selection of individual death as an altruistic adaptation was utterly implausible. Medawar (1952) mocked Weismann's (1891) idea: "He canters twice around the perimeter of a vicious circle ... he assumes all but a fraction of what he set out to prove." Following Medawar, Williams (1957) and Kirkwood (1977) contributed the theories accepted by almost all evolutionists today, based on trade-offs and physical limitations within the individual metabolism. All agree that there is a community benefit when an individual dies and vacates its place in the niche, but there is no plausible mechanism to evolve an adaptation based on this benefit because the benefit is broadly distributed over all individuals sharing the niche, while the cost is borne by the individual alone.

But for this theoretical exclusion, the idea of programmed aging would be an attractive explanation for some phenomena of aging. Examples of the evidence for programmed aging are listed in Box 1.

These and other arguments for aging as a genetic program are reviewed by Bredesen (2004), Mitteldorf (2004, 2010*a*), Goldsmith (2013), and Pepper et al. (2013). Thus, the existence of a viable theoretical model for the evolution of aging as an adaptation is of special interest in a field where empirical support for the predominant theories is sporadic. Such a model was presented by Martins (2011), and it invokes a mechanism fundamentally different from four other models published in the past decade (Travis 2004; Trubitsyn 2006; Mitteldorf and Pepper 2009; and Mitteldorf and Goodnight 2012; though the mechanism of Martins was described qualitatively by Libertini as early as 1988).

These other adaptive models were based on population dynamics, which is a fast process (Gilpin 1975), as population sizes can change substantially in a single generation (Hairston et al. 2005). Martins's model was based on evolvability, which is thought to be a slow process, since evolution proceeds on a timescale of many generations. The Martins result is surprising on this account, and this study is intended to investigate the question, how realistic are its assumptions?

Background: The Evolution of Evolvability

Ahead of his time and outside his field (astrophysics), Layzer (1980) first proposed in these pages that natural selection might favor the rate of increase of fitness over evolutionary time, apart from selection for fitness itself. He cited hierarchical genetic architecture as a powerful indication that evolvability has been a target of selection, and he described the mechanism by which this might have come about ("hitchhiking" [Barton 2000], though he did not use the word). It was 16 years later that Wagner and

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Box 1: Examples of the evidence for programmed aging

- The genetic basis for aging is conserved across such great spans of evolutionary distance as to render pleiotropy an implausible explanation (Guarente and Kenyon 2000; Kenyon 2001) and mutational load an irrelevance.
- Evidence for pleiotropy of known aging genes is weak (Kirkwood 2005; Blagosklonny 2010). In fact, pleiotropic benefits have only been discovered for a small proportion of genes that shorten life span (Curtsinger et al. 1995; Stearns 2000), and several examples are documented in which a wild-type allele shortens life span and also lowers fertility (Spitze 1991; Bronikowski and Promislow 2005; Hanson and Hakimi 2008)
- The high fitness cost of aging in the wild (Ricklefs 1998; Bonduriansky and Brassil 2002; Nussey et al. 2012) is inconsistent with the once-dominant mutation accumulation theory and steepens the challenge to the pleiotropic theories as well.
- The existence of programmed aging in protists, in the form of cellular senescence (Clark 1999, 2004) defies classical evolutionary theory. The association of cellular senescence with increased mortality in humans (Cawthon et al. 2003; Fitzpatrick et al. 2007; Kimura et al. 2008), despite the fact that cellular senescence offers no protection against cancer (Mitteldorf 2013), suggests a form of programmed aging that has persisted since the Cambrian explosion.
- Apoptosis in yeast cells under stress has been documented as an altruistic aging program (Fabrizio et al. 2004).
- An inverse association between fertility and life span is predicted by the disposable soma (Kirkwood 1977) and other theories of metabolic trade-off. But this correlation is observed in neither animals (Ricklefs and Cadena 2007) or humans (Gavrilova et al. 2004; Mitteldorf 2010*b*).
- Animals are able to extend life span under some conditions of hardship and environmental challenge, including caloric restriction (Calabrese and Baldwin 1998; Calabrese 2005; Masoro 2005, 2007). Frequently the life extension comes at minimal cost in fertility (Flatt 2009), especially for males (Weindruch and Walford 1988; Masoro 2003). The ability of the body to extend life span under stress hints that, in the absence of stress, the body harbors a latent capacity for longer life that is not activated because of genetic programming (Mitteldorf 2001).

Altenberg (1996), unaware of Layzer's precedent, independently proposed some of the same ideas, and biochemical advances in the interim helped them to make their case more convincingly, using genetic examples. Evolvability became a new area of evolutionary study.

Adaptations that promote evolvability at a direct and immediate cost to individual fitness include, famously, sexual reproduction. There is broad agreement that the evolutionary basis for sexual reproduction is related to its contribution to evolvability, but there is yet no agreement about how sex might have evolved (Williams 1975; Bell 1982; Margulis and Sagan 1990; Peck 2004; Hartfield and Keightley 2012). In particular, in dioecious species, sex imposes a steep individual cost, a factor of 2 (far greater than the cost of aging in the wild). Individual-based evolutionary analysis suggests it is difficult to see how such a large fitness cost could be offset quickly enough to prevent the fixation of clonal or hermaphroditic reproduction. Although there is still no satisfactory and general explanation for evolution of dioecious sex, there is little doubt that sex emerged in a process of natural selection. Could whatever process led to the evolution of sex also have produced programmed aging?

The mapping of genotype to phenotype is also a crucial evolvability adaptation, because it affects the way in which the feedback of selection works on the raw material of variation (Altenberg 1995; Wagner and Zhang 2011). Both these sources demonstrate that the simplest mappings that we might devise in the abstract would not provide a viable basis for evolution as we know it. Yet the extant mapping cannot have evolved by incremental mutations in nuclear DNA; rather, it reflects the holistic system of gene transcription, developmental timing, self-organizing cell structures, and other processes that are yet poorly understood. Though the evolution of such holistic attributes does not fit easily within models, the genotype/phenotype map has nevertheless evolved in such a way as to make evolution possible and even efficient.

The hypothetical mechanism of Lamarckian inheritance was attractive to Darwin as well as Lamarck (1809) because it offers a very substantial advantage in evolvability.[1] For a century after Weismann's experiments, Lamarckism was believed not to exist in nature; but in recent years, many examples of Lamarckian epigenetic inheritance have been documented (Jablonka 1999; Henderson and Jacobsen 2007; Jablonka and Raz 2009), and substantial evidence points to the ability of bacteria to deploy transposable elements, modifying their own nuclear genome in response to environmental stress (Shapiro 2011).

Similarly, other recognized adaptations that have been interpreted as promoting evolvability include different mutation rates for core metabolism and peripheral traits (Shapiro 2011), adaptive mutation rates that depend on environmental cues (Sniegowski et al. 1997), and hierarchical organization of genes (with Hox genes on top and layers of subordinate instructions under them; Ruddle et al. 1994). Selective mechanisms for each of these fundamental features of life remain unexplained, though there is little doubt that their adaptive purpose is connected to evolvability. These

[1] In the last paragraph of *The Origin of Species*, Darwin mentions "use and disuse" as a source of directed variation, supplementing the force of natural selection. In an 1876 letter to Moritz Wagner, Darwin wrote "In my opinion, the greatest error which I have committed has been not allowing sufficient weight to the direct action of the environments, i.e. food, climate, etc., independently of natural selection.... When I wrote the 'Origin,' and for some years afterwards, I could find little good evidence of the direct action of the environment; now there is a large body of evidence" (quoted in F. Darwin 1892, p. 278).

precedents make plausible the acceptance of aging as another evolvability feature, even though standard theoretical frameworks offer no selective mechanism.

Evolvability was also the implicit basis for the early ideas of Weismann (1891), which he never spelled out with the mechanistic specificity that would be de rigeur in any modern treatise on the subject. Weismann's ideas were dismissed over ensuing decades, including disavowal by Weismann himself (Kirkwood and Cremer 1982). The idea that evolvability could be the basis for evolution of aging was first revived in the modern era by Libertini (1988), and similar ideas with greater physiological detail were expounded by Skulachev (1997) and Bowles (1998, 2000). Goldsmith (2013) has self-published and continually updated a volume on the subject. All these were qualitative descriptions of the mechanism. Mitteldorf and Pepper's (2007) Red Queen model was an individual-based quantitative realization of a special case of selection for diversity as it contributes both to evolvability and pathogen resistance. It was only in 2011 that a general numerical model for evolution of aging based on evolvability was demonstrated by Martins (2011).

Martins Model and Motivation for this Study

The significance of the Martins model is that it is a demonstration of a doubly counterintuitive result. Orthodox evolutionary theory based on individual selection categorically dismisses all mechanisms by which aging might evolve as an adaptation in its own right. But even in the context of multilevel selection theory (Wilson 1997), population turnover would seem to be a weak basis for evolutionary selection. In the paradigm of Price/Wilson (Price 1970; Sober and Wilson 1998; Traulsen and Nowak 2006), group selection for altruism becomes a viable force to the extent that the benefits of altruism are focused on individuals that carry the same altruistic gene. This does not seem to be the case for any model for evolution of aging based on evolvability. If the altruistic act is simply to die early and open a vacancy in the niche, there is no guarantee that this vacancy should be filled by another individual with short life span. The Martins model relies solely on population viscosity to focus the altruistic benefit.

The selective basis in the Martins model lies in the rate of increase of fitness. The advantage in the rate of increase of fitness becomes apparent only in evolutionary time; meanwhile, the substantial individual cost of early death is borne immediately. It is difficult to see how the trait of aging can survive individual selection long enough for its advantage to accrue.

Perhaps for this reason, before Martins (2011), there had never been a published model that successfully evolved aging based on population turnover and progressive evolution. This absence of explicit models was underscored by the many qualitative accounts (Libertini 1988; Skulachev 1997; Bowles 1998; Goldsmith 2013) of population turnover as a basis for the evolution of aging, going back to Weismann (1891). Meanwhile, theories for evolution of aging based on mechanisms that are more rapid and efficient than progressive evolution leapt ahead with detailed, quantitative models. Some were based on Weismann's idea of eliminating nonperforming individuals in the population (Travis 2004; Dytham and Travis 2006); others were based on the ability of aging to dampen the volatility of population dynamics, avoiding extinctions (Mitteldorf 2006; Trubitsyn 2006); and one model (Mitteldorf and Pepper 2009) invoked the Red Queen mechanism (van Valen 1973; Ridley 1993) that had been applied previously to explain the evolution of sex.

The model of Martins is based on cellular automata on a two-dimensional viscous grid. A constantly changing environment assures that each agent's adaptations become outmoded during its lifetime, and it can be replaced by offspring of a neighbor that has mutated appropriately to the new environment. This replacement, by assumption, proceeds more efficiently if the older agent dies and vacates a space in the niche locally. Martins showed that these simple rules are sufficient to give short-lived agents an aggregate selective advantage over longer-lived agents. His simple and elegant demonstration challenged the long-held assumption that aging could never evolve as an adaptation in its own right. However, some features of the model make it difficult to determine whether it may be considered as an explanation for the general phenomenon of aging. In particular, the environment changes at a high rate that appears to limit the general applicability of the model.

In this study, we strip the Martins model to its essence in order to investigate the reason for its effectiveness. We were able to eliminate entirely its most questionable assumption, the rapidly changing environment. We introduce an evolving gene for a life-span continuum, improving over the original model of binary choice between short and long lives. We then analyze features of the simplified model in relation to real biological organisms to ask, to what extent does this model capture general phenomena of the biosphere?

Heuristic Description of this Model

Individual organisms that are genetically programmed to die on a fixed schedule have suppressed fitness, but populations in which everyone dies on a fixed schedule enjoy a higher rate of population turnover and hence can incorporate adaptive changes more quickly. In many ecologies, the effective generation time is not controlled by individual reproductive characteristics but by the rate at

which vacancies appear in the niche, permitting recruitment. The rate of population turnover (and thus the rate of fitness increase) is not under control of the individual's genome but is determined instead by the average life span in a local neighborhood that may include individuals that age and die at diverse rates. Thus, an individual-based model with geographic population structure is the minimum system that can model the effect.

A fixed maximum population, so that reproduction is limited by crowding, is an essential feature of the model. This creates intense competition for space in the niche, such that each new offspring must either find a vacancy or another individual less fit than itself in order to grow successfully to maturity. There is a stochastic component of the replacement dynamic, so that even if a new individual is more fit than the individual it seeks to replace, there is a probability $p < 1$ that it will succeed. Without this rule, there can be no advantage in vacating a site, since a fitter young organism would always be able to displace a less-fit elder. Of course, the model assumes a spectrum of harmful and beneficial mutations, such that at least some offspring are more competitive than their parents.

Aging cannot evolve in a panmictic population, and population viscosity is crucial to the effect that we model. Some of our runs are initialized with aging and nonaging populations that are separated geographically; in other runs, sufficient clustering emerges from the local dynamic of the model itself to support evolution of aging; and in other runs, the aging populations do not concentrate well enough or last long enough to overcome their individual-level handicap.

Mechanics of the Model

Generalities

Competition takes place on a two-dimensional square grid with edges identified to create a toroidal topology. Each cell may be occupied by at most one individual. Individuals are characterized by a birthday, a base "competitiveness" (which may be modified with age), and a life span.

Think of "competitiveness" as an instantaneous measure of fitness, the individual's present ability to survive and compete in the local environment. We do not use the term "fitness" because fitness depends additionally on life span and the local environment.

In one computational cycle, a random site is chosen, and, if it is occupied, the occupant has a probability m of suffering (random background) mortality. If it does not die, it has an opportunity to reproduce (clonally). The offspring may mutate to a higher competitiveness ($+1$, probability $= 1/(1 + D)$) or a lower competitiveness (-1, probability $= D/(1 + D)$). A site for reproduction is chosen randomly from a 9-point square neighborhood centered on the parent. If the target site is empty, reproduction is successful. Otherwise, the competitiveness of the offspring is compared to the competitiveness of the target site's present occupant. If the new individual has equal or lower competitiveness, reproduction fails. If the new individual has a higher competitiveness than the site's present occupant, then reproduction may succeed, with probability p (or fail with probability $1 - p$).

Quantitative Details

Grid size is $128 \times 128 = 16{,}384$. For convenience, time is measured in units of 16,384 computational cycles, so that on average each individual has about one opportunity to reproduce per time step.

Each individual has a programmed life span (ranging from 2 time steps to a very large number, effectively ∞), after which it dies, vacating its site.

In some runs, a variety with long life span was matched against an identical variety with shorter life span in a binary contest. In other runs, life span was an evolving gene, with small mutations in a life span gene each time reproduction takes place. When life span was an evolving gene, it was permitted to mutate within a specified range (with a ceiling comfortably beyond the maximum age attained by individuals on the grid).

Deaths are counted and categorized as age related or otherwise. An age-related death occurs at the end of the programmed life span. Other deaths are either replacement by a fitter competitor or random background deaths. The proportion of all deaths that are age related is our measure of whether aging is an important part of the demographic dynamics. When life span is an evolving gene, it is this number that is our measure of whether the simulated process has evolved aging or not.

There is an opportunity for reproduction into an occupied site only if the competitiveness of the offspring is higher than the competitiveness of the site's former occupant. In this case, the probability of replacement is p, with $p = 1/2$ in almost all our runs. We performed a few tests with a range of p from 0.05 up to 1.0.

In some runs, competitiveness was assumed to increase with age, modeling growth and learning in the real world. In this case, it can be difficult to displace an entrenched older individual. Sometimes an unrealistic result emerged where some individuals were unable to reproduce, but they also could not be displaced because their competitiveness had grown so large. In these cases, the specification of a small background death rate completely changed the evolutionary dynamic.

Experiments with the Model

One-on-One Contest of Aging versus Nonaging

Replicating Martins (2011), we ran a series of binary contests, including competition but no mutation. Half the population was initialized with an infinite life span, and the other half a fixed, finite life span. Ratio of positive (beneficial) to negative (detrimental) mutations was set to $D = 1$, replacement probability was $p = 0.5$, competitiveness growth with age was $g = 0$, and background mortality was set to $m = 0$. We distinguished two cases, where the agers and nonagers were initially randomly mixed or separate. For the separate case, aging was found to prevail over nonaging for life span down to 2.7 (in time units as described above). For shorter life spans, the direct individual disadvantage dominated, and for longer life spans the collective advantage was more important. For the case of mixed initial conditions, the transition occurred around 2.9, and results were slightly more stochastic at the boundary.

Agers and nonagers prevailed equally often when life span was greater than about 12, because so few agents attained that age that life span did not matter. Below this value, agers prevailed more often than nonagers, increasing their success with decreasing age (fig. 1). Data underlying this and all figures are deposited in the Dryad Digital Repository, http://dx.doi.org/10.5061/dryad.9898r (Mitteldorf and Martins 2014).

Evolving a Gene for Life Span

Once again with $D = 1$, $p = 0.5$ and $g = 0$, $m = 0$, we allowed a gene for life span to evolve over 200,000 time steps. A variety of initial conditions was tried, until we gained confidence that the steady state configuration did not depend on initial conditions. Life span found an average value of 3.59, fluctuating with a standard deviation of 0.20. Over the life of the simulation, the proportion of deaths attributable to senescence (PSD) was 53.4% of all deaths.

We introduce the indicator PSD, the proportion of senescent deaths. This is a dimensionless measure of the extent to which senescence is significant to the demography. It is important to have such a measure because time in our model is measured in arbitrary units and because life span in the biosphere varies over a factor of more than 10^6. Field studies commonly invoke this same measure of the demographic importance of senescence in the wild (Promislow 1991; Ricklefs 1998; Bonduriansky and Brassil 2002, 2005).

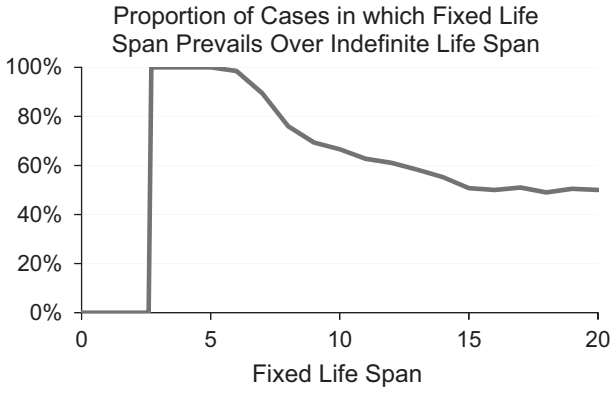

Figure 1: Results of head-to-head competition between fixed life span and indefinite life span. When the fixed life span is below 2.7, the shorter-lived variety always loses. For life span between 2.7 and 5, fixed life span always prevails over indefinite life span. For values >6, the advantage becomes gradually less pronounced, because fewer and fewer individuals live long enough for their life span limit to matter. The curve asymptotes to 50% for large values.

Varying Replacement Probability

We repeated experiment 2, varying the probability p that a new offspring will replace a live occupant of lower competitiveness. We found that evolved life span did not vary much over a range of p between 0.20 and 0.80. For low replacement probability $p < 0.20$, evolved life span rose, and for $p > 0.80$, evolved life span rose and also became less well defined. For $p = 1$, it is not possible to evolve a finite life span, because there is no advantage to aging. This is because an offspring of higher competitiveness can always replace an established individual of lower competitiveness, so there is no advantage to vacating the site via programmed death. (In fact, there is a disadvantage to vacating the site, because it permits the accession of an offspring with lower fitness.) Hence, for values of p approaching 1, the evolution of limited life span was noisy and uncertain, especially for high values of background mortality m (fig. 2*a*, 2*b*).

Varying the Random Background Death Rate

We repeated experiment 2, varying the probability m that an individual will die in each computational cycle. We found that evolved life span varies directly with mortality m, so that senescent mortality tends to complement background mortality. Both contribute to the population turnover rate, and thus to evolvability (fig. 3).

Note that this complementary relationship between background death rate and evolved senescence is characteristic of adaptive theories of aging. A high background death rate leads to a *longer* evolved life span. This contrasts

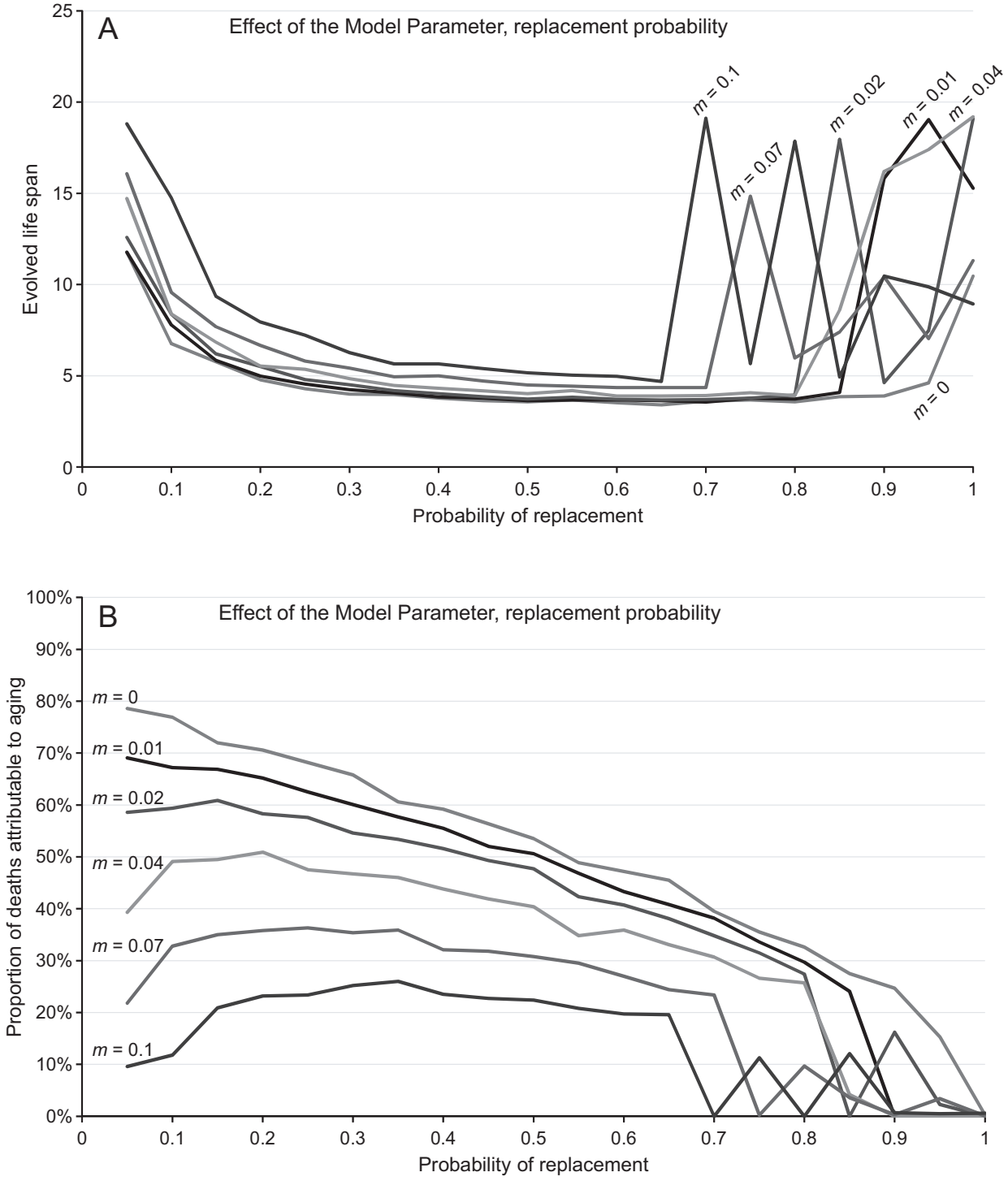

Figure 2: *A*, Evolved life span is plotted against the replacement probability p on the X-axis. Lines represent different values of background mortality m, with the first to spike (at $p = 0.7$) corresponding to the highest value $m = 0.10$, and the bottom line corresponding to $m = 0$. *B*, Proportion of deaths attributable to senescence is plotted against the replacement probability p on the X-axis. Curves represent different values of background mortality m, with the top curve corresponding to the lowest value, $m = 0$, and the bottom curve the highest, $m = 0.1$.

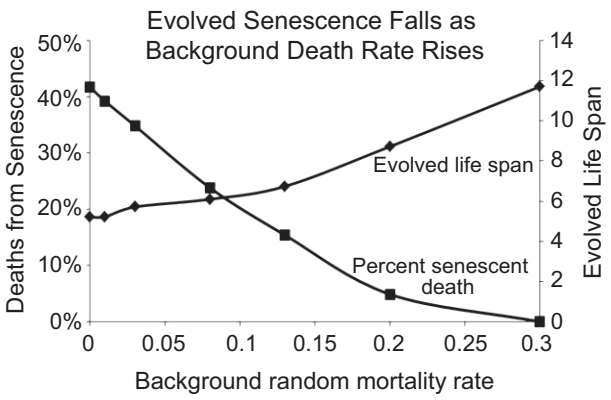

Figure 3: As background death rate increases, evolved life span increases (refer to right axis) and the proportion of deaths attributable to senescence falls (left axis).

with classical theories, in which a high background death rate leads to a *shorter* evolved life span. The classical relationship was first predicted by Williams (1957) and detected in a natural population by Austad (1993). It has been found to hold in inter-species comparisons, for example between arborial and terrestrial mammals. But the complementary relationship (consistent with our model) has also been noted, especially in comparisons of the same species in different environments (Reznick et al. 2000; Bryant and Reznick 2004; Bronikowski and Promislow 2005; Moorad and Promislow 2010; Chen and Maklakov 2012; Walsh et al. 2012).

Relationship between Life Span and Rate of Evolution

We checked our hypothesis that the selective advantage of shorter life span is based on a higher rate of increase in competitiveness over evolutionary time. We chose cases to run in which the inherent variability is high, so that without changing any parameters we can see fluctuations in life span. Competitiveness is a variable that is constantly increasing through the run. We asked, does the differential rate of competitiveness growth fluctuate in tandem with life span? We found correlations in the range approximately $-0.70 < r < -0.99$. Figure 4 is a typical scatterplot from experiment 3 above, for case $p = 0.15$, $m = 0.04$, in which $r = -0.88$.

Effect of Growth in Competitiveness during an Individual Lifetime

In this experiment, we simulated the fact that individuals of most species grow larger and more competitive with age, and (were it not for aging) they present an ever-growing challenge for young offspring seeking to recruit a place in the niche. In our model, competitiveness increases linearly with age, continuing without limit. (In nature, just a few species continue growing over their lifetimes: clams, lobsters, most trees, and possibly sharks.)

In our model, each individual has a basic genetic competitiveness and a phenotypic manifestation that grows with age. The phenotypic value determines whether the individual can be replaced, but it is the genetic basis that must evolve. If competitiveness increases with age, it will frequently happen that a newborn individual with higher innate competitiveness will not be able to displace an established individual of lower innate competitiveness, because after age is factored in, the phenotype of the older individual may be more competitive. The inability of new individuals with better genetics to establish themselves becomes a drag on the pace of evolution.

Within our model, aging supplies a crude solution to this dilemma, eliminating the older individual when his age-adjusted competitiveness would otherwise have made it difficult to displace, and vacating a site for a young individual of any genetic competitiveness. But in most iteroparous life, aging is a more elegant solution, more effectively evolvable, because the competitiveness of each individual gradually fades with age, creating a graded competition for selective replacement that optimizes the mechanism of progressive evolution (Skulachev 1999).

We found a U-shaped curve for evolved life span in relation to the rate of growth: a modest rate of growth promotes the evolution of aging, but a higher growth rate inhibits evolution of aging. The reason for the shorter evolved life spans is that age-related growth in competitiveness suppresses population turnover, creating the imperative to remove older individuals. But if competitiveness is growing at too fast a rate, the oldest individuals can become an ensconced population that is unremovable

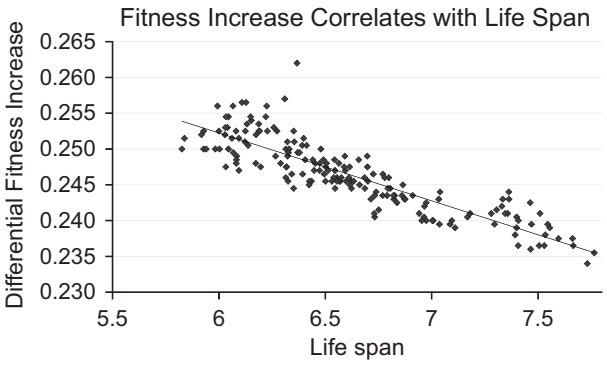

Figure 4: Our hypothesis is that selection for shorter life span derives from an increased rate of growth of competitiveness growth. Here is a typical scatterplot of competitiveness growth versus life span extracted from a single run. Correlation $r = -0.88$.

and demographically important. They cannot reproduce, because their genetic competitiveness is a few generations behind the times, but they can form a barrier that makes the nonaging population uninvasible. (In populations with short life span, of course, this group does not exist.) The lower the rate of random mortality, the more prevalent are these elders (fig. 5*a*). We would like to make predictions about comparative life histories from this result, but the U-shaped result and the indeterminacy of timescale add ambiguity to the predictions. Further complicating the prediction is the fact that we model only a life span and not a mortality function that changes over the life span. We might conjecture that the right side of the U is consistent with the theoretical prediction of Vaupel et al. (2004) that indeterminate growth and rising fertility should be associated with low PSD.

Data from this same experiment can be arrayed to demonstrate the quasi-linear relationship between rate of evolution and life span. In figure 5*b*, each line represents a regression fit for a single value of the growth rate of competitiveness. If both variables (competitiveness growth and life span) are included in a two-variable regression, the overall $r^2 = 0.98$.

Varying Ratio of Bad : Good Mutations and Growth in Competitiveness

The original model of Martins was criticized because it incorporates an unrealistically low ratio of bad : good mutations. To what extent does the ability to evolve senescence within this model depend on a low ratio?

In all the experiments above, ratio D of bad : good mutations has been set $= 1$. In this series, we let D vary over 2 orders of magnitude. The simulation runs much more slowly with large D, since detrimental mutations cause reproduction to fail a large proportion of the time. As expected, we found that large values of D inhibited the ability of the model to evolve short life spans and high proportions of senescent deaths (fig. 6). This is because, with high D, a vacancy created through senescent death is likely to be filled by an individual of lower fitness than the parent, because there are so many more of these. This drags down the rate of increase of competitiveness over time within senescing populations.

Affirmative selection for senescence could be rescued, however, when the model option for growth in competitiveness with age (described in the previous section) was reintroduced. The model then robustly evolves high levels of PSD $> 20\%$. Values of D up to $200 : 1$ successfully evolved high PSD for modest values of g = growth in competitiveness. In fact, $D = 200$ required a lower value for g, because the turnover rate was slowed by high D, so that the g had a longer life span over which to act. This is the reason for the upward tails at the right of all but the lowest lines in the plot of figure 6.

(For much higher ratios, $D > 200$, the model ground to a standstill, with old, established individuals blocking the grid and preventing any new reproduction. Evolution of higher competitiveness was stopped in its tracks.)

Sudden Death at a Programmed Age versus Gradual Senescence

We asked whether, within our model, the ability of programmed death to be selected in preference to immortality was dependent on the particular implementation as sudden death, as opposed to gradual senescence. We compared our base model with three implementations of gradual senescence: (1) competitiveness declines linearly after a fixed age, making it increasingly likely that the individual will be displaced by a newborn offspring. (2) The probability of death rises linearly after a fixed age. (3) The probability of replacement of an individual with a newborn of higher competitiveness (p) increases linearly beyond a fixed age.

Recall that a newborn offspring presents itself at a site adjacent to its parent and compares its genetic competitiveness to the competitiveness of the site's present occupant. If the old occupant has greater or equal competitiveness, the newborn dies without finding a place on the grid. If the newborn has greater competitiveness, then it has a fixed probability p of replacing the old occupant. It is p that becomes an age-dependent variable in implementation 3.

Implementation 1 replaces the above rule entirely with a simpler rule, while options 2 and 3 retain the basic rule described above. Implementation 1 was found to evolve senescence only in limited cases, and inconsistently. Implementations 2 and 3 were found to be as robust as the sudden-death implementation of aging. Implementation 3 (but not 2) was able to prevail in head-to-head competition versus the strongest competitor with sudden death (in which life span was fixed at 3.59).

These results suggest that sudden death is not essential for the ability of our model to evolve senescence as a group-selected adaptation. However, they also underscore the dependence of the result on the particular rule of competition in the model, especially the fact that a new individual can only be assured of a place on the lattice if its former occupant has died. This was also a feature of the original model of Martins (2011).

Discussion

Is the Model Realistic?

The most important features of the model are local competition and the fact that reproduction succeeds at a low

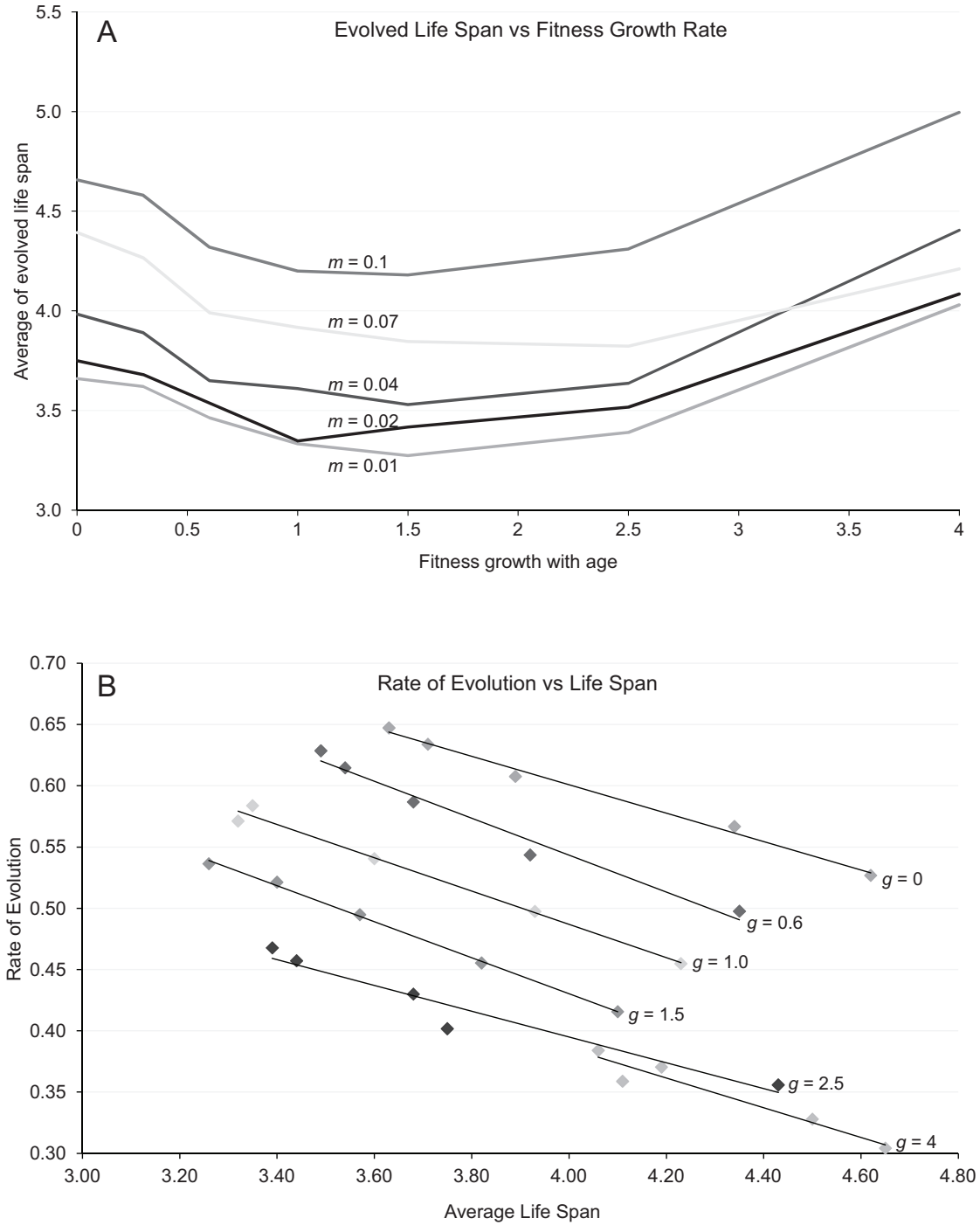

Figure 5: *A*, Evolution of shortened life span is supported by the growth of competitiveness with age. In the absence of aging, the elders can become an ensconced subpopulation that blocks population turnover and slows the pace of evolution. This effect is more pronounced for lower values of random mortality, because the ensconced population lasts longer. But when the rate of growth of competitiveness is too high, the effect can actually inhibit the evolution of aging, because the presence of highly competitive elders makes the nonaging population uninvasible. The curves are in order of increasing m, from $m = 0.01$ at the bottom to $m = 0.10$ at the top. *B*, Rate of increase of competitiveness is extracted from the same data reported in figure 4*a*. Each line represents a single value for g, the rate of growth of competitiveness. Overall R^2 for the two-variable regression is 0.98.

Figure 6: The proportion of deaths attributable to senescence is plotted as a function of D, the ratio of bad : good mutations. Even for high values of D, aging can evolve if individuals grow in competitiveness over time, making them difficult to displace. The rate of fitness growth that is necessary to see this effect actually decreases with higher D because high D implies a slower rate of population turnover, so growth in competitiveness has more time to act. Beginning at the bottom right side and counting up, the four curves in this plot correspond to $g = 0$, 0.01, 0.03, and 0.10, respectively.

rate due to intraspecific competition, hence the rate of vacancies in the niche created by senescence can contribute substantially to the effective population turnover rate. These are both credible and general features of the real world. Figure 5 introduces another realistic feature that may be important to the evolution of senescence: individuals begin their lives small, weak, and undeveloped; they are unprepared to compete with mature members of the same species, even when the genetic component of their competitiveness is superior to the mature competitor. This effect is likely to be an important impediment to progressive evolution, and senescence provides a remedy.

An important motivation for this model was to relax the most questionable feature of the model of Martins (2011), the assumption of a rapidly changing environment. Our model does not assume any change in the environment.

Like most evolutionary models, this one assumes a rate of beneficial mutations that is unrealistically high. It has become conventional to use a high rate of beneficial mutations, merely for the sake of computational efficiency. In this case, however, the rate of beneficial mutations is extreme (at $D = 1$; equal probabilities of bad and good mutations). This raises a question whether the high value of D merely speeds up the operation of the model or whether the positive results actually depend on a high D. Experiment 7 was designed to address this issue. We show that the model robustly evolves senescence for high D only if provision is made for $g > 0$ (i.e., that the young are at a disadvantage in competitiveness.)

Why Do We See Evolved Life Span Rise with External Mortality?

Why does our model (fig. 3) exhibit a behavior opposite to what is usually observed in the biosphere? The essential reason is that in the lab and in natural experiments, high incidental mortality places a premium on rapid reproduction. Where this leads to shorter life span, the result must be attributed to pleiotropy: direct selection for rapid reproduction constitutes indirect selection for shorter life span (Williams 1957). But in our model, rate of reproduction is fixed and pleiotropy is absent. (Otherwise it would not qualify as a demonstration of selection for adaptive aging.) It should be no surprise, then, that higher death rates from incidental mortality imply lower death rates from aging in a context where reproduction is fixed, population is fixed, and hence the total death rate is fixed.

Our results may be related to the reason that Reznick (2004) found more rapid senescence associated with a lower rate of background mortality, only in the sense that both are constrained by the demographic requirement that total death rate must be equal to birth rate. But we do not claim a more general significance for the complementary relationship that appears in our model. In experiments and in field studies, higher rates of incidental mortality frequently lead to shorter life spans. To recreate this effect, pleiotropy might be added to the model "by hand" as an assumption. A novel alternative (Wagner and Zhang 2011) is that pleiotropy might be an evolved adaptation, selected for the sake of enforcing senescence and

preventing runaway selection (Seymour and Doncaster 2007) for longer life span. Mitteldorf (2012) cites a precedent for this kind of "second-order" adaptation in the fact that dioecious sex evolved based on the (community's) need to preserve diversity, avoid selfing, and prevent reversion to hermaphroditism.

Difficulty of Making Specific Predictions for Comparative Biology

Life histories unfold over a timescale that is scaled largely by allometry (West et al. 1997) and demographics. If predictions are to be derived from this model, they must be about scale-free measures of senescence such as PSD. For example, we would not seek to explain why squirrels live longer than rats but to predict that the PSD of squirrels should be higher than that of rats. Published data on PSD is still relatively thin, because measurement of life span can be done in captivity, while measurement of PSD requires labor-intensive field studies.

Vaupel's group (Jones et al. 2014) recently published a survey of scale-free life histories. Their central display shows a chart of various scale-free mortality curves, arranged from high PSD at the top to low PSD at the bottom. The top of the chart includes, predictably, humans but also sea birds and guppies. Also belonging on top (though not part of their survey) would be caribou (*Rangifer tarandus*), swans (*Cygnus columbianus*), and alpine sheep (*Ovis dalli*; PSD was computed implicitly from data in the appendix of Ricklefs 1998). It is not apparent what, besides their patterns of senescence, humans, fulmars, guppies, and alpine sheep might have in common. Scaled to a common time frame, lions and water fleas also have mortality curves that are very similar. The bottom of the chart displays species with low PSD, including plants and sessile animals, but also frogs, hermit crabs, and a great tit. The authors conclude (Jones et al. 2014, p. 169), "Although it has been predicted that evolution should inevitably lead to increasing mortality and declining fertility with age after maturity, there is great variation among these species, including increasing, constant, decreasing, humped and bowed trajectories for both long- and short-lived species. This diversity challenges theoreticians to develop broader perspectives on the evolution of ageing."

If there is a message from these data, it is that natural selection has been free to mold life histories into many different patterns, both with and without senescence. Hamilton's (1966) proof that evolution inevitably generates senescence is shown to be false, as is Vaupel's (2004) proof that senescence is impossible. There is no obvious evidence of the constraints that are commonly assumed in pleiotropic theories.

These data are consistent with programmed aging in the limited sense that there are no physical constraints or ineluctable trade-offs that would enforce a particular life-history pattern. Perhaps consideration of aging as an adaptation can help free evolutionary theory to account for the diversity of life-history patterns found in nature.

Broader Implications of Evolvability

Evolvability as a target of natural selection has been recognized for nearly 20 years and has been described as a plausible principle for more than 30. There is no countercurrent in the field denying that natural selection relies on evolvability adaptations in order to be able to function with its observed efficiency. (Contrast this to the ongoing resistance to multilevel selection [Dawkins 2012], and the categorical dismissal of adaptive theories for aging [Ricklefs 2010; Baudisch and Vaupel 2012; Dowling 2012].) And yet the radical implications of the fact that evolvability has evolved are rarely discussed. Evolvability, like aging, offers benefits in the very long term, but its costs accrue in the short term. This is exactly the sort of conflict that, according to classical evolutionary theory, is almost always resolved in favor of the short term. The fact that evolvability has indisputably evolved should be cause for us to question what has now become a standard presumption: that short-term advantage to the individual always trumps long-term advantage to the population.

Evolution of evolvability requires multilevel selection (MLS), because evolvability is a property not of individuals but of lineages in a deme. But the mechanism of selection for evolvability is far more radical than mainstream MLS, based on the Price equation (Price 1970, 1972). Full recognition of the importance of selection for evolvability and integration of this principle into the field will have deep and far-reaching consequences for our understanding of nature and the science of life.

It is in this context that our model must be understood. We see that aging contributes to evolvability. We do not yet fully understand the mechanism that could have led to selection of aging as an evolvability adaptation, but at least aging is in the good company of so many other evolvability adaptations that seem to have evolved on this basis but for which we do not have a detailed mechanistic understanding. Other evolvability adaptations in this category include: the structure of the genome with Hox genes and transposable elements (Pepper 2003), mutation rates that vary with environmental cues (Shapiro 2011) and across the genome (Sniegowski et al. 1997), neo-Lamarckian inheritance (Jablonka 1999; Shapiro 2011), Masel's (2005) "evolutionary capacitance," sex (Bell 1982), various barriers to selfing (Grosberg and Hart 2000; Pound et al. 2002), mate selection instincts (Milinski 2006), and other adaptations that act to promote population diversity.

Since Williams (1957), pleiotropy has been regarded as a coincidental overlapping of gene function that has, by chance, supplied opportunities for aging to evolve. But Wagner's (2011) suggestion that the pleiotropic structure of the genome might be optimized for evolvability turns the relationship between pleiotropy and aging on its head, opening the possibility that pleiotropy of senescence-related genes is itself an evolved adaptation, the purpose of which is to assure that a lineage does not succumb to the excesses of individual selection and evolve a life span that is too long for demographic stability or a population turnover rate that is too low to support ongoing adaptive change (Mitteldorf 2012).

Although detailed mechanisms for the evolution of evolvability remain largely unknown, it is conceptually a bootstrapping process, or positive feedback loop. The efficiency of short-term individual selection must be suppressed in order to provide time for long-term lineage-level benefits to accrue. This process is self-reinforcing in the sense that blunting of short-term advantages allows time for further evolvability adaptations to manifest their benefits. Thus, the existence of other evolvability adaptations not only renders natural selection for senescence more plausible, they also may contribute directly to the mechanism by which senescence might evolve.

Future Directions

The simulation we present is potentially important as a counterexample to the common assumption that life-history evolution always works to maximize r (or a comparable measure of reproductive fitness). If, indeed, there are plausible mechanisms by which aging might evolve as a group-selected adaptation, then this should prompt a rethinking of the evolutionary theory of aging and a reinterpretation of experiments that might find their most natural explanation in the context of genetically programmed aging. Prominent researchers have put forth well-reasoned arguments that the standard model of natural selection based on inclusive fitness theory is incomplete and that other evolutionary mechanisms ought to be considered for inclusion in the canon (Gould and Eldredge 1993; Margulis 1997, 2009; Jablonka 1999; Woese 2004; Nowak 2006; Wilson and Wilson 2007; Bonduriansky and Day 2009; Shapiro 2011). We look forward to progress toward a broadened vision of the operation of natural selection, within which the hypothesis of aging as an evolvability adaptation may be fully evaluated.

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