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Senescence as an adaptation to limit the spread of disease

Josh Mitteldorf *, John Pepper

Department of Ecology & Evolutionary Biology, University of Arizona, Tucson, AZ 85720, USA

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ABSTRACT

Aging has the hallmarks of an evolved adaptation. It is controlled by genes that have been conserved over vast evolutionary distances, and most organisms are able to forestall aging in the most challenging of environments. But fundamental theoretical considerations imply that there can be no direct selection for aging. Senescence reduces individual fitness, and any group benefits are weak and widely dispersed over non-relatives. We offer a resolution to this paradox, suggesting a general mechanism by which senescence might have evolved as an adaptation. The proposed benefit is that senescence protects against infectious epidemics by controlling population density and increasing diversity of the host population. This mechanism is, in fact, already well-accepted in another context: it is the Red Queen Hypothesis for the evolution of sex. We illustrate the hypothesis using a spatially explicit agent-based model in which disease transmission is sensitive to population density as well as homogeneity. We find that individual senescence provides crucial population-level advantages, helping to control both these risk factors. Strong population-level advantages to individual senescence can overcome the within-population disadvantage of senescence. We conclude that frequent local extinctions provide a mechanism by which senescence may be selected as a population-level adaptation in its own right, without assuming pleiotropic benefits to the individual.

1. Introduction

On its face, senescence of the soma has all the attributes of an evolutionary adaptation for its own sake:

- It is controlled by genes that are highly conserved over vast evolutionary distances (Guarente and Kenyon, 2000; Kenyon, 2001; Budovsky et al., 2007).
- Many specific genes that cause aging in the wild have been catalogued, and it has been demonstrated that when they are disabled in laboratory animals, the animals live longer than controls. For some of these genes, a pleiotropic cost has been identified, but for others there is no known cost (Walker et al., 2000; Holzenberger et al., 2003; Marden et al., 2003; Liu et al., 2005; Hekimi, 2006).
- The additive genetic variance for mortality is low, and decreases with age (measured in flies, but probably true for all animals) (Promislow et al., 1996; Tatar et al., 1996).
- Animals are able to forestall aging in the most challenging environments, especially starvation. This implies that when the body is not challenged, there is an unused, latent capacity to extend life span, suggesting a plastic genetic program for aging. (Mitteldorf, 2004a; Masoro, 2007)

For these and other reasons, it has been proposed that senescence has the hallmarks of an evolved adaptation (Skulachev, 1997; Bredesen, 2004; Mitteldorf, 2004a, 2009; Longo et al., 2005). In the face of this evidence, evolutionary theorists have maintained that such a hypothesis is excluded on theoretical grounds: that there is no plausible evolutionary mechanism by which senescence could have evolved as an independent adaptation. (In a recent review, Bourke, 2007 catalogs many hypothesized evolutionary mechanisms and finds none of them satisfactory as general explanations for programmed aging.) In the present study, we inquire whether a mechanism already well-accepted in another context—the Red Queen Hypothesis for the evolution of sex—is able to evolve senescence.

The effects of senescence on individual fitness are wholly negative, so if senescence is to evolve as an adaptation, it must be at the group level. Senescence benefits the rate of evolution, increases diversity, and shortens the effective generation time. The idea of senescence as a group-level adaptation dates back to Weismann et al. (1891). But traditional comparison of the above listed group-level benefits (e.g. via the Price (1970) Equation or Hamilton's (1964) Rule) leads to the conclusion that the benefits are far too diffuse and too slow to counter-balance the individual

* Corresponding author.
E-mail addresses: josh@mathforum.org (J. Mitteldorf), jpepper1@email.arizona.edu (J. Pepper).

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costs. The only inclusive fitness benefit from 'altruistic death' results when a slot in a population is freed up so that another individual is permitted to mature which might otherwise have been crowded out. But there is no guarantee that the individual that takes the place of the altruistic suicide is a close relative. If any benefit is to be gained from this substitution, it is a long-term benefit of population diversity, or the rate of population adaptation. Meanwhile, the cost is borne very directly and immediately by the individual that actually carries the aging gene. Williams (1957), Maynard Smith (1976) and many who followed them were quite correct to dismiss this tradeoff as implausible as a selective mechanism for aging.

To make these arguments quantitative in a model, consider a fixed-density grid, in which every site is occupied by either an ager or a non-ager. In typical 'viscous models' (Taylor, 1992; van Baalen and Rand, 1998; Mitteldorf and Wilson, 2000), individuals are fixed to a site through their life spans, and replication occurs at any vacant neighbor site. In such models, it is common to define a benefit that is conferred on all neighbors by the carrier of an altruistic allele (Rousset, 2004). But in the case of altruistic death, the only benefit that is conferred is to make a site available for reproduction. The site that is thus vacated is *always* vacated by an altruist. The probability of filling that site with an altruist must be ≤ 1. Therefore, Hamilton's Rule implies that the allele for altruistic death carries a *net cost* in inclusive fitness. It follows that aging (or altruistic death) cannot be selected in any fixed-density viscous model.

One way in which this conclusion can be evaded is to assume that older individuals become damaged over time. If the ability to reproduce declines with age, then it can be a winning proposition to replace an older, ineffective reproducer with a younger relative (Travis, 2004; Penteriani et al., 2009). These models may be interesting in their own right, but as explanations for the universal phenomenology of aging they suffer from a key defect: they beg the question of accumulated damage. It is not programmed death *per se* that cries out for an explanation (though programmed death at a defined age can be a useful mathematical model for studying aging); rather aging in the real world includes a failure to repair somatic and cellular systems that are eminently repairable, certainly at lower cost than the fully-amortized cost of creating an adult offspring via reproduction. Indeed, Vaupel et al. (2004) presents a proof that individually optimized life histories must always evince ever-increasing fertility and decreasing mortality! It is the failure to grow ever stronger and more fertile—the failure even to maintain current faculties—that is the essence of aging, posing a challenge to evolutionary theory. Historically, Weismann et al. (1891) were the first to propose that aging exists to eliminate damaged individuals from the population; but a few years later, he realized that his thinking had been circular, and his later writings no longer reflect this viewpoint (Kirkwood and Cremer, 1982). No evolutionary explanation for aging can be satisfactory which assumes declining function as a point of departure.

The model of Kirchner and Roy (1999) is also in this class. They posit a pathogen which causes sterility but not death, prevalence of which rises rapidly with age. Although the rationale is different, the selective mechanism is similar: older individuals crowd the niche while being reproductively incompetent. In the Kirchner model, the old pose an additional burden on their deme by providing a reservoir of disease that can infect individuals that are still young and fertile. This is an interesting precedent, but lacks sufficient generality to be considered an important mechanism for selection of a near-universal life history attribute.

If aging as an independent adaptation cannot evolve within the range of validity of the Price Equation and Hamilton's Rule, yet we are convinced by the phenomenology that senescence *did* evolve as an adaptation, what theoretical options remain? We seek an answer in terms of strong population dynamic effects. Traditional population genetic analysis (including the Price Equation (Price, 1970) and multilevel selection theory (Wilson, 1997)) assumes populations that are in quasi-steady state, with slow, differential population change. When this assumption is relaxed, we are free to contemplate population dynamics, which may be smooth or violently erratic.

There are two phenomena in nature that can trigger sudden population declines (including extinction) when population density exceeds a threshold level: famine and epidemics. We have previously considered famine as a key to understanding evolution of aging in predator species (Mitteldorf, 2004b, 2006). Predator/prey interactions can lead to chaotic population dynamics if predator population growth proceeds too rapidly in response to the availability of prey. This may provide powerful motivation for evolution of senescence.

In the present work, we invoke a very different model to analyze the effect of epidemics on the evolution of senescence. In our model, lethal epidemics spread with an efficiency that is highly sensitive to population density. In order to limit population density and avoid the devastation of epidemics, any of three life history factors may be deployed: (1) lowered birth rate, (2) increased (age-independent) mortality rate, and (3) senescence. Of the three, we find that selection prefers the last.

2. Intellectual heritage of the present epidemic models

We situate the present work at the intersection of two lineages, from the worlds of evolutionary theory and computational biology. From the literature on the evolution of sex, we draw on the theory that sexual recombination evolved for the purpose of promoting diversity in order to protect a population from microbial epidemics, the so-called 'Red Queen' hypothesis. From the literature of numerical modeling and physics, we have adopted a model of disease transmission and epidemics.

2.1. The Red Queen

The evolution and maintenance of sexual reproduction is recognized as a substantial challenge to evolutionary theory. It is generally recognized that sex cannot evolve via traditionally-recognized population genetic mechanisms (Williams, 1975; Maynard Smith, 1978; Bell, 1982). In its common bimorphic form among higher animals with separate sexes, sexual reproduction carries a fitness cost of a full factor of two; on the other side of the equation, the benefits of sex accrue many generations downstream in a diverse lineage. If costs and benefits are weighed using standard kin selection criteria, sex appears to be a losing proposition. So candidate explanations for sex operate outside the range of validity of standard population genetic assumptions. One of the best-accepted candidates for a mechanism by which sex may have evolved is the Red Queen[1] hypothesis (van Valen, 1973). The Red Queen hypothesis posits that multicellular organisms with long life cycles must maintain population diversity in order to protect against pathogens, which evolve much more rapidly because of their short life cycles. Pathogens that are narrowly adapted to infect a particular genotype can spread rapidly through homogeneous populations, causing local extinctions. Thus they provide a powerful incentive at the group

[1] The name derives from a line in Lewis Carroll's fantasy, *Through the Looking Glass*. The Red Queen says to Alice, "Here, you see, it takes all the running you can do, to keep in the same place. If you want to get somewhere else, you must run at least twice as fast as that!"