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Senescence as an adaptation to limit the spread of disease

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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

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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!"

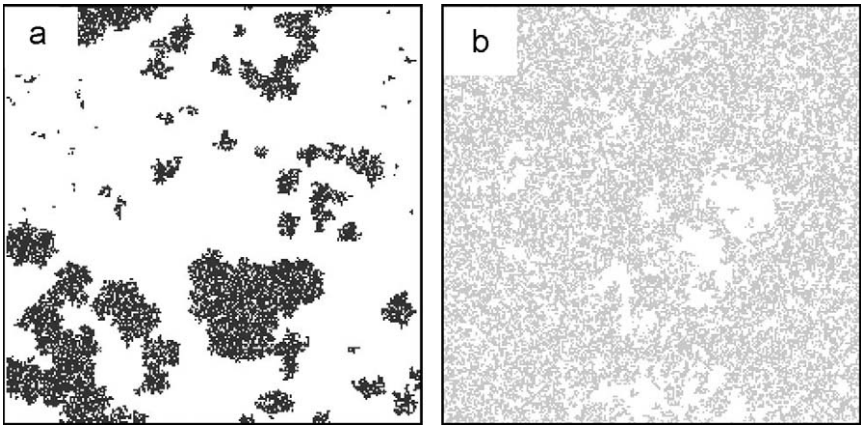

Fig. 1. Adapted from Socolar et al. (2001). This figure illustrates the two qualitatively different regimes, determined in our model by the life span. When life span is long (a) local density is high and epidemics spread efficiently. Occupancy is in isolated patches because patches are destroyed efficiently before they can merge to fill the grid. When life span is short (b), local density is low enough to keep epidemics contained. So epidemics produce holes in a uniformly-filled background, and the holes are quickly re-filled from the edges.

level to maintain immunologic diversity. Sexual reproduction contributes to this end by recombining genomes, providing unique and diverse genomes for each member of a community.

The same Red Queen mechanism that provides a powerful selective force for the evolution of sex also favors the evolution of senescence. Senescence contributes to epidemic resistance in two separate ways:

- Population density contributes to the transmission of disease. Senescence lowers population density by increasing the death rate; moreover, it does so in a way independent of stochastic causes of mortality in the environment. Senescence at the population level can contribute to leveling the death rate in fluctuating environments.
- Senescence contributes to a shorter effective generation time, thereby increasing population turnover and enhancing genetic diversity.

The fitness cost of senescence is high (Ricklefs, 1998; Bonduriansky and Brassil, 2002), but not so high as the cost of sex. If we accept the Red Queen hypothesis as a viable explanation for the evolution of sex, may we also regard it as a possible explanation for the evolution of senescence? This is the subject of the present inquiry.

2.2. Self-organized percolation

The first numerical model of catastrophic limits to population density was due to Henley (1993). He described his model in terms of trees on a Cartesian grid and 'forest fires' that spread through a chain of nearest-neighbor interactions. The model emerged from a branch of computational physics called *percolation theory*, because it deals with the existence of contiguous pathways through a 2- or 3-dimensional medium. As long as the average occupancy of the grid remained low, fires were contained; but when occupancy became too dense, fires could spread unchecked over broad regions. Henley coined the term 'self-organized percolation' to describe the system's attraction to the threshold density for wide transmission.

Rand et al. (1995) describe a class of host/pathogen models, in which pathogens infect a population arrayed on a grid, and once again identify a critical density above which the host population becomes unsustainable. The authors emphasize ways in which behavior of their models contrasts with the predictions of mean-field approaches, where relationships are derived as though every individual experienced an average environment. "In such spatial systems, the agents can configure their own environment in a way that produces both heterogeneity and complexity and stabilizes their population dynamics. It is natural to conjecture that all of this might have profound effects on evolutionary phenomena by, for example, altering selective pressure, stabilizing some mean-field unstable configurations…"

Socolar et al. (2001) describe a model which combines the biologically relevant features of Rand et al. (1995) and Henley (1993), incorporating both local reproduction and local transmission of infections. In Socolar's model, agents live on a Cartesian grid and reproduce to vacant neighbor sites, at a rate controlled by an evolving 'fertility' gene. Similarly, an evolving gene for 'mortality' controls the rate of random events removing the occupant of a site. With low probability ($\sim 10^{-6}$–10^{-4}) an epidemic can begin at a selected site, from which it spreads through every available contiguous pathway of occupied sites, killing all agents in its path. These authors identified two qualitatively distinct dynamic regimes of the parameter specifications: In one parameter regime, the grid remains uniformly filled at low density, and epidemics are well-confined, producing a temporary hole that is quickly filled in from the edges. In the other regime, the density is higher, but epidemics spread globally, wiping out all but a few isolated individuals that happen to have no nearest neighbors at the time of the epidemic. These survivors seed a patchy re-growth after the epidemic, in which populations emerge as dense, isolated spots, growing until they either merge with neighboring spots, or are wiped out by the a subsequent epidemic. The latter regime is thus characterized by large empty spaces between dense colonies, while the former regime appears as a uniform tapestry of lower density (Fig. 1).

Socolar explored the evolution of a constant, age-independent mortality rate under genetic control. The present inquiry extends his model to explore evolution of senescence.

3. Description of the model

Sites are arrayed on a two-dimensional, $n \times n$ grid, with opposing edges identified to form a torus. Each site may be vacant or may be occupied by a single model organism. In each computational cycle, a site is chosen at random, and if the site is

occupied, one of three events may occur: (1) reproduction, (2) death, or (3) the origin of an epidemic. Reproduction occurs at a random neighbor site, creating a viscous population structure with relatedness that varies with physical proximity (Rousset, 2000, 2002). If the chosen site is already occupied, the reproduction fails. This feature creates a dynamic in which rate of reproduction increases with vacancy rate. Death may occur either because of background mortality, or because the organism's genetically programmed life span has expired. Epidemics spread through a contiguous pathway of occupied sites. In some variations, individuals are assigned a heritable *susceptibility* genome, and then the rule is that epidemics spread only among individuals with identical *susceptibility* genomes. Epidemics are the source of the model's highly non-linear behavior, generating selective effects that promote altruism.

The probabilities that govern the selection of one of these three events determine the dynamics of the model. The probability b of reproduction was controlled by a gene in some runs, but after we determined that it tended to evolve to a maximum, we fixed b such that every selected organism which does not die or originate an epidemic is given an opportunity to reproduce. Similarly, we experimented with the background, random mortality rate m as a gene, and found that it evolves toward zero when a *lifespan* gene was available as an alternative, better-regulated source of mortality. The probability of an epidemic is a parameter of the model, fixed as constant within any given run.

Thus in most of our runs, the organisms' genomes included just one or two genes: The first controls *lifespan*, implemented in our simple model as a threshold function. The *lifespan* gene is represented as a floating point number. An organism will vacate its site immediately when its age exceeds its genetically programmed *lifespan*. In some experiments, there is a second *susceptibility* gene, described above, which controls epidemic transmission and is otherwise neutral. Epidemics kill the originator, and then explore all neighbor sites; if a genetically identical *susceptibility* gene is found, the epidemic kills the neighbor and continues to spread recursively through the grid. (Evolution of pathogens is not modeled explicitly, but novel pathogens are assumed to appear stochastically and to be adapted to match the *susceptibility* allele of the organism in which they first appear.)

4. Dynamics of the model

In the Introduction above, we identified two mechanisms by which senescence protects a population from microbial epidemics. The first is population density control, and we have isolated this mechanism in a version of our model in which there is no genetic variation at the *susceptibility* locus.

4.1. No diversity—epidemics controlled by population density only

When life span is freed to evolve, individual selection pushes it higher, and the population consequently grows denser. But contagion is highly sensitive to population density in our model, and when life span passes a threshold value, the next epidemic spreads through a large swath, wiping out the entire region in which life span is long. Then other regions, where, by chance, life span is still a bit shorter, continue to grow with far less damage from epidemics. Thus a dynamic steady state is attained where average life span across the grid remains bounded by the threshold value that can hold epidemics in check.

In the simplest geometry, each site has four neighbors. If two or more of those neighbor sites are occupied, then the epidemic has an opportunity to be transmitted through the site, and continues to spread. But sites with just one occupied neighbor can form firewalls that limit the spread of an epidemic. Ignoring neighbor correlations, we guess roughly that sites with less than two neighbors are common when the grid is less than 50% full. Empirically, we find that the boundary between Socolar's two dynamic domains (high and low transmissibility) occurs at an occupancy rate of about 54%.

As emphasized by Socolar et al. (2001) the model behaves in ways that are explosively non-linear and difficult to predict. It is the chain of epidemic contagion along contiguous pathways that makes the model intractable (and, therefore, interesting as an example of complexity). The current variant subsumes this highly non-linear behavior, and resists analytic treatment. We would like to understand the model in terms of Hamilton's rule: costs, benefits and relatedness. Costs and benefits are easy to determine, but relatedness of the beneficiary to the altruist is, for this model, quite intractable. This is because the benefit derives from those rare occasions when the vacancy created by an individual's death is crucial in blocking the spread of an epidemic. The beneficiaries are all those individuals further along the chain of contiguity that would have been infected but for this individual's altruistic death, and their relatedness to the target altruist resists analysis.

However, if the geometry of contagion can be set aside, other aspects of the model may yield to analytic approximations. We may understand the relationship between life span and population density in the absence of epidemics, and thus gain intuition about how life span may be limited. In a series of appendices, we derive three successive approximations to predict the grid's rate of occupancy in the absence of epidemics.

The spread of an epidemic at the smallest scale is controlled by the micro-environment of the individual. Let q be the probability of finding a site occupied when looking at a random site adjacent to a random occupied site. In Appendix A, we relate q to the global occupancy p and the neighbor correlation R, and show that

$$q = p + R - pR$$

We seek to predict q from m, the programmed lifespan which, in our model, is an evolved individual attribute. During its life span, an agent is selected for an opportunity to reproduce an average of m times. Reproduction fails if it is attempted in a neighbor site that is already occupied, so the probability of reproduction succeeding is just $(1–q)$. In steady state, there must be one birth for each death, so

$$m(1-q) = 1 \quad \text{or} \quad q = 1 - 1/m \tag{2}$$

High population density makes the population susceptible to epidemics. Empirically, we find that the boundary between Socolar's two dynamic domains occurs when q is about 0.62. Below this value, selection is dominated by the individual tendency to maximize reproduction by maximizing life span. Above this value, the population becomes unsustainable, as the probability of widespread epidemics increases rapidly. When epidemics are restored to the model, we find that the values of life span m that evolve are just above 3, corresponding to $q = 0.67$, as predicted.

We may refine the prediction by looking at the detailed probability distribution of which q is the mean. We define q_i as the probability that an occupied site has exactly i neighbors, where i ranges from 0 to 4. q is the expectation of q_i : $q = \frac{1}{4}\sum iq_i$. Most interesting is q_1, the proportion of agents that have exactly one neighbor. Such sites serve as firewalls, halting the spread of an epidemic. An epidemic that spreads to a cell that has only one neighbor cannot proceed further.

In Appendix B, we derive predictions for a full set of probabilities q_i, derived from m in the absence of epidemics as above. The method is to treat q_i as a vector and compute an

instantaneous transition matrix T defined as a differential change of q_i in the 5-dimensional space[2] where q_i lives. Elements of T are probabilities for reproduction and for death among the neighbors of an occupied site. We seek to characterize the grid's steady-state condition (in the absence of epidemics) by finding fixed points where the set of q_i remains constant over time. The transition matrix represents the instantaneous, differential change in a vector q_i. It can be integrated over finite time t to yield $\exp(tT)$, defined formally as $\lim_{\delta t\to 0}(1+\delta tT)^{t/\delta t}=\exp(tT)$. Steady state occurs at fixed points of the matrix $\exp(tT)$. (The value of t does not matter, since any eigenvector for one value of t is an eigenvector for all t.) In practice, we may compute $\exp(tT)$ as a Taylor series, which converges rapidly for small values of t

$$\exp(tT)=1+tT+\frac{1}{2!}t^2T^2+\frac{1}{3!}t^3T^3+\cdots \tag{3}$$

Eigenvectors of $\exp(tT)$ have been computed by beginning with an arbitrary vector and multiplying repeatedly by $\exp(tT)$ until the result converges. (This strategy may be familiar to readers who have worked with Lesley matrices.)

This method is approximate because in reality an occupied site does not have infinite time in which to bring its environment to steady state before it dies. However, we find that the approximation is excellent for long life spans, and even for life spans as short as $m=2$, the method yields a serviceable approximation to q_i.

4.2. Epidemics controlled by diversity as well as population density

In this version of our model, a rule for propagation of epidemics prescribes that contagion is between adjacent sites of identical genomes only. In theory, epidemics could be controlled by a combination of vacancies and diversity, but we find in practice that diversity relieves the need to control density, so contagion is controlled predominantly by diversity in this version of the model.

Beginning from any distribution of genotypes, the grid tends to self-organize into genetically homogeneous domains, because the rule for reproduction keeps offspring close by. Epidemics take down a domain at a time. The larger a domain, the more likely it is to be wiped out by an epidemic. Hence epidemics help to enhance diversity, and diversity helps to mitigate epidemics. When either the total death rate or the mutation rate is high, domains can break apart, forming domain boundaries that limit the spread of epidemics independent of diversity.

After a domain succumbs to an epidemic, it is re-filled from neighboring domains. If the mutation rate is high, the grid will maintain sufficient diversity to avoid extinction; but the lower the mutation rate, the more turnover the population requires in order to sustain a level of diversity that will protect against epidemics.

When mortality from background death rate plus programmed lifespan is too high, the population cannot sustain itself; but when mortality from these two sources is too low, the population grows too dense and too homogeneous; each epidemic then takes down a larger domain. This, too, can lead to extinction.

When either of the two sources of mortality is allowed to evolve, mortality is pushed lower by individual selection. But lower mortality in a region then triggers larger epidemics, creating countervailing selection pressure from a higher level. Depending on model parameters, the result can be a stable balance at a modest mortality level, or wide fluctuations in both mortality and total population, or fluctuations that are wider still can drive the population to extinction.

[2] Actually, a 4-dimensional subspace in which the sum of the probabilities q_i is constrained to equal unity, $\sum q_i=1$.

We capture the behavior of the diversity model with the following approximate analysis: Denote the random death rate as d, and express the fixed life span as m, the epidemic rate as e. Then the total death rate is approximated as $(d+1/m+eN)$, where N is a measure of a typical size of a genetically homogeneous patch which succumbs to an epidemic. In steady state, the average birth rate must equal the death rate.

Consider now the diversity of the population, defined as the total number of distinct immune genotypes represented. This quantity must always be increasing or else collapsing to zero. The condition for diversity to be increasing is that new mutations must come along faster than homogeneous populations of their progenitors are destroyed by epidemics. This means that the mutation rate μ times the total birth (death) rate must be larger than the population death rate from epidemics:

$$\mu(d+1/m+eN)>e \tag{4}$$

One way to satisfy this criterion is for the patch size N to be larger than $1/\mu$. If this condition does not hold, then empty spaces that come from multiple stricken patches will grow larger and larger until it becomes probable that in the course of refilling the hole there is at least one mutation. This is a costly solution, in that it leaves a great deal of empty (unproductive) space.

Alternatively, the patch size can be maintained at a size small compared to $1/\mu$ so long as the total death rate "between epidemics" $(d+1/m)$ is sufficiently high. This represents a solution with lower volatility, since each epidemic takes down a smaller patch. Because the rate at which a patch is filled is proportional to its linear dimension, while its area (population) is proportional to the square of its linear dimension, the small patch size also offers a higher time-averaged occupancy rate. The combination of time-averaged population density and resistance to epidemics is a good surrogate for fitness. Hence this high-mortality solution may be able to out-compete the low-mortality solution. This suggests that selection operating in the model will produce a complementary relationship between evolved life span m and the prescribed background death rate d. It also suggests that the (prescribed) mutation rate must exceed the (prescribed) epidemic rate in order for such solutions to exist. All these predictions are borne out in our simulation results, though the model's behavior is contingent on small variations in parameters and rules. For example, there are some conditions for which the life span m evolves longer values until the entire population is driven to extinction.

5. Numerical results

5.1. Senescence evolves in preference to either lower birth rate or higher death rate

Population density can be controlled at levels that keep epidemics at bay either by moderating the birth rate, by increasing the age-independent mortality rate, or by decreasing the programmed life span.

When we allowed genes for birth rate and life span to evolve simultaneously, birth rate increased to its maximum value, allowing life span to shoulder the entire burden of population control. This is because lowering the birth rate hurts the ability of the population to recover from epidemics and to expand into empty territory, while life span control is capable of maintaining porosity in the grid with less impact on the free expansion rate.

When we allowed genes for age-independent mortality and life span to evolve simultaneously, once again shorter life span was selected, as age-independent mortality evolved toward zero. This is true whether there is just one immune genotype or many. The reason for this is less clear within the model rules. We

speculate that the reason for this advantage is once again in the dynamic of free expansion into unoccupied territory. For an expanding patch in which death is only from life span limit m, the expanding front of new organisms is uniformly young and thus has a low death rate, forming a barrier to invasion until the territory is established. This provides an advantage in head-to-head competition against another population into the same territory, in which death is a random event unrelated to age.

In addition, the present model does not capture some aspects of the real biosphere that make senescence a much better tool for controlling population than age-independent mortality. In real life, background mortality is not a constant, as modeled here, but fluctuates deeply with environmental conditions. In biological practice, to increase "background mortality" means to weaken the organism against one or more environmental threats, which risks extinction during times when environmental conditions are most challenging. Senescence offers a way to level the death rate in good times and bad. During the harshest times, few individuals live long enough for senescence to be relevant; thus senescence does not add appreciably to the risk of extinction. But in times when there are few external threats, more individuals live long enough for senescence to take its toll.

Hormesis may be defined as a form of phenotypic plasticity entailing over-compensation in harsh environmental conditions. In times of greatest environmental challenge, the senescence program is moderated so that challenged individuals actually live longer than unchallenged individuals. Examples include starvation, physical exertion, dietary protein deprivation, exposure to disease and to toxins (Luckey, 1999; Calabrese and Baldwin, 2002; Masoro, 2007). All these conditions lead to slower rates of aging and lowering of the death toll from senescence during times when the mortality from other causes is high. Thus has senescence been refined in natural selection as a program to compress population swings.

5.2. Senescence evolves to complement a low mortality rate

When background mortality is treated as a constant, we find that the death rate from senescence evolves to complement it. Specifying large values of background mortality results in evolution of long life span m, and inversely. These results are plotted in Fig. 2.

This result was anticipated by Travis (2004), but it runs directly counter to the classical prediction of Williams (1957) and to field studies by Austad (1993) and others (Dudycha and Tessier, 1999; Stearns, 2000; Blanco and Sherman, 2005) Intriguingly, there are circumstances—perhaps common in nature—where the classical prediction appears to fail, and lower extrinsic mortality has the paradoxical result of promoting the evolution of a shorter intrinsic life span (Promislow, 1991). Reznick et al. (2004) reports that guppies extracted from high-predation sites in the Amazon have longer intrinsic life spans than guppies from neighboring sites that lack predators (Mitteldorf and Pepper, 2007). More generally, Ricklefs (1998) reports that the proportion of deaths attributable to senescence in the wild is negatively correlated with extrinsic mortality, in a review of bird and mammal field studies. The evidence may be strong enough to justify a radical hypothesis, based on population dynamics rather than traditional population genetics: perhaps senescence is playing a complementary role, contributing to population homeostasis by maintaining the overall death rate in the face of fluctuating incidental mortality.

5.3. Evolved life span as a function of epidemic rate

Another model parameter that affects the evolved life span is the frequency with which novel pathogens are introduced, the epidemic rate. Frequent epidemics offer good feedback, so that life span limits can evolve reliably; infrequent epidemics may fail to punish evolved longevity until it is too late, and extinction can result.

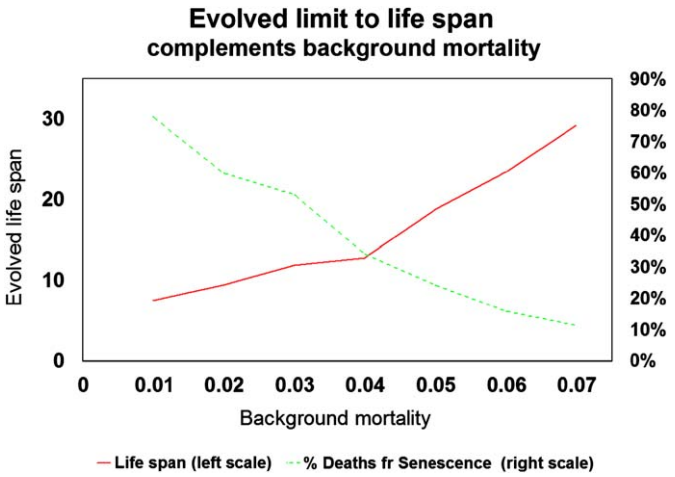

Fig. 2. When background mortality is low, there is more selection pressure to shorten life span (in order to hold down population density and contain epidemics). Senescence complements background mortality, contributing to population homeostasis. (Model parameters: lifespan mutation prob = 0.1 with range = 0.03; single susceptibility genotype, 9-point neighborhoods; fertility = 1; epidemic prob = 3.16×10^{-5}).

Evolved life span is rather insensitive to the rate of epidemics. As epidemic frequency is varied over two orders of magnitude, evolved life span changed by just a few percent (Fig. 3). Epidemic transmission is so sensitive to population density that population density is confined within a narrow range. Since life span determines population density (there was no background mortality in these runs), life span is also confined to a narrow range.

5.4. Sensitivity to mutation rate

We varied the mutation rate at the *lifespan* locus and found that the mean life span that emerges from selection is little changed as mutation rate is varied over three orders of magnitude from 10^{-4} to 10^{-1}. Of course, lower mutation rates take longer to evolve, and the lowest values in this range tend to make the population fragile and sensitive to initial conditions. That higher mutation rates produce slightly longer mean life spans can be explained as a kind of mutational load: longer-lived mutants persist awhile on the basis of their individual selective advantage before they are eliminated by elevated epidemic severity.

Varying the mutation rate at the *susceptibility* locus has a modest effect on evolved life span. Higher mutation rates mean that fewer life cycles are necessary to maintain diversity, as described above in the section *Dynamics of the model* (Fig. 4).

5.5. Effect of dispersal range

Dytham and Travis (2006) and Travis and Dytham (1998) have studied the interaction between dispersal and evolution of cooperation, showing that altruism that is blind and local can evolve more easily when dispersal range is limited (and that limited dispersal can evolve as an adaptation to motivate cooperation). When kin remain tightly clustered, the probability that the beneficiary of altruism will be another altruist is enhanced. In our model, dispersal distance corresponds to the size of the neighborhood in which offspring are distributed; hence

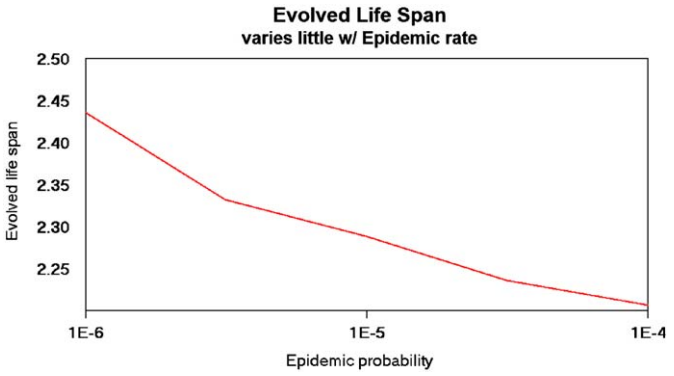

Fig. 3. As epidemic rate varies over two orders of magnitude, the limits to life span that evolve remain within a narrow 10% range. Epidemics that are less frequent are so much more damaging that the death toll is hardly changed. The reason for this behavior is that epidemic transmission is a very steep function of population density; so life span evolves so as to keep population density within a narrow range. (Model parameters: lifespan mutation prob = 0.1 with range = 0.02; single susceptibility genotype, 9-point neighborhoods; fertility = 1.)

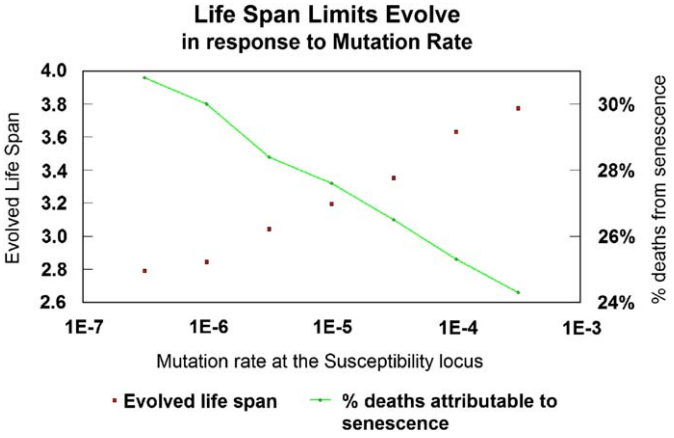

Fig. 4. Life span evolves in response to mutation rates for immune diversity. Higher mutation rates lead to longer life spans, but once again the effect is modest, with three orders of magnitude change in mutation rate accounting for less than a factor of two in life span. (Model parameters: lifespan mutation prob = 0.1 with range = 0.03; 8-bit susceptibility genotype, 9-point neighborhoods; fertility = 1; epidemic prob = 3.16×10^{-5}.)

general considerations suggest that, in our model, smaller neighborhood size would lead to stricter shorter evolved life span. But our results indicate the opposite.

There is a second effect of dispersal range in our model: epidemics spread far more easily with the wider neighborhoods, and a corresponding definition of contiguity. In fact, the larger neighborhoods sharply limit the population density that is robust to epidemics, facilitating the evolution of life span limits that is the subject of our investigation.

All the data plotted above were derived with nine-point neighborhoods, in the form of a 3×3 square. In order to study the effect of dispersal, we ran variants of the model with smaller cross-shaped (von Neumann) neighborhoods of size 5 and larger 25-point neighborhoods (5×5 square).

The larger neighborhoods evolve a shorter life span. If we think just in terms of relatedness and multilevel selection dynamics, this is a paradoxical result. The resolution is that larger neighborhoods permit epidemics to spread more widely, forcing population densities to remain lower.

When the neighborhood is expanded for the purpose of offspring dispersal, but epidemics are limited to spreading via

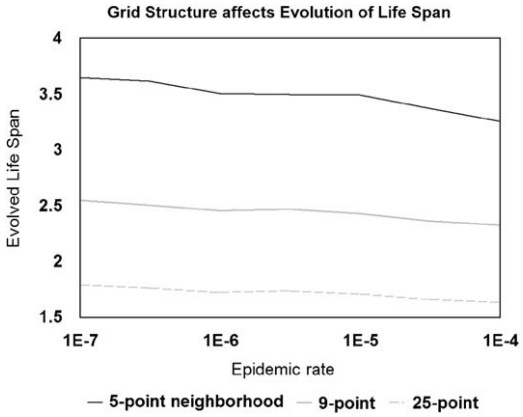

Fig. 5. Smaller neighborhood size limits dispersal rate among kin, which should facilitate evolution of limits on life span. But neighborhood size also affects transmission of epidemics, and this turns out to be a stronger effect. Shorter life spans evolved with 9-point square neighborhoods than with 4-point von Neumann neighborhoods. For yet larger 25-point square neighborhoods, evolved life span was even shorter, but frequent extinctions frustrated our data collection. The bottom line in the plot was extrapolated from incomplete computational results. (Model parameters: lifespan mutation prob = 0.1 with range = 0.03; single susceptibility genotype, fertility = 1; epidemic prob = 3.16×10^{-6}.)

von Neumann contiguity (i.e., in the 5-point neighborhood only), the effect is to permit longer individual life spans to evolve. In this configuration, the population could easily evolve off a cliff, as life spans increased to the point where epidemics spread too broadly, resulting in global extinction (Fig. 5).

6. Discussion

Most mainstream population geneticists believe it is not possible that senescence could have evolved as a group-level adaptation. This theoretical judgment appears sound in the context of constant total populations and differential changes in gene frequency, which are standard assumptions in standard population genetic models. However, many of these same scientists believe that the Red Queen is a credible explanation for the evolution of sex (Ridley, 1993), even though it cannot be framed or modeled in that context. The Red Queen mechanism essentially involves deep population fluctuations and local extinctions that result from infectious epidemics.

Many prominent evolutionary theorists (Ridley, 1993, p. 331; Bell, 1997) who remain skeptical of the potency of group selection in other contexts maintain an exception for evolution of sex. Williams (1975) is quite explicit about this, as is Maynard Smith (1989, p. 243). None of these authors explains why evolution of sex should be a unique exception. The possibility remains open that whatever mechanism evolved sex may have shaped other prominent aspects of advanced life forms.

Like sex, senescence offers a benefit for population diversity, which can limit the spread of epidemics. In addition, senescence provides a benefit that sex does not, in helping to stabilize population densities as environmental conditions vary over time. Modern estimates of the individual cost of senescence are substantial (Ricklefs, 1998; Bonduriansky and Brassil, 2002), but still lower than the 'cost of males'. Hence, we propose that, if the Red Queen is capable of evolving sex, she is also capable of evolving senescence.

In our model, epidemics can wipe out entire (homogeneous) populations in a short time; and the severity of epidemics is approximated by a step function, rising steeply when population density exceeds a threshold value. These two properties of epidemics fundamentally change the rules of selection.

If population density is held below an externally imposed limit, this creates a powerful group-selective force in direct opposition to individual selection for higher fertility and longer life span. Population control cannot be achieved without substantial cost to individual fitness. (Indeed, the most robust classical measure of individual fitness is population density ***K*** (Benton and Grant, 2000), and other measures of fitness such as ***r*** and $\boldsymbol{R_0}$ are closely tied to population density in our model, as in the real world.)

So, if selection acts to hold population density below a threshold, this fundamentally changes the nature of the game. Indeed, nothing less could permit the direct selection of an attribute as detrimental to individual fitness as senescence or sex.

Radical theories require powerful evidence. The mechanism proposed herein is radical in that it is outside the range of standard population genetic assumptions. But we make no claim that our computational model constitutes powerful evidence; rather, the compelling evidence is in the phenomenology of aging, which indicates a purposeful adaptation (Mitteldorf, 2004a, 2009; Skulachev, 1997; Bredesen, 2004; Longo et al., 2005), rather than an unavoidable deterioration or a side-effect of other adaptations. Once this empirical point is recognized, we suggest that the mechanism outlined herein is among the least radical solutions to the conundrum of adaptive aging.

Acknowledgments

We received detailed suggestions about an earlier version of this paper, and much helpful guidance from Peter D. Taylor and Justin Travis.

Appendix A. Calculation of neighbor correlation *R* in a grid unperturbed by epidemics

This is a derivation of the neighbor correlation R, defined as $R=(\langle x_1x_2\rangle-\langle x^2\rangle)/(\langle x^2\rangle-\langle x\rangle^2)$ in a grid where occupied sites reproduce in each time step into (unoccupied) neighbor sites, and deaths occur randomly, without regard to neighbor occupancy.

Here x is defined to be 1 if a cell is occupied and 0 if vacant. x_1x_2 is 1 if both a cell and its neighbor are occupied, 0 otherwise. $\langle x_1x_2\rangle$ represents the value of this quantity averaged over all von Neumann neighbor pairs. $\langle x\rangle$ is just the proportion of cells in the grid that are occupied, and $\langle x^2\rangle$ is the same as $\langle x\rangle$.

We write $p=\langle x\rangle=\langle x^2\rangle$ for the rate of occupancy, and define q as the conditional probability of finding a site occupied when looking adjacent to an occupied site. In these terms, $R=(pq-p^2)/(p-p^2)$, hence $q=\langle x_1x_2\rangle/\langle x\rangle=p+R-pR$.

In our model, with fixed life span and no epidemics, a birth rate $b=1$ corresponds to the specification that whenever a cell is randomly selected, it will reproduce into a randomly selected neighbor site, provided that cell is unoccupied. Hence the probability of creating a new organism in a time step is the probability that the random adjacent cell is vacant, which, by our definition, is $(1-q)$. The rate at which cells will be vacated is $1/m$, where m is the programmed life span expressed in time steps. The birth rate and death rate are equal in steady state, so $1/m=(1-q)$.

Substituting for q its formula above in terms of p and R, we derive the desired expression for R in terms of p and m:

$$R=\frac{(q-p)}{(1-p)}=\frac{(1-1/m-p)}{(1-p)}$$

This is an exact expression (for an infinite grid) that is borne out in our simulation results.

In a simulation, we specify m, and then p and R are measured properties of the grid. The formula relating R to p is only half of what we might hope to predict; it remains to compute both R and p from first principles, given m. An approximate expression is derived in Appendix B.

Appendix B. Approximate calculation of the probability distribution for the number of occupied neighbors (out of 4) of an occupied cell, in a grid unperturbed by epidemics

In Appendix A, we defined q as the probability of finding an occupied cell when looking adjacent to an occupied cell. For purposes of the current derivation, we further refine q to examine the distribution of occupancy next to an occupied cell. Specifically, let q_i represent the probability that exactly i neighbor cells (out of 4) are occupied. The index i runs from 0 to 4. The probabilities sum to unity $\sum q_i=1$, and the quantity previously defined as q is the expectation value $q=\frac{1}{4}\sum iq_i$.

Our method will be to derive a differential transition matrix T for a vector of probabilities q_i, and seek fixed points (eigenvectors) of that transition matrix in steady state. Elements T_{ij} of the transition matrix are proportional to the probability per unit time that a birth or death will change the number of neighbors around an occupied cell from i to j. The transition matrix can be integrated over finite time by composition of an arbitrarily large number of infinitesimal transition probabilities. The result can be written formally as $\exp(T)$. By analogy with the exponential function of a scalar,

$$\exp(T)=\lim_{n\to\infty}(1+T/n)^n=1+T+\frac{1}{2!}T^2+\frac{1}{3!}T^3+\cdots$$

Fixed points of the matrix $\exp(T)$ can be approximated (similarly to fixed points of a Leslie matrix) by beginning with an arbitrary vector q_i and multiplying by $\exp(T)$ repeatedly until the result remains constant to any desired degree of accuracy.

(This method is an approximation and not an exact solution because each central, occupied site has itself a finite lifetime, and the steady-state value of q_i are realized only asymptotically. We have found, nevertheless, that the results of this procedure offer an excellent approximation to the measured distribution q_i when life spans m are long, and a fair approximation even when m is near the limit of the shortest viable life span.)

B.1. Construction of the transition matrix

Each element T_{ij} of the transition matrix represents a probability per unit time that an occupied central site will progress from having i neighbors to j neighbors. We define time units such that each lattice site is hit once on average in each time unit.

The matrix T can be constructed as a linear combination of the birth matrix B and the death matrix D. The single parameter m (programmed life span) of our numerical model determines the proportion in which the matrices B and D are combined to form the full matrix T.

The birth matrix B can be constructed as follows: If there are 0 neighbors to begin with, then the probability of planting a seed in a vacant neighbor site is unity, so the element $B_{10}=1$ expresses the certainty of reproductive success. There must be a corresponding element $B_{00}=-1$, expressing the fact that state with 0 neighbors is certain to be supplanted, and assuring the conservation of probability. Similarly, if the central site has 1 occupied neighbor (out of 4) when it is selected for a birth event, then the probability is $\frac{3}{4}$ that reproduction will be successful, hence $B_{21}=\frac{3}{4}$

and $B_{11} = -\frac{3}{4}$. The remainder of the matrix is constructed with the same logic.

$$B = \begin{bmatrix} -1 & 0 & 0 & 0 & 0 \\ 1 & -0.75 & 0 & 0 & 0 \\ 0 & 0.75 & -0.5 & 0 & 0 \\ 0 & 0 & 0.5 & -0.25 & 0 \\ 0 & 0 & 0 & 0.25 & 0 \end{bmatrix}$$

Similarly, the death matrix D can be constructed. Implicitly, we assume (a further approximation) that the birth times of neighbors may be considered uncorrelated to the birth time of the central site. Hence deaths of each of the occupied neighbors is a random event with equal probability per unit time. If zero cells are occupied, there is no one to die, hence $D_{i0} = 0$ for all values of i. If one cell is occupied, there is a $\frac{1}{4}$ chance that this site will be selected for death, prompting the transition from $1 \rightarrow 0$ occupied neighbors. Hence $D_{01} = \frac{1}{4}$ and $D_{11} = -\frac{1}{4}$. Continuing in this fashion,

$$D = \begin{bmatrix} 0 & 0.25 & 0 & 0 & 0 \\ 0 & -0.25 & 0.5 & 0 & 0 \\ 0 & 0 & -0.5 & 0.75 & 0 \\ 0 & 0 & 0 & -0.75 & 1 \\ 0 & 0 & 0 & 0 & -1 \end{bmatrix}$$

The full transition matrix T is a linear combination of B and D, with the relative proportion determined by the ratio of death to birth opportunities. For example, if $m = 3$, then 3 time units pass during the life span of each individual, so it has enough time to reproduce itself twice (including its own death as -1).[3] In this case $T = 2B+D$ can be computed as

$$T = \begin{bmatrix} -2 & 0.25 & 0 & 0 & 0 \\ 2 & -1.75 & 0.5 & 0 & 0 \\ 0 & 1.5 & -1.5 & 0.75 & 0 \\ 0 & 0 & 1 & -1.25 & 1 \\ 0 & 0 & 0 & 0.5 & -1 \end{bmatrix}$$

Note that it is only the relative proportions of B and D that enter into the calculation, because the unit of time is arbitrary. Put another way, any eigenvector of $\exp(T)$ will also be an eigenvector of $\exp(aT)$ for any scalar a.

The next step is to exponentiate T, and we calculate

$$\exp(T) = \begin{bmatrix} 0.1766 & 0.0479 & 0.0130 & 0.0035 & 0.0010 \\ 0.3833 & 0.3025 & 0.1359 & 0.0515 & 0.0179 \\ 0.3120 & 0.4078 & 0.4214 & 0.2592 & 0.1261 \\ 0.1129 & 0.2060 & 0.3456 & 0.4889 & 0.3938 \\ 0.0153 & 0.0359 & 0.0840 & 0.1969 & 0.4613 \end{bmatrix}$$

(In practice, the numerical calculation proceeds more stably if we compute $\exp(0.1T)$ and then iterate the multiplication ten times more often. The calculation of $\exp(T)$ must be coded by hand in extended precision, or computed within *Mathematica*, whereas the calculation of $\exp(0.1T)$ can be performed in any spreadsheet, using the truncated Taylor series.)

Finally, we determine fixed points of $\exp(T)$ by beginning with an arbitrary probability vector q_i and iteratively multiplying by $\exp(T)$ until the product converges on a solution.

$$q_i = \begin{bmatrix} 0.0123 \\ 0.0988 \\ 0.2963 \\ 0.3951 \\ 0.1975 \end{bmatrix}$$

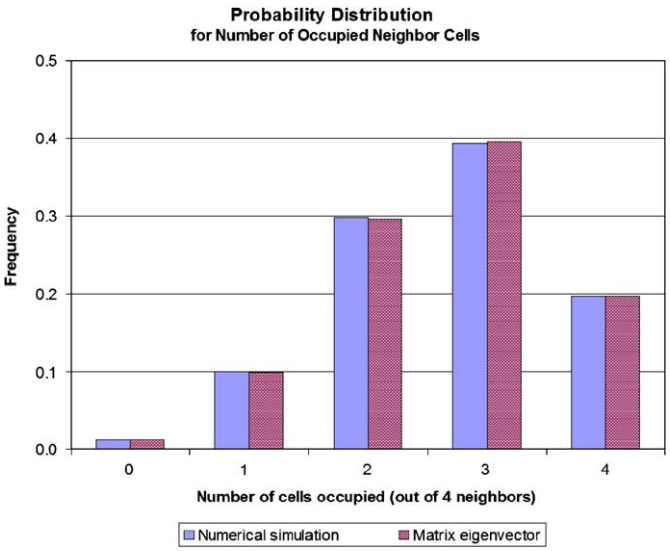

Fig. 6. Predictions of matrix model compared to numerical results for frequency of different numbers of occupied nearest neighbor cells (out of 4).

In Fig. 6, these probabilities are compared to the frequencies compiled from a numerical simulation for agents with life span all equal to 3 and no epidemics.

The expectation value $q = \frac{1}{4}\sum iq_i$ can be calculated from the above vector, yielding $q = 0.667$, and (considering our starting condition $m = 3$) corroborating the formula $1/m = (1-q)$, derived in Appendix A.

References

Austad, S., 1993. Retarded senescence in an insular population of Virginia opossums. J. Zool. London 229, 695–708.
Bell, G., 1982. The Masterpiece of Nature: The Evolution and Genetics of Sexuality. University of California Press, Berkeley.
Bell, G., 1997. Selection: The Mechanism of Evolution. Chapman and Hall, New York.
Benton, T., Grant, A., 2000. Evolutionary fitness in ecology: comparing measures of fitness in stochastic, density-dependent environments. Evol. Ecol. Res. 2, 769–789.
Blanco, M.A., Sherman, P.W., 2005. Maximum longevities of chemically protected and non-protected fishes, reptiles, and amphibians support evolutionary hypotheses of aging. Mech. Ageing Dev. 126 (6–7), 794–803.
Bonduriansky, R., Brassil, C.E., 2002. Senescence: rapid and costly ageing in wild male flies. Nature 420 (6914), 377.
Bourke, A., 2007. Kin selection and the evolution of aging. Ann. Rev. Ecol. Evol. Syst. 38, 103–128.
Bredesen, D.E., 2004. The non-existent aging program: how does it work? Aging Cell 3 (5), 255–259.
Budovsky, A., Abramovich, A., et al., 2007. Longevity network: construction and implications. Mech. Ageing Dev. 128 (1), 117–124.
Calabrese, E.J., Baldwin, L.A., 2002. Defining hormesis. Hum. Exp. Toxicol. 21 (2), 91–97.
Dudycha, M.L., Tessier, A., 1999. Natural genetic variation of life span, reproduction, and juvenile growth in Daphnia. Evolution 53, 1744–1756.
Dytham, C., Travis, J.M., 2006. Evolving dispersal and age at death. Oikos 113, 530–538.
Guarente, L., Kenyon, C., 2000. Genetic pathways that regulate ageing in model organisms. Nature 408 (6809), 255–262.
Hamilton, W.D., 1964. The genetical evolution of social behaviour. I. J. Theor. Biol. 7 (1), 1–16.
Hekimi, S., 2006. How genetic analysis tests theories of animal aging. Nat. Genet. 38 (9), 985–991.

[3] We have found in practice that simply subtracting 1 from the programmed life span yields exactly the correct proportion for combining B and D matrices, but we are less than fully satisfied with this explanation for why the procedure works in terms of the "excess births" after the central individual replaces itself.

Henley, C., 1993. Statics of a "self-organized" percolation model. Phys. Rev. Lett. 71, 2741–2744.
Holzenberger, M., Dupont, J., et al., 2003. IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice. Nature 421 (6919), 182–187.
Kenyon, C., 2001. A conserved regulatory system for aging. Cell 105 (2), 165–168.
Kirchner, J.W., Roy, B.A., 1999. The evolutionary advantages of dying young: epidemiological implications of longevity in metapopulations. Am. Nat. 154 (2), 140–159.
Kirkwood, T.B.L., Cremer, T., 1982. Cytogerontology since 1881: a reappraisal of August Weismann and a review of modern progress. Hum. Genet. 60 (2), 101–121.
Liu, X., Jiang, N., et al., 2005. Evolutionary conservation of the clk-1-dependent mechanism of longevity: loss of mclk1 increases cellular fitness and lifespan in mice. Genes Dev. 19 (20), 2424–2434.
Longo, V.D., Mitteldorf, J., et al., 2005. Programmed and altruistic ageing. Nat. Rev. Genet. 6 (11), 866–872.
Luckey, T.D., 1999. Nurture with ionizing radiation: a provocative hypothesis. Nutr. Cancer 34 (1), 1–11.
Marden, J.H., Rogina, B., et al., 2003. Conditional tradeoffs between aging and organismal performance of Indy long-lived mutant flies. Proc. Natl. Acad. Sci. USA 100 (6), 3369–3373.
Masoro, E.J., 2007. The role of hormesis in life extension by dietary restriction. Interdiscip. Top. Gerontol. 35, 1–17.
Maynard Smith, J., 1976. Group selection. Q. Rev. Biol. 51, 277–283.
Maynard Smith, J., 1978. The Evolution of Sex. Cambridge University Press, Cambridge, UK.
Maynard Smith, J., 1989. Evolutionary Genetics. Oxford University Press, New York.
Mitteldorf, J., 2004a. Aging selected for its own sake. Evol. Ecol. Res. 6, 1–17.
Mitteldorf, J., 2004b. Chaotic population dynamics and the evolution of aging. In: Ninth International Conference on Artificial Life. MIT Press, Boston MA.
Mitteldorf, J., 2006. Chaotic population dynamics and the evolution of aging: proposing a demographic theory of senescence. Evol. Ecol. Res. 8, 561–574.
Mitteldorf, 2009. Evolutionary origins of aging. In: Fahy, G.M. (Ed.), Approaches to Controlling Aging Springer, Berlin, Heidelberg, New York (in press).
Mitteldorf, J., Pepper, J., 2007. How can evolutionary theory accommodate recent empirical results on organismal senescence? Theory Biosci. 126 (1), 3–8.
Mitteldorf, J., Wilson, D.S., 2000. Population viscosity and the evolution of altruism. J. Theor. Biol. 204 (4), 481–496.
Penteriani, V.F., Otalora, M.F., et al., 2009. When individuals senesce: the 'Florida effect' on stable populations of territorial, long-lived birds. Oikos 118 (3), 321–327.
Price, G.R., 1970. Selection and covariance. Nature 227 (5257), 520–521.
Promislow, D.E., 1991. Senescence in natural populations of mammals: a comparative study. Evolution 45 (8), 1869–1887.
Promislow, D.E., Tatar, M., et al., 1996. Age-specific patterns of genetic variance in Drosophila melanogaster. I. Mortality. Genetics 143 (2), 839–848.
Rand, D.A., Keeling, M., et al., 1995. Invasion, stability and evolution to criticality in spatially extended, artificial host–pathogen ecologies. Proc. Roy. Soc. B 259 (1354), 55–63.
Reznick, D.N., Bryant, M.J., et al., 2004. Effect of extrinsic mortality on the evolution of senescence in guppies. Nature 431 (7012), 1095–1099.
Ricklefs, R., 1998. Evolutionary theories of aging: confirmation of a fundamental prediction, with implications for the genetic basis and evolution of life span. Am. Nat. 152, 24–44.
Ridley, M., 1993. The Red Queen. Penguin, London.
Rousset, F., 2002. Inbreeding and relatedness coefficients: what do they measure? Heredity 88 (5), 371–380.
Rousset, F., 2004. Genetic Structure and Selection in Subdivided Populations. Princeton University Press, Princeton NJ.
Rousset, F.B.S., 2000. A theoretical basis for measures of kin selection in subdivided populations: finite populations and localized dispersal. J. Evol. Biol. 13, 814–825.
Skulachev, V.P., 1997. Aging is a specific biological function rather than the result of a disorder in complex living systems: biochemical evidence in support of Weismann's hypothesis. Biochemistry (Moscow) 62 (11), 1191–1195.
Socolar, J., Richards, S., et al., 2001. Evolution in a spatially structured population subject to rare epidemics. Phys. Rev. E. 63 (041908), 1–8.
Stearns, S.C., 2000. Life history evolution: successes, limitations, and prospects. Naturwissenschaften 87 (11), 476–486.
Tatar, M., Promislow, D.E., et al., 1996. Age-specific patterns of genetic variance in Drosophila melanogaster. II. Fecundity and its genetic covariance with age-specific mortality. Genetics 143 (2), 849–858.
Taylor, P., 1992. Altruism in viscous populations: an inclusive fitness model. Ecol. Evol. 6, 352–356.
Travis, J.M., 2004. The evolution of programmed death in a spatially structured population. J. Gerontol. A Biol. Sci. Med. Sci. 59 (4), 301–305.
Travis, J.M., Dytham, C., 1998. The evolution of dispersal in a metapopulation: spatially explicit, individual-based model. Proc. Roy. Soc. B 265 (1390), 17–23.
van Baalen, M., Rand, D.A., 1998. The unit of selection in viscous populations and the evolution of altruism. J. Theor. Biol. 193 (4), 631–648.
van Valen, L., 1973. A new evolutionary law. Evol. Theor. 1, 1–30.
Vaupel, J.W., Baudisch, A., et al., 2004. The case for negative senescence. Theor. Popul. Biol. 65 (4), 339–351.
Walker, D.W., McColl, G., et al., 2000. Evolution of lifespan in C. elegans. Nature 405 (6784), 296–297.
Weismann, A., Poulton, E.B., et al., 1891. Essays Upon Heredity and Kindred Biological Problems. Clarendon press, Oxford.
Williams, G., 1957. Pleiotropy, natural selection, and the evolution of senescence. Evolution 11, 398–411.
Williams, G., 1975. Sex and Evolution. Princeton University Press, Princeton NJ.
Wilson, D.S., 1997. Introduction: multilevel selection theory comes of age. Am. Nat. 150 (s1), S1–S21.