Programmed aging cannot be favored by natural selection in a fixed environment

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Aging is thought to be a consequence of intrinsic breakdowns in how genetic information is processed. But mounting experimental evidence suggests that aging can be slowed. To help resolve this mystery, I derive a universal mortality equation that governs the dynamics of an evolving population with a given maximum age. I solve it analytically and find that, remarkably, the structure of the solution is independent of the choice of fitness function. I confirm the solution computationally for three different fitness functions. I prove that, in a fixed environment, programmed aging cannot confer a long-term benefit.

Why do we get old? Darwin's theory of evolution is the result of mutation, inheritance and selection. It doesn't refer to death explicitly, but dying is a consequence of competition for finite resources, or when one life becomes the resource for another. Some mutants, ill equipped to cope with their environment, simply break down.

This accounts for the pervasiveness of death, but it says nothing about the universality of aging. The explanation for aging is fraught with debate. On the one hand, the canonical view is that aging is the result of intrinsic breakdowns in how genetic information is processed [1–5]. The selective pressure against these breakdowns declines throughout adult lifespan, in line with the future expected reproductive output [3].

On the other hand, many scientists believe that aging is programmed [6–12] Rather than being a fundamental and unavoidable attribute of biological life, aging is actively sought by evolution because it is advantageous. This group rejects the genetic breakdown argument because, while plausible, we don't know how much breakdown is imposed by the laws of physics. Biological life is, after all, one instance of a self-replicating machine, and our understanding of the thermodynamic constraints on such systems is poor [13, 14]. Once heretical, programmed aging is gaining traction because of a range of interventions that reverse aging markers [15]. At the same time, research in the field is surging, thanks to significant investment by longevity companies such as Altos Labs [16].

Several models have been put forward to support programmed aging [8], which were reviewed in detail by Kowald and Kirkwood [3]. These models "have relied extensively on simulation techniques rather than on mathematical analysis. While analytical (mathematical) models generally have the advantage of clarity, they quickly become intractable when the phenomenon to be analysed depends on features such as spatial effects, which are at the heart of several of the claims made in favor of programmed aging" [3]. Spatial effects, while part of any physical manifestation of life, can have unforeseen consequences, such as kin selection, whereby reproductive benefit is transferred to relatives. This can cloud more basic aspects of the benefits of aging.

In this article I provide a simple mathematical framework for answering fundamental questions about the evolutionary benefits of programmed aging. My model is independent of the choice of fitness function and does not invoke spatial effects. I purposefully do not address how a population might evolve from an immortal one to a mortal one, which concerns the challenge of group selection. Potential mechanisms for doing so include violating mean-field assumptions commonly used in evolutionary biology [8]. Rather, I want to settle a more basic question: from an evolutionary perspective, is aging a trait worth fighting for in the first place? This is an important question, because if programmed aging is favored by natural selection, rather than being an inevitable consequence of genetic breakdowns, then it may be possible to devise genetic and pharmacological interventions to prolong life and combat disease.

In this article I do four things. First, I derive a simple mortality equation that governs the transition matrix $\mathbf{Q}$ of an evolving population with maximum age a. It is

$$(\mathbf{I} + \mathbf{MF} - \mathbf{Q})\mathbf{Q}^a = \mathbf{MF},$$

where $\mathbf{I}$ is the identity matrix, $\mathbf{M}$ is the mutation matrix shown in Fig. 1 and $\mathbf{F}$ is a diagonal matrix with the genotype fitnesses along the diagonal. This equation is remarkable because it only assumes mutation, inheritance and selection; it applies for any fitness function. Second, I solve the mortality equation in terms of the spectrum of eigenvalues of the transition matrix $\mathbf{Q}$, which completely determines the dynamics. I provide a geometric characterization of how these eigenvalues change as the maximum allowed age a increases, shown as the lines in Fig. 3. The solution has a special property: while the spectrum of eigenvalues depends on the fitness, how they change with the maximum age a is independent of the fitness. Third, I test my analytic solution of the mortality equation by explicitly solving it computationally for three different fitness functions: uniform fitness, Hamming fitness and overlap fitness. This is shown as the points in Fig. 3. The analytic solution is confirmed in all cases. Fourth, I show that, in a fixed environment, programmed aging cannot be favored by natural selection, regardless of the choice of fitness function. I conclude with three directions for future work, including an approach to understanding aging in a changing environment.

Mutation

In my model, we have a population of reproducing individuals with binary genotypes of length n. Thus there are 2^n different possible genotypes. For example for $n = 3$, these are $000, 001, 010, \ldots, 111$. The population vector is given by $\mathbf{p} = (p_1, \ldots, p_{2^n})$, which is the size of the subpopulations with genotypes $1, \ldots, 2^n$. For $n = 3$, p_1 is size of the subpopulation with genotype 000, p_2 is size of the subpopulation with genotype 001, and so on. Offspring are identical to their parents apart from a single point mutation in the genotype, that is, each child has one spelling mistake.

The process of mutation in the population can be captured by the mutation matrix $\mathbf{m}$, shown in Fig. 1. The 1s in each row–or equally column—indicate the different parents that can give birth to that row's genotype, keeping in mind that an offspring differs from its parent by a single bit. For example, for $n = 3$, the child genotype 001 can arise from mutations in the parents 000, 011 and 101, since these are the only genotypes that are one bit-flip away.

Eventually we will want our mutation matrix to be normalized, meaning that all the rows and columns add to one. But for now it is convenient to work with the unnormalized mutation matrix $\mathbf{m}$, and later normalize it by just dividing $\mathbf{m}$ by n to get $\mathbf{M}$. The mutation matrix $\mathbf{m}$ can be defined recursively in block form:

$$\mathbf{m}_{n+1} = \begin{pmatrix} \mathbf{m}_n & \mathbf{I}_n \\ \mathbf{I}_n & \mathbf{m}_n \end{pmatrix}, \quad \mathbf{m}_1 = \begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix}, \tag{1}$$

where $\mathbf{m}_n$ and $\mathbf{I}_n$ are $2^n \times 2^n$ and $\mathbf{I}$ is the identity matrix. We can find the eigenvalues of $\mathbf{m}$ as follows. Let $p_{\mathbf{m}_n}$ be the characteristic polynomial of $\mathbf{m}_n$, the roots of which

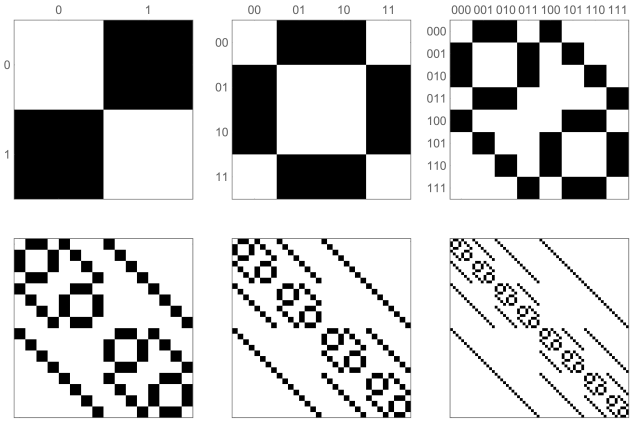

FIG. 1: **The first six unnormalized mutation matrices m.** These $2^n \times 2^n$ matrices, where white and black indicate 0 and 1, act to diffuse a population across genotype space via point mutations. The rows correspond to the all 0s genotype at the top to the all 1s genotype at the bottom, and likewise for the columns. The six panels are for genomes of size $n = 1$ to $n = 6$. The normalized mutation matrix is $\mathbf{M} = \mathbf{m}/n$, so that the columns and rows all add up to one.

are the eigenvalues of the matrix. Then

$$\begin{aligned} p_{\mathbf{m}_{n+1}}(\lambda) &= \det \begin{pmatrix} \lambda\mathbf{I}_n - \mathbf{m}_n & -\mathbf{I}_n \\ -\mathbf{I}_n & \lambda\mathbf{I}_n - \mathbf{m}_n \end{pmatrix} \\ &= \det(\mathbf{m}_n - (\lambda-1)\mathbf{I}_n) \cdot \det(\mathbf{m}_n - (\lambda+1)\mathbf{I}_n) \\ &= p_{\mathbf{m}_n}(\lambda)|_{\lambda=\lambda-1} \cdot p_{\mathbf{m}_n}(\lambda)|_{\lambda=\lambda+1}, \end{aligned}$$

where $p_{\mathbf{m}_0} = \lambda$. Thus the characteristic polynomial $p_{\mathbf{m}_{n+1}}$ is the product of $p_{\mathbf{m}_n}$ evaluated at $\lambda - 1$ and $p_{\mathbf{m}_n}$ evaluated at $\lambda + 1$. This recursive step can be understood visually though a Pascal's triangle of terms: the product of the terms in row n is the characteristic polynomial $p_{\mathbf{m}_n}$, where the rows start at 0:

$$\begin{array}{ccccccccc} & & & & \lambda & & & & \\ & & & \lambda-1 & & \lambda+1 & & & \\ & & \lambda-2 & & \lambda^2 & & \lambda+2 & & \\ & \lambda-3 & & (\lambda-1)^3 & & (\lambda+1)^3 & & \lambda+3 & \\ \lambda-4 & & (\lambda-2)^4 & & \lambda^6 & & (\lambda+2)^4 & & \lambda+4. \end{array} \tag{2}$$

We immediately see that the eigenvalues of $\mathbf{m}_n$ are $n, n-2, n-4, \ldots, -n$, with degeneracies $\binom{n}{0}, \binom{n}{1}, \ldots, \binom{n}{n}$. So the eigenvalues of $\mathbf{M}_n = \mathbf{m}_n/n$ are $1, 1-\frac{2}{n}, 1-\frac{4}{n}, \ldots, -1$, with the same degeneracies. The principal eigenvector of $\mathbf{M}_n$ is $(1, 1, 1, \ldots)$.

Selection

An environment amounts to an assignment of a fitness to each genotype, where genotypes with the same fitness are said to have the same phenotype. To give preferential treatment to certain genotypes, we need to define a fitness function. The fitness of each individual is determined by the distance of the genotype g from some target genotype $\tilde{g}$ which is optimally suited to the environment. The closer g is to the optimum $\tilde{g}$, the higher is the individual's fitness, and therefore reproduction rate, which is proportional to fitness. As the population reproduces and mutates, it drifts towards the vicinity of this optimum $\tilde{g}$. The way in which it does so critically depends on the kind of distance that is used. In principle any fitness can be related to a distance function, even if it is just a lookup table.

Let $\mathbf{f} = (f_1, \ldots, f_{2^n})$ be the vector of fitnesses for the 2^n genotypes, where $f_i \in [0, 1]$. Then the fitness matrix $\mathbf{F}$ is the diagonal matrix with $\mathbf{f}$ along the diagonal.

Let the maximum age a be the number of times that an individual reproduces before dying. Let's assume, for now, that $a = 1$. Then the distribution of the population at time t gets transformed to an updated distribution at time $t + 1$ according to the transition matrix $\mathbf{MF}$:

$$\mathbf{p}(t+1) = \mathbf{MF}\mathbf{p}(t). \tag{3}$$

While the key results in this article are independent of the specific fitness function $\mathbf{F}$, it is illustrative to consider actual examples. In Fig. 2 I show the matrices $\mathbf{M}$, $\mathbf{F}$ and $\mathbf{MF}$ for three different fitness functions: uniform, Hamming and overlap fitness. Later we will explain what these are and use them to test our theory.

Starting from a given initial population distribution at time $t = 0$, we can determine the distribution at time t by repeatedly applying the matrix $\mathbf{MF}$, or just raising it to a power:

$$\mathbf{p}(t) = (\mathbf{MF})^t \mathbf{p}(0).$$

The steady state distribution, which we reach in the limit of large t, is given by the principal eigenvector of the matrix $\mathbf{MF}$, and the long term growth rate is given by the eigenvalue of $\mathbf{MF}$ with the largest magnitude.

The mortality equation

The matrix $\mathbf{MF}$ tells us how a population with maximum age $a = 1$ evolves. What we really want, however, is to understand how a population evolves for an arbitrary a. I now derive a matrix polynomial which governs the transition matrix $\mathbf{Q}$ for a population with $a \geq 1$.

Let's start by considering $a = 2$. Let $\mathbf{x_1}$ be the size of the subpopulation with age 1 and genotypes $1, \ldots, 2^n$, and $\mathbf{x_2}$ be the size of the subpopulation with age 2 and genotypes $1, \ldots, 2^n$. Individuals with ages 1 and 2 can give birth, but all offspring are born with age 1. Let $\mathbf{p} = \mathbf{x_1} + \mathbf{x_2}$ be the total population size. Then

$$\mathbf{x_1}(t+1) = \mathbf{MF}\mathbf{p}(t) \quad \text{and} \quad \mathbf{x_2}(t+1) = \mathbf{x_1}(t). \tag{4}$$

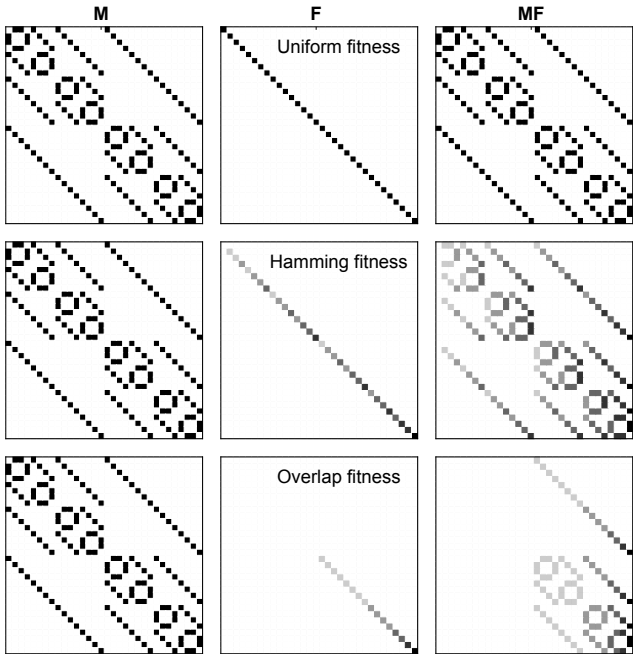

FIG. 2: **Mutation matrix M, fitness matrix F and their product for different fitness functions.** In all cases the genome length is $n = 5$, and $\mathbf{M}$ is the same in each row. **Uniform fitness.** The fitness is equal to 1 for all genotypes. **Hamming fitness.** The fitness is the fraction of bits at which the genotype and the target genotype 11111 match. **Overlap fitness.** The fitness is the length of the longest initial substring over which the genotype and the target genotype 11111 match, divided by n. (For clarity, we show the non-zero entries of $\mathbf{M}$, which are $1/n$, as black rather than gray.)

Inserting these into $\mathbf{p}(t+1) = \mathbf{x_1}(t+1) + \mathbf{x_2}(t+1)$ gives

$$\mathbf{p}(t+1) = \mathbf{MF}\mathbf{p}(t) + \mathbf{x_1}(t).$$

Incrementing both sides by one time step and again applying eq. (4) gives

$$\mathbf{p}(t+2) = \mathbf{MF}\mathbf{p}(t+1) + \mathbf{MF}\mathbf{p}(t). \tag{5}$$

Our goal is to obtain the transition matrix $\mathbf{Q}$ for which $\mathbf{p}(t+1) = \mathbf{Q}\mathbf{p}(t)$. Writing (5) in terms of $\mathbf{Q}\mathbf{p}(t)$, we find $\mathbf{Q}^2\mathbf{p}(t) = \mathbf{MF}(\mathbf{Q} + \mathbf{I})\mathbf{p}(t)$, and so $\mathbf{Q}$ satisfies

$$\mathbf{Q}^2 = \mathbf{MF}(\mathbf{I} + \mathbf{Q}).$$

We can take a similar approach for general maximum age a. Now we need to keep track of a subpopulation vectors, with ages $1, \ldots, a$. We use $\mathbf{x_1}, \ldots, \mathbf{x_a}$ to indicate these vectors. Individuals of all ages can give birth, but all offspring are born with age 1. Let

$$\mathbf{p}(t) = \mathbf{x_1}(t) + \ldots + \mathbf{x_a}(t) \tag{6}$$

be the total population size, of all ages. Then

$$\mathbf{x_1}(t+1) = \mathbf{MF}\mathbf{p}(t) \quad \text{and} \quad \mathbf{x_{i+1}}(t+1) = \mathbf{x_i}(t). \tag{7}$$

Inserting these into eq. (6) evaluated at time $t+1$ gives

$$\mathbf{p}(t+1) = \mathbf{MF}\mathbf{p}(t) + \mathbf{x_1}(t) + \ldots \mathbf{x_{a-1}}(t).$$

Incrementing the time by 1 and again applying eq. (7),

$$\mathbf{p}(t+2) = \mathbf{MF}\mathbf{p}(t+1) + \mathbf{MF}\mathbf{p}(t) + \mathbf{x_1}(t) + \ldots \mathbf{x_{a-2}}(t).$$

Repeating this process until all of the $\mathbf{x}$s are converted to $\mathbf{p}$s, we obtain

$$\mathbf{p}(t+a) = \mathbf{MF}(\mathbf{p}(t+a-1) + \ldots + \mathbf{MF}(\mathbf{p}(t).$$

Then, with $\mathbf{p}(t+1) = \mathbf{Q}\mathbf{p}(t)$, $\mathbf{Q}$ satisfies

$$\mathbf{Q}^a = \mathbf{MF}(\mathbf{I} + \mathbf{Q} + \ldots + \mathbf{Q}^{a-1}). \tag{8}$$

Since, for a general matrix $\mathbf{A}$,

$$\mathbf{I} + \mathbf{A} + \ldots + \mathbf{A}^{a-1} = (\mathbf{A}^a - \mathbf{I})(\mathbf{A} - \mathbf{I})^{-1},$$

we can write

$$(\mathbf{I} + \mathbf{MF} - \mathbf{Q})\mathbf{Q}^a = \mathbf{MF}. \tag{9}$$

I call eq. (9) the mortality equation, and it is one of the two main results of this article. Its concision belies its power. It gives the transition matrix for a population with maximum age a in terms of the transition matrix or a population with maximum age 1, for any fitness function $\mathbf{F}$. Notice that while the compact eq. (9) has degree $a + 1$, it can always be reduced to degree a by dividing through by $\mathbf{Q} - \mathbf{I}$ to give eq. (8).

Solving the mortality equation

With our mortality equation in hand, what kind of

meaning can we extract from it? It is unusual in that it is a polynomial equation in terms of matrices rather than numbers: $\mathbf{I}$ and $\mathbf{MF}$ play the role of 1 and a constant, and we are solving the polynomial for $\mathbf{Q}$. However, matrix polynomials are subject to most of the same machinery used to solve ordinary polynomials, with extra care required when taking roots.

Taking roots of a matrix works as follows. A matrix $\mathbf{A}$ is diagonalizable if there exists an invertible matrix $\mathbf{P}$ and a diagonal matrix $\mathbf{\Lambda}$ such that $\mathbf{A} = \mathbf{P}\mathbf{\Lambda}\mathbf{P}^{-1}$. The roots of such an $\mathbf{A}$ are then $\sqrt[i]{\mathbf{A}} = \mathbf{P}\sqrt[i]{\mathbf{\Lambda}}\mathbf{P}^{-1}$, where $\sqrt[i]{\mathbf{\Lambda}}$ just amounts to taking the roots of the diagonal elements, bearing in mind to take all i roots of each.

There is a family of a solutions to the mortality equation, which we denote $\mathbf{Q}_1, \ldots, \mathbf{Q}_a$. For $a = 2$, $\mathbf{Q} = (\mathbf{M} \pm \sqrt{\mathbf{M}^2 + 4\mathbf{M}})/2$. Even though $\mathbf{M}$ and $\mathbf{F}$ are real, the $\mathbf{Q}_i$ and their eigenvalues can be complex.

Fortunately, there is a shortcut for computing the eigenvalues of $\mathbf{Q}_i$ from those of $\mathbf{MF}$. By the Cayley Hamilton theorem, the eigenvalues of $\mathbf{Q}_i$ have the same functional relation to the eigenvalues of $\mathbf{MF}$ as the matrix $\mathbf{Q}_i$ does to the matrix $\mathbf{MF}$. For a given eigenvalue λ of $\mathbf{MF}$ (recall there are 2^n such eigenvalues), there is a family of a solutions, or roots, to the analogue to eq. (9), but for numbers rather than matrices:

$$(1 + \lambda - \mu)\mu^a = \lambda. \tag{10}$$

The eigenvalues of $\mathbf{Q}_1$ are the first root of eq. (10) for each of the λ; those of $\mathbf{Q}_2$ are the second root for each of the λ; and so on. Eq. (10) is the second of the two main results of this article. Notice that, as for the matrix $\mathbf{Q}$ in eq. (9), eq. (10) has degree $a+1$. But it can always be reduced to degree a by dividing by $\mu - 1$ to give $\mu^a = \lambda(1 + \mu + \ldots + \mu^{a-1})$. The solution $\mu = 1$ is spurious, and we neglect it in what follows.

Writing eq. (10) as $\mu^a = \lambda/(1 + \lambda - \mu)$, and recalling $\lambda \leq 1$, we see that the equation has only one positive real root, disregarding the spurious $\lambda = 1$. This is because the monomial and the shifted hyperbola intersect at 1 and one other positive point. The positive real root is the one with the largest magnitude, as I prove in more recent work showing that the complex roots are of secondary importance [17].

The positive real solutions of eq. (10) are plotted in Fig. 3. For $a = 1$, eq. (10) reduces to $\mu = \lambda$. This is expected, since for $a = 1$ the transition matrix $\mathbf{Q}$ is just $\mathbf{MF}$. This eigenvalue relation is the bottom line in Fig. 3. For $a = \infty$, we can also solve for μ explicitly. We know that $\mu > 1$, because otherwise μ^a in eq. (10) vanishes but $1 + \lambda - \mu$ is finite. So μ^a is infinite, meaning $1 + \lambda - \mu$ must vanish, that is, $\mu = \lambda + 1$. This is the top line in Fig. 3. For intermediate values of a, the positive eigenvalues μ are between these two lines. For $a = 2$, $\mu = (\lambda + \sqrt{\lambda^2 + 4\lambda})/2$. As a grows, the lines are successively higher, ultimately converging to $\mu = \lambda + 1$.

Testing our theory with three fitness functions

To test the grey lines in Fig. 3, which are the dominant root of eq. (10), I wrote a program to explicitly compute the transition matrices $\mathbf{Q}$ for three very different fitness functions: uniform fitness, Hamming fitness and overlap fitness, described below. I then computed the spectrum of eigenvalues of these matrices and found that they agree exactly with prediction, as shown in Fig. 3,

First, I considered uniform fitness, in which every genotype has fitness 1 ($\mathbf{F} = \mathbf{I}$). Uniform fitness diffuses the population over the hypercube, smoothing it out towards a uniformly distributed population. The spectrum of eigenvalues for uniform fitness is shown in Fig. 3A.

Second, I considered the Hamming fitness h. This corresponds to a natural notion of distance: the number of edges on the hypercube that must be traversed to get from one corner to another. The Hamming fitness is one minus $1/n$ times the Hamming distance between some genotype g and the optimal genotype $\tilde{g}$, that is, the fraction of bits at which g and $\tilde{g}$ match. For example, if $\tilde{g}$ is 01100 and g is 11000, then $h = 3/5$. The spectrum of eigenvalues is shown in Fig. 3B.

Third, I considered the overlap fitness v. This is $1/n$ times the length of the longest initial substring over which some genotype g and the optimal genotype $\tilde{g}$ match. For example, if $\tilde{g}$ is 01100 and g is 01010, then the longest initial overlap is 2, since the first two bits of g and $\tilde{g}$ match but not the first three, and $v = 2/5$. The overlap fitness is unusual in that it allows jump discontinuities: one mutation in the first part of the string can change the fitness from high to low or low to high. The spectrum of eigenvalues is shown in Fig. 3C.

Discussion

The mortality equation provides a framework for gaining quantitative insights into the consequences of programmed aging. Its most striking aspect is its universality. It tells us how the spectrum of eigenvalues governing the dynamics of the population changes, independent of the choice of fitness function. The fitness $\mathbf{F}$ alone governs the horizontal placement of the eigenvalues in Fig. 3, whereas the maximum allowed age a alone governs their vertical placement. Shifting a causes the eigenvalues to jump up and down vertically between the lines. This is a key and surprising property, because in general quantitative claims about evolving systems assume a specific fitness function, unlike the situation here.

In a fixed environment, the long-term growth rate of the population is set by the largest eigenvalue μ of $\mathbf{Q}$. As Figs. 3 illustrates, this increases with the maximum age a, starting from $\mu = \lambda$ for $a = 1$ and asymptotically approaching $\mu = \lambda + 1$ as a approaches ∞. In the long run, the growth rate of the population increases with a, and the fastest growing population is the immortal one. In a fixed environment, there is no evolutionary advantage afforded by programmed aging.

This immediately raises the question of whether there is an advantage in a changing environment, where the population is continually out of equilibrium [19, 20].

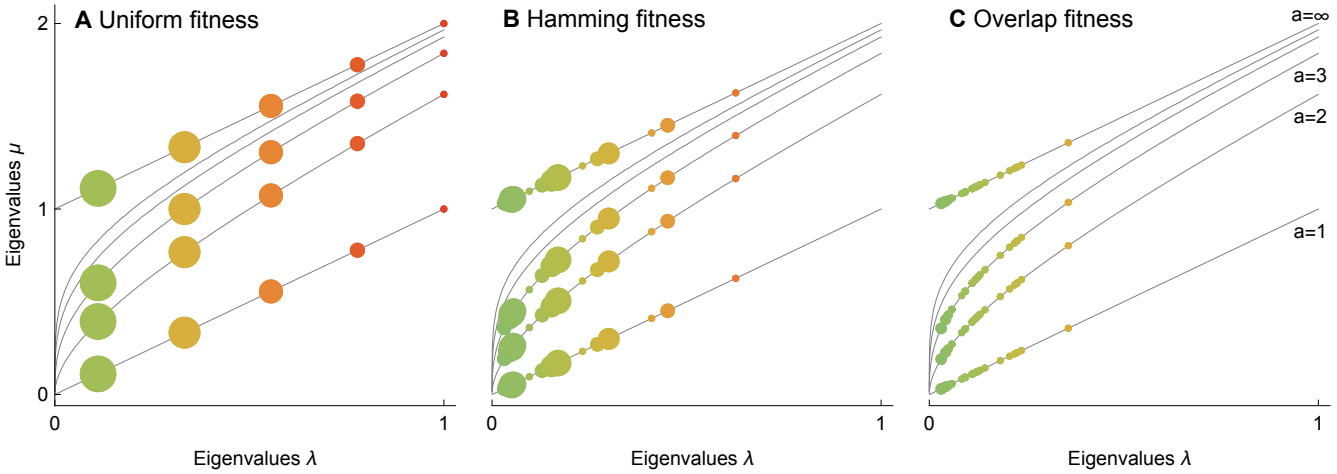

FIG. 3: **Dominant eigenvalues for different maximum ages. Theory.** For any eigenvalue λ of the transition matrix $\mathbf{MF}$ ($a = 1$), the only positive eigenvalue μ of the transition matrix $\mathbf{Q}$ ($a \geq 1$) is given by the lines, which are solutions to eq. (10). Remarkably, the fitness $\mathbf{F}$ alone determines the horizontal placement of the eigenvalues, but the maximum allowed age a alone determines their vertical placement. **Confirmation.** I tested these predictions by explicitly solving the mortality equation computationally for three different fitness functions: uniform, Hamming and overlap fitness. For each, I show the spectrum of positive real eigenvalues for $a = 1$, 2, 3 and ∞, and genome length $n = 9$, which perfectly matches the theory. The degeneracy of each eigenvalue is proportional to the disk radius cubed.

The answer is surprisingly elusive. On the one hand, the equilibration time plays an important role, because the ability to adapt quickly can compensate for a slower growth rate. This is analogous to how, in a race around Britain, a slower yacht can still win by tacking faster. On the other hand, for programmed aging to be beneficial, there must exist some modes which grow more slowly for higher maximum age a.

The mortality equation possesses an abundance of structure, beauty and predictive power. It has the potential to spark significant new research activity on fundamental aspects of aging. In particular, here are three challenges worthy of further investigation. One, mentioned above, is understanding the approach to equilibrium in a changing environment. As I prove in more recent work [17], a population equilibrates faster as the maximum age a decreases. But more work is needed to characterize the different modes.

A second challenge is to find an exact solution for a specific fitness function—a kind of "hydrogen atom" of the mortality equation. This would help clarify under what conditions, if any, programmed aging is favored by natural selection. The Hamming fitness is an attractive candidate, but other choices of the fitness function may prove more tractable.

A third challenge is modeling the effect of kin selection. The mortality equation can be generalized to account for kin selection by inserting a constant in front of $\mathbf{I}$ in eq. (9). Initial considerations suggest that even a small amount of kin selection could shift the balance in favor of programmed aging.

A mathematical theory of evolvability is one of the most important challenges of our times [21]. Understanding the causes and susceptibility of programmed aging is a key step to devising interventions to prolong life and combat disease.

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