The age-specific force of natural selection and biodemographic walls of death

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W. D. Hamilton's celebrated formula for the age-specific force of natural selection furnishes predictions for senescent mortality due to mutation accumulation, at the price of reliance on a linear approximation. Applying to Hamilton's setting the full nonlinear demographic model for mutation accumulation recently developed by Evans, Steinsaltz, and Wachter, we find surprising differences. Nonlinear interactions cause the collapse of Hamilton-style predictions in the most commonly studied case, refine predictions in other cases, and allow walls of death at ages before the end of reproduction. Haldane's principle for genetic load has an exact but unfamiliar generalization.

biodemography | hazard functions | senescence

The best-known formula at the intersection of genetics and demography is doubtless W. D. Hamilton's "age-specific force of natural selection," the starting point for the models in ref. 1 applied in this paper. Hamilton (2, 3) differentiated a measure of fitness, Lotka's intrinsic rate of natural increase, with respect to an increment to age-specific mortality at an age a. Thus, he obtained a linear approximation for loss in fitness due to any deleterious mutations that raised mortality at an age a. The greater the loss in fitness, the faster should mutant alleles be selected out of a population, and the fewer should be found at equilibrium as recurring mutations balance natural selection.

By this route, Sir Peter Medawar's concept of mutation accumulation as an evolutionary reason for senescence takes on mathematical form. As in refs. 4–6, richly developed in ref. 7, the idea involves genetic load produced by large numbers of mildly deleterious mutations occurring at widely separated loci, each with some small age-specific effect on vital schedules.

Hamilton's work has been assessed and extended by Baudisch (8). Sophisticated genetic models of mutation–selection balance are available (9). Demographers mainly put up with less sophisticated models of the genome in return for more refined treatments of age-specific structure, as we do here. Age-specific predictions for vital schedules may be robust to details of genetic specification, in line with a principle of Haldane (10), which equates the population loss in fitness from genetic load to the total mutation rate, independent of the form of action of mutations.

Current interest has been stimulated by the expansion of biodemography, reviewed in refs. 11–14, and by the appreciation of two widely occurring cross-species commonalities in graphs of mortality rates as functions of age: exponential increase at adult ages (the "Gompertz–Makeham" mortality pattern) and plateau-like shapes at older ages. Working with an appealingly simple specification, Brian Charlesworth (15) gave an elegant demonstration that Gompertz–Makeham mortality could be predicted exactly by the Hamilton-based linear approximate model. He also proposed an optional fix that would lead to plateaus at extreme ages. In Charlesworth's setting, a "wall of death" with infinite mortality rates and zero survivorship can occur only at an upper age limit to fertility, if one is imposed.

The theory built on Hamilton's formula thus offers one route toward accounting for remarkable cross-species demographic regularities. However, Hamilton's formula fails to be self-consistent. Its reliance on linear approximation requires total increments to age-specific mortality to stay small where the formula predicts them to grow large.

Nonlinearity is woven into the fitness measure. As deleterious mutations arise, their overall effect differs from the sum of their individual effects. Diminished survival at any one reproductive age necessarily leaves less reproduction to be lost by a drop in survival at any other reproductive age. This interaction, a key feature of mutation accumulation, is set to zero in the linear framework. If total effects were small enough, the conclusions might be broadly accurate, but the theory rests on the opposite principle: These small individual effects accumulate to completely reshape the mortality curve. Furthermore, the linear approximation finesses the treatment of population heterogeneity and genetic variance on which the mechanism of natural selection actually depends.

In ref. 1 we developed a fully nonlinear, explicitly heterogeneous, age-specific model for mutation accumulation. In this paper we apply our model to Hamilton's and Charlesworth's setting. Despite the inconsistencies in the linear approximate model, it has seemed reasonable to hope that salient features of its predictions would be preserved. Simulations by Charlesworth (15) incorporating some nonlinear interactions have bolstered this belief. The expression for the generalized age-specific force of natural selection that we derive also encourages us to expect similarities. However, hopes deceive. We go on to establish four conclusions, all of them surprising:

- In cases that have been thought to lead directly to Gompertz–Makeham mortality, the linear model breaks down under the weight of nonlinear interactions. An equilibrium ceases to exist, and accumulating mutations drive survival to zero at every adult age.
- Cases exist in which walls of death occur before any prespecified oldest age for reproduction.
- Plateaus appear not so much as an option but as an obligate feature of those mutation accumulation models for which equilibria exist.
- Generalization of Haldane's principle requires a new functional form.

Like the linear models, our nonlinear model is an infinite-population model in continuous time. It is presented in ref. 1 (chapter 2) and shown in chapters 5–8 to be a limiting form of standard discrete-generation genetic models such as those of refs. 16 and 17 in an asymptotic regime where selection and mutation are weak relative to recombination. The representation of the genetic structure is kept somewhat stylized to allow elaboration of the demographic structure. The model follows in the tradition of the classic paper of Kimura and Maruyama (18). Inheritance is diploid, with random mating and weak selection, but fitness is calculated for haploid

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individuals, allowing questions of dominance between alleles to be set aside. At each of a large or infinite number of sites is found either a wild-type or a deleterious mutant allele. Alleles with the same effect on the hazard function are treated as if they were copies of the same allele, although found at different sites. Back mutation is taken to be negligible.

A randomly selected member of the population carries some collection of such mutant alleles, and the state of the population is described by a joint probability distribution for the counts of alleles of different kinds, that is, of alleles acting at different ages. The linear models posit Poisson distributions, consistent with a derivation found on p.137 of ref. 19. Our model recovers this Poisson property for solutions via assumptions about recombination spelled out formally in ref. 1 (chapter 4).

Genetic recombination matters in nonlinear models. The effect of recombination acting on a more rapid time scale than mutation and selection is to erase linkage disequilibrium among sites involved in the mutation accumulation process. Such sites would be expected to be sparsely distributed and widely separated on chromosomes, so the assumption accords with common sense. An alternative nonlinear model without recombination is presented in ref. 20. In that model, distributions for allele counts are not Poisson, the counterpart of the force of natural selection is a complicated object depending on a whole suite of probabilities, and absence of mixing allows the persistence of subpopulations untouched by mutation, bypassing *Theorems 1, 2,* and *3*. Charlesworth's models, although not explicitly adducing recombination, incorporate Poisson distributions consistent with the assumptions about recombination adopted here.

Hamilton's Formula

A description of Hamilton's formula is the starting point for the understanding of our results. Some demographic terminology is helpful. Let ζ be a random variable that represents the lifespan of an individual picked at random from a population, or from a subpopulation sharing some attribute. The survivorship function $\ell_x := \mathbb{P}\{\zeta > x\}$ is the probability of survival from birth to age x. The cumulative hazard at age x is $-\log \ell_x$. The hazard function itself at age x is minus the derivative of the logarithm of the survivorship, when the derivative exists. The product of the survivorship function ℓ_x with the age-specific fertility rate f_x is the net maternity function $f_x \ell_x$. Fertility for males is taken to be governed by the rates for their female mates. The models do not explicitly segregate individuals by sex. Fertility vanishes below an age of maturity $\alpha \geq 0$, and sometimes a maximum age of nonzero fertility β is also imposed. The area under the net maternity function ($\int_0^\infty f_x \ell_x \, dx$) is the net reproduction ratio, or NRR. The NRR measures generational replacement, the ratio of the size of the next generation to the current one.

If the survivorship function ℓ_x and fertility schedule f_x do not change over time, then they lead to a population with an unchanging proportional distribution of ages called a stable population. The growth rate of the stable population (the slope of the logarithm of population size over time) is Lotka's intrinsic rate of natural increase r. Lotka's r is the unique real root of the Euler–Lotka equation $1 = \int e^{-r\,x} f_x \ell_x \, dx$—the unique real zero of the logarithm of the Laplace Transform of the net maternity function. On evolutionary time scales, the parameter r is assumed to have been close to zero, the growth rate of a stationary population.

In Hamilton's setting, the effect on age-specific mortality of each mutant allele is taken to be concentrated at a single age, in what we call "point-mass increments." Notionally speaking, the increments are like Dirac delta functions added onto the hazard function. Formally, a step function with a single upward step of size η at an age m is added onto the cumulative hazard function. The age of onset m can be used to index the corresponding mutant allele. Like the cumulative hazard, f_x and ℓ_x need not be continuous functions of age, but age itself is continuous, not discrete. We rule out point masses or "birth pulses" in fertility that could prevent convergence to stable populations.

Differentiating Lotka's r with respect to η at $\eta = 0$ yields Hamilton's formula for the force of natural selection $w(m)$ at age m:

$$w(m) = \int_m^\infty f_y \ell_y e^{-ry} \, dy \Big/ \int_0^\infty y \; f_y \ell_y e^{-ry} \, dy.$$

The denominator, the mean age of childbearing in the stable population, is an expression for generation length. With time measured in generations and Lotka's rate set to the stationary value $r = 0$, $w(m)$ is $\int_m^\infty f_y \ell_y \, dy$, the expected number of offspring produced after age m by an individual chosen at random from the population, offspring that would be lost by death at age m. In Hamilton's formula, f_x and ℓ_x are baseline schedules, unadjusted for mutational effects.

As we have said, Hamilton's expression gives a linear approximation to the fitness cost of mutations that add point-mass increments. The loss from N such mutations is being approximated by $N\eta$ times $w(m)$, even though the fitness itself depends exponentially on N and η. Deleterious mutations are taken to be occurring at a rate q, and accumulating. For outflow $N\eta w(m)$ due to selection to balance inflow q due to mutation at equilibrium, the linear model sets $N \approx q/(\eta w(m))$. The approximation for the increment to the hazard function is then $N\eta = (\eta q)/(\eta w) = q/w$, independent of the size η of the effect (15).

Hamilton's formula applies in principle to favorable as well as to deleterious mutations. However, outside the context of mutation accumulation the formula is uninformative with respect to age-specific shapes of vital schedules. Any recurring favorable mutation eventually goes to fixation. The rapidity of fixation does not matter to the ultimate contribution.

The following simple example, of prime importance, highlights the approximations at stake. Baseline survivorship, now denoted by $\ell_x(0)$, results from a constant exogenous hazard of level λ and equals $\exp(-\lambda x)$. Fertility is constant at $f_x \equiv f$, with $f = \lambda$ to achieve a stationary population, that is, $r = 0$. Then, with time measured in generations, $w(m) = e^{-\lambda m}$.

The quantity $w(m)$ is the total net fertility beyond age m. For Hamilton, $w(m)$ serves as a selective cost per unit increment in hazards. The loss in fertility among individuals carrying N alleles that each impose a burst in hazards at age m of size η is approximated by $N\eta$ times the per-unit cost. If losses added up in this linear fashion, losses from $N\eta$ units would balance a rate q of new mutations only if $N\eta w(m) = q$, resulting in $N\eta = q \exp(\lambda m)$, yielding finally a total fitness cost of q.

We can also calculate the loss in fertility for this example directly. A burst of hazards at age m reduces survivors proportionately at all ages above m, entailing a loss in fertility of $(1 - \exp(-q \exp(\lambda m)))\exp(-\lambda m)$. When m is big, N is big, and this loss in fertility is much less than the value q arising from the linear model. This mismatch is the inconsistency noted in the Introduction. With late-acting mutations, the linear model requires large numbers of alleles to achieve mutation–selection balance, and large numbers of alleles defeat the linear approximation.

A natural next step would be to dispense with the approximation and solve directly for N from the nonlinear formula for selective cost. The marginal cost of an additional allele of any type could be measured, not with respect to baseline hazards, but with respect to hazards generated by equilibrium numbers of other mutations. This strategy is half the story behind our nonlinear model. The other half pertains to heterogeneity. The count N is not fixed but random, assumed to be Poisson-distributed in the linear model and shown to be Poisson-distributed in ref. 1. Fertility costs of hazard increments need to be calculated

taking into account this variability in genetic load across members of the population. Together, these two innovations are at the heart of the nonlinear model.

Returning to our example, consider now the predictions of the linear approximate model when mutations with effects concentrated at age m occur at a uniform rate q for each positive m. We still have $N(m)\eta = q\exp(\lambda m)$ because the linear assumption keeps the presence of other alleles from affecting the selective pressure on each one. Alleles acting at m affect the cumulative hazard at ages $x > m$. If in this example $\theta(m,x)$ is the indicator function equaling 1 when $x > m$ and zero else, the $N(m)$ alleles contribute $q\exp(\lambda m)\,\theta(m,x)$ to the cumulative hazard, and the total contribution at x is given by $\int q\exp(\lambda m)\,\theta(m,x)\,dm$. Integrating over m and differentiating with respect to x gives the increment to the hazard function itself, $h(x) = q\,e^{\lambda x}$. The overall predicted hazard is the sum of a constant baseline hazard λ and an exponential (Gompertz–Makeham) age-specific increment, as derived by Charlesworth (15).

As we shall see, the main steps in this derivation have their counterparts in the nonlinear model, as do the refinements due to Charlesworth, mentioned in the Introduction. The results in the following section, however, reveal dramatic differences in outcomes.

Results

Nonlinear Force of Natural Selection. Formal specification of our model within the general framework of ref. 1 is provided in *Materials and Methods*. Proofs are given in *SI Text*. For our results, what matters is the nonlinear force of natural selection $F_r(m)$, the counterpart of the Hamilton $w(m)$. In general $m \in \mathcal{M} = \mathbb{R}^+$ indexes mutations by their age of effect (not genome position), and $r \in L_+^\infty(\mathcal{M})$ (the space of essentially bounded nonnegative measurable functions on $\mathcal{M}$) represents a population mean density for mutations, as they are distributed over the range of possible ages. (This r, essentially replacing N by its mean value, has no connection to Lotka's r.) Similarly, $q \in L_+^\infty(\mathcal{M})$ represents a rate of new mutations. The novelty is that F, unlike w, depends on all of r, and so on all of the mutant alleles already present. When r_t represents the density at time t, starting from $r_0 \equiv 0$, the derivative of $t \mapsto r_t$, the increase due to new mutations minus the decrease due to natural selection, satisfies a nonlinear dynamical equation:

$$\frac{dr_t(m)}{dt} = q(m) - r_t(m)F_{r_t}(m). \qquad [1]$$

What is F? For $r \in L_+^\infty(\mathcal{M})$, we have $F_r : \mathcal{M} \to \mathbb{R}^+$, a map derived from a selective cost function S defined in *Materials and Methods*. In a sense made precise there, $S(g)$ records the decrement to the NRR associated with a fixed collection of mutant alleles g. The random collection of mutant alleles carried by a randomly chosen individual is a Poisson point process G on $\mathcal{M}$ with intensity measure $r(m)\,dm$. (The points of the random scatter G are elements of $\mathcal{M}$, not instants of time.) Our force of selection $F_r(m)$ is the average marginal increase in selective cost to an individual with random genotype G, due to adding an extra mutant allele of type m. It equals

$$F_r(m) = \int_\alpha^\infty \left(1 - e^{-\eta(m)\theta(m,x)}\right) f_x\,\mathcal{L}_x^{(r)}\,dx, \qquad [2]$$

where $\mathcal{L}_x^{(r)}$ represents the aggregate survivorship function for the population. Writing $\ell_x(g)$ for the survivorship of an individual carrying the collection of mutant alleles g and using $\mathbb{E}_r$ to denote averages over realizations G of a Poisson point process with intensity r,

$$\mathcal{L}_x^{(r)} := \mathbb{E}_r\left[\ell_x(G)\right] = \ell_x(0)\exp\left(-\int_{\mathcal{M}} \left(1 - e^{-\eta(m')\theta(m',x)}\right) r(m')\,dm'\right). \qquad [3]$$

In general, $\eta(m)$ gives the size and $\theta(m,x)$ gives the shape of an age-specific increment to the cumulative hazard at age x from mutant allele m, η being positive and bounded and θ, called the effect "profile," being nonnegative, bounded, and monotone nondecreasing in x for fixed m. The baseline net maternity function $f_x\ell_x(0)$ is assumed to be integrable and bounded with support $[\alpha,\beta]$, where $0 \le \alpha < \beta \le \infty$, and $\ell_x(0) > 0$ for $x < \beta$.

Bounded equilibria are covered in ref. 1 (chapter 3). We are concerned here with more inclusive asymptotics, in which the mean density of mutant alleles may grow without bound for effects at ages where remaining fertility drops toward zero. Starting from $r_0 \equiv 0$, our r_t is monotone nondecreasing in t for each m, and so increases to some r_* with values in $[0,\infty]$ (*SI Text*, *Lemma 1*). For every age x, $\mathcal{L}_x^{(r_t)}$ is monotone nonincreasing in t. The limit $\mathcal{L}_x^*$ is the aggregate survivorship function at equilibrium, a nonincreasing function of age x that reaches zero at some $\omega \le \infty$. When ω is finite, it is the age of a wall of death at which the cumulative hazard goes to infinity and aggregate survivorship reaches zero.

When we specialize to Hamilton's case of point-mass increments and identify m with the age of onset, $\theta(m,x)$ is the indicator function for $\{m < x\}$. The last two equations both simplify. The integral over x in Eq. **2** comes to run from m to infinity and the integral over m' in Eq. **3** comes to run over ages from α to x. The total increase h in the aggregate population hazard at age y implied by any intensity r is $h(y) := (1 - e^{-\eta(y)})\,r(y)$. When baseline survivorship is differentiable, we arrive at a decomposition of the aggregate hazard as a sum of independent competing risks $\lambda(y)$ due to baseline hazards and $h(y)$ due to genetic load. When h is calculated from a candidate equilibrium intensity $r = r_* = \lim r_t$, point-mass profiles imply $h < \infty$ on (α,ω) and $h = \infty$ on (ω,∞).

For simplicity, we generally omit juvenile mortality and let λ and q start at age α. Using h we define a monotone nonincreasing function:

$$T(m) := \int_m^\infty f_x \exp\left(-\int_\alpha^x \left[\lambda(y) + h(y)\right] dy\right) dx. \qquad [4]$$

The function $T(m)$ is the expected remaining fertility at age m. In the case of constant fertility it is proportional to the column for "remaining person-years" in the population life table. The equilibrium condition for point-mass increments can be written in terms of the h and T functions defined from r_* in the form

$$q(m) = h(m)\,T(m). \qquad [5]$$

The equilibrium equation does not involve η, and so the equilibrium hazard rate is independent of the sizes of effects as in Hamilton's model.

Equilibrium Collapse. As we have seen, an elementary linear model with point-mass increments leads exactly to Gompertz–Makeham hazards under the linear approximate model. It may be surprising, then, that accounting for nonlinear interactions does not just shift the equilibrium but prevents the existence of any equilibrium in this elementary case and generalizations of it, no matter how tiny the background rate of mutations.

Theorem 1. *Let the mutation rate $q(m)$ be bounded below by a constant $q_0 > 0$ beyond an age of maturity $\alpha \ge 0$ and vanish for $m < \alpha$. For some $\eta_0 > 0$ let the action profiles θ and effect sizes η satisfy*

$$\theta(m,x) = 0 \text{ for } x \le m,$$
$$\eta(m)\theta(m,x) \ge \eta_0 > 0 \text{ for } x > m.$$

Then, starting from $r_0 \equiv 0$, the intensity function $r_t(m)$ diverges monotonically to infinity as $t \to \infty$ for all $m > \alpha$.

Full proofs are given in *SI Text*. In the case with $\eta(m) \equiv 1$, and $\theta(m,x) = 1_{\{m<x\}}$ we show that if ω were greater than α, then the equilibrium equation would lead to the contradiction $\lim_{m\uparrow\omega} T(m) > 0$. The comparisons lemma 3.15 from ref. 1 extends this result to the more general θ and η of the theorem.

Charlesworth (15) relaxed the assumption of point-mass increments and treated increments drawn from a translation family, in which the counterpart of $\theta(m,x)$ vanishes for $x < m$ and depends only on $x - m$. Gompertz–Makeham hazards were still predicted at older ages beyond a threshold age. We conjecture that *Theorem 1* can be extended to cover such cases as well.

Early Walls of Death. In the light of *Theorem 1*, the question arises whether the full nonlinear model ever allows a bounded equilibrium r_* on a bounded but nonempty subset $\mathcal{M}_*$, with a corresponding wall of death such as the linear approximate model predicts at and only at a maximum age of nonzero fertility. The answer to this question is yes. The examples in the next theorem are artificial but theoretically revealing. In contrast to the implications of the linear model, under the nonlinear model a wall of death can occur at an age before the end of reproduction.

Theorem 2. *For each $\omega \in (\alpha, \infty)$ there exists a choice of mutation rate function $q(m)$ that yields a solution r_t to Eq. **1** with the properties that as $t \to \infty$ we have $r_t \uparrow r_* < \infty$ on $\mathcal{M}_* = (0, \omega)$ and $r_t \uparrow \infty$ on (ω, ∞) and as $m \uparrow \omega$ we have $r_*(m) \to \infty$. A family of such solutions can be constructed with point-mass profiles, constant positive f, λ, and η on (α, ∞), and $r_0 \equiv 0$.*

The proof in *SI Text* exploits a differential equation for T and constructs a family of examples indexed by a shape parameter ϕ in (0, 1). For a fixed level of constant baseline hazard λ, we can arrange for a wall of death to occur at any given age ω beyond α by adjusting the total selective cost s in $(0, \infty)$ to make $\omega = (\alpha + (1-\phi)^{-1}\lambda)^{-1} \log(1 + 1/s)$ and tuning fertility f to a level $\lambda(1+s)$. It turns out that we can make

$$r_*(m) = \frac{\lambda\phi s/(1-e^{-\eta})}{(1+s)\exp(\lambda(1-\phi)(m-\alpha)) - s}$$

by setting

$$q(m) = (\lambda\phi s)^{1/(1-\phi)}\left((1-e^{-\eta})r_*(m)\right)^{-\phi/(1-\phi)}$$

for $m \le \omega$ and $q(m) = \lambda > 0$ for $\omega < m$. Notice that $q(\alpha) = \lambda\phi s$. This mutation rate function is pinched down to zero at ω and then bounces back for ages of onset beyond ω. The bounce-back is essential. If, instead, $q(m)$ remained at zero beyond ω, the wall of death would disappear. For ages x well below ω, the predicted hazards approximate a Gompertz–Makeham form. Near the wall of death, hazards increase more rapidly than exponentially. Derivatives of all orders go to infinity. This behavior is particularly striking, because the linear approximate model would predict no wall of death at all.

Mutation rates that drop sufficiently rapidly with ages of onset will prevent walls of death in the absence of an upper limit to ages of reproduction. Indeed, Eqs. **4** and **5** allow us to start with a fairly arbitrary target shape for $h(y)$ and find a set of mutation rates $q(y)$ that will generate it.

Plateaus. A natural way to avoid collapse, less contrived than tailoring the rate function, is to assume that action profiles do not entirely vanish at young ages even though their effects may be concentrated late in life. As long as the profiles are not themselves unbounded, such a condition implies the existence of late-age plateaus. A proof that early-age effects guarantee the existence of equilibria has already been given in ref. 1, section 3.9. For completeness, we restate it here:

Suppose the integral of $q(m)$ is finite and sufficiently small and suppose

$$\sup_{m,x} \eta(m)\theta(m,x) < \infty \text{ and}$$
$$\inf_m \inf_{x \in B} \eta(m)\theta(m,x) > 0$$

for some set B with $\int_B f_x \ell_x(0)\,dx > 0$, and suppose $\sup_m q(m)$ is finite. Let $r_0 \equiv 0$. Then there exists $r_* \in L^\infty_+(\mathcal{M})$ such that $r_t \uparrow r_*$ Lebesgue almost surely and $H(x) = -\log \mathcal{L}_x^{(r_*)}$ is bounded by a constant times x.

As in refs. 21 or 15, ubiquitous small early-age effects have long been recognized as an option that would erode Gompertzian increase in mortality rates and instate plateaus. The results in this paper showing equilibrium collapse in their absence suggest that such effects are not merely allowed, but required.

Haldane's Principle. In the face of mutation accumulation, any equilibrium is a state in which inflow due to continuing mutation is balanced by outflow due to selection, allele by allele. In the linear approximate model, each mutant allele has a fixed cost, unaffected by other alleles. Summing over alleles, the total inflow at equilibrium, that is, the total mutation rate, has to equal the sum of these fixed costs, which, under the linearity assumption, would be the total selective cost. That is a classical version of Haldane's principle.

In our nonlinear model, outflow of each allele is driven not by its fixed cost but by its marginal selective cost, which is reduced by the presence in the genome of other deleterious alleles. The greater the supply of mutant alleles, the less the marginal cost of each one. The total mutation rate at equilibrium still has to equal the sum of the costs. However, the sum of the marginal costs is not the total selective cost, but something less than it. Remarkably, the sum turns out to have its own simple mathematical form, yielding a nonlinear generalization of Haldane's Principle.

Theorem 3. *Let $r_t \uparrow r_*$ on $\mathcal{M}_* \subseteq \mathcal{M}$ as $t \to \infty$ from $r_0 \equiv 0$, with $r_t \uparrow \infty$ elsewhere and $\mathcal{L}_x^{(r_t)} \downarrow \mathcal{L}_x^*$, with fertility rates that imply stationarity at equilibrium. Then the total mutation rate for mutations held in mutation–selection balance (belonging to $\mathcal{M}_*$) equals the sum of $\log(1 + \mathbb{E}_{r_*}[S(G)])$ and the relative entropy of the equilibrium net maternity function relative to the normalized baseline net maternity function. That is,*

$$\int_{\mathcal{M}_*} q(m)\,dm = \log(1+s) + \int_\alpha^\omega Q_x \log\left(\frac{1}{Q_x}\right)\frac{\ell_x(0) f_x}{1+s}\,dx, \qquad [6]$$

with $s = \mathbb{E}_{r_*}[S(G)]$ and $Q_x = (f_x \mathcal{L}_x^*)/(f_x \ell_x(0)/(1+s))$.

The proof in *SI Text* depends on being able to integrate the right-hand side of Eq. **1** solely over m in $\mathcal{M}_*$, substituting from Eqs. **2** and **3**. The right-hand side of Eq. **6** can be expanded in integrals of powers of the age-specific reduction in survivorship $\Delta_x = 1 - \mathcal{L}_x^*/\ell_x(0)$

$$\int_{\mathcal{M}_*} q(m)\,dm = s - \int_\omega^\infty f_x \ell_x(0)\,dx - \int_\alpha^\omega \left((1/2)\Delta_x^2 + (1/6)\Delta_x^3 + \cdots\right) f_x \ell_x(0)\,dx.$$

The first term on the right is the total loss in fitness. The second term subtracts the portion resulting from zeroing out fitness

contributions from ages beyond any wall of death. The third subtracts the contributions from interactions among alleles. The subtractions bring the total loss in fitness down to the total mutation rate for those mutations kept at finite intensity by natural selection.

Closed-form expressions are available for the special family of cases characterized by *Theorem 2*. The overall loss in fitness due to genetic load is $s = \mathbb{E}_{r_*}[S(G)]$. The loss of the contributions to fitness beyond the wall of death at ω amounts to $s(1+1/s)^{-\phi/(1-\phi)}$. The total rate of mutations with onset before the wall of death is given by ϕ times Gauss's hypergeometric function with parameters 1, $1/(1-\phi)$, $1+1/(1-\phi)$, and $-1/s$. If we hold s and λ fixed and take ϕ close to zero, then to first order in ϕ the total mutation rate for mutations acting before ω matches the loss in fitness from mutations acting before ω. Their common value is $\phi s \log(1+1/s)$. In other words, we recover Haldane's principle in its original form when mutation rates are very low.

Discussion

In the words of Charlesworth (15), "the 'mutation accumulation' theory, first proposed by Medawar, [...] refers to the fact that deleterious alleles with effects restricted to late stages of life equilibrate at higher frequencies at mutation–selection balance than alleles that act earlier [...]." The results here show that there is an unexpected and far-reaching difference between effects restricted to late stages and effects only concentrated at late stages, carrying with them some small crucial share of early-age effects.

We can visualize the disappearance of equilibria in the absence of early-age effects in several ways: with respect to age, with respect to time, or with respect to the shape of the mutation rate function.

Consider the picture with respect to age. At sufficiently advanced ages, remaining net fertility necessarily drops below any mutation rate that is bounded below. If the force of selection depends only on remaining net fertility, selection cannot balance mutation, and such ages must lie beyond a wall of death. However, if we try to construct an equilibrium with some specific wall of death, we find too little remaining net fertility very close to the wall to balance mutation there. Each wall of death implies an earlier one. The instability propagates down through the whole reproductive span, and our construction unravels.

A complementary picture emerges with respect to time. A steady influx of mutations affects the whole reproductive span. Hazards begin to increase linearly with time at all ages. At older ages, where selective pressure is always low, this linear increase continues unabated, whereas at younger ages it is slowed for a while by outflow due to natural selection. At a snapshot in time, hazards lie low for a stretch of ages, climb at ages where remaining net fertility is dropping off, and link up with the old-age segment. As time goes by, the climbing phase shifts down to younger and younger ages, until the hazard rate at every adult age comes to be marching toward infinity.

Details of the dynamics depend on assumptions about fertility. We may hold fertility fixed over time, but we have to recognize that no fixed fertility level is sufficient for stationary population growth at equilibrium when there is no equilibrium. Unbounded accumulation of mutations across the whole reproductive span drives any population to extinction. We may instead let fertility levels adjust over time to maintain stationarity with current values of the hazard, on the assumption that feedback between resources and population growth operates on a faster time scale than mutation and selection. Under this scenario, the climbing phase in the snapshot of the hazard function steepens with age and time as it shifts to younger ages, and the fertility level required for stationarity heads toward infinity.

A third picture relates to shape. The family of examples constructed in *Theorem 2* have mutation rate functions that are nearly constant over age but that are pinched to zero at a point. The pinching has a characteristic steepness that turns out to produce an equilibrium on a subset of ages ending in a wall of death. The nearer the mutation rate function to constancy, the nearer is the wall of death to the age at maturity, the shorter the reproductive lifetime, and the higher the fertility level required for stationarity. To reach the case of a wholly constant mutation rate function the brief high burst of fertility before death would have to turn into a delta function or point mass at the age of maturity, followed by immediate death.

Such a stylized life history, called the "salmon limit" by Tuljapurkar (22), is a far cry from the smooth Gompertz–Makeham equilibrium predicted by the linear approximate model. Nonlinear interactions make the Gompertz–Makeham form collapse.

This outcome depends on recombination. Recombination spreads the deleterious alleles throughout the population, leaving no lineages untouched by a surfeit of late-acting mutant alleles. In the absence of recombination, as shown in ref. 20, a minority group of high-fitness lineages can keep the aggregate population hazard finite at younger ages in the face of constant mutation rates and a late-age wall of death. However, in the presence of recombination as specified in our model, even a tiny rate of production of mutant alleles with arbitrarily late ages of effects cannot be balanced by natural selection, and leads to collapse of the equilibrium.

Our results on equilibrium collapse invite comparison with the well-known phenomenon of Mueller's ratchet. The ratchet destroys any equilibrium distribution of genotypes in nonsexually reproducing populations of finite size subject to genetic drift. Our results pertain to sexually reproducing populations of infinite size, that is, of sufficient size that genetic drift can be ignored. As with the ratchet, the lesson from our results is to point to the evolutionary need for processes to counteract collapse.

The generic antidote to collapse in our context comes in the form of small early-age manifestations of deleterious effects concentrated at later ages. The fascinating concomitant is that such early-age trace effects leave their signature in late-age plateaus in hazard functions. Plateaus appear not as a convenient add-on but as something like an obligate feature of mutation accumulation models with equilibria.

It seems logical that organisms should acquire mechanisms that push the age of onset of ill effects from numerous minor defects associated with genetic load toward later ages. However, our analysis suggests that such mechanisms, if carried to extremes, have bad evolutionary repercussions.

For species like humans, with substantial postreproductive survival, theories that emphasize mutation accumulation face the challenge of accounting for the absence of a wall of death at the end of reproduction. Early-age trace effects can remove walls of death, but the challenge remains in the persistence of exponentially increasing hazards well beyond the end of reproduction and the extreme late ages at which plateaus occur. The importance of postreproductive ages of nurturance, perhaps especially of grandmothers, is likely part of the explanation. In social species, transfers within sharing groups and across generations have a bearing on optimal life strategies. However, it would be a mistake to think that they can reshape the age-specific force of natural selection, linear or nonlinear, for the obvious reason that each mutation in the genome of an individual does not simultaneously appear in the genomes of all other members of a sharing group. Recombination erodes any potential for group selection in this setting.

It seems to us likely that effects of accumulating mutations in humans are now seen at postreproductive ages bearing age-specific signatures that were imprinted at earlier epochs when their contributions were more rapidly lethal at younger ages. Sizes of effects under our models have little impact, and sometimes no impact, on predicted hazard functions, but they have

major impact on rates of turnover. For each allele, the reciprocal of the nonlinear age-specific force of natural selection indicates a typical clearance time. For the small effects posited by the theory, this can amount to thousands of generations. Future models may be able to make these ideas more concrete by supplementing mutation accumulation with explicit models of how genetic change affects vitality throughout the life course.

Empirical studies among humans are beginning to characterize genetic diversity at lower and lower thresholds of allele frequency. Early indications (e.g., ref. 23) are for heavy representation of rare, so-called private alleles. These are the kinds of alleles modeled by mutation accumulation theory.

A long-term goal is to integrate the nonlinear models for mutation accumulation examined here with models for other contributors to senescent processes. Mutation accumulation does not act in isolation. It reshapes vital schedules that themselves reflect cellular and organismic processes and considerations of life-history optimization in interactions with environments. Mathematical modeling of mutation accumulation is a point of departure for further enhancements of our evolutionary understanding of senescence.

Materials and Methods

Our model is the general model in ref. 1 specialized to demographic selective costs treated there in sections 1.4 and 3.9 and developed further here. For such cost functions theorems 2.9 and 2.10 and remark 2.13 establish the existence and uniqueness of a solution $r_t(m)$ that is continuously differentiable in t and satisfies the dynamic Eq. **1** for all t and m.

Each individual in our infinite population carries some finite batch of deleterious mutant alleles specified by an element g in $\mathcal{G}$, the space of integer-valued Borel measures on $\mathcal{M}$. Alleles in the batch are those with $g(m) \geq 1$. We use the word "genotype" as shorthand to refer to g. A member who carries no mutant alleles is said to carry the "null genotype" $g = 0$, with wild-type alleles at every site. Selective cost S, as defined below, is a function of g. The symbol $\delta_m \in \mathcal{G}$ denotes a unit mass at m, so the marginal selective cost of m is given by $S(g + \delta_m) - S(g)$.

Care is necessary with respect to the definition of fitness costs in the presence of heterogeneity. With linear approximations are being used, it makes no difference whether costs are based on Lotka's r or on the NRR. Charlesworth (ref. 7, pp. 136–146) gives a careful examination of first-order and second-order terms. For nonlinear models, the choice does make a difference. As Charlesworth points out (ref. 6, p. 930), the NRR is the appropriate fitness measure for our purposes. The alleles are not invading a population but are being held at equilibrium frequencies. Measuring selective cost by reductions in the NRR makes frequencies agree with classical formulas for single-locus models.

The demographic meaning may be clarified through stable population theory. The population members who carry a particular collection of mutant alleles make a contribution to the next generation given by their mutation-dependent NRR. Thanks to new mutations as well as to recombination, their offspring do not carry identical collections of alleles. Groups of carriers are broken up each generation, before they establish their own special stable age structure or their own special values of Lotka's r, the growth rate that occurs with a stable age structure. At equilibrium all groups of carriers share the same growth rate, because their numbers are replenished by new mutations to balance their loss in numbers due to natural selection. For this reason, the NRR, rather than r, determines selective costs for mutation accumulation:

$$S(g) := \int f_x \, \ell_x(0) \, dx - \int f_x \, \ell_x(g) \, dx. \qquad [7]$$

The cumulative hazard function defined for a subpopulation of individuals with genotype g is formed by starting with the cumulative baseline hazard and adding a term $\eta(m')\,\theta(m', x)$ for each m' in g. In demographic language, alleles act like independent competing risks in a multiple decrement life table. Alternatives positing proportional hazards are studied in Baudisch (ref. 8, chapter 2). Converting from cumulative hazards to survivorship $\ell_x(g)$, we have

$$\ell_x(g) := \ell_x(0) \exp\left(- \sum_{m' \in g} \eta(m') \, \theta(m', x) \right). \qquad [8]$$

By ref. 1, the distribution of genotypes under our model is given by a Poisson point process G on $\mathcal{M}$, whose distribution is fully determined by its intensity r. By Eq. **8**, the net maternity function resembles a Laplace transform for the distribution of G. This Poisson process expectation can be taken in closed form, as, for instance, in ref. 24 (p. 227), leading to Eq. **3** for aggregate survival and Eq. **2** for the age-specific force of natural selection

$$F_r(m) = \mathbb{E}_r[S(G + \delta_m) - S(G)]. \qquad [9]$$

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