

The Age-Specific Force of Natural Selection and Walls of Death

Kenneth W. Wachter, Steven N. Evans, and
David R. Steinsaltz
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Abstract

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 non-linear demographic model for mutation accumulation of Evans et al. (2007), we find surprising differences. Non-linear 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.

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1 The Force of Selection

The best-known formula at the intersection of genetics and demography is doubtless W. D. Hamilton's "age-specific force of natural selection". Hamilton (1966) 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 any one specific age. 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 Medawar (1952), Finch (1990), or Charlesworth (2000), 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. As developed by Brian Charlesworth (1994) this framework guides the interpretation of many experiments in aging research and population genetics. A recent perspective is offered by Flatt and Promislow (2007). For definitions, see Section 2.

Hamilton's work, reprinted in Hamilton (1995), has been assessed and extended by Baudisch (2008). Sophisticated genetic models of mutation-selection balance are covered in an authoritative book by Bürger (2000). 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 are sometimes robust to details of genetic specification, in line with a principle of Haldane (1937) 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 Wachter and Finch (1997), Vaupel et al. (1998), Carey (2003), and Carey and Tuljapurkar (2003).

The theory built on Hamilton's formula is, in short, a centerpiece for demographic research. But 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.

Non-linearity is built 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 all effects were small enough, little accuracy would be lost, but the prediction turns out to be for large cumulative effects from small individual ones. Richly suggestive as it is, Hamilton's formula can only be

taken so far and no further. How far is too far? The answer has remained in doubt.

In Evans et al. (2007) we developed a full non-linear age-specific model for mutation accumulation. In this paper we apply our model to Hamilton's setting, in which the effect on age-specific mortality of each deleterious mutation is concentrated at a single age. As explained shortly, these effects are called "point-mass increments" and they are added onto the continuous-age version of mortality rates called the "hazard function". This specification is not a realistic one for actual mutations, but it is of central interest given its dominant role in prior work. A companion paper in preparation applies the new model to cases with more plausible specifications of distributed mutational effects. With point-mass increments, we are fortunate to obtain closed-form expressions, a particular advantage since numerical simulations may not readily reveal whether finite solutions do or not exist.

The most studied case with point-mass increments was put forward by Charlesworth (2001). He showed that the widely-observed Gompertz-Makeham form for age-specific mortality would be predicted exactly by the linear approximate model if one took mutation rates, background hazards, and fertility all constant across ages beyond an age of maturity. The Gompertz-Makeham form has a hazard function rising exponentially with age added onto a constant background level. Charlesworth was able to generalize the Gompertz-Makeham prediction beyond the point-mass setting. In his framework, a "Wall of Death" with infinite hazards and zero survivorship could occur, at but not before an upper age limit to fertility, if such an age limit were imposed. Charlesworth's elegant results with the linear approximate model have shaped thinking in biodemography.

Our paper presents three main findings for the full non-linear model with point-mass increments, all of them surprising:

1. In the elementary case with constant rates, the linear model breaks down when non-linear interactions are taken into account. An equilibrium ceases to exist, and accumulating mutations drive survival to zero at every adult age.
2. When provisions are introduced that preserve survival at some adult ages, a "Wall of Death" can occur before rather than at the oldest age of reproduction.

3. A generalization of Haldane's Principle holds exactly but it takes an unfamiliar form.

These results demonstrate the limitations of the traditional approach grounded in Hamilton's formula. They furnish guidance for constructing more realistic specifications of mutational action. It is especially revealing to learn that Gompertz-Makeham hazard functions cannot withstand certain simple kinds of sustained mutational pressure when interactions are taken into account. In the interpretation which we shall offer, equilibrium solutions disappear because they collapse to something outside the model specification. The "missing" equilibrium is a stylized life history in which all fertility is concentrated in a burst at a single age, followed by immediate death, a life history which Tuljapurkar (1997) calls "the salmon limit".

Like the linear models, our non-linear model is an infinite-population model in continuous time. The representation of the genetic structure is kept somewhat stylized in order to allow ramification of the demographic structure. The model follows in the tradition of Kimura and Maruyama (1966). Inheritance is diploid, with random mating, weak selection, and fitness calculated for individuals rather than for mating pairs. At each of a large or infinite number of sites is found either a wild-type or a dominant deleterious mutant allele. Alleles with the same effect on the hazard function are treated as if they were copies of the same allele, though 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 page 137 of Durrett (2002). Our model recovers this Poisson property for solutions, in a sense explained in Section 3. The property follows from an assumption called "Free Recombination," spelled out in Evans et al. (2007).

Genetic recombination makes no difference when interactions are all suppressed by linear approximations, but it matters in non-linear models. Under Free Recombination, recombination is assumed to act on a more rapid timescale than mutation and selection, erasing linkage disequilibrium among sites involved in the mutation accumulation process. An alternative non-linear model without recombination is presented in Steinsaltz et al. (2005) but will not be treated in this paper.

When age like time is taken to be continuous, adding an increment to the hazard function “at” an age a does not strictly make sense. The remedy is to think of adding a point mass or “delta function” of some size η to the hazard function, equivalent to adding onto the cumulative hazard function a step function with a single upward step of size η at age a . Hamilton’s formula then follows by differentiating Lotka’s r with respect to η applying implicit differentiation to the Euler-Lotka Equation which defines r . In the application of our model to Hamilton’s setting, the mutational effects are point-mass increments.

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. Transient effects are possible, but those would depend on independent definition of some origin for time. Parallel studies of fertility are also of interest but outside our present scope. Here we concentrate on deleterious mutations affecting survival and their demographic consequences.

2 The Linear Approximation

Our non-linear model is derived from dynamic equations in Evans et al. (2007) and may be regarded as a limiting form of standard discrete-population genetic models such as those of Barton and Turelli (1991) and Kirkpatrick et al. (2002) in the asymptotic regime of weak selection and mutation. Although the derivation is complicated, the formulas for predicted hazards are simple. They are presented in Section 3. An informal account of why the answers take the shape they do is offered in this section through an examination of the linear approximation built into Hamilton’s formula.

For the convenience of readers, we review some demographic terminology. Let ζ be a random variable that represents the life-span of an individual picked at random from a population, or from a subpopulation sharing some attribute. The *survivorship function* $l_x := \mathbb{P}\{\zeta > x\}$ is the probability of survival from birth to age x . The *cumulative hazard* at age x is $-\log l_x$. 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* $f_x l_x$. Fertility for males is taken to be governed by the rates for their female mates. The models do not explicitly segregate individuals by sex. The area under the Net Maternity Function (that is, $\int_0^\infty f_x l_x dx$) 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 $1 = \int e^{-rx} f_x l_x dx$. That is, r is the unique real zero of the logarithm of the Laplace Transform of the Net Maternity Function. On evolutionary timescales, the parameter r is assumed to have been close to zero, the growth rate of a *stationary population*.

Hamilton's expression for the force of natural selection is a function of the age a at which the effect of a mutant allele is assumed to be concentrated. It is calculated from background or extrinsic schedules for l_x and f_x , called the *baseline* schedules. If time is measured in units of generations, with generation length equal to the stable population mean age at childbearing, and if Lotka's parameter r is set to the stationary level $r = 0$, the force of selection reduces to the simple form $w(a) = \int_a^\infty f_x l_x dx$, the expected number of offspring produced after age a by an individual chosen at random from the population, offspring that would be lost by death at age a . With time in units of generations, the expression is the same whether the fitness measure being differentiated is Lotka's r or the Net Reproduction Ratio.

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

(2001) for a full account.

A contradiction arises because mutational effects of tiny size imply equilibrium increments to the hazard function of hefty size. Small values of η , which ought to help the approximation, strain it by bolstering the equilibrium value for n . The force on any one of n alleles acting at a responds to alterations to the survivorship function due to the other $n - 1$ alleles, as well as to alterations due to alleles acting at other ages. In other words, interaction terms enter the calculation. For consistency, w ought to be computed from a new l_x , reflecting these alterations. But then we would have new increments to the hazard function and need a new new l_x , over and over.

The hazard function at equilibrium computed from the survivorship function for the population as a whole may be written as a sum of a contribution $\lambda(x)$ due to baseline risks and increments $h(x)$ due to the mutant alleles distributed across the population. The linear approximation based on Hamilton's formula puts

$$h(a) \approx \frac{\nu(a)}{w(a)} = \frac{\nu(a)}{\int_a^\infty \exp\left(-\int_0^x \lambda(y) dy\right) f_x dx} \quad (1)$$

Since all increments affect selective costs, a guess at correction might be to replace the baseline hazard with the total hazard, leading to an equation with h on both sides:

$$h(a) = \frac{\nu(a)}{\int_a^\infty \exp\left(-\int_0^x (\lambda(y) + h(y)) dy\right) f_x dx} \quad (2)$$

This guess turns out to be the actual equation for h with point-mass increments in the full non-linear model.

The simplicity of Equation (2) hides some subtleties. The function h in (2) is the hazard function computed from the population survivorship function. Also called the "aggregate" hazard function, it differs from the average hazard function. Across the population, the set of mutant alleles present in each individual is random. Different members carry different genetic loads. Without such heterogeneity, natural selection would have nothing to select. Members carrying heavier loads tend to die at younger ages. This process of "demographic selection" makes hazards observed among survivors lower than hazards evaluated by averaging over the distribution of alleles inherited

at birth. It is not obvious whether formulas should feature the average hazard or the aggregate hazard. As shown in Section 3, the non-linear model picks out the aggregate hazard, as a consequence of computing a statistical expectation value for the marginal cost of each mutant allele.

Another point concerns the specification of fitness costs in the presence of heterogeneity. When linear approximations are being used, it makes no difference whether costs are based on Lotka's r or on the Net Reproduction Ratio, the NRR . Pages 136 to 146 of Charlesworth (1994) give a careful examination of first-order and second-order terms. For non-linear models, the choice does make some difference. As Charlesworth (2000) points out on page 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 background to the specification of selective costs may be clarified by reference to 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, since 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.

We are now in a position to preview our chief results. In the linear theory, the force of selection $w(a)$ is non-zero for any age at which the net maternity function calculated from the baseline schedules is non-zero. Non-zero $w(a)$ implies finite equilibrium numbers of mutant alleles acting at each age a . Numbers may tend to infinity as a approaches the last age of reproduction, imposing a "Wall of Death" at that age but not before. Late-acting mutations have no impact on the numbers of earlier-acting mutations. Selective pressure at an age abutting on the Wall of Death is calculated as if there were no Wall of Death.

In the full non-linear theory, in contrast, a Wall of Death, by erasing all

net reproduction beyond itself, reduces selective pressure against mutations acting at slightly younger ages. Reduced pressure may mean that selection cannot balance the rate of new mutations and equilibrium conditions cannot be satisfied at a younger age. The Wall of Death at the older age comes to imply a Wall of Death already at a slightly younger age. If this chain of implication proceeds unchecked through younger and younger ages, it may mean that no equilibrium solution with finite mean numbers of mutations exists at all. We say that “the solution unravels”, or, more precisely, that an attempt to solve for the equilibrium distribution of mutant alleles in the population unravels. We show in Section 5 that such pathology can in fact occur.

Unraveling can be prevented in some biologically sensible ways. But equilibrium mean numbers of mutations can still go to infinity at ages before the last age of net reproduction, as we show in Section 6. A Wall of Death may be found at earlier ages than the linear framework permits.

Mutation accumulation has the appealing property that predictions are insensitive to some of the details of specification. Working with genetic models without age structure, Haldane (1937), page 341, announced that

“... the loss of fitness to the species depends entirely on the mutation rate and not at all on the effect of the gene upon fitness of the individual carrying it ...”

He found the sum total of mutation rates at different sites to be approximately equal to the resulting decrement in the logarithm of fitness, a measure of “genetic load” essentially equivalent to our selective cost.

Haldane worked with two alleles per site and imposed a strong assumption about independence of mutational effects. Generalizations to multi-allele models are proved on pages 105 to 112 and 143 to 153 of Bürger (2000), and a version holds in the age-specific linear framework. In our non-linear model with point-mass increments, the aggregate population hazard and the population loss in fitness are strictly independent of the sizes of the increments, as we show in Section 7. The total mutation rate, however, is not equal to the total selective cost, but to a less conventional function of the demographic schedules.

3 The Non-Linear Model

We now present the non-linear model from Evans et al. (2007) and show how it leads to the equation (2) for predicted aggregate hazards in the special case of point-mass increments.

Mutant alleles m , distinguished by their age-specific effects, are drawn from a space \mathcal{M} . In our point-mass setting, m corresponds to an age of action or “age of onset”, a point on the real line, and \mathcal{M} is the positive real line itself. Each individual carries some finite batch of mutant alleles denoted by the letter g , and we use the word “genotype” as shorthand to refer to it. A member who carries no mutant alleles is said to carry the “null genotype” $g = 0$, with wild-type alleles at every site.

An individual sampled at random from the population carries a random batch of points G . The count of points of G in any interval of \mathcal{M} is a random variable. The mean of this random variable is given by the area within the interval under a curve ρ called the *intensity*. (Technically speaking, ρ is a density with respect to Lebesgue measure on the line.) In the non-linear model under the assumption of Free Recombination, Evans et al. (2007) prove that the random counts in disjoint intervals are independent random variables with Poisson distributions. Such a *Poisson point process* is uniquely determined by its intensity. It can also be defined for more general choices for \mathcal{M} including sample spaces for stochastic processes. The points of the Poisson process are points of age, not points of time. The Poisson property holds at any given time and also at equilibrium, if an equilibrium exists. Background on Poisson processes may be found in textbooks like Kallenberg (2002), Chapter 12.

Each application of the general model requires three ingredients: the age-specific profiles for the actions of mutant alleles, the rate at which new mutations enter the population, and the selective cost which gradually drives mutant alleles out of the population.

Here each mutation profile is written as a function $\kappa(m, x)$ of the index m and an age variable x . The function $\kappa(m, x)$ is multiplied by a size factor $\eta(m)$ and added onto the cumulative hazard function. In other words, 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 $\eta(m)\kappa(m, x)$ for each point m in the batch of points g . In demographic language, alleles act like independent competing risks in a multiple decrement life table. Other interesting forms of action including proportional hazards are studied by Baudisch (2008), Chapter 2.

In this paper, following Hamilton, we take the profile $\kappa(m, x)$ to be a step function with a unit step at the age of onset for m , corresponding to a point-mass increment to the hazard itself. Equations do not depend on this special choice for κ until Equation (9) at the start of Section 4.

The number of new mutations per generation with m from some interval of \mathcal{M} is given by the area within the interval under a curve $\nu(a)$ called the *mutation rate*. Like the intensity ρ , the mutation rate is a density with respect to Lebesgue measure. As in the elementary cases studied by Charlesworth (2001), we usually take $\nu(m)$ to be constant or nearly constant across ages within the reproductive span because we are interested in structure that arises from the logic of natural selection rather than from structure arbitrarily built into assumed mutation rates. Concentrating on adult mortality, we make ν vanish for ages of onset below some age at maturity α at which fertility and exogenous baseline mortality commence. The level of fertility is tuned to produce a stationary population at equilibrium, cancelling out effects of juvenile mortality and letting us omit them here.

The selective cost function S is a non-negative function of g , here taken equal to the decrement in the *NRR* due to the mutant alleles included in g . This choice was explained in Section 2. Formulas are given in Equations (5) and (6) below.

Since a Poisson point process is uniquely determined by its intensity, the theorems in Evans et al. (2007) allow the population over time to be described by an equation for the intensity $\rho_t(m)$ over time. This dynamic equation involves an expectation value, written \mathbb{E}_ρ , which averages over the random genotypes G of randomly selected members of the population, using the intensity function for the Poisson process:

$$\frac{d\rho_t(m)}{dt} = \nu(m) - \rho_t(m)\mathbb{E}_{\rho_t} [S(G + \delta_m) - S(G)] \quad (3)$$

The symbol $G + \delta_m$ denotes a genotype with all the mutant alleles in G plus one copy of m , using δ_m to stand for the measure which puts mass 1 on the point m . Equation (3) sets change equal to inflow minus outflow, with

inflow given by the mutation rate and outflow given by mean numbers times the marginal selective cost of each additional mutant allele. An equilibrium intensity ρ , if one exists, has the left-hand side equal to zero, requiring ρ to satisfy

$$\nu(m) = \rho(m) \mathbb{E}_\rho [S(G + \delta_m) - S(G)] \quad (4)$$

We calculate predicted hazard functions at equilibrium by substituting demographically meaningful expressions for $S(g + \delta_m)$ and $S(g)$ for each fixed g . The selective cost function S measures the fitness of genotypes on an implicitly logarithmic scale. We continue to write f_x for the fixed baseline age-specific fertility schedule and $\lambda(x)$ for the baseline hazard rate, so that the survivorship function for the null genotype is given by $l_x(0) = \exp(-\int_0^x \lambda(a)da)$.

The function S can be defined to equal

$$S(g) := \int f_x l_x(0) dx - \int f_x l_x(g) dx \quad (5)$$

The integrals are all taken over ages for which the integrands are non-zero. The function $l_x(g)$, the probability of survival to age x for members with genotype g , is derived from hazards that include increments from mutations in g . We add up the increments on top of the baseline to form the cumulative hazard, insert a minus sign, and exponentiate to recover the survivorship:

$$l_x(g) := l_x(0) \exp\left(-\sum_{m' \in g} \eta(m') \kappa(m', x)\right) \quad (6)$$

The prime on m is a reminder not to confuse the index of summation with the mutant allele m whose marginal cost we seek to calculate.

Adding a copy of some particular mutant allele m to the alleles already in g multiplies this survivorship by $\exp(-\eta(m)\kappa(m, x))$, with a marginal cost equal to

$$S(g + \delta_m) - S(g) = \int_\alpha^\infty (1 - e^{-\eta(m)\kappa(m, x)}) f_x l_x(g) dx \quad (7)$$

The theory tells us that our non-linear counterpart to Hamilton's age-specific force of natural selection is the expectation value of this marginal

cost, formed by letting g range over randomly selected genotypes G from the Poisson point process. The integrand factors into a fixed part involving only the extra allele m and a random part involving only G , namely the net maternity $f_x l_x(G)$ for the subpopulation with genotype $g = G$. By Equation (6), 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, on page 227 of Kallenberg (2002):

$$\mathbb{E}_\rho [l_x(G)] = l_x(0) \exp \left(- \int_{\mathcal{M}} (1 - e^{-\eta(m')\kappa(m',x)}) \rho(m') dm' \right) \quad (8)$$

4 Solutions with Point Mass Profiles

In Section 3, the expressions do not depend on the form of κ . Now we specialize to point-mass profiles. The step-function form for κ leads to further simplification. We substitute from Equation (7) in the equilibrium formula, Equation (4), replacing m with its age of onset a .

$$\nu(a) = \rho(a) \int_\alpha^\infty (1 - e^{-\eta(a)\kappa(a,x)}) \mathbb{E}_\rho [f_x l_x(G)] dx \quad (9)$$

The step function preceding the expectation value restricts the range of integration to $x > a$, replacing α by a , since the integrand vanishes for x below the age of onset. The random factor also simplifies, since the integral over \mathcal{M} in Equation (8) can be replaced by an integral over ages from α to x . It can be written in terms of the increment h to the aggregate hazard discussed at length in Section 2. The increment h is defined by

$$h(x) := -\frac{d}{dx} \log (\mathbb{E}_\rho [l_x(G)/l_x(0)]) \quad (10)$$

We can express the aggregate population survivorship function in terms of h :

$$\mathbb{E}_\rho [l_x(G)] = \exp \left(- \int_\alpha^x [\lambda(y) + h(y)] dy \right), \quad (11)$$

We have decomposed the aggregate population hazard into independent competing risks λ due to baseline and h due to genetic load. When we substitute (11) in (9) and compare with (8), we see how h depends on ρ and η :

$$h(y) := (1 - e^{-\eta(y)})\rho(y) \quad (12)$$

Furthermore, we see that Equation (9) is equivalent to the expression introduced in Section 2, Equation (2). As promised, we have derived the equation for h from the general equations of the non-linear model.

We now specialize our choices of baseline schedules for the sake of our main applications. We choose a value for α , the age of maturity below which exogenous baseline mortality and fertility are taken to vanish. Beyond α , the baseline hazard is taken to be a constant λ and fertility is taken to be a constant f tuned to produce a stationary population at equilibrium. We begin by imposing no upper age limit on fertility and later consider cases with fertility set back to zero beyond an age $\beta < \infty$.

Our goal in the rest of this section is to rewrite the equilibrium equation for h in a form that is easier to solve in special cases. We introduce notation for the indefinite integral of the aggregate population survivorship function (11).

$$T(a) := \int_a^\infty \exp\left(-\int_\alpha^x [\lambda + h(y)] dy\right) dx \quad (13)$$

This quantity $T(a)$, often written T_a , is the same as the column for “remaining person-years lived” in the population life table. Since for simplicity we have been omitting juvenile mortality, life expectancy ξ at the age of maturity α is the same as $T(\alpha)$ and equal to the reciprocal of the level of constant fertility required for stationarity:

$$\xi = T(\alpha) = T(0) - \alpha = 1/f. \quad (14)$$

The equilibrium condition (9) can now be written in terms of $h(a)$ and $T(a)$:

$$\nu(a) = h(a) \int_a^\infty f \exp\left(-\int_\alpha^x (\lambda + h(y)) dy\right) dx = h(a) f T(a) \quad (15)$$

Since $-T'(a)$ is the survivorship function and minus the derivative of log survivorship is the aggregate hazard, $\lambda + h(a)$ is $T''(a)/T'(a)$. The equilibrium condition (9) therefore implies that $T(a)$ must satisfy a non-linear second-order differential equation:

$$\nu(a) = \left(\frac{T''(a)}{T'(a)} - \lambda\right) f T(a) \quad (16)$$

Solution of this differential equation is facilitated by exploiting the monotonicity of $T(a)$ to change variables from age a to person-years $\tau = T(a)$. We make use of the inverse function T^{-1} which is defined to satisfy $T^{-1}(T(a)) = a$ and $T(T^{-1}(\tau)) = \tau$. The symbol \circ denotes composition of functions: $T^{-1}(T(a))$ is the same as $T^{-1} \circ T(a)$. Aggregate survivorship is expressed as a function of τ by composing the derivative of $T(a)$ with the inverse of $T(a)$:

$$L(\tau) := -T' \circ T^{-1}(\tau) \quad (17)$$

With this definition, $L(T(a)) = \mathbb{E}_\rho[l_a(G)]$. The function L is easy to interpret. The last τ person-years lived by members of a cohort are lived by the fraction L of the members.

The derivative of $L(\tau)$ with respect to τ comes out to be the hazard expressed as a function of τ :

$$L'(\tau) = \frac{T'' \circ T^{-1}(\tau)}{-T' \circ T^{-1}(\tau)} = h \circ T^{-1}(\tau) + \lambda \quad (18)$$

From the definition of ξ , we have $L(\xi) = 1$. The function L must also satisfy the boundary condition $L(0) = 0$ with $L(\tau) > 0$ for $\tau > 0$. At an age to which no one survives, there are no remaining person-years to live.

We can rewrite $\nu = hfT$ in the form $h = \nu/(fT)$, substitute for h , and express both sides as functions of τ :

$$L'(\tau) = \lambda + \frac{\nu \circ T^{-1}(\tau)}{f\tau} \quad (19)$$

5 Unraveling

The simplest case of mutation accumulation with point-mass profiles takes the mutation rate ν to be a constant ν_0 at all reproductive ages.

In the linear framework, this case is the starting-point for the notable results of Charlesworth (2001), discussed in Section 1. With a constant background hazard at adult ages, we have baseline survival, remaining person-years lived, and Hamilton's force of natural selection all going down exponentially with age. With a constant mutation rate in the numerator and the

force in the denominator of the linear approximate formula, Equation (1), we have the mean intensity of mutations and the increment to the population hazard both going up exponentially with age, achieving a total hazard equal to an exponential plus a constant, a Gompertz-Makeham form.

What impact do the non-linear interactions suppressed in Hamilton's formula turn out to have on this important prediction? We seek solutions to Equation (9) with $\nu(a) \equiv \nu_0$.

Plugging in a constant for ν , the solution to the differential equation (19) including a constant of integration A is given by

$$L(\tau) = \lambda\tau + (\nu_0/f) \log(\tau) + A \quad (20)$$

We expect to determine the constant of integration from the initial condition $L(\xi) = l_\alpha = l_0 = 1$, since $T(\alpha) = \xi$. We also expect to set $f = 1/\xi$ to tune the population growth rate to stationary levels. A puzzle arises, because ξ , the life expectancy at maturity, is as yet an unknown quantity that should be determined by the equations, while it appears that different values of ξ can correspond to different choices for A . But a deeper problem intervenes. The quantity $\log(\tau)$ goes to minus infinity as the remaining person-years of life τ go to zero, forcing there to be some non-zero value of τ for which $L(\tau)$ vanishes. But our model requires that $L(\tau) = 0$ only when $\tau = 0$. We cannot have further person-years to be lived when no survivors remain. This contradiction shows that the non-linear model has no equilibrium solution in this elementary case. This unexpected finding is the first of our main results.

We can visualize the disappearance of an equilibrium in several ways, with respect to age, with respect to time, or with respect to the shape of the mutation rate function.

The picture with respect to age has been mentioned in Section 2. We give a sketch rather than a formal argument. We seek to construct a solution satisfying the equilibrium condition (15) restricted to some late range of ages $[z, \infty)$ and then seek to extend the construction backward to earlier ages. At late ages, selective pressure is driven to low levels by the background hazard as well as by any late-acting alleles. Beyond some sufficiently late z , we expect the pressure to be too weak to be balancing a rate of new mutations that does not drop with age. We therefore expect infinite h and a Wall of Death. At the next earlier ages, the elimination of later reproduction by the

Wall of Death again leaves weak selective pressure. The interaction between older and younger ages, missing from the linear approximate model, puts $T(a)$ near zero. Low $T(a)$ requires high $h(a)$ to make $h(a)fT(a)$ as large as ν_0 but high $h(a)$ implies even lower $T(a)$, demanding, as it turns out, that the Wall of Death be earlier. Each Wall of Death implies an earlier Wall of Death, the instability propagates down through the whole reproductive span, and our construction unravels.

A complementary picture with respect to time is implied by the dynamic equation (3) with the null genotype as starting state. A steady influx of mutations affects the whole reproductive span, and $h_t(a)$ begins to increase over time like $\nu_0 t$ 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 maintained by substantial values of $fT_t(a)$. The function $h_t(a)$ at a snapshot in time has an age profile which keeps low for a stretch of ages, climbs as $T_t(a)$ drops off with age, and settles out at $\nu_0 t$. As time goes by, the climbing phase accompanying the drop in $T_t(a)$ 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 $h_t(a)$, on an assumption that feedback between resources and population growth operates on a faster timescale than mutation and selection. Under this scenario, the climbing phase in the age profile of $h_t(a)$ steepens with age and time as it shifts to younger ages, and the fertility level heads toward infinity.

A third way of picturing the disappearance of an equilibrium makes use of results from the next section about mutation rate functions with different shapes. Section 6 displays a family of examples in which the mutation rates are nearly constant but not exactly constant. Each mutation rate function has a drop down to zero with some characteristic steepness which turns out to produce an equilibrium with 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. In order 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 (1997), is a far cry from the smooth Gompertz-Makeham equilibrium from the linear approximate model. Non-linear interactions make the Gompertz-Makeham form collapse, leaving no smooth equilibrium for the elementary case of constant mutation rates with point-mass increments.

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 Steinsaltz et al. (2005), 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.

It is remarkable that the collapse of the equilibrium in our model with Free Recombination does not depend on the magnitude of the uniform mutation rate ν . Even the tiniest such rate cannot be balanced by the force of natural selection. The elementary case with constant mutation rates and point-mass increments is the most studied case for the linear approximate model. The transforming effect of non-linear interactions for this case of all cases is a dramatic *denouement*.

6 Walls of Death

Unraveling can be avoided in several biologically reasonable ways, already adumbrated, for instance, in Wachter (1997), pages 11ff. There may not be mutant alleles whose effects are entirely concentrated at or above an age of onset. An “entry cost” of some small loss of fitness at young ages associated with all later-acting mutations will keep unraveling in check. Restricting ages of onset to some finite subset of discrete ages will also suffice. Here we examine another alternative, mutation rates for point-mass increments that remain only nearly constant with age of onset and drop to zero at what comes to be the end of life.

We construct a family of cases with nearly constant mutation rates by seeking forms for the remaining person-years function $T(a)$ satisfying Equation (19) consistent with a predetermined relationship between $T(a)$ and $\nu(a)$. We then construct $\nu(a)$ to validate this relationship and deduce $h(a)$ from $T(a)$. Our cases are indexed by a positive exponent θ less than or equal to 1. Our intended relationship between $T(a)$ and $\nu(a)$ for $a > \alpha$ takes the form

$$\nu(a) = \nu_0 (T(a)/T(\alpha))^\theta \quad (21)$$

When θ is close to zero, the rate starts at $\nu(\alpha) = \nu_0$ and remains nearly constant until close to the end of life.

With ν as in Equation (21), the differential equation (19) takes the form

$$L'(\tau) = \lambda + (f\xi)^{-1} \nu_0 (\tau/\xi)^{\theta-1} \quad (22)$$

Its solution is

$$L(\tau) = \lambda\tau + (f\xi\theta)^{-1} \nu_0 \xi^{1-\theta} \tau^\theta + A \quad (23)$$

Applying our boundary condition $L(0) = 0$ implies $A = 0$. With $f\xi = 1$ for stationary growth and $L(\xi) = 1$ by the definition of ξ , life expectancy at maturity is given by

$$\xi = \frac{1}{\lambda + \nu_0/\theta} \quad (24)$$

Higher mutation rates lower life expectancy, as they should, and so does slower tapering of the mutation rates with lower θ . With no mutations, $\nu_0 = 0$, survival drops exponentially at the rate λ , and $\xi = 1/\lambda$.

We can express a as a function of τ , because we now know the derivative of a with respect to τ , the reciprocal of $-L(\tau)$.

$$a - \alpha = \int_{T(\alpha)}^{T(a)} \frac{-d\tau}{L(\tau)} = \int_{T(a)}^{\xi} \frac{d\tau}{\lambda\tau + (f\xi\theta)^{-1} \xi^{1-\theta} \nu_0 \tau^\theta} \quad (25)$$

This expression can be integrated in closed form and the answer inverted to give τ as a function of age. We change notation for age from a to x for subsequent clarity:

$$\tau(x) = \xi \left(\left(1 + \frac{\nu_0}{\lambda\theta}\right) (\exp(-\lambda(1-\theta)(x-\alpha))) - \frac{\nu_0}{\lambda\theta} \right)^{1/(1-\theta)} \quad (26)$$

When we substitute into $L'(\tau)$, we find the contribution of genetic load to the hazard rate to be

$$h(x) = \frac{\nu_0 \exp(\lambda(1-\theta)(x-\alpha))}{(1 + \nu_0/(\lambda\theta)) - \nu_0/(\lambda\theta) \exp(\lambda(1-\theta)(x-\alpha))} \quad (27)$$

The hazard rate goes to infinity as x approaches

$$\omega = \alpha + \frac{1}{\lambda(1-\theta)} \log \left(1 + \frac{\lambda\theta}{\nu_0} \right) \quad (28)$$

For $\theta < 1$, ω is the age of a Wall of Death.

We now need to write down a mutation rate ν as a function of age which satisfies the posited relationship with T and leads to (27) as an equilibrium solution. The posited relationship follows easily by raising $\tau(x)/\xi$ from (26) to the power θ . However, this relationship does not tell us how to define $\nu(x)$ beyond the age ω at which τ vanishes.

It is tempting to define $\nu(x) \equiv 0$ beyond ω , but if baseline fertility remains positive beyond ω , the resulting equilibrium will not be the limit over time of the dynamical process starting from the null genotype. Late-age fertility will keep $h_t(a)$ bounded and prevent the Wall of Death. A second alternative is to terminate the baseline reproductive span at an age β equal to ω . As with the linear approximate model, a limiting Wall of Death does then occur at the end of reproduction.

A third alternative is to set $\nu(x)$ back equal to some positive constant after its drop to zero at ω . The rate is pinched to zero at ω rather than cut off. The dynamical process starting from the null genotype does then converge to the equilibrium given by (27). This alternative is of theoretical interest, showing as it does that a Wall of Death can occur before rather than at the last age of reproduction in the full non-linear model.

The behavior of our family of cases as the exponent θ approaches zero has been discussed in Section 5. The mutation rate becomes more and more nearly constant and the Wall of Death at ω moves down to the age of maturity, wiping out all fertility.

For ages x well below the Wall of Death, the denominator of Equation (27) is nearly constant, and the hazard along with the constant baseline contribution approximates a Gompertz-Makeham form. As x comes closer to the

Wall of Death, the hazard function becomes hyperexponential. Derivatives of all orders go to infinity.

The predicted hazards from the linear model with the same form for ν have exponential increase at the same rate as the numerator in Equation (27). If no upper age limit is imposed on the reproductive span, the Gompertz pattern continues out to infinity. If an upper age limit is imposed, the linear model has a Wall of Death at that age, but not before.

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, Equation (15) allows us to start with a fairly arbitrary target shape for $h(a)$ and find a set of mutation rates $\nu(a)$ which will generate it. The case $\theta = 1$ from our family of cases has an exponentially declining mutation rate which produces an increment to the hazard rate that is constant over age.

7 Haldane's Principle

Our equilibrium condition (15) encapsulates a notable result. In our non-linear model with point-mass increments, if an equilibrium exists, the aggregate population hazard maintained by mutation-selection balance at equilibrium does not depend on the sizes $\eta(a)$ of the mutational effects.

This result generalizes a property of linear approximate models, but in a surprising direction. Scaling up the size of the effect of a mutation increases the selective pressure against it and reduces its expected frequency. In the linear setting, the expected hazard, that is, the average hazard averaged across the population, is insensitive to $\eta(a)$. Doubling $\eta(a)$ halves the expected frequency $\rho(a)$ and leaves the expected hazard $\eta(a)\rho(a)$ unchanged. In our full non-linear setting, it is not the expected hazard but the aggregate population hazard that comes out to be invariant to changes in $\eta(a)$.

The difference between aggregate and expected hazards is a preoccupation of social scientists. It is due to demographic selection or culling, already discussed in Section 2. The population is heterogeneous. Some members have genotypes with more mutant alleles and lower net reproduction. Others have fewer mutant alleles and higher net reproduction. The heterogeneity

is what allows natural selection to operate over time, and it is also what produces demographic selection with increasing age. Members with more mutant alleles die at younger ages, and survivors to later ages carry smaller than average sets of mutant alleles. The aggregate population hazard, based on proportions surviving, is lower at advanced ages than the expected hazard, which averages over all members, irrespective of survival.

In the linear framework, one way of calculating overall selective costs makes them equal the total mutation rate. The contribution from a number $\nu(a)/(\eta w(a))$ of mutant alleles acting at a , each with a cost $\eta w(a)$, amounts to $\nu(a)$, and the integral over ages of onset equals the total mutation rate. However, calculating selective cost directly from the predicted hazard gives a different answer, reflecting the inconsistencies built into the linear approximations.

In the full non-linear model, the change in expected frequency $\rho(a)$ which compensates for a change in effect size $\eta(a)$ is only approximately linear in $1/\eta(a)$. But the non-linearity of the change exactly balances the non-linear effect of culling. Cases in which most population members carry only a handful of mutant alleles, each with a large effect, lead to the same aggregate hazard as cases in which almost all population members carry a huge number of mutant alleles, each with a tiny effect. The variance in net reproduction across the heterogeneous population is very different in the two settings, but the aggregate hazard, the most readily observable outcome, is the same.

The total mutation rate, obtained by integrating over m , turns out to equal a function of the aggregate population survivorship $\mathbb{E}_\rho[l_x(G)]$. The expectation is taken over the Poisson point-process distribution for G determined by the equilibrium intensity ρ .

$$\nu(M) = \int_\alpha^\infty (-\log(\mathbb{E}_\rho[l_x(G)/l_x(0)])) f_x \mathbb{E}_\rho[l_x(G)] dx \quad (29)$$

The right-hand side is a fertility-weighted version of life-table entropy, described with references in the textbook by Keyfitz and Caswell (2005), pages 80–82 and 166. In a sense, this equation is a generalization of Haldane's Principle to our age-dependent models for mutation-selection balance under Free Recombination with point-mass profiles. The quantity equal to the total mutation rate, however, is not the overall loss of fitness for the population. The overall loss in fitness depends only on the aggregate population hazard

rate, so it remains independent of the sizes of mutational effects as Haldane posited, but not entirely independent of the age pattern of mutation rates.

8 Conjectures and Conclusions

The derivations in this paper show that non-linear interactions can make a profound difference to patterns of senescent mortality produced from mutation accumulation. Breakdowns can occur not only when rates of deleterious mutations are high but, in the simplest cases, whenever they are not zero.

The setting with point-mass mutations is the one most thoroughly studied in the past, going back to Hamilton himself. It is a stylized setting. Do our main conclusions hold when the age-specific effects of deleterious mutations are not concentrated at single ages but spread across a range?

We conjecture that unraveling does occur not only with point-mass profiles but with profiles from translation families of the kind also treated by Charlesworth (2001). Let the functions $\kappa(m, x)$ each vanish below some age of onset $a(m)$ and have the same shape above it, being shifted versions of some template. We expect that a mutation rate ν constant over ages of onset still leads to unraveling. We also expect that the shapes can vary to some extent and that the strict absence of effects below the ages of onset is the feature that drives models to unravel. With mutation rates that taper with age, such absence leads to early Walls of Death.

A reasonable way for nature to avoid such pathologies would be for deleterious mutations to have small effects of at least some minimal level at young ages even when their main effects are concentrated later. Such a requirement would keep genetic loads from growing to infinity. In the process, it would introduce a tendency for hazard rates to tend toward plateaus at high ages, Charlesworth (2001) suggested this condition within the linear framework as a way of generating plateaus. With the non-linear model, the argument becomes stronger. The necessity to avoid unraveling becomes a reason for expecting plateaus.

We have seen that Gompertz-Makeham hazards arise quite easily at young and medium ages from our non-linear model with point-mass profiles and tapering mutation rates. We conjecture that they also arise with distributed

mutational profiles of a more realistic kind. Applications of our model with richer families of profiles will be presented in a sequel.

A number of aspects in the application of our non-linear model await examination. These include

- possible closed-form solutions with point-mass profiles augmented with fixed early-age selective costs;
- inclusion of mutations depressing fertility as well as augmenting hazards, with point-mass profiles and with more realistic profiles;
- extension of the results of Baudisch (2008) for effects that act multiplicatively on hazards, exploiting the full non-linear model;
- comparisons of predicted hazards between our model with Free Recombination and the alternative model without recombination;
- study of intermediate assumptions about recombination and their implications for unraveling and Walls of Death;

A larger goal is to begin to integrate the non-linear 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.

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