

Solvable Senescence Model Showing a Mortality Plateau

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We present some analytic results for the steady states of the Penna model of senescence, generalized to allow genetically identical individuals to die at different ages via an arbitrary survival function. Modeling this with a Fermi function (of modest width) we obtain a clear mortality plateau late in life: something that has so far eluded explanation within such mutation accumulation models. This suggests that factors causing variable mortality within genetically identical subpopulations, which include environmental effects, may be essential to understanding the mortality plateau seen in many real species.

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A common feature of the life history of multicellular organisms is the progressive decline in the various physiological processes once the reproductive phase is complete. This process of aging has attracted considerable attention [1–5], particularly after work from the Human Genome project identified specific “clock genes” [6] which regulate human aging. In addition to these underlying genes, the environment can play a part. For example, experimental studies [7,8] have shown that organisms subject to a reduction in caloric intake without essential nutrient deficiency display an extension of maximum life expectancy. How, then, do the effects of evolution and/or the environment “pick out” a particular profile of senescence?

Two major theories of aging prevail, the “mutation accumulation,” where mutations affecting old ages accumulate thanks to a weaker reproductive selection, and the “antagonistic pleiotropy,” where a gene, beneficial in youth, is deleterious in old age [4]. Traditional mutation accumulation theories lead to an exponentially increasing mortality with age, the so-called Gompertz Law [1]. However, it has been experimentally observed that the rate of mortality, while obeying the Gompertz Law up to an intermediate age, often shows an unexpected drop at an advanced age. This drop, valid for many species from human to medflies, gives rise to a “mortality plateau,” somewhat at odds with theory [9–12]. As a result, antagonistic pleiotropy has been suggested as an essential part of aging [4,13].

In 1995, with computer simulation in mind, Penna proposed a mutation accumulation model of senescence, which quickly became widespread [14]. Gompertz behavior has been reported for the standard Penna model [15], and variations on the model were proposed to account for demographic features [16–18], as well as catastrophic mortality [19,20]. However, a major shortcoming of the Penna model [21] was examined only recently: According to the model, all members of a genetically identical population must die exactly at the same age, which is

obviously untrue. Recent attempts in removing this determinism within the Penna model gave rise to a gently decelerating old age mortality, without reproducing a satisfactory mortality plateau [22].

Here we present a general formulation and an exact solution to the Penna model, which, together with a simple Fermi survival function, gives rise to a convincing mortality plateau. The introduction of a gene-dependent survival curve (replacing a single parameter, the deterministic age of death) enlarges the parameter space for simulations considerably. This makes analytical results all the more valuable, especially those that do not depend on the survival function chosen.

Below, we first consider a particular version of the Penna model (by setting the mortality threshold $T = 1$), and present for it an exact analytic solution. Furthermore, this solution is robust against changes in the survival function. In the case of a Fermi function for survival, we show the presence of an extended mortality plateau. The generalization of the analytic solution to $T > 1$ is then given.

In the original Penna model [14], each individual carries a string of binary numbers, which stays fixed for that individual's lifetime. A “1” for the i th bit represents the effect of a harmful gene which causes the individual to be struck by a heritable disease upon reaching the age of i . Thus, as an individual ages, its bit string is sequentially examined and diseases are accumulated. The individual expires upon encountering the T th deleterious bit, where T is a preset mortality threshold. Qualitatively, T represents the number of heritable diseases required to make an individual nonviable; within the original model, if the T th 1 occurs at the l th bit, the individual will survive precisely to age l and no more. As long as it survives, the individual has a probability (rate) b to give birth. The offspring inherits the same bit string from the parent except for some mutations occurring at a small rate β . In simulations, the birth rate b is often regulated by a “Verhulst factor” to prevent either population explosion

or decay [1]. A different Verhulst factor, reducing populations of all ages at every time step (but with a fixed birth rate), has also been used, for which the Penna model can be formulated analytically into an eigenvalue equation and solved numerically [23].

In the $T = 1$ limit, the population can be described by a probability function $n(l)$ of the first deleterious bit occurring at position l . Equivalently, $n(l)$ is simply the number of such l -type individuals at any particular time. Then the evolution of $n(l)$ is given by

$$\frac{dn(l)}{dt} = bn(l)e^{-\beta l} - \frac{n(l)}{l} + b(1 - e^{-\beta})e^{-\beta l} \sum_{l'=l+1}^{\infty} n(l'), \quad (1)$$

where the first term corresponds to the mutation-free reproduction; the second term gives the mortality, where $1/l$ is the average rate of mortality for an l -type (which assumes the population changes slowly in the lifetime of an individual); the third term represents the switching from l' to l due to a single mutation [24]. Note that there is no noise in this equation. Hence it describes the thermodynamic limit of a large population in which deterministic dynamics is recovered. Note also that, in a stationary state of the original Penna model, l -types are distributed uniformly over all ages up to l at which they promptly die, so the mortality rate is exactly $1/l$. However, our formulation is more general in that l -types may have an arbitrary survival function provided their mortality rate averages to $1/l$. (This is the same as demanding the average life expectancy for an l -type to be l , which we may take as the definition of l .) As in the original Penna model, only bad mutations (from 0 to 1) have been included.

For a stationary state, the constant introduction of bad mutations is balanced by the longer reproductive lifetime of healthier individuals. Setting $dn/dt = 0$, Eq. (1) can be solved exactly to give the recursion relation

$$\frac{n(l+1)}{n(l)} = \frac{l+1}{l} \frac{e^{\beta l} - b l}{e^{\beta(l+1)} - b(l+1)e^{-\beta}}. \quad (2)$$

Before going further, we need to examine the interdependence of the mutation and birth rates β and b . Obviously a very large b coupled with a negligible β would result in an exponential population growth. A stationary state requires a specific combination of β and b . An extremely long-lived individual (large l) produces many offspring in total (proportional to l), but mutation reduces the probability of it reproducing itself accurately by an exponential factor ($e^{-\beta l}$). This means that a very large l cannot maintain itself and must rely instead on mutated reproduction of even fitter individuals. Such a cascade is not possible in a finite population which must, at any time, contain a maximum $l = l_{\max}$; the above argument shows that, if too large initially, this will decrease with time until the l_{\max} subpopulation is indeed self-sustaining. The evolution equation (1) for this subpopulation then reads

$$\frac{dn(l_{\max})}{dt} = g(l_{\max}) n(l_{\max}), \quad (3)$$

where the growth rate function $g(l) \equiv be^{-\beta l} - 1/l$, and a steady state demands $g(l_{\max}) = 0$; namely,

$$be^{-\beta l_{\max}} - 1/l_{\max} = 0. \quad (4)$$

Next we argue that for a steady state in the thermodynamic limit, we should have

$$g(l_{\max} - 1) < 0; \quad g(l_{\max} + 1) \leq 0. \quad (5)$$

Without the first condition, the subpopulation with $l = l_{\max} - 1$ would grow thanks to the extra proliferation of $l_{\max} - 1$ as a result of a mutation to l_{\max} . The second condition ensures the stability of $l_{\max} + 1$ upon approaching steady state. In the continuum limit, this is equivalent to demanding that the derivative of $g(l)$ should be zero.

These conditions are well confirmed by our numerical simulations of the Penna model. However, if $n(l_{\max} + 1)$ falls to zero discontinuously significantly before the steady state is reached, then the second condition in Eq. (5) might not be strictly required. This is unlikely in the thermodynamic limit and we ignore such contingencies from now on. It would also happen if a maximum bit-string length less than l_{\max} were imposed in a simulation; see below.

Equations (4) and (5) together lead to

$$\frac{1}{e^{\beta} - 1} \leq l_{\max} < \frac{1}{e^{\beta} - 1} + 1, \quad (6)$$

which implies a unique integer value for l_{\max} given any β . Whenever $1/\beta$ is an integer, it lies in the above specified range, and Eqs. (4) and (5) greatly simplify to

$$l_{\max} = 1/\beta; \quad b = \beta e, \quad (7)$$

where only one of l_{\max} , β and b is a free variable. Choosing β and b such that $l_{\max} = 20, 30$, the result of the recursion relation (2) is plotted in Fig. 1, with normalization $\sum_l n(l) = 1$.

Our simulation results are obtained following the method proposed by Penna [14], where mutation rate is prespecified as is the maximum string length l_{sim} (often set to 32). However, a Verhulst factor is included to regulate the birth reproduction rate and the system finds its own stationarity by adjusting the birth rate. The string length dependence has been investigated by computer simulation, but no universal results were found [25]. Our analysis suggests that the results depend on the value of l_{sim} in relation to l_{\max} , which is set by the mutation rate, Eq. (7). If $l_{\text{sim}} > l_{\max}$, no string length effect is expected as the final bits of the string do not affect the system. Therefore, the most efficient simulation is performed when l_{\max} approaches l_{sim} from below.

With the original Penna model, the only mortality at age x occurs to individuals with $l = x$; these have number density $n(l)/l$ and mortality rate 1. In other words, the survival function of an l -type is a square function with a height of 1 and width l . The normalized mortality at x is therefore

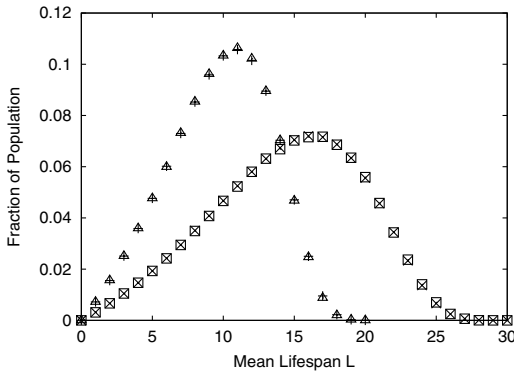


FIG. 1. Life span distribution $n(l)$ for $l_{\max} = 20$ (+), 30 (x), compared with simulations (boxes). Simulation size 10^7 , averaged over 10 runs.

$$\mathcal{M}(x) = \frac{n(x)/x}{\sum_{l=x}^{\infty} n(l)/l}, \quad (8)$$

where the denominator gives the total number of individuals living at the age x , and the numerator gives the number of individuals dying at the age x . The resulting population mortality exhibits a Gompertz-like behavior up to an intermediate age but then slows down as l_{\max} is approached [15]; see Fig. 2. But since the mortality at this point reaches 1, there is no population left to continue the incipient plateau and only its onset is observed.

However, Eqs. (2)–(7) make no assumption about the survival function of an l -type and apply equally well to, say, a Fermi function [17,18]:

$$f(x, l) = \frac{\mathcal{N}}{1 + \exp[(x - \tilde{l})/w\tilde{l}]},$$

where w is its width in units of the Fermi level \tilde{l} . \mathcal{N} ensures $f(0, \tilde{l}) = 1$, and \tilde{l} is chosen so that the average life span $\sum_x f(x, l) = l$. In fact, $\tilde{l} = l$ to within terms of order $\exp[-1/w]$; the latter are safely ignored in the following plots, where we choose small w 's as examples of modest influence of environmental factors on the life expectancy of genetically identical individuals. The analysis leading to the recursion result [Eq. (2)] stands, and the mortality function corresponding to Fig. 2 is plotted in Fig. 3.

A pronounced mortality plateau is now observed. By varying w in a reasonable range of 0.01–0.5 and the

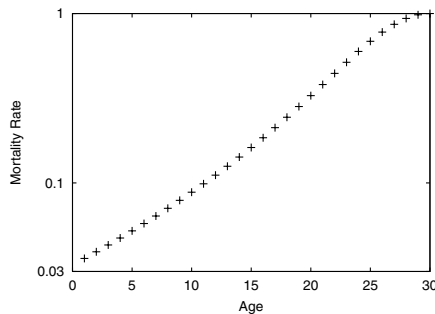


FIG. 2. Mortality rate with $l_{\max} = 30$ (note log scale).

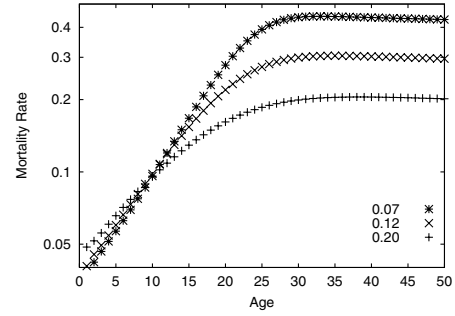


FIG. 3. Mortality rate for Fermi survival functions of different width w , and $l_{\max} = 30$.

choice of b , which in turn determines $n(l)$, it is possible to obtain different shapes of this mortality plateau which resemble those observed experimentally in various species [9]. The different values of w could be easily justified as the species-dependent susceptibility to environmental variations, as well as other factors. Thus, the Penna model, coupled to a Fermi survival function, is sufficient to account for the plateau observed in mortality for different species.

Now we extend the analysis to the multidisease cases where $T > 1$. In this scenario, the obvious extension of our existing theory is to write $n(l_1, l_2, \dots, l_T)$ which gives the number of individuals with deleterious bits at positions l_1, l_2, \dots, l_T on their “genetic” strings. And a similar, albeit more complex, evolution equation can be constructed. However, it is immediately evident that the final l_T holds a special position as this is the bit which determines the individual’s death. In contrast, the positions of other deleterious bits are less significant, in fact so insignificant as to inspire an ansatz,

$$n_T(l) = n(l_1, l_2, \dots, l),$$

for the steady state. Neglecting multiple mutations which will be addressed elsewhere [26], we find that the relevant generalization of Eq. (1) reduces to

$$0 = \frac{dn_T(l)}{dt} = bn_T(l)e^{-\beta(l-T+1)} - \frac{n_T(l)}{l} + bT(1 - e^{-\beta})e^{-\beta(l-T+1)} \sum_{l'=l+1}^{\infty} n_T(l'). \quad (9)$$

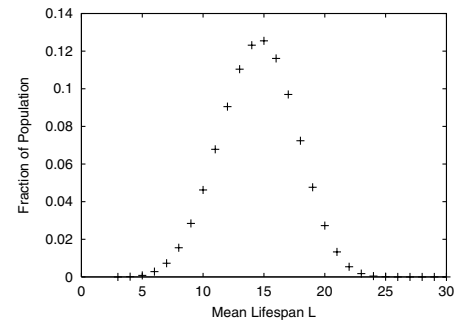
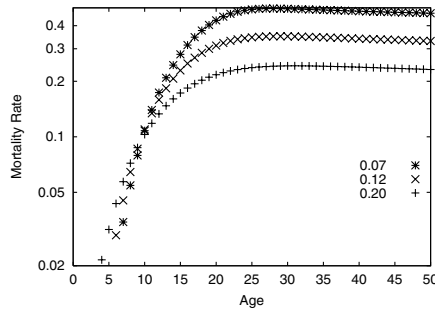


FIG. 4. Life span distribution function $C_{T-1}^l n_T(l)$ for $T = 4$.

FIG. 5. Mortality rate for $T = 4$.

Our notation means $n_1(l) \equiv n(l)$, defined earlier. The ansatz implies that the distribution function $n(l_1, l_2, \dots, l)$ depends merely on the position l and not on any of the others. It is possible that there are other solutions not contained in the ansatz; without claiming uniqueness we note that our simulations show the ansatz leads to a valid solution. Equation (9) can be solved to give the recursion

$$\frac{n_T(l+1)}{n_T(l)} = \frac{l+1}{l} \frac{e^{\beta(l-T+1)} - bl}{e^{\beta(l-T+2)} - b(l+1)(1-T+Te^{-\beta})}.$$

Since for every l there are different combinations of having the remaining $T-1$ mutations, the correct normalization is now $\sum_l C_{T-1}^l n_T(l) = 1$, where C_{T-1}^l is the number of combinations of choosing $T-1$ out of a total of l , and $C_{T-1}^l n_T(l)$ gives the weighted probability of finding an l -type. The stability criterion for the multi-disease case reads

$$l_{\max} = 1/\beta; \quad b = \beta e^{1-\beta(T-1)}, \quad (10)$$

which recovers Eq. (7) for $T = 1$. Choosing $l_{\max} = 30$ as before and $T = 4$, we plot the weighted mutation distribution function in Fig. 4. The mortality rate with the same Fermi survival function as before is presented in Fig. 5.

In conclusion, we have analyzed the $T = 1$ case of the Penna model, finding a nontrivial steady state solution for an arbitrary l -dependent survival function, and gained by ansatz similar solutions for the general T case. Our result suggests the mortality plateau arises from a variation in the mortality within genetically identical subpopulation. Our analysis also shows the importance of the maximum sustainable longevity l_{\max} , set by the mutation rate, which determines, for example, whether there is any effect of the bit-string length l_{sim} used in simulations (there is such an effect only if $l_{\text{sim}} < l_{\max}$). It is hoped that the analytic solution presented here will provide guidance for further simulations. In our own future work we will describe the continuum limit (in l) of the theory presented here and deal with other, more technical aspects of the Penna

model such as multiple mutations and the Verhulst factor coupled with noise [26].

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