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# Life histories and the evolution of aging in bacteria and other single-celled organisms

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**Abstract**

The disposable soma theory of aging was developed to explore how differences in lifespans and aging rates could be linked to life history trade-offs. Although generally applied for multicellular organisms, it is also useful for exploring life history strategies of single-celled organisms such as bacteria. Motivated by recent research of aging in *E. coli*, we explore the effects of aging on the fitness of simple single-celled organisms. Starting from the Euler-Lotka equation, we propose a mathematical model to explore how a finite reproductive lifespan affects fitness and resource allocation in simple organisms. This model provides quantitative predictions that have the potential for direct comparison with experiment, providing an opportunity to test the disposable soma theory more directly.


*Keywords:* Bacteria; Life history; Mathematical model; Replicative senescence; Euler-Lotka equation

## 1. Introduction

Single-celled organisms, as well as any organisms where the soma and the germ line are not separate, were once expected to be immortal (Williams, 1957). Later it was observed that some asymmetrically dividing single-celled organisms, such as *Saccharomyces cerevisiae* (Mortimer and Johnston, 1959) and *Caulobacter crescentus* (Ackerman et al., 2003) age and die. Therefore, it was hypothesized that the distinction between organisms that age and those that do not depends upon asymmetry in reproduction (Partridge and Barton, 1993). Recent research by Stewart et al. (2005) indicates that even bacteria that appear to divide symmetrically, such as *Escherichia coli*, actually produce functionally asymmetric cells during cell division. They identified one of the cells as the aging parent cell that produces offspring that are ''rejuvenated,'' and found evidence that these older cells reproduce more slowly as they age, and may even stop reproducing.

Current theories of aging seek to combine principles of evolution with theories from physiology, microbiology, and genetics (Rauser et al., 2005). For instance, the mutation accumulation theory of aging hypothesizes that lethal genetic mutations which affect organisms late in life will not be selected against, because the force of selection decreases with age. Over time, these negative, late-acting mutations can accumulate, resulting in increased mortality as organisms age (Medawar, 1952). The antagonistic pleiotropy theory takes this a step further and hypothesizes that these late acting mutations may be selected for if they benefit an organism earlier in life (Williams, 1957; Hamilton, 1966, 1996). On the other hand, the reliability theory of aging and longevity hypothesizes that over time organisms wear out and eventually fail due to the loss of irreplaceable parts (Gavrilov and Gavrilova, 1991, 2001).

Another theory is the disposable soma theory of aging (Drenos and Kirkwood, 2005; Finch and Kirkwood, 2000; Kirkwood, 1981). This theory predicts that because organisms have a finite amount of energy to use for all life functions, there is a trade-off between repairing and maintaining the soma or reproducing. If energy is used to maintain the soma, there might not be enough energy to reproduce, and vice versa. We therefore expect that the optimal allocation strategy, which would maximize the representation of an organism's genes in future generations, will not be one that allows an organism to maintain the soma indefinitely.

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These theories make similar predictions about how aging and lifespan will evolve in response to extrinsic mortality. For instance, if an organism experiences high natural mortality, natural selection will result in greater investment in offspring than in soma. High natural mortality is also predicted to encourage earlier maturation, so an organism will be less likely to die before having an opportunity to reproduce. Organisms with low natural mortality are predicted to maintain the soma for longer, produce offspring less frequently, and experience longer lives. However, disposable soma theory also predicts how natural mortality is expected to influence life span and reproductive schedules, and gives insight into responses to aging in terms of allocation of resources for repair and maintenance.

## 2. Fitness models of bacteria and simple organisms

Quantitative models can be useful for exploring how evolutionary trade-offs shape aging and senescence in these simple organisms. In this paper we utilize a simple mathematical model to explore the effect of senescence, in the form of finite reproductive lifespan, on bacterial fitness and resource allocation. We first introduce a baseline model without aging to provide a point of reference with which to compare the model with aging, then present a model of life histories of simple organisms that includes aging.

### 2.1. The baseline model: population without aging

Various approaches are available for modeling life-history strategies (Charlesworth, 1980; Roff, 2002; Stearns, 1992). We use the Euler-Lotka equation to explore the effects of life history choices on fitness of single-celled organisms. Our selected measure of fitness is the intrinsic rate of natural increase, for populations living in a constant environment with age-dependent reproduction and mortality schedules, denoted by $r$. The Euler-Lotka equation in continuous time is given by:

$$1 = \int_0^\infty \mathrm{e}^{-rx} l_x b_x \mathrm{d}x. \tag{1}$$

Here the probability of surviving to age $x$ is denoted as $l_x$ and the rate of production of offspring by an individual of age $x$ is $b_x$.

Before examining a model with aging, we review a baseline model that assumes infinite reproductive potential. Kirkwood (1981) proposed a simple model of bacterial fitness for cells that divide perfectly symmetrically, based upon (1), with appropriate choices of $b_x$ and $l_x$ for a clonally reproducing population. First, let $l_x$ be an exponentially decreasing survival probability, $l_x = \mathrm{e}^{-mx}$, where $m$ is the constant extrinsic mortality rate. The birth rate depends upon the doubling time, $T$. If an individual bacteria survives to time $T$, it divides. Since the division is perfectly symmetric, we cannot tell the difference between the two resulting cells. We therefore consider both of the cells to be identical offspring, and the original bacteria is essentially "dead" (rather like a semelparous organism). If the offspring have the same doubling time as the original cell, an appropriate "birth" rate would therefore be $b_x = 2\delta(x - T)$, where $\delta(\cdot)$ is the Dirac delta function.[1] With these expressions for $l_x$ and $b_x$ the Euler-Lotka Eq. (1) becomes:

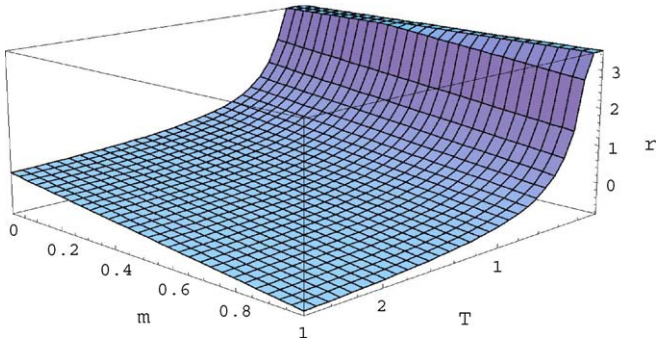


Fig. 1. The intrinsic rate of natural increase, $r$, as a function of the doubling time, $T$, and the mortality, $m$.

$$2\mathrm{e}^{-(m+r)T} = 1. \tag{2}$$

In Fig. 1, we show this functional relationship between fitness, $r$, mortality rate, $m$, and doubling time, $T$. As $m$ and $T$ increase, $r$ decreases. As $T \to 0$, $r \to \infty$ regardless of the value of $m$. As $m$ and $T$ increase, $r$ decreases.

Trade-offs between mortality and reproduction can be explored by examining how resource allocation impacts the mortality rate and doubling time of the bacteria. We denote the fraction of resources allocated for growth and reproduction by $\rho$, and the fraction allotted for maintenance/repair and survival by $1 - \rho$. Following Kirkwood (1981), we parameterize the mortality, $m$, and doubling time, $T$, in terms of $\rho$ as:

$$T(\rho) = \frac{T_0}{\rho} \tag{3}$$

$$m(\rho) = \frac{m_0}{1 - \rho}. \tag{4}$$

Here, $T_0$ can be thought of as the minimum possible time it would take for the bacteria to reproduce if all of its resources are allocated to growth; $m_0$ is the minimum mortality of the bacteria if all resources are allocated to survival. Solving for $r$ in (2) with the expressions for $T$ and $m$ in (3)–(4) yields:

$$r = \frac{\rho}{T_0} \ln 2 - \frac{m_0}{1 - \rho}. \tag{5}$$

[1] The Dirac delta function is defined as a unit impulse at some point $x_0$ such that:

$$\delta(x - x_0) = 0, \quad x \neq x_0$$
$$\int_{-\infty}^{\infty} \delta(x - x_0)\mathrm{d}x = 1,$$

and given an arbitrary function $f(x)$:

$$\int_{-\infty}^{\infty} f(x)\delta(x - x_0)\mathrm{d}x = f(x_0).$$

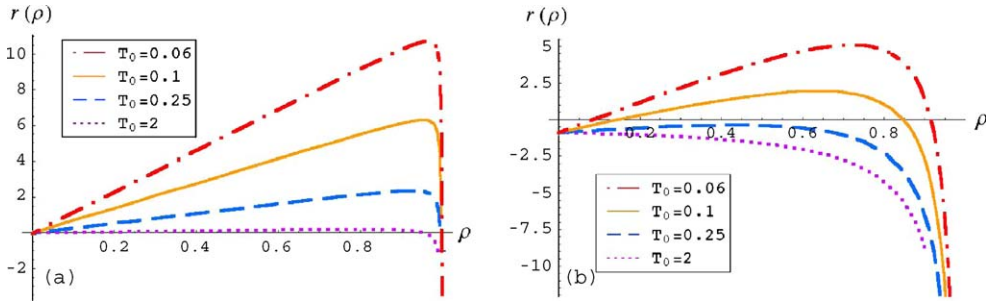


Fig. 2. $r$ as a function of $\rho$ for four values of $T_0$ = (2, 0.25, 0.1, 0.06) for (a) $m_0 = 0.015$, (b) $m_0 = 0.9$. High values of $T_0$ correspond to the lowest curves in each plot, and small $T_0$ to higher curves.

Maximizing (5) with respect to $\rho$ gives the optimal resource allocation, $\rho^*$:

$$\rho^* = 1 - \left(\frac{T_0 m_0}{\ln 2}\right)^{1/2}, \tag{6}$$

and the corresponding value of $r_{\max}$,

$$r_{\max} = \frac{1}{T_0}(\ln 2 - 2(m_0 T_0 \ln 2)^{1/2}). \tag{7}$$

If $T_0$ and $m_0$ are constants, $r(\rho)$ will follow curves similar to those depicted in Fig. 2. We can see from Eq. (6) and Fig. 2 that if there is any mortality (i.e. $m_0 > 0$) the optimal strategy will never be to dedicate all resources to reproduction, i.e. $\rho^* < 1$. Also, from Eq. (6) we see that the optimal allocation strategy is determined by the product $m_0 T_0$. In an environment with low mortality, it can be optimal to invest most resources in reproduction ($\rho^* \to 1$), as we show in Fig. 2a, even if the generation time is relatively long (lowest curve). However, if the mortality is high and/or the doubling time is long, the optimal resource allocation may be to use more resources for survival ($\rho^* \to 0$) (Fig. 2b). Furthermore, the maximum fitness, $r_{\max}$, is more sensitive to the value of the minimum doubling time, $T_0$, than to the minimum mortality rate, $m_0$, so we expect that there would be stronger selection to reduce $T_0$ than $m_0$.

## 3. Effects of limited reproduction on the fitness of simple organisms

We now explore how the fitness of unicellular organisms, measured by the intrinsic rate of natural increase and denoted by $\tilde{r}$, is affected by finite reproductive life span. For simplicity, we assume that the only effect of aging is limited reproduction, and that mortality is constant across all age classes. Additionally we assume that the doubling time is constant.

Starting from the Euler-Lotka Eq. (1) we first assume, as in the baseline model, an exponentially decreasing survival rate. We modify the birth rate, $b_x$, to take into account a functional asymmetry in cell division. The cell is able to divide and produce a single offspring in a given fixed doubling time $T$, then again at times $2T$, $3T$, etc. We define cellular "age", $a = 1, 2, \ldots, a_{\max}$, as the number of times the cell has doubled, where $a_{\max}$ is the maximum number of times it can split.

Additionally, we assume that the offspring is "rejuvenated", in that its initial age is set to zero, instead of to the maternal age. The birth rate is then a sum of delta functions spaced a distance $T$ apart:

$$b_x = \sum_{a=1}^{a_{\max}} \delta(x - aT). \tag{8}$$

This, together with the previous expression for $l_x$, inserted into (1) gives:

$$\begin{aligned} 1 &= \int_0^\infty e^{-\tilde{r}x} e^{-mx} \sum_{a=1}^{a_{\max}} \delta(x - aT)\,dx \\ &= \sum_{a=1}^{a_{\max}} e^{-(\tilde{r}+m)aT} \end{aligned}. \tag{9}$$

Evaluating the sum in Eq. (9) results in:

$$e^{(\tilde{r}+m)T} = 2 - e^{-(\tilde{r}+m)Ta_{\max}}. \tag{10}$$

This equation has two solutions for $a_{\max} \geq 1$. A trivial solution exists when $\tilde{r} = -m$. This solution corresponds to population in a steady state such that the intrinsic rate of natural mortality exactly balances extrinsic mortality. All other solutions depend upon the maximum age, $a_{\max}$, the mortality rate, $m$, and the doubling time, $T$. Since Eq. (10) does not have an exact closed form solution, we explore the relationships between fitness and other parameters using numerical solutions or analytic approximations. In Fig. 3, we show the numerical solution to Eq. (10) for various combinations of $a_{\max}$, $m$, and $T$. The value of $\tilde{r}$ varies considerably depending upon the combination of these three parameters. Variation of $T$ and $a_{\max}$ have the most impact upon $\tilde{r}$, as we show in Fig. 3a. Small perturbations of $a_{\max}$ when $a_{\max}$ is small has a much larger impact upon $r$ than perturbations of $a_{\max}$ when $a_{\max}$ is large. When $a_{\max} \to \infty$, Eq. (10) reduces to Eq. (2), and $\tilde{r} \to r$. In other words, infinite reproductive lifespan and perfectly symmetrical cell division are equivalent.

In contrast to the large influence of the doubling time on fitness, variations in the mortality, $m$, act to shift $\tilde{r}$ up or down a fixed amount when $T$ is held constant (Fig. 3b). Because mortality acts on all age classes equally, there is no decrease in the force of selection on older age classes when the mortality is high.

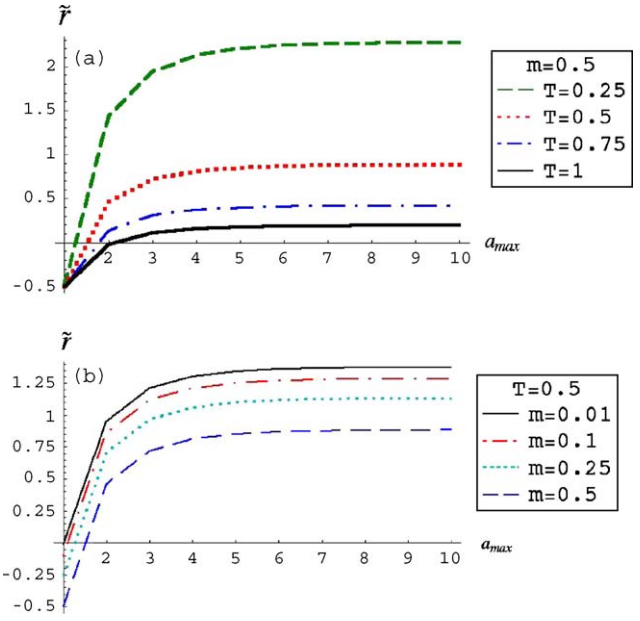


Fig. 3. $\tilde{r}$ vs. $a_{\max}$ for (a) $m = 0.5$, $T = (0.25, 0.5, 0.75, 1)$ and (b) $T = 0.5$ and $m = (0.5, 0.25, 0.1, 0.01)$.

Since $\tilde{r} \to r$ as $a_{\max}$ increases, we can approximate the second solution of Eq. (10) in terms of $r$ for large values of $a_{\max}$ using Newton's method. The first order approximation to Eq. (10) is:

$$\tilde{r} \approx r - \frac{1}{T} \frac{2^{-a_{\max}}}{\ln 2 + a_{\max} 2^{-a_{\max}}}. \tag{11}$$

As can be seen in Fig. 4, this approximation is remarkably good over a wide range of values of $a_{\max}$, so further approximations are not necessary. This approximation also gives us some idea of the values of $a_{\max}$ that are "large". Where

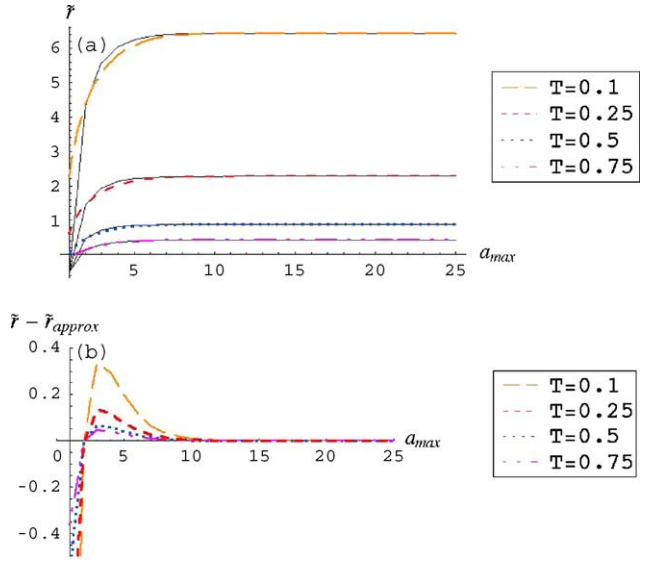


Fig. 4. (a) Analytic approximation (dashed lines) and numerical solution (solid lines) of $\tilde{r}$ vs. $a_{\max}$ for $m = 0.5$ and $T = (0.1, 0.25, 0.5, 0.75)$. (b) The difference between the numerical solution and analytic approximation, $\tilde{r} - \tilde{r}_{\text{approx}}$, for the same values as in (a).

the approximation is valid, $a_{\max}$ must be large enough to make the difference in fitness between the aging bacteria and the immortal bacteria, $r - \tilde{r}$, very small, corresponding to values of $a_{\max} \geq 10$.

Using this approximation, we can look at fitness changes when an additional replication is added,

$$\Delta\tilde{r} = \tilde{r}(a_{\max} + 1) - \tilde{r}(a_{\max}), \tag{12}$$

to learn more about how selective pressure might influence the value of $a_{\max}$. This is similar to the approach used by Hamilton (1996) and Charlesworth (1980, 2000) to explore how natural selection shapes fecundity and mortality as a function of age. The numerical solution is shown in Fig. 5. We can also use Eq. (11) to find an analytic approximation.

$$\Delta\tilde{r} \approx \frac{2^{-a_{\max}-1}}{T} \left( \frac{2}{\ln 2 + a_{\max} 2^{-a_{\max}}} - \frac{1}{\ln 2 + (a_{\max} + 1) 2^{-a_{\max}-1}} \right) \tag{13}$$

From both the numerical solution and analytic approximation, we can see that the value of additional replications declines rapidly as the maximum number of possible replications, $a_{\max}$, increases (Fig. 5). This indicates that the selective pressure to increase $a_{\max}$ above 10 or 20 should be small.

Since the fitness of the aging and immortal bacteria are very close when $a_{\max}$ is large, we would expect that the allocation strategies would be similar as well. Let us denote the allocation strategy of an aging bacteria by $\tilde{\rho}$. Substituting (3) and (4) into (10) gives a relationship between $\tilde{r}$, $\tilde{\rho}$, $m_0$, $T_0$, and $a_{\max}$:

$$\exp\left( \left( \tilde{r} + \frac{m_0}{1 - \tilde{\rho}} \right) \frac{T_0}{\tilde{\rho}} \right) = 2 - \exp\left( - \left( \tilde{r} + \frac{m_0}{1 - \tilde{\rho}} \right) \frac{T_0}{\tilde{\rho}} a_{\max} \right). \tag{14}$$

Unlike the baseline model without aging, Eq. (14) does not have an exact closed form analytic solution. In Fig. 6, we show a numerical solution for the fitness of the aging bacteria, $\tilde{r}$, as a function of the fraction of resources allocated for reproduction, $\tilde{\rho}$, for various values of $a_{\max}$, $m_0$, and $T_0$. The fitness measure, $\tilde{r}$,

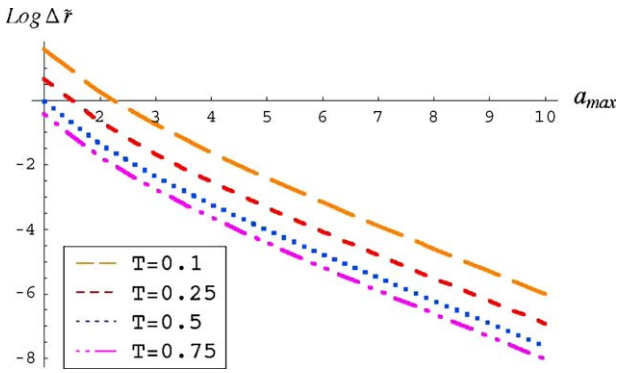


Fig. 5. Fitness gained by the organisms by increasing the maximum number of doublings from $a_{\max}$ to $a_{\max} + 1$, i.e. $\Delta\tilde{r} = \tilde{r}(a_{\max} + 1) - \tilde{r}(a_{\max})$.

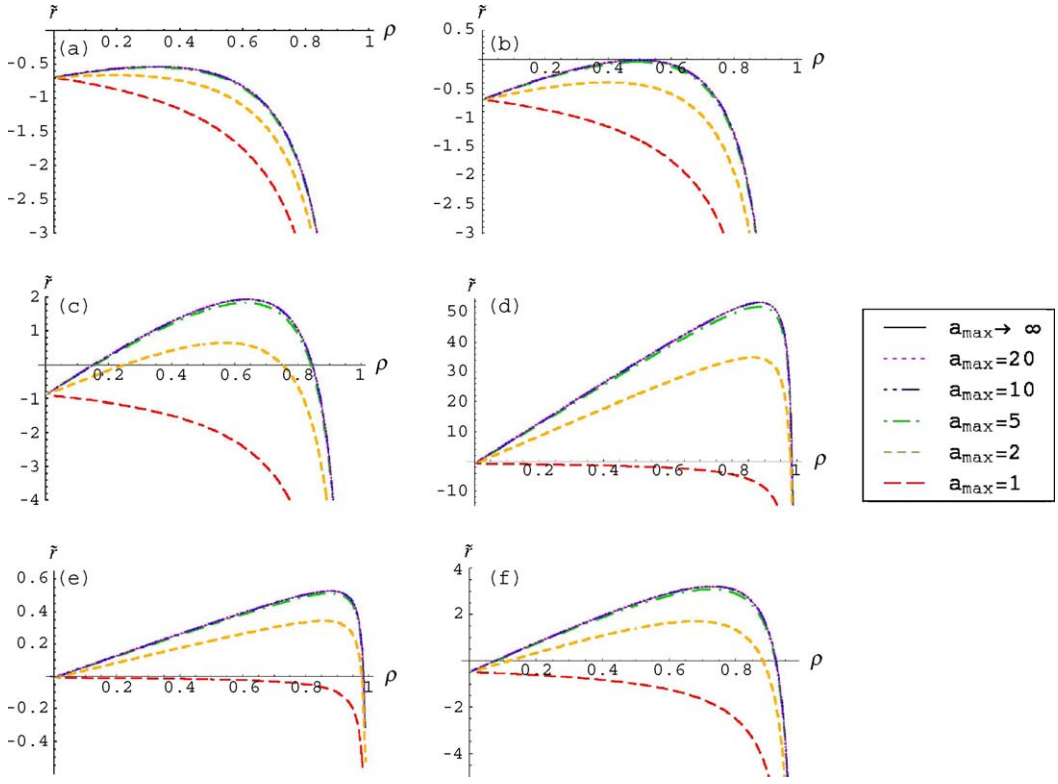


Fig. 6. Effects of $a_{max} = (1, 2, 5, 10, 20)$ on $\tilde{r}(\tilde{\rho})$ and $r(\rho)$ (solid black line) for (a) $m_0 = 0.7$, $T_0 = 0.45$; (b) $m_0 = 0.7$, $T_0 = 0.25$; (c) $m_0 = 0.9$, $T_0 = 0.1$; (d) $m_0 = 0.9$, $T_0 = 0.01$; (e) $m_0 = 0.01$, $T_0 = 1$; and (f) $m_0 = 0.5$, $T_0 = 0.1$.

increases dramatically as $a_{max}$ initially increases from $a_{max} = 1$. However, for higher values of $a_{max}$ (e.g. $a_{max} = 10$ or 20), $\tilde{r}$ hardly varies. Thus there is a lower return in fitness for more opportunities to reproduce. Additionally, notice that as $a_{max}$ increases, the peak in $\tilde{r}$ becomes more pronounced, and shifts towards higher values of $\tilde{\rho}$. Thus, bacteria that have more opportunities to reproduce gain more fitness from focusing resources on reproduction than those that cannot.

We can quantify how aging shifts the optimal allocation strategy away from the value determined in Eq. (6) for immortal bacteria. If we differentiate Eq. (14) with respect to $\tilde{\rho}$, and evaluate it at the optimal strategy, $\tilde{\rho}^*$, so that $(\mathrm{d}\tilde{r}(\tilde{\rho}^*))/\mathrm{d}\tilde{\rho}^* = 0$, we find an implicit expression for the maximum fitness, $\tilde{r}(\tilde{\rho}^*) = \tilde{r}_{max}$, as a function of $\tilde{\rho}^*$:

$$((2\tilde{\rho}^* - 1)m_0 - \tilde{r}_{max}(1-\tilde{\rho}^*)^2) \times \left[\mathrm{e}^{(\tilde{r}_{max}+m(\tilde{\rho}^*))T(\tilde{\rho}^*)} + a_{max}\mathrm{e}^{-(\tilde{r}_{max}+m(\tilde{\rho}^*))T(\tilde{\rho}^*)a_{max}}\right] = 0. \quad (15)$$

Since the sum of exponential terms in (15) can never be equal to zero, we conclude that

$$(2\tilde{\rho}^* - 1)m_0 - \tilde{r}_{max}(1-\tilde{\rho}^*)^2 = 0,$$

and therefore $\tilde{r}_{max}$ is related to $\tilde{\rho}^*$ by

$$\tilde{r}_{max} = \frac{2\tilde{\rho}^* - 1}{(1-\tilde{\rho}^*)^2}m_0. \quad (16)$$

When $a_{max} \to \infty$, we regain (6). As previously discussed, increasing the maximum cellular age, $a_{max}$, results in an increase in the difference between the fitness of the immortal bacteria, $r$, and the fitness of the aging bacteria, $\tilde{r}$, decreases. In particular, for large values of $a_{max}$ we saw that $r \to \tilde{r}$. We can also see in Fig. 6 that when $a_{max} \approx 10$ the peaks in the fitness curves are very close, so that $r_{max} \approx \tilde{r}_{max}$, and occur at about the same value of the allocation strategy, i.e. $\tilde{\rho}^* \approx \rho^*$.

This suggests that we can find approximate expressions for $\tilde{\rho}^*$ and $\tilde{r}_{max}$ by examining the difference between $r_{max}$ and $\tilde{r}_{max}$:

$$r_{max} - \tilde{r}_{max} = r(\rho^*) - r(\tilde{\rho}^*) + r(\tilde{\rho}^*) - \tilde{r}(\tilde{\rho}^*). \quad (17)$$

Writing (17) in this way allows us to use the approximation from Eq. (11) to determine the value of a small parameter, $\epsilon$, in our approximation. Substituting Eqs. (5), (11) and (16) into (17) and rearranging gives:

$$\frac{2\tilde{\rho}^* - 1}{(1-\tilde{\rho}^*)^2}m_0 \approx \frac{\tilde{\rho}^* \ln 2}{T_0} + \frac{m_0}{1-\tilde{\rho}^*} + \frac{\tilde{\rho}^*}{T_0}\epsilon$$

where $\epsilon = (2^{-a_{max}})/(\ln 2 + a_{max}2^{-a_{max}})$. Solving this expression for $\tilde{\rho}^*$, we find:

$$\tilde{\rho}^* \approx 1 - \left(\frac{m_0 T_0}{\ln 2 - \epsilon}\right)^{1/2} \approx \rho^* - \frac{1}{2}\left(\frac{\ln 2}{m_0 T_0}\right)^{1/2}\epsilon. \quad (18)$$

From this we also find an approximate expression for $\tilde{r}_{\max}$, similar to Eq. (7):

$$\tilde{r}_{\max} \approx \frac{1}{T_0}(\ln 2 - \epsilon - 2(m_0 T_0(\ln 2 - \epsilon))^{1/2}). \quad (19)$$

This analytic approximation gives results that are close to those obtained numerically, especially for large values of $a_{\max}$. When $T_0 = 0.05$ and $m_0 = 0.5$, the approximation performs the least well when $a_{\max} = 5$, as we might have guessed since this is when $r - \tilde{r}$ is largest (Fig. 4). In this case the numerical solution is $(\tilde{\rho}^*, \tilde{r}_{\max}) = (0.8077, 8.31959)$ compared to the analytic approximation $(\tilde{\rho}^*, \tilde{r}_{\max}) = (0.804836, 8.00324)$. As $a_{\max}$ increases, the approximation improves. For instance, when $a_{\max} = 20$, the numerical solution is $(\tilde{\rho}^*, \tilde{r}_{\max}) = (0.8101, 8.58945)$, and the analytic approximation is $(\tilde{\rho}^*, \tilde{r}_{\max}) = (0.810086, 8.59738)$, a difference of less then 0.1% in $\tilde{r}_{\max}$ and less than 0.002% in $\tilde{\rho}^*$.

The analytic approximation for $\tilde{\rho}^*$ can be used to explore how the bacterial mortality rate under an optimal allocation strategy depends upon $a_{\max}$. Substituting Eq. (18) into (4) gives:

$$\tilde{m}^* = m(\tilde{\rho}^*) \approx \left(\frac{m_0}{T_0}\right)^{1/2} (\ln 2 - \epsilon)^{1/2} \quad (20)$$

where the mortality under this optimal strategy for the aging bacteria is denoted by $\tilde{m}^*$.

In Fig. 7 we show $\tilde{m}^*$ as a function of $a_{\max}$. For a given value of $a_{\max}$, as $T_0$ decreases the optimal allocation strategy results in higher overall mortality rates. That is, an organism with shorter minimum doubling times is likely to live through most of its reproductions, so it gains more from shifting resources to decrease the doubling time further, letting the mortality rate rise. On the other hand, when $T_0$ is large, the organism is better served by keeping the mortality rate low. This way it can survive through as many reproductions as possible, even though this increases the time between reproductions. Additionally, when $a_{\max}$ is small, it is to the organism's advantage to keep the mortality lower so it can survive through more of its possible reproductions. As $a_{\max}$ increases, however, it becomes less necessary to survive for all of the possible reproductions, and instead it is optimal to allow the mortality rate to increase so the doubling time can be decreased.

Also notice that as $a_{\max}$ increases, $\tilde{m}^*$ approaches the mortality under the optimal strategy for bacteria that do not age ($\tilde{m}^* \to m^*$), but the mortality rate for the bacteria with infinite

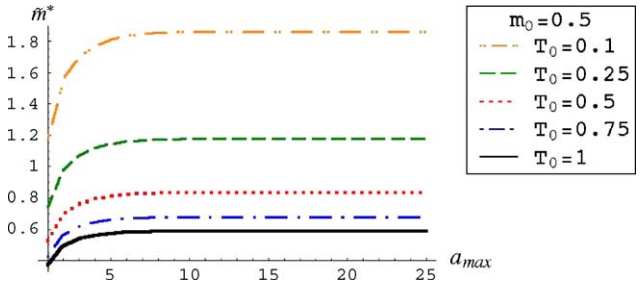


Fig. 7. Mortality under the optimal strategy for the aging bacteria, $\tilde{m}^*$ as a function of $a_{\max}$ for $m_0 = 0.5$, $T_0 = (0.1, 0.25, 0.5, 0.75, 1)$.

reproductive capability is always higher than that of the aging bacteria. This is counterintuitive, since it would seem to be to the organism's advantage to survive for as long as possible and get many opportunities to reproduce. However, the high value of the first few reproductions together with the trade-off between mortality and reproduction results in an optimal strategy that increases the mortality of the infinitely reproducing bacteria compared to the aging bacteria. So although high extrinsic mortality does not influence the value of later reproductions in this model, it does influence the pay-off from allocation of resources for repair, especially when the maximum number of possible reproductions is small. In these cases, higher mortality results in a greater investment in repair and survival, leading to a decrease in the absolute mortality experienced by the organism. When the mortality is lower, however, the organism does not gain as much benefit from repair processes, and instead allocates resources for reproduction.

### 3.1. Discussion

Here we have proposed a simple mathematical model to explore how aging, in the form of finite reproductive life span, affects fitness in unicellular organisms, particularly in bacteria. This allows us to explore, explicitly, predictions of the disposable soma theory of aging for systems that are fairly simple and easy to manipulate.

The model has three major assumptions: (1) some kind of asymmetry in cell division, regardless of the source, that can enable us to differentiate between an "old" and a "young" cell; (2) that the young cell is somehow rejuvenated; (3) mortality is age independent. The first two assumptions are general enough to make this model applicable to various unicellular organisms, not just bacteria. The model could be generalized by relaxing the third assumption to include some kind of age dependent mortality.

This model allows us to quantify how senescence, specifically finite replicative ability, affects fitness of unicellular organisms, and provides a framework for quantifying how other traits associated with aging can affect fitness. Given the assumptions about the form of $l_x$ in the Euler-Lotka equation, as well as the relationships between mortality, doubling rate, and resource allocation, this model predicts that the organism's ability to manipulate the doubling time $T$ has the greatest impact upon fitness. If the doubling time is short, even if the mortality is high, as is shown in Fig. 6d, the bacteria's fitness is considerably higher than in a system with lower mortality, but longer doubling time (Fig. 6e and f). Thus we expect for there to be strong selection for lower values of the minimum doubling time, $T_0$, but little selection for lower values of the minimum mortality rate, $m_0$.

We also find that bacteria experience surprisingly little loss of fitness when reproductive opportunities are reduced (Figs. 3 and 6). For most combinations of the minimum mortality rate, $m_0$, and minimum doubling time, $T_0$, $a_{\max} \approx 10$ or 20 is large enough to confer almost exactly the same amount of fitness to the bacteria as would an ability to reproduce indefinitely (Fig. 6). Most of the bacteria's fitness is gained the first few

times it doubles, and the amount gained in each subsequent doubling decreases rapidly, because after an organism has reproduced a few times, the lineages produced from the first few offspring are growing exponentially, so the fitness gained from producing a single new offspring now is much smaller in comparison. Therefore, we expect that if there were a resource cost associated with increasing the maximum number of possible doublings, then investing resources to survive to double the first few times would be better than investing additional resources to try to maintain cell integrity indefinitely.

This pattern of lower fitness payoff per additional chance at replications is not only found when using $r$ as a measure of fitness. We can examine the expected lifetime reproductive success (LRS)

$$\mathrm{LRS} = \sum_{i=1}^{a_{\max}} \mathrm{e}^{-mTi} = \frac{\mathrm{e}^{-mT}\left(1 - \mathrm{e}^{-mTa_{\max}}\right)}{1 - \mathrm{e}^{-mT}}.$$

This fitness measure exhibits much of the same qualitative behavior as the intrinsic rate of natural increase, $r$, as a function of the maximum reproductive age: when $a_{\max}$ increases, the fitness increases, rapidly asymptoting towards a maximum value. However, in this case, the asymptote of the fitness and the value of later reproduction are influenced by the mortality, $m$, and the doubling time, $T$, equally.

Studying the impacts of aging and resource allocation on fitness for bacteria is appealing for a number of reasons. Bacterial systems are relatively simple. They also are ideal for experimental manipulation. Metabolism and repair activity should be fairly straightforward to measure, giving indications of how bacteria allocate resources. Genetic manipulation of bacterial systems is also possible, which allows more direct measurement of the parameters in the model. Because generation times are short, bacterial systems also allow for replicate experiments at a reasonable cost. Thus, bacterial systems are ideal model systems for ecology (Jessup et al., 2004).

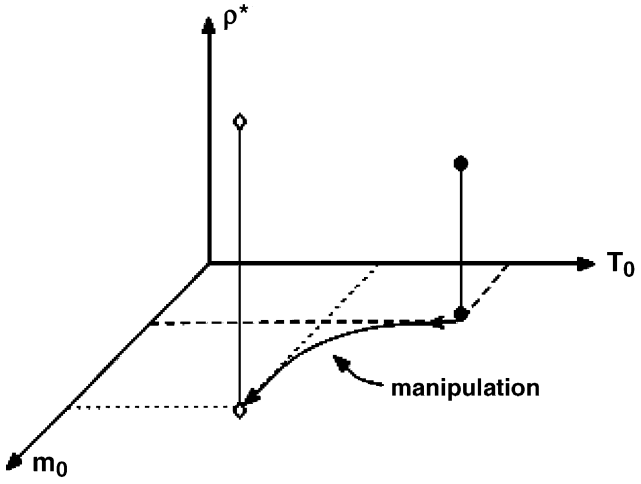


Fig. 8. Schematic of an experiment to test predictions of our model. The experimental system starts out with particular values of $m_0$ and $T_0$, and a corresponding value of $\rho^*$. After an experimental manipulation, the system has new values of $m_0$ and $T_0$. A new value of $\rho^*$ is then measured, and compared to model predictions.

It should be possible to test many of our model predictions experimentally (see Fig. 8). The laboratory environment that the bacteria experiences could be manipulated in order to ''set'' values of $m_0$ and $T_0$. For instance, temperature affects the rates at which chemical reactions occur and thus affects $T_0$. Other factors, such as nutrient levels, salinity, and oxygen levels, could also determine $T_0$ and $m_0$. Then, assuming that the organisms act in a way which is approximately optimal, the optimal allocation strategy could be measured via gene expression or some other proxy, and compared to the model predictions. For example, *E. coli* and other bacteria undergo drastic metabolic changes (stringent response) during amino acid starvation (Magnesson et al., 2005). During the stringent response, genes responsible for proliferation and growth are down-regulated while genes responsible for survival and virulence are up-regulated. These responses are thought to be mediated by a small nucleotide, guanosine tetraphophate (ppGpp) (Magnesson et al., 2005). Measurement of gene expression or levels of signaling molecules such as ppGpp may be appropriate as proxies for $\tilde{\rho}^*$ in order to test the predictions of the model, specifically the quantitative predictions of allocation strategies presented here.

Our simple model has the advantage of being analytically tractable. Although numerical results for complex models are fairly easy to obtain, it can be difficult to understand and quantify the roles of model parameters. Good analytic approximations, such as those found above for $\tilde{r}$, $\tilde{r}_{\max}$, and $\tilde{\rho}^*$, allow us to explore the effects of parameter variation in a very concrete way that might not be available for more complex models.

This simple model is only a first step in understanding how aging impacts bacterial fitness. It predicts that the fitness of individuals that only reproduce a few times is comparable to the fitness of those that reproduce many times, and that selection for large values of $a_{\max}$ should be small. This raises two important questions.

First, why do these organisms reproduce as many times, and survive for as long, as they do? Second, what other factors influence replicative life span? Looking at more complicated versions of this model may give insight into the answers to these questions. For instance, the current model does not consider the effects of variable environmental conditions, density effects, or of increasing doubling times or mortality rates as a function of age. Also, here we assume no dependence of $a_{\max}$ on $\rho$, i.e. there is no cost associated with increasing $a_{\max}$. These could be important factors in the development of bacterial life histories. However, in spite of these limitations, this model gives insight into why bacteria do not exhibit infinite lifespans, and suggests directions for further exploration.

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