Evolutionary Advantage of Cell Size Control

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We analyze the advantage of cell size control strategies in growing populations under mortality constraints and show that growth-dependent mortality can select for accurate size control. We determine how mortality, noise, and nongenetic heritability of cell size impact long-term population growth. We derive an analytical expression for the optimal cell size. We demonstrate that size heritability enables selection to act on the distribution of cell sizes in a population to avoid viability thresholds and adapt to size- and growth-dependent mortality landscapes.

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Cells of bacteria and other organisms grow exponentially in size before dividing [1,2]. Noise in cell division timing is therefore expected to yield increasingly large variations in cell size over time, yet single cell lineages maintain a narrow distribution of cell sizes over many generations [3–6]. While strategies [7–10] and molecular mechanisms [11–14] that underlie cell size control are being elucidated, it is presently unknown what selective advantage they confer in nature. Specifically, in free-living microbes such as bacteria, if exponential biomass growth can be achieved by any number of cells, what evolutionary benefit does the control of cell size contribute to a growing population? This question underlies our understanding of the evolutionary determinants of cell size and the origins of cell size control.

Starting from a single, exponentially growing cell that lacks a size control mechanism, the resulting population's average biomass growth rate would not depend strongly on how frequently cells divide; rather, it would largely depend on the mean growth rate of the size of single cells. However, if the process of cell growth comes with some mortal risk, division events can reduce the probability of extinction along each lineage by distributing the risk across a population. By this reasoning, selection will favor lineages that divide as frequently as possible. Since cells cannot be too small due to biophysical constraints—e.g., there must be enough room for their DNA and proteins—the presence of mortality could select for cell size control. In particular, we expect a control mechanism that enables cells to be as small as physically possible to be advantageous. As the minimum viable size of cells is approached, errors in cell size control will become increasingly costly as they can result in nonviable cells. Natural selection should favor minimizing the errors and evolutionarily tuning the control mechanism to avoid such viability thresholds. This argument thus identifies a general advantage of accurate cell size control. Yet, different control strategies, e.g., "sizer" or "adder," can efficiently minimize size control errors [3–5,7,9,15–19], and it has therefore been an outstanding question whether one strategy broadly confers a fitness advantage relative to another.

In this Letter, we introduce a simple model that represents the above evolutionary forces and study its implications using simulations, numerics, theory, and comparison with experiments. We demonstrate that the presence of growth-dependent mortality is sufficient to determine a finite optimal cell size that maximizes long-term population growth, thus providing an evolutionary mechanism that selects for cell size control. We show that nongenetic heritability of cell size enables selection to act on the cell size distribution to avoid viability thresholds and enhance population growth in different mortality landscapes. We discuss implications for evolution of size control mechanisms.

The statistics of size control in isolated single cells can be observed experimentally in a "mother machine" device [1,6]. Starting from a given birth size l, each cell grows exponentially in size and divides symmetrically. Given a parent cell's birth size l, the cell size control mechanism determines Δ, a random variable corresponding to the size added before cell division. The offspring's birth size l' is determined by the size relation, $l' = (l + \Delta)/2$. Iterating this control process leads to a stable birth-size distribution in isolated single cells. In an adder mechanism, cells attempt to add a fixed size before dividing; hence Δ and l are independent random variables, while l' and l are positively correlated. In a sizer mechanism, cells attempt to elongate to a fixed target size before dividing; hence l' and l are independent, while $\Delta\,(= 2l' - l)$ is negatively correlated with l. We define the control functions, $C_A(\Delta)$ and $C_S(l')$, which are the probability distributions of Δ in the adder model and of l' in the sizer model, respectively. We first analyze these two key examples and then generalize to a broad class of size control strategies.

We model a population of cells growing in the presence of mortality constraints. Active cell growth involves

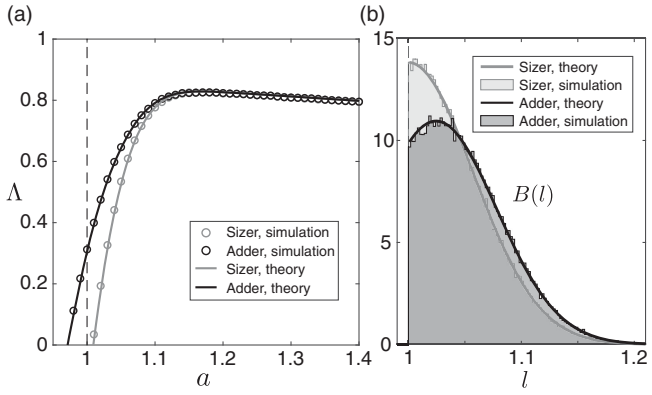

FIG. 1. Population growth of adder and sizer mechanisms with growth-dependent mortality. (a) Population growth rate Λ is shown as target birth size a is varied in simulations (points), compared with predictions (curves) from numerical solution of Eq. (2). Dashed line indicates $l_{\min} = 1$. Cells grow exponentially in size at rate $\lambda_0 = 1$. Control functions $C_S(l')$ and $C_A(\Delta)$ are Gaussian with mean a and variances σ_S^2 and σ_A^2, respectively, chosen to yield identical birth-size distributions in isolated cells [23]. Parameters are $\sigma_A = 0.1$, $\sigma_S = \sigma_A/\sqrt{3} = 0.058$, and $\beta = 0.1$. (b) Population birth-size distributions measured in simulation (shaded) and predicted by Eq. (2) (curves) for $a = l_{\min}$, with parameters as in (a).

remodeling basic cellular structures, e.g., the cell wall of bacteria, and renders cells more susceptible to environmental stresses such as antibiotics [20,21]. Mortality in our model is determined by a constant β characterizing growth-dependent mortality, where the probability of cell death during a growth increment δl is given by $\beta\,\delta l$ [22], and by a viability threshold $l_{\min}$, such that cells with birth size $l < l_{\min}$ are not viable. As cells grow and divide, the population size $N(t)$ increases exponentially, and its long-term growth rate is $\Lambda \equiv (1/t)\ln N(t)$, in the limit of large t.

For sizer and adder mechanisms that generate identical birth-size distributions in isolated cells, we compared the long-term growth rate of their populations as the target birth size a was varied [Fig. 1(a)]. We found that, for values of $a \gg l_{\min}$, the two curves nearly overlap and decrease linearly with a. As a approaches $l_{\min}$, however, the curves separate and the adder mechanism exhibits a pronounced advantage over the sizer. Strikingly, if we set the target birth size precisely at the viability threshold $a = l_{\min}$, the sizer population does not grow as half of its cells are born with $l' < l_{\min}$, yet the adder population has a positive growth rate. Moreover, the adder population can grow exponentially even for a range of target birth sizes $a < l_{\min}$ over which the sizer population goes extinct. This suggests that, although the two size control mechanisms are equally precise, the structure of single cell lineages that they generate differs in a critical way. Indeed, when $a = l_{\min}$, the distribution of birth sizes in the population has a peak at $l = l_{\min}$ for the sizer mechanism, but in the adder mechanism the peak is shifted to a value higher than $l_{\min}$ [Fig. 1(b)].

To understand these behaviors more generally, we analyzed population lineage structures using the transfer operator approach [24], which was previously used to study populations structured by age or size [25,26]. A single cell lineage $\xi = (l_1, l_2, \ldots, l_n)$ is specified by a series of cell divisions, where the i th division yields a cell with birth size l_i. We let the kernel $K(l', l)$ denote the expected number of offspring of birth size l' for a parent of birth size l. We let $B_t(l')$ denote the expected number of births at time t with birth size l', corresponding to lineages ending with l'. Each birth with size l' at time t results from a parent cell of birth size l that grew and divided at size $2l'$. The parent itself was born at time $t - \tau$, where $\tau = (1/\lambda)\ln(2l'/l)$; hence

$$B_t(l') = \int K(l', l) B_{t-\tau}(l) p(\lambda) dl d\lambda, \tag{1}$$

where we assume that the single cell growth rate, λ, is independent of birth size and has probability distribution $p(\lambda)$. In rod-shaped bacteria such as *Escherichia coli*, which maintain a constant cell width, l is measured by the cell length and λ is known as the elongation rate; experiments indicate that λ and l are nearly uncorrelated in constant conditions [2,15]. We analyze steady-state population growth, for which $B_t(l) \simeq e^{\Lambda t} B(l)$, where $B(l)$ is the population's composition of birth sizes l. Below, we assume a constant elongation rate λ_0, i.e., $p(\lambda) = \delta(\lambda - \lambda_0)$; for variable λ see [27]. Defining $\psi(l) \equiv l^{\Lambda/\lambda_0} B(l)$ and $\alpha \equiv (\Lambda/\lambda_0)\ln 2$, Eq. (1) yields

$$\psi(l') = e^{-\alpha} \int K(l', l)\psi(l) dl, \tag{2}$$

where e^{α} is the top eigenvalue of the kernel $K(l', l)$ and ψ is the associated right eigenfunction.

We study kernels that take the following form:

$$K(l', l) = z e^{-\beta(2l'-l)} \theta(l' - l_{\min}) C(l', l), \tag{3}$$

where the growth-dependent mortality β acts on the added size $\Delta = 2l' - l$, the viability threshold at $l_{\min}$ is enforced by the Heaviside step function θ, and the control function $C(l', l)$ gives the $l \to l'$ transition probability in isolated cell lineages. The constant z is used to distinguish lineages within a population, where each binary cell division generates two offspring ($z = 2$), from isolated single cell lineages ($z = 1$); we assume $z = 2$ unless otherwise specified [40]. We initially analyze a bivariate Gaussian family of control functions,

$$C(l', l) \equiv \frac{1}{\sqrt{2\pi\sigma^2(1-\rho^2)}} e^{-\frac{[l'-l\rho-a(1-\rho)]^2}{2(1-\rho^2)\sigma^2}}. \tag{4}$$

The parameter ρ is the correlation of parent-offspring birth length, where $\rho = 0$ or $1/2$ yields the previous sizer or

adder kernels, respectively. These control functions yield a Gaussian stable birth size distribution in isolated lineages, with mean a and variance σ^2, for any value of correlation $-1 < \rho < 1$, and thus span a continuous range of possible control mechanisms [41]. Numerical solution of Eq. (2) correctly predicts simulation results (Fig. 1).

We now analyze Eq. (2) to obtain the top eigenvalue of the kernel. For the special case of the sizer ($\rho = 0$), the kernel is separable such that $K(l', l) = \psi(l')\tilde{\psi}(l)$, with $\tilde{\psi}(l) = e^{\beta l}$ and $\psi(l') = zg(l')e^{-2\beta l'}\theta(l' - l_{\min})$, where $g(x) \equiv (2\pi\sigma^2)^{-1/2}e^{-(x-a)^2/(2\sigma^2)}$. Computing the top eigenvalue, we obtain $\alpha = \ln[\int \tilde{\psi}(l)\psi(l)dl]$, which can be evaluated exactly. However, for the general case ($\rho > 0$), there does not appear to be an analytical solution, and we proceed to develop the following scaling approximation. By analogy with polymers, we model the lineages as rigid rods with a certain persistence length [42]. We assume that offspring perfectly inherit their parent's birth size for r generations. Each such "block" of r monomers corresponds to a single, random choice of birth size l, and the blocks are therefore independent just like the individual monomers in the sizer model; we call this the "rigid correlated sizer" (RCS) approximation. To match parent-offspring correlation ρ to the RCS block size r, we set $r = (1-\rho)^{-1}$. At the level of blocks, parameters are rescaled via $\beta \leftrightarrow r\beta$, $z \leftrightarrow z^r$, and $\alpha \leftrightarrow r\alpha$, and substituting in the expressions above yields

$$\alpha_{\mathrm{RCS}} = \ln z - \beta a + \frac{r\beta^2\sigma^2}{2} + \frac{1}{r}\ln\left[\frac{1}{2}\mathrm{erfc}\left(\frac{l_{\min} - a + r\beta\sigma^2}{\sigma\sqrt{2}}\right)\right], \tag{5}$$

where $\mathrm{erfc}(x) \equiv (2/\sqrt{\pi})\int_x^\infty e^{-l^2}dl$ is the complementary error function. We then obtain $\Lambda_{\mathrm{RCS}} = \lambda_0\alpha_{\mathrm{RCS}}/\ln 2$.

The RCS approximation correctly predicts that an adder population can grow at the viability threshold while a sizer population cannot. Specifically, $\Lambda_{\mathrm{RCS}} = \lambda_0(1 - 1/r)$ at $a = l_{\min}$ for $\beta = 0$; hence $\Lambda_{\mathrm{RCS}} = 0$ for sizer and $\Lambda_{\mathrm{RCS}} = \lambda_0/2$ for adder. For comparison, the numerically computed value for adder is $\Lambda = 0.47\lambda_0$. We can alternatively treat r as a free parameter determined by matching the numerically computed value of Λ at the viability threshold. With this choice, the RCS closely approximates the growth rates for the adder model with different values of σ [Fig. 2(a)], as well as for kernels with different values of ρ [Fig. 2(b)]; we emphasize that the RCS is exact for the sizer kernel. Moreover, it predicts that at $a = l_{\min}$ for $\beta = 0$ the growth rate Λ does not depend on σ, consistent with numerical results [Fig. 2(a)].

Deviations between numerics and the RCS approximation are related to having a fixed rather than a flexible block size. To see this, we relaxed the RCS by allowing inheritance of birth size to be a random process, namely, with probability h the birth size is inherited, and with probability $1 - h$ the offspring is assigned a random birth size according to $g(l')$. We refer to this as the "flexible correlated sizer" (FCS); its kernel was previously studied in models of correlated cell division times [43,44] where ψ and α can be computed [28], though generally not in closed form. We find that the FCS approximation is slightly more accurate than RCS at intermediate values of a (Fig. 2). We note that, since RCS and FCS models assume that blocks are uncorrelated and do not capture details within blocks, they fail to approximate the eigenfunction itself; to this end, perturbation theory may be applicable (see [28] for details).

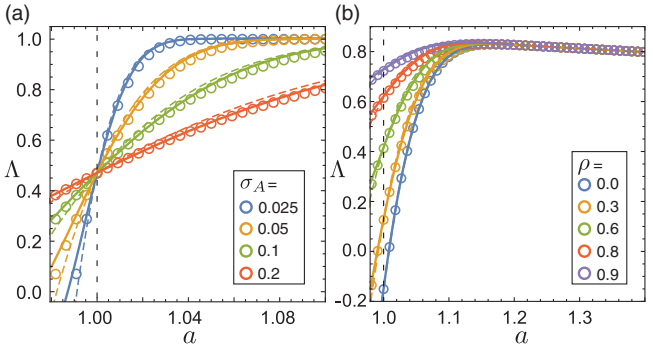

FIG. 2. Analytical results for correlated sizer approximations. Numerical results (points) and analytical approximations (RCS, dashed curves; FCS, solid curves) shown for long-term growth rate, Λ, as a function of target birth size, a. Vertical dashed line at $l_{\min} = 1$. (a) Results for the adder model ($\rho = 1/2$) with $\beta = 0$, $\lambda_0 = 1$, and σ_A as indicated in the key. Approximations use $\sigma = \sigma_A/\sqrt{3}$, $r = 1.887$ (RCS), and $h = 0.384$ (FCS); see [28] for $\beta = 0.1$. (b) Results for different values of ρ with $\beta = 0.1$. Parameter values ρ are indicated in the key, $\lambda_0 = 1$, $\sigma = 0.058$; see [28] for $\beta = 0$.

The selective benefits of cell size control can now be inferred from Eq. (5). In the absence of mortality ($\beta = 0$), Λ increases monotonically with a, indicating that arbitrarily large cell sizes would be favored to avoid the viability threshold. Size control therefore does not confer an advantage in this regime. In the presence of mortality ($\beta > 0$), size control is beneficial as there exists an optimal birth size a_{opt} that maximizes Λ [28], given by

$$a_{\mathrm{opt}} \approx l_{\min} + \sigma\sqrt{\ln[1/(2\pi r^2\beta^2\sigma^2)]} \tag{6}$$

for $r\beta\sigma \ll 1$. The optimal cell size balances a trade-off between mortality, which selects against large cells, and noise in cell size control, which selects against small cells. Furthermore, Eq. (5) shows that the quality of size control is under selection as reducing the noise σ moves a_{opt} closer to the viability threshold and increases Λ. The presence of a viability threshold and growth-dependent mortality thus select for accurate size control.

Would evolution tend to minimize σ as much as physiologically feasible, or does a nonzero value of σ confer

benefits? For example, if mortality β fluctuates in time, the peak of the mortality function will vary, and the long-term optimal cell size a_{opt} will deviate from the instantaneous optimum. In this case, noise in cell size control may be beneficial. To obtain analytical results, we consider a simple model in which survival of cells with birth size l is given by $f(l) \equiv e^{-\frac{1}{2}[(l-l_s)/\sigma_s]^2}$ and the position of peak survival l_s is normally distributed with mean $\bar{l}_s$ and variance Σ^2. Computing the long-term growth rate and optimizing over a and σ, we obtain $a_{\mathrm{opt}} = \bar{l}_s$, while σ_{opt} exhibits a continuous transition from zero for $\Sigma < \Sigma_*$ to $\sigma_{\mathrm{opt}} > 0$ for $\Sigma > \Sigma_*$, where $\Sigma_* \simeq \sigma_s$ [28]. Thus, if variability of l_s is larger than the width of the survival function, a nonzero optimal value of σ exists. Maintaining a limited amount of noise in cell size control can thus be advantageous in a fluctuating environment.

Would evolution favor increasing r arbitrarily, or are there constraints that select against high values of size heritability? For low mortality rates ($\beta\sigma \ll 1$), Eq. (5) shows that the strength of selection on r is driven by avoidance of the viability threshold and given by $\partial\alpha/\partial r \approx -r^{-2}\ln[\frac{1}{2}\mathrm{erfc}(-Z/\sqrt{2})]$, where $Z \equiv (a - l_{\mathrm{min}})/\sigma$. Thus, as r increases there will be diminishing returns for further increase in heritability. We therefore expect r to evolve until $\partial\alpha/\partial r$ is smaller than any fitness costs associated with mutations that increase r. For example, based on experimentally measured values of Z, we find that the strength of selection to increase r is high in the vicinity of a sizer ($r = 1$), where $\partial\alpha/\partial r$ can be as large as 7% per generation, while for $r > 4$, the strength of selection is much lower with $\partial\alpha/\partial r < 0.4\%$ [28]. While the precise evolution of r will depend on many factors, the above analysis points to evolutionary trade-offs that maintain a limited amount of cell size heritability $r > 1$. Consistent with this, experiments show that, in different species and growth conditions, $r = 1.9$–4.2 (*Escherichia coli*) and 1.5–3.0 (*Bacillus subtilis*) [28]. This range of values corresponds to $\rho = 0.35$–0.76, reflecting adderlike size control in these species.

In summary, the theory introduced here identifies how cell size control can be selected for and shaped over evolutionary timescales. We showed that growth-dependent mortality in the presence of a viability threshold selects for accurate cell size control. The optimal size relation (6) predicts what cell size would evolve over long timescales for a fixed level of noise, mortality, and nongenetic heritability in our model. Cell sizes can also adapt physiologically over much shorter timescales, e.g., in different nutrient conditions [45,46], and our analysis of experimental data shows that the optimal size relation is consistent with such physiological adaptation [28]. We demonstrated that nongenetic heritability of cell size increases a population's ability to adapt to mortality landscapes. Experimental perturbations of *E. coli*'s native cell division machinery [12,47], as well as simulated network evolution of simple cell cycle models [10], indicate a high capacity for size homeostasis mechanisms to adapt. On the basis of our findings, we expect that mortality landscapes present in nature select for and shape cell size control mechanisms in different species and environments.

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