Modeling the Growth of Organisms Validates a General Relation between Metabolic Costs and Natural Selection

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Metabolism and evolution are closely connected: if a mutation incurs extra energetic costs for an organism, there is a baseline selective disadvantage that may or may not be compensated for by other adaptive effects. A long-standing, but to date unproven, hypothesis is that this disadvantage is equal to the fractional cost relative to the total resting metabolic expenditure. We validate this result from physical principles through a general growth model and show it holds to excellent approximation for experimental parameters drawn from a wide range of species.

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Discovering optimality principles in biological function has been a major goal of biophysics [1–6], but the competition between genetic drift and natural selection means that evolution is not purely an optimization process [7–9]. A necessary complement to elucidating optimality is clarifying under what circumstances selection is actually strong enough relative to drift in order to drive systems toward local optima in the fitness landscape. In this Letter, we focus on one key component of this problem: quantifying the selective pressure on the extra metabolic costs associated with a genetic variant. We validate a long hypothesized relation [10–12] between this pressure and the fractional change in the total resting metabolic expenditure of the organism.

The effectiveness of selection versus drift hinges on two nondimensional parameters [13]. (i) The first is the *selection coefficient* s, a measure of the fitness of the mutant versus the wild-type. Mutants will have on average $1+s$ offspring relative to the wild-type per wild-type generation time. (ii) The second is the *effective population* N_e of the organism, the size of an idealized, randomly mating population that exhibits the same decrease in genetic diversity per generation due to drift as the actual population (with size N). For a deleterious mutant ($s<0$) where $|s| \gg N_e^{-1}$, natural selection is dominant, with the probability of the mutant fixing in the population exponentially suppressed. In contrast if $|s| \ll N_e^{-1}$, drift is dominant, with the fixation probability being approximately the same as for a neutral mutation [7]. Thus, the magnitude of N_e^{-1} determines the "drift barrier" [14], the critical minimum scale of the selection coefficient for natural selection to play a non-negligible role.

The long-term effective population size N_e of an organism is typically smaller than the instantaneous actual N and can be estimated empirically across a broad spectrum of life: it varies from as high as 10^9-10^{10} in many bacteria, to 10^6-10^8 in unicellular eukaryotes, down to $\sim 10^6$ in invertebrates and $\sim 10^4$ in vertebrates [12,15]. The corresponding 6 orders of magnitude variation in the drift barrier N_e^{-1} has immense ramifications for how we understand selection in prokaryotes versus eukaryotic organisms, particularly in the context of genome complexity [16–18]. For example, consider a mutant with an extra genetic sequence relative to the wild type. We can separate s into two contributions, $s=s_c+s_a$ [12]: s_c is the baseline selection coefficient associated with the metabolic costs of having this sequence, i.e., the costs of replicating it during cell division, synthesizing any associated mRNA/proteins, as well as the maintenance costs associated with turnover of those components; s_a is the correction due to any adaptive consequences of the sequence beyond its baseline metabolic costs. For a prokaryote with a low drift barrier N_e^{-1}, even the relatively low costs associated with replication and transcription are often under selective pressure [11,12], unless $s_c<0$ is compensated for an $s_a>0$ of comparable or larger magnitude [19]. For the much greater costs of translation, the impact on growth rates of unnecessary protein production is large enough to be directly seen in experiments on bacteria [1,20]. In contrast, for a eukaryote with sufficiently high N_e^{-1}, the same s_c might be effectively invisible to selection, even if $s_a=0$. Thus, even genetic material that initially provides no adaptive advantage can be readily fixed in a population, making eukaryotes susceptible to noncoding "bloat" in the genome. But this also provides a rich palette of genetic materials from which the complex variety of eukaryotic regulatory mechanisms can subsequently evolve [12,21].

Part of the explanatory power of this idea is the fact that the s_c of a particular genetic variant should in principle be predictable from underlying physical principles. In fact, a

very plausible hypothesis is that $s_c \approx -\delta C_T/C_T$, where C_T is the total resting metabolic expenditure of an organism per generation time, and δC_T is the extra expenditure of the mutant versus the wild type. This relation can be traced at least as far back as the famous "selfish DNA" work of Orgel and Crick [10], where it was mentioned in passing. But its true usefulness was only shown more recently, in the notable works of Wagner [11] on yeast and Lynch and Marinov [12] on a variety of prokaryotes and unicellular eukaryotes. By doing a detailed biochemical accounting of energy expenditures, they used the relation to derive values of s_c that provided intuitive explanations of the different selective pressures faced by different classes of organisms. The relation provides a Rosetta stone, translating metabolic costs into evolutionary terms. And its full potential is still being explored, most recently in describing the energetics of viral infection [22].

Despite its plausibility and long pedigree, to our knowledge this relation has never been justified in complete generality from first principles. We do so through a general bioenergetic growth model, versions of which have been applied across the spectrum of life [23–25], from unicellular organisms to complex vertebrates. We show that the relation is universal to an excellent approximation across the entire biological parameter range.

Growth model.—Let $\Pi(m(t))$ [unit: W] be the average power input into the resting metabolism of an organism (the metabolic expenditure after locomotion and other activities are accounted for [24]). $\Pi(m(t))$ can be an arbitrary function of the organism's current mass $m(t)$ [unit: g] at time t. This power is partitioned into maintenance of existing biological mass (i.e., the turnover energy costs associated with the constant replacement of cellular components lost to degradation) and growth of new mass (i.e., synthesis of additional components during cellular replication) [26]. Energy conservation implies

$$\Pi(m(t)) = B(m(t))m(t) + E(m(t))\frac{dm}{dt}, \qquad (1)$$

here $B(m(t))$ [unit: W/g] is the maintenance cost per unit mass, and $E(m(t))$ [unit: J/g] is the synthesis cost per unit mass. We allow both these quantities to be arbitrary functions of $m(t)$.

Though we will derive our main result for the fully general model of Eq. (1), we will also explore a special case: $\Pi(m(t)) = \Pi_0 m^\alpha(t)$, $B(m(t)) = B_m$, $E(m(t)) = E_m$, with scaling exponent α and constants Π_0, B_m, and E_m [25]. Allometric scaling of $\Pi(m(t))$ with $\alpha = 3/4$ across many different species was first noted in the work of Max Kleiber in the 1930s [27], and with the assumption of time-independent $B(m(t))$ and $E(m(t))$ leads to a successful description of the growth curves of many higher animals [23,24]. However, recently there has been evidence that $\alpha = 3/4$ may not be universal [28,29]. Higher animals still exhibit $\alpha < 1$ (with debate over $\alpha = 2/3$ vs $3/4$ [30]), but unicellular organisms have a broader range $\alpha \lesssim 2$. Thus, we will use the model of Ref. [25] with an arbitrary species-dependent exponent α. While the resulting description is reasonable as a first approximation, particularly for unicellular organisms, one can easily imagine scenarios where the exponent and maintenance costs might vary between different developmental stages [31]. For the case of maintenance in endothermic animals, which in our approach includes all non-growth-related expenditures, more energy per unit mass is allocated to heat production as the organism matures [32], effectively increasing the cost of maintenance. In the Supplemental Material, Sec. V [33] we show how the generalized model works in this scenario, using experimental growth data from two endothermic bird species [72]. Thus, it is useful to initially consider the model in complete generality.

Baseline selection coefficient for metabolic costs.—To derive an expression for s_c for the growth model of Eq. (1), we first focus on the generation time t_r, since this will be affected by alterations in metabolic costs. t_r is the typical age of reproduction, defined explicitly for any population model in the Supplemental Material, Sec. I [33], where we relate it to the population birth rate r through $r = \ln(R_b)/t_r$ [73,74]. Here R_b is the mean number of offspring per individual. Let $\epsilon = m_r/m_0$ be the ratio of the mass $m_r = m(t_r)$ at reproductive maturity to the birth mass $m_0 = m(0)$. For example, in the case of symmetric binary fission of a unicellular organism, $R_b \approx \epsilon \approx 2$ (see the Supplemental Material, Sec. III [33] for a discussion of ϵ in more general models of cell size homeostasis). Since $m(t)$ is a monotonically increasing function of t for any physically realistic growth model, we can invert Eq. (1) to write the infinitesimal time interval dt associated with an infinitesimal increase of mass dm as $dt = dmE(m)/G(m)$ where $G(m) \equiv \Pi(m) - B(m)m$ is the amount of power channeled to growth, and we have switched variables from t to m. Note that $G(m)$ must be positive over the m range to ensure that $dm/dt > 0$. Integrating dt gives us an expression for t_r

$$t_r = \int_{m_0}^{\epsilon m_0} dm \frac{E(m)}{G(m)}. \qquad (2)$$

If we are interested in finding s_c for a genetic variation, we can focus on the additional metabolic costs due to that variation. For the purposes of calculation, this means treating the mutation as if it does not alter biological function in any other respect, including the ability of the organism to assimilate energy for its resting metabolism through uptake of nutrients or foraging. If the mutation actually had only metabolic cost effects, the full selection coefficient $s = s_c$. However, generically mutations can affect both metabolic costs and power input (and/or other adaptive aspects), so $s = s_c + s_a$, with a correction term s_a due to the adaptive effects [12]. In the latter case, s_c can still

be calculated as shown below (ignoring adaptive effects) and interpreted as the baseline contribution to selection due to metabolic costs. While we do not focus on s_a here, our theory can be readily extended to consider adaptive contributions as well, as illustrated in the Supplemental Material, Sec. VII [33], including aspects like spare respiratory capacity. This broader formalism is summarized in Fig. S3 of the Supplemental Material [33].

Proceeding with the s_c derivation, the products of the genetic variation (i.e., extra mRNA transcripts or translated proteins) may alter the mass of the mutant, which we denote by $\tilde{m}(t)$. The left-hand side of Eq. (1) remains $\Pi(m(t))$, where $m(t)$ is now the *unperturbed* mass of the organism (the mass of all the prevariation biological materials). The power input $\Pi(m(t))$ depends on $m(t)$ rather than $\tilde{m}(t)$ since only $m(t)$ contributes to the processes that allow the organism to process nutrients, in accordance with the assumption that power input is unaltered in order to calculate s_c. It is also convenient to express our dynamics in terms of $m(t)$ rather than $\tilde{m}(t)$, since the condition defining reproductive time t_r remains unchanged, $m(t_r) = \epsilon m_0$, or in other words when the unperturbed mass reaches ϵ times the initial unperturbed mass m_0. Thus, Eq. (1) for the mutant takes the form $\Pi(m(t)) = \tilde{B}(m(t)) + \tilde{E}(m(t))dm(t)/dt$, where $\tilde{B}(m(t)) = B(m(t)) + \delta B$ and $\tilde{E}(m(t)) = E(m(t)) + \delta E$ are the mutant maintenance and synthesis costs. For simplicity, we assume the perturbations δB and δE are independent of $m(t)$, though this assumption can be relaxed. In the Supplemental Material, Sec. IV [33], we show a sample calculation of δB and δE for mutations in *Escherichia coli* and fission yeast involving short extra genetic sequences transcribed into noncoding RNA. This provides a concrete illustration of the framework we now develop.

Changes in the metabolic terms will perturb the generation time, $\tilde{t}_r = t_r + \delta t_r$, and consequently the birth rate $\tilde{r} = r + \delta r$. The corresponding baseline selection coefficient s_c can be exactly related to $\tilde{s}_c \equiv -\delta t_r/t_r$, the fractional change in t_r, through $s_c = R_b^{\tilde{s}_c/(1-\tilde{s}_c)} - 1$ (see the Supplemental Material, Sec. I [33]). This relation can be approximated as $s_c \approx \ln(R_b)\tilde{s}_c$ when $|\tilde{s}_c| \ll 1$, the regime of interest when making comparisons to drift barriers $N_e^{-1} \ll 1$. In this regime $\tilde{s}_c \approx \delta r/r$, the fractional change in birth rate. While we focus here on the simplest case of exponential population growth, where $\tilde{s}_c$ is time independent, we generalize our approach to density-dependent growth models, where $\tilde{s}_c$ varies between generations, in the Supplemental Material, Sec. VI [33]. $\tilde{s}_c$ can be written in a way that directly highlights the contributions of δE and δB to $\tilde{s}_c$. To facilitate this, let us define the average of any function $F(m(t))$ over a single generation time t_r as $\langle F \rangle \equiv t_r^{-1} \int_0^{t_r} dt F(m(t))$. Changing variables from t to m, like we did above in deriving Eq. (2), we can write this equivalently as $\langle F \rangle = \int_{m_0}^{\epsilon m_0} dm F(m) p(m)$, where $p(m) \equiv t_r^{-1} dt/dm = t_r^{-1} E(m)/G(m)$. The value $p(m)dm$ is just the fraction of the generation time that the organism spends growing from mass m to mass $m + dm$. Expanding Eq. (2) for t_r to first order in the perturbations δE and δB, the coefficient $\tilde{s}_c = -\delta t_r/t_r = -\sigma_E \delta E/\langle E \rangle - \sigma_B \delta B/\langle B \rangle$, with positive dimensionless prefactors

$$\sigma_E \equiv \langle E \rangle \langle E^{-1} \rangle, \qquad \sigma_B \equiv \langle B \rangle \langle \Theta^{-1} \rangle. \tag{3}$$

Here $\Theta(m) \equiv G(m)/m$, and $F^{-1}(m) \equiv 1/F(m)$ for any F. The magnitude of σ_B versus σ_E describes how much fractional increases in maintenance costs matter for selection relative to fractional increases in synthesis costs. We see that both prefactors are products of time averages of functions related to metabolism. See the Supplemental Material, Sec. II [33] for a detailed derivation of Eq. (3), and also Eq. (4) below.

Relating the baseline selection coefficient to the fractional change in total resting metabolic costs.—The final step in our theoretical framework is to connect the above considerations to the total resting metabolic expenditure C_T of the organism per generation time t_r, given by $C_T = \zeta \int_0^{t_r} dt \Pi(m(t)) = \zeta t_r \langle \Pi \rangle$. To compare with the experimental data of Ref. [12], compiled in terms of phosphate bonds hydrolyzed [P], we add the prefactor ζ which converts from units of J to P. Assuming an ATP hydrolysis energy of 50 kJ/mol under typical cellular conditions, we set $\zeta = 1.2 \times 10^{19}$ P/J. The genetic variation discussed above perturbs the total cost, $\tilde{C}_T = C_T + \delta C_T$, and the fractional change $\delta C_T/C_T$ can be expressed in a form analogous to $\tilde{s}_c$, namely $\delta C_T/C_T = \sigma'_E \delta E/\langle E \rangle + \sigma'_B \delta B/\langle B \rangle$, with

$$\sigma'_E \equiv \langle E \rangle \langle \Pi \rangle^{-1} \langle \Pi E^{-1} \rangle, \qquad \sigma'_B \equiv \langle B \rangle \langle \Pi \rangle^{-1} \langle \Pi \Theta^{-1} \rangle, \tag{4}$$

where again the prefactors are expressed in terms of time averages over metabolic functions. The connection between s_c and $\delta C_T/C_T$ can be constructed by comparing Eq. (3) with Eq. (4). We see that $\tilde{s}_c = -\delta C_T/C_T$ for all possible perturbations δE and δB only when $\sigma_E = \sigma'_E$ and $\sigma_B = \sigma'_B$. We derive strict bounds on the differences between the prefactors (Supplemental Material, Sec. II [33]), which show that the relation is exact when (i) $\Pi(m)$ is a constant independent of m, and/or (ii) $E(m)$ and $\Theta(m)$ are independent of m. Outside these cases, the relation $\tilde{s}_c \approx -\delta C_T/C_T$ is an approximation. To see how well it holds, it is instructive to investigate the allometric growth model described earlier, where $\Pi(m(t)) = \Pi_0 m^\alpha(t)$, $E(m(t)) = E_m$, $B(m(t)) = B_m$.

Testing the relation in an allometric growth model.—We use model parameters based on the metabolic data of Ref. [12], covering a variety of prokaryotes and unicellular eukaryotes. These data consisted of two quantities, C_G and C_M, which reflect the growth and maintenance contributions to C_T. Using Eq. (1) to decompose $\Pi(m(t))$, we can

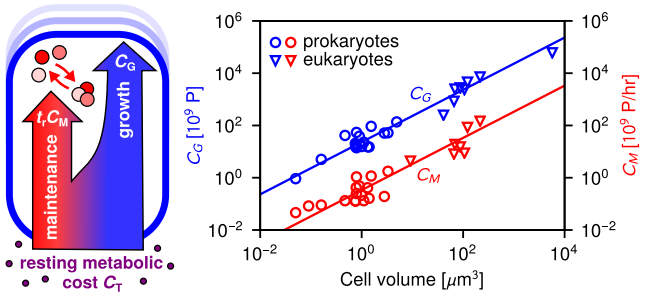

FIG. 1. The growth C_G (blue) and maintenance C_M (red) contributions to an organism's total resting metabolic cost $C_T = C_G + t_r C_M$ per generation time t_r. The symbols (circles = prokaryotes, triangles = unicellular eukaryotes) represent data tabulated in Ref. [12]. C_G and C_M have units of 10^9 P (phosphate bonds hydrolyzed) and 10^9 P/h, respectively. The lines represent best fits to the theoretical expressions for C_G and C_M from the allometric growth model.

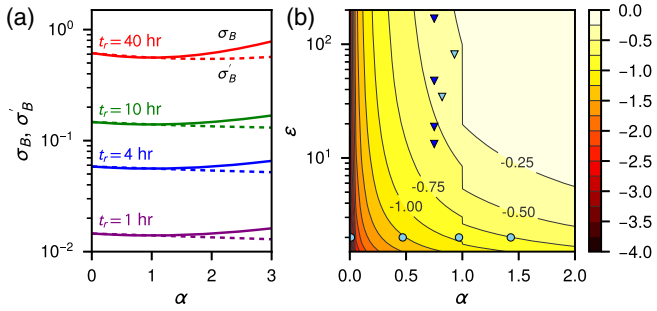

FIG. 2. (a) σ_B (solid curves) from Eq. (3) and σ'_B (dashed curves) from Eq. (4) versus α, for the allometric growth model with $E_m = 2600$ J/g, $B_m = 7 \times 10^{-3}$ W/g, and $\epsilon = 2$. At any given α, the parameter Π_0 for each pair of curves (different colors) is chosen to correspond to particular reproductive times t_r, indicated in the labels. (b) Contour diagram showing the logarithm of the maximum possible discrepancy $\log_{10}|1 - \sigma'_B/\sigma_B|$ for any allometric growth model parameters, as a function of α and ϵ. To illustrate biological ranges α and ϵ, the symbols correspond to data for various species (circles = unicellular, triangles = multicellular) drawn from the growth trajectories analyzed in Ref. [25] (light blue) and Ref. [23] (dark blue). See the Supplemental Material, Sec. III [33] for a detailed species list.

write $C_T = C_G + t_r C_M$, where $C_G = \zeta \int_{m_0}^{\epsilon m_0} dm E(m) = \zeta(\epsilon - 1) m_0 E_m$ is the expenditure for growing the organism, and $C_M = \zeta \langle Bm \rangle = \zeta B_m \langle m \rangle$ is the mean metabolic expenditure for maintenance per unit time. C_G and C_M scale linearly with cell volume (Supplemental Material, Sec. III [33]), and best fits to the data, shown in Fig. 1, yield global interspecies averages $E_m = 2600$ J/g and $B_m = 7 \times 10^{-3}$ W/g. As discussed in the Supplemental Material [33], these values are remarkably consistent with earlier, independent estimates, for unicellular and higher organisms [24,25,75,76].

Since $E(m(t)) = E_m$ is a constant in the allometric growth model, $\sigma_E = 1$ from Eq. (3), and $\sigma_E = \sigma'_E$ holds exactly from Eq. (4). So the only aspect of the approximation that needs to be tested is the similarity between σ_B and σ'_B. Figure 2(a) shows σ_B versus σ'_B for the range $\alpha = 0$–3, which includes the whole spectrum of biological scaling [28] up to $\alpha = 2$, plus some larger α for illustration. For a given α, the coefficient Π_0 has been set to yield a certain division time $t_r = 1$–40 h, encompassing both the fast and slow extremes of typical unicellular reproductive times. In all cases, σ'_B is in excellent agreement with σ_B. For the range $\alpha \leq 2$, the discrepancy is less than 15%, and it is in fact zero at the special points $\alpha = 0$, 1. Clearly the approximation begins to break down at $\alpha \gg 1$, but it remains sound in the biologically relevant regimes. Note that σ_B values for $t_r = 1$ h are ~ 0.01, reflecting the minimal contribution of maintenance relative to synthesis costs in determining the selection coefficient for fast-dividing organisms. This limit is consistent with microbial metabolic flux theory [77], where maintenance is typically neglected, so $\tilde{s}_c = -\delta C_T / C_T$ exactly (since only $\sigma_E = \sigma_{E'} = 1$ matters). As t_r increases, so does σ_B and hence the influence of maintenance costs, so by $t_r = 40$ h, σ_B is comparable to σ_E.

To make a more comprehensive analysis of the validity of the $\tilde{s}_c \approx -\delta C_T / C_T$ relation, we do a computational search for the worst case scenarios: for each value of α and ϵ, we can numerically determine the set of other growth model parameters that gives the largest discrepancy $|1 - \sigma'_B/\sigma_B|$. Figure 2(b) shows a contour diagram of the results on a logarithmic scale, $\log_{10}|1 - \sigma'_B/\sigma_B|$, as a function of α and ϵ. Estimated values for α and ϵ from the growth trajectories of various species are plotted as symbols to show the typical biological regimes. While the maximum discrepancies are smaller for the parameter ranges of unicellular organisms (circles) compared to multicellular ones (triangles), in all cases the discrepancy is less than 50%. To observe a serious error (σ'_B a different order of magnitude than σ_B), one must go to the large α, large ϵ limit (top right of the diagram) which no longer corresponds to biologically relevant growth trajectories.

Validity of the relation in more complex growth scenarios.—Going beyond the simple allometric model, Supplemental Material, Sec. V [33] analyzes avian growth data, where the metabolic scaling exponent varies between developmental stages. We find $\sigma_E = \sigma'_E = 1$ and the discrepancy $|1 - \sigma'_B/\sigma_B| \leq 30\%$. Supplemental Material, Sec. VI [33] considers density-dependent growth, illustrated by examples of bacteria competing for a limited resource in a chemostat and predators competing for prey. Remarkably, when these systems approach a stationary state in total population and resource or prey quantity, we find $\sigma_E = \sigma'_E = 1$, $\sigma_B = \sigma'_B = (B_m \ln R_b)/(E_m d \ln \epsilon)$, where d is the dilution rate in the chemostat, or the predator death rate. The simple expression for σ_B allows straightforward estimation of the maintenance contribution to

selection. For the chemostat that contribution can be tuned experimentally through the dilution rate d.

We thus reach the conclusion that the baseline selection coefficient for metabolic costs can be reliably approximated as $s_c \approx -\ln(R_b)\delta C_T/C_T$. As in the original hypothesis [10–12], $-\delta C_T/C_T$ is the dominant contribution to the scale of s_c, with corrections provided by the logarithmic factor $\ln(R_b)$. Our derivation puts the relation for s_c on a solid footing, setting the stage for its wider deployment. It deserves a far greater scope of applications beyond the pioneering studies of Refs. [11,12,22]. Knowledge of s_c can also be used to deduce the adaptive contribution $s_a = s - s_c$ of a mutation, which has its own complex connection to metabolism [78] (see also the Supplemental Material, Sec. VII [33]). The latter requires measurement of the overall selection coefficient s, e.g., from competition or growth assays, and the calculation of s_c from the relation, assuming the underlying energy expenditures are well characterized. The s_c relation underscores the key role of thermodynamic costs in shaping the interplay between natural selection and genetic drift. Indeed, it gives impetus to a major goal for future research: a comprehensive account of those costs for every aspect of biological function, and how they vary between species, what one might call the "thermodynome." Relative to its more mature omics brethren—the genome, proteome, transcriptome, and so on—the thermodynome is still in its infancy, but fully understanding the course of evolutionary history will be impossible without it.

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