The trade-off between rate and yield in the design of microbial metabolism

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Abstract

Extra energy devoted to resource acquisition speeds metabolic rate, but reduces the net yield of energy. In direct competition, microbial strains with high rates of resource acquisition often outcompete strains with slower resource acquisition but higher yield, reducing the net output of the group. Here, I use mathematical models to analyse the genetic and demographic factors that tip the balance toward either rate or yield. My models clarify the widely discussed roles of kin selection and the spatial structure of populations. I also emphasize the strong effect of two previously ignored factors: demographic aspects of colony survival and reproduction strongly shape the design of metabolic rate and efficiency, and competitive mutants within long-lived colonies favour rate over yield, degrading the efficiency of the population.

Prior work emphasized the role of competition between strains in the trade-off between rate of resource acquisition and net yield of energy (Pfeiffer *et al.*, 2001). For example, a microbe can make more of a cell surface transporter to increase its rate of nutrient acquisition (Wong *et al.*, 2009). That extra energy devoted to nutrient transport reduces the net yield at which the nutrient is changed into usable energy. Because direct competition tends to favour rapid resource acquisition, the potential for competitive degradation in metabolic efficiency has led to much discussion about the processes that favour high rate versus high yield (Pfeiffer *et al.*, 2001; MacLean & Gudelj, 2006; Gudelj *et al.*, 2007; Schuster *et al.*, 2008b).

I begin by showing that, in the absence of competition, the rate-yield trade-off is also important in the metabolic design of a single strain that consumes a resource. When a strain is alone, demography determines the balance between rate and yield. For example, a colony that lasts a long time gains most from efficient yield. By contrast, short-lived colonies are often favoured to emphasize rapid resource acquisition

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over long-term efficiency. Stated this way, it is easy to see that demography is important. However, the quantitative understanding of demographic factors and their interaction with competition between strains has not been emphasized with regard to metabolic design. A comprehensive quantitative theory will greatly expand opportunities for experimental analysis of the trade-off between rate and yield in metabolic pathways.

Consider first the dynamics of a single microbial strain that consumes a resource. The density of the resource with respect to the total volume of the system is x. In the absence of consumption by the microbes, the resource increases at rate σ up to a maximum density. I scale all densities so that the maximum resource density is one. The total density of the microbe's transporter is y; the transporter can take up the resource in proportion to xy, the binding of the resource, x and the transporter, y. Thus, the dynamics of the resource is given by $\dot{x} = \sigma(1-x) - xy$, where the dot denotes the change with respect to time (see Appendix).

The microbe splits acquired resource into a fraction, f, devoted to increasing the transporter, and a fraction, $1-f$, devoted to increasing total biomass, b. Thus, the dynamics of the resource, x, transporter, y, and biomass, b, is given by

$$\dot{x} = \sigma(1-x) - xy$$
$$\dot{y} = xyf - \delta y \qquad (1)$$
$$\dot{b} = xy(1-f) - \gamma b,$$

where the transporter decays at rate δ, and the biomass decays through cellular death at a rate γ.

The issue here concerns the allocation, f, to production of the transporter and increased rate of resource acquisition versus the allocation, $1 - f$, to the production of biomass. What value of f maximizes fitness? To answer this question, we must measure fitness over a period of time by summing up the probability of surviving to each future point in time, $S(t)$, multiplied by the reproductive success (fecundity) at that time, $F(t)$. We also weight the sum by $e^{-\lambda t}$, the discount to future reproduction in proportion to the growth rate of the total population, λ.

To analyse a simple case, suppose the colony dies at a constant rate, d, in which case $S(t) = e^{-dt}$, where, without loss of generality, I have absorbed any consequences of population growth, λ, into the parameter d. For fecundity, assume that the success of the colony in sending out dispersers that establish new colonies is proportional to total biomass, $b(t)$. Then fitness is

$$w = \int e^{-dt} b(t) \mathrm{d}t. \qquad (2)$$

Consider the case in which a small number of microbes colonize a patch with a fixed initial resource level, x_0. No new resources flow into the patch, $\sigma = 0$. The microbes will grow until the resource is used up. Assume that, over the time period of interest, the transporter and the total biomass do not decay significantly, thus $\delta = \gamma \approx 0$. In this case, we only need to study how f, the division of resource into transporter (rate) and biomass (yield), affects fitness.

Figure 1 shows the value f^* that maximizes fitness. The lowest curve in each panel corresponds to the case discussed so far, in which each colony begins with a single genetically uniform clone. With a clone, we have maximum genetic relatedness among colony members measured by the coefficient of relatedness, $r = 1$. In Fig. 1a, when colony survival is short, f^* is high, emphasizing rapid use of resources before impending colony death. As the survival of the colony increases, natural selection weights more strongly total yield at the expense of rate. Therefore f^* declines with increasing survival.

Figure 1b shows the same analysis, but with a lower initial amount of resource. With less resource, the colony does not produce significant biomass when total survival time is short, so no value is shown for f^*. As survival rises, emphasis on rate, f^*, is at first low, because in a short time period, the optimal strategy is to use the initial small amount of transporter to transform all resource into yield, without adding to the transporter density. With further increase in survival, the emphasis switches to very high rate, shown as a rise in f^*, because the best
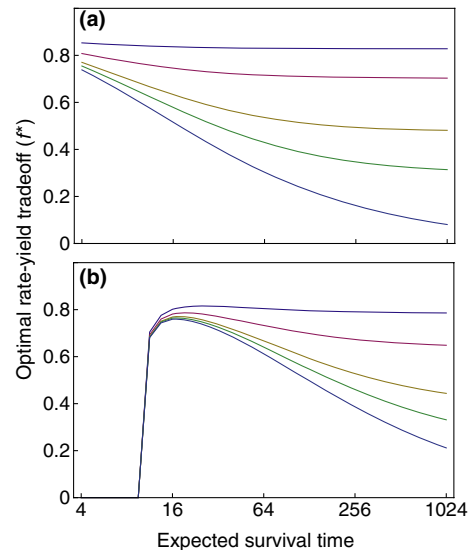

Fig. 1 Evolutionarily stable trade-off between rate and yield in relation to colony survival and genetic population structure. The x axis shows the expected lifetime of a colony, measured by $1/d$ in Eqn 2, where time is expressed in nondimensional units scaled by αk from Eqn 4. In each panel, the curves show different values of the coefficient of relatedness: from top to bottom, $r = 0, 0.5, 0.8, 0.9, 1$. (a) The initial value of the resource is $x(0) = 1$. (b) The initial value of the resource is $x(0) = 0.1$. Other parameters from Eqn 1: $\sigma = \delta = \gamma = 0$, and the initial value of the transporter for each type is $y_i(0) = 10^{-5}$. With these parameters, there is an initial fixed resource and no further resource inflow, and there is no cell death. The initial value of biomass, $b_i(0)$, does not influence the results.

strategy is to build up the transporter so that resource can be transformed into biomass as quickly as possible. With greater survival, the emphasis increasingly turns back toward long-term yield, with a decline in f^*. These simple examples show that, even in a genetically uniform clone, the optimal trade-off between rate and yield can vary in interesting ways.

What happens when we allow genetic mixtures that cause a decline in the relatedness coefficient, r? It is generally understood that competition between genotypes leads to a stronger emphasis on rate over yield, because genotypes that extract resources more rapidly outcompete neighbours (Pfeiffer *et al.*, 2001; West *et al.*, 2007; Schuster *et al.*, 2008a). Although this point has been mentioned several times, and occasionally analysed by computer simulation, no simple quantitative evaluation has been presented. A quantitative framework would facilitate experimental evaluation and comparison of the importance of genetic mixtures in relation to other processes. MacLean emphasized the significance of this topic in the final sentence of his comprehensive review of the field (MacLean, 2008): '[I]t would be desirable to integrate the theoretical literature on the rate-yield trade-off with kin selection theory by developing kin selection models that explicitly incorporate the density-dependent

costs and benefits of altruism that are such a prominent feature of this social conflict' (see also Ross-Gillespie *et al.*, 2009).

Suppose two different genotypes occur in a population. The common type has a particular rate-yield trade-off given by $f*$. For what value of $f*$ can the common type outcompete any rare type with a different trade-off, $\hat{f}$? In other words, what is the value of $f*$ that is evolutionarily stable and thus is a reasonable candidate for what we may expect to observe (Maynard Smith, 1982)?

I calculate the evolutionarily stable value, $f*$, for the following case. In each patch, suppose the initial amount of transporter is divided equally into two parts. Each part is of either the common or the rare type; both parts may be of the same type. The spatial association between types in patches can be fully described by the correlation coefficient, r, which, in this case, is equivalent to the coefficient of relatedness from kin selection theory (Hamilton, 1970; Frank, 1998). In microbial populations, we can roughly think of r as the probability that two randomly chosen neighbouring microbes descended from a recent common ancestor. Thus, members of a clone have a relatedness of $r = 1$, as long as the time back to the common ancestor is not long enough to have allowed significant divergence by mutation and selection. An equal mixture of two clones leads approximately to $r = 1/2$.

With these definitions, an evolutionarily stable trade-off occurs when

$$w(f*,f*) \geq rw(\hat{f},\hat{f}) + (1-r)\,w(\hat{f},f*), \qquad (3)$$

where the two arguments to w describe the types that initialize a patch. For example, $w(f*,f*)$ is the fitness of the common type in a patch in which all initial types are the same common type. By contrast, $w(\hat{f},f*)$ is the fitness of the rare type when in a patch co-colonized by the common type. The weights r and $1-r$ describe the relative frequencies of the two different patch compositions in which the rare type occurs. For the common type, being in a mixed patch is so rare compared with patches that have only the common type, that we can ignore the mixed patches in the overall fitness of the common type. The Appendix describes how to calculate w.

We find an evolutionarily stable rate-yield trade-off by searching for a value of $f*$ that satisfies Eqn 3. Figure 1 illustrates the important interaction between relatedness, r, and aspects of colony demography. In each panel, spatial association is perfect in the bottom curve, $r = 1$; relatedness declines as the curves move from the bottom to the top. Thus, lower relatedness and more mixing between types favours rate over yield. However, the strength of this relatedness effect depends on how long colonies survive. In short-lived colonies, high rate dominates and is only weakly modulated by relatedness. By contrast, in long-lived colonies, either high rate or high yield may be favoured according to the level of relatedness in colonies.

If colonies live long enough, then natural selection may act on different timescales (Levin & Bull, 1994). Within colonies, faster, more competitive mutants can increase in frequency, even if such mutants fare poorly over the long run and do not increase in the population. Longer colony lifetimes emphasize the shorter within-colony timescale, favouring rate over yield and degrading the overall efficiency of the population. One can think of a colony as a multicellular aggregation, in which 'somatic' mutants arise that grow faster than their progenitors. Those highly competitive somatic mutants impose an inevitable tax on multicellular cooperation. The problem concerns how the magnitude of this tax grows over time in relation to the multicellular aggregate's survival and reproduction.

Figure 2 illustrates the consequences of within-colony mutation. Each curve shows the rate-yield trade-off, $f*$, that maximizes fitness. Here, there is no mixture at colony foundation, $r = 1$. In each colony, the optimal type generates mutants at rate μ, in which mutants with phenotype $\tilde{f}$ have a higher rate of resource acquisition and lower yield (see Appendix). The longer a colony survives, the greater the competition for resources between the founding type, $f*$, and the higher-rate mutants, $\tilde{f}$. As competition from mutants increases, the
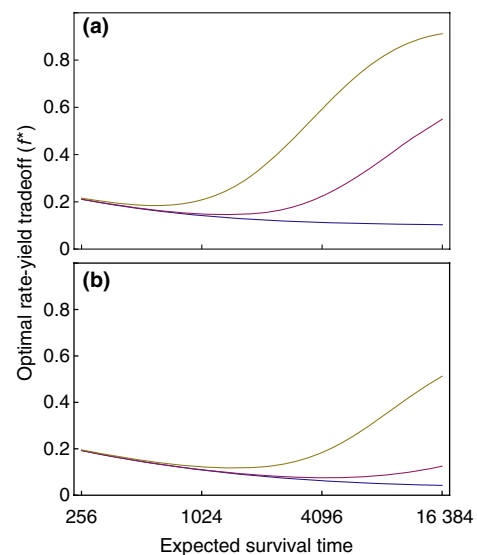

Fig. 2 The role of mutation in the trade-off between rate and yield. In each panel, the curves from bottom to top correspond to a mutation rate of $\mu = 0, 10^{-6}, 10^{-5}$. (a) Faster turnover of transporter and biomass leads to more cell division and greater expansion of mutant clones, increasing the competitive pressure for resource acquisition imposed by the mutants and raising the optimal value of $f*$. (b) Slower turnover of transporter and biomass leads to less pressure from mutants and lower optimal values, $f*$. In this case, there is continual resource inflow, $\sigma > 0$, otherwise the mutant clones do not expand. See Appendix for parameter values.

optimal value f^* rises to provide the founding type with greater success against the high-rate mutants.

These analyses emphasize three key processes in metabolic design. First, the genetic structure of populations determines the extent of direct competition between genotypes, in which greater competition favours rate over yield. The kin selection coefficient, r, elegantly quantifies the competitive intensity.

Second, colony demography translates aspects of competition and efficiency into the survival and reproduction components of fitness. In the models here, the longer a colony survives, the more heavily natural selection favours efficient yield over rate. Other demographic scenarios may occur. For example, a group of pathogens may be favoured to grow as quickly as possible to achieve a density at which the colony can secrete sufficient immunomodulatory molecules to circumvent attack by host immunity. In this type of colony demography, rate may be favoured early in the colony life cycle, whereas efficiency may be favoured later in the life cycle.

The third process follows from mutation within colonies. Greater mutation rate, longer colony lifetime, and more rapid cellular turnover all intensify the competition between wild-type and mutant genotypes within colonies. Such somatic mutation imposes a tax on colony efficiency, tipping the balance toward greater rate of resource acquisition at the expense of efficiency and yield.

Previous models demonstrated that, to understand most social traits, one must study the interaction between kin or group selection and demography (Frank, 1998, 2010). Here, the word 'social' simply means a tension between competition and cooperation. Analyses of social traits in a demographic context have particularly emphasized problems such as parasite virulence, sex ratios, and the widely applicable tragedy of the commons.

Microbial metabolism often has a strongly social component because of the rate-yield trade-off. Many other microbial traits have the same sort of social aspect, for example, bacterial secretions to build biofilms or to take up free iron (West et al., 2007). However, most models and empirical studies of social microbial traits have focused entirely on aspects of genetic structure and kin selection, and have not set their analyses into a proper demographic framework. In this article, I demonstrated the essential role of demography in such problems, and how demography interacts with a simple description of population structure in terms of kin selection. I also showed that mutation in long-lived colonies may have a very strong effect on the evolutionary dynamics of social traits.

With regard to the particular analyses in this article, the mathematical models make clear predictions about metabolic design. These predictions can be tested by the rapidly expanding field of experimental microbial evolution (Elena & Lenski, 2003). In addition, many aspects of pathogen life history are shaped by the trade-off between rapid growth and efficient resource use through the molecular design of pathogenic mechanisms (Frank & Schmid-Hempel, 2008). The demographic models in this paper provide testable hypotheses about pathogen life history, another rapidly growing area of microbial biology.

Acknowledgments

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Appendix

Nondimensional definitions

The full system for Eqn 1 is

$$\dot{x}' = \sigma'(k - x') - \alpha x' y'$$
$$\dot{y}' = \alpha x' y' f - \delta' y' \qquad (4)$$
$$\dot{b}' = \alpha x' y'(1 - f) - \gamma' b'$$

Define nondimensional quantities for densities $x = x'/k$, $y = y'/k$, and $b = b'/k$. Let the usual dimensional measure of time be τ, and define a nondimensional time scaling as $t = \tau \alpha k$. Scale rates to nondimensional form as $\sigma = \sigma'/(\alpha k)$, $\delta = \delta'/(\alpha k)$ and $\gamma = \gamma'/(\alpha k)$. Substitute these values into the full system given in this section. These steps yield the nondimensional system in Eqn 1.

Solution for use of fixed resource

If in Eqn 1 we set $\sigma = \delta = \gamma = 0$, we obtain the solution

$$x(t) = \frac{x_0(f x_0 + y_0)}{f x_0 + y_0 e^{t(f x_0 + y_0)}}$$
$$y(t) = y_0 + f[x_o - x(t)] \qquad (5)$$
$$b(t) = b_0 + (1 - f)[x_o - x(t)].$$

Multiple genotypes

If there are n different genotypes with different trade-offs, f_i, for $i = 1, \ldots, n$, then the dynamics of all types is given by extension of Eqn 1 as

$$\dot{x} = \sigma(1 - x) - x \sum y_i$$
$$\dot{y}_i = x y_i f_i - \delta y_i \qquad (6)$$
$$\dot{b}_i = x y_i (1 - f_i) - \gamma b_i.$$

The fitness of the ith type in a particular patch is

$$w_i = \int e^{-dt} b_i(t) dt, \qquad (7)$$

where the fitness depends on the initial values of the different y_i in the patch. Differences in initial b_i only change final fitness values by a constant and can be ignored with regard to searching for how changes in the f_i influence fitness. To find the best value of f, we would have to calculate the fitness of all types over all initial patch compositions in the population. That calculation is not difficult, but our question here concerns how spatial associations between the f values influence the rate-yield trade-off favoured by natural selection.

Genetic structure of populations

For the particular assumptions given in the main text, we find an evolutionarily stable rate-yield trade-off by searching for a value of f^* that satisfies Eqn 3. To analyse cases in which the alternative types have varying frequencies, and the initial compositions of the patches vary, we apply the same concept as in Eqn 3, but we must consider all initial patch compositions and their relative contributions to the fitnesses of each type. In this more complex case, the spatial associations summarized by r still come into play, but the quantitative effect of spatial associations on the favored value of f will vary in relation to other demographic and rate-process assumptions.

Mutation within colonies

In Eqn 6, let there be $n = 2$ distinct types, with type 1 as the wildtype and type 2 as a mutant. Modify the change in y for type 1 as $\dot{y}_1 = x y_1 f_1 - \delta y_1 - \mu y_1$ and for type 2 as $\dot{y}_2 = x y_2 f_2 - \delta y_2 + \mu y_1$, where $\mu = \mu'/(\alpha k)$ is the nondimensional measure of mutation given the mutation rate of μ'. Let the mutant phenotype, f_2, be such that the ratio $f/(1-f)$ is twice as great for the mutant compared to the wildtype, yielding $f_2 = 2f_1/(1+f_1)$. In the text, $f_1 = f^*$ and $f_2 = \tilde{f}$.

In Fig. 2, the common parameter values for both panels are as follows: $\sigma = 1$, $x(0) = 1$, $y_1(0) = 10^{-4}$, $b_1(0) = 10y(0)$, $y_2(0) = b_2(0) = 0$, $r = 1$, and the integration of fitness in Eqn 7 is calculated to a maximum value of $t = 40\,000$. In Fig. 2a, the rates of transporter and biomass turnover are $\delta = \gamma = 0.01$ and in Fig. 2b, $\delta = \gamma = 0.001$. As the rates of turnover decline, the colony more closely approaches the case in which a fixed resource is used up as the colony grows from the initial colonizers to a fixed, final population. As turnover rates increase, more cell death and replacement birth occur, increasing the opportunity for the expansion of mutant clones. Changes in σ and in the initial values of x, y_1 and b_1 have little consequence for the results, as long as the values of σ and y are not too small.

The solution method finds f^* such that no other value has higher fitness when colonies are founded by a single genotype, $r = 1$. A colony founded by genotype f^* may eventually contain a significant or even majority fraction of the mutant, $\tilde{f}$. Those mutants, when founding a new colony, have lower fitness than the optimal type. Mutant colonies themselves generate further mutants with even higher values of f. Thus, with increasing mutation rate, colony survival rate, and cellular turnover rate, the population may harbor an increasingly complex polymorphic mixture of phenotypes maintained by a balance between selection, which favors f^*, and mutation, which generates a spectrum of variants. In this case, one can think of the colony mutation rate as potentially very high, because rare cellular mutations may increase significantly in frequency throughout the lifetime of a colony.