Growth tradeoffs produce complex microbial communities without direct interactions

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The distribution of fitness effects for mutations is often believed to be key to predicting microbial evolution. However, fitness effects alone may be insufficient to predict evolutionary dynamics if mutations produce nontrivial ecological effects which depend on the composition of the population. Here we show that variation in multiple growth traits, such as lag times and growth rates, creates higher-order effects such the relative competition between two strains is fundamentally altered by the presence of a third strain. These effects produce a range of ecological phenomena: an unlimited number of strains can coexist, potentially with a single keystone strain stabilizing the community; strains that coexist in pairs do not coexist all together; and the champion of all pairwise competitions may not dominate in a mixed community. This occurs with competition for only a single finite resource and no other interactions. Since variation in multiple growth traits is ubiquitous in microbial populations due to pleiotropy and non-genetic variation, these higher-order effects may also be widespread, especially in laboratory ecology and evolution experiments. Our results underscore the importance of considering the distribution of ecological effects from mutations in predicting microbial evolution.

Keywords: microbial growth; microbial ecology; higher-order effects; coexistence; non-transitive selection

I. INTRODUCTION

The relative simplicity and experimental tractability of microbes make them convenient for studying fundamental ecological and evolutionary questions. One such question concerns the distribution of fitness effects across mutations [1], which has been measured in various microbial systems [2–6]. The ultimate goal is to use this distribution to predict the evolutionary dynamics of a population, such as microbes evolving resistance to an antibiotic. This approach assumes mutants are fully characterized by selection coefficients relative to a wild-type, which can be used to predict the population dynamics of any number of segregating mutants. However, ecologists have long recognized the possibility that the selection coefficients between pairs of strains can be altered by the presence of additional strains [7–11]. These "higher-order" effects may cause a community to be fundamentally different than the sum of its pairwise interactions and may play an important role in stabilizing coexisting communities [12, 13]. Therefore the distribution of ecological effects, rather than mere fitness effects, may be essential to accurately predict the evolutionary dynamics of a population.

Most well-known ecological effects in microbes are mediated by cross-feeding interactions or the consumption of multiple resources [14]. For example, long-term coexistence of distinct strains is often believed to depend on the existence of at least as many resource types as coexisting strains, according to the "principle of competitive exclusion" [15, 16]. However, theoretical and experimental work has demonstrated that tradeoffs in life-history traits alone — for example, growing quickly at low concentration of a resource versus growing quickly at high concentrations, but with only a single resource type and no other interactions — are sufficient to produce not only stable coexistence of two strains [17–20] but also non-transitive selection [21], in which pairwise competitions of strains can exhibit "rock-paper-scissors" behaviors [22].

Variation in multiple growth traits, such as lag time, exponential growth rate, and yield (resource efficiency), is pervasive in microbial populations [23–25]. Not only are single mutations known to be pleiotropic with respect to these traits [26, 27], but even genetically-identical lineages may demonstrate significant variation [28, 29]. The ecological effects of such variation, however, are unknown in large populations with many distinct strains simultaneously competing, as is generally the case for microbes.

Here we study a model that shows how covariation in growth traits can produce complex microbial communities without any direct interactions among cells beyond competition for a single limiting resource. We focus on variation in lag times, exponential growth rates, and yields since they are the traits most easily measured by growth curves of individual strains [30]. We show that covariation in these traits creates higher-order effects such that the magnitude and even the sign of the selection coefficient between a pair of strains may be changed by the presence of a third strain. These higher-order effects can produce nontrivial ecological phenomena: an unlimited number of strains can coexist, potentially with a single "keystone" strain stabilizing the community [31, 32]; strains that coexist in pairs do not coexist in a community all together; and the champion of all pairwise competitions may not dominate in a mixed community. Our model can be combined with high-throughput measurements of microbial growth traits across mutants to make

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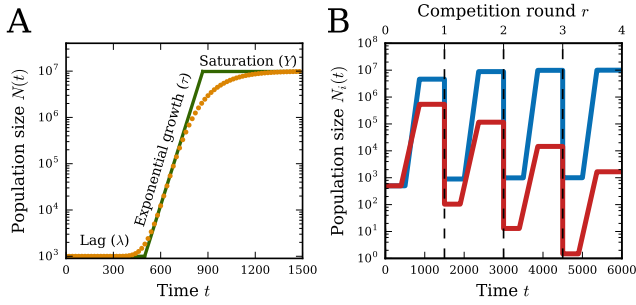* To whom correspondence should be addressed. Email: shakhnovich@chemistry.harvard.edu

FIG. 1. **Model of growth and selection.** (A) Approximation of a hypothetical growth curve (orange points) by the minimal three-phase model (green). Each phase is characterized by a quantitative trait: lag time λ, growth time τ (reciprocal growth rate), and yield Y at saturation. (B) Growth curves of two competing strains over multiple rounds of competition in the model. Vertical dashed lines mark the beginning of each round, where the population is diluted down to the same initial population size with new resources.

Definition	Notation
Lag time of strain i	λ_i
Exponential growth time (reciprocal growth rate) of strain i	τ_i
Yield (cells per resource) of strain i	Y_i
Density of strain i at beginning of competition round	x_i
Density of resources per cell at beginning of competition round	ρ
Effective exponential growth time of whole population (harmonic mean)	$\bar{\tau} = \dfrac{\sum_k \frac{x_k}{Y_k}}{\sum_k \frac{x_k}{Y_k \tau_k}}$
Effective yield of whole population (harmonic mean)	$\bar{Y} = \dfrac{1}{\sum_k \frac{x_k}{Y_k}}$
Growth-lag tradeoff	$c = -\left(\dfrac{\lambda_i - \lambda_j}{\tau_i - \tau_j}\right)$

TABLE I. **Summary of key notation.**

more accurate predictions of the distribution of ecological effects and, in turn, evolutionary dynamics. Altogether these results show how fundamental properties of microbial growth are sufficient to generate complex ecological behavior, underscoring the necessity of considering ecology in studies of microbial evolution.

II. METHODS

We consider a microbial population consisting of multiple strains with distinct growth traits, all competing for a single limiting resource. These strains may represent different microbial species living in a community, mutants of the same species, or even genetically-identical cells with purely phenotypic variation. We approximate the growth of each strain i by the minimal model in Fig. 1A, defined by a lag time λ_i, exponential growth time τ_i (reciprocal growth rate, or time for the strain to grow e-fold), and yield Y_i, which is the population size supported per unit resource (*Supplementary Methods* Sec. S1) [33]. Therefore the amount of resources strain i has consumed by time t is $N_i(t)/Y_i$, where $N_i(t)$ is the population size of strain i. Growth stops when the amount of resources consumed by all strains equals the initial amount of resources; we define the initial density of resources per cell as ρ. Although it is possible to consider additional growth traits such as a death rate or consumption of a secondary resource, here we focus on the growth traits λ_i, τ_i, and Y_i since they are most often reported in microbial phenotyping experiments [24, 34]. See Table I for a summary of all key notation.

The selection coefficient between a pair of strains i and j measures their relative ability to compete for resources [35, 36]:

$$s_{ij} = \log\left(\frac{x_i'}{x_j'}\right) - \log\left(\frac{x_i}{x_j}\right), \tag{1}$$

where x_i is the density (fraction of the whole population) of strain i at the beginning of the competition and x_i' is the density at the end. If new resources periodically become available, as occur in both laboratory evolution experiments and natural "seasonal" environments [33], then the population will undergo cycles of lag, growth, and saturation (Fig. 1B). We assume each round of competition begins with the same initial density of resources ρ; the population grows until all the resources are consumed, and then it is diluted down to the original size again. We also assume the growth traits λ_k, τ_k, Y_k of each strain remain the same over multiple competition rounds. The selection coefficients in Eq. 1 measure the rate of change of a strain's density x_i over many rounds of these competitions (*Supplementary Methods* Sec. S2).

III. RESULTS

A. Contribution of multiple growth traits to selection

We can solve for the selection coefficients in Eq. 1 in terms of the strains' traits $\{\lambda_k, \tau_k, Y_k\}$, the initial strain densities $\{x_k\}$, and the initial density of resources per cell ρ (*Supplementary Methods* Sec. S3):

$$s_{ij} \approx s_{ij}^{\text{lag}} + s_{ij}^{\text{growth}} + \sum_k s_{ijk}^{\text{coupling}}, \tag{2a}$$
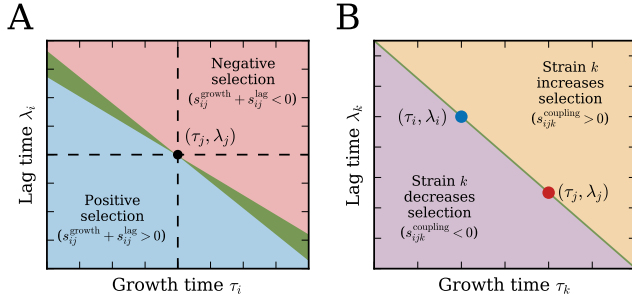
FIG. 2. **Selection in growth-lag trait space.** (A) Diagram of selection on growth and lag for strain i relative to strain j. Trait values of strain j are marked by a black dot in the center. If the traits of strain i lie in the blue region, i is positively selected over strain j, while if strain i lies in the red region, it is negatively selected. If strain i lies in the green region, it is conditionally neutral with j (positively selected at some densities and negatively selected at others). (B) Diagram of growth and lag times for strain k relative to two other strains i (blue) and j (red). If the traits of strain k lie in the orange region (above the straight line joining i and j), then its coupling term $s_{ijk}^{\text{coupling}}$ (Eq. 2b) increases the total selection coefficient of i over j, while if k lies in the violet region (below the straight line), then it decreases the selection of i over j.

where

$$s_{ij}^{\text{lag}} = -\frac{\bar{\tau}}{\tau_i \tau_j} \Delta\lambda_{ij},$$

$$s_{ij}^{\text{growth}} = -\frac{\bar{\tau}}{\tau_i \tau_j} \Delta\tau_{ij} \log\left(\rho\bar{Y}\right), \qquad (2b)$$

$$s_{ijk}^{\text{coupling}} = -\frac{\bar{\tau}\bar{Y}}{\tau_i \tau_j} \frac{x_k}{\tau_k Y_k} \left(\Delta\tau_{ik}\Delta\lambda_{kj} - \Delta\lambda_{ik}\Delta\tau_{kj}\right).$$

Here $\Delta\lambda_{ij} = \lambda_i - \lambda_j$ and $\Delta\tau_{ij} = \tau_i - \tau_j$ denote the pairwise differences in lag and growth times, while

$$\bar{\tau} = \frac{\sum_k \frac{x_k}{Y_k}}{\sum_k \frac{x_k}{\tau_k Y_k}}, \qquad \bar{Y} = \frac{1}{\sum_k \frac{x_k}{Y_k}} \qquad (3)$$

are, respectively, the effective exponential growth time (reciprocal growth rate) and effective yield for the whole population (*Supplementary Methods* Sec. S4). Since both of these quantities are harmonic means over the population, they are dominated by the smallest trait values. Therefore the effective growth time $\bar{\tau}$ for the whole population will be close to the growth time of the fastest-growing strain (smallest τ_k), while the effective yield $\bar{Y}$ will generally be close to the yield of the least-efficient strain (smallest Y_k).

As Eq. 2 indicates, selection consists of three distinct additive components. The first is selection on the lag phase s_{ij}^{lag}, which is nonzero only if i and j have unequal lag times. The second is selection on the growth phase s_{ij}^{growth}, which is similarly nonzero only if i and j have

unequal growth times. The relative magnitude of selection on growth versus lag is modulated by the density of resources ρ and the effective population yield $\bar{Y}$:

$$\frac{s_{ij}^{\text{growth}}}{s_{ij}^{\text{lag}}} = \frac{\Delta\tau_{ij}}{\Delta\lambda_{ij}} \log\left(\rho\bar{Y}\right). \qquad (4)$$

In particular, increasing the resources ρ leads to an increase in the magnitude of relative selection on growth versus lag, since it means the growth phase occupies a greater portion of the total competition time.

If i and j are the only two strains present, then the total selection on strain i relative to j is the net effect of selection on the lag and growth phases: $s_{ij} = s_{ij}^{\text{lag}} + s_{ij}^{\text{growth}}$ [21]. Figure 2A qualitatively shows this selection coefficient as a function of strain i's lag and growth traits relative to those of strain j. If strain i's traits fall in the blue region, the overall selection on it relative to strain j will be positive, while if strain i's traits fall in the red region, it will be negatively selected relative to strain j. Between these two regions lies a "conditionally-neutral" region (green), where strain i will be positively selected at some densities and negatively selected at others [21]. The slope of the conditionally-neutral region is $\log\left(\rho\bar{Y}\right)$ according to Eq. 4.

B. Pairwise selection coefficients are modified by additional strains through higher-order effects

If more than two distinct strains are present, then selection between i and j is modified by higher-order effects from the other strains. These modifications occur through three mechanisms, all fundamentally a consequence of having a finite resource. The first mechanism is through changes to the effective population growth time $\bar{\tau}$, which rescales all selection coefficients (Eq. 2b). For example, the addition of a strain with much faster growth will reduce the time all strains have to grow (Eq. 3), and thereby decrease the magnitude of all selection coefficients. The second modification is through the effective population yield $\bar{Y}$. Like $\bar{\tau}$, $\bar{Y}$ is a harmonic mean over strains, and similarly it will be significantly reduced if a strain with very low yield is added. This may change even the signs of some selection coefficients since changes in $\bar{Y}$ modify the relative selection on growth versus lag between strains (Eq. 4).

Higher-order effects in $\bar{\tau}$ and $\bar{Y}$ are non-specific in the sense that these parameters are shared by all pairs of strains in the population. In contrast, the third type of modification is through the terms $s_{ijk}^{\text{coupling}}$, which couple the relative growth and lag traits of a pair i and j with a third strain k (Eq. 2b). This effect is specific, since each additional strain k modifies the competition between i and j differently, depending on its growth traits and density x_k. We can interpret this effect graphically by considering the space of growth and lag times for strains i,

j, and k (Fig. 2B). If strain k lies above the straight line connecting strains i and j in growth-lag trait space, then the coupling term will increase selection on whichever strain between i and j has faster growth (assumed to be strain i in the figure). This is because strain k has relatively slow growth or long lag compared to i and j, thus using fewer resources than expected. This then leaves more resources for i and j, which effectively increases the selection on growth rate between the two strains beyond the s_{ij}^{growth} term. If strain k instead lies below the straight line, then it increases selection on the strain with slower growth, since k uses more resources than expected. For example, even if strain i has both better growth and better lag compared to strain j, a third strain k could actually reduce this advantage by having sufficiently short lag. Note that the coupling term is zero if all three strains have equal growth times or equal lag times. These coupling effects will furthermore be small if the relative differences in growth and lag traits are small, since $s_{ijk}^{\mathrm{coupling}}$ is quadratic in $\Delta\tau$ and $\Delta\lambda$ while s_{ij}^{lag} and s_{ij}^{growth} are linear. In the following sections, we will demonstrate how these three higher-order mechanisms lead to nontrivial ecological dynamics.

C. Growth tradeoffs produce stable communities of multiple strains on a single resource

Selection is frequency-dependent since each s_{ij} in Eq. 2 depends on the densities $\{x_k\}$ [21]. It is therefore possible for a community of strains to be stable at certain combinations of densities (*Supplementary Methods* Sec. S5, Fig. S1). The strains must have a linear tradeoff between lag and growth times (Fig. 3A):

$$\lambda_i = -c\tau_i + \mathrm{constant} \qquad (5)$$

for all i and some parameter $c > 0$, which we define as the growth-lag tradeoff. The resource density ρ must also fall in the range (Fig. 3B)

$$\frac{e^c}{\max_k Y_k} < \rho < \frac{e^c}{\min_k Y_k}. \qquad (6)$$

Note that $\rho > 1/\min_k Y_k$ is necessary as well, since if ρ is below this limit there will be insufficient resources for some strains to grow at all. Since this limit is always lower than the upper bound in Eq. 6 (because $c > 0$), there will always be some range of ρ at which all strains coexist. While real strains will not exactly obey Eq. 5, even noisy tradeoffs cause effective coexistence over a finite time scale (*Supplementary Methods* Sec. S5, Fig. S2).

Intuitively, coexistence occurs because strains consume resources in such a way to exactly balance selection on lag and growth for all pairs of strains. The linear growth-lag tradeoff across all strains from Eq. 5 causes the higher-order coupling terms $s_{ijk}^{\mathrm{coupling}}$ of the selection coefficient

to be zero (Fig. 2B). It also means there is some value of the effective yield $\bar{Y}$ that will enable $s_{ij}^{\mathrm{growth}} + s_{ij}^{\mathrm{lag}} = 0$ for all pairs i and j; this critical value of the effective yield is $\bar{Y} = e^c/\rho$ (Eq. 4, *Supplementary Methods* Sec. S5). The constraint on resource density ρ (Eq. 6) ensures that the population can actually achieve this required effective yield given the yield values of the individual strains.

D. Community stability may hinge on a single keystone strain

Coexistence will be stable against small density fluctuations if there is also a tradeoff in growth and yield (*Supplementary Methods* Sec. S6, Fig. S3), in addition to the growth-lag tradeoff (Eq. 5). An even stronger perturbation is to remove one strain entirely. The stability of ecosystems in response to removal of a strain or species has long been an important problem in ecology; in particular, species whose removal leads to community collapse are known as "keystone" species due to their importance in stabilizing the community [31, 32].

Coexisting communities in our model will have a keystone strain for a certain range of resource density ρ. Figure 3B shows a diagram of competition outcomes across ρ values for four hypothetical strains (blue, red, green, orange): if ρ is in the orange or blue ranges, then removal of the strain of corresponding color (orange or blue) will cause collapse of the community (all remaining strains but one will go extinct), since ρ will no longer satisfy Eq. 6 for the remaining strains. Therefore the orange or blue strain is the keystone. However, if ρ is within the gray region, then the community is robust to removal of any single strain. This shows that the keystone must always be the least- or most-efficient strain (smallest or highest yield Y_k) in the community. Figure 3C shows the population dynamics with each strain removed from a coexisting community where the orange strain is the keystone.

Besides removal of an existing strain, another important perturbation to a community is invasion of a new strain, either by migration or from a mutation. If the growth and lag times of the invader lie above the diagonal line formed by the coexisting strains' traits (e.g., as in Fig. 3A), then the invader will quickly go extinct (*Supplementary Methods* Sec. S7). This would be true even if the invader has a growth time or lag time shorter than those of all the resident strains. On the other hand, if the invader lies below the diagonal line in growth-lag trait space, then it will either take over the population entirely or coexist with one of the resident strains if it is sufficiently close to the diagonal line. It cannot coexist with more than one of the resident strains, since all three points by assumption will not lie on a straight line in the growth-lag trait space.
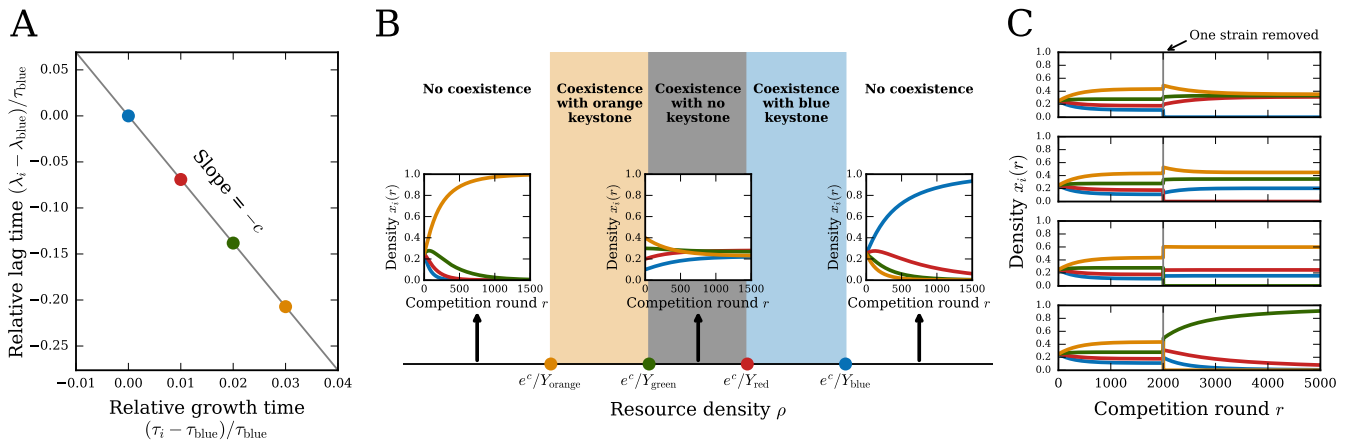
FIG. 3. **Coexistence of multiple strains on a single resource.** (A) Growth and lag times of four strains (blue, red, green, orange). For them to coexist in a community, these traits must have a linear tradeoff with slope $-c$ (Eq. 5). (B) Diagram of competition outcomes as a function of resource density ρ. Each inset shows the dynamics of the strains' densities $x_i(r)$ over rounds of competition r for a particular value of ρ. All four strains will coexist if ρ is in the range defined by Eq. 6 (shaded regions). If ρ is in the orange or blue regions, coexistence hinges on a single keystone strain of corresponding color (orange or blue), while if ρ is in the gray region, coexistence is robust to loss of any single strain. (C) Density dynamics of the same four strains with resource density ρ in the orange region of (B), so that the orange strain is the keystone. All four strains coexist together at first, then at competition round 2000 one strain is removed (different in each panel) and the remaining strains are allowed to reach their steady state. See *Supplementary Methods* Sec. S11 for parameter values.

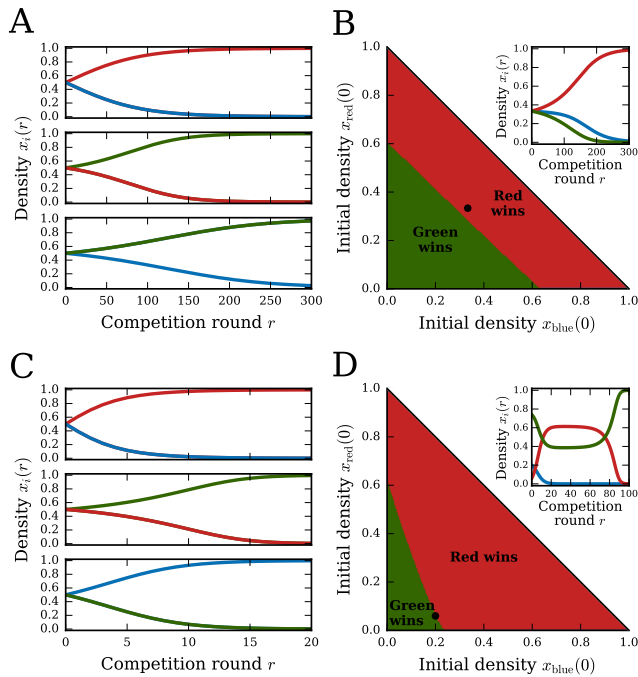### E. Pairwise competitions do not predict community behavior

A fundamental issue for microbial ecology and evolution is whether pairwise competitions are sufficient to predict how a whole community will behave [7, 9, 10]. For example, if several strains coexist in pairs, will they coexist all together? Or if a single strain dominates all pairwise competitions, will it also dominate in the mixed community? We now show that competition for a single limiting resource with tradeoffs in growth traits is sufficient to confound these types of predictions due to the higher-order effects in the selection coefficient (Eq. 2).

Strains that coexist in pairs will generally not coexist all together. Strains i and j that coexist as a pair are characterized by a particular growth-lag tradeoff $c_{ij} = -\Delta\lambda_{ij}/\Delta\tau_{ij}$ (Eq. 5). For a set of these pairs to coexist all together, these tradeoffs must all be equal, which will generally not be the case. However, if the growth-lag tradeoffs are equal for all pairs, then the strains can indeed coexist in a community, but not at the same resource densities as for the pairs (*Supplementary Methods* Sec. S8).

Pairwise champion may not dominate in the community. In a collection of strains, there may be one "champion" strain that wins all pairwise competitions. This champion, however, may not prevail in a mixed competition of all strains. For example, in Fig. 4A the green strain beats the blue and red strains individually with a "hoarding" strategy — slower growth, but shorter lag with lower yield — but together the blue and red strains consume resources efficiently enough to use their faster

growth rates to beat green (Fig. 4B). This is a unique consequence of higher-order ecological effects: the presence of the red strain actually changes the sign of the selection coefficient between green and blue (from positive to negative), and the blue strain similarly changes the sign of selection between green and red. In this example it occurs via modifications to the effective population yield $\bar{Y}$. Even if the strains have identical yields, it is possible for the pairwise champion to lose the mixed competition over short time scales due to effects from the growth-lag coupling terms $s_{ijk}^{\text{coupling}}$ (*Supplementary Methods* Sec. S9, Fig. S4).

Selection can be non-transitive. It is also possible that there is no pairwise champion among a set of strains, meaning that selection is non-transitive [22]. For example, in Fig. 4C, red beats blue and green beats red, but then blue beats green, forming a rock-paper-scissors game [37, 38]. This outcome relies crucially on the existence of tradeoffs between growth traits, so that no single growth strategy always wins (*Supplementary Methods* Sec. S10, Fig. S5). In this example, red beats blue by having a shorter lag time, green beats red by growing faster and using resources more efficiently (higher yield), and blue beats green by having shorter lag and hoarding resources (lower yield). Non-transitivity in this model occurs only for pairwise competitions where each strain starts with equal density ($x_i(0) = 1/2$); invasion competitions, where each strain competes against another starting from very low density (as would occur in an invasion by a migrant or a new mutant), do not demonstrate this type of non-transitivity (*Supplementary Methods* Sec. S10, Fig. S5).

FIG. 4. **Pairwise competitions do not predict community behavior.** (A, B) Example of three strains (blue, red, green) with a single pairwise champion (green). Panel (A) shows density dynamics $x_i(r)$ for binary competitions, while panel (B) shows outcome of ternary competition as a function of initial conditions: red marks space of initial densities where the red strain eventually wins, while green marks initial densities where green eventually wins. Inset: density dynamics starting from equal initial densities (marked by black dot in main panel). (C, D) Same as (A, B), but for three strains without a pairwise champion (non-transitivity). See *Supplementary Methods* Sec. S11 for parameter values.

Non-transitive competitions are particularly confounding for predicting the behavior of a mixed community. Since there is no clear champion, non-transitive pairwise competitions are often hypothesized as the basis for oscillations or coexistence in mixed communities [22, 37, 38]. However, a non-transitive set of strains will not coexist all together in our model. Which strain wins, though, is not directly predictable from the pairwise selection coefficients, and in fact may depend on the initial conditions. For example, Fig. 4D shows the outcomes of ternary competitions for a non-transitive set of strains as a function of their initial densities. If green starts at sufficiently high density, then it wins the mixed competition, but otherwise red wins. In the inset we show one such ternary competition, with initial conditions on the boundary between the red and green regimes. Here the outcome is very sensitive to the initial conditions, since higher-order effects from the decaying blue population draw the red and green strains toward their unstable coexistence point, where they temporarily remain until the blue strain goes extinct and either red or green eventually wins.

IV. DISCUSSION

Ecological effects of growth trait variation. Variation in multiple growth traits is widespread in microbial populations [23–25], since even single mutations tend to be pleiotropic with respect to these traits [26, 27]. Genetically-identical cells can also demonstrate significant growth variation [28, 29]. We have shown how this variation, with competition for only a single finite resource and no other interactions, is sufficient to produce a range of ecological phenomena, such as coexistence, keystones, non-transitivity, and other collective behaviors where a community is more than the sum of its parts. This is because variation in multiple growth traits creates higher-order effects in which the pairwise selection coefficients themselves change in the presence of other strains. This goes beyond the effects of ordinary clonal interference [39]; for example, even the sign of the selection coefficients may change due to these higher-order effects, so that a strain that is the best in pairwise competitions actually goes extinct in the mixed community (Fig. 4A,B). For example, a mutation that is apparently beneficial against the wild-type alone may not only appear to be less beneficial in the presence of other mutations, but it could even appear to be deleterious. These results highlight the importance of considering the mutational distribution of ecological effects, rather than just fitness effects relative to a wild-type, for predicting evolutionary dynamics.

The ability to coexist on a single limiting resource contradicts the principle of competitive exclusion [15, 16]. While previous work indicated that two strains may stably coexist through tradeoffs in growth traits [17–21], here we have shown that an unlimited number of strains can in fact coexist through this mechanism, and that coexistence may be multi-stable at a range of densities. Our work also supports the hypothesis that higher-order effects should be widespread in microbial ecosystems [7, 9]. Experimental tests for these effects and the predictive power of pairwise competitions remains limited, however. A recent study found that pairwise competitions of soil bacteria generally did predict the behavior of three or more species together [10], although there were important exceptions. Our results suggest an avenue for future investigations of this problem.

Tradeoffs between growth traits. Tradeoffs among lag, growth, and yield underlie many key outcomes of the model, such as stable coexistence. The prevalence of these tradeoffs in microbial populations has been the subject of many previous studies, especially due to interest in the r/K (growth-yield) selection problem. Models of metabolic constraints do imply a tradeoff between growth rate and yield [40, 41], while models of the lag phase suggest a synergy, rather than a tradeoff, with the growth phase ($c < 0$ in Eq. 5) [42–44]. While some experimental results have agreed these predictions, others have found the opposite trends or no trends at all [23–27]. In general, some sets of microbial strains certainly

realize tradeoffs, but it remains unclear whether tradeoffs are routinely generated by random mutations or emerge through evolution.

Applications to experimental ecology and evolution. Given a collection of microbial strains, we can measure their individual growth curves to determine their growth traits [30], and then predict the population dynamics of any combination of strains using our model. If we also know the distribution of mutational effects on growth traits, we can further predict evolutionary dynamics to determine what patterns of traits are likely to evolve, which can be compared with experimental data [23–26]. In contrast to another recent computational method [45], which also aims to predict competitions from individual growth curves, our results are analytical and therefore provide greater insight into the contribution of different growth traits to selection and evolutionary dynamics.

Our results are especially relevant to evolution and ecology experiments where populations undergo periodic growth cycles. While the importance of interference among mutants has been widely studied in these experiments [6, 39], it is generally assumed that each mutant is described by a fixed selection coefficient independent of the background population, since the relative genetic homogeneity of the population suggests there should be no additional ecological interactions beyond competition for the limiting resource. But since even single mutations will produce variation in multiple growth traits, our results show that higher-order effects should actually be widespread in these populations. Even genetically-identical populations may experience higher-order effects due to stochastic cell-to-cell variation [28, 29, 42], although the effects will fluctuate from one round of competition to the next assuming cell-to-cell variation does not persist over these timescales. While natural populations likely contain more complex interactions beyond competition for a single resource between different strains or species, our results here can nevertheless serve as a null model for detecting these interactions [19].

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AUTHOR CONTRIBUTIONS

MM and EIS designed research; MM performed calculations; MM wrote the manuscript. Both authors edited and approved the final version.

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