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How do microbes grow in nature? The role of population dynamics in microbial ecology and evolution

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Abstract

The growth of microbial populations in nature is dynamic, as the cellular physiology and environment of these populations change. Population dynamics have wide-ranging consequences for ecology and evolution, determining how species interact and which mutations fix. Understanding these dynamics is also critical for clinical and environmental applications in which we need to promote or inhibit microbial growth. We first address the latest efforts and outstanding challenges in measuring microbial population dynamics in natural environments. We next summarize fundamental concepts and empirical data on how population dynamics both shape and are shaped by evolutionary processes. Finally, we discuss the role of tradeoffs in microbial population dynamics, which may reveal physiological constraints and help to maintain ecological diversity. We find that current evidence for tradeoffs in population dynamics is limited, but that consideration of the evolutionary context of these tradeoffs is necessary for designing future experiments that can better address this problem.

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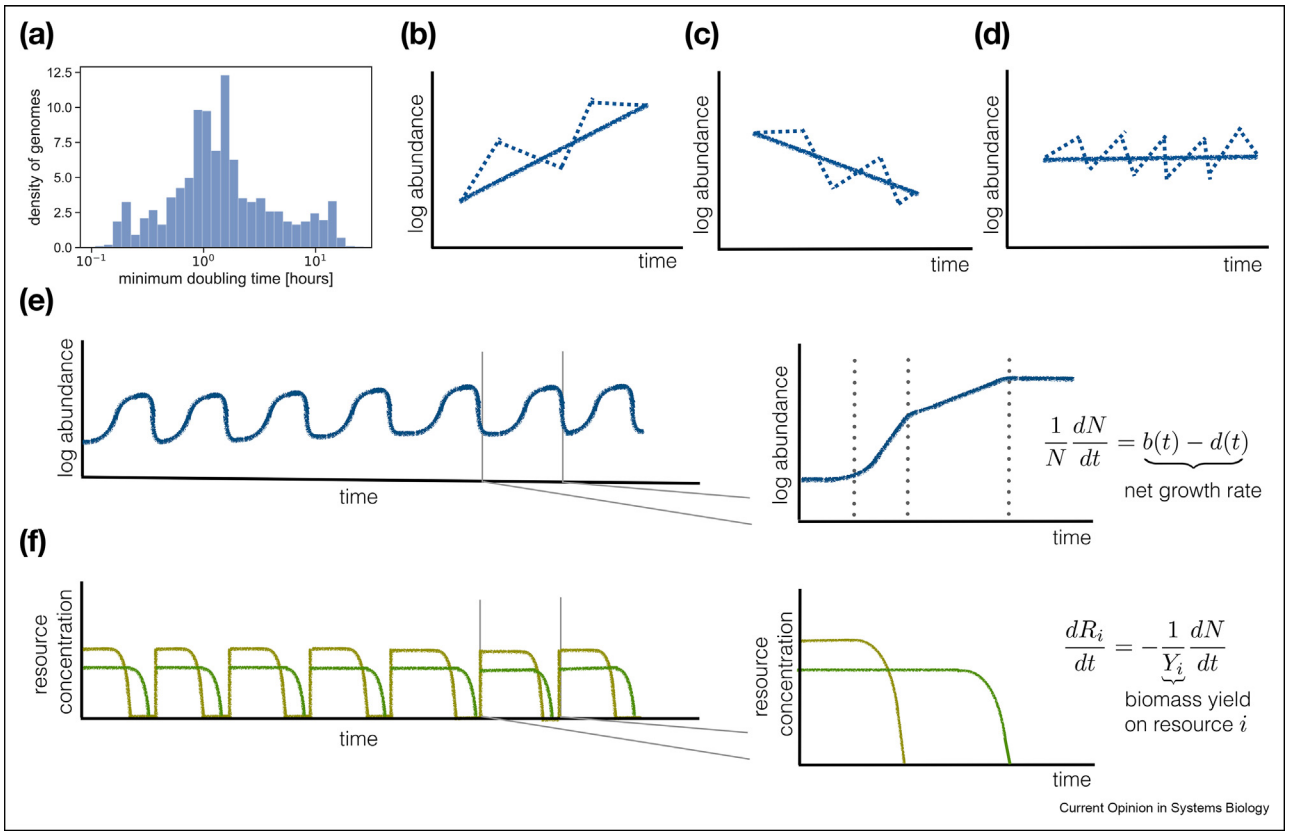
Microbes, Population dynamics, Natural environments, Microbial ecology, Microbial evolution, Tradeoffs.

What are the population dynamics of microbes in natural environments?

The focus of microbiology has shifted in the last decade from the study of tractable but simplified laboratory environments to the properties of microbes in their natural environments [1–3]. Evidence suggests that microbial populations in these environments are highly dynamic: individual taxa can grow 20-fold over the course of a week in the surface ocean [4] or fluctuate fourfold each day in the human gut microbiome [5]. Current estimates of minimum doubling times for most known microbes range from tens of minutes to tens of hours (Figure 1a) [6]. However, we are still beginning to assemble a detailed quantitative picture of what these population dynamics look like [7]. Since natural populations are always dispersed in space and contain genetic variation even within species, here we focus on the growth of microbial populations aggregated at a particular spatial and phylogenetic resolution. While understanding the variation of population dynamics across short spatial scales or between closely related lineages (including genetically identical single cells) is an important problem, it is beyond the scope of the work we discuss here.

There are three main scenarios for a population's growth: positive net growth (Figure 1b), as occurs for strains colonizing new environments such as the infant gut [8] or germ-free animal models [9]; negative net growth (Figure 1c), as has been observed for microbial taxa in anaerobic wastewater treatment [10]; or approximately zero net growth such that abundance remains constant (Figure 1d), which is the only scenario feasible over long times. Zero net growth can arise either because birth rates and death rates are balanced at every time point (solid line in Figure 1d) or because birth and death occur asynchronously, such that the population spends some short periods of time undergoing net birth and other periods undergoing net death while maintaining zero net growth over long periods of time (dashed line in Figure 1d). Indeed, there is the possibility of different short-term behaviors for all of these long-term scenarios (solid versus dashed lines in

Figure 1



Fundamental aspects of microbial population dynamics. (**a**) Distribution of minimum doubling times for ~200,000 prokaryotic genome sequences from the EGGO Database [6], as predicted from the codon usage bias of each genome. (**b**) Schematic abundance trajectory (solid line) for a microbial population with a positive net growth rate, given by the slope of the log abundance over time ($d\log N/dt$). An alternative trajectory with short-time variation in net growth rate but the same total change in abundance is plotted on top (dotted line). (**c**) Similar to panel (**b**), but for a population with negative net growth rate. (**d**) Similar to panel (**b**), but for a population with zero net growth rate. (**e**) Schematic time series of abundance for a microbial population with zero net growth rate on long time scales but with short-time cycles of birth and death. In the right-hand panel, a zoomed-in view is shown of a single growth cycle where the dotted lines mark discrete phases of growth, along with a general differential equation for the absolute abundance N according to its time-dependent birth rate $b(t)$ and death rate $d(t)$. (**f**) Same as panel (**e**), but showing the time series of two abiotic resource concentrations (dark green and yellow green) that drive microbial growth in panel (**e**). The differential equation describes the dynamics of the resource concentration R_i as it is depleted by biomass growth, according to the biomass yield Y_i (new biomass produced per unit resource).

Figures 1b,c). It is often useful to break down these short-term dynamics into discrete phases, each with an approximately constant growth rate (Figure 1e) [11]. We can then describe the trajectory of growth, a high-dimensional object, as a lower-dimensional set of traits (e.g., growth rates, lag times, etc.) corresponding to discrete growth phases [12,13].

Measuring the population growth rate and distinguishing the three scenarios (Figure 1b–d) is in principle straightforward given time-series data on absolute abundances. Unfortunately, measuring the absolute abundance of microbial strains in natural environments remains difficult since traditional omics methods only provide relative abundance [14], despite recent advances to calibrate these protocols for absolute abundance by adding foreign cells or DNA sequences to the sample [8,10,14–16]. However, the more fundamental obstacle to measuring growth dynamics is insufficient time resolution. For example, the gut microbiome of a single person can be sampled at best every six hours [5] (although an average time series of resolution every two hours can be reconstructed from replicate samples [17]), but this frequency is insufficient to capture short growth phases of 2–3 cell divisions. One possible solution to these problems has been to simulate natural environments in the laboratory [18], where direct absolute abundance measurements are easier.

An alternative strategy to the time-series approach relies instead on inferring the instantaneous birth rate of a population from a covariate property measured from a single "snapshot" in time. For example, the age distribution in a population of plants or animals at a single

time point can be used to estimate the birth rate [19]. In the case of microbes, Korem et al. [20] used a mechanistic model of cell division to identify the ratio of maximum to minimum read coverage over the genome (known as the peak-to-trough ratio) as a proxy for birth rate. This method performed well for *Escherichia coli* in lab environments, and the method has since been extended to work with draft genomes [21,22] and lower read coverage [23,24], but neither of these implementations performed as well in additional experiments with *Synechococcus* [25] and a diverse marine community [24,26]. One key limitation of the peak-to-trough ratio is that it cannot be converted into a birth rate unless the period of DNA replication is known [20], which may vary across species and environments.

Since the instantaneous birth rate is a global regulator of many cellular processes, snapshot methods have also tried to correlate the birth rate with other cell properties such as gene expression [27], proteome allocation [28], or other omics data [29]. For these methods to measure birth rates in natural environments, they must be trained with measured birth rates from these habitats. Such benchmarking data sets are currently lacking, but they will have to use time series of absolute abundance [26] or other methods that already provide calibrated growth rates. Insight into the birth rate of natural populations also comes from environmental biogeochemistry, using nutrient turnover rates in sediments [30] or by adding isotope-labeled nutrients as chemical tracers [31,32].

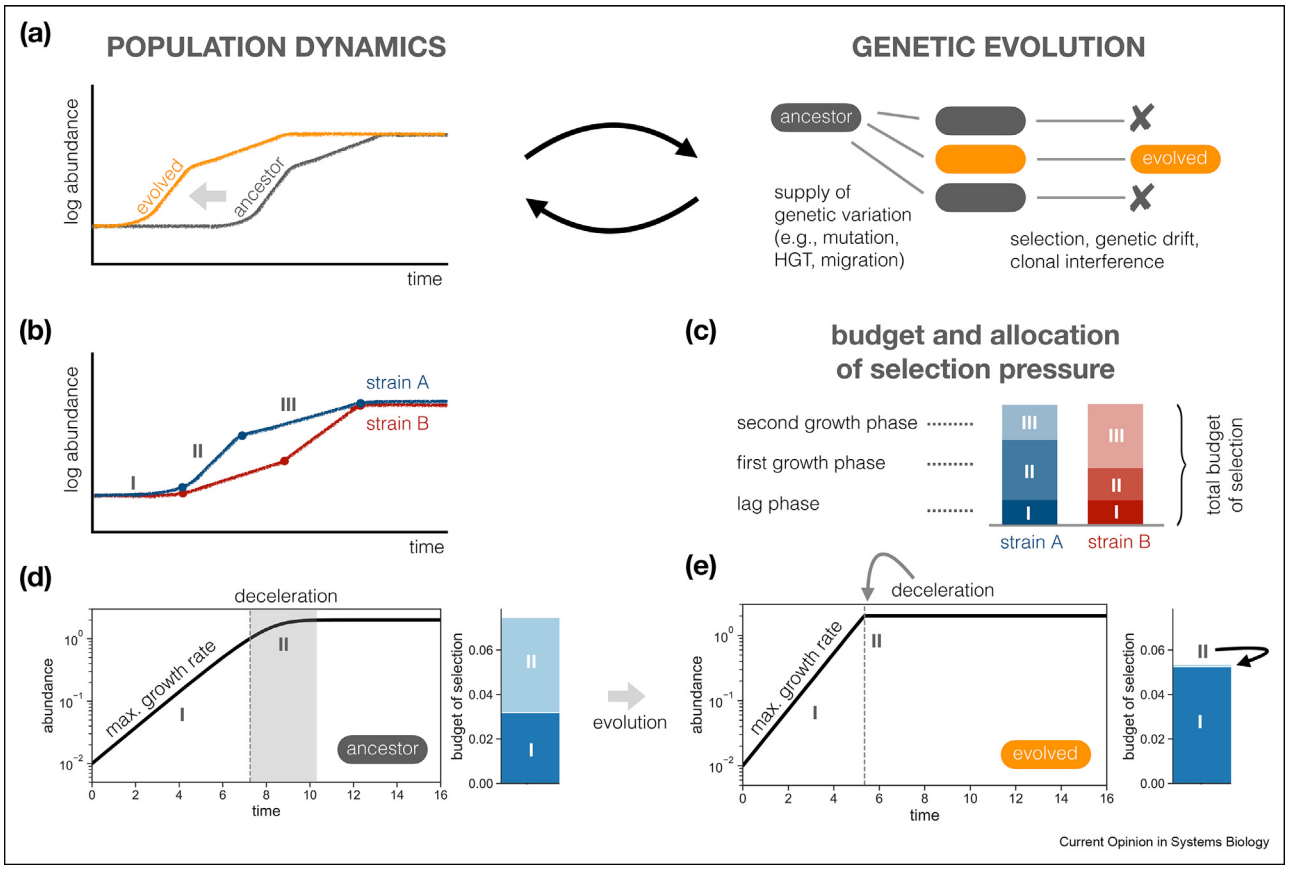
A final category of methods for determining population dynamics aims not to infer instantaneous birth rates in samples but rather to infer properties of growth from evolved patterns in genomes. One such method uses the accumulation of mutations in a genome as a clock to determine the historical birth rate of the species, assuming that mutations occur only during cell divisions and are largely neutral [33]. Other methods of this type infer the maximum potential birth rate of a species. The best genomic pattern here appears to be codon usage bias [6,34]. Figure 1a shows an example of these data. However, when tested in benchmark marine species, the predicted maximum birth rate falls short of matching the birth rate measured from absolute abundance data [26]. This may be because of qualitative differences between the environmental conditions used for the training data [34] and the species' true natural environments, or because the organism simply grows at rates much slower than their maximum due to nutrient limitation or other inhibiting factors. Besides codon usage bias, rRNA copy number provides another genomic pattern that can show a moderate correlation with birth rate in literature data [35,36], but mostly fails to predict the actual birth rate measured by isotope-labeled heavy water in a soil community [36].

What causes population growth to vary with time? Changes in the supply of resources are a likely factor in many systems. For example, populations may grow fast right after a pulse of resources but then decelerate and eventually stop growing once they deplete the resources (Figure 1f). Understanding population dynamics in natural environments therefore requires understanding resource dynamics as well. One major question here is whether natural resource dynamics are more "chemostat-like"—where the rate of resource influx is fast compared to the rate of population birth and death, leading to an approximately constant resource abundance—or more "batch-like," where the resource influx is slow compared to population growth (i.e., resources arrive in infrequent pulses) [37]. Identifying which nutrients are limiting growth is also an important question, especially for the problem of promoting or inhibiting the growth of microbial populations. For example, recent work has suggested that nitrogen is the primary limiting nutrient for microbes in mammalian guts [38], but it is also possible that multiple nutrients could simultaneously co-limit growth [39]. Whereas nutrients control population dynamics from the bottom-up, other biological players in the environment like phages, predators, and host immune systems can serve as top-down controls of microbial populations. This is particularly relevant for microbial pathogens, whose death rate, for example, has been found to depend strongly on the activity of host phagocytes [40].

What is the feedback between microbial population dynamics and evolutionary processes?

As with all aspects of biology, we must understand microbial population dynamics in the context of evolutionary processes. On the one hand, population dynamics affect key aspects of evolution (Figure 2a): the population size determines the supply rate of new mutations and other sources of genetic variation (e.g., horizontal gene transfer), as well as the strength of demographic fluctuations (genetic drift) associated with that variation. Population dynamics also determine how selection acts on genetic variation by setting both the total selection "budget"—the overall magnitude of selection on a mutation over a time period, which is proportional to the number of generations over which that mutation competes with its ancestor [41–43]—and the allocation of that selection budget across traits affected by the mutation (Figure 2b,c). For example, strain A (blue) in Figure 2b undergoes more generations during growth phase II than in phase III and hence has greater selection on mutations affecting traits for phase II (Figure 2c), while strain B (red) undergoes more generations in phase III and hence has greater selection on that phase. Different patterns of resource supply and mortality also play major roles. For example, Letten and Ludington [37] recently demonstrated in a model that

Figure 2



Feedback between microbial population dynamics and evolution. (**a**) Schematic diagram for the feedback between population dynamics (left panel) and evolutionary processes (right panel). In the ancestral population (gray growth curve on the left, gray cell on the right), there is a supply of new genotypes (gray and orange cells) through spontaneous mutations, horizontal gene transfer (HGT), or migration, but only one of them (orange cell) survives subsequent processes of selection, genetic drift, and clonal interference to reach fixation while the others go extinct (gray crosses). Population dynamics set key parameters of this process such as the population mutation rate, strength of genetic drift, and selection. But the outcome of genetic evolution (right panel) also influences the population dynamics in turn (left panel) by changing the population growth traits. For example, the evolved population (orange curve, left panel) may have a shorter lag time compared to the growth of the ancestor (gray curve). (**b**) Schematic growth curves for two species with different patterns of growth phases. Strains A (blue line) and B (red line) both have the same lag phase (marked as I), but strain A experiences greater growth in the first phase of exponential growth (II), whereas strain B has more growth in the second phase of exponential growth (III). (**c**) Schematic of the total budget and allocation of selection pressure for the two growth curves in panel (**b**). The height of the bars represents the total magnitude ("budget") of selection on a spontaneous mutation that appears on the backgrounds of strains A and B. The composition of the bars shows the contribution of each growth phase (in Roman numerals) to selection in a mutant. (**d**) Simulated growth curve under the Monod model of growth rate $g(R) = g^{\max} \cdot R/(R + K)$ for an ancestral strain where the half-saturation concentration K is approximately equal to the initial resource concentration R_0 [43]. We mark the two phases of the growth dynamics: phase I, where growth is approximately at the maximum growth rate, and phase II, where the growth rate decelerates to zero as the resource is depleted. As a bar plot on the right shows, the selection budget for a mutation that increases the maximum growth rate $g^{\max}$ and decreases the half-saturation concentration K by 1%. (**e**) Same as panel (**d**), but for an evolved microbial strain that has a much lower half-saturation concentration, $K/R_0 \approx 0.01$. In this evolved strain, the population dynamics have changed such that the phase of deceleration (II) is almost negligible due to the low value of the trait K. As such, there is little selection allocated to this phase, as shown in the bar plot on the right.

population dynamics with constant resource supply and mortality (chemostat-like conditions) select for different compositions of strains than population dynamics with pulsed resource supply and mortality (batch-like conditions).

However, population dynamics not only shape, but are also shaped by, evolution, as mutations affecting growth traits fix. For example, evolution could change the length or growth rate of different growth phases (Figure 2a). What patterns of population dynamics should we expect to emerge from evolution? Evolution occurs in two main steps (Figure 2a). First, genetic variation in growth traits is supplied to the population, usually through spontaneous mutations, horizontal gene transfer, or migration, but there can also be cryptic genetic variation whose phenotypic effects are revealed after a change in environment. Evolved trait patterns can be strongly

influenced by biases in the supply of growth trait variation alone. For example, growth phases may evolve to be shorter compared to lag phases if there are more mutations that affect growth rates than mutations that affect lag times. Previous studies have measured the supply of variation in growth traits for various combinations of traits, including lag times, growth rates, and yields for gene deletion strains of *E. coli* [44–47] and *Saccharomyces cerevisiae* [48], a collection of yeast hybrids [49], and a set of *E. coli* strains with point mutations in the adenylate kinase protein [50].

In general, these measurements show that mutations are almost always pleiotropic, affecting multiple phases of growth simultaneously. A key question about these measurements is whether mutation effects for different traits are correlated, especially in the form of a tradeoff, which we discuss in the next section. However, these data sets are relatively limited in scope and number due to the difficulty of performing high-throughput measurements of growth traits for large mutant libraries; since current omics methods for growth dynamics are insufficiently accurate (as discussed in the previous section), these measurements typically require imaging or tracking optical absorbance or fluorescence in microplates. Improving these methods or otherwise expanding the scale of these experiments is a critical need for future work. We also expect mechanistic models that can predict how mutations affect growth traits—for example, based on whole-genome metabolism [51] or intracellular resource allocation [52]—to play a crucial role in addressing questions beyond the practical constraints of empirical measurements.

Given a supply of genetic variation in growth traits, that variation is then shaped by selection, genetic drift, and other population genetic processes (e.g., clonal interference) into the evolved patterns of traits (Figure 2a). Laboratory competition experiments can empirically measure aspects of these processes, but they are especially amenable to mathematical models since the evolved trait patterns generally do not depend on molecular or cellular details. In particular, competition experiments and models have determined the total budget and allocation of selection across different traits (Figure 2b,c), such as lag times versus growth rates [41,47,53], maximum growth rates versus deceleration rates [43,54], and secondary growth phases such as fermentation versus respiration in yeast [42,55].

How much of the evolved population dynamics is due to the mutation supply versus selection on the growth traits? Evolution experiments in both *E. coli* [56,57] and *S. cerevisiae* [58,59] found significantly different amounts of evolutionary change on different growth traits under selection, suggesting that the mutation supply was limited for some of those traits. However, practical limitations on measurements, as aforementioned, have constrained the scale of these experiments. Thus, we still need more data on growth traits within and between evolved populations, ideally over long evolutionary trajectories, to comprehensively address this question.

Altogether, population dynamics and evolution form a feedback loop (Figure 2a) [42]: population dynamics set constraints for evolution over short times, but then evolution changes those constraints over long times. Previous work on the evolution of the half-saturation concentration K (concentration of a limiting nutrient at which growth rate is half its maximum) in the Monod growth response provides a useful example [43]. Initially, the trait K determines the population dynamics by controlling the phases of maximum growth and deceleration, which shape evolution by determining the allocation of selection for mutations to each of these phases (Figure 2d). But as the trait K evolves to lower concentrations, the population dynamics change as well: the phase of deceleration becomes shorter, until the population dynamics are almost entirely at maximum speed (Figure 2e). This means there is little selection for additional mutations in K.

Are there tradeoffs in microbial population dynamics?

When considering patterns of evolved growth traits for microbial populations, tradeoffs between these traits are one of the most important possibilities. For example, one species could grow faster but another species could use resources more efficiently (rate-yield tradeoff) [60], or one species could grow faster when resources are abundant while another species could grow faster when resources are scarce (rate-affinity tradeoff) [54,61]. Species could also have tradeoffs between their growth on different resources altogether [55,62,63].

Tradeoffs matter for two main reasons: First, they can reflect an underlying physiological or biophysical constraint on cells. For example, the rate-yield tradeoff has been hypothesized because of a thermodynamic constraint in energy metabolism [60]. Another common scenario is that if cells have only a fixed amount of resources to invest in metabolism for two different nutrients, then different genotypes can have different investment strategies, creating a tradeoff between growth on those different nutrients. The second reason tradeoffs in population dynamics matter is that they can underlie complex ecological interactions between genotypes. In particular, growth tradeoffs enable the exploitation of distinct spatial or temporal niches—such that different species have growth advantages at different points in space or time—which can allow those species to stably coexist [54,60,62]. These mechanisms are especially important to ecology because they may explain the maintenance of species diversity with few resources. However, growth tradeoffs can produce other complex ecological dynamics as well, including

multistability, non-transitive selection, and higher-order interactions [41,42,53].

There are several different forms of tradeoffs when considering microbial population dynamics, depending on what type of variation (genotypic or environmental) one considers and at what biological scale. We enumerate the possibilities and their interpretations in Box 1 and Figure 3. In general, tradeoffs across spontaneous mutations (Figure 3a,d) or environments (Figure 3g) are most relevant for revealing underlying constraints, while tradeoffs across genotypes within populations (Figure 3b,d) are necessary for realizing complex ecological dynamics such as stable coexistence.

What tradeoffs in microbial population dynamics are actually realized? Existing data shows that tradeoffs across genotypes occur sometimes but are not widespread among closely related genotypes. A rate-affinity tradeoff in population growth rates at high and low concentrations of resources has been reported in a few systems [67], while other studies have actually found synergies across genotypes [68] or no correlation at all [43]. Tests for rate-yield tradeoffs [57,69–75] and

Box 1. Types and interpretations of tradeoffs in microbial population dynamics.

A tradeoff between two quantitative traits *X* and *Y* of population dynamics is a negative correlation in the values of those traits across some set of samples. Here we focus on traits that directly describe the population dynamics of microbes (e.g., lag time and doubling time), but some previous studies have focused on traits at molecular or cellular scales (e.g., rates of metabolic pathways or nutrient uptake) on the assumption that they correlate with traits of population growth [65]. However, this is often not the case (see Figure S12 and the Discussion section in Ref. [43]), so one must be cautious about extrapolating tradeoffs or other patterns across biological scales.

There are two major types of tradeoffs in population growth traits, which differ in the variation across samples they represent and hence their interpretations.

1. **Genotypic tradeoffs.** In this case, one considers traits across a set of samples representing different genotypes (Figure 3a–c). We test the existence of a tradeoff between two growth traits (e.g., lag time and minimum doubling time of a growth curve, Figure 3d) by measuring the traits for all genotypes in the set. A genotypic tradeoff exists if there is a negative correlation between those traits across genotypes (Figure 3e). Tradeoffs of these types in population dynamics traits appear to be rare, at least across closely related sets of genotypes. One can choose the set of genotypes in various ways, but there are three most common types of genetic variation, each having a different meaning for a tradeoff.
   (a) **Tradeoff across spontaneous mutations** (Figure 3a). Here, the samples are spontaneous mutations on the background of a single reference genotype. This represents the genetic variation that arises spontaneously in a population during evolution (Figure 2a), and therefore it is an important determinant of the mutations that actually fix in the population. Since this set of genotypes is not biased by selection or other evolutionary processes, a tradeoff here is indicative of an underlying constraint. For example, if *X* and *Y* are growth rates on two different carbon sources, then a tradeoff across spontaneous mutations may occur because the different mutants reflect different investments of a fixed pool of cellular resources into the metabolism of each carbon source. Figure 3f shows growth rates and reciprocal lag times across a set of *E. coli* strains with point mutations in the adenylate kinase protein [50]; while some subsets of these mutations exhibit tradeoffs, the whole set does not at a statistical level, suggesting there is no underlying constraint on both lag and growth.
   (b) **Tradeoff across standing variation within a population** (Figure 3b). These genotypes are those that co-occur within a single, evolving population at a single point in time. This set of genotypes reflects both the supply of spontaneous mutations (i.e., the pattern of traits in Figure 3a) and the outcome of selection and other evolutionary processes (Figure 2a). Tradeoffs here can therefore be due to tradeoffs at the level of spontaneous mutations, tradeoffs induced by selection, or both. As a result, one cannot deduce underlying constraints from tradeoffs at this level. Since this set represents genotypes that actually co-occur in a population at the same time, these tradeoffs represent opportunities for coexistence or other ecological dynamics associated with tradeoffs (e.g., multistability, non-transitive selection, higher-order interactions) [41,42,53,54].
   (c) **Tradeoff across independent populations** (Figure 3c). These genotypes come from independently evolving populations. Like the previous case, these genotypes represent the combined outcome of mutation supply and selection, but because these genotypes do not co-occur in the same population, they may demonstrate a different pattern of traits compared to those within populations (Figure 3b). This could be due to stochastic differences in the number of accumulated mutations between populations [47], but it could also be due to environmental variation that exists between the populations. As a result, tradeoffs across this type of variation are usually difficult to interpret.
2. **Environmental tradeoffs.** These tradeoffs correspond to negative correlations of traits for a single genotype across multiple environmental trajectories or treatments (Figure 3g,h). Note that this requires defining traits *X* and *Y* in a way that matches across environmental variation. As with tradeoffs across spontaneous mutations, tradeoffs across environments can also represent underlying constraints. For example, Basan et al. [64] found an environmental tradeoff for a single *E. coli* strain between its growth rate *X* in various carbon sources and the reciprocal lag time *Y* after shifting to a different carbon source (Figure 3i), which they explain in terms of a constraint on the underlying metabolic regulation.

We finally note that individual cells and populations are characterized by more than just two traits, and so one must consider the possible effects of dimensional reduction when evaluating two-dimensional tradeoffs as discussed here. In particular, if there is no tradeoff between two traits, there could still be another type of constraint that is only apparent when considering a higher-dimensional set of traits [55]. Even if there is a tradeoff between two traits, the consequences for ecology and evolution may be unclear from that data alone, as there can be hidden variation in a third trait also under selection. The dimensionality of trait space relevant for mutations and selection remains an important topic for research [66].

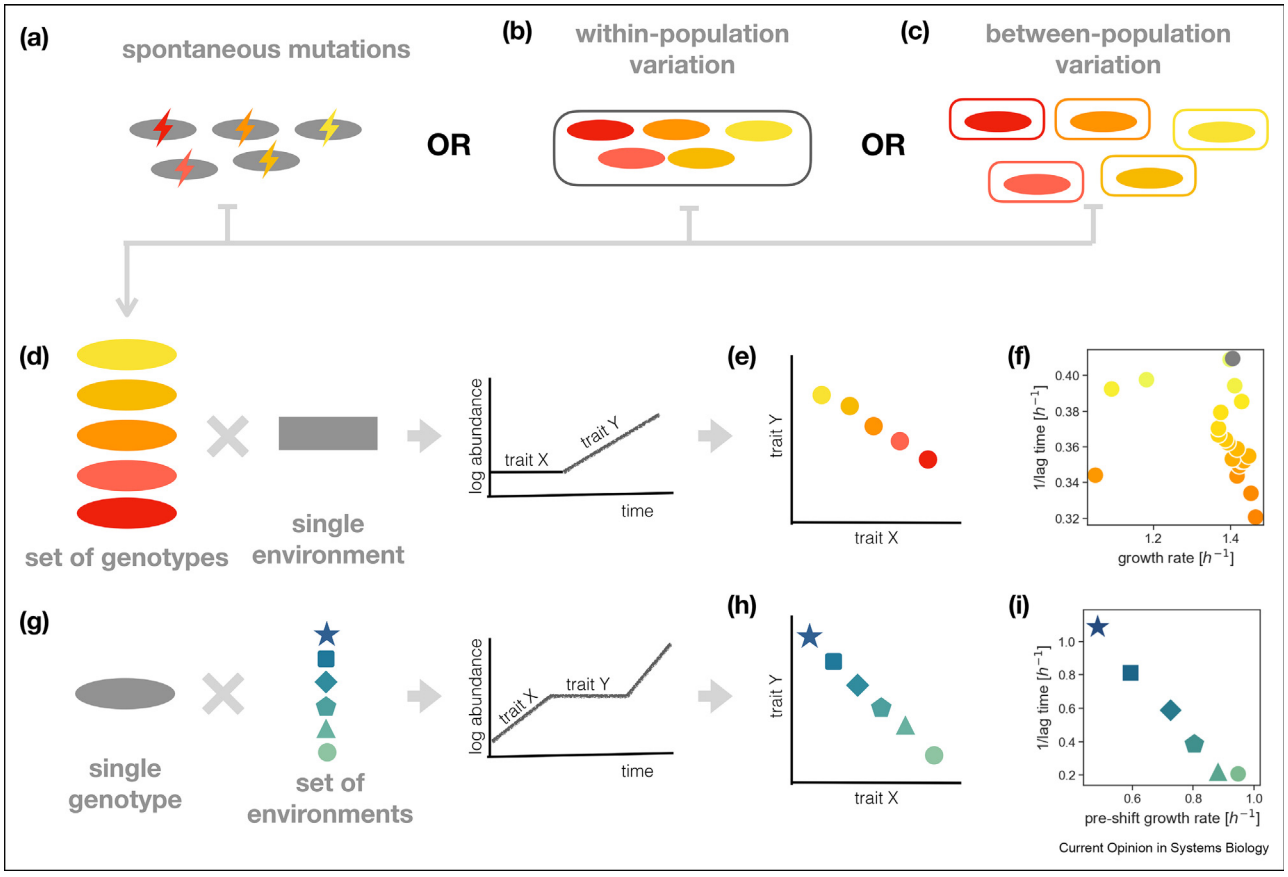
tradeoffs between lag times and growth rates [49,50,68,70,76] have also found mixed results (e.g., Figure 3f).

We believe there are two major causes for the inconclusive status of many tradeoffs. First, tradeoffs do not necessarily translate across biological scales. Some of the proposed tradeoffs in microbial growth, such as rate-yield and rate-affinity, were initially formulated for molecular- or cellular-scale processes such as metabolic pathways, but traits at those scales do not directly correspond to growth traits for whole cells or populations [43,65].

Second, many discussions of tradeoffs have conflated different types of genetic variation (Box 1 and Figure 3a–c), whose interpretations are quite different. Tradeoffs across spontaneous mutations (Figure 3a) should directly reflect underlying physiological constraints, but tradeoffs across genotypes within or between populations (Figure 3b,c) depend on both the supply of spontaneous mutations *and* the selection on these traits (Figure 2a). For example, even if there is a tradeoff across spontaneous mutations, there may be no tradeoff in evolved populations if selection favors generalist trait combinations over specialists. Moreover, a tradeoff across lineages within evolved populations can emerge in the absence of a tradeoff across spontaneous mutations if the trait combinations of the lineages are selectively neutral with respect to each other [47].

Future work on this topic will therefore require high-throughput measurements of growth traits (rather than uptake or metabolic traits) across well-defined sets of genetic variants, ideally in systems where libraries of

Figure 3



Types of tradeoffs in microbial population dynamics. (**a**) An example set of genotypes (gray cells) that vary by spontaneous mutations (lightning bolts) on the same background genotype. (**b**) An example set of genotypes (colored cells) that all co-occur in the same population (gray box). (**c**) An example set of genotypes (cells of different colors) that occur in independent populations (colored boxes). (**d**) Schematic procedure for measuring a tradeoff across genotypes (colored cells) in a single environmental condition (gray box). For each genotype, the two growth traits *X* and *Y* are identified from the strain's growth curve (gray line). (**e**) Schematic of data showing a tradeoff across genotypes between two traits, *X* and *Y*. (**f**) Measured growth rate (x-axis) and reciprocal lag time (y-axis) for a set of *E. coli* genotypes that differ by single mutations in their adenylate kinase protein [50]. The gray dot marks the ancestral strain. (**g**) Schematic procedure for measuring a tradeoff across environments (colored shapes) for a single genotype (gray cell). For each environmental treatment, two traits *X* (here shown as initial growth rate in first phase) and *Y* (here shown as reciprocal lag time after a shift to a second growth phase) are estimated from the growth curve (gray line). (**h**) Schematic of data showing a tradeoff across environments between the two traits *X* and *Y*. (**i**) Measured growth rate before nutrient shift to acetate (x-axis) and reciprocal lag time after shift to acetate (y-axis) for *E. coli* under six different pre-shift carbon sources (colors) [64].

spontaneous mutants and evolved lineages can be directly compared. In particular, this would be valuable for collections of strains or species that are already known to coexist in the same community, so we can test how much of this coexistence can be explained by any growth tradeoffs [41,53,54,62].

Outlook

Understanding the population dynamics of microbes in natural environments holds the promise of helping us control microbial growth in clinical and environmental systems—for example, by promoting the growth of commensal bacteria or inhibiting the growth of a pathogen. However, future progress will hinge on our ability to make these measurements more accurate and systematic; we expect this will require a combination of experimental innovations as well as insights from modeling, especially in terms of identifying better snapshot biomarkers of cellular birth and death. We have also learned a great deal, both theoretically and empirically, about how ecology and evolution may give rise to these observed population dynamics. Here we also look forward to improvements in high-throughput growth phenotyping, especially for large mutant libraries and within-community strain libraries, as well as multiscale modeling that can predict mutation effects on growth traits. Together these steps will help us toward our ultimate goal of a quantitative and predictive theory of microbial population dynamics.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data is from previously published papers, which are cited therein.

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This article provides a comprehensive study of genomic codon usage bias as a predictor of maximum birth rates in an enormous collection of microbial species. Reusing a training data set of maximum growth rates for ~200 microbial taxa measured under laboratory conditions (negligible death), the authors build a statistical regression model to predict the maximum birth rate for any sequenced microbial genome. It is a landmark paper as it connects the physiological variable of growth to modern-day omics data. It makes a powerful case for more measurements of growth rates, especially in natural environments, to eventually use similar frameworks to predict the growth of microbial populations in nature.

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This is a case study of microbial population dynamics in a wastewater reactor, using a combination of metagenomics and spike-in to estimate taxon-specific death rates from scratch. In particular, this demonstrates how population dynamics depend on the choice of time scale: despite the net negative growth over 30 days, there is net positive growth during the first day, suggesting that natural populations can experience short phases of growth and that resolving these phases requires sampling every few hours or less.

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This article provides a thorough discussion of current methods to measure absolute abundance from sequencing data using the spike-in of cells or DNA sequences. Written in the format of a technical review, the article stands out for formulating the information lost by only

measuring relative abundances and providing a step-by-step guide for complementing standard metabarcoding protocols with spike-ins to measure absolute abundance. The more widely absolute abundance is measured, the more we can learn about population dynamics, and the authors provide a practical guide for adding absolute abundance to the toolkit of microbial ecology measurements.

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This gives a mathematical overview of growth rate estimators used in age-structured populations and a potential inspiration for developing snapshot methods beyond the peak-to-trough ratio. In the introduction, the authors present a summary of historic approaches to estimating generation times and the conceptual problems that come with them. It is a worthwhile read for historical context, and although the population dynamics are mostly focused on larger organisms such as humans, the concept of inferring growth rates from the distribution of age may be more universal.

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This study proposes and implements an interesting "snapshot" method for inferring the instantaneous growth rate of a population from metagenomics data. The idea is that faster-growing cells will have more overlapping DNA replication cycles, which leads to a greater copy number of the genome near the origin of replication (peak of read coverage) relative to the terminus of replication (trough of read coverage). Using a mathematical model of this process based on a previously published work, the authors show that they can accurately infer growth rates of *E. coli* in both chemostat and batch cultures. While the method does not perform as well for other systems, they nevertheless find the method suggests significant growth rate differences for mouse and human gut microbiomes under different treatments or disease states.

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The authors assemble a naturalistic data set of growth rates, measured through absolute abundance in controlled incubation of seawater, across 101 marine taxa. This provides a ground truth for the growth rate and allows the authors to test existing software implementations of the peak-to-trough ratio (PTR), which largely fail to capture the instantaneous population growth rate. A key lesson here is that all tested methods for the PTR fail to a similar degree, suggesting that the issue for this method of growth rate estimation does not lie within the bioinformatics processing but rather in the conceptual insufficiency of the PTR as a single metric to capture growth.

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This study is an exemplary application of stable-isotope probing (qSIP) to track 300 taxa in their birth, death, and net growth by incubating a soil sample with heavy water. Under this experimental analog of summer rain, most taxa experience net negative growth rates (death) that differ from species to species, suggesting that phases of death are in fact phases of natural selection and species in natural environments can outcompete their community members both in the growth phase and in the death phase.

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The authors devise a clever approach for inferring historical average birth rates for species. The method assumes that the mutation rate of an organism during its evolutionary history is the same as its mutation rate in a laboratory experiment. Thus, by taking the ratio of a mutation rate inferred from a phylogeny (in units of clock time, such as years) and a mutation rate measured directly in a laboratory experiment (in units of generations), they can calculate the number of generations per year, which is the birth rate. While the authors could only perform this calculation directly on a few organisms due to the availability of laboratory measurements of mutation rates, they extrapolated their results statistically to obtain a distribution of birth rates that is quantitatively consistent with measurements obtained by other methods (e.g., codon usage bias).

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The authors simulate the assembly of a microbial community under both chemostat-like dynamics (constant resource supply and mortality) and batch-like dynamics (pulsed resource supply and mortality). They find that these two regimes produce significantly different community compositions, as a proof-of-principle for the importance of population and resource dynamics.

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The authors collected a set of single adaptive mutations from an evolution experiment in *S. cervisiae*. They can infer the contribution of different growth phases (fermentation, respiration, and stationary phase) to the relative fitness of each mutant by varying the length of the growth cycle, a clever method that enables these measurements to be done in bulk using sequencing rather than by measuring the growth curves of all mutants as separate monocultures. The authors then map the distribution of mutants in the growth phase trait space to determine whether the mutants form a Pareto front, which would indicate an underlying tradeoff. They find that while some mutations can in fact improve all traits simultaneously relative to the ancestor, the mutants collectively imply a constraint on the ability to improve all traits simultaneously beyond a limit. This work has one of the highest-throughput data sets and the clearest discussion of tradeoffs in microbial growth.

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The authors measured the growth of 186 marine heterotrophic bacteria on 135 carbon sources. They find the diversity of the strains' metabolic preferences collapses into a low-dimensional space, mainly the one-dimensional space of preference for sugars versus organic acids. The authors explain the sugar-acid preference in terms of the number of genes in corresponding metabolic pathways. Besides demonstrating a within-population tradeoff that could facilitate coexistence, this work shows how such growth traits may be predicted from genomic features.

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The authors grow *E. coli* at steady state using different glycolytic carbon sources and then rapidly shift them to growth on acetate, a gluconeogenetic carbon source. They find that there is a tradeoff across these environmental conditions, such that the faster the population was growing before the shift, the longer it takes to start growing after the shift, which they explain in terms of the underlying metabolic pathway. These results are one of the most quantitatively elegant demonstrations of a tradeoff in microbial population dynamics.

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