

Ecological systems biology: The dynamics of interacting populations

Jonathan Friedman and Jeff Gore

Abstract

Ecological systems biology integrates theory and experiments in simple laboratory systems to study how interactions between individuals determine the emergent properties of complex biological communities. This approach reveals parallels between ecological dynamics that result from interactions between populations, and evolutionary dynamics which result from analogous interactions within a population. Tractable microbial systems enable systematic testing of theoretical predictions, and identification of novel principles. Notable examples include using a cooperatively growing yeast population to detect theoretically predicted early-warning indicators preceding sudden population collapse, validating predicted spatial expansion patterns using two yeast strains which exchange essential metabolites, and the recent realization that coevolution of predators and prey qualitatively alters the oscillations that are observed in a rotifer-algae system.

Addresses

Physics of Living Systems, Department of Physics, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

Corresponding authors: Friedman, Jonathan (yonatanf@mit.edu); Gore, Jeff (gore@mit.edu)

Current Opinion in Systems Biology 2017, 1:114–121

This review comes from a themed issue on **Future of systems biology**

Edited by **Arnold Levine**

For a complete overview see the [Issue](#) and the [Editorial](#)

Available online 8 December 2016

<http://dx.doi.org/10.1016/j.coisb.2016.12.001>

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Keywords

Ecology, Evolution, Microbial communities, Interactions, Cooperation, Mutualism, Predator-prey.

Introduction

Systems biology aims to understand complex biological systems by studying the interactions between the components that make up these systems. For example, in molecular systems biology, interactions between cellular components such as genes and proteins are studied to determine cellular properties such as adaptability and robustness. Analogously, ecological systems biology involves studying interactions within and between species to elucidate community-level properties such as di-

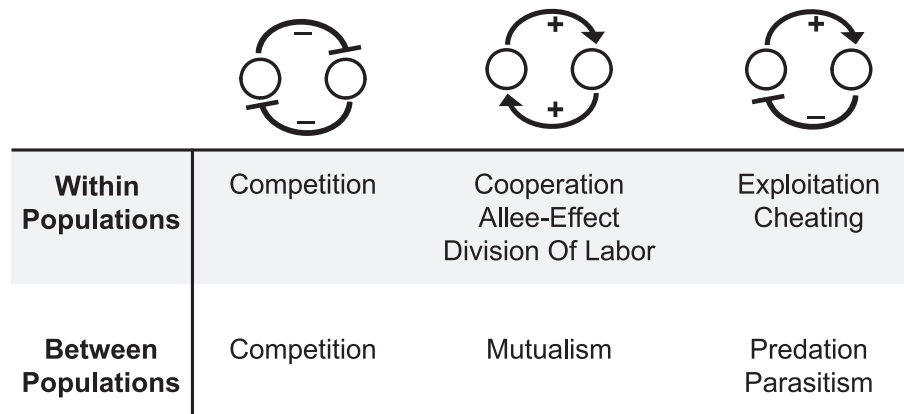
versity and stability. To do so, the ecological systems biology approach is to tightly integrate theory and experiments in simple laboratory systems, in which general principles can be tested systematically. Since they offer the fast time scale and experimental control required to implement this approach [1,2], much of the recent progress in the field has been achieved using microbial systems. But microbes are far more than a convenient model system: microbial communities play key roles in human health and global nutrient cycles [3], and developing a quantitative understanding of how these communities form, function and evolve is of crucial importance [4]. While this manuscript focuses on microbial systems, the insights gleaned using these systems are broadly applicable to ecological system, including cancerous cells within multicellular organisms [5].

Ecological interactions can broadly be classified according to whether the interacting partners promote or hinder each other's growth, regardless of the mechanistic details of the particular species involved [6] (Figure 1). By focusing on qualitative interactions, one can identify parallels between ecological dynamics that result from interactions between populations, and evolutionary dynamics which result from analogous interactions within a population. In the following sections, we highlight qualitative phenomena resulting from different interaction types, recent experimental demonstrations of these phenomena, and potential future research directions.

Competition and cooperation in clonal populations

Clonal populations are composed of genetically identical individuals, which have overlapping growth requirements. Therefore, negative interactions, such as resource competition (Figure 2A), are expected to be prevalent within such populations. However, positive interactions, where individuals promote each other's growth, also occur within clonal populations, where it is commonly referred to as cooperation. For example, when deriving energy from the disaccharide sucrose, cells of the yeast *S. cerevisiae* promote each other's growth by extracellularly breaking down the sucrose into monosaccharides which are available to the entire population [7] (Figure 2B). A variety of mechanisms can give rise to positive interactions, including protection from predators, degradation of antibiotics, and increasing extracellular nutrient availability via secretion of digestive enzymes or chelators that liberate scarce elements such as iron [8].

Figure 1



Similar interaction types occur within and between populations. We classify Interactions according to whether interacting partners promote (arrow) or hinder (blunt arrow) each other's growth, and provide the common terminology used to describe these interaction when they occur within and between populations.

The dynamics of cooperating populations can be qualitatively different from those of competing ones. First, in competing populations, crowding effects, such as resource depletion and waste accumulation lead to a monotonic decrease in per-capita growth rate with population density (Figure 2C). In contrast, at low densities, cooperating populations experience an increase in per-capita growth with population density (Figure 2D), a phenomenon known as the Allee effect [9].

Due to this interdependence between individuals, there may be a minimal number of individuals required to establish a viable cooperative population, whereas no such minimal size exists for competing populations. Consequentially, as environments deteriorate, competing populations experience a gradual decline in population size (Figure 2E), whereas cooperating ones may undergo a sudden collapse [10] (Figure 2F). Lastly, when growing into new territory, competing populations are “pulled” forward by a small number of individuals growing at the population front, whereas cooperating populations are “pushed” forward by individuals arriving from the bulk of the trailing population. Theory predicts that these distinct modes of expansion lead to difference in the velocity and shape of the advancing front [11], as well as to a higher degree of genetic diversity being maintained in cooperating populations [12]. The former effects have recently been observed experimentally [13], whereas the latter has yet to be directly demonstrated.

Positive interactions create opportunities for “cheaters” who exploit the public goods created by cooperators without contributing to them [14]. How, then, is cooperation maintained in the presence of such cheaters? In the case of yeast consuming sucrose, the sugar is broken down close to the surface of cooperating

cells, which get preferential access to the resulting monosaccharides [7]. This partial “privatization” of the public goods can give an advantage to cooperators when they are rare and prevent them from going extinct. Several other mechanisms for maintaining cooperation have been recently explored, including spatial structure, group selection, and horizontal gene transfer [15–19].

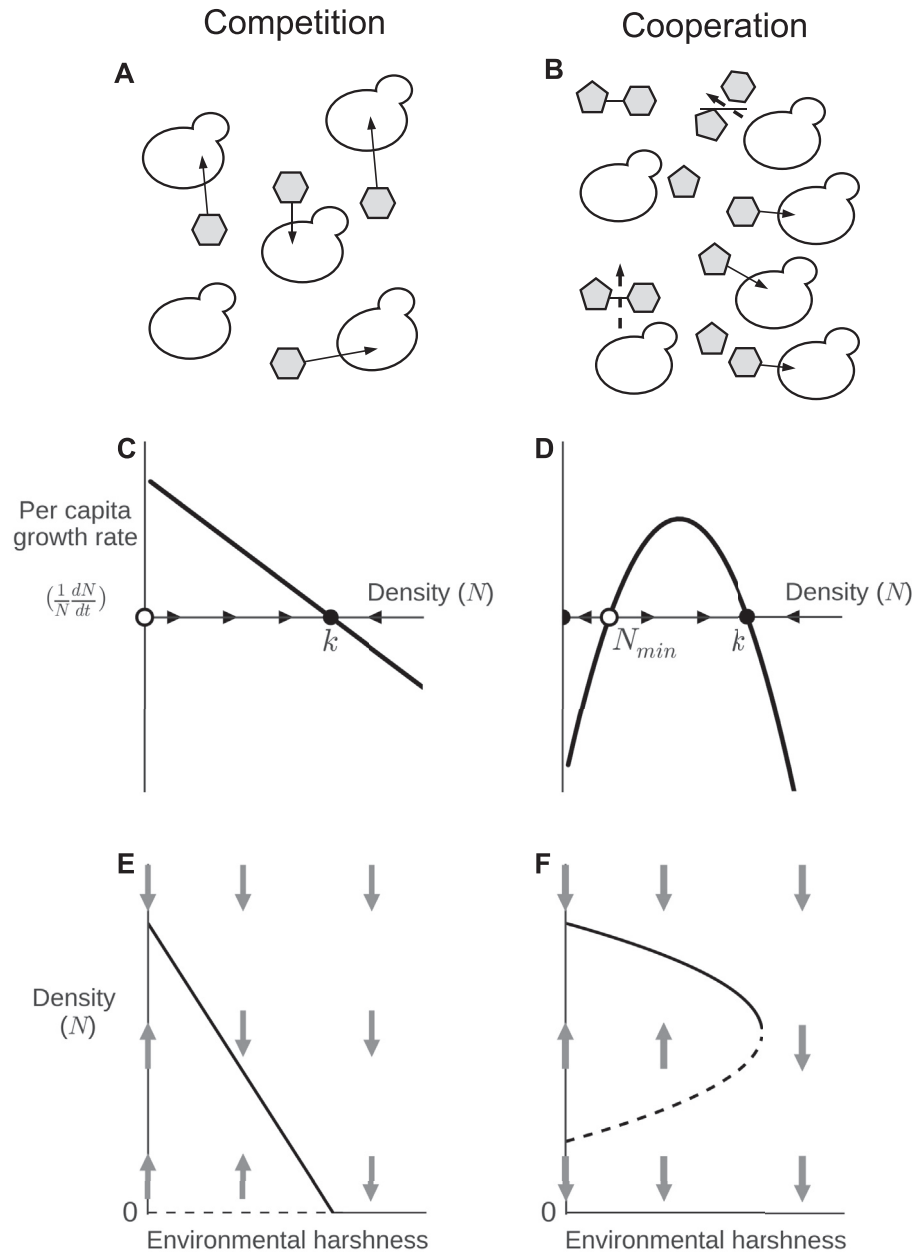
Competing populations

Competition is perhaps the most common natural interaction [20]. Similar to the maintenance of cooperation within a population, the maintenance of species diversity in communities is a fundamental question in ecology. For resource competition in well-mixed environments, theory predicts that the number of coexisting species cannot exceed the number of limiting resources. This theoretical expectation was validated in simple lab systems, where interactions are dominated by competition for known limiting resources [21]. Spatial or temporal heterogeneity are predicted to increase the number of coexisting species, though there are few experimental tests of these mechanisms [22,23].

In addition to competition for exploitation of shared resources, species can directly interfere with each other's growth by mechanisms such as the secretion of toxins [24]. In contrast to resource competition, in which the outcome is typically independent of the initial species abundances, this “interference” competition can lead to a bistable outcome, with exclusion of initially rare species [25]. The prevalence of such interactions among soil bacteria of the genus *Streptomyces* has recently been demonstrated experimentally [26].

While resource competition and direct interference differ in their mechanistic details, both can be captured

Figure 2



The dynamics of cooperating populations can be qualitatively different from those of competing ones. A model system for studying the cooperative dynamics is the yeast *S. cerevisiae* (ovals), which can either grow competitively or cooperatively. Competition occurs when it derives energy from glucose (filled hexagons), which is imported directly into the cell (A). More complex sugars, such as sucrose (linked hexagons linked to pentagons) must be first broken down extracellularly, leading to cooperative growth of the population (B). When cells compete, the per-capita growth rate declines monotonically with population density (C), whereas in cooperating populations the per-capita growth rate initially increases with population density, potentially leading to a minimal viable population density (D). Therefore, as environments deteriorate, competing populations experience a gradual decline in population size (E), whereas cooperating ones may undergo a sudden collapse (F). Solid and dashed lines indicate stable and unstable equilibrium population densities, respectively.

using the competitive Lotka-Volterra (LV) model [27]. This simple, phenomenological model can capture the various qualitative outcomes typically observed in competition experiments: competitive exclusion, coexistence, or bistability. The model provides intuition

regarding how the competitive outcome relates to the difference between the strengths of inter- and intra-population competition. For example, two species are expected to coexist if they compete with each other less strongly than each species competes with itself.

Mutualisms

As within a clonal population, distinct populations may not only compete, but also promote each other's growth. These populations could correspond to different species, or they could correspond to sub-populations within a species, but in either case the dynamics can be determined by the mutualistic interaction. Such positive interactions are thought to be common among microbes [28]. In the lab, strains that exchange essential amino acids are often used to study mutualisms (e.g. [29,30]). In these systems each strain requires an amino acid secreted by the other strain (Figure 4A and C).

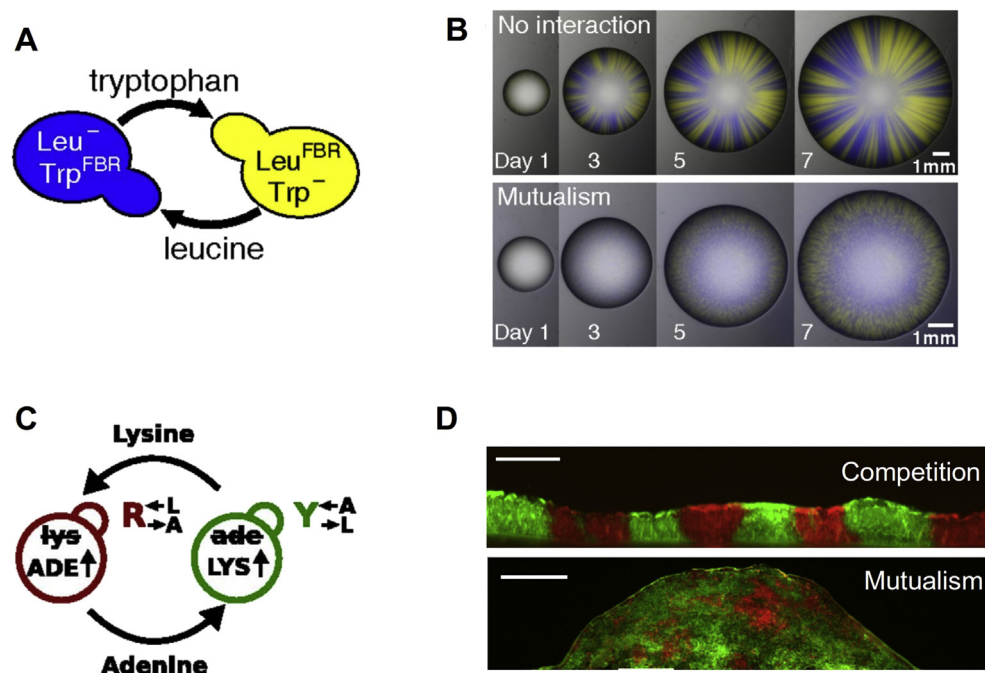
Since they involve an interdependency between populations, mutualisms are a stabilizing force that can prevent extinctions and promote community diversity [31]. This stabilizing effect is also predicted in spatially expanding populations: diversity is predicted to be lost from competing populations due to stochastic spatial segregation of the competing population that occurs at the expansion front, where the effective population size is small. Strong mutualisms are predicted to maintain diversity by preventing this segregation, since no single population cannot expand on its own [32]. This effect has recently been confirmed experimentally using two separate amino acid cross-feeding yeast systems [29,30] (Figure 3A and C). When amino acids were supplied externally, the mutualism was abolished, and the strains segregated during a spatial expansion (Figure 3B and D

top). In contrast, when no amino-acids were supplied, the strains established a mutualism, and remained intermixed while expanding (Figure 3B and D bottom).

Mutualistic interactions can lead to dynamics that are distinct from those of competing populations. As in the case of the Allee effect within populations, a minimal population size may be required to establishing a mutualism. This effect was demonstrated experimentally using a system composed of two strains of the bacteria *E. coli* which form a cross-protection mutualism, in which each strain degrades a different antibiotic, to which the other strain is susceptible [33]. This mutualism enables the strains to coexist in environments (i.e. antibiotic concentrations) in which neither strain can survive on its own. However, in a periodically changing environment, the relative fractions of the strains can display oscillations spanning over three orders of magnitude, which can lead to population collapse.

Mutualisms are hypothesized to arise naturally due to selective pressures for gene loss within a population [34], and in some cases can be beneficial to the entire community due to more efficient division-of-labor [35,36]. However, they can be exploited by cheaters from within one of the mutualistic populations, or by an external population, raising questions regarding their evolutionary stability. The evolutionary stability of

Figure 3



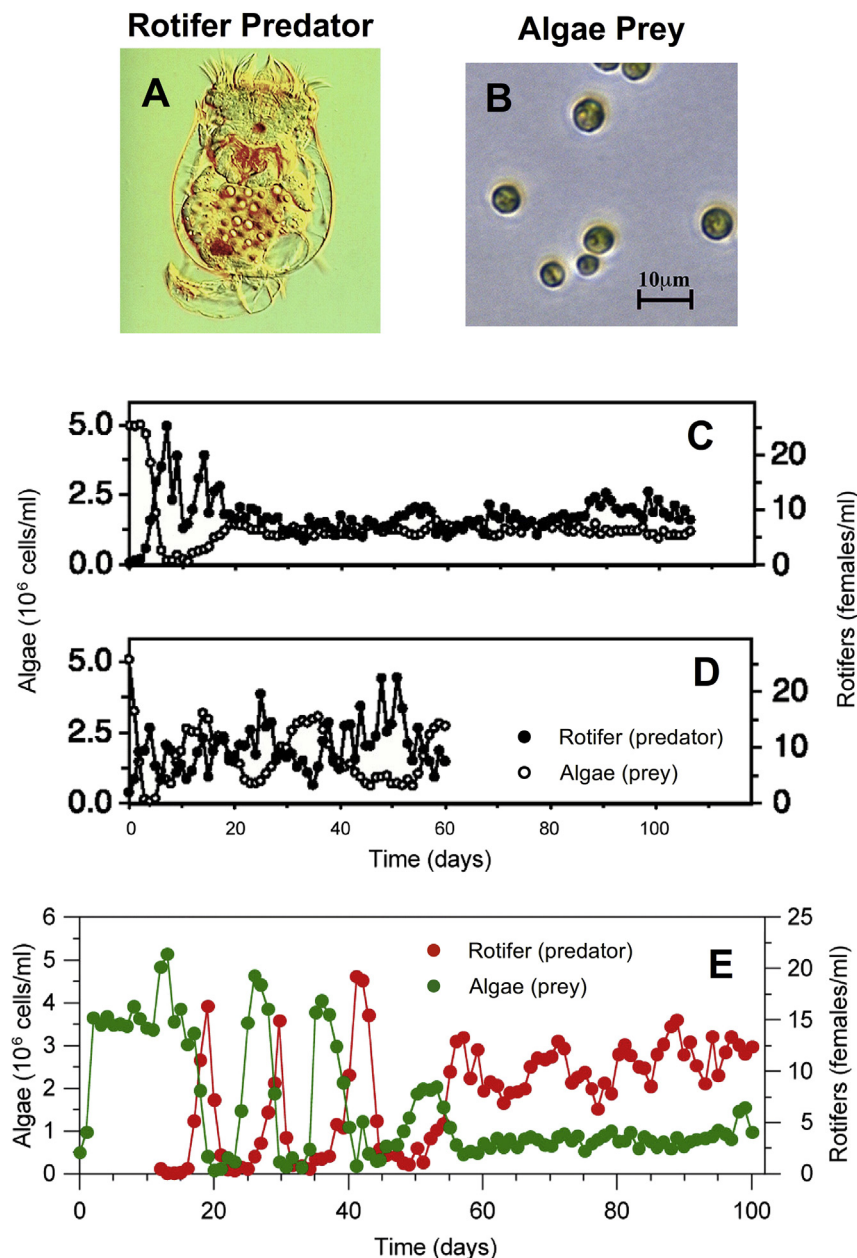
Mutualistic interactions prevent demixing during range expansions. (A) Schematic of the yeast amino-acid cross-feeding mutualism used in [30], where each yeast strain secretes an amino acid the other strain is not able to synthesize on its own. (B) Mutualistic partners remain mixed during a spatial expansion (bottom), whereas spatial segregation occurs when the mutualism is abolished by the addition of external amino-acids. (C–D) A similar result was observed in [29] using a similar yeast cross-feeding system. Panels A and B are adapted from [30], panels C and D are modified from [29].

synthetic cross-feeding mutualisms has recently been explored using the yeast mutualism between strains [37], and a novel system involving two distinct bacterial species [38]. In both systems, the mutualism could not persist in a well-mixed environment, and non-contributing phenotypes took over the population. The mutualism was stabilized in a spatially structured environment, where the cross-feeding strains were spatially segregated from non-producers.

Predators and parasites

Predators and parasites grow at the expense of their prey or host. Theory suggests that such interactions could either lead to oscillations or to stable population sizes. Using a microbial system composed of a rotifer predator (Figure 4A) grazing on a single-celled green algae (Figure 4B), Fussman et al. [39] experimentally demonstrated that both of these outcomes can indeed be observed in a single system by varying the

Figure 4



Oscillations in predator-prey systems can be modified and even obscured by prey evolution. A predator-prey system composed of a rotifer (A) preying on algae (B) displayed either stable (C) or oscillatory (D) dynamics at different experimental conditions. These oscillations differ from theoretical expectations since the two populations oscillated 180° out of phase, rather than the expected pattern of the prey oscillating 90° ahead of the predator. (E) Further experiments in this system demonstrated that rapid prey evolution can even lead to “cryptic” oscillations in which subpopulations of the prey oscillate, but the total prey population (green line) appears stable. In this experiment the transition to cryptic oscillations occurred after ~60 days. Panel A taken from Robinson R (2007). PLOS Biol, 5:e255. Panel B adapted from Chioccioli M, Hankamer B, Ross IL (2014). PLoS one, 9:e97269. Panels C and D adapted from [39], and panel E adapted from [41].

experimental conditions (Figure 4C and D). However, the observed oscillations had two features that were not consistent with classical predator-prey models: the oscillations were much slower than expected and the two populations oscillated 180° out of phase rather than the expected pattern of the prey oscillating 90° ahead of the predator. Further modeling predicted that diversity and internal dynamics within the prey population could account for both of these surprising features [40]: at low predator density the prey population is mostly composed of fast growing individuals, which are outcompeted by a more resistant subpopulation when predators abound. In an impressive interplay between theory and experiment, these authors later experimentally demonstrated that they could recover “classic” predator-prey oscillations by using isogenic prey populations [41,42]. Further experiments in this system demonstrated that rapid prey evolution can even lead to “cryptic” oscillations in which subpopulations of the prey oscillate, but the total population appears stable [41] (Figure 4E).

Similar dynamics can occur in host-parasite interactions, as such systems also consist of a combination of a negative and positive interaction. For example, bacteria and phage populations have also been shown to oscillate, yet in some cases there can again be cryptic oscillations in which oscillations of different host genotypes occur despite stable overall population sizes [41]. In addition, bacterial resistance and phage infectivity can evolve over time [43]. This coevolution can lead to expanding resistance and infectivity ranges (termed arms-race dynamics), or ones that shift over time to target or evade abundant types (termed fluctuating-selection dynamics). Recent experiments suggest that arms-race dynamics are favored in well-mixed conditions [44], but the general determinants and consequences of such coevolutionary dynamics are not yet well-understood.

Conclusions

In this manuscript, we have highlighted how a combination of theory and laboratory experiments can elucidate the ecological and evolutionary dynamics resulting from interactions within and between populations, and the parallels between these two processes. To date, much of the work has focused on basic interactions patterns involving a small number of populations. Future work will focus on elucidating the dynamics and patterns that arise due to more complex interactions in more diverse assemblages.

Interactions are often the net result of several distinct mechanistic processes that occur simultaneously. Since the balance between these processes typically depends on environmental conditions, a given ecological system can display qualitatively different behaviors in different environments. For example, cross-feeding yeast

populations secrete amino acids needed for the growth of their partner, while competing for additional resources. Changing the external supply of amino acids alters the balance of these opposing processes and leads to qualitative changes in the interaction from mutualistic, to parasitic, to competitive [30,45]. However, we are only beginning to investigate the effects of such mixed interactions in fluctuating or spatially structured environments, as well as their evolution.

We have mostly considered pairs of populations interacting in isolation, but natural communities are composed of a diverse set of interacting populations. The presence of additional populations can qualitatively alter the community dynamics. For example, competitive cycles (“Rock-Paper-Scissors” interactions) can lead to coexistence of all three populations [46,47]. Additional populations can modify the effective interactions between populations, for example by serving as sources or sinks for public goods, thus affecting the stability of cooperation and mutualisms [48]. Another common mechanism for interaction modification in microbes is degradation of secreted toxins [49]. While theory suggests that interaction modifications can have a significant impact on community structure [50], this has not yet been demonstrated experimentally.

The number of potential interactions grows combinatorially with the number of types in a community. Therefore, even characterizing interactions in diverse assemblages is a major challenge [51]. Being able to infer interactions directly from genomes could remove this hurdle, and further be used to identify ways to engineer desired interactions between existing populations. An emerging approach for achieving this goal is dynamic flux-balance analysis, which models individuals’ metabolic activities based on the repertoire of enzymes present in their genomes [52]. This approach was used to predict the structure of a community composed of three bacterial species, which interacted through secreted metabolites [53]. While it shows tremendous potential, the predictive power of this framework has not yet been systematically evaluated.

We are only beginning to understand the forces and processes that shape the assembly and function of diverse natural communities. While progress has been made by studying natural communities in situ, and simple populations in the lab, our ability to identify unifying principles and truly predictive models has been hindered by the lack of tractable model systems in which we can “turn experimental knobs”. Synthetic communities, composed of several interacting species may fill this gap [54]. Such systems offer a balance between the complexity of natural communities and the controllability needed to directly test theoretical ideas, and allow for the tight integration between theory and experiments central to the systems biology approach.

Acknowledgements

We would like to thank members of the Gore laboratory for critical discussions and comments on the manuscript. This work was supported by the DARPA BRICS program (Program Code: TRS-01 under Contract No. HR0011-15-C-0091), an NIH New Innovator Award (DP2 AG044279), an NSF CAREER Award (PHY-1055154), a Sloan Research Fellowship (BR2011-066), the Pew Scholars Program (2010-000224-007) and the Allen Investigator Program.

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