

Eco-evolutionary dynamics of complex social strategies in microbial communities

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Microbial communities abound with examples of complex social interactions that shape microbial ecosystems. One particularly striking example is microbial cooperation via the secretion of public goods. It has been suggested by theory, and recently demonstrated experimentally, that microbial population dynamics and the evolutionary dynamics of cooperative social genes take place with similar timescales, and are linked to each other via an eco-evolutionary feedback loop. We overview this recent evidence, and discuss the possibility that a third process may be also part of this loop: phenotypic dynamics. Complex social strategies may be implemented at the single-cell level by means of gene regulatory networks. Thus gene expression plasticity or stochastic gene expression, both of which may occur with a timescale of one to a few generations, can potentially lead to a three-way coupling between behavioral dynamics, population dynamics, and evolutionary dynamics

Introduction

Microbes are not only social organisms,¹ but they may also be strategic gamers. Many instances have been found in recent years of evolutionary games, situations where the fitness of a particular microbe depends on the complex interplay between its actions (its strategy) and those of the other microbes in the population. To name a few examples, the budding yeast *S. cerevisiae* plays a snowdrift game when collectively degrading complex extracellular sugars;²⁻⁵ *Pseudomonas fluorescens* play a stag-hunt, or coordination game when they form biofilms on the air-water interface;⁶ signaling games allow *Vibrio fischeri* to coordinate via low cost quorum sensing molecules before making energetically expensive investments, such as synthesizing bioluminescent proteins within jellyfish.⁷

Most research on microbial games has indeed focused on their evolutionary importance. However, it is becoming increasingly clear that these social interactions may also have important ecological consequences. Due to the rapid evolutionary

dynamics that are typical in microbes, and to the fact that the payoffs of the different strategies in a social game often depend on the size of the population,⁸⁻¹¹ the ecological and evolutionary dynamics may be strongly coupled via feedback loops. Therefore, the outcomes of the social games played by microbes may have ecological, as well as evolutionary consequences, and the two need to be studied together in a unified approach: that of eco-evolutionary dynamics.

A second important aspect of microbial social dynamics is the fact that microbes can implement complex social strategies. While they lack a central nervous system to help them make decisions, microbes have gene regulatory networks that allow them to adopt different phenotypic states in response to their environment and the actions of other microbes.^{3,12} This genetically coded ability to adopt different phenotypes in response to the actions taken by the other cells in the population, allows these relatively simple unicellular organisms to go beyond simple (i.e., always cooperate with others, always defect) evolutionary strategies. Interestingly the behavioral process of selection of a phenotype among the many alternatives allowed by the genotype, (a process that is often referred to as “cellular decision making”¹³), also occurs with timescales that are comparable to those of population and evolutionary dynamics; for instance, switching between alternative phenotypic states can occur with timescales in the order of one to a few generations.¹⁴ In consequence, there is the potential for microbial behavioral dynamics to interface with population and evolutionary dynamics,¹⁵ in a complex three-way feedback loop whose consequences are yet unknown.

The goal of this mini-review is to put the spotlight onto these two aspects of microbial sociobiology: first, we discuss recent findings on the interplay between ecology and evolution of social microbial traits. In the second part, we discuss how complex strategies may be implemented by gene regulatory networks, and hypothesize what their effect may be on the evolutionary dynamics of social behaviors in microbial communities, and how they may affect ecological interactions and rewire ecological networks in a short timescale.

Eco-Evolutionary Dynamics of Social Microbial Traits

Eco-evolutionary dynamics, the study of the coupling between population dynamics and evolutionary dynamics, has been discussed within the scientific community for many

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years,¹⁶ though it has been recently rediscovered in part due to the empirical evidence in support of rapid evolution in the wild.¹⁷⁻¹⁹ The core idea of eco-evolutionary dynamics is that when population dynamics and evolutionary dynamics occur on similar timescales, they may affect each other and be linked together by an eco-evolutionary feedback loop.

The significance of eco-evolutionary dynamics is most readily understood in terms of density-dependent selection, where changes in population density can lead to changes in fitness. Examples of positive effects of population density on fitness include the enhanced ability to mine the environment for nutrients, and improved defense against predators when microbes form tight groups such as flocs or biofilms.^{6,20,21} Examples of negative density-dependent fitness include the increased probability of pathogen transfer, or the enhanced competition for resources at high population densities. In some instances, fitness depends non-monotonically on density, reaching peaks at intermediate densities and displaying positive density dependence at low densities, but negative density dependence at large population densities.^{22,23} Given that the payoffs for the various strategies in social games often depend on the size of the interacting population eco-evolutionary feedbacks are expected theoretically in the context of ecological public goods games.⁸⁻¹¹

Experimentally, a few studies have confirmed some of the theoretical predictions and found evidence of eco-evolutionary interactions connected to social games.²³⁻²⁵ However, our understanding of the role that eco-evolutionary dynamics of social microbial traits may have on microbial ecology is still very limited. One of the best-characterized examples of social microbial games concerns *Saccharomyces cerevisiae*. These yeasts have a multigene family of SUC genes, which code for a periplasmic invertase enzyme that catalyzes the breakdown of sucrose into glucose and fructose. Once sucrose is hydrolyzed, fructose and glucose can then be imported and directly metabolized by the individual cells in the population. The SUC genes are highly polymorphic.^{2,26} In the context of microbial games, a specific variant of this gene, SUC2, is of particular interest due to its presence in the most common laboratory strains and its protected chromosomal location near the centromere. The expression of this gene represents a cooperative action in the social sense.² By producing and releasing invertase into the periplasmic space between the cell membrane and cell wall, the producer creates a supply of monosaccharides that is not only available to itself, but also to its neighbors. While the producer retains a small percentage (1%) of the all the glucose and fructose that it makes,³ the majority of the monosaccharides diffuse away and become a public good. This diffusion and accumulation of sugars in the environment has a significant impact on the growth rate of the population. At low population density (and thus low density of the enzyme invertase), the extracellular concentrations of glucose and fructose are low, and most of the glucose imported by the cells is derived from each cell's hydrolysis of sucrose. At high population density the population produces enough glucose to sustain rapid growth rates.^{3,22,23,27}

The transformation of the environment from sucrose dominated to a mainly glucose and fructose dominated environment

is achieved cooperatively by a population of invertase expressing cells. As it is often the case with cooperative behaviors, cooperators that break down sucrose can be exploited by non-cooperative "cheaters," or "free-loaders," which consume fructose and glucose but do not express invertase. In spite of the competition from cheaters, cooperators have a higher fitness than cheaters when the population density is low, and the medium consists mainly of non-hydrolyzed sucrose. Under these conditions, cooperators replicate faster than cheaters, thanks to the small fraction of glucose and fructose that they are able to capture after sucrose hydrolysis. This leads to the initial evolutionary advantage of cooperators when their density is low, which results in a slow but steady growth in numbers of cooperators in the population.²³ However, as the density of cooperators increases so does the public supply of glucose and fructose. Environments with high concentrations of glucose and fructose favor cheater phenotypes, which can grow rapidly on the glucose and fructose without having to pay the metabolic cost of producing invertase. This leads to an increase in cheaters at the expense of cooperators that eventually reduces the number of cooperators in the population; and with them the public goods (glucose and fructose) to the point where cheating is no longer favorable, and the eco-evolutionary feedback loop can begin again.²³ The consequences of this eco-evolutionary feedback extend beyond iterative dynamics. Under some conditions the equilibrium between cheaters and cooperators can be near the separatrix that divides the eco-evolutionary phase space between stable equilibria and population collapse,²³ making the whole population more prone to extinction in response to environmental perturbations (Fig. 1). It is worth noting here that the possibility that the evolution of cooperation may lead to population collapse has also been experimentally found as well in other single-species microbial ecosystems.^{24,28}

The observed eco-evolutionary trajectories behave just as expected by an ecological public goods game. This may perhaps be surprising, given that the biochemical details that describe the interaction between cooperators and cheaters in yeast, as well as the experimental design²³ (unlike in the model, yeast cells do not form local interaction groups and the system is well mixed) and the physical constraints in these experiments do not adjust to the assumptions by the model. This speaks highly of the ability of this model to capture the essential features of public goods interactions, which are characterized by an Allee-effect-like, non monotonic dependence of the fitness of cooperators on their density, and by a higher fitness of cooperators at low density and a higher fitness of the cheaters at high density.^{8,9} Notably, a simple ad hoc phenomenological model that just captured these two features was also able to reproduce the experimentally observed dynamics. However, the same features emerge naturally and without imposing any ad hoc assumptions from the ecological public goods game studied by Hauert and Doebeli.^{8,9}

In addition to affecting the resilience of a population, evolution of cooperation in sucrose breakdown may affect other ecological parameters. In a recent study, MacLean and Gudelj²⁷ found that the evolutionary competition between cooperators

and cheaters had important effects on another ecological parameter: ecosystem productivity (in this case, measured as an increase in total biomass). When considered as a single population, mixed cultures of cheaters and cooperators growing in plates were found to lead to larger net populations than would be achieved by pure cooperators.⁴ A similar, though in this case transient effect was also observed in well-mixed populations.²³ In equilibrium, this second study found that both mixed and pure cooperator cultures had very similar population sizes, with the slight advantage being for the pure cooperator populations.

The sucrose system has also been used to investigate the interplay between the evolution of cooperation and ecological interactions between different species. In another experiment that explores the effect of ecology on the evolution of cooperation, Celiker and Gore investigated a two-species ecosystem of *S. cerevisiae* and *E. coli* growing together in sucrose. The authors found that the presence of the bacteria limit the density of yeast.²⁹ This ecological effect leads to lower densities of yeast, thus promoting the evolutionary success of cooperation.

Complex Social Strategies in Microbial Populations

In the previous section, we discuss the competition between “cooperator” strains that produce a public good, and “free loader” strains that take advantage of it without contributing to its production. However, the picture is more nuanced than this, and microbial social strategies can be more complex than simply “always defect” or “always cooperate.” In spite of their relatively simple nature, even unicellular microbes are able to make sophisticated behavioral decisions and implement complex social strategies, with the aid of gene regulatory networks. These complex strategies are characterized by phenotypic plasticity¹⁵: the social behavior or phenotype adopted by a microbe depends on the behaviors of the other microbes in the population. In some instances, the social strategies adopted by a microbe may be characterized by a continuum of expression levels of the cooperative genes as a function of the actions of other cells in the population. In other instances, microbes may choose between a set of alternative phenotypes (which can vary in the degree of cooperation), stabilized by (genetic) positive and negative feedback loops. Here we present some examples that have been recently discussed in the literature and which we believe are particularly promising in order to help us understand the evolutionary dynamics of social microbial behavior.

The first example concerns ferric uptake in *P. aeruginosa*. In a set of recent studies, Kümmerli et al.¹² have demonstrated that extracellular iron scavenging proteins are released in greater or smaller levels depending on the amount of iron in the local environment. This finding indicates that cooperative release of iron scavenging proteins is not unconditional, but depends on the environment; an environment that is in turn transformed by the collective actions of all of the cells in the population. Phenotypic plasticity also allows microbes to tune their level of investment in a public good in response to the presence or absence of other species in the population and the phenotypes adopted by those other species. For instance, *P. aeruginosa*

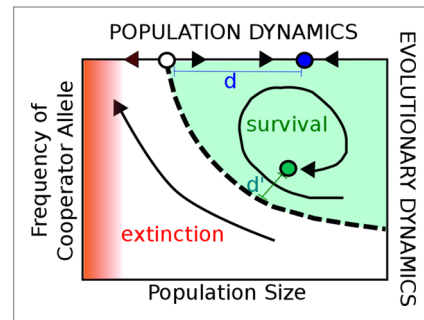


Figure 1. Eco-evolutionary phase diagram of a cooperative-cheater evolutionary interaction. We depict a schematic of the eco-evolutionary dynamics phase portrait for an ecological public goods game. The plot is based on the experimental findings of Sanchez and Gore^{23,52} and it is consistent with theoretical predictions by Hauert and coworkers.^{8,9} Note that while the yeast evolutionary dynamics at constant population size are consistent with a snowdrift game, the dependence of the payoffs on population density adjusts to the expectations from the ecological public goods game described in.^{8,9} The phase diagram contains two regions: one where trajectories lead to stable coexistence between cooperators and cheaters (green zone above the separatrix), and a second region where trajectories lead to population collapse (represented here by the shaded red region). This portrait reveals that, whereas evolutionary coexistence between cheaters and cooperators is possible, the resulting ecosystem is closer to the separatrix (characterized by the distance d') than a population of pure cooperators (blue dot) is to the unstable fixed point (white dot). The reader is referred to references^{23,53} for further details about the construction of this phase diagram.

has been found to upregulate the secretion of iron scavenging molecules when in presence of *S. aerus*, which acts as an interspecific cheater.^{30,31} Finally, the ability to switch phenotypes between the expression of two alternative iron scavenging molecules³² has also been reported to be superior evolutionarily to conditionally expressing each phenotype in fluctuating environments. Thus, phenotypic plasticity allows *P. aeruginosa* to maximize its fitness by allowing it to differentially adopt a different social strategy depending on the environmental conditions, which in turn may be affected by the combined actions of all cells, leading to the potential for feedback between behavior and ecology.

A second example of complex social strategizing takes us back to the sucrose degradation by *S. cerevisiae*. While the models used to understand cooperation in this system assume cooperation to be constitutive for the sake of simplicity (also note that within the experimental constraints imposed by previous researchers, expression of invertase is approximately constant), it is known that the expression of invertase (and thus the degree of cooperation) can be modulated by the amount of glucose in the environment: the higher the glucose concentration is, the lower the expression of *SUC2*.³ This represents a particularly appealing example of a complex social strategy implemented by gene regulatory circuits: As the cells transform their environment by increasing the extracellular concentrations of sucrose and fructose, they can also modify their behavior by reducing the expression levels (and the cost associated to it) of the enzyme invertase. This regulation mimics the winning strategy in a snowdrift game: cooperate when the majority of cells in

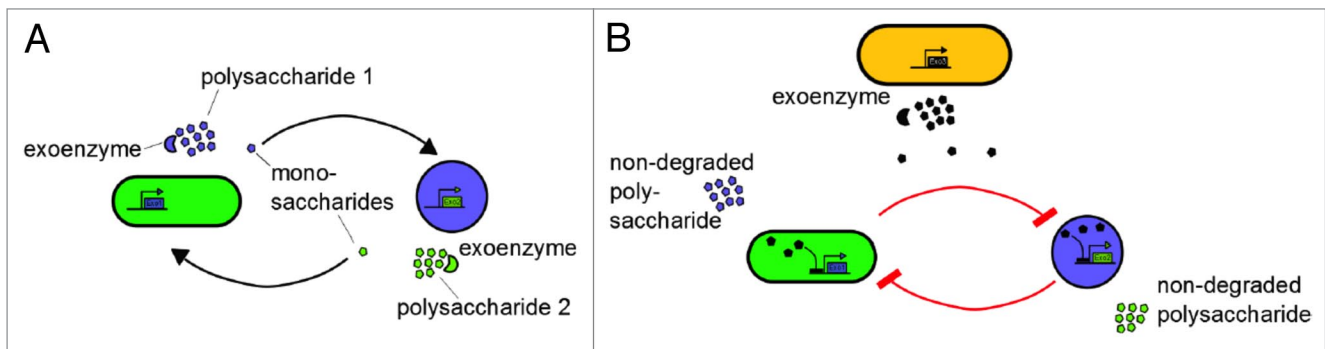


Figure 2. Phenotypic plasticity can rapidly rewire microbial ecological networks (A) A possible mechanism of mutualism between two microbial species. Each secretes an extracellular enzyme that breaks down a different polysaccharide. The released products can be utilized by both species, leading to cross-feeding and a synergistic mutualism between them. (B) A third species (orange) secretes another exoenzyme that frees a higher quality carbon source. This leads to catabolite repression and thus eliminates the synergism, leading instead to competitive growth on the new carbon source.

the population are defecting, and defect when they are cooperating.³ It is possible that this complex strategy (as opposed to a “simple” strategy consisting on unconditional cooperation) may help the cooperators to fare better when competing against the cheaters. Whether or not this is the case, and what the “optimal” gene regulatory function would be in the presence of cheaters, remains to be investigated and represents a promising area of future research.

Although most studies of sucrose breakdown cooperation in *S. cerevisiae* focus on the invertase gene *SUC2*, other members of the *SUC* family provide similar functionality and may present a unique opportunity for evolutionary studies.² With the exception of *SUC2*, members of the *SUC* family are located in the sub-telomeric region.³³ It has been found that *SUC* genes in these subtelomeric regions can be epigenetically silenced.³⁴ This epigenetic silencing represents an important form of phenotypic plasticity from the perspective of evolutionary theory: it allows lineages to temporarily deviate from their genetically-encoded cooperative strategy. In terms of the *SUC* gene family, *S. cerevisiae* might be capable of adopting a “cheater” strategy by both epigenetic and genetic means. This possibility remains to be investigated, but evidence that stochastic phenotype switching is possible in another cooperative, sub-telomeric gene in yeast (i.e., *FLO11*) has been recently presented,³⁵ which suggests the possibility that this might also be the case in subtelomeric *SUC* genes. Even in the unimodally expressed *SUC2*,³ the degree of cell-to-cell variability and of stochastic fluctuations in invertase expression could be quite large, on the basis of the presence of a TATA box and several transcription factor binding sites in its regulatory sequence.³⁶ It has been recently found that both of these promoter architectural motifs may lead to elevated noise in gene expression in yeast.^{37–39}

A third example of complex social strategizing is quorum sensing. Quorum sensing is a fairly pervasive mechanism in microbial communities for coordinating population-level behaviors.⁴⁰ This signaling mechanism allows populations to cheaply coordinate cooperative behaviors by producing signaling molecules with low metabolic cost as opposed to a higher-cost quorum-induced behavior (such as production of

bioluminescent proteins).⁴¹ Individual cells produce and secrete signaling molecules (i.e., autoinducers), which they also sense. Variations in population density correlate with variations in concentration of signaling molecules. This allows individuals to trigger changes in gene expression as a function of quorum density, where such changes can be coordinated over all members of a quorum. One of the most commonly cited examples of coordinated microbial behavior guided by quorum sensing is *Vibrio fischeri*, which bioluminesces upon reaching a sufficiently sized quorum. Quorum sensing systems are also vulnerable to cheaters. The production and secretion of signaling molecules is costly, and introduces a growth penalty on cooperators. In a game theoretic model, Brown and Johnstone demonstrate the impact of population size and intracolony relatedness on cooperativity.⁴² Relatedness is found to be a significant factor in determining signaling strength and cooperativity. The emergence of signaling systems is another challenging area of research, where theoretical models suggest that the ability to transition from non-communicative to communicative populations is significantly less likely than the ability to maintain signaling in an already communicative population.⁴³ However, care must be taken when describing molecular interactions between microbes as signaling, where nuances discriminate between molecular cues, signals, and coersions.⁴⁴

Discussion: Ecological Implications of Cellular-Decision Making in Social Behaviors

Gene regulatory networks allow microbes to implement complex social strategies; these include both continuous tuning of the investment in a public good by the regulation of cooperative genes,⁴⁵ as well as the choosing among alternative, discrete phenotypes driven by stochastic switching.^{46,47} In both of these instances, the dynamics of phenotype switching can occur within a timescale of one to a few microbial generations, which is comparable to the timescale of evolutionary and population dynamics. Therefore, it is conceivable that phenotypic dynamics (changes in the adopted phenotype at the level of a single cell) may also be coupled with ecological and evolutionary dynamics

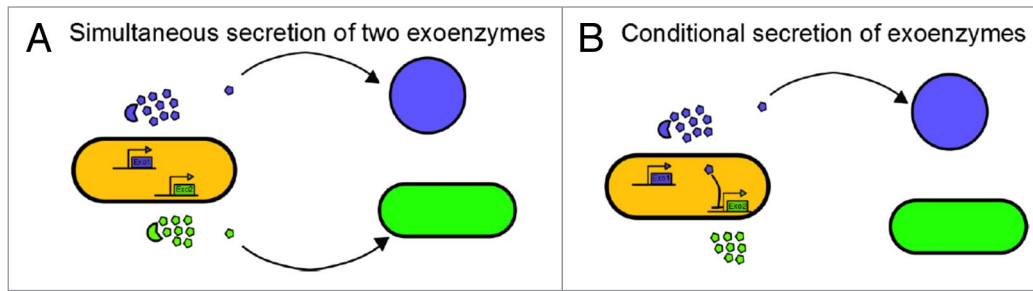


Figure 3. The patterns of exoenzyme secretion may affect the kinds of ecological interactions between species. (A) A “producer” microbe secretes two exoenzyme species simultaneously. The metabolites freed up by each enzyme preferentially feed a different commensal species, allowing for their coexistence. (B) An evolutionary change in the promoter region leads to the repression of one of the enzymes by the products of the other. This leads to a sequential release (rather than simultaneous) and eliminates one of the two interactions and the possibility for coexistence between the two commensal bacteria.

in a three-way feedback loop. Furthermore, we believe that phenotypic dynamics of social traits may have profound ecological implications, allowing for rapid re-wiring of microbial ecological networks over a timescale of just one or a few generations.

Two possible scenarios where phenotypic dynamics may affect eco-evolutionary dynamics are illustrated in **Figures 2 and 3**. In the first such scenario we consider a synergistic “public goods” interaction between two bacteria, which cross feed each other via the secretion of extracellular glycosidases that break down two different polysaccharides (**Fig. 2**). The sudden arrival of a better carbon source (perhaps secreted by a third species) may make it unnecessary to pay the cost of secreting the enzymes. Instead of cooperating, the two species would now compete for the higher quality sugar. This hypothetical situation is quite plausible; for instance, catabolite repression is a widespread regulatory process by which bacteria shut down operons responsible for metabolizing lower-quality sugars when a better quality sugar is available. It is thus likely that synergistic interactions can be suddenly transformed into competitive interactions by the repression of single operons on the mutualistic species. A second attractive possibility is suggested by recent experiments that indicate that very simple mutational processes can transform a transcriptional activator into a transcriptional repressor, or turn a constitutive gene into a regulated one.⁴⁵ As before, it is plausible that evolutionary changes in cellular decision making circuitry could rapidly re-wire ecological networks within a very short time. For instance, consider the case of a bacterium that contains more than one “public good” gene; to keep with the previous example, consider these code the expression of two different exoenzymes that break down two different polysaccharides releasing nutrients to the environment. Rather than secreting the two exoenzymes constitutively at the same time, a bacterium can “learn” to secrete them sequentially, thanks to mutations that allow the cells to downregulate the expression of one of the exoenzymes when the other exoenzyme is being expressed (See **Figure 3**). This would in turn affect any commensal bacteria that depend on the monosaccharides released by the producer strain. Thus, without the need to lose a social gene, and just by acquiring the ability to regulate its expression, a bacterium can change its ecological interactions with the various partners with which it coexists.

These two examples are just illustrations of what the consequences of coupling between population, evolutionary, and phenotypic dynamics may be in microbial communities. While we have no direct evidence of this three-way feedback yet, many results, particularly those reviewed above concerning plasticity in the expression of iron scavenging proteins, suggest that phenotypic dynamics occurring over a one to a few generations timescale may be a major force in determining social interactions between microbes.

The specific examples of complex social interactions that we have discussed above come mainly from laboratory experiments with exceedingly simple, single-species ecosystems. The advantage of these reductionist experiments is that they allow us to put theoretical predictions to the test, and thus allow us to advance in firmer ground by benchmarking our theoretical understanding of eco-evolutionary dynamics in social microbial communities. There is every reason to believe that these interactions are very important in natural communities as well. Processes such as the decomposition of complex organic matter involve the secretion of extracellular enzymes that break down this complex matter and release smaller nutrients, which become public goods. For instance, bacteria such as *Akkermansia muciniphila* (an important commensal of the human gut and a biomarker for a healthy intestinal track) grow in the human colon by breaking down the complex human glycoproteins that form the matrix of the intestinal mucosa.⁴⁸ Since the small sugars released by the action of these enzymes may benefit other species (as well as potentially “cheater” *A. muciniphila* mutants),⁴⁹ public goods interactions similar in nature to those in the sucrose system in yeast may likely ensue. Similar public goods mediated ecological interactions also take place in oral cavity: several *Streptococcus* species secrete extracellular glycosidases that break down salivary mucin glycans and allow the oral microbiome to survive even periods of prolonged starvation.⁵⁰ The fact that bacteria may adopt complex (in this case probabilistic) social strategies in the wild is supported by the observation of stochastic expression of a lethal strategy (a fraction of cells commit suicide to allow other members of a clonal population of *Salmonella typhimurium* to infect the host).⁵¹ In this case, stochastic phenotypic switching is critical for the “self-destruction cooperation” strategy to be successful.

Microbes represent the majority of biomass on Earth, and they are most commonly found forming complex communities consisting of many different species interacting with each other. A small number of microbial ecologies have been discussed in this review, exemplifying the complex strategies often followed by seemingly simple unicellular organisms, and the eco-evolutionary dynamics resulting from these social interactions. While the game dynamics of some of these systems have been confirmed, most still require quantitative evidence of game dynamics. By understanding microbial games quantitatively, not only will we further understand the role of microbes within us from

teeth to gut, but our own role in interacting with these strategic organisms. After all, pound-for-pound microbes occupy more of this planet than humans.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

- West S, Diggle S. The social lives of microbes. *Annu Rev Ecol Syst* 2007; 38:53–77; <http://dx.doi.org/10.1146/annurev.ecolsys.38.091206.095740>
- Greig D, Travisano M. The Prisoner's Dilemma and polymorphism in yeast SUC genes. *Proc. R. Soc. B Biol. Sci.* 271, S25–26 (2004).
- Gore J, Youk H, van Oudenaarden A. Snowdrift game dynamics and facultative cheating in yeast. *Nature* 2009; 459:253–6; PMID:19349960; <http://dx.doi.org/10.1038/nature07921>
- MacLean RC, Fuentes-Hernandez A, Greig D, Hurst LD, Gudelj I. A mixture of “cheats” and “co-operators” can enable maximal group benefit. *PLoS Biol* 2010; 8:e1000486; PMID:20856906; <http://dx.doi.org/10.1371/journal.pbio.1000486>
- Koschwanez JH, Foster KR, Murray AW. Sucrose utilization in budding yeast as a model for the origin of undifferentiated multicellularity. *PLoS Biol* 2011; 9:e1001122; PMID:21857801; <http://dx.doi.org/10.1371/journal.pbio.1001122>
- Rainey PB, Rainey K. Evolution of cooperation and conflict in experimental bacterial populations. *Nature* 2003; 425:72–4; PMID:12955142; <http://dx.doi.org/10.1038/nature01906>
- Parsek MR, Greenberg EP. Sociomicrobiology: the connections between quorum sensing and biofilms. *Trends Microbiol* 2005; 13:27–33; PMID:15639629; <http://dx.doi.org/10.1016/j.tim.2004.11.007>
- Hauert C, Holmes M, Doebeli M. Evolutionary games and population dynamics: maintenance of cooperation in public goods games. *Proc. R. Soc. B Biol. Sci.* 273, 2565–2571 (2006).
- Hauert C, Wakano JY, Doebeli M. Ecological public goods games: cooperation and bifurcation. *Theor Popul Biol* 2008; 73:257–63; PMID:18221761; <http://dx.doi.org/10.1016/j.tpb.2007.11.007>
- Wakano JY, Nowak MA, Hauert C. Spatial dynamics of ecological public goods. *Proc Natl Acad Sci U S A* 2009; 106:7910–4; PMID:19416839; <http://dx.doi.org/10.1073/pnas.0812644106>
- Zhang F, Hui C. Eco-evolutionary feedback and the invasion of cooperation in prisoner's dilemma games. *PLoS One* 2011; 6:e27523; PMID:22125615; <http://dx.doi.org/10.1371/journal.pone.0027523>
- Kümmerli R, Jiricny N, Clarke LS, West SA, Griffin AS. Phenotypic plasticity of a cooperative behaviour in bacteria. *J Evol Biol* 2009; 22:589–98; PMID:19170825; <http://dx.doi.org/10.1111/j.1420-9101.2008.01666.x>
- Perkins TJ, Swain PS. Strategies for cellular decision-making. *Mol Syst Biol* 2009; 5:326; PMID:19920811; <http://dx.doi.org/10.1038/msb.2009.83>
- Vardi N, Levy S, Assaf M, Carmi M, Barkai N. Budding yeast escape commitment to the phosphate starvation program using gene expression noise. *Curr Biol* 2013; 23:2051–7; PMID:24094854; <http://dx.doi.org/10.1016/j.cub.2013.08.043>
- Cavaliere M, Poyatos JF. Plasticity facilitates sustainable growth in the commons. *J R Soc Interface* 2013; 10:20121006; PMID:23365195; <http://dx.doi.org/10.1098/rsif.2012.1006>
- Haldane JB. The relation between density regulation and natural selection. *Proc R Soc Lond B Biol Sci* 1956; 145:306–8; PMID:13359386; <http://dx.doi.org/10.1098/rspb.1956.0039>
- Grant P, Grant B. Evolution of character displacement in Darwin's finches. *Science (80-)*. 313, 224–226 (2006).
- Reznick DN, Ghalambor CK, Crooks K. Experimental studies of evolution in guppies: a model for understanding the evolutionary consequences of predator removal in natural communities. *Mol Ecol* 2008; 17:97–107; PMID:17725576; <http://dx.doi.org/10.1111/j.1365-294X.2007.03474.x>
- Schoener T. The newest synthesis: understanding the interplay of evolutionary and ecological dynamics. *Science (80-)*. 331, 426–429 (2011).
- Smukalla S, Caldara M, Pochet N, Beauvais A, Guadagnini S, Yan C, Vincens MD, Jansen A, Prevost MC, Largé JP, et al. FLO1 is a variable green beard gene that drives biofilm-like cooperation in budding yeast. *Cell* 2008; 135:726–37; PMID:19013280; <http://dx.doi.org/10.1016/j.cell.2008.09.037>
- Becks L, Ellner SP, Jones LE, Hairston NG Jr. The functional genomics of an eco-evolutionary feedback loop: linking gene expression, trait evolution, and community dynamics. *Ecol Lett* 2012; 15:492–501; PMID:22417636; <http://dx.doi.org/10.1111/j.1461-0248.2012.01763.x>
- Dai L, Vorselen D, Korolev K, & Gore J. Generic indicators for loss of resilience before a tipping point leading to population collapse. *Science (80-)*. 336, 1175–1177 (2012).23. Sanchez A, Gore J. feedback between population and evolutionary dynamics determines the fate of social microbial populations. *PLoS Biol* 2013; 11:e1001547; PMID:23637571; <http://dx.doi.org/10.1371/journal.pbio.1001547>
- Fiegna F, Velicer G. Competitive fates of bacterial social parasites: persistence and self-induced extinction of *Myxococcus xanthus* cheaters. *Proc. R. Soc. B Biol. Sci.* 270, 1527–1534 (2003).
- Ross-Gillespie A, Gardner A, Buckling A, West SA, Griffin AS. Density dependence and cooperation: theory and a test with bacteria. *Evolution* 2009; 63:2315–25; PMID:19453724; <http://dx.doi.org/10.1111/j.1558-5646.2009.00723.x>
- Carlson M, Botstein D. Organization of the SUC gene family in *Saccharomyces*. *Mol Cell Biol* 1983; 3:351–9; PMID:6843548
- MacLean RC, Gudelj I. Resource competition and social conflict in experimental populations of yeast. *Nature* 2006; 441:498–501; PMID:16724064; <http://dx.doi.org/10.1038/nature04624>
- Waite AJ, Shou W. Adaptation to a new environment allows cooperators to purge cheaters stochastically. *Proc Natl Acad Sci U S A* 2012; 109:19079–86; PMID:23091010; <http://dx.doi.org/10.1073/pnas.1210190109>
- Celiker H, Gore J. Competition between species can stabilize public-goods cooperation within a species. *Mol Syst Biol* 2012; 8:621; PMID:23149686; <http://dx.doi.org/10.1038/msb.2012.54>
- Harrison F, Paul J, Massey RC, Buckling A. Interspecific competition and siderophore-mediated cooperation in *Pseudomonas aeruginosa*. *ISME J* 2008; 2:49–55; PMID:18180746; <http://dx.doi.org/10.1038/ismej.2007.96>
- Mashburn LM, Jett AM, Akins DR, Whiteley M. *Staphylococcus aureus* serves as an iron source for *Pseudomonas aeruginosa* during in vivo coculture. *J Bacteriol* 2005; 187:554–66; PMID:15629927; <http://dx.doi.org/10.1128/JB.187.2.554-566.2005>
- Dumas Z, Ross-Gillespie A, Kümmerli R. Switching between apparently redundant iron-uptake mechanisms benefits bacteria in changeable environments. *Proc. R. Soc. B Biol. Sci.* 280, 1055 (2013).
- Carlson M, Celenza JL, Eng FJ. Evolution of the dispersed SUC gene family of *Saccharomyces* by rearrangements of chromosome telomeres. *Mol Cell Biol* 1985; 5:2894–902; PMID:3018485
- Louis EJ. The chromosome ends of *Saccharomyces cerevisiae*. *Yeast* 1995; 11:1553–73; PMID:8720065; <http://dx.doi.org/10.1002/yea.320111604>
- Octavio LM, Gedeon K, Maheshri N. Epigenetic and conventional regulation is distributed among activators of FLO11 allowing tuning of population-level heterogeneity in its expression. *PLoS Genet* 2009; 5:e1000673; PMID:19798446; <http://dx.doi.org/10.1371/journal.pgen.1000673>
- Bu Y, Schmidt MC. Identification of cis-acting elements in the SUC2 promoter of *Saccharomyces cerevisiae* required for activation of transcription. *Nucleic Acids Res* 1998; 26:1002–9; PMID:9461460; <http://dx.doi.org/10.1093/nar/26.4.1002>
- Sanchez A, Garcia HG, Jones D, Phillips R, Kondev J. Effect of promoter architecture on the cell-to-cell variability in gene expression. *PLoS Comput Biol* 2011; 7:e1001100; PMID:21390269; <http://dx.doi.org/10.1371/journal.pcbi.1001100>
- Sanchez A, Choubey S, Kondev J. Regulation of noise in gene expression. *Annu Rev Biophys* 2013; 42:469–91; PMID:23527780; <http://dx.doi.org/10.1146/annurev-biophys-083012-130401>
- Sanchez A, & Golding I. Genetic Determinants and Cellular Constraints in Noisy Gene Expression. *Science (80-)*. 342, 1188–1193 (2013).
- Waters CM, Bassler BL. Quorum sensing: cell-to-cell communication in bacteria. *Annu Rev Cell Dev Biol* 2005; 21:319–46; PMID:16212498; <http://dx.doi.org/10.1146/annurev.cellbio.21.012704.131001>
- Diggle SP, Griffin AS, Campbell GS, West SA. Cooperation and conflict in quorum-sensing bacterial populations. *Nature* 2007; 450:411–4; PMID:18004383; <http://dx.doi.org/10.1038/nature06279>

42. Brown S, Johnstone R. Cooperation in the dark: signalling and collective action in quorum-sensing bacteria. *Proc. R. Soc. B Biol. Sci.* 268, 961–965 (2001).
43. Harrington KI, Ozisik AP, Pollack J. The Effects of Finite Populations and Selection on the Emergence of Signaling. in *Proc. Artif Life* 2012; XIII:194–201
44. Diggle S, Gardner A, West S, Griffin A. Evolutionary theory of bacterial quorum sensing: when is a signal not a signal? *Proc. R. Soc. B Biol. Sci.* 362, 1241–1249 (2007).
45. Garcia HG, Sanchez A, Boedicker JQ, Osborne M, Gelles J, Kondev J, Phillips R. Operator sequence alters gene expression independently of transcription factor occupancy in bacteria. *Cell Rep* 2012; 2:150–61; PMID:22840405; <http://dx.doi.org/10.1016/j.celrep.2012.06.004>
46. Ozbudak EM, Thattai M, Lim HN, Shraiman BI, Van Oudenaarden A. Multistability in the lactose utilization network of *Escherichia coli*. *Nature* 2004; 427:737–40; PMID:14973486; <http://dx.doi.org/10.1038/nature02298>
47. Acar M, Becskei A, van Oudenaarden A. Enhancement of cellular memory by reducing stochastic transitions. *Nature* 2005; 435:228–32; PMID:15889097; <http://dx.doi.org/10.1038/nature03524>
48. Derrien M, Collado MC, Ben-Amor K, Salminen S, de Vos WM. The Mucin degrader *Akkermansia muciniphila* is an abundant resident of the human intestinal tract. *Appl Environ Microbiol* 2008; 74:1646–8; PMID:18083887; <http://dx.doi.org/10.1128/AEM.01226-07>
49. Png CW, Lindén SK, Gilshenan KS, Zoetendal EG, McSweeney CS, Sly LI, McGuckin MA, Florin TH. Mucolytic bacteria with increased prevalence in IBD mucosa augment in vitro utilization of mucin by other bacteria. *Am J Gastroenterol* 2010; 105:2420–8; PMID:20648002; <http://dx.doi.org/10.1038/ajg.2010.281>
50. Bradshaw DJ, Homer KA, Marsh PD, Beighton D. Metabolic cooperation in oral microbial communities during growth on mucin. *Microbiology* 1994; 140:3407–12; PMID:7881558; <http://dx.doi.org/10.1099/13500872-140-12-3407>
51. Diard M, Garcia V, Maier L, Remus-Emsermann MN, Regoes RR, Ackermann M, Hardt WD. Stabilization of cooperative virulence by the expression of an avirulent phenotype. *Nature* 2013; 494:353–6; PMID:23426324; <http://dx.doi.org/10.1038/nature11913>
52. Chen A, Sanchez A, Dai L, Gore J. Dynamics of a producer-parasite ecosystem on the brink of collapse. *arXiv Prepr. arXiv1306.3465* (2013). at <<http://arxiv.org/abs/1306.3465>>
53. Allen B, Nowak MA. Cooperation and the fate of microbial societies. *PLoS Biol* 2013; 11:e1001549; PMID:23637573; <http://dx.doi.org/10.1371/journal.pbio.1001549>