Theory of cooperation in a micro-organismal snow-drift game

Zhenyu Wang and Nigel Goldenfeld
Department of Physics, Center for the Physics of Living Cells and Institute for Genomic Biology, University of Illinois at Urbana-Champaign, Loomis Laboratory of Physics, 1110 West Green Street, Urbana, Illinois, 61801

We present a mean field model for the phase diagram of a community of micro-organisms, interacting through their metabolism so that they are, in effect, engaging in a cooperative social game. We show that as a function of the concentration of the nutrients glucose and histidine, the community undergoes a phase transition separating a state in which one strain is dominant to a state which is characterized by coexisting populations. Our results are in good agreement with recent experimental results, correctly predicting quantitative trends and the phase diagram.

PACS numbers: 87.23.Cc, 87.18.Gh

Cooperative phenomena in biology are difficult to treat because of the complexity and heterogeneity of the interactions, but a qualitatively successful approach is cooperative game theory—the effort to encapsulate the complex interactions into parameters describing the binary outcome of pairwise interactions between individuals[1–7]. The central element in game theory is the payoff matrix, which describes the score accruing to each member of an interacting pair depending upon their action in the game. For example, in the Prisoner's Dilemma, the two players can either "cooperate" or "defect". Cooperation yields a reward R, whilst if both defect, they receive a punishment P. If one defects and the other cooperates, the defector receives a temptation T while the cooperator receives the sucker's payoff S. If $T > R > P > S$, then there is a dilemma: a rational player would defect to receive the highest payoff independent of the state of the other player, so that if both parties play rationally, each will end up with the punishment P. However, if they had both cooperated, they would have received the reward R. Two-body interactions are paradoxical in cooperative games, a forceful indicator of how collective effects can override selfish one-body behavior.

Such seemingly abstract games have biological realizations in the dynamics of microbes and viruses. In a pioneering study, Turner and Chao[8, 9] demonstrated that an RNA virus ϕ6 is engaging in the Prisoner's Dilemma by measuring the payoff matrix. In their experiment, ϕ6 is a wild-type complete strain, capable of producing all the necessary intracellular products for infection, and acts as a cooperator. ϕH2 is a mutant strain, which evolves a defective strategy when cultured at high miltiplicities-of-infection. During the co-infection of a microbial host by these two strains, the fitness of the whole community increased initially, but dropped eventually. The final drop was unexpected because in evolution fitness usually increases. The dilemma was explained using game theory. By constructing the payoff matrix according to the measured mean fitness at different initial ratios of the two strains, the authors showed that the virus was effectively trapped in the Prisoner's Dilemma, which caused the final drop. To escape the dilemma, several years later, the same authors[10] cultured another strain ϕL1 to compete with ϕH2. This time the payoff matrix obeyed the inequalities $T > R > S > P$ and so conformed to the condition for the so-called Snowdrift Game, in which coexistence of the two strains were observed.

In these two experiments, the payoff matrices are measured, but not manipulated. However, in a recent experiment, the payoff matrix was actually manipulated by genetically engineering *Saccharomyces cerevisiae* (budding yeast)[11]. Budding yeast's primary carbon intake is a monosaccharide, such as glucose and fructose. In a monosaccharide-absent environment, dormant genes are derepressed, enabling the digestion of alternative nutrients, such as disaccharide lactose and sucrose[12]. In the experiment, wild-type cooperative strains have an intact *SUC2* gene, which codes for the enzyme invertase to hydrolyze sucrose into glucose and fructose. However, 99% of the product from sucrose hydrolysis is released back into the media, giving rise to the possibility that mutant defectors with the *SUC2* gene knocked out could make use of the metabolite without having to pay the price of manufacturing glucose. In order to tune the cost of cooperation and hence the payoff matrix, the authors engineered cooperators to be a histidine auxotroph, which relies on histidine importation from the media. Having an intact histidine gene, defectors are not affected. Thus limitation of histidine concentration in the media coerces the metabolism of cooperators, increases the cost of cooperation, and thus affects the payoff matrix. By changing the glucose and histidine concentration provided with a fixed portion of sucrose, the authors empirically obtained a transition from the dominance of defectors, which corresponds to the Prisoner's Dilemma, to the coexistence of both strains, which is a Snowdrift Game. The ability to manipulate collective properties of the microbial world by genetic engineering is impressive, but what is lacking is a predictive understanding of the direct dependence of cooperator fraction on nutrition concentrations.

The purpose of this paper is to build up a phenomeno-

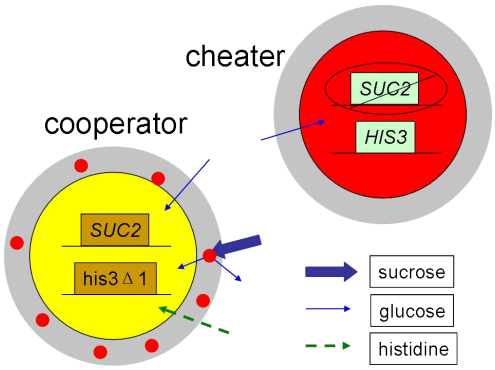

FIG. 1: (Color online) Experimental design of the two strains and sucrose metabolism[11].

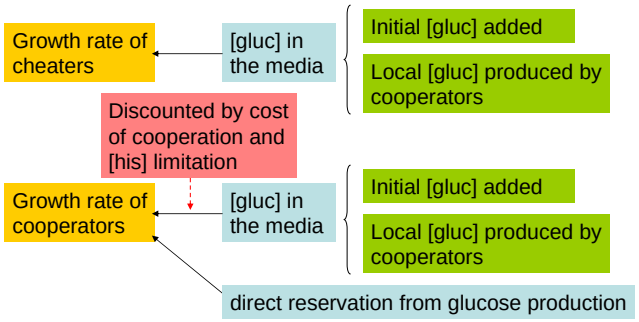

FIG. 2: (Color online) Flow chart for the construction of growth rates for defectors and cooperators, respectively.

logical model linking game theory and experimental measurable quantities. We calculate the population structure, i.e. the fraction for cooperators and defectors, at different glucose and histidine concentrations, and reproduce the phase diagram for the transition from dominance of a single strain to coexistence of both. We resort to game theory at the phenomenological level because the collective effects here are highly nonlinear due to complex metabolism. Our model implies a consistent nonlinearity responsible both for the yeast growth and glucose production.

The interactions between cooperative and defective strains are complicated for the following two reasons. First, there are two sources of nutrition supplies sucrose and glucose(Fig. 1). Sucrose is easy to model because it has a single source and single mode of consumption, originating from the media and being consumed only by cooperators. However, glucose has two sources: the initial glucose added into the media, and the local glucose increment from sucrose decomposition by cooperators. The actual glucose concentration surrounding yeast cells depends on the cooperators' metabolism and concentration, whose relation is not clearly known. Second, in sucrose hydrolysis, cooperators suffer a negative cost in invertase synthesis, but at the same time win a positive cost by generating glucose for themselves. The balance between the positive and negative cost is subtle and hard to handle. In order to circumvent these two obstacles, we model a simple situation where the two strains are at the same nutrition level. This should be applicable to the experimental situation because cooperative strains ultimately live on the monosaccharide glucose no matter if it is absorbed from the surrounding media or decomposed from sucrose. In this way, our system can be simplified as a coexistence problem of two strains living on the same nutrition glucose.

Next we use game theory to identify the conditions for coexistence. The key here is to construct a payoff matrix with experimental data. Here, the two strains are engaging in a cooperative game: if the payoff for defectors exceeds that of cooperators, defectors will dominate; if the payoff for cooperators exceeds that of defectors, cooperators will dominate. Therefore only when the payoffs for cooperators and defectors are equal to each other, will coexistence be achieved. The payoff for players is the mean fitness for species, which is measured as the growth rate. Thus, our next task is to construct the dependency of growth rates on experimental observable quantities.

The first input into the calculation is the measured nonlinear dependency of growth rate b (hr^{-1}) on glucose concentration g (%)[11]:

$$b = \gamma_1 g^{\alpha}, \tag{1}$$

where $\gamma_1 = 0.44$, and $\alpha = 0.15$. The nonlinearity $\alpha = 0.15$, which may come from the metabolism of the yeasts, is more or less unexpected[13]. Although the nonlinear relation, and the coefficients as well, were measured for mutant cheaters in a media of 5% sucrose and various concentrations of glucose, we assume that the basic nonlinearity still applies in a mixed community. Hence we import it into our model as a starting point for the construction of growth rates. Next, we add wild-type cooperators to the above media of mutant cheaters (see Fig. 2). The cooperators generate glucose from sucrose hydrolysis. From the perspective of the defectors, glucose concentration increases and the increment goes up with the increase in cooperator fraction. At first glance, one might assume that the increment is linearly proportional to the cooperator fraction. However, we argue here that the increment is nonlinear and raised to the power of the same parameter α because sucrose decomposition depends also on the metabolism of cooperators. Then we have

$$b_d = \gamma_1 (g + \gamma_2 f^{\alpha})^{\alpha}, \tag{2}$$

where b_d denotes the growth rate for defectors, γ_2 is a fixed parameter for cooperation, and f is the fraction of cooperators. When the cooperator's metabolism is co-

erced by histidine concentration, we need to give a discount on the increment. Combining the discount with γ_2, we obtain the growth rate for defectors

$$b_d = \gamma_1(g + \gamma f^\alpha)^\alpha, \tag{3}$$

where γ is a general discount, a combined effect of the artificial discount in histidine limitation and the natural cost in cooperation, and γ varies with histidine concentrations.

Finally, we model the growth rate of cooperators (Fig. 2). As mentioned above, cooperators' metabolism is discounted by a ratio γ compared to that of defectors, which leads to

$$b_c = \gamma\gamma_1(g + \gamma f^\alpha)^\alpha, \tag{4}$$

where b_c is the growth rate for cooperators. Up to here, we have put the two strains on the same carrying capacity of glucose and incorporated the cost for cooperation in invertase synthesis, but the obstacle for the positive cost in glucose reservation remains. Such a positive cost depends on metabolism and sucrose concentration. Since the sucrose concentration is fixed in the experiment, we expect a compensation for cooperators, labeled by a constant ζ, depending only on histidine concentrations. ζ might in principle be a function of γ since both depend monotonically on histidine concentration. Including the positive cost for cooperation, we finally obtain

$$b_c = \gamma\gamma_1(g + \gamma f^\alpha)^\alpha + \zeta. \tag{5}$$

Eq. (3) and (5) compose the central part of our model. These two equations show clearly the contribution of wild-type cooperators to the increase in glucose concentration as γf^α, which is nonlinear in the cooperator fraction mediated by histidine limitation. This model balances the discount γ for cooperators, which represents the negative cost, and the introduction of a single-variable function ζ depending on histidine concentration, which represents a positive cost. The positiveness of ζ implies that the engineered yeasts are engaging in a snowdrift game.

In our model of cooperation, we have input three nontrivial arguments: (i) The two α's in Eq.(3) and (5) are the same, implying the same nonlinear mechanism, which might be the metabolic system, in yeasts growth and sucrose decomposition; (ii) The two γ's in Eq. (5) are the same, implying the same discount in yeasts' growth and sucrose decomposition by cost of cooperation mediated by histidine limitation; (iii) ζ is a single-function of histidine concentration, represnting that cooperators are compensated for production of glucose.

Now we verify that these assumptions are consistent with the data. Based on our reasoning from game theory that the growth rates for cooperators and cheaters are

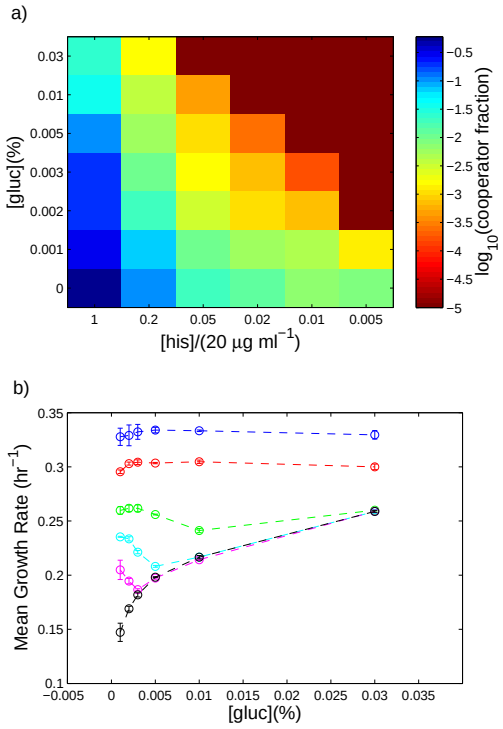

FIG. 3: (Color online) Coexistence of the two strains with the variation in glucose and histidine concentration[11]. (a) Cooperator fraction with the variation in glucose and histidine concentration at equilibrium. (b) Mean growth rate of coculture with different glucose and histidine concentrations at equilibrium.

the same at equilibrium, the growth rates measured in Fig. 3b should be valid for either strain. Interpreting them as the growth rates for defectors, we can import the data in Fig. 3 for various glucose and histidine concentrations into Eq. (3) and calculate the discount γ. According to our argument (i), we expect that γ is the same at the same histidine concentration but different glucose concentrations; this is supported by the standard deviations shown in Table I. We neglect the data for very small cooperator fractions, especially for the extinction of cooperators, such as those when histidine concentration is as low as 0.005, since they will either generate large deviation with very small bias in measurement or cause the cooperation term γf^α to vanish. Averaging among different glucose concentrations, we can see that the discount γ gets smaller when histidine is more dilute. The latter two σ_γ are smaller than the previous two since fewer data are averaged.

Next, we interpret the data in Fig. 3b as growth rates for cooperators and plug in the values of γ shown in Table I into Eq. (5). Our arguments (ii) and (iii) predict that ζ depends only on histidine concentration, which is consistent with the standard deviation for ζ in Table II. The positive cost for cooperators diminishes with the

TABLE I: Negative cost γ for cooperators at various histidine concentrations.

[his]/(20 μg ml^{-1})	1	0.2	0.05	0.02
γ	0.186	0.136	0.0607	0.0274
standard deviation σ_γ	0.02	0.02	0.006	0.006

TABLE II: Postive cost ζ for cooperators at various histidine concentrations.

[his]/(20 μg ml^{-1})	1	0.2	0.05	0.02
ζ	0.269	0.260	0.241	0.222
standard deviation σ_ζ	0.003	0.004	0.007	0.02

limitation in histidine. The latter two σ_ζ are bigger than the previous two since we extend the data for those not incorporated in the calculation of γ in Table I.

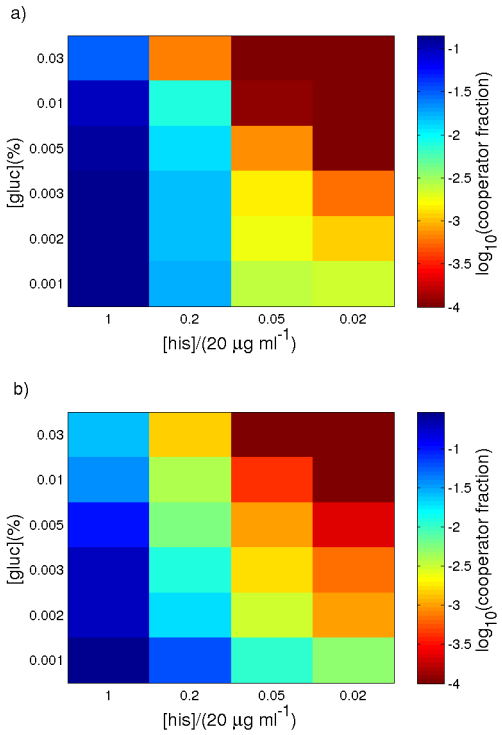

FIG. 4: (Color online) (a) Theoretical result for cooperator fraction at various glucose and histidine concentrations. (b) Experimental result for cooperator fraction at various glucose and histidine concentrations.

With the discounts γ and gain ζ in hand, we can now show the consistency of our theory by calculating the cooperator fraction at equilibrium. Setting $b_d = b_c$ in Eq. (3) and (5), we plot the cooperator fraction in Fig. 4a. As a comparison, we replot the corresponding data from experiment[11] in Fig. 4b. The similarity between the theoretical calculation and experimental measurement is striking and supports our model.

Based on game theory, we have proposed a phenomenological model for wild-type cooperative and mutant defective strains in a mixed media of glucose and sucrose. We circumvented the obstacle of modeling sucrose decomposition, which increases glucose concentration, incurs a cost as invertase syntheses for cooperators, and rewards them with a small fraction of the glucose produced, by attributing positive and negative cost for cooperation to growth rates. Then we constructed a theory of cooperation, determining the dependency of growth rates for defectors and cooperators on experimental quantities such as glucose and histidine concentration. Our calculation of cooperator fraction at equilibrium is consistent with experimental observations, showing the two strains are engaging in a snowdrift game. These methods should be useful in the design of future experiments to manipulate collective properties of micro-organism communities.

We thank Jeff Gore for sharing with us his experimental data. This work was supported in part by the National Science Foundation through grant number NSF-EF-0526747.

[1] J. Smith, *Evolution and the Theory of Games* (Cambridge Univ Pr, 1982).
[2] C. Hauert and G. Szabó, American Journal of Physics **73**, 405 (2005).
[3] R. Axelrod, D. Axelrod, and K. Pienta, Proceedings of the National Academy of Sciences **103**, 13474 (2006).
[4] M. Nowak, Science **314**, 1560 (2006).
[5] J. Prosser, B. Bohannan, T. Curtis, R. Ellis, M. Firestone, R. Freckleton, J. Green, L. Green, K. Killham, J. Lennon, et al., Nature Reviews Microbiology **5**, 384 (2007).
[6] T. Antal, H. Ohtsuki, J. Wakeley, P. Taylor, and M. Nowak, Proceedings of the National Academy of Sciences **106**, 8597 (2009).
[7] A. Traulsen, D. Semmann, R. Sommerfeld, H. Krambeck, and M. Milinski, Proceedings of the National Academy of Sciences **107**, 2962 (2010).
[8] P. Turner and L. Chao, Nature **398**, 441 (1999).
[9] M. Nowak and K. Sigmund, Nature **398**, 367 (1999).
[10] P. Turner and L. Chao, American Naturalist **161**, 497 (2003).
[11] J. Gore, H. Youk, and A. Van Oudenaarden, Nature **459**, 253 (2009).
[12] J. Gancedo, Microbiology and Molecular Biology Reviews **62**, 334 (1998).
[13] E. Frey, Physica A: Statistical Mechanics and its Applications **389**, 4265 (2010).