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Theory of cooperation in a micro-organismal snowdrift game

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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 reproducing quantitative trends and predicting the phase diagram.

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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." Mutual cooperation yields a reward R, whereas 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. If the the payoff matrix instead obeyed the inequalities $T > R > S > P$, then the rational strategy is to do the opposite of the other player. This condition leads to the so-called snowdrift game, which corresponds to a coexistence of players.

Such seemingly abstract games have biological realizations in the dynamics of microbes and viruses. In a recent experiment, a game theory payoff matrix was manipulated by genetically engineering *Saccharomyces cerevisiae* (budding yeast) [8]. Budding yeast's primary carbon intake is a monosaccharide, such as glucose or fructose. In a monosaccharide-absent environment, dormant genes are derepressed to digest alternative nutrients, such as disaccharide maltose and sucrose [9]. In the experiment, wild-type cooperative strains have an intact SUC2 gene, which codes enzyme invertase to hydrolyze sucrose into glucose and fructose. However, 99% of the product 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 histidine auxotrophs, relying on histidine importation from the media. Because they have 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 phenomenological 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 use phenomenological game theory because the collective effects here are highly nonlinear due to complex metabolism. Our model implies a consistent nonlinearity responsible for both yeast growth and glucose production.

The interactions between cooperative and defective strains are complicated for the following two reasons. First, there are two kinds of nutritional molecules: sucrose and glucose, as sketched in Fig. 1. Sucrose is easy to handle 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 amount added into the media and the local increment from sucrose decomposition by cooperators. The actual glucose concentration surrounding yeast cells depends on the cooperators' metabolism and concentration, whose relation is unknown. Second, in sucrose hydrolysis, cooperators experience a cost to synthesize invertase but at the same time gain in generating glucose for themselves. The balance between the cost and benefit 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

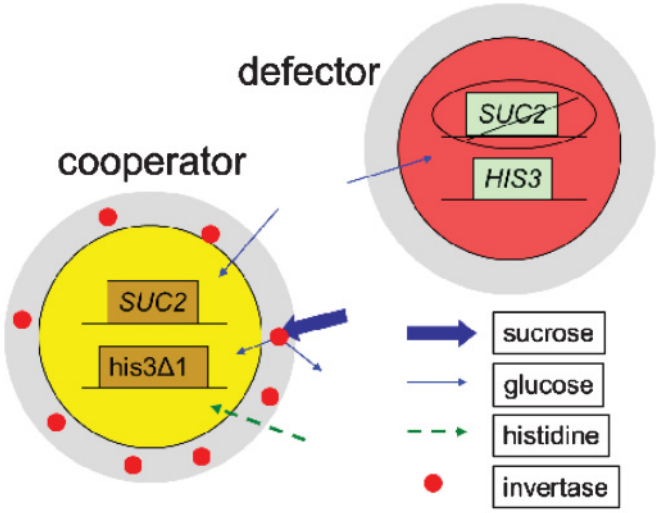

FIG. 1. (Color online) Schematic of nutrient flows in the experiment of Ref. [8]. Sucrose is hydrolyzed in the periplasmatic space (grey) of cooperators. The majority of the glucose produced diffuses back to the media, from which both strains import glucose.

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 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 both parties are equal will coexistence be achieved. The payoff for players is the mean fitness for strains, which is measured as the growth rate. Thus, our next task is to construct the dependency of growth rates on experimental observable quantities. We do this below using a mean-field theory, modeled after the way in which cooperative interactions leading to ferromagnetism are described by an effective local field that adds to the externally applied magnetic field (see, e.g., Ref. [10]).

The first input is the nonlinear dependency of growth rate b (h^{-1}) on glucose concentration g (%) according to the experiment [8]:

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

where $\gamma_1 = 0.44$, $\alpha = 0.15$, and g is 0.001–0.03%. In Eq. (1), the growth rate b varies nonlinearly with glucose concentration g. The nonlinear power α is unusual and reflects cellular constraints, such as the nonlinear performance of hexose transporters and catabolic pathway enzymes. We cannot use first principles system biology to justify the nonlinear α, because the basic metabolic networks etc are not well enough understood. Instead, we make a very simplified assumption: We interpret the nonlinearity as primarily reflecting aspects of the efficiency of hexose transporters across the cell membrane. Hence, Eq. (1) implies that translocation flux rate through the membrane is proportional to the concentration raised to a nonlinear power α. Note that in principle such translocation processes are influenced by the metabolism of the cells, but for now we regard that as negligible.

Second, we include the presence of cooperators. Now, there are two sources of glucose. Besides the initial glucose added into the media, cooperators also produce glucose from sucrose decomposition. At the mean-field level, every cooperator manufactures glucose at about the same rate. We assume that this rate does not have a significant dependence on the metabolism of cells; because the amount of invertase in each cell is not influenced by the metabolism, we assume that the performance of invertase is also not significantly influenced by the metabolism. Since the sucrose concentration is kept the same throughout the experiment, there is no need for us to explore the detailed form of such a production rate. The total glucose produced inside all the cooperator cells is thus proportional to the cooperator fraction f. Equation (1) implies that the glucose imported into the cell scales as g^{α} due to the cellular constraints on the molecular translocation process. The same translocation passage limits the glucose output from cooperators, as evidenced by the report that the diffusion coefficient through the cell wall is anomalously small, estimated to be $\frac{1}{20}$ of that in water [8]. Hence, the flux of glucose released is proportional to the glucose produced inside the cells raised to the power α. Since the glucose manufactured inside the cells is proportional to the cooperator fraction f, the glucose contribution from cooperators is proportional to f^{α} with some coefficient of proportionality. We denote the coefficient as γ. As we note in the discussion about Eq. (1), the translocation process is affected by the metabolism of the cells. The coefficient γ, in this way, represents a general discount factor due to metabolism, which is a combined effect of the artificial discount in histidine limitation and the natural cost in cooperation. Hence, we obtain the growth rate for defectors

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

where γ is a general discount factor that varies with histidine concentration, reflecting the artificial discount in histidine limitation and the natural cost of cooperation.

Third, we analyze the situation for cooperators. Compared with defectors, when they import glucose from the media, the translocation process is influenced by the metabolism, as we learn from Eq. (1). Such a discount, representing a combined effect of the artificial discount in histidine limitation and the natural cost in cooperation, is represented by the same γ as in Eq. (2), because the same cellular processes are involved. Thus, we obtain

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

where b_c is the growth rate for cooperators. Last, we recall that there is a small amount of glucose that cooperators reserve for themselves. This amount is determined by the sucrose concentration and the cell's metabolism and transport processes, which are mediated by the histidine concentration. Since the sucrose concentration is always 5% during the experiment, we denote the benefit for a single cooperator cell by ζ, a single-variable function of histidine concentration only. Including this benefit for cooperation, we finally obtain

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

Equations (2) and (4) compose the central part of our model, including the contribution of cooperators to the increase in glucose concentration by the term γf^{α}. This

TABLE I. Cost γ for cooperators at various histidine concentrations.

his/(20 μg ml^{-1})	γ	Standard deviation σ_γ
1	0.19	0.02
0.2	0.14	0.02
0.05	0.061	0.006
0.02	0.027	0.006

TABLE III. Benefit ζ for cooperators at various histidine concentrations.

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

model balances the cost γ for cooperators with the benefit ζ, both depending only on histidine concentrations. Note that as the cooperator fraction f increases, more glucose is trapped in cooperators, but the amount per cooperator does not change. The positivity of ζ is essential for the survival of cooperators, which makes it possible for the two engineered strains to engage in a snowdrift game.

In our model of cooperation, we have input three nontrivial arguments: (i) The two α's in Eqs. (2) and (4) are the same, representing the same translocation passage limitation on the glucose flux both into and out of yeast cells. (ii) The two γ's in Eq. (4) 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-variable function of histidine concentration, representing that cooperators are compensated for production of glucose.

Our arguments above motivated points (i)–(iii) assuming that it is primarily the phenomenology of transport of glucose through the cell membrane which is the growth-rate determining factor. However, in principle, other metabolic effects can be present. To test whether our assumptions are self-consistent and represent a good representation of the data, we compare the predictions of our equations with the data.

Ideally, we would like to be able to calculate the cooperator fraction as a function of glucose and histidine concentrations (Fig. 3(b) of Ref. [8]) from theory, but this would require a detailed description of the metabolism and growth dynamics of the organisms to obtain the parameters. As an alternative approach, we input experimental data to our equations and verify the consistency of our modeling by checking the standard deviations for different sets of data. Based on our reasoning from game theory that the growth rates for cooperators and defectors are the same at equilibrium, the measured growth rates of cocultures as a function of glucose and histidine concentrations (Fig. 3(c) of Ref. [8]) should be valid for either strain. Interpreting them as the growth rates for defectors, we can import the data in Figs. 3(b) and 3(c) of Ref. [8] for various glucose and histidine concentrations into Eq. (2) and calculate the discount γ. According to our argument (i), we predict that γ should be 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. By averaging among different glucose concentrations, we can see that the discount γ gets smaller when histidine is more dilute. The first two σ_γ are calculated with six data points where glucose concentration (%) ranges from 0.001 to 0.03. The latter two are smaller than the first two since fewer data are averaged. The smallness of the standard deviations has not been hardwired into our model and substantiates our assumption (i) because otherwise they might be orders of magnitude larger, as we

TABLE II. Large standard deviation σ_γ to fit Eq. (5) in violation of assumption (i).

his/(20 μg ml^{-1})	γ	Standard deviation σ_γ
1	1.8	1.5
0.2	12	9
0.05	12	7
0.02	8	4

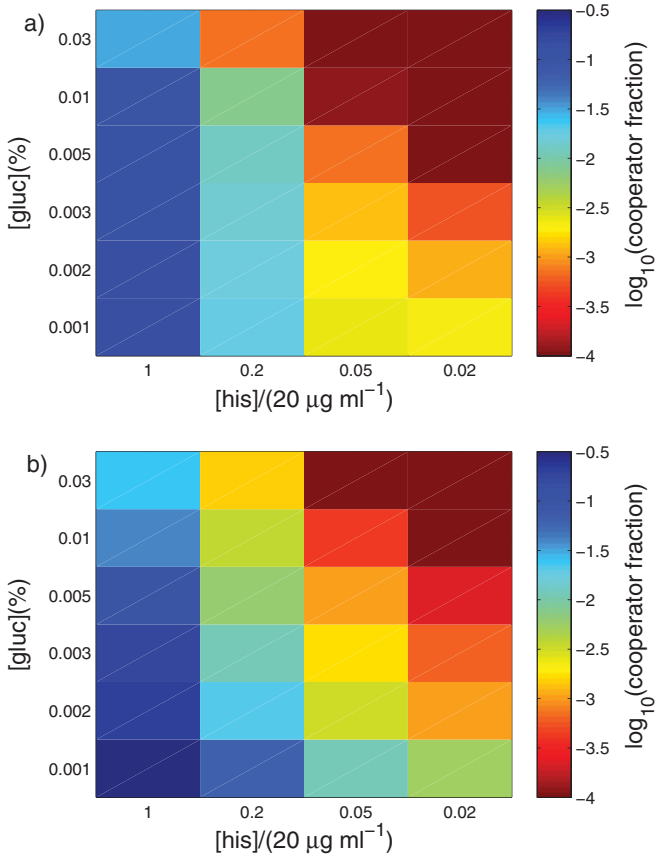

FIG. 2. (Color online) (a) Theoretical result for cooperator fraction at various glucose and histidine concentrations. (b) Corresponding experimental result for cooperator fraction at various glucose and histidine concentrations.

illustrate as follows. We show in Table II the average of γ and its corresponding standard deviation σ_γ if the increment of glucose concentration varied not with the same power α, as we have assumed in our model, but linearly with cooperator fraction, as we might have initially guessed,

$$b_d = \gamma_1(g + \gamma f)^\alpha, \tag{5}$$

or even quadratically

$$b_d = \gamma_1(g + \gamma f^2)^\alpha. \tag{6}$$

The standard deviations σ_γ in Table II are at least two orders of magnitude larger than those in Table I and are even higher for the fit to Eq. (6). The comparison among these tables demonstrates that the standard deviation is a good test of our assumption and hence justifies the self-consistency of our theory.

Next, we interpret the data in Fig. 3(c) of Ref. [8] as growth rates for cooperators and plug in the values of γ shown in Table I into Eq. (4). Our arguments (ii) and (iii) predict that ζ depends only on histidine concentration, which is consistent with the standard deviation for ζ in Table III. The benefit for cooperators diminishes with the 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. Overall, however, these consistency checks are successful, a result that we emphasize is not "built in" to our theory.

With the cost γ and gain ζ in hand, we can now predict the cooperator fraction at equilibrium. Setting $b_d = b_c$ in Eq. (2) and (4), we plot the predicted cooperator fraction in Fig. 2(a). As a comparison, we replot the corresponding data from experiment [8] in Fig. 2(b). The similarity between the theoretical calculation and experimental measurement is striking and supports our model.

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 cost and benefit for cooperation to growth rates. Then we determined the dependency of growth rates for defectors and cooperators on experimental quantities such as glucose and histidine concentrations. Despite our approximations, such as averaging over different glucose concentrations, the resulting calculation of cooperator fraction at equilibrium is consistent with experimental observations. So what did we actually predict? By requiring that $b_d = b_c$, we thus found, *in a noncircular way*, the condition for the phase boundary separating the prisoner's dilemma phase from the snowdrift phase of the system. Our mean-field arguments also predict the trend, that is, the sign of $\partial f/\partial g$ for fixed histidine concentration. These methods could be useful in the design of future experiments to manipulate collective properties of micro-organism communities.

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