Published in final edited form as:

Bull Math Biol. 2012 July ; 74(7): 1469–1484. doi:10.1007/s11538-012-9721-5.

Game Dynamic Model for Yeast Development

Yuanyuan Huang and Zhijun Wu

Department of Mathematics Program on Bioinformatics and Computational Biology Iowa State University, Ames, Iowa 50011, USA

Abstract

Game theoretic models, along with replicator equations, have been applied successfully to the study of evolution of populations of competing species, including the growth of a population, the reaching of the population to an equilibrium state, and the evolutionary stability of the state. In this paper, we analyze a game model proposed by Gore et al. (2009) in their recent study on the co-development of two mixed yeast strains. We examine the mathematical properties of this model with varying experimental parameters. We simulate the growths of the yeast strains and compare them with the experimental results. We also compute and analyze the equilibrium state of the system and prove that it is asymptotically and evolutionarily stable.

Keywords

Evolutionary game theory; evolution of cooperation; replicator equations; Nash-equilibrium; evolutionarily stable states; co-existence of mixed yeast strains

1. Introduction

Game theory, originally developed in economics, has been applied to many other scientific fields including ecology, psychology, sociology, and political sciences. In 1940s, John von Neumann and Oskar Morgenstein (1944) investigated the zero-sum games and proved the existence of the optimal strategies. In 1950s, John Nash (1950) considered more general games and showed the existence of the equilibrium solution, called the Nash equilibrium. Later in 1970s, John Maynard Smith and George R. Price (1973) introduced game theory to biology and proposed the concept of evolutionarily stable state, which laid the foundation for evolutionary game theory. The latter, along with replicator equations, has been applied successfully to the study of evolution of populations of competing species, including the growth of a population, the reaching of the population to an equilibrium state, and the evolutionary stability of the state (Nowak, 2006a).

The evolution of cooperation has been an area of intensive research in the past several decades (West et al., 2006). General rules have been studied in terms of kin selection, direct and indirect reciprocity, network selection, and group selection (Nowak, 2006b). Special strategies have been discovered such as the tit for tat strategies in the repeated prisoner's dilemma games (Axelrod and Hamilton, 1981) and the restrictions of dispersal, movement, and interaction for the co-existence of competing species (Nowak and May, 1992; Durrett and Levin, 1997; Kerr et al., 2002; Hauert and Doebeli, 2004). The cooperative behaviors have been explained in game theoretic models and verified in experiments with model bacteria and yeast systems (Rainey and Rainey, 2003; Griffin et al., 2004; Maclean and Gudelj, 2006; Diggle et al., 2007; Santorelli et al., 2008; Gore et al., 2009).

In particular, Gore et al. (2009) investigated the evolution of cooperation using a deliberately designed system of two competing yeast strains. What special about this work is the following: First, the designed system depends on several experimental parameters. Therefore, by varying the parameters, the system's behavior can be changed from a mutual benefit game to a snowdrift game and from a snowdrift game to a prisoner's dilemma game. Then, cooperation can be investigated in different game settings. Second, the authors showed that if a simple matrix game model was used, there might be only two types of games, the mutual benefit game or prisoner's dilemma game. The snowdrift game is not implied in this model, while in the experiments the system behaved most time like a snowdrift game. Therefore, the authors derived a nonlinear payoff function for the game, i.e., a nonlinear game model, with a more accurate description of the system's behaviors.

While Gore et al. (2009) focused on experimental results, this paper is a further theoretical stretch of their work. In this paper, we examine the mathematical properties of the proposed game model with varying experimental parameters. We simulate the growths of the yeast strains and compare them with the experimental results. We also compute the equilibrium states of the system and analyze their stabilities. We show that the equilibrium state of the snowdrift game is evolutionarily stable, which is not so obvious when the model is given in a nonlinear form.

In what follows in this section, we introduce some basic concepts in game theory. In Section 2, we describe the yeast experiments in Gore et al. (2009). We describe their model and show some of their results. In Section 3, we describe the methods for computing the growths and equilibrium states of the yeast system. We present our computational results and compare them with the experimental ones. In Section 4, we analyze the model and prove the asymptotic and evolutionary stabilities of the equilibrium states. We conclude the paper in Section 5 and make some additional remarks.

For introduction, let's consider a simple two-player two-strategy game. Then, the outcomes of the game can be measured by a pair of payoff functions that depend on the strategies of the players. Let π_1 and π_2 be the payoff functions for player 1 and 2, respectively. Let $x = (x_1, x_2)^T$ be the player 1's choice of strategies, playing strategy 1 with probability x_1 and strategy 2 with probability x_2 , and $x_1 + x_2 = 1$. Let $y = (y_1, y_2)^T$ be the player 2's choice of strategies, playing strategy 1 with probability y_1 and strategy 2 with probability y_2 , and $y_1 + y_2 = 1$. Then, the payoffs for player 1 and 2 will be $\pi_1(x, y)$ and $\pi_2(y, x)$, respectively. If π_1 is equal to π_2 , the game is called symmetric, i.e., the payoff will be the same for a pair of competing strategies no matter which player chooses which strategy. For a biological game, a player could be a certain species; a strategy could be a certain genotypic or phenotypic feature; and the payoff function could be the fitness function defined in terms of resource gain or reproduction success.

In any case, each player competes to maximize his payoff, but can only achieve it when the other player can no longer reduce his gain with a counter strategy. If both players reach such a point, the game is said to reach equilibrium or more specifically Nash equilibrium, and the strategies of the players are called the optimal strategies. Consider a symmetric game. Define $S_x = \{x \mid 0 \leq x_i \leq 1, \sum_i x_i = 1\}$. Then, a game reaches Nash equilibrium if there are optimal strategies x^* in S_x for player 1 and y^* in S_y for player 2 such that

$$\pi(x^*, y^*) \geq \pi(x, y^*), \forall x \in S_x \quad \text{and} \quad \pi(y^*, x^*) \geq \pi(y, x^*), \forall y \in S_y. \quad (1)$$

Usually, the payoffs for all the pairs of competing strategies can be given in a matrix U with U_{ij} being the payoff for strategy i against strategy j . The payoff function π can then be defined as the average payoff of the player when he chooses strategy x against the other

player's strategy y , i.e., $\pi(x, y) = x^T U y = \sum_i (x_i \sum_j U_{ij} y_j)$. In this case, the game is called a matrix game. Otherwise, the payoff function can be in a general nonlinear form.

A game is called a prisoner's dilemma game (PD) if each player chooses to be a cooperator or defector to counter the other: A cooperator gains substantially (with a payoff, say 4) if the opponent also cooperates, but loses the most (with a payoff, say -1) if the opponent defects. A defector gains the most (with a payoff, say 5) if the opponent cooperates, and does not lose that much as the cooperator (with a payoff, say 1) if the opponent defects. So a safe guard is to always play a defector, for nobody wants to take a risk to cooperate but become a loser when the opponent defects.

A game is called a mutual benefit game (MB) if each player chooses to be a cooperator or defector, but the payoff outcomes are very different from PD: A cooperator gains (with a payoff, say 5) no matter what the opponent chooses to be. A defector always loses (with a payoff, say 3) no matter what the opponent is. As a result, both players will choose to play cooperators.

A snowdrift game is played when two players act as two drivers whose cars are blocked by the snow on the road. Each of them needs to decide if he should go out to remove the snow or stay in the car to wait until the other driver clears the road. In this game, a defector (who stays in the car) takes advantage (with a payoff, say 5) if the opponent cooperates (removing the snow), but the worst scenario is when the opponent also defects and then both get stuck in the car (with a payoff, say 0). A cooperator benefits (with a payoff, say 3) if the opponent also cooperates, but would benefit more if he were a defector. Besides, he may get worse (with a payoff, say 1) if the opponent defects. In such cases, the cooperators are attempted to be defectors, and the defectors have to cooperate sometimes if there is no cooperator. As a result, a good scenario would be for the player to sometimes cooperate and sometimes defect, to obtain an optimal amount of benefit.

2. Yeast Development as a Snowdrift Game

Gore et al. (2009) designed an experiment with two mixed yeast strains in sucrose culture. The wild type cells, considered as cooperators, hydrolyze sucrose into glucose and fructose with protein invertase. They consume only a small portion (about 1%, called the capture rate) of the products. The rest of the glucose and fructose diffuses into the culture. The mutant cells, considered as defectors, do not have the gene *SUC2* that produces protein invertase and therefore, cannot make glucose or fructose. The wild type cells are also made histidine auxotroph (with defected *HIS3* genes) so they have an additional fitness cost due to histidine anabolic deficiency. The cost is high when the histidine concentration in culture is low (see Fig. 1).

In general, the growth of the mutant strain depends on the wild type strain, but the mutant strain will outgrow the wild type if the culture is maintained with high concentration glucose and low concentration histidine, because the wild type cells incur a fitness cost due to invertase production as well as histidine anabolic deficiency. In this case, the interaction between the wild type cell and the mutant cell is more like a prisoner's dilemma game (PD), and the mutant cells, the defectors, eventually take over the whole population, assuming the high glucose concentration of the culture is maintained. On the other hand, if the glucose concentration in culture is low and the histidine concentration is high, the wild type cells will eventually win, because they have the advantage of consuming their own glucose or fructose directly while the "cost of living" due to histidine anabolic deficiency is not so high. This makes the interaction between the two types of cells a mutual benefit game (MB).

In Gore et al. (2009), the authors were able to change several experimental parameters including the glucose and histidine concentrations in culture. The authors found that for a large range of parameter values, the interaction between the two types of yeast cells maintained a snowdrift game (SG) instead, and the two strains co-existed at equilibrium. More specifically, with a reasonable concentration of glucose and histidine in culture, the authors observed the increase of the wild type strain when it started from a small fraction and the decrease from a large fraction, and it reached an equilibrium fraction no matter what fraction it started (see Fig. 2).

Note that by the equilibrium of the yeast system in experiment we mean a relative stable state of the system after a sufficiently long time. It is an approximately estimated equilibrium state, and in the yeast experiment, was roughly the state after 6 days.

To build a game model for a biological system, the population is usually assumed well mixed so that each individual can interact with any others. An individual is designated as one of the players, say player 1, while the population as another, say player 2. The types of species in the population can be considered as the types of strategies, and each individual can choose to be a certain type of species (i.e., a certain strategy) or to be a mixed type of species (i.e., a mixed strategy). Such a game is called a population game or an evolutionary game or a game against the field (Hofbauer and Sigmund, 1998; Webb, 2007). For the system of two yeast strains, assume that all yeast cells are well mixed. Then, the system can be considered to have two strategies: f fraction of wild types (cooperators) and $(1-f)$ fraction of mutants (defectors). Each individual cell can be considered to play a mixed strategy, with probability f to be a wild type and $(1-f)$ to be a mutant. Clearly, when the system reaches equilibrium, $f = f^*$.

Let ϵ be the capture rate and f the fraction of the cooperators (the wild types). Let the payoff (growth rate) of the cooperators be P_C and of the defectors (the mutants) be P_D . Then, a simple game model for the yeast system of interest can be defined such that

$$P_C = \epsilon + f(1 - \epsilon) - c, \quad P_D = f(1 - \epsilon). \quad (2)$$

where c is the cost for cooperation. Consider P_C and P_D to be the functions of f and h , with $h = 1 - f$. Then, $P_C(f, h) = f(1 - c) + h(\epsilon - c)$ and $P_D(f, h) = f(1 - \epsilon) + h \cdot 0$. Let the strategy of an individual cell be $(f, h)^T$, where $h = 1 - f$. Then, the average payoff for the cell against a population of strategy $(f, h)^T$ can be written as

$$\pi = f^0 P_C(f, h) + h^0 P_D(f, h). \quad (3)$$

Let $x = (f, h)^T$ and $y = (f, h)^T$. Define a payoff matrix,

$$U = \begin{bmatrix} 1 - c & \epsilon - c \\ 1 - \epsilon & 0 \end{bmatrix}.$$

Then, the average payoff in (3) can be written in the following form,

$$\pi(x, y) = x^T U y. \quad (4)$$

Based on the general properties of two by two matrix games, it is not hard to see that this payoff function defines a PD game if the cost is high ($c > \epsilon$) and a MB game if the cost is low ($c < \epsilon$). However, in Gore et al. (2009), it was observed that the yeast strains behaved

more of a snowdrift game. Therefore, the matrix game does not seem to be a suitable model for the yeast system of interest. Indeed, Gore et al. (2009) proposed a nonlinear game model that matched the observed behaviors of the yeast strains. In this model, the payoff functions P_C and P_D are defined in the following form:

$$P_C(f, h) = [g + (1 - g)(\varepsilon + f(1 - \varepsilon))]^\alpha - c, \quad P_D(f, h) = [g + (1 - g)f(1 - \varepsilon)]^\alpha, \quad (5)$$

where an additional parameter g is also introduced to account for the dependency of the payoffs on the glucose concentration g of the culture, and the payoff functions are made nonlinear by using a fractional power $\alpha = 0.15$. The glucose concentration g of the culture is measured in milligrams per 100 milliliters and is maintained via routine artificial adjustment in the experiment. Consider the following two equations:

$$[g + (1 - g)(1 - \varepsilon)]^\alpha = 1 - c, \quad g^\alpha = [g + (1 - g)\varepsilon]^\alpha - c. \quad (6)$$

The first one holds when the whole population becomes cooperators ($f = 1$) at equilibrium ($P_C = P_D$). The second one holds when the whole population becomes defectors ($f = 0$) at equilibrium ($P_C = P_D$). The two equations define two curves in the c - ε plane. The payoff functions define a MB game when the (c, ε) pair is above the first curve and a PD game when it is below the second curve. When the (c, ε) pair is in between the two curves, a snowdrift game (SG) is played as it is observed in the experiment (see Fig. 3).

3. Computer Simulation

Suppose that the growth rates of cooperators and defectors are given as the formulas in (5). Then, the average payoff function for a cell of strategy $x = (f, h)^T$ against a population of strategy $y = (f, h)^T$ can be written as

$$\begin{aligned} \pi(x, y) &= f^\circ P_C(f, h) + h^\circ P_D(f, h) \\ &= f^\circ [g + (1 - g)(\varepsilon + f(1 - \varepsilon))]^\alpha - f^\circ c + h^\circ [g + (1 - g)f(1 - \varepsilon)]^\alpha. \end{aligned} \quad (7)$$

By the definition of Nash equilibrium and the fact that $x^* = y^*$ when the system reaches equilibrium, we then have y^* as an equilibrium state of the system if and only if

$$\pi(y^*, y^*) \geq \pi(y, y^*), \quad \forall y \in S_y \quad (8)$$

where $S_y = \{y : 0 \leq \sum_i y_i = 1\}$. Define $S_{y^*} = \{y \in S_y : \sum_{i \in \text{supp}(y^*)} y_i = 1\}$, where $\text{supp}(y^*) = \{i : y_i^* > 0\}$. Then, we also have an important property for y^* as stated in the following theorem.

Theorem 3.1 If a population game defined by a payoff function π reaches (Nash) equilibrium with an optimal strategy y^* , then $\pi(y^*, y^*) = \pi(y, y^*)$, $\forall y \in S_{y^*}$.

This theorem is called the equal payoff theorem in evolutionary game theory. A proof can be found in standard textbooks such as Webb (2007). The theorem implies that if y^* is an optimal strategy, then $\pi(y, y^*) = \pi(y', y^*)$, $\forall y, y' \in S_{y^*}$. For a two-strategy game, if $y^* = (f^*, h^*)^T$ is an optimal strategy and $f^*, h^* > 0$, then $S_{y^*} = S_y$. Let $y_C = (1, 0)^T$ and $y_D = (0, 1)^T$. Then, y_C, y_D are in S_{y^*} and $\pi(y_C, y^*) = \pi(y_D, y^*)$. It follows that for the payoff function π defined in (7),

$$[g + (1 - g)(\varepsilon + f^*(1 - \varepsilon))]^\alpha - c = [g + (1 - g)f^*(1 - \varepsilon)]^\alpha. \quad (9)$$

This is equivalent to the condition when $P_C(f^*, h^*) = P_D(f^*, h^*)$.

For computer simulation, the equation in (9) gives an important condition for the computation of the equilibrium fraction f^* of the yeast game if the parameters g , ϵ , and c are given. Indeed, in Gore et al. (2009), ϵ was estimated to be around 0.01. Then, if glucose and histidine concentrations were set to certain values, the corresponding equilibrium fraction could be observed after the system settled down for several days (Rigorously speaking, the observed equilibrium fraction in finite time is only an approximated equilibrium fraction). Figure 4 shows the experimentally observed cooperator fractions f^* at equilibrium with varying glucose and histidine concentrations in a color-coded graph. From this graph, we see that in low histidine and high glucose, the cooperator fractions f^* are almost zero and the defectors win, implying that the game is PD. On the other hand, in high histidine and low glucose, the cooperator fractions f^* are almost one and the cooperators win, implying that the game is MB. In between, the two strains co-exist, and the game is SG.

Conversely, using condition (9), if g and ϵ are given and f^* is known, the cost c , dependent of the histidine concentration, may be determined. We call this process an inverse game: determine the parameters that define the payoff function, given the optimal strategies at equilibrium. It is called the inverse game because it corresponds to an inverse problem in mathematical terms (Aster et al., 2005). Such a problem can be as important as a direct problem, for often in biological games, we can observe or measure the equilibrium states at least approximately, but we do not know anything about the payoff rules, which in fact are what we want to learn and discover. From condition (9), the cost c can be determined given ϵ , g , and equilibrium fraction f^* using the following formula:

$$c = [g + (1 - g)(\epsilon + f^*(1 - \epsilon))]^\alpha - [g + (1 - g)f^*(1 - \epsilon)]^\alpha. \quad (10)$$

Figure 5 shows the values of c in a color-coded graph calculated using formula (10) with the values of f^* shown in Fig. 4. Note again that these equilibrium fractions are observed ones in experiment and are approximately estimated values. From this figure, we see that the values of c are high for low histidine and high glucose (red regions) and are low for high histidine and low glucose (blue regions). With high cost, the system certainly tends to be like a PD game, while with low cost, it is more of a MB game. In between, the system behaves as a SG game with (the wild type) cooperators co-existing with (the mutant) defectors.

Once all the parameters in the payoff functions are determined, the equilibrium fraction f^* and hence h^* can be computed based on Theorem 3.1 or more specifically, on condition (9) for the yeast problem. However, in order to learn how the yeast strains have developed from some initial state to an equilibrium state, we have to solve a system of replicator equations that describes the dynamic properties of the population changes of the species.

A general principle for constructing a system of replicator equations for a given population of species is that the growth rate for each species relative to its current population is proportional to the payoff advantage of this species over the average payoff of the whole population. Let y_i be the population fraction of species i , $i = 1, \dots, n$, where n is the total number of species. Then, the replicator equations can be written in the following form

$$y_i' / y_i = \pi(e_i, y) - \pi(y, y), \quad i = 1, \dots, n, \quad \sum_i y_i = 1. \quad (11)$$

For the yeast problem, $n = 2$, $y = (f, h)^T$, $\pi(e_1, y) = P_C(f, h)$, $\pi(e_2, y) = P_D(f, h)$, and $\pi(y, y) = fP_C(f, h) + hP_D(f, h)$. We then have

$$f' / f = P_C(f, h) - f P_C(f, h) - h P_D(f, h), \quad (12)$$

$$h' / h = P_D(f, h) - f P_C(f, h) - h P_D(f, h). \quad (13)$$

Given the fact that $f + h = 1$, the above equations can be reduced to one:

$$f' = f(1 - f) [P_C(f, 1 - f) - P_D(f, 1 - f)]. \quad (14)$$

Let $P(f) = P_C(f, 1 - f) - P_D(f, 1 - f)$. Then, equation (14) can also be written as

$$f' = f(1 - f) P(f), \quad (15)$$

where

$$P(f) = [g + (1 - g)(\varepsilon + f(1 - \varepsilon))]^\alpha - c - [g + (1 - g)f(1 - \varepsilon)]^\alpha \quad (16)$$

depends on the parameters ε , g , and c . By fixing the values for these parameters, we can solve a corresponding equation (15) for any initial fraction f_0 , to obtain a trajectory for f changing from f_0 in certain time period. In particular, we can also find possible fixed points (or limiting points) for f from equation (15) when the growth rate of f is zero, i.e., either $f = 0$, or $f = 1$, or f is such that $P(f) = 0$. It follows from the following theorem that a Nash equilibrium point must be a fixed point, but a fixed point may not necessarily be a Nash equilibrium point.

Theorem 3.2 A strategy y^* is a fixed point of the system of replicator equations (11) if it is a Nash-equilibrium strategy for the game defined by the payoff function π .

The proof for this theorem is straightforward, since if y^* is an equilibrium strategy, by Theorem 3.1, $\pi(y^*, y^*) = \pi(y, y^*)$, $\forall y$ in S_{y^*} including $\forall e_i$ in S_{y^*} , and then, the equations in (11) are all equal to zero when $y = y^*$. More detailed and related discussions on the fixed points of the replicator equations can be found in standard textbooks such as Webb (2007).

The following are the computational results we have obtained from our simulation. These results agree well with the experiment results reported in Gore et al. (2009) and hence validate the proposed game model. In addition, the simulation allows us to not only predict all possible equilibrium states of the system but also track the dynamic changes of the yeast system in a continuous time period.

Figure 6 (b) shows the solution curves for the equation in (15) with varying values of glucose concentration of the culture, while the value for $\varepsilon = 0.01$ and histidine concentration is fixed to $0.05\times$, where $\times$ means times the normal histidine concentration, which is $20\mu\text{g/mL}$. The simulations are all started with an initial cooperator fraction $f_0 = 10^{-1}$. Then, if glucose concentration is relatively low (0.001%), the defector fraction grows and the cooperator fraction f decreases to an equilibrium fraction. When the glucose concentration is increased, the cooperator fraction at equilibrium decreases (not as demanded yet costly for co-existence). When it is increased to 0.03%, the cooperator fraction at equilibrium is almost zero (below 10^{-4} after 5 days). All these results agree well with the experimental observations as displayed in Fig. 6 (a).

Figure 7 (b) shows the solution curves for the equation in (15) with varying values of histidine concentration instead, while the value for $\epsilon = 0.01$ and glucose concentration is fixed to 0.003%. The simulations are all started with an initial cooperator fraction $f_0 = 10^{-1}$. Then, if histidine concentration is relatively high ($> 0.2\times$), the cooperators maintain their population to equilibrium. When the histidine concentration is decreased, the cooperator fraction f decreases from its initial fraction to equilibrium, and in general, the lower the histidine concentration, the smaller the cooperator fraction at equilibrium (costly to maintain). When it is decreased to $0.005\times$, the cooperator fraction at equilibrium is close to 10^{-5} in 5 days, while the experimentally observed one is close to 10^{-4} . Overall, these results agree well with the experimental observations as displayed in Fig. 7 (a).

Note that in Fig. 6 and Fig. 7, the computed trajectories are shown only in 6 days, in order to compare with the experimental ones. They also end slightly higher than the experimental curves, because they are supposed to converge to the observed equilibrium fractions as the time goes to infinity.

Figure 8 (b) shows the equilibrium fractions f^* obtained using condition (9) with varying values for glucose and histidine concentrations, while the value for $\epsilon = 0.01$. The condition (9) holds when $0 < f^* < 1$ and two yeast strains co-exist. Therefore, the curves for histidine concentrations $1.0\times$ and $0.2\times$ match with experimentally observed equilibrium fractions well, decreasing relatively slowly as the glucose concentration increases. When the histidine concentration further decreases, the equilibrium fraction is supposed to approach to zero quickly as glucose concentration increases. Indeed, for example, when the histidine concentration is decreased to below $0.02\times$, the equilibrium fractions become zero for all glucose concentrations higher than 0.005%. Otherwise, a true fractional cooperator equilibrium strain is found. All these results agree well with the experimentally observed equilibrium fractions as displayed in Fig. 8 (a).

4. The Stability of Equilibrium

We focus on the stability of the equilibrium states of the snowdrift game for the yeast problem. To be self-contained, we first introduce some stability terms and theorems without proofs and refer the readers to Hofbauer and Sigmund (1998) and Webb (2007) for more details.

Definition 4.1 A solution y^* for a system of replicator equations (11) is called a fixed point if $y_i^{*'} = y_i^* [\pi(e_i, y^*) - \pi(y^*, y^*)] = 0$, $\forall i = 1, \dots, n$.

Definition 4.2 A fixed point y^* for a system of replicator equations (11) is said to be asymptotically stable if for any $\epsilon > 0$, there is $\delta > 0$ such that $\|y(t) - y^*\| < \epsilon$ for all $t > 0$ whenever $\|y(0) - y^*\| < \delta$ and if $y(t) \rightarrow y^*$ as $t \rightarrow \infty$.

Note that by this definition, asymptotically stable for a fixed point y^* simply means that a small deviation or perturbation $y(t)$ from y^* will remain arbitrarily close to y^* for all t and converge to y^* as t goes to infinity. However, it is hard to verify the asymptotic stability of a fixed point directly from its definition. The following theorem, called Lyapunov Theorem, is often used in stability analysis.

Theorem 4.1 A fixed point y^* for a system of replicator equations (11) is said to be asymptotically stable if there is a function $V(y) \geq 0$ with $V(y) = 0$ if and only if $y = y^*$ such that $V_t'(y) \leq 0$ with $V_t'(y) = 0$ if and only if $y = y^*$.

Definition 4.3 A strategy y^* for a population game defined by a payoff function π is called a Nash equilibrium point if $\pi(y^*, y^*) \geq \pi(y, y^*)$, $\forall y$ in $S_y = \{y \geq 0: \sum_i y_i = 1\}$.

Definition 4.4 A Nash equilibrium point y^* for a population game defined by a payoff function π is said to be evolutionarily stable if for any y in S_y , $y \neq y^*$, $\pi(y, \epsilon y + (1-\epsilon)y^*) < \pi(y^*, \epsilon y + (1-\epsilon)y^*)$, for any $\epsilon > 0$ sufficiently small.

Note that evolutionary stability is a stronger stability term than asymptotic stability. It was first proposed by John Maynard Smith and George R. Price (1973) for measuring the stability of equilibrium states of a biological system and later justified as a general stability measure. However, the definition does not provide a simple way for verifying evolutionary stability. The following theorem is one among many others that can be used more directly for formal proofs.

Theorem 4.2 A Nash equilibrium point y^* for a population game defined by a payoff function π is said to be evolutionarily stable if and only if $\pi(y^*, y) > \pi(y, y)$ for any y in S_y , $y \neq y^*$, and y in a small neighborhood of y^* .

Note again that as a system of replicator equations corresponds to a population game, the fixed points for a system of replicator equations and their asymptotic stabilities have close relationships with the Nash equilibrium points for the corresponding population game and their evolutionary stabilities. In fact, as stated in the following theorems, an evolutionarily stable Nash equilibrium point must be an asymptotically stable fixed point; an asymptotically stable fixed point must be a Nash equilibrium point; and a Nash equilibrium point must be a fixed point. However, the reverse of any of these statements may not always valid.

Theorem 4.3 An asymptotically stable fixed point for a system of replicator equations is a Nash equilibrium point for the corresponding population game.

Theorem 4.4 An evolutionarily stable Nash equilibrium point for a population game is an asymptotically stable fixed point for the corresponding system of replicator equations.

Theorem 4.5 Let $\mathbf{F}$ be the set of fixed points, $\mathbf{N}$ the set of Nash equilibrium points, $\mathbf{A}$ the set of asymptotically stable fixed points, and $\mathbf{E}$ the set of evolutionarily stable Nash equilibrium points for a given population game and its corresponding system of replicator equations. Then, $\mathbf{F} \supset \mathbf{N} \supset \mathbf{A} \supset \mathbf{E}$.

We now consider the game model for the yeast problem. Consider the replicator equation (15) for the model. By the definition of fixed points, this equation has three fixed points: $f=0$, $f=1$, $f=f^*$ such that $P(f)=0$. It is easy to verify that $P'(f) < 0$ and therefore, $P(f)$ is a monotonically decreasing function. Assume that $0 < f^* < 1$. Then, f' is positive and f increases to f^* for $0 < f < f^*$ and f' is negative and f decreases to f^* for $f^* < f < 1$, as can be depicted in Fig. 9. The point f^* must be a stable point. We state this fact more formally in the following theorem.

Theorem 4.6 The fractional fixed point f^* for the replicator equation in (15) of the yeast game is asymptotically stable.

Proof Let $V(f) = P^2(f)$. Then, $V(f) > 0$ for all $f \neq f^*$ but $V(f^*) = 0$. Also, since $P'(f) < 0$ and $f' = f(1-f)P(f)$, we have $V'_f(f) = V'_f(f)f' = 2f(1-f)P^2(f)P'(f) < 0$ for all $f \neq f^*$ but $V'_f(f^*) = 0$. It follows from Theorem 4.1 that f^* is an asymptotically stable fixed point. $\square$

Let $y^* = (f^*, h^*)^T$, where $h^* = 1 - f^*$. Then, by Theorem 3.1, y^* is an optimal mixed strategy for the yeast game, since $\pi(y^*, y^*) = \pi(e_i, y^*) = \pi(y, y^*)$, $\forall y$ in S_y . In other words, y^* is a fractional Nash equilibrium point for the yeast game, corresponding to the co-

existing state of the yeast strains. In the following theorem, we prove that this state is also evolutionarily stable.

Theorem 4.7 The optimal mixed strategy y^* of the yeast game defined by the nonlinear payoff function in (7) is an evolutionarily stable strategy.

Proof Let f be any cooperator fraction and f^* . Since $P(f)$ is a monotonically decreasing function, we have $(f^* - f) P(f) > 0$. The latter is equivalent to

$$(f^* - f) [P_c(f, h) - P_d(f, h)] > 0 \text{ or } (f^* - f) P_c(f, h) - (f^* - f) P_d(f, h) > 0,$$

which further reduces to

$$f^* P_c(f, h) + (1 - f^*) P_d(f, h) > f P_c(f, h) + (1 - f) P_d(f, h).$$

The left-hand side of the above inequality is exactly the payoff function $\pi(y^*, y)$, where $y^* = (f^*, h^*)^T$ and $y = (f, h)^T$, while the right-hand side is $\pi(y, y)$. We then have $\pi(y^*, y) > \pi(y, y)$, for all $y \neq y^*$. By Theorem 4.2, y^* is an evolutionarily stable strategy. $\square$

5. Concluding Remarks

In this paper, we have examined several mathematical properties of the nonlinear game model proposed by Gore et al. (2009). While Gore et al. (2009) focused on experimental results, this paper is a further theoretical stretch of their work. The contributions of this paper can be summarized as follows.

First, we have analyzed the mathematical properties of the nonlinear game model proposed by Gore et al. (2009) and determined the values of the cost factor c in the payoff functions with varying experimental parameters, the glucose and the histidine concentrations in culture, using the experimentally observed yeast fractions at equilibrium. The calculations were not complicated, but the process of determining one or more parameters that define the game model using the dynamic properties such as the equilibrium states were emphasized. Termed as an inverse game, the process can be important for general game theoretic modeling of biological systems. Considered as an inverse problem, issues such as the existence of the inverse solutions, the uniqueness of the solutions, and the stability of the problem can be important for general models, either linear or nonlinear (Aster et al., 2005).

Second, with the determined cost factor c , the payoff function is well defined. Then, we have been able to compute the yeast fractions at equilibrium based on the game theory principles and obtain their dynamic trajectories by solving a system of replicator equations. We have obtained these results with a fixed glucose concentration but varying histidine concentrations and also with a fixed histidine concentration but varying glucose concentrations. The results were not just simple recoveries of the experimental outcomes. In fact, they can be generated with arbitrary parameter values and in continuous time intervals.

Third, we have compared our computational results with the experimental ones reported in Gore et al. (2009). Both sources of results agreed well, confirming the theoretical model as well as the simulation results. In Gore et al. (2009), a nonlinear game model is proposed because it admits a snowdrift game for a large range of parameter values. It is therefore important to verify computationally if this model can indeed lead to similar equilibrium states and dynamic trajectories of the yeast strains as observed in experiments.

Fourth, with the model validated computationally, we have been able to prove that the co-existing equilibrium state of the yeast strains is asymptotically and evolutionarily stable, which is not so obvious when the game is modeled in a nonlinear form. The stability, especially the evolutionary stability, is a critical issue for evolutionary game dynamics. It is a rigorous measure for how strong a given biological system is against any mutant invasion, but the proof for such a property often requires some mathematical techniques. On the other hand, the proof is only based on the theoretical model, and the true stability of the system is yet to be verified by experiment, which may not be easy to do as well.

Finally, the paper is written in a more expository form, with both biological and mathematical accounts, while certain level of mathematical rigorousness is maintained. The paper invites interests from biological and mathematical communities in evolutionary game theory and its applications in biological modeling. Further extension of this work can be interesting as well such as applying the studied game model to the yeast strains in a 2D plane. The outcomes can be different from what we have so far observed either experimentally or computationally, because of the effect of the scale of the local movement and interaction (Nowak and May, 1992; Durrett and Levin, 1997; Kerr et al., 2002; Hauert and Doebeli, 2004).

Acknowledgments

We would like to thank Prof. Jeff Gore for kindly giving us the Matlab code for generating some of the graphical results in their paper and for providing helpful suggestions and advices for how to proceed in our computation. This work is partially supported by the NIH/ NIGMS grants R01GM072014 and R01GM081680 and by the NSF/ DMS grant DMS0914354.

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Fig. 1. A mixed culture of two yeast strains

One is the wild type and the other mutated. The wild type inverts sucrose into glucose and fructose (producing food). The mutated only takes glucose and fructose (without producing them). The wild types are called cooperators, while the mutated cheaters. The wild type strain has a gene *SUC2* for producing sucrose invertase, while the mutated strain lacks *SUC2* and therefore, cannot invert sucrose. The wild type has a defective *HIS3* gene and can only take histidine from outside to grow and thereby incurs an additional fitness cost. (From Gore et al., 2009)

Fig. 2. The co-existence of two yeast strains

(a) If started with a high population, the cooperator fraction decreases. If started with a low portion, the cooperator fraction increases. Somewhere in between, there must be an equilibrium state of nonzero cooperator fraction. (b) If the cost is high (in low histidine concentration), the equilibrium fraction tends to be low (RED). If the cost is low (in high histidine concentration), the equilibrium fraction tends to be high (BLUE). (From Gore et al., 2009)

Fig. 3. The nonlinear game model for yeast development

With low efficiency e and high cost c , cheaters win (PD). With high efficiency e and low cost c , cooperators win (MB). In between, the two strains co-exist, reaching equilibrium (SG). (From Gore et al., 2009)

Fig. 4. Cooperator fractions at equilibrium

The experimentally observed cooperator fractions at equilibrium with varying glucose and histidine concentrations are shown in a color-coded graph. From this graph, we see that in low histidine and high glucose, the cooperator fractions are almost zero and the defectors win, implying that the game is PD. On the other hand, in high histidine and low glucose, the cooperator fractions are almost one and the cooperators win, implying that the game is MB. In between, the two strains co-exist, and the game is SG. (From Gore et al., 2009)

Fig. 5. Color-coded cost values

The values for cost c are calculated using Formula (10). From this graph, we see that the c values are high for low histidine and high glucose (red regions) and are low for high histidine and low glucose (blue regions). With high cost, the system certainly tends to be like a PD game, while with low cost, it is more of a MB game. In between, the system behaves as a SG game with (the wild type) cooperators co-existing with (the mutant) defectors.

Fig. 6. Dynamic changes of cooperator fractions

Shown in (b) are the simulated trajectories of cooperator fractions with varying values of glucose concentration, where the value for $\epsilon = 0.01$ and histidine concentration is fixed to $0.05 \times$. The simulations are all started with an initial cooperator fraction $f = 10^{-1}$. Then, if glucose concentration is relatively low (0.001%), the defector fraction grows and the cooperator fraction decreases to an equilibrium fraction. When the glucose concentration is increased, the cooperator fraction at equilibrium decreases (not as demanded yet costly for co-existence). When it is increased to 0.03%, the cooperator fraction at equilibrium is almost zero (below 10^{-4} after 5 days). All these results agree well with the experimental observations as displayed in (a) (from Gore et al., 2009).

Fig. 7. Dynamic changes of cooperator fractions

Shown in (b) are the simulated trajectories of cooperator fractions with varying values of histidine concentration, where the value for $\epsilon = 0.01$ and glucose concentration is fixed to 0.003%. The simulations are all started with an initial cooperator fraction $f_0 = 10^{-1}$. Then, if histidine concentration is relatively high ($> 0.2\times$), the cooperators maintain their population to equilibrium. When the histidine concentration is decreased, the cooperator fraction decreases from its initial fraction to equilibrium, and in general, the lower the histidine concentration, the smaller the cooperator fraction at equilibrium (costly to maintain). When it is decreased to 0.005 $\times$, the cooperator fraction at equilibrium is close to 10^{-5} in 5 days, while the experimentally observed one is close to 10^{-4} . Overall, these results agree well with the experimental observations as displayed in (a) (from Gore et al., 2009).

Fig. 8. Equilibrium fractions

Shown in (b) are the computed cooperator fractions at equilibrium with varying values for glucose and histidine concentrations, while the value for $\epsilon = 0.01$. The curves for histidine concentrations 1.0 $\times$ and 0.2 $\times$ match with experimentally observed equilibrium fractions well, decreasing relatively slowly as the glucose concentration increases. When the histidine concentration further decreases, the equilibrium fraction is supposed to approach to zero quickly as glucose concentration increases. Indeed, for example, when the histidine concentration is decreased to below 0.02 $\times$, the equilibrium fractions become zero for all glucose concentrations higher than 0.005%. Otherwise, a true fractional cooperator equilibrium strain is found. All these results agree well with the experimentally observed equilibrium fractions as displayed in (a) (from Gore et al., 2009).

Fig. 9. Stability of equilibrium state

There are three fixed points: $f=0$, $f=1$, $f=f^*$ such that $P(f)=0$ for equation (15). Assume that $0 < f^* < 1$. Then, f' is positive and f increases to f^* for $0 < f < f^*$ and f' is negative and f decreases to f^* for $f^* < f < 1$. The point f^* must be a stable point.