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Games of life and death: antibiotic resistance and production through the lens of evolutionary game theory Peter L Conlin¹, Josephine R Chandler² and Benjamin Kerr¹



In this review, we demonstrate how game theory can be a useful first step in modeling and understanding interactions among bacteria that produce and resist antibiotics. We introduce the basic features of evolutionary game theory and explore model microbial systems that correspond to some classical games. Each game discussed defines a different category of social interaction with different resulting population dynamics (exclusion, coexistence, bistability, cycling). We then explore how the framework can be extended to incorporate some of the complexity of natural microbial communities. Overall, the game theoretical perspective helps to guide our expectations about the evolution of some forms of antibiotic resistance and production because it makes clear the precise nature of social interaction in this context.

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Introduction

Although antibiotic resistance has been traditionally viewed as asocial, recent studies show that in some important cases antibiotic resistance is in fact the product of social interactions $[1,2,3^{\bullet\bullet},4,5]$. For example, an extracellular enzyme that inactivates an antibiotic can protect both the bacterium that produces it and its neighbors [6,7]. In such cases, drug susceptibility depends on social context. Social interactions are also important in the case of antibiotic production, where the density of producers can considerably impact the survival of sensitive competitors.

Here we demonstrate how evolutionary game theory $[8^{\bullet\bullet},9]$, a mathematical framework focused on social

interaction, is particularly helpful in understanding evolutionary outcomes in circumstances where antibiotic resistance and production involve a social dimension. Evolutionary game theory has been successfully applied to study topics including the evolution of cooperation [10,11], ritual fighting among animals [12], and more recently to the study of microbial interactions [13–18], but its usage in cases of antibiotic resistance and production is less common. In the following sections, we will review some basic features of game theory, highlight microbial systems that exhibit classical game dynamics, discuss natural features that increase the complexity of the framework, and suggest some possible areas of interest for future study.

Game theory basics

In classical game theory [19], a game is a contest between individual players. Each player employs a strategy that yields some payoff. Generally the payoff to a player using a given strategy depends on the strategy employed by its partner(s). A simple illustration of this can be seen in the child's game rock–paper–scissors, which is a two-player game with three strategies. This game is nontransitive: each strategy beats one other strategy and is beaten by the third. Specifically, Rock crushes Scissors, Scissors cuts Paper, and Paper covers Rock. Were you to play this game with a friend, your payoff would be given by the following table (or payoff matrix):

| | Your partner's strategy | | |
|---------------|-------------------------|-------|----------|
| | Rock | Paper | Scissors |
| Your strategy | | | |
| Rock | Draw | Lose | Win |
| Paper | Win | Draw | Lose |
| Scissors | Lose | Win | Draw |

This game illustrates how the payoff of one player's strategy can be conditional on the strategy of another player. Playing Rock is exactly the right thing to do if your partner plays Scissors, but is precisely the wrong thing to do if your partner decides on Paper.

In evolutionary game theory, the focus shifts from the handful of players in a single game to a very large population of individuals playing many instances of a game in parallel [8^{••}]. The strategies are genetically determined and the payoffs are expressed in terms of fitness, which can be organized into a fitness matrix (similar to the payoff matrix above). The most successful





Two-player two-strategy evolutionary games. (a) The fitness matrix for a game between producers (P) and nonproducers (N) of a public good (see Supplement for details). This matrix conforms to the Prisoner's Dilemma. Fitness of a focal player depends not only on its genotype (blue or red rows) but also the genotype of its partner (columns). (b) Predicted population dynamics of a simple game theoretical model, given the fitnesses in part a (see Supplement for details). Despite its initial proportion, the producer approaches extinction. The vertical line segment to the right is identical to the *y*-axis of the graph and large circles represent equilibria. Because N will invade a population of mostly P (top arrow), fixation for P is an *unstable* equilibrium (unfilled circle). Because P fails to invade a population of mostly N (bottom arrow), fixation for N is a stable equilibrium (filled circle) and N is an ESS. (c) A generic fitness matrix for a two-strategy two-player game. The fitness of a focal P individual (blue entries) is *w* and *y* when paired with a partner of genotype P and N, respectively. The fitness of a focal N individual (red entries) is *x* and *z* when paired with P and N, respectively. (d–g) Here we rotate the vertical line segment of part b clockwise by 90°. If w < x, N will invade a population of P. If y > z, P will invade a population of N. On the other hand, if w > x or y < z, then P or N, respectively, is an ESS. (d) For the Prisoner's Dilemma, P fixation is unstable and N is stable to invasion (i.e., N the sole ESS). (e) When the fitness inequalities are reversed, N fixation is unstable and P is the sole ESS, (f) When both fixation states are unstable (i.e., no ESS), sither strategy can dominate depending on whether the initial proportion of P is above or below the unstable equilibrium (purple unfilled circle). Such dynamics are termed bistable.

genotype has the most offspring. Because offspring inherit the strategy of their parent, successful genotypes increase in proportion in the population. When a genotype that is very rare employs the most successful strategy, it is said to 'invade' the population. Under certain conditions (see Supplement I), the fitness matrix contains all the information necessary to predict such evolutionary invasion [20,21].

To illustrate the idea, we consider a two-player game in which it is possible for an individual to produce a compound (termed a 'public good') that benefits itself and its partner. There are two genotypes in this game: producers (**P**) and nonproducers (**N**), and one possible fitness matrix is shown in Figure 1a. This fitness matrix assumes that the cost of production outweighs the benefit a producer receives from its own production. When **P** is common and **N** is rare, both genotypes tend to pair up with **P** partners when pairs form randomly. Because genotype **N** has a higher fitness than genotype **P** in such matches (i.e., 4 > 3 in Figure 1a), **N** can invade. Conversely, when **N** is common and **P** is rare, genotype **P** fails to invade because it has a lower fitness than N (i.e., 1 < 2 in Figure 1a). In this case, we say that N is stable to invasion, and genotype N is termed an Evolutionarily Stable Strategy (ESS). In this example, a pair of producers has higher collective fitness than a pair of nonproducers (as in Figure 1a). This is an instance of the famous Prisoner's Dilemma^a [10]. Despite initial proportions, N is predicted to drive P to extinction (Figure 1b). Here, evolution is predicted to eliminate public good production, lowering average fitness in the process.

More generally, inequalities in the fitness matrix govern whether each genotype is an ESS. In a two-strategy twoplayer game (Figure 1c) there are four possible ESS configurations (Figure 1d–g). Each configuration corresponds to a distinct evolutionary outcome. Specifically, the form of the fitness matrix determines whether a certain genotype dominates, whether coexistence is predicted, or whether initial genotype proportions matter. That is, the nature of the game informs us about evolution of the population. In the next few sections we will illustrate this connection, where we discuss cases of antibiotic resistance and production as simple games, revisiting some of the evolutionary behavior shown in Figure 1.

Antibiotic resistance: the dilemma of being 'snowed in'

A common mechanism of antibiotic resistance in bacteria involves the production of an enzyme that deactivates the antibiotic [22,23]. For instance, β -lactamase hydrolyzes β -lactam antibiotics (e.g., ampicillin). This enzyme is costly to produce and can work outside the producing cell [24], and thus might be considered a public good. (Note, even if detoxification of the drug occurs exclusively within the cell it can still be considered a public good because it detoxifies the local environment [25,26].) We discussed costly public good production in the context of the Prisoner's Dilemma (Figure 1a), which makes a clear evolutionary prediction: in a population of producers and nonproducers, the producers are driven to extinction (Figure 1b). Does the β -lactamase system conform to the predictions of the Prisoner's Dilemma?

Recent studies of β -lactamase production in *Escherichia coli* have shown that producer and nonproducer cells can coexist in an environment containing ampicillin [1,3^{••}] Indeed, Yurtsev *et al.* [3^{••}] found that producer cells settled to a stable equilibrium regardless of initial proportions (Figure 2a). This is not consistent with the predictions of the Prisoner's Dilemma, as producers have a relative growth advantage when rare [15]. This deviation can be explained by the finding that the

antibiotic-degrading enzyme is primarily contained in the periplasmic space of the producing cell [6,24]; thus, there is partial 'privatization' of the public good (Figure 2b). When producers are rare, their private detoxification yields an advantage over the nonproducers that depend solely on public detoxification.

The dynamics exhibited in the above experiments can be understood as a Snowdrift game^b [27,28]. In this game, two drivers are stuck behind a snowdrift. Each has the option of staying in their car or clearing a path. The payoff is always greater if you choose to do the opposite of your opponent. Analogously, when there are many producing cells in a population it pays to not produce, as the cost of production is avoided (compare entries in the first column of Figure 2c). Conversely, when there are many nonproducing cells in a population it pays to produce, as greater protection from the antibiotic is achieved (compare entries in the second column of Figure 2c). If interactions occur randomly, then average fitnesses of the two strategies cross as the producer proportion increases (Figure 2d) and a stable equilibrium is predicted (Figures 2e and 1f). When moving from the Prisoner's Dilemma (Figure 1d) to the Snowdrift game (Figure 1f) the ordering of fitnesses of the two genotypes when paired with a nonproducer has flipped (compare payoff matrices in Figures 1a and 2c). Given that partial privatization is common among many public good systems [15,26,29], the Snowdrift game may be widely applicable in natural systems [28,30[•]].

In the case of *E. coli* β -lactamase production, the experimentally described stable interior equilibrium is consistent with a Snowdrift game (Figure 2a). However it should also be noted that the results shown in Yurtsev *et al.* display dynamics that would not be predicted from a simple Snowdrift game (for instance, when started at a low proportion, β -lactamase producers rise to a high proportion before decreasing to the interior equilibrium). This suggests the two-player game framework is oversimplified; however, more detailed models (incorporating antibiotic deactivation dynamics and modeling the growth rate of the nonproducer as a function of antibiotic concentration) can faithfully generate experimental results (see [3**]).

Yurtsev *et al.* [$3^{\bullet \bullet}$] also showed that the stable equilibrium shifts in response to changes in drug concentration. Specifically, the fitness of nonproducers (red entries in Figure 2c) decreases as drug concentration increases. Above a certain level of the drug, the fitness of the producer becomes higher than the nonproducer across all possible scenarios (i.e., a shift from Figure 1f to e). This would lead to the eventual fixation of the producer

^a The Prisoner's Dilemma was originally introduced by Merrill Flood and Melvin Dresher in 1950 as part of the Rand Corporation's research on game theory.

^b The Snowdrift game is also known as the Hawk–Dove game [8^{••}] or the game of Chicken [78].





Snowdrift game. **(a)** Results of a laboratory experiment tracking the proportion of bacteria producing an antibiotic-inactivating enzyme (β -lactamase). In the presence of the antibiotic (ampicillin), the producers and nonproducers coexist, approaching the same final proportions despite their initial fractions (data reproduced with permission from Yurtsev *et al.* [3**]). **(b)** In this cartoon, we consider two genotypes: producers of an antibiotic-inactivating extracellular enzyme (blue cells) and nonproducers (red cells). Shown are three possible pairwise interactions in the presence of an antibiotic (top) and the outcome of each interaction (bottom). A producer benefits neighboring cells by inactivating the antibiotic (purple shading represents enzyme concentration), but also receives greater private protection (indicated by the purple 'halo'). **(c)** The fitness matrix for the cartoon in part b is shown. Compared with Figure 1a, the producer now has a higher fitness when the partner is a nonproducer because the enzyme (public good) is partially privatized. This arrangement of fitnesses is known as the Snowdrift game. **(d)** Predicted average fitnesses of each genotype given random interaction (note that the end points are the values in part c). The small empty circles correspond to points where the average fitness is not strictly defined (e.g., where producers or nonproducers are absent). The point where the red and blue lines cross corresponds to a producer proportion where the fitness of each genotype is equal; thus, this point is an equilibrium. **(e)** Predicted population dynamics of a simple game theoretical model, given the average fitnesses in part d. The proportion of producers increases when producers are rare and decreases when producers are common. Thus, the producer proportion reaches a stable interior equilibrium, regardless of the initial fraction. There is no pure strategy ESS here (see also Figure 1f).

despite its starting proportion (an outcome predicted for the so-called Harmony game [31]).

Antibiotic production: choosing sides in a deadly game

In the previous section we considered a public good that can protect other cells from antibiotics, but many bacteria also produce their own proteinaceous antibiotics [32,33]. A strain that produces such a toxin (known as a bacteriocin) carries genes for both toxin production and immunity, while a nonproducing strain has neither and consequently avoids associated costs [34]. In a mixed population of producers and nonproducers the bacteriocin kills only nonproducing types. Given that producers compete with nonproducers for limited resources, producers can help one another by destroying mutual competitors. In this light, bacteriocins can be seen as an indirect 'public good' [35,36]. However, as we shall see, this kind of public good game has very different dynamics than any we have previously considered.

In a study of bacteriocin production (colicin E3) in *E. coli*, Chao and Levin [37^{••}] found that the outcome of competition between the producer and a sensitive nonproducer was dependent on initial genotype proportions. In contrast to the case of β -lactamase production where the producing strain has an advantage when rare, they found that the producer only had an advantage when fairly common (>2%). For a rare producer, the cost of production outweighs the diluted benefit of colicin



Choosing Sides. (a) In this cartoon, the two genotypes are producers of a toxin (blue cells) and sensitive nonproducers (red cells). Three possible pairwise interactions (top) result in different outcomes (bottom). A nonproducer is killed by the producer's toxin (where gray shading indicates toxin concentration), whereas the producer is immune to its own toxin. The producer does incur a growth cost for production; thus, the producer is less fit when paired with itself than the nonproducer when paired with itself. (b) The fitness matrix for part a is shown. A producer has a higher fitness when the partner is a producer (first column), while the nonproducer has a higher fitness when the partner is a nonproducer (second column). This arrangement of fitnesses is similar to the Choosing Sides game. (c) Predicted average fitness of each genotype given random interaction. The point where the red and blue lines cross is an equilibrium. (d) Predicted population dynamics of a simple game theoretical model, given the average fitnesses in part c. The proportion of producers increases when producers are common and decreases when producers are rare. Thus, the producer proportion either approaches 0 or 1, depending on the initial fraction. The internal equilibrium is unstable and there are two ESSs: production and nonproduction (see also Figure 1g).

production. For a common producer, the concentrated toxic benefit offsets the production costs. Thus, the fitness payoffs are such that each genotype does better when matched with its own type (Figure 3a,b). If interactions occur randomly, each genotype is fitter than the other when common (Figure 3c), which leads to a bistability (Figures 3d and 1g).

The payoff structure here is roughly equivalent to the 'coordination' game^c called Choosing Sides, which

involves two drivers speeding toward each other on a dirt road [38]. Each driver must choose a direction to swerve (Left or Right) in order to avoid a crash. If both execute the same swerving maneuver they will manage to pass each other, but if they choose differing maneuvers they will collide. A rare nonproducer in a population of colicin producers fares poorly in the same way a Right Swerver fares poorly in a population of Left Swervers, and vice versa.

Complex games I: more strategies

The experiments presented above involve only two strategies, but new strategies can readily evolve in large populations of bacteria. The addition of new strategies to a game involves adding additional rows and columns to the payoff matrix (consider moving from a 2×2 to a

^c Coordination games are a class of games with multiple equilibria. Another well-known coordination game is the Stag Hunt game [79]. Note that the payoff structure of a coordination game is exactly opposite to that of the Snowdrift game (which belongs to a class of games called 'anti-coordination' games).





Spatial games. (a) An experiment tracking the proportion of colicin E3 producers in liquid culture. If the producers start above a critical fraction (\sim 0.02), then the producers drive the sensitive nonproducers extinct. Otherwise, the producers go extinct (data reproduced with permission from Chao and Levin [37**]). (b) When the same community is propagated in a structured environment (soft agar), the producers increase despite initial proportion. (c) A second experiment tracking the density of three genotypes. In a well-mixed flask, the sensitive nonproducer (S) quickly goes extinct (due to the ubiquitous toxin) and then the producer (P) is outcompeted by the resistant nonproducer (R) (data reproduced with permission from Kerr *et al.* [41]). (d) All three genotypes are maintained at high density when the community is propagated on the surface of an agar plate. (e) Time series photographs of a representative replicate of the RPS community propagated on agar. (Top row) The changing spatial configuration of the experimental community is shown in this first panel of photographs. Because borders could be identified where P interacted with R or S, the direction of clump movement over transfers could be inferred. (Bottom row) 'Chasing' between clumps is highlighted in this second panel. The borders where P chased S are colored in purple and the borders where R chased P are in green.

 3×3 payoff matrix). For example, colicin resistance mutations occasionally arise in sensitive populations of *E. coli* [32,39,40]. When the resistant strain has a fitness intermediate between the sensitive and producer strain, the new strategy can lead to a cyclical dynamic [41,42]. Specifically, the sensitive strain outgrows the resistant strain, the resistant strain outgrows the producer, and a sufficiently common producer displaces the sensitive type through toxic killing in a relationship analogous to the game of rock-paper-scissors. The strategy set gets even larger still when further evolution of the three genotypes is considered [43-47].

Of course, natural microbial communities contain a diverse assortment of species with much richer strategy sets than we have considered [48]. This is beginning to be explored with pairwise studies of antibiotic production and resistance in co-occurring species from natural communities [49–54]. By constructing large interaction matrices with this type of data, the nature of the multispecies game is elucidated. In particular, these enlarged payoff matrices provide critical information on the network structure of microbial communities (e.g., the symmetry and transitivity of killing interactions) [49,53,54].

Complex games II: nonrandom interaction

The experiments presented above were conducted under 'well-mixed' conditions where extracellular products were uniformly distributed throughout the microbial community. However, microbes often live in complex biofilms where the distribution of extracellular products may be highly nonuniform [55–58]. Theoretically, limited diffusion and local interaction can completely transform the population dynamics of a system because a producer may disproportionately experience its own products (if dispersal is limited) and the products of its clone mates (if dispersal is limited) [59–61,62°,63°].^d This effect of 'spatial structure' has been illustrated experimentally in two of the examples we previously discussed (and elsewhere [64,65]).

Chao and Levin [37^{••}] showed that spatial structure can promote successful invasion by a colicin producer. In contrast to the bistability observed under well-mixed liquid culture conditions (Figure 4a), the colicin-producing strain always displaced the nonproducing sensitive strain in soft agar (Figure 4b). Even if the producer was at a very low proportion globally, spatial structure gave colicin producers an advantage because the toxin became concentrated around producer microcolonies and killed neighboring nonproducers; subsequently, the producer was able to capitalize on the local resources liberated.

Kerr *et al.* [41] demonstrated that spatial structure can promote the maintenance of diversity in a rock-paperscissors community. In an unstructured habitat (a stirred flask), the distributed toxin rapidly killed the sensitive strain and the resistant strain then displaced the producer (Figure 4c). Diversity was rapidly lost. However, in the structured habitat (the surface of an agar plate), local dispersal gave rise to patches of each cell type, and these patches 'chased' one another according to the rockpaper-scissors relationship (Figure 4d,e). Given that such nontransitive relationships have been reported in natural microbial communities [49,50], it will be interesting to explore the role of spatial structure in the maintenance of diversity within natural systems (see [66-70]).

Complex games III: more players

In this review we have focused on games involving two players. However, interactions among bacteria rarely occur among discrete pairs. For this reason *n*-player games are often useful for modeling bacterial interactions (see Supplement III for the *n*-player case and Supplements II and IV for connections to dynamics in a single well-mixed population). Unlike increasing the number of strategies (which adds rows and columns to the payoff matrix). increasing the number of players requires that the dimensionality of the payoff matrix increase (for example, moving from a 2×2 to a $2 \times 2 \times 2$ payoff matrix). Games involving an arbitrary number of players lead naturally to an explicit consideration of how fitness depends on the density of other players (density-dependent selection).^e Many bacteria have regulatory systems that can be activated at a specific cell density [71], some of which are known to control antibiotic production [72-74]. The relationship between cell density-dependent regulation and antibiotic production and resistance is an area that is just beginning to be explored, but one theoretical model suggests that linking antibiotic production to cell density may be important for competition because it can help to delay the cost of producing the antibiotic, thus improving the fitness of the producing cell ([75], but see [76,77]). Another area for future study related to density issues is

^d In this section we focus on the effects of limited dispersal but it is important to note that non-random interaction can be achieved in ways besides limited dispersal. For example, producing types may preferentially interact with other producers via homophilic binding as is seen in several microbes [80,81] including bacteria [82].

^c Consider a 2-strategy game (with strategies labeled **A** and **B**) that can be played with 2, 3, 4, 5, ..., *n* players. One can see that keeping track of the 2-, 3-, 4-, 5-, ..., *n*-dimensional payoff matrices will quickly become unwieldy. An obvious simplifying alternative is to describe the fitness of an individual as a function of densities of strategies within its group. For instance, the fitness of an individual implementing strategy $X \in \{A, B\}$ would be described by a function $\omega_X(n_A, n_B)$, where n_Y is the number of players employing strategy $Y \in \{A, B\}$ in the group of our focal X player. When such functional descriptions are possible, we replace the large (potentially infinite) collection of matrices with 2 functions each of dimensionality 3. In general, the density-dependent functional description would involve *s* functions each of dimensionality *s* + 1, if *s* is the number of strategies in the game.

the role of signaling in the production of antibiotic resistance phenotypes [4,5].

Conclusions

We demonstrate how evolutionary game theory can be a useful framework for understanding cases of antibiotic resistance and production that involve social interaction. We illustrated that the population dynamics found in microbial experiments are predicted by different twostrategy, two-player games. Certainly, the consideration of more strategies, more players and more complex interaction are promising directions for future research. Nonetheless, we feel that there is also value in the very simplest models. Specifically, these simple games define different categories of social interaction with different resulting dynamics. The game theoretical perspective focuses our attention on the precise nature of interaction, which can guide our expectations about the evolution of some forms of antibiotic resistance and production.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.mib.2014.09.004.

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