Alma Mater Studiorum - Università di Bologna

Evolutionary Game Theory application for microbes in intestinal microbiota

Complex Systems and Network Science

Marco Costante
marco.costante@studio.unibo.it
ID: 0000973866

Abstract

The human intestinal microbiota plays an important role in the health of the host. When the homeostasis is disturbed, it is related to many diseases. Although the latest results of metagenomic sequencing have begun to reveal the diversity of microbial composition related to health and disease states, species-specific interactions and system dynamics still pose a huge challenge to solve the complexity of the human microbiota. Taking the infection of *Clostridium difficile* in the human intestinal microbiota as an example, it is possible to apply evolutionary game theory to understand the phenotypic variation and dynamic progress of the microbiota.

1 Introduction

The human intestinal microbiota contains at least 1011 bacteria per gram of intestine, and they play a key role in the development and maintenance of system homeostasis. The mutually beneficial relationship between the host and the microbiota is constantly regulated by the metabolites produced by the microorganisms. These complex and dynamic interactions greatly affect the host's susceptibility to diseases.

One of the disorders of intestinal flora caused by a single strain is the infection of *Clostridium difficile*, which is resistant to antibiotics. It is generally believed that antibiotic treatment can deplete the intestinal commensal bacteria and provide *C. difficile* with a growth advantage, after which *C. difficile* can release its toxin to inhibit the susceptible microbiota. Unfortunately, although antibiotic treatment is initially effective in treating *C. difficile* infection, it usually recurs within 3 months. Another basic feature of the microbial community is the interaction between microorganisms in various communities. This interaction determines future changes in the composition of microorganisms. From the perspective of biomolecules, the

interspecies exchange of metabolites should play an important role in the evolution and dynamics of the intestinal microbial community. This leads to symbiosis, parasitism, symbiosis or competitive interaction of specific species. Symbiotic bacteria constantly compete with pathogenic bacteria for attachment sites and nutrients on the surface of intestinal epithelial cells for optimal proliferation; they can even directly inhibit each other by secreting antibacterial compounds. In view of this complexity, a theoretical framework is needed to summarize individual behaviors at the community level. Using evolutionary game theory, it is possible to observe that the growth rate of each member of the microbial community is usually affected by the abundance of other members of the community. Focusing on the *C. difficile* infection model, various scenarios that rely on the interaction between different bacterial phenotypes are discussed.

2 Model

A minimal model is proposed in order to capture the dynamics of the human gut microbiota challenged by *C. difficile* infection. The symbiotic microbiota model has been simplified into two phenotypic groups: antibiotic-sensitive bacteria (denoted as **CS**) and antibiotic-resistant bacteria (denoted as **CT**). In addition, it is also considered the third group of pathogens (denoted as **PA**) to represent the possible existence of *Clostridium difficile*. Unless the balance of the intestinal microbiota is disturbed, the number of PA bacteria is usually low. In each case, the model parameters are assumed as constant in time and the overall mixing is assumed to be good.
According to evolutionary game theory, the existence of each phenotype group will affect the growth rate of each group. In other words, the fitness of each phenotype depends on the frequency of each phenotype. In this 3-player game, the payoff can be expressed as a 3 x 3 matrix, described as the effect of the interaction on the growth rate of each phenotype.

2.1 Payoff matrix

The payoff matrix is defined as follows:

	CS	**CT**	**PA**
CS	0	c	e
CT	a	0	f
PA	b	d	0

The diagonal of the payoff matrix is zero, because each phenotype has a neutral effect on its own growth rate. The values of the payoff matrix is based on the following rules and assumptions:

- CS and CT bacteria depend on each other for optimal proliferation, resulting in positive values for "a" and "c" in the payoff matrix. The resulting two-player game has only CS and CT phenotypes, which obtain direct benefits from cooperative behavior, thus forming an evolutionary stable strategic state (coexistence). This is consistent with the observation that if the proportion of PA cells is negligible, there is a stable coexistence between CS and CT cells.

- Regarding the pair-wise interaction between CS and PA: in the absence of antibiotic administration, the CS population usually suppresses the PA population. However, when antibiotics were used, the PA population replaced the CS population. The resulting two-player game is very similar to the prisoner's dilemma, in which the two strategies (or participants) cannot coexist stably. In other words, there can only be one evolutionary stable strategy. Therefore, it is assumed that one player gains and the other player loses, represented by the opposite signs of CS vs. PA ("e") and PA vs. CS ("b").

- Similarly, when the CS population is suppressed by antibiotics, there may be two situations: (1) PA and CT compete for resources, so the benefits of PA and CT ("d") and CT and PA ("f") are negative ; (2) PA uses CT to obtain resources, so the returns of PA and CT ("d") are positive, while the returns of CT and PA ("f") are negative. Therefore, in any case, it is assumed that the CT population declines in the presence of PA cells and has a negative return "f".

2.2 Reduced payoff matrix

It is possible to readjust the original payoff matrix by factors (a, c, -f) so that $\beta = -b/a = e/(-f)$ and $\alpha = d/c$. Then the minimum payout matrix becomes:

	CS	**CT**	**PA**
CS	0	1	β
CT	1	0	-1
PA	$-\beta$	α	0

Among them, α and β can be positive or negative numbers. If the sign of α is positive (or negative), the PA population may increase (or decrease) in the presence of CT bacteria. Similarly, the fitness acquired (or lost) of CS bacteria from PA bacteria depends on whether β is positive (or negative). In the minimum payoff matrix, the payoff of the CS group during the interaction is exactly the same as the loss of the PA group on the growth rate (β). The biological explanation is that one population may obtain attachment sites or metabolic resources from another population, and which population will take over is determined by the presence of antibiotics.

2.3 Noise

The addition of noise in the model, modifies the possibility that an agent randomly selects the strategy with a small probability. The inclusion of noise in the system can sometimes significantly change its dynamic behavior. In addition, as a positive side effect, adding a small amount of noise to the model usually makes the analysis of its dynamics easier.

3 Evolution analysis

3.1 Healthy stability ($\beta > 0$)

In this situation the PA population benefits from the presence of CT bacteria ($\alpha > 0$) but is inhibited by the presence of CS bacteria ($\beta > 0$). The system will have a stable equilibrium corresponding to the healthy coexistence of CS and CT bacteria, with little or no PA bacteria.
When approaching equilibrium, the progress of dynamics slows down. From a clinical point of view, the ideal goal is to eradicate pathogenic bacteria (PA) or at least stabilize at a low PA ratio. Figure 1 shows an ideal condition ($\alpha < \beta + 1$), where the PA-free coexistence of CT and CS cells is a stable fixed point.

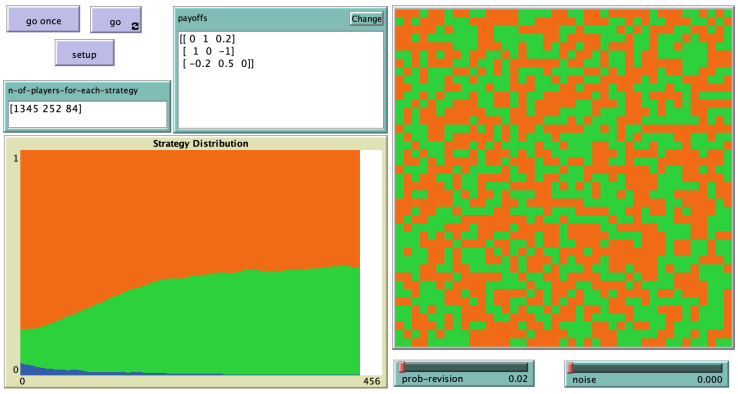

Figure 1: PA benefits from CT, inhibited by CS: $\alpha < \beta + 1$, $\alpha = 0.5$, $\beta = 0.2$

When $\alpha > \beta + 1$, PA, CT and CS cells coexist in equilibrium, as shown in Figure 2. This is a clinically acceptable condition because the ratio of the three phenotypes is balanced regardless of the initial population score.

On the other hand, both CT and CS bacteria may inhibit the growth of PA bacteria by producing toxins or competing for attachment sites and nutrients. In this case, both CT bacteria and CS bacteria inhibit the growth of PA populations ($\alpha < 0$ and $\beta > 0$). Similarly to what happens in the case in which $\alpha < \beta + 1$, the system will have only one stable equilibrium which corresponds to a healthy state without PA bacteria. The dynamic progress of various initial population proportions

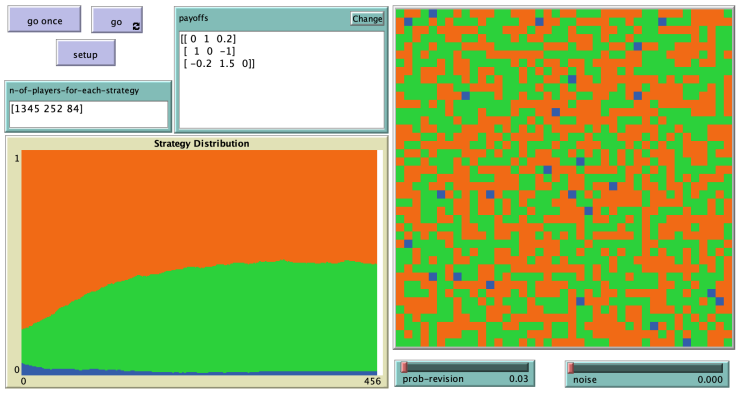

Figure 2: Equilibrium coexistence: $\alpha > \beta + 1$, $\alpha = 1.5$, $\beta = 0.2$

is shown in Figure 3. Regardless of the initial population ratio, the system will be restored to the healthy state of the CS and CT dominated communities.

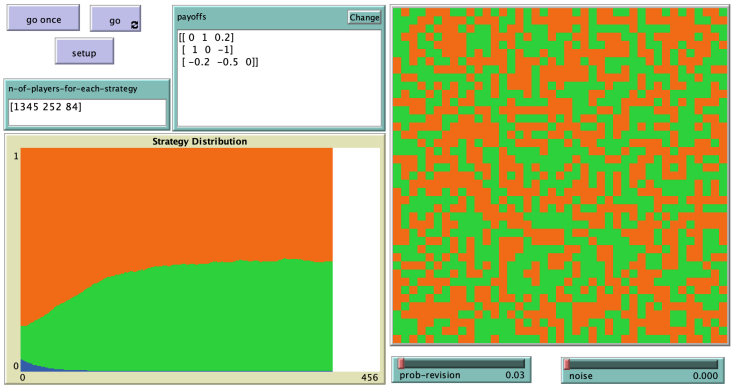

Figure 3: PA inhibited by CT and CS bacteria: $\alpha < 0$ and $\beta > 0$, $\alpha = -0.5$, $\beta = 0.2$

In these scenarios, an higher revision probability value speeds up the attainment of the equilibrium state, even though it introduces some fluctuations. Introducing noise, the expected equilibrium state is no longer guaranteed, leading to a coexistence of the three populations.

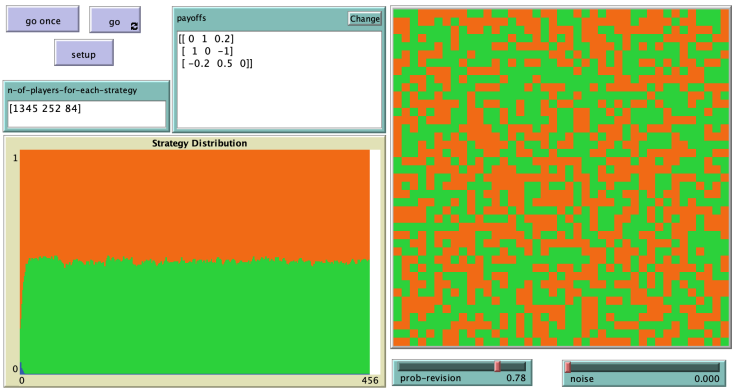

Figure 4: PA benefits from CT, inhibited by CS, in case of higher probability revision: $\alpha < \beta + 1$, $\alpha = 0.5$, $\beta = 0.2$

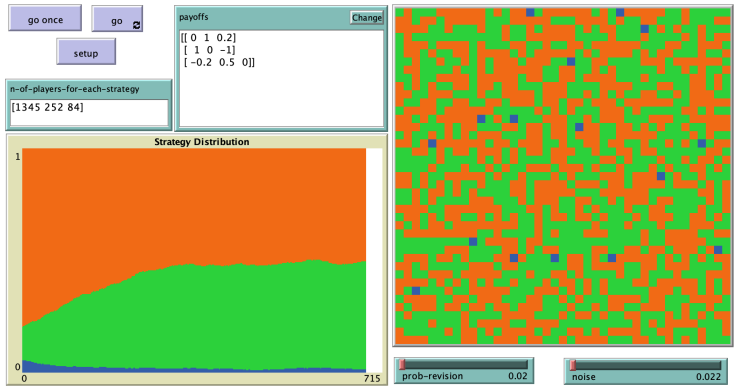

Figure 5: PA benefits from CT, inhibited by CS, with the presence of noise: $\alpha < \beta + 1$, $\alpha = 0.5$, $\beta = 0.2$

3.2 From healthy to dysbiotic state ($\alpha > 0$ and $\beta < 0$)

In this scenario it is considered the case where the PA population benefits from the presence of CT bacteria ($\alpha > 0$) and CS bacteria ($\beta < 0$). This can happen, for example, if PA bacteria require metabolites produced by CT and CS populations for optimal growth. If PA bacteria benefit only moderately from CT bacteria ($\alpha < \beta + 1$), the system can tolerate a certain degree of PA infection. Indeed, if the proportion of PA is low, PA bacteria will eventually be extinguished, which is conducive to a stable community composed of only CS and CT. However, if the proportion of PA is too high, PA bacteria will eventually dominate the community.

If PA bacteria benefit greatly from CT bacteria ($\alpha > \beta + 1$), regardless of the initial population ratio, PA will eventually dominate the community.

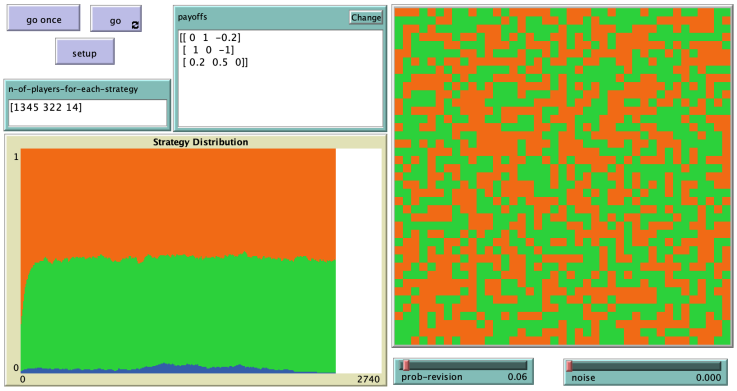

Figure 6: Small PA population benefits moderately from CT bacteria: $\alpha < \beta + 1$, $\alpha = 0.5$, $\beta = -0.2$

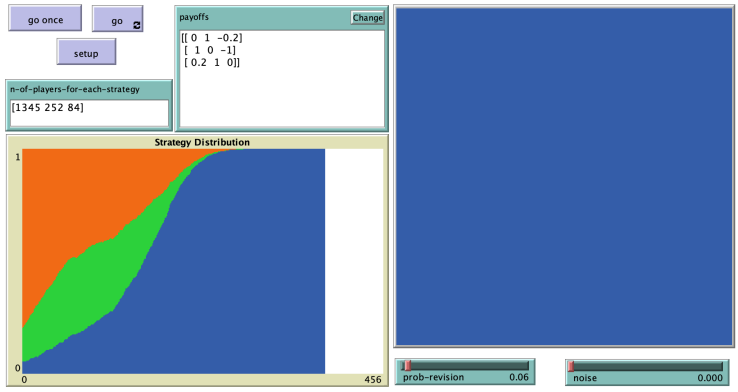

Figure 7: PA population benefits greatly from CT bacteria: $\alpha > \beta + 1$, $\alpha = 1$, $\beta = -0.2$

When PA bacteria benefit moderately from CT bacteria, an higher revision probability value speeds up the attainment of the equilibrium state between CS and CT populations, introducing some fluctuations. In case PA population benefits greatly from CT bacteria, the revision probability is responsible for a faster equilibrium achievement. With the introduction of noise, the expected equilibrium state is no longer guaranteed in both scenarios, ending up with a coexistence of the three population with some fluctuation.

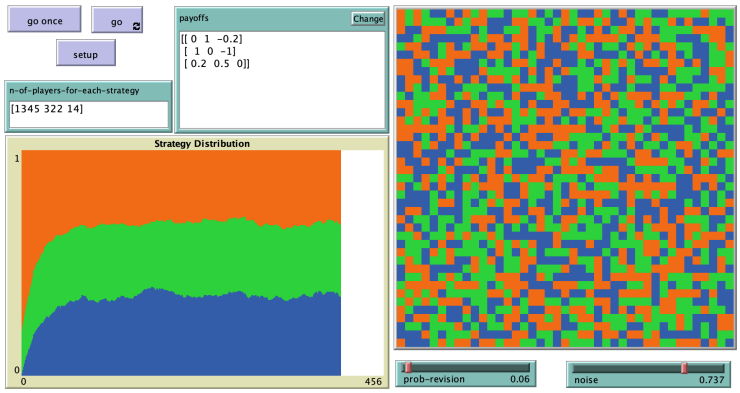

Figure 8: Small PA population benefits moderately from CT bacteria, with the presence of noise: $\alpha > \beta + 1$, $\alpha = 1$, $\beta = -0.2$

3.3 Two stable states: healthy and dysbiotic ($\alpha < 0$ and $\beta < 0$)

The last situation is where the PA population is inhibited by the presence of CT bacteria ($\alpha < 0$) but benefits from the presence of CS bacteria ($\beta < 0$).
If the interaction of the three phenotype groups is weak ($\alpha < \beta+1$ and $\alpha(\beta+1) < 1$), the dynamic behavior is similar to Figure 6, and it can tolerate a certain degree of PA infection. Regardless of the CS or CT score, the low-level PA will be extinguished. High levels of PA will take over the microbial community.

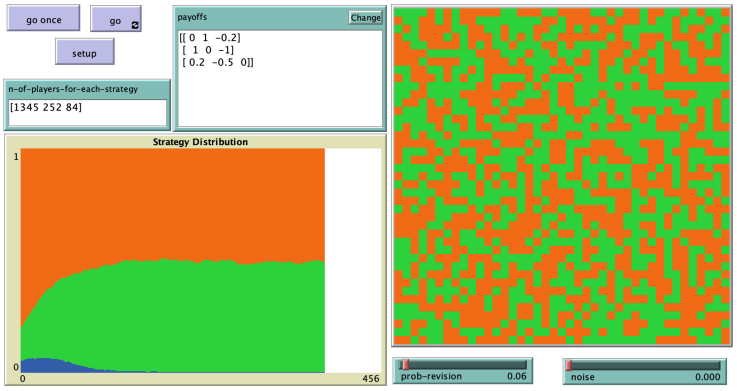

Figure 9: Low interaction of the three phenotype populations, with low level of PA bacteria: $\alpha < \beta + 1$ and $\alpha(\beta + 1) < 1$, $\alpha = -0.5$, $\beta = -0.2$

When CT bacteria moderately inhibits PA bacteria ($\alpha > \beta+1$ and $\alpha(\beta+1) > 1$) and the PA frequency starts from a low level, the state of the system will depend on the CT frequency. If the CT frequency is high enough, the system flows to a healthy state, and the two healthy phenotypes coexist. Otherwise, the system will flow into

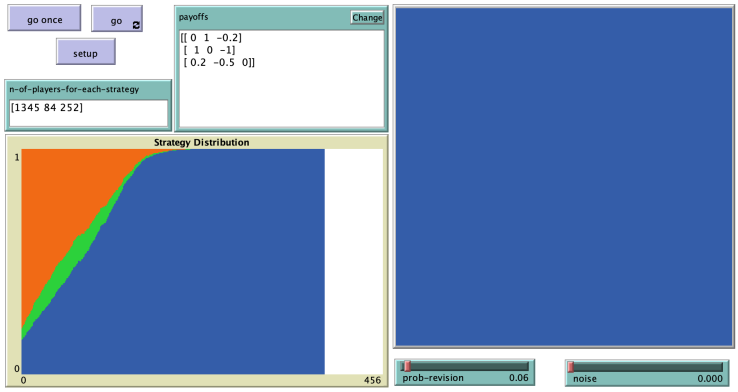

Figure 10: Low interaction of the three phenotype populations, with high level of PA bacteria: $\alpha < \beta + 1$ and $\alpha(\beta + 1) < 1$, $\alpha = -0.5$, $\beta = -0.2$

a state of ecological imbalance, and PA will eventually dominate the population.

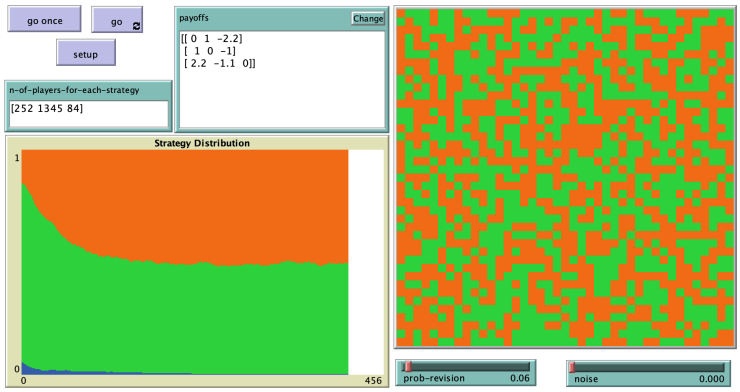

Figure 11: CT bacteria moderately inhibits PA bacteria, with high level of CT population: $\alpha > \beta + 1$ and $\alpha(\beta + 1) > 1$, $\alpha = -1.1$, $\beta = -2.2$

If CT bacteria strongly inhibits PA bacteria ($\alpha < \beta + 1$ and $\alpha(\beta + 1) > 1$), the system has a certain degree of tolerance to PA infection. As long as the CT level is higher than 15% of the overall population, the PA unit will go out. Otherwise, PA cells will dominate the entire system.

In these scenarios, an higher revision probability value speeds up the achievement of the expected equilibrium states, introducing some fluctuations in case of coexistence of CT and CS populations. With the introduction of noise, the expected equilibrium state is no longer guaranteed in every scenario, ending up with a coexistence of the three population with some fluctuations, depending on the noise value.

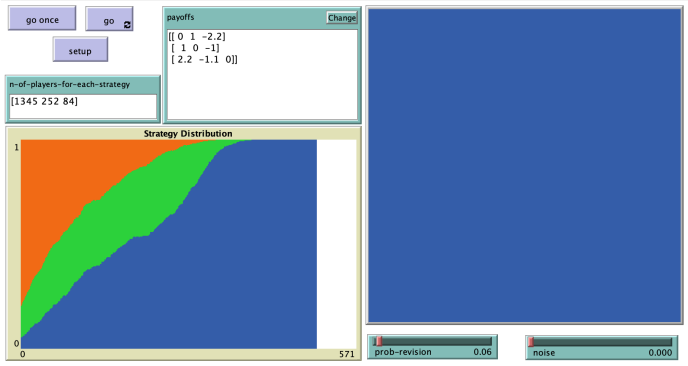

Figure 12: CT bacteria moderately inhibits PA bacteria, with low level of CT population: $\alpha > \beta + 1$ and $\alpha(\beta + 1) > 1$, $\alpha = -1.1$, $\beta = -2.2$

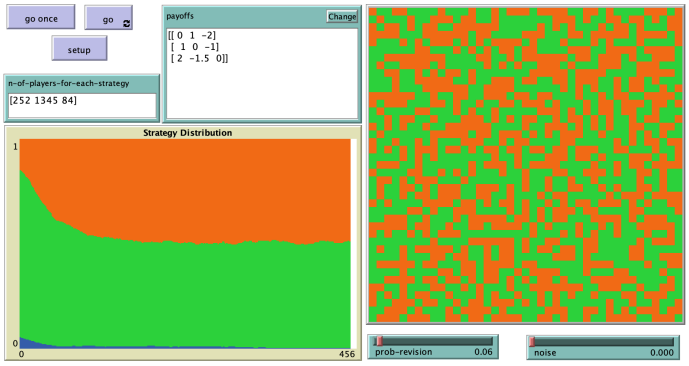

Figure 13: CT bacteria strongly inhibits PA bacteria, with CT level at 15% of the overall population: $\alpha < \beta + 1$ and $\alpha(\beta + 1) > 1$, $\alpha = -1.5$, $\beta = -2$

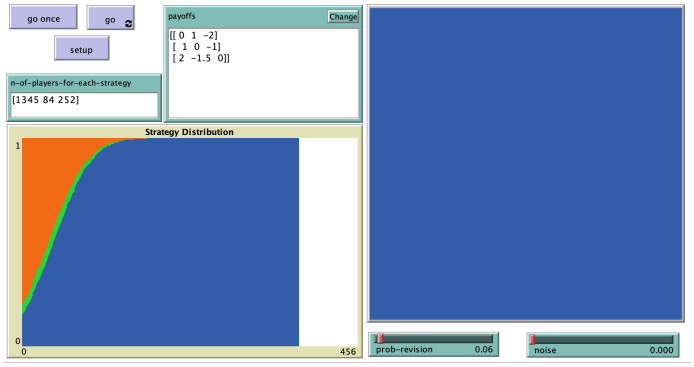

Figure 14: CT bacteria strongly inhibits PA bacteria, with CT level at less than 15% of the overall population: $\alpha < \beta + 1$ and $\alpha(\beta + 1) > 1$, $\alpha = -1.5$, $\beta = -2$

4 Discussion

In these experiments are present various scenarios based on the relative gain or loss of PA phenotypic adaptability represented by the α and β values. The parameters α and β and the composition of the population determine whether the system can recover from a sudden disorder caused by pathogen invasion or antibiotic interference.

If antibiotics are used, the balance of the microbial system will be disturbed. Pathogens such as *Clostridium difficile* are usually suppressed by symbiotic bacteria (especially CS) until antibiotics gradually eradicate most of the antibiotic-sensitive CS bacteria. When CS weakens ($\beta < 0$), two situations may occur: (1) PA strongly uses CT ($\alpha > \beta + 1 > 0$), and then *C. difficile* infection occurs; (2) CT competes with PA ($\alpha < 0$). If CT sufficiently inhibits PA, *C. difficile* infection may not occur. Therefore, the result of the competition can be determined by the value of α.

This model provides some potential therapeutic insights: when the system has only one stable equilibrium, the system will return to a unique "absolutely stable" state after disturbance. When the system has two stable equilibrium states, it is important to consider whether the fixed equilbrium of dysbiosis is globally stable or just metastable, and which clinical interventions will transform the system into a state that will flow to the desired healthy fixed state. This feature is often overlooked in clinical practice, and generally follows the strategy of "providing antibiotics immediately when pathogen infection is detected". A better understanding of population dynamics can help reducing the overuse of antibiotics and the resulting emergence of antibiotic resistance. In the highly simplified scenario described by this model, if it is effectively possible to adjust the system parameters α and β by re-adjusting the host biochemical environment or by taking probiotics, therefore the system can be used to eradicate PA cells and CT cells with the help of CS.

References

[1] David Ross Amy Wu. "Evolutionary Game between Commensal and Pathogenic Microbes in Intestinal Microbiota". In: *Games* (2016). DOI: 10.3390/g7030026.

[2] William H. Sandholm Luis R. Izquierdo Segismundo S. Izquierdo. "Agent-Based Evolutionary Game Dynamics". In: (2019).