# The Phage's Dilemma

This problem set is loosely based on a system described by Turner & Chao (1999), *Nature* 398: 441-443. (You can also find a short summary by Nowak & Sigmund on p. 367 of the same issue.) RNA phage $\phi 6$ (a virus) infects *Pseudomonas phaseolicola* (a bacterial species), replicating intracellularly and then causing the cells to burst, spreading phage to nearby cells.

Phage replication depends upon certain enzymes that are coded by the phage genome. The "cooperator" genotype produces a full complement of enzymes and allows them to diffuse through the bacterial cell, making them available for use by other phage genotypes. The "defector" genotype produces less of this resource, instead hoarding the enzyme produced by nearby cooperators.

The following questions ask you to use the tools of evolutionary game theory to interpret data measuring phage fitness and to make predictions about the fate of phage strains. You do not need to have read the Turner & Chao paper in order to do this problem set. Chapter 4 of the textbook may be of use in answering the questions.



All logs shown are in base $e$. Please show all work and represent your answers in simplest possible form.

**Question #1 (25 points)**

For this question, assume that the population of phage infecting each cell is very large and looks like the phage population overall.

Given two phage strains, S1 and S2, suppose we have the following payoff matrix:

| | S1 | S2 |
|---|---|---|
| S1 | $f+\alpha$ | $f+\beta$ |
| S2 | $f+\gamma$ | $f$ |

The above payoffs represent the fitnesses of coinfecting phage (phage particles that infect the same bacterial cell). For instance, if a single S1 particle infects a cell that is otherwise inhabited entirely by S2 phage, then the expected number of S1 particles released from the cell that will later infect another host cell is $(f+\beta)$.

**1a) (3 points)** What is the fitness of an S1 particle that infects a cell that is host to a population of 75% S1 and 25% S2?

**1b) (3 points)** Let $x$ be the portion of the population that is strain S1. Calculate $\phi$, the average fitness of the population.

**1c) (7 points)** Suppose that we have designed an experiment to measure the immediate growth rate in number of total phage, given an initial frequency $x$ of S1 and $(1-x)$ of S2. The experiment shows that $\phi$ decreases linearly in $x$.

Based on your answer to **(1b)**, what does the result of this experiment tell us about the payoff matrix?

**1d) (7 points)** Suppose that further experiments show that the payoff matrix can be represented in the following "canonical prisoner's dilemma" form, with $b > c > 0$. (We relabel S1 as C for cooperator, S2 as D for defector.) $x$ is the portion of phage that are cooperators.

| | C | D |
|---|---|---|
| C | $f + b - c$ | $f - c$ |
| D | $f + b$ | $f$ |

**The *relative fitness* of C versus D is defined as the time derivative of** $\log\left(\frac{x}{1-x}\right)$**.** Show, using the replicator equation, that the relative fitness of strain C is a constant. Calculate its value.

**1e) (5 points)** If $f = 100$, $b = 10$, and $c = 2$, how long will it take for the portion of C to decrease from $x_0 = 0.9$ to $x_1 = 0.1$?

**Question #2 (40 points)**

In a later paper (*Am. Nat* 161: 497-505), Turner & Chao demonstrate that cooperation in phage can evolve under low multiplicities of infection (MOI, the average number of phage that infect each host cell). This question explores how this result is possible.

For this question, assume that the total number of phage is very large, but the MOI is a finite number, $\bar{k}$. The number of phage coinfecting host cell $h$ is $k_h$. (Treat $k_h$ as the *total number* of phage co-infecting the host cell, including the "focal phage" whose fitness you are asked to calculate below.)

Use the following prisoner's dilemma payoff matrix (with $b > c$), and assume that phage "play against" all coinfecting phage, including themselves. Assume that the fitness of a phage depends on the *fraction* of its coinfectors (including itself) that are cooperators or defectors, not the total number. (The maximum payoff that a phage can get in any particular host is therefore $b$.)

| | C | D |
|---|---|---|
| C | $b - c$ | $-c$ |
| D | $b$ | $0$ |

**2a) (10 points)**

**i)** Suppose that a single cooperator is the only phage to infect a cell. What is its fitness? **(2 points)**

**ii)** Suppose that a single defector is the only phage to infect a cell. What is its fitness? **(2 points)**

**iii)** Suppose that $b = 7$, $c = 4$. If $k_h = 1$ for all host cells $h$, how long will it take for the portion of phage that are cooperators to increase from $x_0 = 0.01$ to $x_1 = 0.99$? **(6 points)**

**2b) (30 points)**

Let $x$ be the portion of phage in the total population that are cooperators. Assume that $x_h$, the portion of phage infecting host $h$ that are cooperators, is determined by randomly sampling $k_h$ phage from the population, each one with a probability $x$ of being a cooperator (*i.e.*, $x_h$ is a binomial random variable).

**i)** Calculate $E_k(\mathrm{C}, x)$, the expected fitness of a cooperator in a host cell infected with $k$ phage, in terms of $x$, $b$, $c$, and $k$. **(7 points)**

**ii)** Calculate $E_k(\mathrm{D}, x)$, the expected fitness of a defector in a host infected by $k$ phage, in terms of $x$, $b$, $c$, and $k$. **(6 points)**

**iii)** Calculate $\Delta = E(\mathrm{C}, x) - E(\mathrm{D}, x)$, the expected fitness difference between a cooperator and a defector, assuming that each infects a random cell (not necessarily the same cell). You may express your answer in terms of $b$, $c$, and any desired statistics of the distribution of $k$. **(15 points)**

**iv)** Based on your answer to part (iii), how large must the ratio $\frac{b}{c}$ be in order for cooperators to increase in frequency in the total population (ignoring stochastic effects)? **(2 points)**

**Question #3 (35 points)**

Now we return to the setting in which MOI is very large ($k \to \infty$), so that defectors always beat cooperators.

Suppose that a third strain ("S") arises, giving us the following payoff matrix:

| | C | D | S |
|---|---|---|---|
| C | $b-c$ | $-c$ | $b$ |
| D | $b$ | $0$ | $0$ |
| S | $0$ | $b$ | $b-c$ |

Use the parameters $b = 3$, $c = 1$.

**(i)** Write down the replicator equations for this game. **(5 points)**

**(ii)** Using Mathematica or your programming language of choice, plot the frequencies of each strategy over time. Use initial conditions $x_C = x_D = x_S = \frac{1}{3}$, and plot for 300 timesteps. (Please give us just one static plot on one set of axes, with three curves corresponding to the three frequencies. Make sure to label each curve. You do not need to submit your Mathematica code.) **(14 points)**

**(iii)** Based on your plot in (ii), sketch (by hand) the dynamics of the system on the population simplex $S_3$. (Make clear the qualitative features of the dynamics, and label all fixed points as stable or unstable. You do not need to formally prove anything here – just rely on your observations of the system.) **(8 points)**

**(iv)** Describe the dynamics that you observe (two sentences only). **(8 points)**

**Extra Credit (8 points)**

Use the system from Question #3, with parameters $b = 2$, $c = 1$. Suppose that we start out with $x_C = 0$, $x_S = x \in (0, 0.5)$, and $x_D = 1 - x$. How long will it take for the frequency of strain S to double?

Take a look at the doubling time that you computed, as a function of $x$. Examine how the function behaves near $x = 0.5$. Why does it behave this way? (One or two sentences)