IMO 1 Exam 3

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While tumor cells disregard homeostatic rules in the tissues they invade, there is often heterogeneity in regards to their genes and their phenotypes and these phenotypes can impact how they interact with each other. Using a game theory approach, model a hypothetical situation where a tumor population lives in a tissue with very few metabolic resources. The population of tumor cells is made of cells that, when having to share resources with other cells, prefers not to compete with them and do not take those resources. On the other hand, other cells can be very aggressive and fight for those resources secreting cytotoxic molecules. The result is that the more aggressive cells might have to incur in a cost when dealing with other aggressive cells as a result of those cytotoxic molecules whereas the less aggressive cell types never have to pay that cost but often do not get the benefit of using the available resources.

1 Question 1

Identify a canonical GT game that could easily describe this situation.

1.1 Solution

Characteristics of the game:

Strategies = phenotypes.
Phenotypes are: Aggressive (A) and Non-aggressive (N).

Payoffs are defined as:
Aggressive cells have lower payoff when interacting with other Aggressive cells than with the non-aggressive ones.

- **a: A vs. A $\rightarrow$ Negative payoff**. Cytotoxic granules kill the target cell. Here I am assuming that the cost for competition is greater than the benefit from obtaining resources during the "fight", because cells are in a tissue with few metabolic resources.
- **b: A vs. N $\rightarrow$ positive payoff**. Benefit, N cells don't compete. A doesn't share resources.

Non-aggressive cells don't compete with aggressive ones but share resources with other non-aggressive cells.

- **c: N vs. A $\rightarrow$ No payoff**. Don't compete with A. Don't get benefit from resources.
- **d: N vs. N $\rightarrow$ Positive payoff**. This payoff is smaller than the one A gets when facing N, because in that case A gets all the resources, here N share resources with other N.

In general, games are defined by inequalities. From the analysis above $b > d > c > a$, this case correspond to the **Hawk–Dove game**. The Hawk-Dove game is described as a competition for a shared resource where the contestants can choose either conciliation (in our case Non-Aggressive phenotype) or conflict (Aggressive phenotype). https://en.wikipedia.org/wiki/Chicken_(game)

2 Question 2

Write down a payoff table describing the game theoretical model.

2.1 Solution

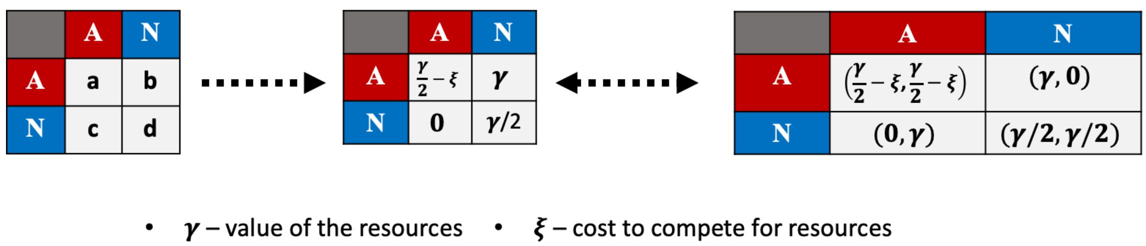

Figure 1: Payoff table of the problem, where γ is the value of the resources and ξ is the cost aggressive cells have to pay to compete for resources with other aggressive cells. As stated before, in question 1, the cost to compete is greater than the value of the available resources, $\xi > \gamma$.

3 Question 3

Write down replicator equations describing the dynamics of this game.

3.1 Solution

The total population of tumor cells is:

$$N = n_1 + n_2 \tag{1}$$

where n_1 and n_2 are the number of aggressive and non-aggressive cells respectively.
Defining the fraction of cells of each phenotype as:

$$X_1 = \frac{n_1}{N} \tag{2}$$

$$X_2 = \frac{n_2}{N} \tag{3}$$

Therefore by dividing by N (1), and using equations (2) and (3):

$$X_1 + X_2 = 1 \tag{4}$$

The replicator equations can be obtained taking the time derivative of equations (1), (2), and (3), together with the fact that the variants n_i $(i = 1, 2)$ grow exponentially with fitness f_i, i.e. $\dot{n}_i = f_i n_i$. Then, the replication equations are:

$$\dot{X}_1 = X_1(f_1 - \langle f \rangle) \tag{5}$$

$$\dot{X}_2 = X_2(f_2 - \langle f \rangle) \tag{6}$$

where $\langle f \rangle$ is the average fitness:

$$\langle f \rangle = X_1 f_1 + X_2 f_2 \tag{7}$$

In game theory, the fitness is related with the payoff matrix components in the following manner:

$$f_1 = aX_1 + bX_2$$

$$f_2 = cX_1 + dX_2$$

Using the payoff matrix in figure 1, the fitness are:

$$f_1 = \left(\frac{\gamma}{2} - \xi\right) X_1 + \gamma X_2$$

$$f_2 = \frac{\gamma}{2} X_2$$

The replicator equations can be further simplified using the equations (7) and (4). Therefore one of the following equations can be used to solve completely the system since $X_1 + X_2 = 1$:

$$\dot{X}_1 = X_1(1 - X_1)(f_1 - f_2) \tag{8}$$

Or

$$\dot{X}_2 = X_2(1 - X_2)(f_2 - f_1) \tag{9}$$

Therefore the replicator equation (8) for this game is:

$$\begin{aligned}\dot{X}_1 &= \left(\frac{\gamma}{2} - \xi\right) X_1^2(1 - X_1) + \frac{\gamma}{2} X_1(1 - X_1)^2 \\ &= X_1(1 - X_1)\left(-\xi X_1 + \frac{\gamma}{2}\right)\end{aligned}$$

Where the relative fitness is:

$$f_1 - f_2 = -\xi X_1 + \frac{\gamma}{2}$$

4 Question 4

Imagine a treatment that reduce the amount of metabolic resources even more. Model that and describe what the impact would be.

4.1 Solution

	A	**N**
A	$\frac{\gamma-\delta}{2} - \xi$	$\gamma - \delta$
N	**0**	$\frac{\gamma - \delta}{2}$

Figure 2: Payoff table of the problem with treatment, where γ is the value of the resources, ξ is the cost aggressive cells have to pay to compete for resources with other aggressive cells, and δ is the amount of resources that the treatment deplete.

In this case, the relative fitness is:

$$f_1 - f_2 = -\xi X_1 + \frac{\gamma - \delta}{2}$$

So, the replicator equation (8) for this game is:

$$\dot{X}_1 = X_1(1 - X_1)\left(-\xi X_1 + \frac{\gamma - \delta}{2}\right)$$

This means that the amount of aggressive cells X_1 will decrease faster over time, meanwhile the amount of non-aggressive cells increase faster over time.

Figure 3 shows the coexistence of both cell types and the effect of treatment, in which the final amount of non-aggressive cells is greater than the case of no treatment.

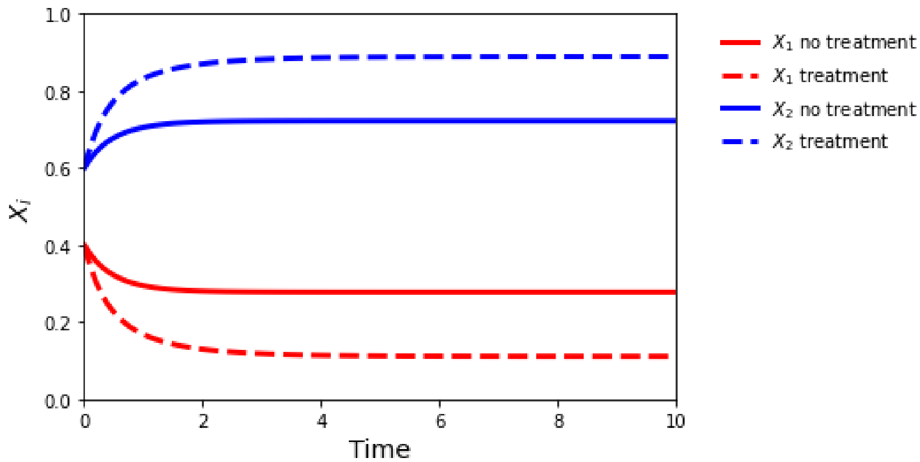

Figure 3: Solutions of replicator equations for this game with $\gamma = 5$, $\xi = 9$, $\delta = 3$, and initial values $X_1 = 0.4$ and $X_2 = 0.6$. Aggressive cell dynamics are in red, and non-aggressive cell dynamics are in blue. The dashed lines correspond to the case of treatment and the solid lines when there is no treatment.