Applying Linear Goods Games to Tumor Models

Suzanna Semaan

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1 Abstract

A hallmark of tumor cells is their ability to rapidly evolve. Maximum tolerated dose (MTD) based treatments apply a constant dosage of chemotherapy drugs and often result in higher rates of drug resistance over time due to tumor cells' rapid evolution. This paper presents a model for tumor growth based on evolutionary game theory (EGT) and examines long-term dynamics of three tumor cell strategies: glycolytic cells, aerobic cells overproducing VEGF, and non-VEGF overproducing aerobic cells. Using the framework of an anti-correlated double goods game, this model from Kaznatcheev et al. introduces new heterogeneous dynamics that have not been observed in previous two-strategy games and emphasizes the importance of treatment timing in this scenario.

2 Background

We think of tumors as a homogenous mass of cancer cells, but in reality these cells form a diverse population. Treatments often depend on the characteristics of cancer cells found in a tissue sample which, due to this diversity, may not be representative of the entire tumor population. This paper seeks to use evolutionary game theory to model differences in tumor cell behavior and answer the question: What are the necessary conditions for each type of tumor cell to be successful over time? In this paper, we will consider glycolytic, VEGF over-producers, and non-VEGF producing aerobic cells and find conditions that lead to each of their evolutionary success.

Glycolysis is a metabolic process that converts glucose into ATP (energy) and pyruvate, acidifying the environment by releasing $H+$ ions as a byproduct. Tumors engage in glycolysis even when oxygen is available despite its lower ATP yield when compared to aerobic respiration, a phenomenon called the Warburg Effect. It has been hypothesized that the evolutionary benefit of the Warburg effect comes from the acidification of the environment resulting from the release of $H+$ ions; acidic environments degrade the cell membranes of healthy cells, allowing cancer cells to reproduce at a higher rate. Therefore glycolytic cells face the cost of a lower ATP yield while benefiting the entire population of tumor cells by acidifying the environment, a classic public goods game. A brief note: glycolysis in the presence of oxygen is called *aerobic glycolysis*, but so as to not confuse glycolytic cells with cells that use aerobic respiration (which we call aerobic cells), we will refer to cells using glycolysis in the presence of oxygen strictly as glycolytic cells.

Vascular endothelial growth factor (VEGF) is a hormone that stimulates the formation of blood vessels. Some cancer cells have been observed to overproduce VEGF, which would increase oxygen availability and benefit any aerobic (i.e. non-glycolytic) cells in the tumor. Indeed, tumors require

a blood supply to grow more than 1-2mm in mass, emphasizing the importance of VEGF overproduction to the tumor's success. Aerobic ells that do not overproduce VEGF benefit from the overproduction of VEGF by its neighbors without paying the cost of expending energy. Due to the cost of overproducing VEGF and the fact that all aerobic cells benefit from vascularization, VEGF is classified as a club good; that is, a good whose benefit is restricted to a subset (a particular club) of the population.

Notably, vascularization and glycolysis are related since "the benefits of oxygen affect the degree of hypoxia and thus the relative cost of glycolysis when compared with aerobic metabolism" (Kaznatcheev 2017). With this in mind, we can continue with a description of the model.

3 Model

Due to the relatedness of glycolysis and vascularization, we can frame the intra-tumor dynamics as a double goods game, where VEGF is a club good and acid from glycolysis is a public good. Since cells need to defect from the public goods game (not producing acid via glycolysis) to benefit from the club good (increased oxygen from VEGF overproduction), these games are anti-correlated. Consider a cell interacting with n neighboring cells; let $A_n(k) = \frac{b_a k}{n}$ be the benefit to each cell from increased acidity if k cells are glycolytic and $V_n(k) = \frac{b_v k}{n}$ be the benefit to aerobic cells if k cells are overproducing VEGF with cost c. The three pure strategies are thus

1. (GLY) Glycolytic cells: Non-aerobic cells interacting with n_G other GLY cells have payoff $A_n(n_G + 1)$, since they have no benefit from VEGF production.
2. (VOP) VEGF over-producers: Aerobic cells that over-produce VEGF, and thus do not produce any acid. These cells pay a cost c and have payoff $A_n(n_G)+V_{n-n_G}(n_V+1)-c$ when interacting with n_G glycolytic cells and n_V other VOP cells.
3. (DEF) Non-VEGF Aerobic cells: Aerobic cells that do not over-produce VEGF, benefitting both from VEGF overproduction and increased acidity due to glycolysis with payoff $A_n(n_G)+V_{n-n_G}(n_V + 1)$.

Note that we do not specifically quantify the cost of glycolysis as the difference in ATP production, as this difference can be factored into the chosen value of b_a.

Using a binomial distribution to represent random assortment of cells, we have that the fitness function for the glycolytic strategy is:

$$w_G = \Sigma_{n_G=0}^{n} \binom{n}{n_G} \underbrace{x_G^{n_G}(1-x_G)^{n-n_G}}_{\text{prob. cell is GLY vs. aerobic}} \cdot \underbrace{A(n_G+1)}_{\text{payoff to GLY cells}} = \underbrace{\langle A(n_G+1)\rangle_{n_G \sim \mathbf{B}_n(x_G)}}_{\text{binomial distribution on } n_G}$$

The braces are simplified notation for summation, and we let $\sim \mathbf{B}_n(x_G)$ be the binomial distribution with probability of success x_G. Using this notation for the other two strategies,

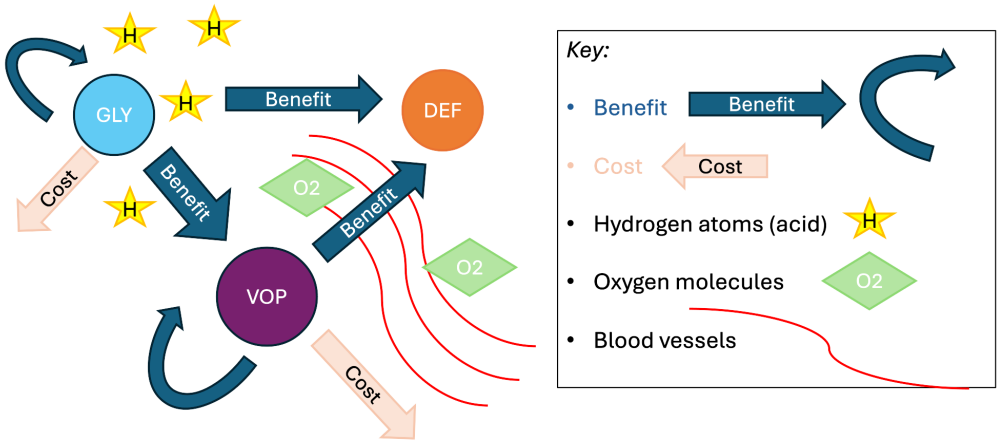

Figure 1: The three strategies, shown with relative benefits and costs.

$$
\begin{aligned}
w_V &= \langle A(n_G+1)\rangle_{n_G\sim\mathbf{B}_n(x_G)} + \langle V_{n-n_G}(n_V+1)\rangle_{(n_G,n_V)\sim\mathbf{M}_n(x_G,x_V)} - c \\
&= \langle \frac{b_a n_G}{n}\rangle_{n_G\sim\mathbf{B}_n(x_G)} + \langle \frac{b_v(n_V+1)}{n-n_G+1}\rangle_{(n_G,n_V)\sim\mathbf{M}_n(x_G,x_V)} - c \\
w_D &= \langle A(n_G+1)\rangle_{n_G\sim\mathbf{B}_n(x_G)} + \langle V_{n-n_G}(n_V+1)\rangle_{(n_G,n_V)\sim\mathbf{M}_n(x_G,x_V)} \\
&= \langle \frac{b_a n_G}{n}\rangle_{n_G\sim\mathbf{B}_n(x_G)} + \langle \frac{b_v(n_V+1)}{n-n_G+1}\rangle_{(n_G,n_V)\sim\mathbf{M}_n(x_G,x_V)}
\end{aligned}
$$

Note that $\sim \mathbf{M}_n(x_G, x_V)$ is the multinomial distribution where x_G is the probability of the first outcome and x_V is the probability of the second outcome.

3.1 Replicator Dynamics

In evolutionary game theory, the replicator dynamics for a population with frequency x are given by $\dot{x} = x(1-x)(f(x)-\phi)$, where $f(x)$ is the fitness of x and ϕ is the average fitness.

For our system, the average fitness between GLY, VOP, and DEF cells is $\langle w\rangle = x_G w_G + x_V w_V + x_D w_D$, yielding the following replicator dynamics:

$$\dot{x}_G = x_G(w_G - \langle w\rangle) \tag{1}$$
$$\dot{x}_V = x_V(w_V - \langle w\rangle) \tag{2}$$
$$\dot{x}_D = x_D(w_D - \langle w\rangle) \tag{3}$$

We factor the dynamics in terms of proportions of glycolytic cells $p = x_G$ and VEGF over-producing aerobic cells $q = \frac{x_V}{x_V + x_D}$ to simplify the system.

$$\dot{p} = \underbrace{p(1-p)}_{\text{prop. of GLY cells vs aerobic}} \cdot \underbrace{(w_G}_{\text{fitness of GLY}} - \underbrace{(qw_V + (1-q)w_D))}_{\text{fitness of aerobic cells}} \tag{4}$$

$$\dot{q} = \underbrace{q(1-q)}_{\text{prop. of VOP vs DEF}} \cdot \underbrace{(w_V - w_D)}_{\text{fitness of VOP vs DEF}} \tag{5}$$

Kaznatcheev supplies a proof that equations (1)-(3) are equivalent to the system in equations (5)-(6). He factors the three-strategy system using a set of compound strategies: $\{(Y_j, W_j, c_j)\}_{j=1}^m$ where c_j is a component function with $\Sigma_{i=1}^n c_j(i) = 1$, Y_j is a weight given by $Y_j = \Sigma_i^n c_j(i)x_i$, y_{ij} is a profile defined as $y_{ij} = \frac{c_j(i)x_i}{Y_j}$, and W_j is a fitness $W_j = \Sigma_{i=1}^n y_{ij}w_i$. He proves that if a set of compound strategies $\{(Y_j, W_j, c_j)\}_{j=1}^m$ factors a set of strategies $\{(x_i, w_i)\}_{i=1}^n$, then the system $\dot{x_i} = x_i(w_i - \langle w \rangle)$ and the system $\dot{Y_j} = Y_j(W_j - \langle W \rangle), \dot{y_{ij}} = y_{ij}(w_i - \langle w \rangle_j)$ describe the same dynamics. This applies specifically to our system of tumor strategies GLY, VOP, and DEF, given in equations (1) - (5). With these systems equivalence, we proceed by finding the replicator dynamics for equations (4) and (5).

4 Results

We continue by solving for equilibrium frequencies by finding where the replicator dynamics equal zero. From equations (4) and (5), we have non-trivial solutions when

$$\begin{aligned} w_G - (qw_V + (1-q)w_D) &= 0 \qquad\qquad (w_V - w_D) = 0 \\ w_G - qw_V - w_D - qw_D &= 0 \\ w_G - w_D - q(w_V - w_D) &= 0 \end{aligned}$$

Therefore, we must calculate $w_G - w_D$ and $w_G - w_D$ to find the equilibrium frequencies. We begin by solving for $w_V - w_D$. We write the payoff function with the binomial distribution.

$$\begin{aligned} w_V - w_D &= \Sigma_{n_G+n_V+n_D} \binom{n}{n_G, n_V, n_D} x_G^{n_G} x_V^{n_V} x_D^{n_D} \underbrace{(A_n(n_G) + V_{n-n_G}(n_V+1) - c)}_{\text{VOP fitness}} - \underbrace{[A_n(n_G) + V_{n-n_G}(n_V)])}_{\text{DEF fitness}} \\ &= \Sigma_{n_G+n_V+n_D} \binom{n}{n_G, n_V, n_D} x_G^{n_G} x_V^{n_V} x_D^{n_D} (V_{n-n_G} - c) \end{aligned}$$

Notice that the term $A_n(n_G)$ cancels out since both VOP and DEF cells receive the same benefit from acidity, and that the difference in benefit from increased vascularization is equal to $V_{n-n_G}(n_V + 1) - V_{n-n_G}(n_V) = V_{n-n_G} = \frac{b_V}{n-n_G+1}$. Writing this in terms of glycolytic and aerobic cells p and $(1-p)$ will help us, since we are only considering the payoffs of VOP and DEF cells in the difference $w_V - w_D$. This simplifies our system to

$$\Sigma_{n-n_G=0}^n \binom{n+1}{n-n_G+1} \underbrace{p^{n_G}}_{\text{Prob. cell is GLY}} \cdot \underbrace{(1-p)^{n-n_G}}_{\text{Prob. cell is aerobic}} \cdot \underbrace{\frac{b_v}{n-n_G+1} - c}_{\text{fitness of aerobic cells}}$$

Again, we factor out the constant $\frac{b_v}{n-n_G+1}$ and subtract the constant c.

$$\frac{b_v}{n-n_G+1}(\Sigma_{n-n_G=0}^{n}\binom{n+1}{n-n_G+1}p^{n_G}(1-p)^{n-n_G})-c$$

We are only interested in the case where we choose n_V+n_D aerobic cells from the population of size $n+1$: since this is the exact number of aerobic cells, there is only one way to do so, namely, when $n_G=0$. Hence, $\binom{n+1}{n-n_G+1}=1$, $p^{n_G}=p^0=1$. We are left with

$$\frac{b_v}{n-n_G+1}(\Sigma_{n-n_G=0}^{n}(1-p)^{n-n_G})-c$$

Since this scenario has the entire population using aerobic respiration, the probability of encountering an aerobic cell is $(1-p^{n+1})$ (because the probability of encountering a glycolytic cell in a population of only GLY strategy is p^{n+1}). Thus we are rewarded with

$$w_V-w_D=\frac{b_v}{n-n_G+1}(1-p^{n+1})-c$$

We continue with w_G-w_D below; we use an alternate form of the fitness equation with the binomial distribution, given by

$$\begin{aligned}w_G-w_D&=\Sigma_{n_G+n_V+n_D}\binom{n}{n_G,n_V,n_D}\underbrace{x_G^{n_G}x_V^{n_V}x_D^{n_D}}_{\text{Prob. of strat. to power of pop. size}}\underbrace{(A_n(n_G+1)}_{\text{GLY fitness}}-\underbrace{[A_n(n_G)+V_{n-n_G}(n_V)])}_{\text{DEF fitness}}\\&=\Sigma_{n_G+n_V+n_D}\binom{n}{n_G,n_V,n_D}x_G^{n_G}x_V^{n_V}x_D^{n_D}[\frac{b_a(n_G+1)}{n+1}-\frac{b_a(n_G)}{n+1}-\frac{b_v(n_V)}{n-n_G+1}]\\&=\Sigma_{n_G+n_V+n_D}\binom{n}{n_G,n_V,n_D}x_G^{n_G}x_V^{n_V}x_D^{n_D}[\frac{b_a}{n+1}-\frac{b_v(n_V)}{n-n_G+1}]\end{aligned}$$

Note that we consider a population of size $n+1$ (since any focal cell is interacting with n_G other GLY cells, n_D other DEF cells, and n_V other VOP cells with $n_G+n_V+n_D=n$), so we divide benefits of increased acidity among $n+1$ cells and of increased oxygen availability among $n-n_G+1=n_V+n_D+1$ cells. Next, we factor out the acidity benefit to glycolytic cells; as it has no dependence on n_G, n_V, or n_D, we may treat this term as a constant: this is our reduced w_G. To find w_G-w_D, we subtract the sum over the aerobic cells, reducing the system in terms of p and q. Note that we break up the sum from $n_V=0$ to n_V+n_D and from n_V+n_D to n, in order to separate the aerobic and glycolytic cases.

$$\begin{aligned}w_G-w_D=&\underbrace{\frac{b_a}{n+1}}_{\text{acidity benefit per cell}}-\Sigma_{n-n_G=0}^{n}\underbrace{\binom{n}{n-n_G}}_{\text{choose }n_G\text{ cells}}\underbrace{p^{n_G}(1-p)^{n-n_G}}_{\text{prob. cell is GLY vs aerobic}}\cdot\\&[\Sigma_{n_V=0}^{n_V+n_D}\underbrace{\binom{n_V+n_D}{n_V}}_{\text{choose }n_V\text{ aerobic cells}}\underbrace{q^{n_V}(1-q)^{n_D}}_{\text{prob. cells is VOP vs DEF}}\cdot\underbrace{\frac{b_v(n_V)}{n_V+n_D+1}}_{\text{oxygen benefit}}]\end{aligned}$$

The fitness of glycolytic cells is now just the binomial distribution on n_G cells. Similarly to the glycolytic case, we sum over the number of aerobic cells, $n - n_G = n_D + n_V$; in particular, only VOP cells contribute to the benefit from increased vascularization b_v. We only consider the case where we choose n_V VOP cells out of $n_V + n_D$ aerobic cells, so the sum reduces to $b_v q(1 - \frac{1}{n_V + n_D + 1})$. Recall that $n_V + n_D = n - n_G$. Consequently,

$$\frac{b_a}{n+1} - \Sigma_{n-n_G=0}^{n} \binom{n}{n-n_G} p^{n_G}(1-p)^{n-n_G} \cdot b_v q(1 - \frac{1}{n-n_G+1})$$

Finally, factoring out $b_v q(1 - \frac{1}{n-n_G+1})$, we have only that $\frac{b_a}{n+1} - \Sigma_{n-n_G=0}^{n} \binom{n}{n-n_G} p^{n_G}(1-p)^{n-n_G}$. We narrow our focus to the case where we pick only aerobic cells out of the population, as only these cells receive a benefit from oxygen; since the entire population we consider is aerobic, it follows that $n_G = 0$ so $p^{n_G}(1-p)^{n-n_G} = 1 \cdot (1 - p^{n+1})$. Since there is only one way to choose all aerobic cells, $\binom{n}{n-n_G} = 1$, and therefore the entire expression reduces to $(1 - p^{n+1})$. This yields our final expression for $w_G - w_D$:

$$w_G - w_D = \frac{b_a}{n+1} - b_v q(1 - \frac{1}{n - n_G + 1})(1 - p^{n+1})$$

Recall that an equilibrium frequncy is achieved when $w_V - w_D = 0$ and when $w_G - w_D - q(w_V - w_D) = 0$. Substituting the above expressions yields

$$w_G - w_D - q(w_V - w_D) = \frac{b_a}{n+1} - b_v q(1 - \frac{1}{n - n_G + 1})(1 - p^{n+1}) - q(\frac{b_v}{n - n_G + 1}(1 - p^{n+1}) - c) = 0$$

$$w_V - w_D = \frac{b_v}{n - n_G + 1}(1 - p^{n+1}) - c = 0$$

We may algebraically simply the first equation as the term $\frac{b_v q}{n-n_G+1}(1 - p^{n+1})$ cancels.

$$\frac{b_a}{n+1} - q b_v - q c = 0$$

$$\frac{b_a}{n+1} - q(b_v - c) = 0$$

This yields an equilibrium frequency of $\frac{b_a}{n+1} = q(b_v - c)$. We proceed with an analysis of long-term behavior:

(1) If $b_a > (b_v - c)(n+1)$, then $\frac{b_a}{n+1} > b_v - c$. Recalling that q is the proportion of VOP cells and consequently that $q \in [0, 1]$, this means that $\frac{b_a}{n+1} > b_v - c \geq q(b_v - c)$, so $\frac{b_a}{n+1} - b_v - c > 0$. In this scenario we have $\dot{p} > 0$, so the population will tend toward the fully glycolytic equilibrium.

(2) If $b_a < (b_v - c)(n+1)$, the population dynamics depend on q. In the case where $b_v > c(n+1)$ (i.e. when $w_V - w_D = \frac{b_v}{n+1} - c > 0$), it follows that $\dot{q} > 0$. This makes $\frac{b_a}{n+1} - q(b_v - c) = \dot{p} < 0$, since q is positive and $b_a < (b_v - c)(n+1)$, so the population will tend towards a fully VEGF-overproducing equilibrium.

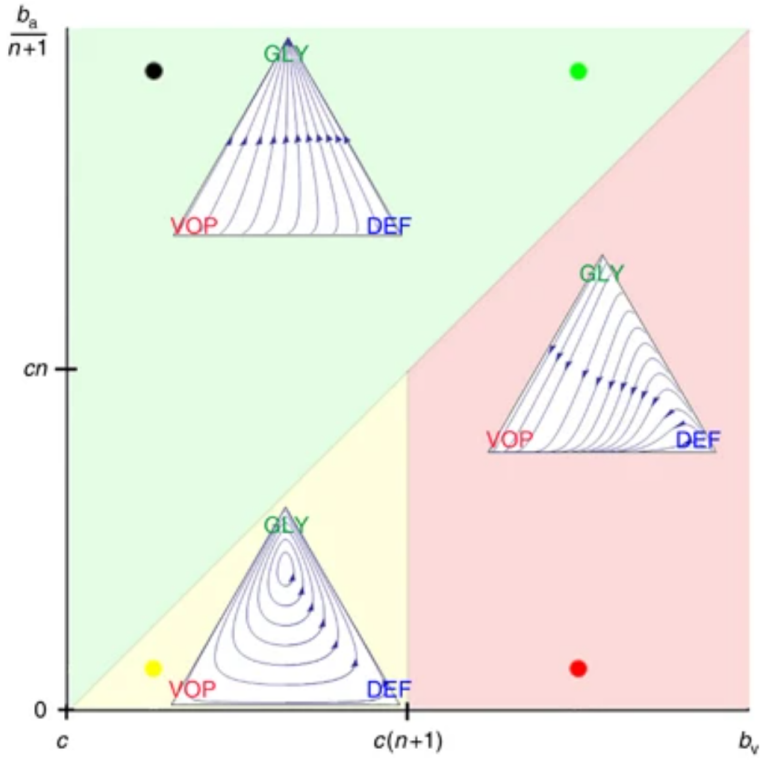

Figure 2: Figure from Kaznatcheev (2017): The values for b_v are varied on the horizontal (x-axis) while the values for $\frac{b_a}{n+1}$ are varied on the vertical (y-axis). The green area corresponds to the fully glycolytic strategy, the red area to the fully VOP strategy, and the yellow area to the cyclic dynamics. Each simplex shows an example of the dynamics in that region. The particular parameters used in each region are: (1) $ba = 37.5, bv = 2, c = 1, n = 4$ for green; (2) $ba = 2.5, bv = 7, c = 1, n = 4$ for red; and (3) $ba = 2.5, bv = 2, c = 1, n = 4$ for yellow.

(3) If $b_a < (b_v - c)(n+1)$ and $b_v < c(n+1)$ and $w_V - w_D = \frac{b_v}{n+1} - c < 0$, the system will have cyclic dynamics, with all three strategies present at all points in time. We show this behavior in the following ternary diagrams; Kaznatcheev [1] shows the system is Hamiltonian and establishes closed orbits around fixed points where the replicator dynamics equal zero.

5 Discussion

From the previous section, we have three distinct possible dynamics:

Fully glycolytic strategy when $\underbrace{\frac{b_a}{n+1}}_{\text{acid benefit per cell}} > \underbrace{b_v - c}_{\text{total benefit to aerobic cells}}$.

Fully VOP equilibrium when $\{ \underbrace{cn}_{\text{total cost of VEGF overproduction}}, \underbrace{\frac{b_a}{n+1}}_{\text{acid benefit per cell}} \} < \underbrace{b_v - c}_{\text{total benefit to aerobic cells}}$.

Cyclic dynamics with all three populations when $\underbrace{\frac{b_a}{n+1}}_{\text{acid benefit per cell}} < \underbrace{b_v - c}_{\text{aerobic cell benefit}} < \underbrace{cn}_{\text{cost of VEGF production}}$.

5.1 Fully Glycolytic Strategy

The fully glycolytic strategy dominates when the acid benefit per cell is higher than the total benefit to aerobic cells. Since the population will tend towards a fully GLY strategy, the timing of the treatment is less important in this case. Kaznatcheev mentions that a strategy targeting GLY cells to create a two-strategy population would be an effective intervention; if glycolysis inhibitors were administered for long enough to drive the GLY strategy to extinction, the two remaining strategies (VOP and DEF) may be easier to treat. Additionally, traditional game theory and [4] show that in a two-player game of VOP vs DEF, the system tends toward the DEF strategy. Glycolysis inhibitors are already being used in cancer treatments [3], with more being sythesized and approved for pre-clinical trials each year, making this a viable treatment option for further trials.

Observe in the case studies (shown in Figure 2) we have this scenario when $b_a = 37.5$ and $b_v = 2$, a significant difference when compared to other scenarios, for example, to fully VOP dynamics when $b_a = 2.5$ and $b_v = 7$. Additionally, we have n, the number of cells, being set to $n = 4$ for computational ease, though this is quite unrealistic. A larger value of n would make the term $\frac{b_a}{n+1}$ smaller, further decreasing the fitness of a fully glycolytic strategy unless b_a is very large, or b_v is very small.

According to Carmeliat (2005), "Tumor vasculature formed under the influence of VEGF is structurally and functionally abnormal. Blood vessels are irregularly shaped, tortuous, have dead ends and are not organized into venules, arterioles and capillaries. They are also leaky and hemorrhagic, which leads to high interstitial pressure. These characteristics mean that tumor blood flow is suboptimal, resulting in hypoxia and further VEGF production" [2]. While VEGF is essential in early stage tumor growth, the fully glycolytic scenario could be realized if, for example, the vasculature from VEGF was badly formed and unable to increase oxygen flow to the tumor, reducing b_v. Additionally, larger tumors have been observed to have hypoxic environments, further decreasing b_v and increasing b_a [3]. It might also be the case that b_a is incredibly high: the rapid growth of cancer cells is theorized to effect oncogenic signals and damage mitochondrial DNA, which would inhibit a cell's ability to use aerobic respiration [3].

5.2 Fully Angiogenic Strategy

This strategy is realized when the total cost of VEGF overproduction and the acid benefit per cell are less than the total benefit to aerobic cells.

Intuitively, this makes sense: if the cost of VEGF overproduction is less than its benefit, then VEGF overproduction is beneficial to tumor cells. To illustrate this, consider another strategy where glycolytic cells overproduce VEGF. The cost of overproduction is the same as the cells in the VOP strategy, but the benefit is lower since glycolytic cells are unable to benefit from the increased oxygen availability. Therefore, glycolytic cells that overproduce VEGF will not be selected for over time;

Kaznatcheev proves this population will be driven to extinction.

Returning to the fully angiogenic strategy, it is also required that the acid benefit per cell is less than the net benefit to aerobic cells for this strategy to dominate. In this case, a treatment that increases the cost of VEGF production, or inhibits angiogenesis altogether, would be effective in driving the tumor cells toward a DEF strategy. Such immunotherapy drugs, like lenalidomide, can block the VEGF receptor and prevent the angiogenesis signaling pathway, stopping the growth of new blood vessels.

5.3 Heterogeneous Strategy

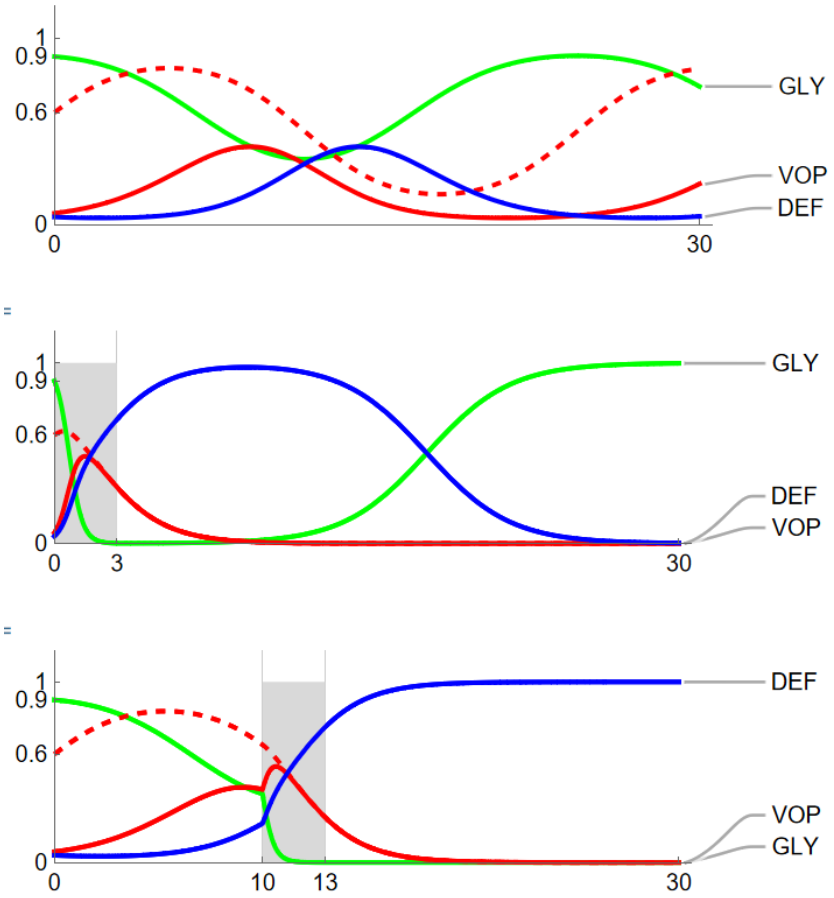

Figure 3: From Kaznatcheev: Tumor dynamics with initial conditions $p(0) = 0.9$, $q(0) = 0.6$ and microenvironment $b_a = 2.5$, $b_v = 2, c = 1$, and $n = 4$. The top plot shows the dynamics in this scenario with no treatment. The center plot shows the dynamics with treatment applied for three time steps beginning at $t = 0$, and the bottom plot shows treatment beginning at $t = 10$, the low point of the GLY cycle. x-axis is time (may be scaled to any units) while the y-axis is the proportion of each cell strategy.

The most interesting dynamics occur in the yellow region in Figure 2, where all three strategies are present in the population. Due to the cyclic dynamics, the timing of treatment becomes important to long term behavior. Kaznatcheev models different treatment regimes with tumor microenvironment $b_a = 2.5$, $b_v = 2, c = 1$, and $n = 4$ and initial conditions $p(0) = 0.9$, $q(0) = 0.6$. With no treatment, the population will have cyclic dynamics. Kaznatcheev considers reducing the GLY cell population using lonidamine, a glycolysis inhibitor, applied at $t = 0$ and $t = 10$. When treatment is applied at $t = 0$, the population of GLY cells is at its highest; although treatment is administered until cell levels are undetectable (with proportion below 10^{-4}), the GLY population completely dominates by $t = 20$, resulting in the opposite effect as desired and a more difficult to treat tumor. In contrast, when treatment is applied at the low phase of the GLY cycle ($t = 10$) for three time steps, the GLY population is driven fully to extinction, leaving only VOP and DEF cells; naturally, the DEF cells dominate, as desired. See Figure 3.

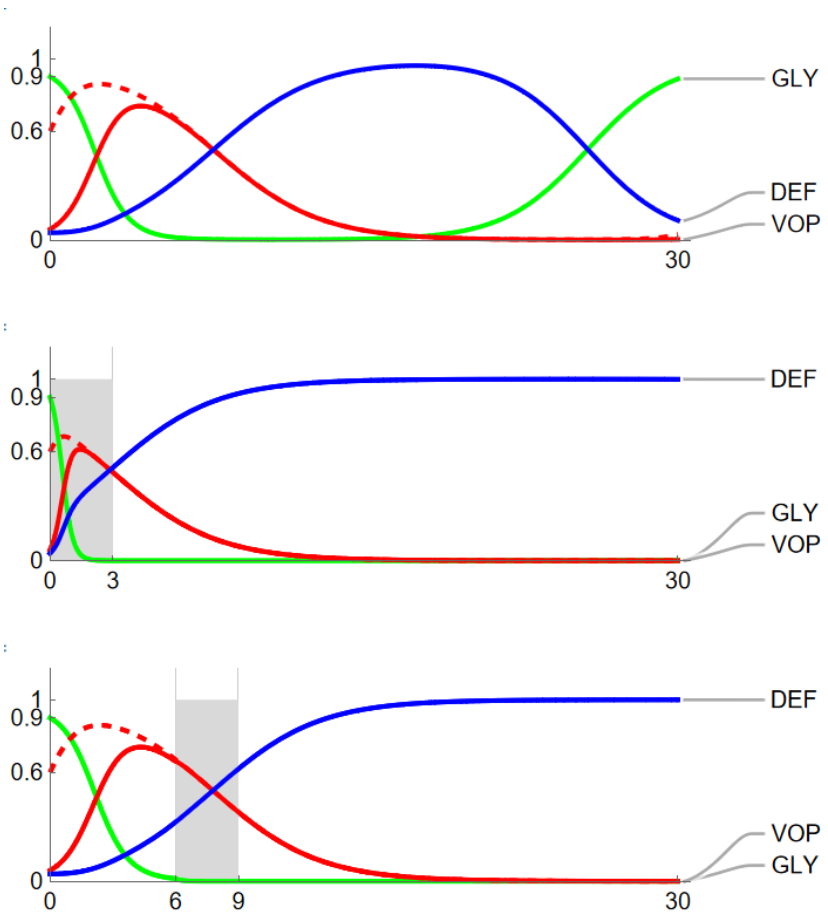

Figure 4: Tumor dynamics with same initial conditions and microenvironment as Figure 3, except with $b_v = 3$ so that $b_v > b_a$. Top plot shows dynamics without any intervention, while middle and bottom plots show anti-glycolytic treatment applied at $t = 0$ and $t = 6$, respectively.

We model a similar scenario, with a tumor microenvironment slightly more friendly to VOP cells with $b_v = 3$ to better understand how treatment regimens change in different tumor microenvironments. In particular, while the previous case study considered $b_a > b_v$, we are considering the case where $b_v > b_a$. As Kaznatcheev says, personalized tumor treatment typically targets the largest subpopulation, which in this case cycles between GLY and DEF. Modeling the same lonidamine treatment with therapy strength 3, we observe similar dynamics: applying treatment both when GLY is decreasing (at $t = 0$) and when GLY is at its lowest (at $t = 6$) results in the elimination of GLY cells and the domination of the DEF strategy. The only treatment regimen that leads to an increase in the GLY population is beginning treatment at peak times in the GLY cycle, like at $t = 25$; in this case, treatment must be administered for longer, 5 time steps, for GLY to be driven fully to extinction. See Figure 5.

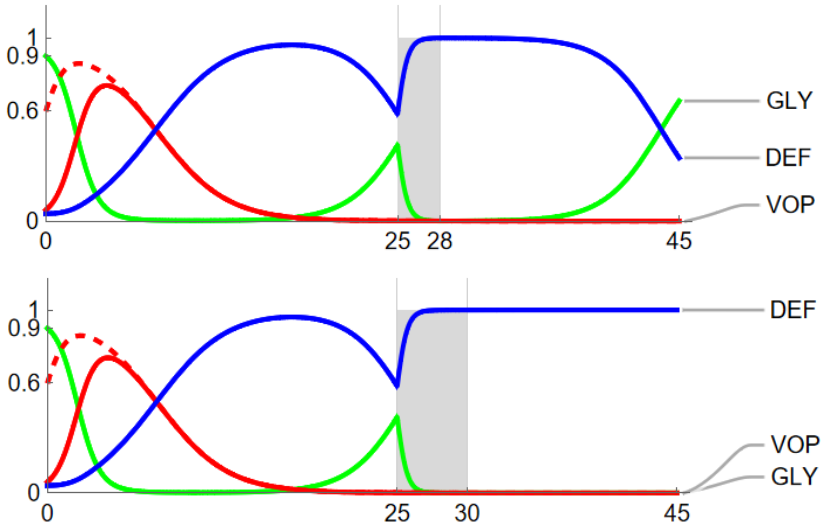

Figure 5: Tumor dynamics with the same microenvironment and initial conditions at Figure 4 when treatment is delayed until $t = 25$. In the top plot, we see a re-emergence of the GLY population, whereas in the bottom plot, where treatment is administered for 5 time units instead of 3, the GLY population is driven to extinction. Note the increased time horizon $t_{max} = 45$ due to the later timing of treatment administration.

Our scenario seems to verify the fact that VOP cells will quickly tend toward extinction when competing with DEF cells and emphasize the importance of glycolysis inhibitors in treating various tumor states. However, I found it interesting that by increasing b_v, it became easier to eliminate GLY and VOP cells. This is likely because the increased payoff of VOP cells lead to an increase in their fitness against the GLY strategy, driving GLY cells to extinction at a faster rate. The timing of glycolysis inhibitors then became less important, allowing for more flexibility; in clinical settings where knowing the exact proportions of each strategy is difficult, the higher chances of successful treatment can be beneficial to the patient. The cost of VEGF overproduction remaining the same between the scenarios in Figure 3 and Figure 4 meant that the DEF cells still have a greater fitness than the VOP cells and lead to their extinction as well. Such a scenario illuminates the possibility of a combined treatment; for example, increasing oxygen availability in the blood while administering

an anti-glycolytic medication. Notably, any such treatment must specifically increase the *benefit* of increased vascularization and not the cost of producing VEGF, otherwise posing the risk of VOP cells dominating over DEF cells.

6 Next Steps

The paired linear-goods game reveals interesting dynamics between GLY and VOP cells that have the ability to better inform treatment regimens depending both on the composition and microenvironment of the tumor. While precise measurement of these parameters is difficult in a clinical setting, this work reveals patterns in qualitative behavior that can be used as a framework for future treatment strategies. As Kaznatcheev says, expanding the evolutionary game theory model itself will depend on clinical trials to determine what precisely is needed. However, other mathematicians have expanded his model using other branches of mathematics:

(1) Gluzman et. al [5] adapted Kaznatcheev's initial EGT model by introducing an objective functional to minimize treatment cost and total time that treatment is applied. They found that the solution was "bang-bang," meaning that the optimal treatment switches between maximum (MTD) and no treatment, with hybrid strategies sometimes resulting in better outcomes than total MTD-based strategies. This extends Kaznatcheev's model of tumor dynamics into formally optimized treatment regimens, a powerful next step for the transition into adaptive therapy approaches over MTD-based approaches.

(2) Wang, Scott, and Vladmirsky [6] use stochastic optimal control to introduce randomness of cancer evolution and maximize the probability of the patient's eventual remission without exceeding a specific drug dosage over time. This stochastic process assumes that the evolution of each strategy of cancer cells is random, with probabilities corresponding to each fitness function.

(3) Sayedi et al. [7] have tested adaptive therapy techniques in mice with endocrine-resistant breast cancer, and found a significant increase in lifespan by altering moderate dosages of two drugs (capecitabine and gemcitabine) compared to high dosages of both drugs simultaneously.

Modeling cancer growth through the lens of evolution allows physicians to administer treatments that consider the rapid evolution that characterizes cancer cells. A desirable next step is to move towards partially-observable states; while it is difficult to know the exact proportions of GLY, VOP, and DEF cells in a tumor, using state variables that can be well-estimated from observation of a related phenomenon (ex. an increased amount of a hormone in the bloodstream) would greatly improve the accuracy of this model. While Kaznatcheev's original model does not factor in acquired drug resistance, future models may do so to understand long-term treatment solutions.

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