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Cheater-altruist synergy in public goods games

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ABSTRACT

Much research has focused on the deleterious effects of free-riding in public goods games, and a variety of mechanisms that suppress cheating behavior. Here we argue that under certain conditions cheating can be beneficial to the population. In a public goods game, cheaters do not pay for the cost of the public goods, yet they receive the benefit. Although this free-riding harms the entire population in the long run, the success of cheaters may aid the population when there is a common enemy that antagonizes both cooperators and cheaters. Here we study models of the interactions between tumor cells, which play a public goods game, and the immune system. We investigate three population dynamics models of cancer growth combined with a model of effector cell dynamics. We show that under a public good with a limiting benefit, the presence of cheaters aids the tumor in overcoming immune system suppression, and explore the parameter space wherein it occurs. The mechanism of this phenomenon is that a polymorphism of cheaters and altruists optimizes the average growth rate of the tumor, which is what determines whether or not the immune response is overcome. Our results give support for a possible synergy between cooperators and cheaters in ecological public goods games.

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1. Introduction

The behavior of social organisms and the influence of cooperation on pathology is an active field of evolutionary biology (Griffin et al., 2004; West et al., 2006; Wingreen and Levin, 2006). Altruism and conflict has been explored within the domains of cancer (Axelrod et al., 2006; Cleary et al., 2014; Merlo et al., 2006; Tomlinson and Bodmer, 1997) and biofilm (Boyle et al., 2015; Buckling et al., 2007; Xavier and Foster, 2007) evolution. Evolution of social behavior is often studied within the context of the tragedy of the commons through a multi-player Prisoner's Dilemma game (Rapoport and Chammah, 1965). Public goods benefit every agent, but more so the free-riders/cheaters that use them without contributing. Assuming there is some cost to the production of the public good by altruists, cheaters will out-compete altruists unless further mechanisms are in place. Since the evolutionary optimal (cooperative) behavior is not a Nash equilibrium, an outstanding question in evolutionary biology is how cooperation can originate and stably persist. Within the literature, there is an abundance of means to do so, such as kin-selection (Queller, 1992), repeated games (Axelrod and Hamilton, 1981), reciprocal altruism (Ale et al., 2013), spatial factors (Nowak and May, 1992) or selection mechanisms (Morsky and Bauch, 2016). However, there has been no research exploring the hypothesis that "cheating" might have indirect benefits to the population as a whole.

Here we use computer simulations to put forth the hypothesis that under certain conditions, cheating behavior can be beneficial. The idea is that a reservoir of altruists can fuel a rapid increase in the population of cheaters. In an infection or tumor, strength in numbers matter. A larger number of pathogens, even if some are cheaters that might eventually jeopardize the fitness of the population, can flip the course of a battle.

We explore this idea within a model of cancer cells cooperating through a public good, and find that through the mechanism of cheating in a public goods game, the population as a whole can better overcome the immune system's response, and thereby grow into a large malignant tumor instead of being kept under control.

Cooperation under the framework of game theory is relevant to cancer dynamics, where cancer cells may cooperate and compete with one another for nutrients and space. In our model, the public good is equally divided amongst all the population and provides a growth benefit to the cells. There is a metabolic cost (and therefore reduced growth rate) applied to the altruists, who are thus less fit than cheaters. Extending this fact evolutionarily, we would expect extinction of the altruistic phenotype. An example of such a public good in cancer is vascular endothelial growth factor (VEGF) (Sartakhti et al., 2017). Tumorigenesis is dependent upon a balance of pro- and anti-angiogenic molecules (Carmeliet and Jain, 2000;

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Folkman, 1995), which are necessary for the production of blood vessels to bring oxygen and nutrients, and remove waste. Angiogenic factors therefore affect growth rates (Herman et al., 2011). They exhibit the tragedy of the commons in that there are altruistic and cheating phenotypes, the public good benefits cells irrespective of their contribution, and cheaters have a higher fitness (growth rate) than altruists.

In the host ecological setting of our social dilemma, we are not only concerned with the issues of competition among cancer phenotypes, but the role of the immune system and mathematical models of immunology (Louzoun, 2007). A variety of interesting cancer-immune system models have been explored in the literature (Eftimie et al., 2016; Foryś, 2002; Kirschner and Panetta, 1998; Kuznetsov et al., 1994; Perelson and Weisbuch, 1997). Cancer cells grow under the limitations of a carrying capacity and facing both innate and adaptive anti-tumor responses by the immune system, including the effectors: natural killer cells (NK cells), macrophages, and T cells (CD8+ T cells). The immune systems dynamics are governed by the production and loss of these effectors.

Here, we extend the model in Kuznetsov et al. (1994) by the incorporation of a public goods game. We explore both linear and Monod (nonlinear) public good growth functions, and adapt two other canonical two-species growth models into our models that are adaptations of the logistic equation (Crow and Kimura, 1970). Depending on the specific growth source used by the microbes, empirical data either supports a linear or Monod growth rate function (Monod, 1949). We find that the models employing the Monod function exhibit a synergy between altruists and cheaters where the public good is more efficiently used to increase the growth rate of the entire population of pathogens. With this effect, the pathogens can overcome the immune response of the host whereas wholly altruistic or cheating populations cannot.

Nonlinearities in benefit functions can turn what is a Prisoner's Dilemma in the linear case into a Volunteer's Dilemma (Archetti and Scheuring, 2010; Diekmann, 1985), where only if the population's public good production is sufficient, the group as a whole benefits. Volunteer's Dilemmas have been shown to produce stable coexistence of cheaters and altruists (though this phenomenon is diminished for large populations sizes as the equilibria are susceptible to small stochastic fluctuations) (Archetti, 2009; Archetti and Scheuring, 2010). The Volunteer's Dilemma has been studied with respect to punishment (Raihani and Bshary, 2011), shared rewards (Chen et al., 2013), voluntary reward funds (Sasaki and Uchida, 2014), and asymmetric player strength (He et al., 2014). Additionally, multilevel selection can favor a polymorphism of cooperators and defectors by maximizing the group donation level when the benefit function is sigmoid (Boza and Számadó, 2010).

Though we have a similar nonlinearity in our Monod function, we do not see a persistence of cheaters and altruists at any of our equilibria. Rather than trying to show coexistence of cheaters and altruists, or how cheating can be suppressed, we show how cheaters are present in the socially optimal situation. The key contribution of this paper is to demonstrate the possibility that cheaters can contribute to the well-being of the entire population.

Although we have chosen to illustrate our argument using cancer models, and interpret all our results in this language, prima facie, the main idea seems very generalizable to other social populations antagonized by a third party. For example, one popular experimental model is the siderophore production in *P. aeruginosa* (Cordero et al., 2012; Kim et al., 2009). Iron is an important and scarce resource for bacteria living in hosts. Thus, they produce siderophores that bind to iron in hemoglobin and other molecules to form iron-siderophore complexes. The bacteria then absorb these complexes. Some bacteria cheat, by not producing (or producing fewer) siderophores. They absorb the iron-siderophore complexes produced by the community as a whole, without contributing to the cost (Boyle et al., 2013). The lower operating cost allows cheating strains to reproduce faster, dominate the population, and lead to an iron-deprived community. Thus, a mixed population of altruists and cheaters could, in principle, overwhelm the immune system and perform better than one with only altruists.

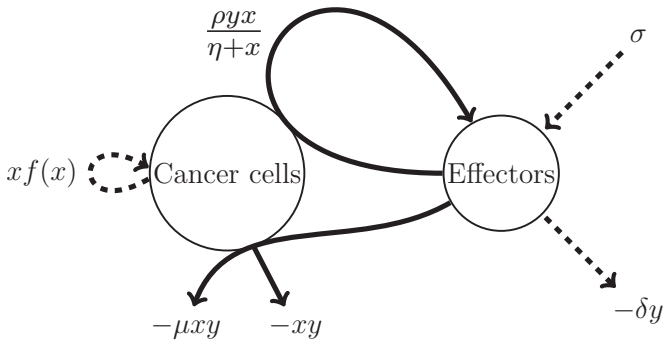

Fig. 1. A pictorial representation of the model without a public good. Solid lines represent cancer-effector interactions, and dashed lines single/no variable terms.

A synergy between cheating and cooperating microbes would have interesting epidemiological implications: Since cheaters cannot survive and grow on their own a new infection would have to be initiated by altruists. After the altruistic population settles in the new host, the pathogen may be kept under control, till a new cheating mutant emerges once again and dominates the immune system.

2. Methods

2.1. Cancer growth models and the immune response

Generally, we can write the growth of a tumor by the function $\dot{x} = xf(x)$, where x is the number of cancer cells, and $f(x)$ determines the growth of the population and density dependence. Three common tumor growth models include the logistic (1a), von Bertalanffy (1b), and Gompertz (1c) equations,

$$f(x) = \begin{cases} r(1 - x/K), & \text{(1a)} \\ rx^{-1/3} - \kappa x, & \text{(1b)} \\ r - \kappa \ln(x), & \text{(1c)} \end{cases}$$

which have each been used successfully within the literature (Eftimie et al., 2011; Gerlee, 2013). We will focus on the logistic model (1a). However, we expect cheater-altruist synergy with other growth models that are qualitatively similar to the phase portrait of Fig. 2 discussed below (i.e. that are bistable). Letting r and K be the growth rate and carrying capacity for the cancer cells, we then add the effects of the immune system, which kills the cancer cells via effectors, y.

Fig. 1 pictorially represents the model. We will examine the same effector dynamics, $\dot{y} = h(x, y)$, as Kuznetsov et al. (1994). Effectors are produced at a basal rate, σ, and die at a rate, δ. A cancer free host thus has an equilibrium $y^* = \sigma/\delta$. In the presence of a tumor, the production of immune agents is determined by the nonlinear activation function, $\rho yx/(\eta + x)$, and immune agents are exhausted at a rate, μx. The immune system attacks the pathogen, and reduces their number at a rate, xy. The dynamics of this system are governed by the following system of equations:

$$\dot{x} = xf(x) - xy, \tag{2}$$

$$\dot{y} = y\left(\frac{\rho x}{\eta + x} - \mu x - \delta\right) + \sigma. \tag{3}$$

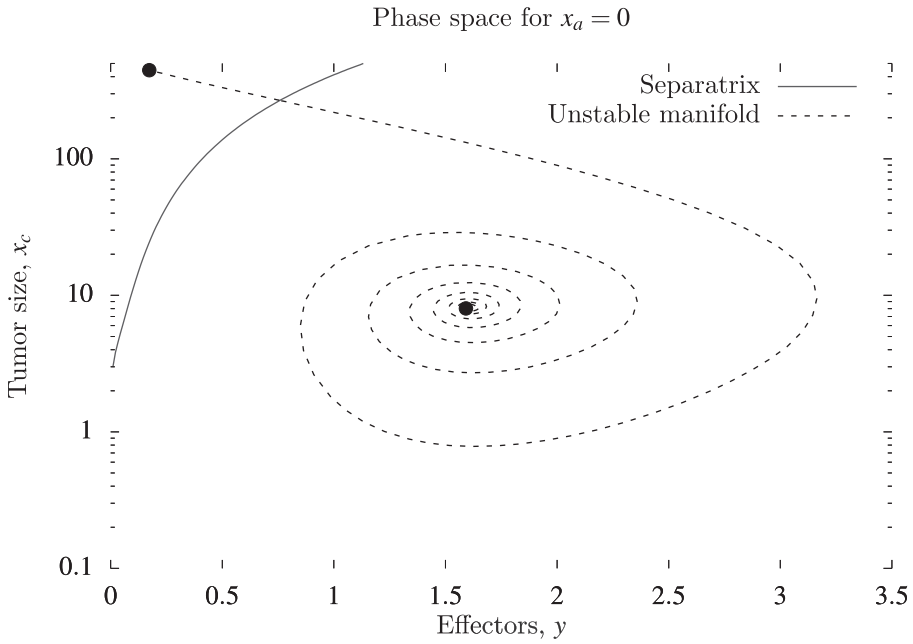

Fig. 2. A phase space of the monomorphic population. The equilibrium at the top left is the malignant tumor; the one to the right is the suppressed tumor. Separating them is the separatrix.

2.2. Public goods games

Here we introduce the public goods game played amongst the cancer cells. Let x_a and x_c be the number of altruists and cheaters, respectively, and $X(x_a, x_c) = x_a + x_c$ the size of the tumor. The growth rate of cheaters is $r(x_a, x_c) = \beta + g(x_a/X)$, which is the sum of a basal growth rate, β, and the benefit from the public good, $g(x_a/X)$, which is a function of the proportion of the population that are altruists. Altruists produce the public good at a cost of $-c$, and thus the growth rate of altruists is $r - c$. We explored two public good growth functions, linear (4a) and Monod growth (4b),

$$g\left(\frac{x_a}{X}\right) = \begin{cases} \dfrac{\alpha x_a}{X}, & \text{(4a)} \\ \dfrac{\alpha x_a/X}{K_\alpha + x_a/X}, & \text{(4b)} \end{cases}$$

where α is the maximum growth rate provided by the public good, and K_α is the half velocity constant. Let $\bar{r}(x_a, x_c) = ((r-c)x_a + rx_c)/X$ be the average rate of growth. In the absence of an immune response and other complications, it is standard to describe the growth and competition by logistic dynamics. Here we separately consider three population models in this class (cf. Crow and Kimura, 1970): r/K selection (5a), weak selection (5b), and interspecific competition (5c),

$$f(x_a, x_c) = \begin{cases} r(1 - X/K), & \text{(5a)} \\ r - X/K, & \text{(5b)} \\ r - \bar{r}X/K, & \text{(5c)} \end{cases}$$

for cheaters, and $r - c$ replaces r for altruists. In r/K selection (5a), the success of one phenotype over the other is determined by both the growth rates and carrying capacities. There is a trade-off between r and K: when close to the carrying capacity, K determines fitness, whereas when the tumor is small, r determines fitness. In weak selection (5b), the population is limited by rK, and this trade-off does not exist. Finally, in interspecific competition (5c), the phenotypes compete against one another for resources. A phenotype with a larger growth rate will curtail the carrying capacity of its competitor.

The immune system does not differentiate between altruistic and cheating cancer cells, and thus effector dynamics are only dependent upon the size of the tumor, i.e. $\dot{y} = h(X, y)$. In general, the model is written

$$\dot{x}_a = x_a f\left(x_a, x_c, (r \circ g)\left(\frac{x_a}{X}\right) - c\right) - x_a y, \tag{6}$$

$$\dot{x}_c = x_c f\left(x_a, x_c, (r \circ g)\left(\frac{x_a}{X}\right)\right) - x_c y, \tag{7}$$

$$\dot{y} = y\left(\frac{\rho X}{\eta + X} - \mu X - \delta\right) + \sigma. \tag{8}$$

A summary of the parameters, variables, and their values can be found in Table 1, which were estimated from experimental data and converted into non-dimensional parameters in Kuznetsov et al. (1994). We have chosen the values of α, K_α, and c in Table 1 to show the synergy between cheaters and altruists in an emphasized way, since this is the main point of our paper. The synergy does not exist across the entire parameter space.

3. Results

Here we discuss the qualitative dynamics of the immune system plus social and anti-social cancer cells, i.e. the equilibria, stability, and invariant surfaces. We follow these analyses with simulation results that depict the synergy (and lack thereof) between altruists and cheaters, and the effects of different parameters on this synergy.

The non-zero equilibria occur for $\dot{x}_a = 0$ and $\dot{x}_c = 0$ when

$$y^* = f\left(x_a^*, x_c^*, (r \circ g)\left(\frac{x_a^*}{X^*}\right) - c\right) = f_a, \tag{9}$$

$$y^* = f\left(x_a^*, x_c^*, (r \circ g)\left(\frac{x_a^*}{X^*}\right)\right) = f_c, \tag{10}$$

respectively. For $c \neq 0$, we cannot have polymorphic equilibria. Evaluating the Jacobian, J, for a monomorphic population $x_i^* > 0$ and $x_j^* = 0$, we find

$$\det(J - \lambda I) = (f_j - f_i - \lambda)\left[\left(x_i^* \frac{\partial f_i}{\partial x_i} - \lambda\right)\left(\frac{\partial h}{\partial y} - \lambda\right) + x_i^* \frac{\partial h}{\partial X}\right]. \tag{11}$$

Assuming that $c > 0$ and f is an increasing function with respect to the growth rate, $f_c > f_a \Rightarrow \lambda_1 > 0$. Thus, the equilibrium $x_a^* > 0$ is unstable; defectors always out-compete cooperators.

Since $g(0/0)$ is undefined and altruist equilibria are unstable with respect to cheaters, we will examine the stability for the non-altruist system (where $r = \beta$) of the non-cancerous state, $(x_c, y) = (0, y^*)$. Evaluating the Jacobian at the critical point $(0, y^*)$, we find

$$\det(J - \lambda I) = (f_c - y^* - \lambda)\left(\frac{\partial h}{\partial y} - \lambda\right). \tag{12}$$

For our choice of h, $\partial h/\partial y|_{x_c^*=0} = -\delta < 0 \Longrightarrow \lambda_3 < 0$. However, since

$f_c(0) - y^* = \beta - \sigma/\delta > 0 \Longrightarrow \lambda_1 > 0$ and thus the non-cancerous state is unstable.

Returning to our choices of f and h, we find the non-zero monomorphic tumor equilibria by solving $\dot{y} = 0$.

$$\begin{aligned}\dot{y} &= f_i[-\mu x_i^{*2} + (\rho - \mu\eta - \delta)x_i^* - \delta\eta] + \sigma(x_i^* + \eta) = 0\\ \Longrightarrow\ & \frac{r_i\mu}{K}x_i^{3*} - r_i\left(\mu + \frac{\rho - \mu\eta - \delta}{K}\right)x_i^{*2}\\ &+\left(\frac{r_i\delta\eta}{K} + r_i(\rho - \mu\eta - \delta) + \sigma\right)x_i^*\\ &+\eta(\sigma - r_i\delta) = 0,\end{aligned} \tag{13}$$

$$\frac{\mu}{K}x_i^{3*} - \left(r_i\mu + \frac{\rho - \mu\eta - \delta}{K}\right)x_i^{*2} + \left(\frac{\delta\eta}{K} + r_i(\rho - \mu\eta - \delta) + \sigma\right)x_i^* + \eta(\sigma - r_i\delta) = 0. \tag{14}$$

Where $r_a = \beta + g(1) - c$ and $r_c = \beta$, (10) and (11) are the cubic functions to find the monomorphic states for the r/K and interspecific competition models, and the weak selection model, respectively (note that since $\bar{r} = r$ in monomorphic populations, (10) applies for both r/K selection and interspecific competition). Using the parameters from Table 1 and Eq. (8) to test for stability, we show the following equilibria in Table 2.

Qualitatively, the model has four fixed points (Table 2): the tumor free state, a suppressed tumor (i.e. corresponds to a dormant/benign state); a large tumor (i.e. a malignant tumor or death of the host); and a saddle point. Fig. 2 depicts the phase space for a monomorphic population of cheaters. The tumor free state is connected to the saddle via a stable manifold. This stable manifold, a separatrix, divides phase space into regions where the tumor succeeds and fails. The unstable manifold spirals into the suppressed state on one side of the separatrix, and connects to the malignant state on the other side. Qualitatively, this picture is the same as in Kuznetsov et al. (1994) with the addition of the altruist dimension.

Fig. 3 shows the regions of suppression (gray) and success (white) of the tumor for all the models we study. The goal here is to check whether a certain *initial* distribution of phenotypes (x_c, x_a) succeeds in defeating the host. The line $x_a = X - x_c$ (with constant X) is overlaid to these plots to show whether changing the composition of the population—without changing the size of the tumor—results in a difference in the fate of the disease.

Interestingly, in some cases we observe that population compositions with an intermediate number of cheaters can place the population in the successful region, while too few or too many cheaters jeopardize the population. In other words, while neither pure altruism nor pure cheating leads to success, a mixture of the two does. We observe this phenomenon in a tumor growing from the public good according to the Monod law, but not for linear growth.

We can explain this phenomenon by examining the equations for the change in the total population, $\dot{X}$, r/K selection and interspecific competition (15a), and weak selection (15b);

Table 1
Summary definitions of parameters and variables.

Parameter/ variable	Value	Definition
α	1.3088	Benefit from the public good
β	1.636	Basal growth rate
δ	0.3743	Death rate of effectors
η	20.19	Activation parameter
K	500	Carrying capacity
K_α	0.5	Monod parameter
μ	0.00311	Inactivation rate
ρ	1.131	Activation parameter
σ	0.1181	Birth rate of effectors
c	0.818	Cost to altruists
$r - c$	–	Altruist growth rate
r	–	Cheater growth rate
$\bar{r}$	–	Average growth rate
x_a	–	10^6 altruists
x_c	–	10^6 cheaters
X	–	Tumor size (10^6)
y	–	10^6 effectors

$$\dot{X} = \begin{cases} \bar{r}X\left(1 - \dfrac{X}{K}\right) - yX, & \text{(15a)}\\ \bar{r}X - \dfrac{X^2}{K} - yX. & \text{(15b)}\end{cases}$$

In linear growth, $\bar{r} = \beta + (\alpha - c)x_a/X$, which is an increasing function with respect to x_a (given $\alpha > c$). Thus, (15a) and (15b) are increasing with respect to x_a. Therefore, the impact of decreasing altruists in favor of cheaters is a decrease in the total population's rate of growth; cheaters harm the population as a whole. However, for Monod growth, we have the function

$$\bar{r} = \beta + \left(\frac{\alpha}{K_\alpha + x_a/X} - c\right)\frac{x_a}{X} \tag{16}$$

with the assumption that $\alpha/(K_\alpha + 1) > c$. With respect to the proportion of altruists, this function has a local maximum at

$$\frac{x_a}{X} = \sqrt{\frac{\alpha K_\alpha}{c}} - K_\alpha > \sqrt{K_\alpha(K_\alpha + 1)} - K_\alpha > 0. \tag{17}$$

Therefore, unlike the linear growth case, the optimal growth rate will occur in the presence of cheaters when $\sqrt{\alpha K_\alpha/c} - K_\alpha < 1$. In general, cheaters are beneficial to the tumor if f is increasing with respect to g and g is decreasing at $x_a/X = 1$.

Fig. 4 shows the results for simulations where we varied the parameters, α (the maximum growth rate from the public good), K_α (the half velocity constant), and c (the cost of public good production). We ran simulations for pure altruist and 5% cheaters populations. We calculated the minimum initial total population size X and X' at which the pure and 5% cheater populations, respectively, became malignant (the stable malignant cheater equilibria in Table 2). The initial number of effectors for these simulations is σ/δ, the non-cancerous state. Thus, our simulations describe a tumor that has evaded an immune response before reaching size X (X') (for a review on how this can happen cf. Marcus et al., 2014). We colored the figures relative to $X' - X$; blue regions are where cheaters are beneficial and red where they are not. The purpose of this figure is to determine the parameter space where cheaters are beneficial.

We observe that for sufficiently large α and small c, cheaters do not benefit — and may in fact hinder — the tumor. For sufficiently high α, the difference between the two initial cases is minimal. Since, even a marginal initial population will overcome the immune response. However, within the region where we observe cheater-altruist synergy, increasing α reduces the synergistic effect. Fig. 5 explains this effect. Note the sharp drop in the separatrix in

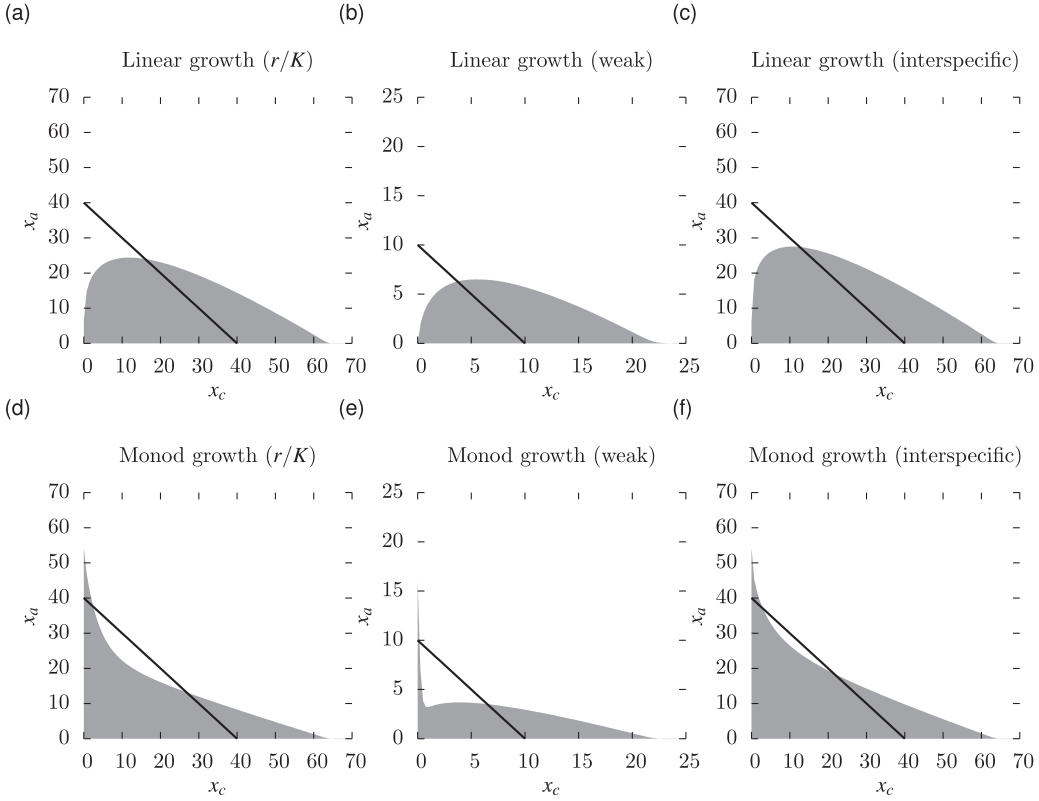

Fig. 3. A mixed population of altruists and cheaters minimizes the tumor size required to overcome the immune system when growth from the public good behaves as a Monod function (d–f). However, this behavior is not observed when the growth function is linear (a–c). The white and gray regions are where the tumor overcomes and is suppressed by the immune system, respectively. The black curves are the isoclines, $x_a = X - x_c$, where $X = 10$ in **b** and **e**, and $X = 40$, otherwise.

Table 2
Summary of fixed points, (x_a^*, x_c^*, y^*), and their stability.

Stability	r/K and interspecific competition	Weak selection	
unstable	$(0, 0, 0.3155)$	$(0, 0, 0.3155)$	
stable	$(8.876, 0, 2.089)$	$(8.898, 0, 2.109)$	Linear
unstable saddle	$(252.4, 0, 1.053)$	$(237.9, 0, 1.651)$	Linear
stable	$(461.8, 0, 0.1625)$	$(1040, 0, 0.04726)$	Linear
stable	$(8.283, 0, 1.663)$	$(8.303, 0, 1.674)$	Monod
unstable saddle	$(265.5, 0, 0.7928)$	$(247.7, 0, 1.195)$	Monod
stable	$(449.3, 0, 0.0.1713)$	$(812.4, 0, 0.06571)$	Monod
stable	$(0, 8.190, 1.609)$	$(0, 8.208, 1.620)$	
unstable saddle	$(0, 267.8, 0.7598)$	$(0, 249.5, 1.137)$	
stable	$(0, 447.1, 0.1730)$	$(0, 783.4, 0.06914)$	

Fig. 5; a small proportion of cheaters is beneficial to the tumor. However, the remainder of the curve shows malign effects of increasing the proportion of cheaters. As we increase α, this phenomenon disappears, and we observe the same qualitative behavior as linear growth.

K_α is negatively correlated with cheater success (Fig. 4). A low half velocity constant implies that the marginal benefit from the public good rapidly decreases as the proportion of altruists increases. As such, cheaters permit a more efficient utilization of the public good in the population. In the linear growth case, this effect cannot occur because the higher the proportion of altruists, the greater the tumor's growth rate. However, where cheaters are harmful, as seen in panels (a), (d), and (g), K_α is negatively correlated with the deleterious effects of cheaters. Cheaters are harmful to the population when α is sufficiently high. As $K_\alpha \to 0$, $g(x_a/X) = \alpha$, which is independent of the proportion of the population that are altruists. Thus, similarly with the other panels, the difference between the outcomes is marginal.

We compared the separatrices for the Monod models of a tumor with the two phenotypes and a tumor with a single phenotype with an intermediate production of the public good in Fig. 6. We plotted the tumor size required to overcome the immune system given an initial proportion of altruists x_a/X for the two (pheno)types case, and a single phenotype with growth rate $\bar{r}(x_a/X)$ (Eq. (12)) where x_a/X is interpreted as a parameter. We denote the latter phenotype the "mixed type." When altruism is low, the two types population is optimal for the tumor. Conversely, when altruism is high, the mixed type population is optimal. If $x_a/X < \sqrt{\alpha K_\alpha / c} - K_\alpha$, then the mixed type will out-compete the two type case. Since, $x_a/X \to 0$ as $t \to \infty$ and (6) is a decreasing function from 0 to $\sqrt{\alpha K_\alpha / c} - K_\alpha$ in the two type case, while the growth rate of the mixed type will not decrease. This figure shows

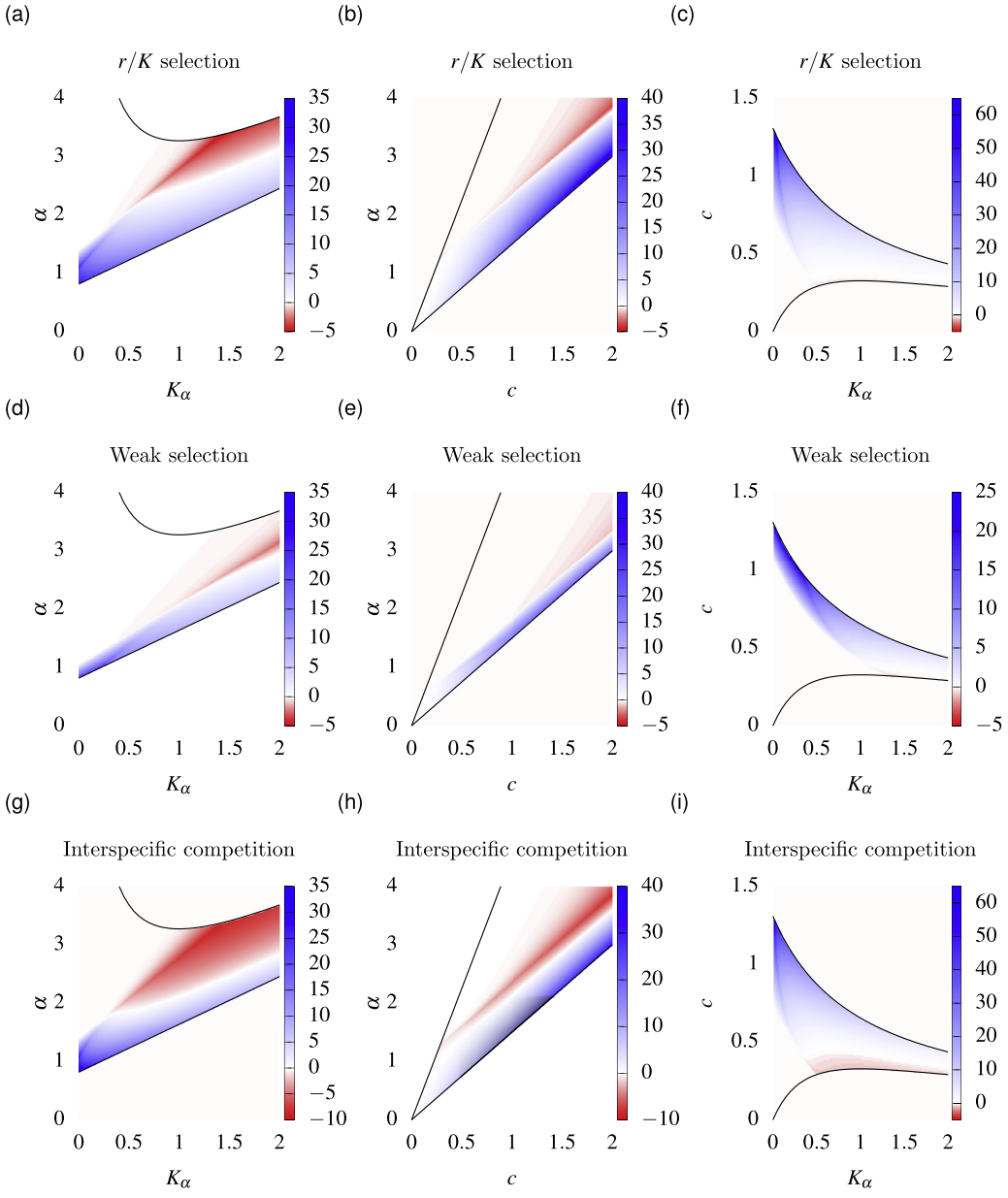

Fig. 4. Comparison of success of a 5% cheater population vs. a pure altruist population for varying parameters α, K_α, and c. The colored regions measure the difference between the initial population size required to overcome immune suppression for the 5% cheater, X, vs. pure altruist populations, X'. The curves define the envelope in which the optimal growth rate occurs for $x_a < 1$ and the pure altruist Monod growth rate is greater than c. Where a parameter is not varied, its value is from Table 1.

that the presence of distinct phenotypes, altruists and cheaters, can be important for the tumor to overcome the immune system (i.e. when altruism is low). However, the minimum for each panel occurs for the mixed type models at an intermediate degree of altruism as we expect from g being nonlinear.

4. Discussion

Previous studies support the hypothesis of frequency dependent selection among cheaters and altruists in microorganisms (Diggle et al., 2007; Levin et al., 1988; Ross-Gillespie et al., 2007). Altruists are less fit in the presence of cheaters, who outperform them. Further, average fitness is negatively correlated with the proportion of cheaters, which reduces virulence (Harrison et al., 2006; Rumbaugh et al., 2009). Our linear growth model qualitatively matches these empirical results. Given these observations, the question arises as to how altruism can be facilitated. However, less discussed, is why both cheating and altruism are prevalent, which is relevant since the prevalence of cheaters may be common (Dugatkin et al., 2005; Velicer et al., 2000).

Much research has explored the use of ecology and evolution against cancer (Korolev et al., 2014), and the mechanisms by which altruism can be facilitated, yet not how cheating can indirectly aid the population. Our approach was to explore how, in host-tumor ecology, if cheaters may be necessary for tumors to overcome the host's immune system. Our problem can be interpreted as a threshold Volunteer's Dilemma in two ways: the benefit to growth is nonlinear in the Monod case, and there is a threshold of altruism at which the population overcomes the immune response (the definition of benefit in this case). However, unlike in other models of Volunteer's Dilemmas (Archetti and Scheuring, 2010) — which can be understood as N person games of Chicken (Hawk-Dove) (Palfrey and Rosenthal, 1984) — we do not observe coexistence

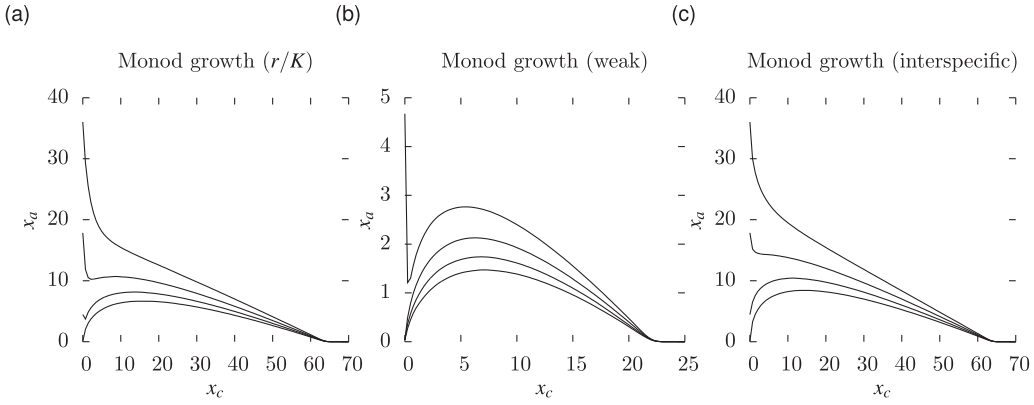

Fig. 5. Comparison of varying benefits from public good growth rates (α) on the separatrix with respect to initial conditions (x_c, x_a). For a given separatrix, below the curve the tumor is contained and above it it is not. All separatrices are in decreasing order from top to bottom of the graphs with increasing α ($\alpha = 1.5,\ 1.75,\ 2$, and 2.25). As α increases, the behavior of the model approaches that of linear growth, i.e. a monomorphic altruistic population is optimal with respect to the tumor. All other parameter values used are from Table 1.

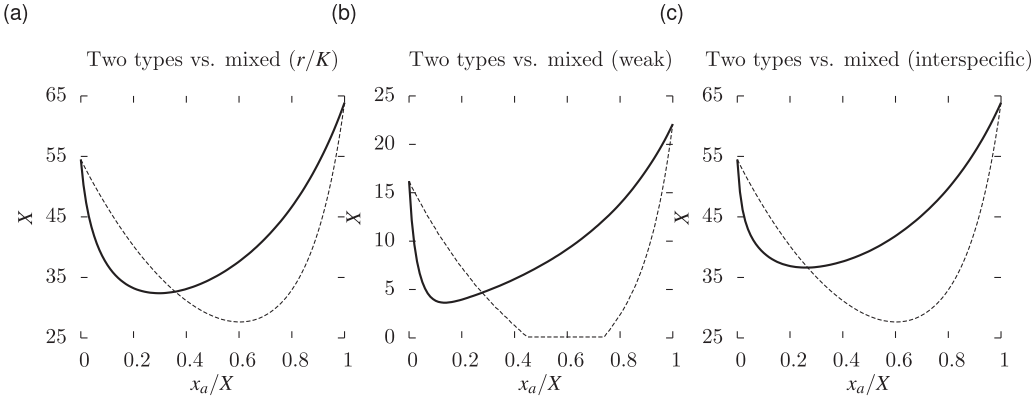

Fig. 6. Comparison of the separatrices of a polymorphic population of two types, altruists and cheaters, at initial condition x_a/X (solid curves), vs. a "mixed type" monomorphic population with growth rate $\bar{r}(x_a/X)$ (Eq. 12, dashed curves). Below the curves, the immune system suppresses the tumor, and above them, it does not. For low altruism, the two types case outperforms the mixed type. And, for high altruism, the mixed type is optimal. All other parameter values used are from Table 1.

of altruists and cheaters. In the long run, cheaters will always out-compete altruists.

We have shown that although cheaters out-compete altruists in a mixed population, such a population can be more harmful than a pure population of altruists or cheaters. This unexpected phenomenon occurs due to the Monod growth nature of the public good. The optimal total population growth rate may be at a mixed population. Although this harms altruists relative to cheaters, it may permit the tumor to resist suppression by the immune system.

We can interpret our model as having two public goods. The first is the altruists' secretion, which increases the growth of individual cells. The second public good is simply provided by the *presence* of tumor cells, regardless of whether they are cheaters or altruists. This is because, the greater the number of cells, the better the tumor can combat the immune system. Thus, though cheaters free-ride with respect to the first public good, they help provide (are cooperative) with respect to the second. As such, the presence of an antagonizing outside force and a collective outcome (suppression or malignancy) can make the cheaters quasi-cooperative.

There are several interesting extensions that this paper does not address: spatial effects (Lieberman et al., 2005), stochasticity, or other effector dynamical equations. Spatial effects, for example, could show surprising results. Spatial considerations in the diffusion of public goods can aid cooperation in tumors (Archetti, 2016). However, though this effect could explain persistence of some degree of altruism, it also could counteract the benefit from cheaters in the Monod case. Spatial effects could also address a weakness of the model, an explanation for the prevalence of altruism at the initial stages of the tumor. Another extension that may address this concern is interactions groups, which have been shown to facilitate cooperation where population density depends on average payoff (Hauert et al., 2006, 2008) (details of an interaction group extension to the model are presented in Appendix B). Additionally, interaction groups could result in interesting cycles of altruism and cheating facilitating the spread of tumors. Such cycling could also be observed by assuming different carrying capacities. A mixed population is required to overcome the immune response, during which the relative number of cheaters is increasing. However, if the carrying capacity for altruists were to be larger than for cheaters, then at large population sizes, the relative fitness advantage of cheaters may vanish. In this interplay, cheaters are *r* selection and altruists *K* selection phenotypes.

Author contributions

B.M. and D.C.V. conceived the theory and carried out the analytical work. B.M. ran the numerical simulations. Both authors wrote and reviewed the manuscript.

Competing interests

The authors declare no competing financial interests.

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Appendix A. Correspondence between parameters and variables, and units

From Kuznetsov et al. (1994):

$$\beta = \frac{0.18 \times 10^7 \text{cells} \times \text{day}}{1.101 \times 10^6 \text{cells} \times \text{day}}, \qquad \rho = \frac{0.1245 \times 10^7 \text{cells} \times \text{day}}{1.101 \times 10^6 \text{cells} \times \text{day}},$$

$$\delta = \frac{0.0412 \times 10^7 \text{cells} \times \text{day}}{1.101 \times 10^6 \text{cells} \times \text{day}}, \qquad \sigma = \frac{1.3 \times 10^{11} \times \text{cells} \times \text{day}}{1.101 \times 10^{12} \times \text{cells} \times \text{day}},$$

$$\eta = \frac{2.019 \times 10^7 \text{cells}}{10^6 \text{cells}}, \qquad x_i = \frac{\text{cells}}{10^6 \text{cells}},$$

$$K = \frac{10^9 \text{cells}}{2.0 \times 10^6 \text{cells}}, \qquad y = \frac{\text{cells}}{10^6 \text{cells}}.$$

$$\mu = \frac{3.422 \times 10^7 \text{cells} \times \text{day}}{1.101 \times 10^{10} \text{cells} \times \text{day}},$$

Appendix B. Interaction groups

The results in the main body of the paper assume mean-field dynamics. However, spatial considerations in the diffusion of public goods can aid cooperation in tumors (Archetti, 2016), and interaction groups in ecological public goods games have been shown to facilitate cooperation where population density depends on average payoff (Hauert et al., 2006, 2008). We extend our model above by introducing interaction groups. Assume that players form interaction groups of size N, at random, where they play the public goods game. The probability of a player finding itself in an interaction group where k of the other $N-1$ players are cooperators is

$$P(x_a = k) = \binom{N-1}{k} \left(\frac{x_a}{X}\right)^k \left(1 - \frac{x_a}{X}\right)^{N-1-k}. \tag{18}$$

Then, on average, for the cheaters and altruists growth rates, r_c and r_a, we have

$$r_c = \beta + \frac{\alpha x_a (N-1)}{NX}, \tag{19}$$

$$r_a = \beta + \frac{\alpha x_a (N-1)}{NX} - c + \frac{\alpha}{N}. \tag{20}$$

Note now that the growth rate for cheaters is not necessarily greater than that of altruists. If the tumor size and interaction group are sufficiently small, altruists are more fit than cheaters. The implication is that altruists can be evolutionarily stable in the benign tumor state while not in the malignant state. The evolutionary story under stochastic conditions that this provides is that any new small tumors will be altruists capable of fueling rapid growth synergistically with cheaters. If a malignant tumor is capable of spreading with via a small offshoot, altruists could reemerge. We thus have a cycle of small tumors and altruism, and malignancy and cheating.

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