IOPscience iopscience.iop.org

Home Search Collections Journals About Contact us My IOPscience

Cancer treatment as a game: integrating evolutionary game theory into the optimal control of chemotherapy

This article has been downloaded from IOPscience. Please scroll down to see the full text article.

2012 Phys. Biol. 9 065007

(http://iopscience.iop.org/1478-3975/9/6/065007)

View the table of contents for this issue, or go to the journal homepage for more

Download details:
IP Address: 128.233.210.97
The article was downloaded on 15/06/2013 at 09:39

Please note that terms and conditions apply.

Phys. Biol. **9** (2012) 065007 (10pp) doi:10.1088/1478-3975/9/6/065007

Cancer treatment as a game: integrating evolutionary game theory into the optimal control of chemotherapy

Paul A Orlando[1], **Robert A Gatenby**[2] **and Joel S Brown**[3]

[1] Biometry Research Group, Division of Cancer Prevention, National Cancer Institute, Executive Plaza North, Suite 3131, 6130 Executive Blvd, MSC 7354, Rockville, MD 20852, USA
[2] Department of Radiology, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612, USA
[3] Department of Biological Sciences, University of Illinois at Chicago, 845 W Taylor Street, Chicago, IL 60607, USA

E-mail: paul.orlando@nih.gov

Received 20 July 2012
Accepted for publication 24 September 2012
Published 29 November 2012
Online at stacks.iop.org/PhysBio/9/065007

Abstract
Chemotherapy for metastatic cancer commonly fails due to evolution of drug resistance in tumor cells. Here, we view cancer treatment as a game in which the oncologists choose a therapy and tumors 'choose' an adaptive strategy. We propose the oncologist can gain an upper hand in the game by choosing treatment strategies that anticipate the adaptations of the tumor. In particular, we examine the potential benefit of exploiting evolutionary tradeoffs in tumor adaptations to therapy. We analyze a math model where cancer cells face tradeoffs in allocation of resistance to two drugs. The tumor 'chooses' its strategy by natural selection and the oncologist chooses her strategy by solving a control problem. We find that when tumor cells perform best by investing resources to maximize response to one drug the optimal therapy is a time-invariant delivery of both drugs simultaneously. However, if cancer cells perform better using a generalist strategy allowing resistance to both drugs simultaneously, then the optimal protocol is a time varying solution in which the two drug concentrations negatively covary. However, drug interactions can significantly alter these results. We conclude that knowledge of both evolutionary tradeoffs and drug interactions is crucial in planning optimal chemotherapy schedules for individual patients.

Introduction

With few exceptions, metastatic cancers remain incurable. Treatments for common epithelial tumors, such as lung, colon, and breast, can be effective initially but almost invariably fail due to evolution of resistance. The mechanisms by which cancer cells achieve resistance are extremely diverse and can vary depending on the mechanism(s) of action and molecular characteristics of the chemotherapeutic drug (for review see Gottesman 2002). Even highly targeted therapy, such as Herceptin for breast cancer patients with the HER/2neu mutations, typically produces only transient response with rapid evolution of adaptive strategies (median time to progression following treatment is 4.9 months, Vogel *et al* 2002). Thus, evolution of resistance to treatment is the ultimate cause of death in patients with disseminated cancers and will likely remain so even with targeted, personalized therapy. We propose cancer therapy can be optimized using treatment strategies based on Darwinian principles that focus on understanding and exploiting evolutionary dynamics of cancer cell response and adaptation to treatment.

Here, we examine a novel conceptual model for optimizing cancer therapy by viewing therapy as a 'game' between the oncologist and the cancer. In principle, the oncologist has a significant advantage in the game because she can understand evolution while the tumor cannot. That is, cancer cells, like any evolving population, are evolutionarily short sighted. They can only evolve in response to what has or is happening and can *never* anticipate future selection forces. Critically, the oncologist *can* think ahead and *can* design

 © 2012 IOP Publishing Ltd Printed in the UK & the USA

strategic, long-term plans that anticipate and even steer the evolutionary and ecological dynamics of the cancer cells.

Here we examine one potential component of the cancer treatment game by focusing on the potential exploitation of evolutionary tradeoffs to the advantage of the oncologist. For instance, if cancer cells face a tradeoff in resistance between two drugs, then it is possible to select for tumor resistance to one of the drugs, while simultaneously increasing tumor susceptibility to a second drug. We refer to this scenario as an evolutionary double bind (Gatenby *et al* 2009).

We view the interactions between the oncologist and a cancer as a differential game and frame this hypothesis using evolutionary game theory to determine how natural selection 'chooses' the strategies that cancer cells deploy. We apply control theory to determine the optimal treatment strategy available to the oncologist.

In this paper we build on the work of Cunningham *et al* (2011) to understand optimal treatment protocols that may result in a double-bind scenario. Previous studies have incorporated the evolution of resistance within an optimal control problem (e.g. Ledzewicz and Schattler 2006). However, these evolutionary dynamics were modeled with compartmental models of resistant and non-resistant, and did not allow for degrees of resistance. In contrast, we use G-functions (Vincent and Brown 2005) to model an evolutionary dynamic with a continuous spectrum of phenotypic resistance. G-functions consider how the fitness' of rare mutants in the population are influenced by the strategies and population sizes of resident phenotypes as well as the environment. Researchers have applied G-functions to cancer to understand how cancer adapts to the environment in a variety of publications over the last decade (e.g. Gatenby and Vincent 2003, Vincent and Gatenby 2008). This paper is the first to apply G-functions in an optimal control framework, to understand how we can use the evolutionary competence of cancer to our advantage.

Here, we model a scenario in which cancer trades off resistance between two drugs. We first explore three different types of tradeoffs in allocation of resistance to two drugs to see the effects on the optimal treatment protocols. The different tradeoffs affect whether cancer cells can allocate additively more, less, or equal amounts when generalizing resistance to two drugs as opposed to specializing to be resistant to a single drug. Tradeoffs are one way that affects how multiple drugs influence the fitness of cancer cells. The relationship between the two drugs in their effects on cancer cells also affects how multiple drugs influence cancer cell fitness. For example, if drugs are synergistic, then all else equal, a cancer cell's fitness is lowest when drugs are combined, and vice versa for antagonistic drugs. Therefore, we also explored the influence of drug interactions combined with the tradeoffs on the optimal treatment protocols. We use these different scenarios to answer a straightforward qualitative therapy question—when is it optimal to give a relatively static treatment of both drugs versus a dynamic treatment, which varies the concentration of drugs over time?

Model description

Eco-evolutionary model of tumor growth with therapy

We use a predator–prey type model to envision tumor growth subject to chemotherapy. In the absence of therapy we imagine that the tumor grows to some carrying capacity described by the logistic growth equation. We then let two different therapies act as 'predators' that induce tumor cell mortality:

$$\frac{\mathrm{d}N}{\mathrm{d}t} = N\left[r\left(1-\frac{N}{K}\right) - d_1 y_1 - d_2 y_2 - \beta y_1 y_2\right].$$

In this model, N is the total tumor population size. The first term inside the brackets is the per capita growth rate of the tumor in the absence of therapy, where r is the intrinsic growth rate and K is the carrying capacity. Chemotherapy influences the per capita death rate of the cells in both additive and non-additive ways. The terms d_1 and d_2 are per capita mortality rates per unit drug concentration for drug 1 and drug 2, respectively, and y_1 and y_2 are the concentrations of drugs 1 and 2, respectively. Since the model has no spatial structure, we implicitly assume that the drug concentrations are equal throughout the tumor. The last term of the per capita growth rate determines the type and magnitude of drug interaction. The sign of β determines whether drugs are antagonistic ($\beta < 0$) or synergistic ($\beta > 0$). With antagonism, the presence of one treatment reduces the direct efficacy of the other and vice-versa. With synergism, each treatment type amplifies the effectiveness of the other at killing tumor cells.

We transform this basic ecological model into an evolutionary model through the use of a fitness generating function or G-function (Vincent and Brown 2005). In this function, tumor cell fitness is defined as per capita growth rate. The G-function models the potential fitness of rare mutant tumor cells. The fitness of a tumor cell is influenced by its heritable phenotype or strategy ($\mathbf{v}$), the resistance strategy of the resident population ($\mathbf{u}$), the cell population size (N), and the concentrations of two therapies (y_1 and y_2). The strategy of the resident population represents the mean phenotype of the population. Given a particular ecological circumstance, the G-function defines the fitness of all potential mutants contained within the phenotypically feasible strategy set (upper and lower bounds on $\mathbf{v}$). This allows us to determine how natural selection will act within a population. For instance, if in a particular ecological circumstance, rare mutant cancer cells with lower resistance have higher fitness than the current resident strategy, and vice versa for mutants with higher resistance, then resistance will decrease by natural selection.

To create the G-function, we make the ecological parameters of the model a function of our evolutionary variables:

$$G(\mathbf{v}, N, y_1, y_2) = r\left(1-\frac{N}{K(\mathbf{v})}\right) - d_1(\mathbf{v})y_1 - d_2(\mathbf{v})y_2 - \beta y_1 y_2.$$

Note that the fitness function for rare mutants does not directly depend on the current resident strategy. We let the phenotypic strategy of a cell be vector valued with two evolutionary variables ($\mathbf{v} = (v_1\ v_2)$). The first is a cell's overall investment in resistance (v_1). And the second is a cell's allocation of resistance to drug 1 (v_2). The resident's

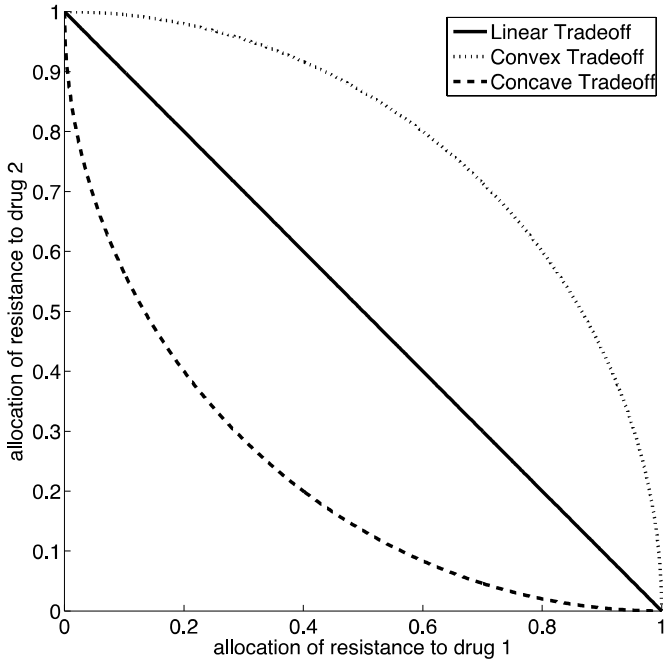

Figure 1. Three different tradeoffs in allocation of resistance between the two drugs.

strategy is also vector valued ($\mathbf{u} = [u_1\, u_2]$) and the variables are analogous to those of the rare mutants. We assume that as a cell increases investment in resistance, per capita birth declines via a declining carrying capacity. The carrying capacity function is given as

$$K = K_{\max} \exp\left(\frac{-v_1^2}{2\sigma_k^2}\right).$$

Where σ_k^2 is the standard variance parameter of a Gaussian function. We also assume that cells face a tradeoff in allocation of resistance between the two drugs. To describe a cell's allocation of resistance to both drugs we use three different functions. Figure 1 shows the three different tradeoff types we use. The first is a linear tradeoff given by

$$v_2^{'} = 1 - v_2.$$

Where $v_2^{'}$ is allocation of resistance to drug 2. With this function, generalizing to accommodate both drugs, or specializing on a single drug is equal in terms of allocation. The second is a concave function given by

$$v_2^{'} = 1 - \sqrt{1 - (v_2 - 1)^2}.$$

With this function cells allocate additively more by specializing as opposed to generalizing. The third is a convex tradeoff given by

$$v_2^{'} = \sqrt{1 - v_2^2}.$$

With this function cells allocate additively more by generalizing as opposed to specializing.

A cell's resistance to a single drug is the product of a cells investment in resistance (v_1) and allocation to that drug (v_2 or v_2'). Drug resistance influences cell fitness by decreasing the cell's per capita mortality rate due to drug toxicity. The cell's per capita mortality rates from non-interactive drug effects are

$$d_1 = \frac{1}{k_1 + v_1 v_2}$$

and

$$d_2 = \frac{1}{k_2 + v_1 v_2^{'}(v_2)},$$

for drugs 1 and 2, respectively. Where k_1 and k_2 are the baseline levels of resistance to drugs 1 and 2 respectively. For simplicity we assume that resistance does not affect drug interactions.

Finally, we derive the evolutionary dynamics that describe how the resident strategy (i.e. phenotype) of the tumor changes with time. The evolutionary dynamic describes how the cancer cells 'choose' their strategy in the game against the oncologist. Following Fisher's fundamental theorem of natural selection, the direction of natural selection is given by the gradient of the fitness function with respect to the fitness of rare mutants. This derivative is evaluated at the strategy of the current resident ($\mathbf{u}$), since this is where the genetic variance is clustered. Thus, an evolutionary dynamic for each evolutionary variable of the resident is given by

$$\frac{\mathrm{d}u_i}{\mathrm{d}t} = s \frac{\mathrm{d}G}{\mathrm{d}v_i}\bigg|_{v_i = u_i}.$$

Where s is a speed parameter, which is larger with increased genetic variance or mutation rate.

Optimal control problem

Using our eco-evolutionary model, we formulate a control problem with the objective of minimizing tumor size at the end of the planning period. The solution to the control problem determines how the oncologist chooses a strategy in the game against the tumor. In addition to the dynamics of the tumor population we add equations for the concentrations of two different drugs, y_1 and y_2 respectively, in the immediate vicinity of the tumor. The oncologist chooses the control variables w_1 and w_2. These are the rates of drug delivery for drugs 1 and 2, respectively. Drug clearance is modeled with basic first order pharmacokinetics, where z_1 and z_2 are per unit drug clearance rates. Furthermore, we place an upper limit on the total amount of drugs that can be present in a patient's system at any one time. This limits drug dosage to avoid toxicity to the patient. Combining these pieces yields the following time-dependent control problem:

Minimize $N(t_\mathrm{f})$

Subject to

$$\frac{\mathrm{d}N}{\mathrm{d}t} = NG|_{\mathbf{v}=\mathbf{u}}$$

$$\frac{\mathrm{d}u_1}{\mathrm{d}t} = s \frac{\mathrm{d}G}{\mathrm{d}v_1}\bigg|_{v_i = u_1}$$

$$\frac{\mathrm{d}u_2}{\mathrm{d}t} = s \frac{\mathrm{d}G}{\mathrm{d}v_2}\bigg|_{v_2 = u_2}$$

$$\frac{\mathrm{d}y_1}{\mathrm{d}t} = w_1 - z_1 y_1$$

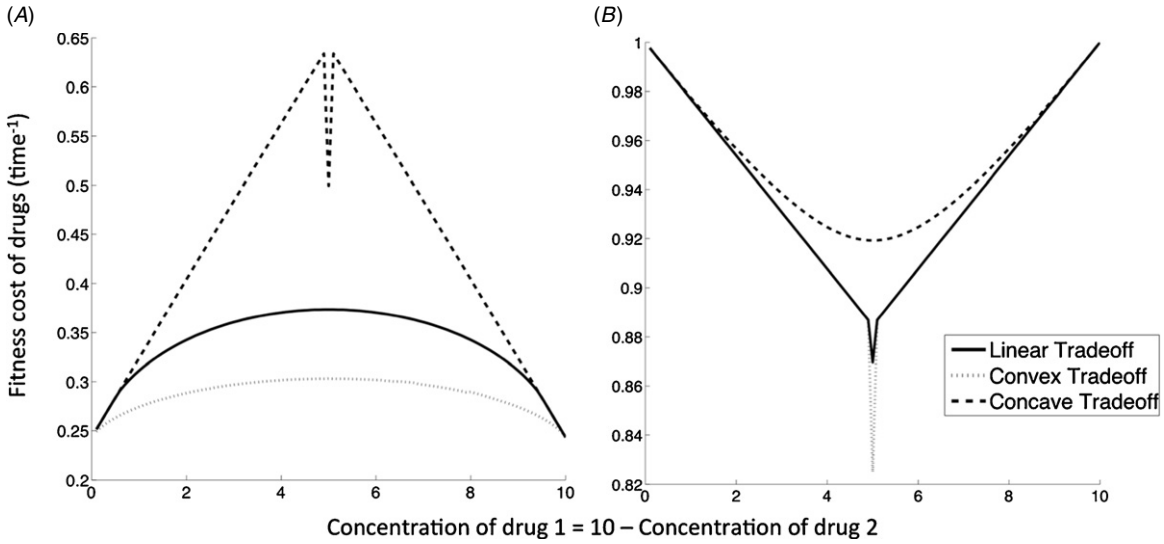

Figure 2. The effects of two drugs on cancer cell fitness in two different scenarios. (*A*) The cancer cells are using their best evolutionary strategy against the combination of drugs. (*B*) The cancer cells have a fixed level of resistance and are using their worst evolutionary strategy in terms of allocation to either drug. The linear, concave, and convex tradeoffs are represented by solid, dashed and dotted lines, respectively. Note that the total concentration of drug 1 and drug 2 is fixed at 10, consistent with the optimization problem. Parameters in common for both panels: $r = 1$, $K_{\max} = 10$, $\sigma_k = 30$, $k_1 = k_2 = 10$, $\beta = 0$. For panel (*B*) $u_1 = 3$.

$$\frac{dy_2}{dt} = w_2 - z_2 y_2$$

$$y_1 + y_2 \leqslant 10$$

$$w_1 \leqslant 10, \quad w_2 \leqslant 10, \quad N(0) = K_{\max}, \quad y_1(0) = 0,$$
$$y_2(0) = 0, \quad u_1(0) = (0), \quad u_2(0) = u_2', \quad t_f \text{ fixed.}$$

We used GPOPS software (Rao *et al* 2010) to numerically solve this control problem.

Table 1. Evolutionary tradeoff definitions.

Evolutionary tradeoff	Definition
Benefit of multitasking	Cancer cells have higher fitness when they generalize resistance in response to a multidrug therapy as opposed to specializing in response to a single drug therapy.
Penalty of multitasking	Cancer cells have higher fitness when they specialize resistance in response to a single drug therapy as opposed to generalizing in response to a multidrug therapy.

Results

Cancer at its best and its worst

We begin by analyzing the G-function model independent of any control by the oncologist. This allows us to gain insight into the effectiveness of potential therapies from the perspective of the cancer cells. Specifically, we optimize the fitness of cancer cells under different ratios of the two drugs (assuming total drug amount must be held constant to limit the combined toxicity) to see how cell fitness varies with different drug combinations. We explore this relationship when cancer cells maximize fitness and when they minimize fitness. These scenarios give us insight into the nature of optimal treatment protocol—whether it should be static or dynamic. We define a static control as a situation in which the oncologist administers the highest possible dose of either or both drugs without aiming to vary concentrations. We define a dynamic control as therapy in which the oncologist explicitly varies drug concentrations over time.

With fitness maximization, we seek to understand if cancer cells have higher fitness when given a single drug versus when given both drugs simultaneously. When cancer cells are given a single drug, their best strategy is a specialized resistance approach. That is, they become maximally resistant to the administered drug but remain susceptible to the alternate drug. On the other hand, when they are given both drugs, their best strategy is to generalize resistance, such that cancer cells are equally resistant to both drugs. Figure 2(*A*) clearly shows that regardless of the allocation tradeoff between the evolutionary variables, the cancer cells have higher fitness as specialists when given a single drug rather than generalists when given both drugs. In other words, the cancer cells face a 'penalty of multitasking', since they are less fit when they try to generalize resistance to both drugs (see table 1). Interestingly, however, with the concave tradeoff the cancer cells face a local 'benefit of multitasking', meaning that even though the cancer cells have higher fitness as specialists rather than generalists, when the cancer cells do generalize, they have higher fitness as balanced generalists (equal resistance to both drugs) as opposed to slightly imbalanced generalists.

These results give insight into the optimal static treatment. Given cancer cells that face an evolutionary 'penalty of multitasking', the best static treatment is to give both drugs simultaneously at maximum dose. For the linear and convex allocation tradeoffs the concentrations of both drugs should be

equal. However, due to the local 'benefit of multitasking' with the concave tradeoff, the concentration of one drug should be slightly higher than the other.

With fitness minimization, the cancer cells are doing the worst that they can in the sense that they have the lowest fitness possible. Exploring fitness minimization gives us insight into the effectiveness of a dynamic treatment strategy. The idea being that if the oncologist varies drug concentrations rapidly, the oncologist can exploit the evolutionary tradeoff by treating cancer with the drug it is most susceptible to. Figure 2(*B*) shows that all of the tradeoff types are susceptible to a dynamic treatment strategy as is ensured by the assumed allocation tradeoff. Regardless of tradeoff type, all of the cells have the lowest fitness when specialized on a single drug and then treated with the alternate drug. Interestingly, for both the linear tradeoff and the convex tradeoff, cancer cells using their worst strategy have significantly reduced drug effects when drugs are given in equal amounts compared to slightly unequal amounts. In conclusion, although the optimal static strategy may be to give equal (or nearly equal) amounts of both drugs, there is potential that a dynamic treatment protocol of switching drugs may work better. In the next section we analyze the optimal solutions of the game between cancer and the oncologist.

Solutions to the control problem without drug interactions

In this section, we numerically solve the control problem with a common set of parameters for the three different allocation tradeoffs. We find that the nature of the solutions is fundamentally different between the concave tradeoff versus the linear and convex tradeoffs. Figure 3 shows the optimal state profiles for the three different tradeoff scenarios. We chose not to show the control profiles, as one can easily deduce them from the state profiles of drug concentrations. Regardless of the type of tradeoff, the optimal state profiles have a common beginning—an increase in both drugs simultaneously at the maximum rate to increase drug concentrations as quickly as possible until the upper limit of drug concentration is hit. After this initial phase, there are differences between the concave and the other two tradeoff types. With a concave tradeoff, immediately after the initial phase, drug 1 is further increased and delivery of drug 2 is stopped. Consequently, the tumor becomes resistant to drug 1 and losses resistance to drug 2. Midway through the planning period delivery of drug 1 is stopped and delivery of drug 2 is initiated at the maximum rate. Here, the oncologist exploits the evolutionary tradeoff between the two drugs, by exploiting the tumors susceptibility to drug 2. The tumor responds by losing resistance to drug 1 and gaining resistance to drug 2.

The linear and convex tradeoffs have almost identical optimal state profiles. After the initial phase of drug increase, there is a constant chattering control, which appears to stochastically vary the drugs just slightly from equal concentrations for the rest of the planning period. Recall that for both the linear and the convex tradeoffs, when the tumor is using a maladaptive strategy, the negative effects of the drugs are significantly more when drug concentrations are slightly unequal. This phenomenon is what drives this bizarre solution. Notice however, that the evolutionary strategies are barely changing as drug concentrations are varied up and down. We were curious as to how much of an improvement this chattering control is over a static control of equal drug concentrations after the initial drug increase phase. We found that there is virtually no difference. With both treatment strategies, the ending tumor population size is equal within three decimal places. Obviously, this subtle difference is not clinically significant, and we can regard the optimal control as static, in that the best strategy is to use as much drug as possible and in equal concentrations.

In conclusion, the differences in evolutionary tradeoffs between the concave allocation tradeoff and the other two tradeoffs drive differences in optimal treatment protocols. The concave allocation tradeoff produces a local 'benefit of multitasking' evolutionary tradeoff. This means that the cancer can do slightly better if both drugs are given together in equal amounts. Thus, the best treatment strategy is a dynamic one, where drug concentrations are varied over time. When the cells adapt to resist the first drug, they are hit with the second drug, which they are not evolutionarily prepared for. Contrary to this, both the convex and linear allocation tradeoffs lead to a 'penalty of multitasking' evolutionary tradeoff. With a 'penalty of multitasking' tradeoff, cancer cells do their worst when both drugs are given together in equal amounts. Thus the optimal treatment protocol is static, where both drugs are maintained at equal levels.

Solutions to the control problem with drug interactions

We also explored the effects of drug interactions on solutions to the optimal control problem. Drug interactions can counteract or enhance the effect of tradeoffs on the relationship between evolutionary variables and fitness. For instance, all of our tradeoffs produce global 'penalties of multitasking'. From the oncologist's point of view, the two drugs are evolutionarily complementary in their effectiveness. A strong enough antagonistic interaction between the two drugs however, will ameliorate this effect, since giving the drugs together lessens their effectiveness even though phenotypically cells are not as adept as generalists. We consider three different scenarios that include drug interactions.

First, we consider the linear tradeoff with an antagonistic interaction, to see if we can force a dynamic control solution. The top panel of figure 4 shows that this is indeed the case. Notice how the antagonistic interaction causes the optimal drug concentrations to be pushed to their extremes.

Next, since the optimal treatment for the concave tradeoff was dynamic, we introduce a synergistic interaction to see if this forces a static optimal control. Again the prediction is correct (middle panel of figure 4), even with a relatively weak interaction between the drugs.

Lastly, we consider the convex tradeoff with an antagonistic drug interaction. Interestingly, we find that in this case the control shifts from a static solution of two drugs to a static solution of a single drug, instead of switching to a dynamic solution.

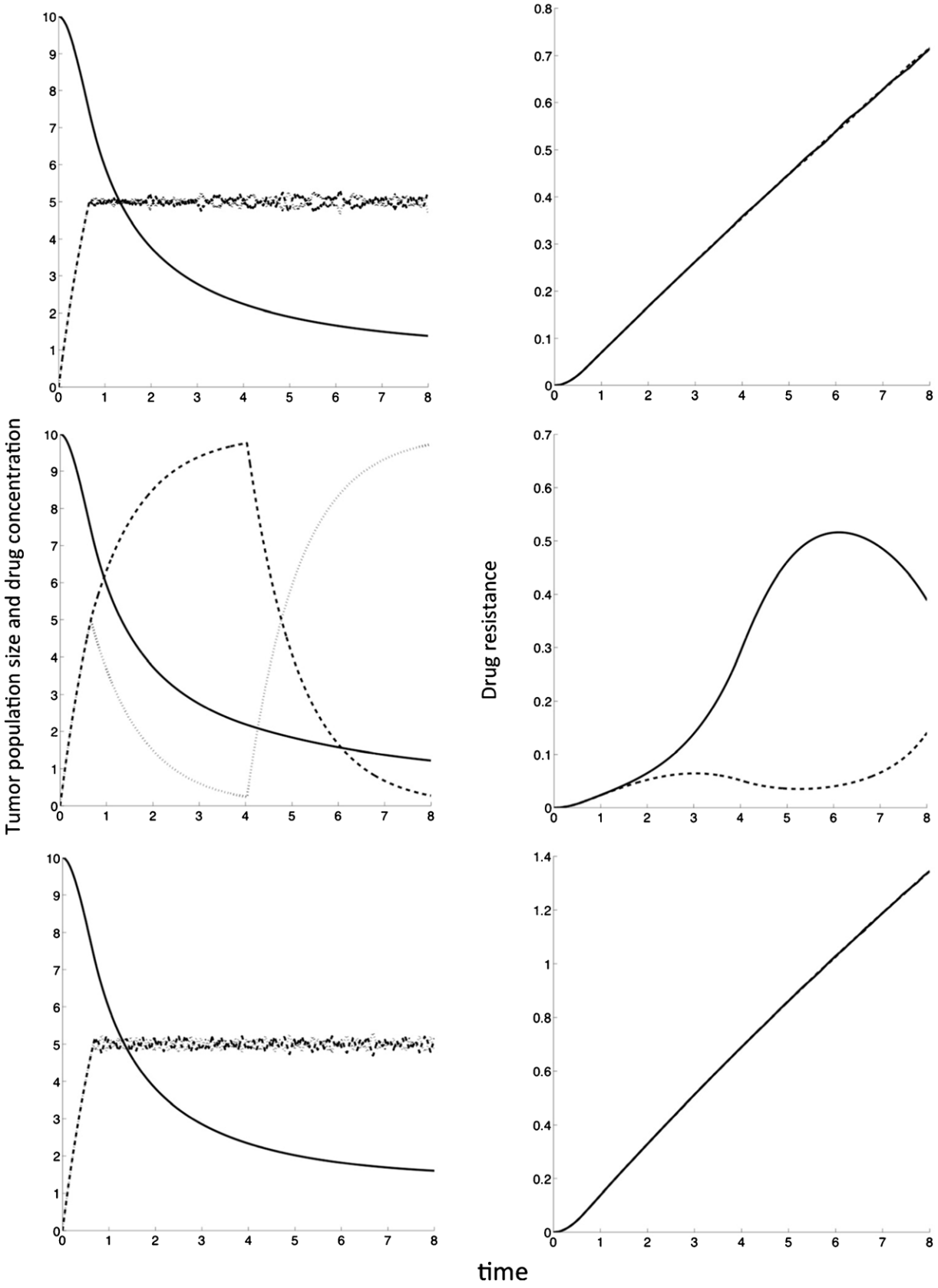

Figure 3. Optimal state profiles for the three different tradeoff types without drug interactions. The left panels show tumor cell densities (solid line) and the concentrations of drug 1 (dashed line) and drug 2 (dotted line). The right panel shows the tumor cells resistance to drug 1 (solid line) and drug 2 (dashed line). The top, middle and bottom panels show the solutions for the linear, concave and convex tradeoffs, respectively. Parameters in common to all panels: $r = 1$, $K_{\max} = 10$, $\sigma_k = 30$, $k_1 = k_2 = 10$, $\beta = 0$, $z_1 = z_2 = 0.9$.

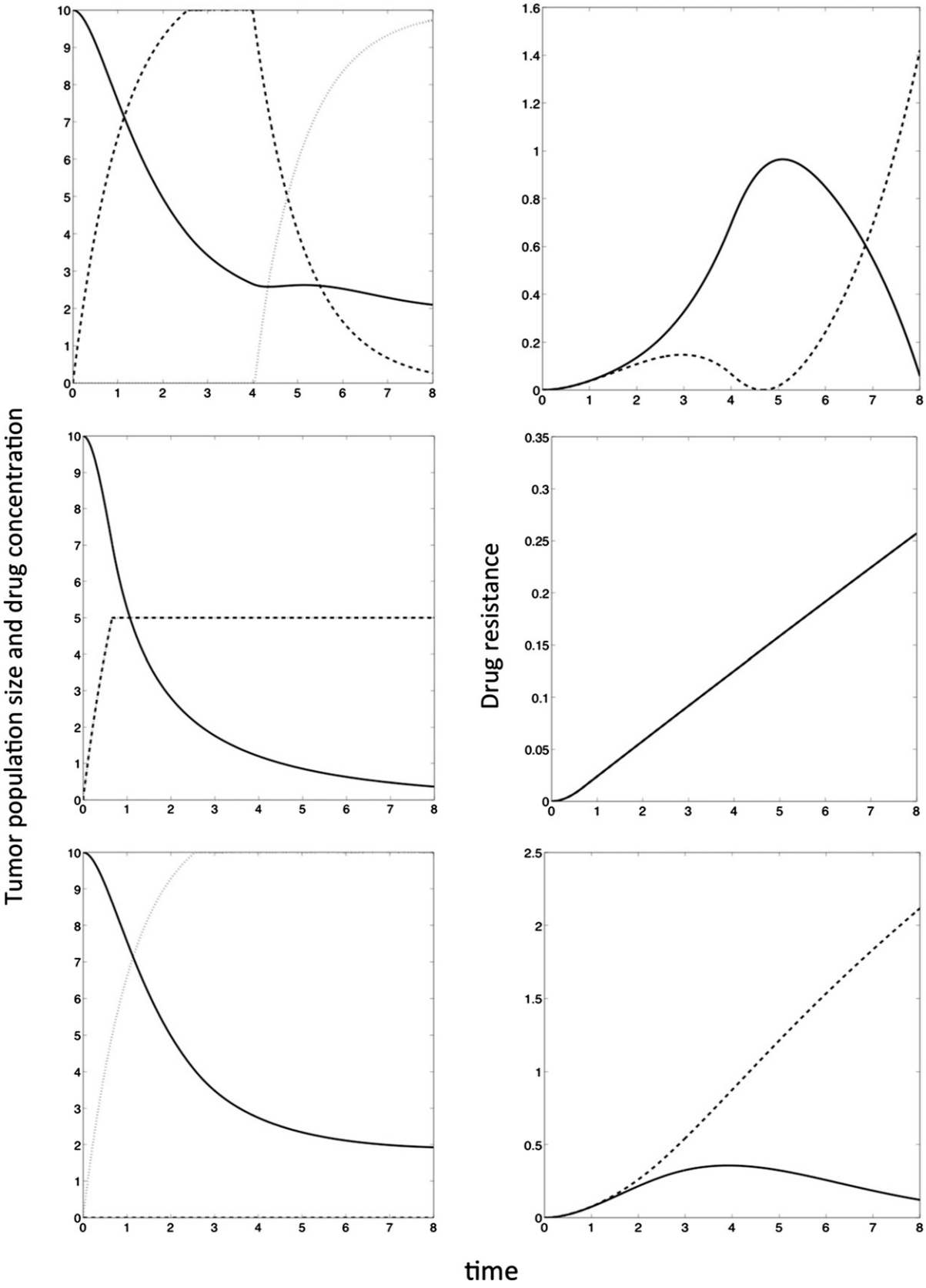

Figure 4. Optimal state profiles for the three different tradeoff types with drug interactions. The left panels show tumor cell densities (solid line) and the concentrations of drug 1 (dashed line) and drug 2 (dotted line). The right panel shows the tumor cells resistance to drug 1 (solid line) and drug 2 (dashed line). The top, middle and bottom panels show the solutions for the linear tradeoff with antagonistic drugs ($\beta = -0.01$), concave tradeoff with synergistic drugs ($\beta = 0.01$), and convex tradeoff with antagonistic drugs ($\beta = -0.01$), respectively. Parameters in common to all panels: $r = 1$, $K_{\max} = 10$, $\sigma_k = 30$, $k_1 = k_2 = 10$, $z_1 = z_2 = 0.9$.

Table 2. Final tumor population sizes under best and worst treatment protocols.

Tradeoff type	Drug interaction	Worst protocol	Best protocol	% Decrease from worst to best
Linear	None	1.42 (*d*)	1.35 (*s*2)	4.92
Linear	Antagonistic	3.21 (*s*2)	2.21 (*d*)	31.2
Concave	None	1.28 (*d*)	1.18 (*d*)	7.81
Concave	Synergistic	0.837 (*d*)	0.332 (*s*2)	60.3
Convex	None	1.85 (*s*1)	1.58 (*s*2)	14.6
Convex	Antagonistic	3.57 (*s*2)	2.00 (*s*1)	44.0

d stands for a dynamic control solution. *s*1 and *s*2 stand for a static control solution of one or two drugs respectively. Parameters for simulations are the same as those used for figures 3 and 4.

Comparing best and worst treatment protocols

Following the lead of Engelhart *et al* (2011) we determine how effective the optimal control solution is by fixing the total amount of drugs over the planning period and investigating the differences between maximizing the final tumor population size at the end of the time period (worst treatment) verses minimizing final the tumor population size (best treatment). We do this for all six scenarios we previously presented (table 2). Most notably, drug interactions strongly inflate the effectiveness of optimal therapy, decreasing tumor size as much as 60% in the case of concave tradeoff with synergistic drug interactions. Without drug interactions, differences in tumor size between the worst and best protocols are minimal. At the extreme, the linear tradeoff yields less than a 5% difference between the two.

Discussion

In this paper, we explore the conceptual model of cancer therapy as an evolutionary game played by the oncologist and the tumor. We specifically model the dynamics that result when tumor cells face an evolutionary tradeoff in resistances between two drugs. We hypothesized that tradeoffs in resistant strategies to two drugs permit the oncologist to exploit the evolutionary responses. Specifically, the application of one drug can promote resistance strategies that increase susceptibility to a second drug, which can then be administered to the detriment of the tumor. We refer to this as an evolutionary double bind. We considered three different resistance allocation tradeoffs to understand how the evolutionary relationships between the drugs affected optimal treatment protocols. Furthermore, we investigated interactions between drugs to see if these ecological effects of the drugs could counteract the effects of the allocation tradeoffs.

Evolutionary tradeoffs and optimal treatment protocols

We found that the concave allocation tradeoff produced a local 'benefit of multitasking'. Specifically, when cells maximized fitness (i.e. using the best phenotypic strategy possible) they had slightly higher fitness (i.e. less negative drug effects) when drugs were administered in equal amounts as opposed to slightly unequal amounts. This led to a dynamic optimal treatment protocol, in which the oncologist used the double bind trap against the tumor.

In contrast, both the linear and convex allocation tradeoffs produce a situation in which cancer cells faced a 'penalty of multitasking'. This means that when the cells were using their best phenotype strategy, they had the lowest fitness (highest negative drug effects) when drugs were administered in equal amounts. This situation intuitively leads to a static optimal treatment where drugs are given in equal amounts.

Cunningham *et al* (2011) discuss an example of a two-treatment therapy, which may represent an evolutionary double bind. They cite a study by Antonia *et al* (2006), which administered a p53 vaccine to patients with small cell lung cancer. Following tumor progression cytotoxic drugs were administered. The study showed that the cytotoxic drug was more effective (response rate of 62% compared to <5% in historical controls) if given following tumor progression after p53 vaccine therapy. This could be an example of exploiting the benefit of multitasking. The therapies were administered sequentially with the second being administered only after failure of the first, which would be optimal when there is a significant benefit of multitasking. Interestingly, our models suggest that if cancer cells face a penalty of multitasking then giving the two treatments simultaneously should result in a better clinical outcome—a prediction that could be tested in follow-up clinical trials.

In current practice, however, an evolutionary double bind may seldom occur in cancer therapy using common chemotherapeutic drugs since multidrug resistance (MDR) due to promiscuous membrane drug transporters (which extrude many different drugs from the cytoplasm) is commonly observed (Gottesman 2002). Thus, tumors composed of cells with multidrug transporters are effectively adapted to a wide range of chemotherapeutic agents. However, not all chemotherapy drugs are substrate for MDR transporters and thus combinations of drugs with different mechanisms of resistance will potentially allow for an evolutionary double bind. Researchers may be able to use insights from evolutionary theory to find such therapy combinations. For example, food and safety are generally evolutionarily complementary (Brown 1992, Brown and Kotler 2004) or in other words they create a 'benefit of multitasking'. Drugs that attack cancer cells' abilities to obtain metabolic substrate (i.e. oxygen and glucose) combined with drugs that are cytotoxic have potential to work as an evolutionary double bind therapy, where the optimal treatment protocol is dynamic. This may be the case with combination anti-angiogenesis and cytotoxic therapies.

Drug interactions can counteract allocation tradeoffs

We found that interactions between the drugs can significantly modify the effects of allocation tradeoffs. For instance, since the linear allocation tradeoff produced an evolutionary penalty of multitasking and thus led to a static optimal treatment protocol, we investigated whether antagonism between the drugs would lead to a dynamic optimal treatment protocol. We found that even a weak antagonistic interaction led to a very dynamic optimal treatment protocol.

Drug–drug interactions appear to be prevalent with cancer chemotherapy. A review article reports 1/3 of chemotherapy patients suffer from drug interactions (Riechelmann and Del Giglio 2009). In this paper, we consider pharmacodynamic type drug interactions. This type of interaction is more elusive and is often discovered only after drugs are already in use (Beijnen and Schellens 2004). Our results stress that it is important to recognize both drug-drug interactions and evolutionary tradeoffs. Since both contribute to how the drugs influence cell fitness, we need to understand how they combine in designing optimal treatment strategies. We showed how drug interactions essentially swamp out the effects of evolutionary tradeoffs. We note that the reverse should also be true. For example if drugs are synergistic in action a oncologist should use both drugs together. However, a strong enough benefit of multitasking evolutionary tradeoff will necessitate a dynamic optimal treatment protocol. Interestingly, the potential role of drug interactions in modifying combination chemotherapy strategies is not typically considered in conventional cancer therapy. Our results suggest this is an important subject for future investigation.

Effectiveness of optimal treatment protocols

Finally, we gauged the usefulness of optimal treatment strategies by fixing the total amount of drug over the planning horizon and comparing the best (minimizing final tumor size) and worst (maximizing final tumor size) treatment protocols. Surprisingly, we found that without drug interactions, even the optimal treatment protocol was not particularly effective. This limited response even to the best available treatment strategy is, in fact, seen in a number of common clinical metastatic cancers including lung, pancreas, renal and colon cancers. It is thus very interesting to note that when drug interactions are included an optimal treatment protocol was substantially more effective.

This suggests that if there are no drug interactions, the specific treatment protocol with a fixed amount of drugs is not too important. However, if there are drug interactions, it is very important to understand the details of the ecology and evolution of the system in planning the best treatment protocol.

Future research directions

A major challenge for this approach is development of empirical methods to investigate optimal control strategies in cancer chemotherapy. In this paper we focus on qualitative results that could be integrated into quantitative models. We predict that the type of evolutionary tradeoff determines the optimal treatment protocol. Empiricists could quantify a fitness tradeoff in the lab (figure (2(*A*)), which are often assessed by measuring components of fitness such as fecundity and death (e.g. Vasi and Lenski 1999). Determining this should give the prediction as to the best treatment protocol. Then dynamic versus static treatments could be compared to see if the prediction is correct. In a more quantitative fashion, a simple eco-evolutionary model could be fit to empirical data. These models could then be used to produce optimization predictions. Then one could compare this to variations of the solution and see how accurate the prediction is. Empirical tests of these results would be a stepping stone to clinical applications of optimal control theory.

In addition to empirical tests, more theoretical development of differential games between an oncologist and cancer are warranted. Specifically, we propose investigation of the consequence of intratumoral cellular heterogeneity as well as different combinations of therapy types on optimal treatment protocols. Individual-based models or partial differential equation models could be used to model spatial heterogeneity and or phenotypic diversity. However, these models are more challenging to accommodate in an optimal control framework. Finally, enforcing a static tumor volume and controlling tumor phenotype is likely a better objective than reducing tumor size, since focusing on tumor size neglects the role of natural selection as the main driver of the progression of cancer.

Acknowledgments

We thank two anonymous reviewers whose comments improved the quality of this paper. This work was supported by grant NIH U54CA143970-01.

References

Antonia S J *et al* 2006 Combination of p53 cancer vaccine with chemotherapy in patients with extensive stage small cell lung cancer *Clin. Cancer Res.* **12** 878–87

Beijnen J H and Schellens J H M 2004 Drug interactions in oncology *Lancet Oncol.* **5** 489–96

Brown J S 1992 Patch use under predation risk: I. Models and predictions *Ann. Zool. Fenn.* **29** 301–9

Brown J S and Kotler B P 2004 Hazardous duty pay and the foraging cost of predation *Ecol. Lett.* **7** 999–1014

Cunningham J J, Gatenby R A and Brown J S 2011 Evolutionary dynamics in cancer therapy *Mol. Pharm.* **8** 2094–100

Engelhart M, Lebiedz D and Sager S 2011 Optimal control for selected cancer chemotherapy ODE models: a view on the potential of optimal schedules and choice of objective function *Math. Biosci.* **229** 123–34

Gatenby R A, Brown J S and Vincent T L 2009 Lessons from applied ecology: cancer control using an evolutionary double bind *Cancer Res.* **69** 7499–502

Gatenby R A and Vincent T L 2003 An evolutionary model of carcinogenesis *Cancer Res.* **63** 6212–20

Gottesman M M 2002 Mechanisms of cancer drug resistance *Annu. Rev. Med.* **53** 615–27

Ledzewicz U and Schattler H 2006 Drug resistance in cancer chemotherapy as an optimal control problem *Discrete Contin. Dyn.* B **6** 129–50

Rao A V, Benson D A, Darby C, Patterson M A, Francolin C, Sanders I and Huntington G T 2010 Algorithm 902: GPOPS, a MATLAB software for solving multiple-phase optimal control problems using the gauss pseudospectral method *ACM Trans. Math. Softw.* **37** 22:1–22:39

Riechelmann R P and Del Giglio A 2009 Drug interaction in oncology: how common are they? *Ann. Oncol.* **20** 1907–12

Vasi F K and Lenski R E 1999 Ecological strategies and fitness tradeoffs in *Escherichia Coli* mutants adapted to prolonged starvation *J. Genet.* **78** 43–9

Vincent T L and Brown J S 2005 *Evolutionary Game Theory, Natural Selection, and Darwinian Dynamics* (Cambridge: Cambridge University Press)

Vincent T L and Gatenby R A 2008 An evolutionary model for initiation, promotion, and progression in carcinogenesis *Int. J. Oncol.* **32** 729–37

Vogel C L *et al* 2002 Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER-2-overexpressing metastatic breast cancer *J. Clin. Oncol.* **20** 719–26