Journal of Theoretical Biology 358 (2014) 166–178

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Modeling oncolytic virotherapy: Is complete tumor-tropism too much of a good thing?

Kenichi W. Okamoto [a,b,*], Priyanga Amarasekare [a], Ian T.D. Petty [c]

[a] Department of Ecology and Evolutionary Biology, University of California, Los Angeles, CA 90095, USA
[b] Department of Entomology, North Carolina State University, Raleigh, NC 27695-7613, USA
[c] Department of Biological Sciences, North Carolina State University, Raleigh, NC 27695-7614, USA

HIGHLIGHTS

- Oncolytic viruses (OVs) selectively infect and lyse tumor cells.
- Complete tumor-tropism is a major goal in developing OVs for cancer treatment.
- We model how OVs also infecting non-cancer cells affect the efficacy of virotherapy.
- OVs exploiting non-tumor cells can clear tumors yet limit damage to normal tissue.
- Tumor-normal cell apparent competition mediated by OVs permits tumor eradication.

ARTICLE INFO

Article history:
Received 29 June 2013
Received in revised form
22 April 2014
Accepted 25 April 2014
Available online 5 May 2014

Keywords:
Oncolytic viruses
Tumor elimination
Apparent competition
Vesicular stomatitis virus

ABSTRACT

The specific targeting of tumor cells by replication-competent oncolytic viruses is considered indispensable for realizing the potential of oncolytic virotherapy. Yet off-target infections by oncolytic viruses may increase virus production, further reducing tumor load. This ability may be critical when tumor-cell scarcity or the onset of an adaptive immune response constrain viral anti-tumoral efficacy. Here we develop a mathematical framework for assessing whether oncolytic viruses with reduced tumor-specificity can more effectively eliminate tumors while keeping losses to normal cell populations low. We find viruses that infect some normal cells can potentially balance the competing goals of tumor elimination and minimizing the effects on normal cell populations. Particularly when infected tissues can be regenerated, moderating rather than completely eliminating the ability of oncolytic viruses to infect and lyse normal cells could improve cancer treatment, with potentially fewer side-effects than conventional treatments such as chemotherapy.

1. Introduction

Two basic approaches are frequently considered when using viruses in cancer treatment. First, replicating or non-replicating viruses that infect tumor cells could be genetically engineered to express genes that render the infected tumor cells more susceptible to immune-mediated killing, chemo- or radioisotope therapy, or prevent angiogenesis. Second, replication-competent viruses can be used to directly lyse infected cells, increasing the viral load and propagating the infection of further tumor cells. Maximizing viral tumor-specificity is a central objective when developing such replication-competent oncolytic viruses that infect and kill tumor cells for cancer therapy (e.g., Sinkovics and Horvath, 2005; Roberts et al., 2006; Vähä-Koskela et al., 2007; Russell et al., 2012). Tumor-specificity can be enhanced in principle by genetically engineering virus strains that exclusively recognize tumor-specific molecules as cellular receptors, or utilizing strains that require a tumor-specific promoter for expressing viral genes needed for replication and subsequent death of the infected cell (e.g., Parato et al., 2005).

The replication of oncolytic viruses during the course of treatment can increase their efficacy, particularly when the tumor cell population size is large. Although each individual virion may have a low probability of infecting a tumor cell, when the population of free virus particles is large, the likelihood that an individual tumor cell will become infected with the virus increases. However, relying on replication-competent viruses to facilitate tumor eradication can carry certain limitations. For instance, when the abundance of tumor host cells falls below a certain threshold, the population of infectious viruses may no

* Corresponding author at: Department of Entomology, North Carolina State University, Raleigh, NC 27695-7613, USA.
E-mail addresses: kenichi_okamoto@ncsu.edu (K.W. Okamoto), amarasek@ucla.edu (P. Amarasekare), itpetty@ncsu.edu (I.T.D. Petty).

http://dx.doi.org/10.1016/j.jtbi.2014.04.030
0022-5193/

longer be sustainable (e.g., Wodarz and Komarova, 2009; Dingli et al., 2009; Wodarz et al., 2012). Moreover, the efficacy of oncolytic virotherapy is constrained by the onset of an adaptive immune response. Such an immune response can, for example, generate large amounts of neutralizing antibodies that render free virus particles impotent (e.g., Ferguson et al., 2012). The combined effects of neutralization by an immune response and scarcity of susceptible host cells can thus ultimately cause viral population extinction. While this may be beneficial from the perspective of minimizing long-term treatment complications, the rapid decline in viral population size may prevent oncolytic viruses from effectively controlling tumors. As a result, the tumor cells may increase from low numbers following viral population extinction, leading to potential relapse.

In patients who have a pre-existing adaptive immune response to an oncolytic virus, infection is prevented or strongly suppressed by the combined effects of neutralizing antibodies on extracellular virus particles and cytotoxic T-lymphocytes (CTLs) that kill virus-infected cells. Thus, a pre-existing adaptive immune response against the virus renders oncolytic virotherapy largely ineffective (e.g., Guo et al., 2010). Furthermore, in patients who have not previously been exposed to the oncolytic virus, a primary adaptive immune response will be initiated shortly after the onset of therapy. Consequently, there is a window of only 5–7 days before virus-specific immune system effectors, antibodies and CTLs, accumulate sufficiently to interfere with virus propagation and the infection begins to wane. Although the adaptive immune response constrains oncolytic virus reproduction, there is ample evidence that successful oncolytic virotherapy also depends on the induction of immune effectors, particularly CTLs, that are directed against tumor cells (e.g., Diaz et al., 2007; reviewed in Prestwich et al., 2009). A therapeutic approach which exploits both these observations is so-called “one-shot” virotherapy, in which a single dose of oncolytic virus is intended to cause tumor clearance. This is achieved through rapid cell lysis prior to the accumulation of adaptive immune system effectors, which is induced either directly by the oncolytic virus or by the innate immune system, combined with the subsequent induction of anti-tumor adaptive immunity (Naik et al., 2012). Indeed, optimal one-shot virotherapy may be expected to require maximizing the viral population size during the 5–7 day window of opportunity for virus propagation before the accumulation of adaptive immune system effectors renders it ineffective.

One approach to rapidly increase the virus population before the onset of an adaptive immune response is to exploit the ability of normal cells to augment oncolytic virus production. In organs capable of self-regeneration (e.g., the liver), infection of normal cells by viruses may be tolerable if such infections can meaningfully facilitate tumor control that would otherwise be difficult. Allowing oncolytic viruses to infect normal cells may result in the propagation of new virus particles, increasing the oncolytic virus population. An increased oncolytic virus population, in turn, can increase the probability that more tumor cells will become infected by the oncolytic virus. Thus, when one host population (e.g., the population of normal cells) can facilitate an increase in the numbers of a shared pathogen (e.g., the oncolytic virus), this increase can thereby have a detrimental effect on a second host population (e.g., the population of tumor cells). Under these conditions, normal cells and tumor cells can be considered to be in apparent competition, which is defined as a reduction in the fitness of one species caused by a second species increasing the numbers of a shared enemy (e.g., Holt, 1977; Chaneton and Bonsall, 2000). Apparent competition has been well studied, both theoretically and empirically, in community ecology (e.g., Holt and Lawton, 1994; Hudson and Greenman, 1998) to describe the dynamics of two prey populations that share a common predator. As a consequence of apparent competition, normal and tumor cells may exert mutually negative effects on each other by sharing a common pathogen (e.g., the oncolytic virus) even in the absence of direct competition for space and nutrients. A key result of apparent competition theory is that the prey species that imposes greater enemy-mediated mortality can drive the other to extinction through an effect similar to competition mediated through resource-use (Holt, 1977). The theory of apparent competition provides an attractive conceptual framework for investigating whether augmenting viral productivity by infecting some normal cells can cause the reduction and eradication (i.e., apparent-competition mediated competitive exclusion) of a tumor cell population.

Historically, oncolytic virotherapy was inspired by clinical reports on tumor remission following infection with pathogenic wild-type viruses (reviewed by Kelly and Russell, 2007). If direct lysing by oncolytic viruses caused reductions in the tumor population in these early studies, variation in total viral load could affect whether tumor remission occurred. If the infection by these viruses of normal cells caused an increase in the virus population, this could result in increased infections of tumor cells and a subsequent reduction in the tumor cell population. Thus, apparent competition may potentially explain some of the historically observed patterns whereby non-specialist wild-type viruses reduced tumor load. Moreover, elucidating the role of apparent competition during oncolytic virus treatment may help explain the findings of recent and future clinical trials using wildtype oncolytic viruses (e.g., Coxsackie virus A21 Shafren et al., 2004 and reovirus Comins et al., 2008).

The non-linearities inherent in the competitive and consumer-resource dynamics that characterize virus-host cell interactions necessitate a mathematical framework that can elucidate the conditions under which oncolytic viruses that infect normal cells can control tumors while simultaneously minimizing the impact on normal cell populations. Such a framework provides a systematic approach linking readily measurable quantities (e.g., viral productivity exploiting a host) to potential treatment outcomes (e.g., likelihood of successful tumor remission, or damage to normal tissue). Mathematical models may therefore provide criteria by which previously untested viruses can be rapidly screened to identify those with the highest potential for success in oncolytic virotherapy. Elucidating the dynamical effects of non-specialist oncolytic viruses on tumor and normal cell populations may also be key to interpreting the outcome of virotherapy trials involving wildtype viruses (Shafren et al., 2004; Comins et al., 2008).

Previous theory has focused largely on the ecological interactions between oncolytic viruses and their susceptible tumor host cell populations. This work has characterized the effect of cancer growth patterns (i.e., whether it is logistic, or Gompertz-type) on successful oncolytic virotherapy, and investigated the stability properties of tumor cell-only and tumor cell-virus equilibria (e.g., Wodarz, 2001; Wu et al., 2001, 2004; Friedman et al., 2006; Bajzer et al., 2008). The potential for oncolytic virus-mediated apparent competition between different cancer cell populations has also received some attention (Wodarz, 2009). These studies have yielded important insights into the balance between tumor cell fitness and the degree of tumor cell virulence of the oncolytic virus required for successful suppression of the tumor. However, none of the previous studies has investigated the potential for indirect, mutually negative interactions via apparent competition between normal cells and tumor cells to affect the course of oncolytic virotherapy. Modeling such pathogen-mediated effects of non-target cells can be key to balancing the damage non-specialist viruses can cause to normal cell populations with prospects for apparent-competition mediated tumor

eradication in a clinically relevant timeframe. A theoretical framework for tumor cell-virus interactions that explicitly incorporates the indirect interactions between tumor cells and normal cells mediated by a shared viral pathogen is therefore critical.

We use our model to compare the ability of oncolytic viruses to become established and reduce tumor load in the presence and absence of tumor-cell specificity. We analyze how the phenotypes of these viruses (e.g., their relative abilities to exploit normal and tumor cells) interact with processes such as viral replication, infection, and the growth and death of normal cells and tumor cells. We model the dynamics for an oncolytic adenovirus, an oncolytic herpes simplex virus (HSV), and an oncolytic vesicular stomatitis virus (VSV) as case studies. We use this comparative approach to identify the conditions under which oncolytic viruses can become established and clear tumors while also keeping the impact on normal cell populations within acceptable levels.

2. Methods

We model the dynamics of an oncolytic virus within the context of its interactions with the populations of tumor cells and normal cells. We integrate key ecological processes, such as the growth of normal cells and tumor cells and an adaptive immune response, with an explicit treatment of how viruses differentially exploit the two cell types.

2.1. Model description

We use as our starting point a model presented in Wu et al. (2001) to characterize an oncolytic virus infecting a population of tumor cells. The model in Wu et al. (2001) is itself an extension of previous models of virus-host interactions (e.g., Nowak and May, 2000), which in turn are based on models of infectious disease dynamics (e.g., Anderson and May, 1979, 1981). Because we seek to model whether the oncolytic virus can exploit normal cells, we extend this model to incorporate the effect of an oncolytic virus on the growth and maintenance of normal cells. Both the tumor and normal cell populations are divided into two subpopulations - cells infected with the oncolytic virus (C_I and H_I for tumor and normal cells infected with the virus, respectively), and cells that are not infected with the oncolytic virus (C_S and H_S for susceptible tumor and normal cells, respectively). When an oncolytic virus can infect both normal and tumor cells, the dynamics of the virus, normal cells, and tumor cells prior to the onset of an adaptive immune response are given by

$$\begin{aligned}
\frac{dH_S}{dt} &= r_H H_S\left(1-\frac{(H_S+H_I)}{K_H}\right)-H_S\beta_H v\\
\frac{dC_S}{dt} &= r_C C_S\left(1-\frac{(C_S+C_I)}{K_C}\right)-C_S\beta_C v\\
\frac{dC_I}{dt} &= \beta_C C_S v-\lambda_C C_I\\
\frac{dH_I}{dt} &= \beta_H H_S v-\lambda_H H_I\\
\frac{dv}{dt} &= b_C\lambda_C C_I+b_H b_C\lambda_H H_I-\beta_H H_s v-\beta_C C_s v-\omega v. \qquad (1)
\end{aligned}$$

In Eq. (1), virions encounter and infect cell-type j at a per-capita rate β_j, while λ_j is the lysing rate of an infected cell of type j, and during the course of the infection (or upon lysing) the virus releases b_j infectious virion propagules from each cell of type j that it infects (i.e., b_j is the burst size for viruses infecting cell type j). For brevity, we refer to the parameter β_j as the infection rate for the remainder of the article. An oncolytic virus capable of exploiting normal cells (i.e., $\beta_H>0$ and $\lambda_H>0$) is defined as the "generalist" virus, and an oncolytic virus only capable of exploiting tumor cells is denoted as the "specialist" virus (i.e., $\beta_H=0$ or $\lambda_H=0$). To facilitate comparison with earlier models of oncolytic viruses (e.g., Wodarz, 2001; Wu et al., 2001, 2004; Friedman et al., 2006; Bajzer et al., 2008; Tao and Guo, 2005), we retain the assumption that infected tumor cells cannot reproduce. For simplicity and to retain symmetry with the behavior of the virus exclusively infecting tumor cells, we assume that normal cells infected with the virus also do not reproduce. We highlight that model (1) implies that when all cells are infected with the oncolytic virus, the cell population will ultimately go extinct. Analyzing how generalist oncolytic viruses affect the population of non-tumor cells is key to assessing the potential risks such viruses can pose during virotherapy.

In Eq. (1), free virus particles are cleared or potentially inactivated by an innate immune response at rate ω. If the virus is not cleared by an innate immune response, the initiation of oncolytic virotherapy is expected to induce a primary adaptive immune response (Prestwich et al., 2009; Ferguson et al., 2012) that further reduces viral transmission between cells. However, the effects of this adaptive immune response on viral dynamics are delayed due to, for instance, the production of sufficient antibodies to have an effect on dynamics (Marchuk, 1997; Perelson and Weisbuch, 1997). Thus, an oncolytic virus can initially propagate in the absence of an adaptive immune response, and the dynamics described by Eq. (1) describe this early transient stage during oncolytic virotherapy. In particular, Eq. (1) characterizes the interactions between viruses and their host cells between the initial administration of viruses until the delayed immune response is activated. Once the adaptive immune response begins to affect viral population dynamics (typically after 7 days – e.g., Janeway et al., 1996), we assume the oncolytic virus is rapidly eliminated. Hence, we restrict our analysis of the dynamical behavior of Eq. (1) prior to the onset of an adaptive immune response. We assume that if tumor elimination fails prior to the onset of an adaptive immune response (i.e., if $C_S(t)>0$ when $t\geq 7$ days), further viral infections will cease and that the tumor subsequently relapses.

Eq. (1) follows Gatenby (1995) and others (e.g., Novozhilov et al., 2006; Dou and Zheng, 2010) in assuming that the growth of the tumor and normal cell populations, in the absence of the virus, can be characterized using logistic growth dynamics. Supplementary Information 1 analyzes the dynamics of the tumor-normal cell interactions in the absence of oncolytic virotherapy, and specifies the conditions under which the tumor cell population can invade into a population of normal cells. In the main text, we model the population of normal cells at the onset of virotherapy as being at the normal cell carrying capacity K_H. Thus, we assume a normal cell population size that is initially at equilibrium, and that normal cell population growth does not occur before the normal cells have been infected and lysed by the generalist oncolytic virus. Modeling the growth of normal cells in this way therefore describes the regeneration of normal tissue (e.g., Gatenby et al., 2006), which can be modeled to occur on the same time scale as tumor growth dynamics (e.g., Gatenby, 1991, 1995). We assume such regeneration occurs only during and after virotherapy. Moreover, although other tumor growth models could potentially be considered (e.g., Wodarz and Komarova, 2009; Komarova and Wodarz, 2010; Rommelfanger et al., 2012), we begin with a logistic growth model for describing growth in the host cell populations for several reasons. First, it captures a decelerating growth rate as tumors increase in size, as is observed experimentally (e.g., Spratt et al., 1993). Second, its dynamics can describe key qualitative predictions of a number of more complex tumor cell-normal cell interaction models that explicitly account for resource supply and utilization (e.g., Kuang et al., 2004). Indeed, as one of the simplest models that can capture key components of cell population dynamics, a logistic model represents a natural starting point

for investigating the virus-mediated interactions between normal cell and tumor cell populations.

3. Model analysis and results

We use a combination of analytical and numerical methods to predict and compare how viruses exhibiting different combinations of per-capita normal cell infection rates (β_H), virulence (λ_H), and burst size (b_H) effect reductions in the tumor burden. We address three key questions pertaining to whether apparent competition could be effective during oncolytic virotherapy:

- What are the conditions under which infection of normal cells by oncolytic viruses facilitates an increase in the virus population size?
- When does the infection of normal cells by oncolytic viruses facilitate tumor removal in a realistic time frame?
- What are the effects of apparent competition on normal cell populations?

3.1. When does infection of normal cells by oncolytic viruses facilitate an increase in the virus population size?

Increasing the virus population size is particularly key during two stages of treatment: (i) during the early stages until the virus population becomes established, and (ii) when tumor cells are not as abundant, as may occur when remnant tumor cells persist following alternative treatments (e.g., surgery, chemotherapy), or after oncolytic viruses have substantially reduced the supply of susceptible tumor cells. Here we assess whether apparent competition between normal cells and tumor cells can facilitate viral population growth during these two treatment stages.

During the early stages of treatment, the ability of the virus to increase when rare could potentially govern whether the virus can cause any reduction in tumor burden. In particular, when the oncolytic viruses are administered intravenously, only a relatively small number of virus particles may ultimately encounter tumor cells. Although direct intratumoral injection may ameliorate such losses, such injections are not always clinically feasible due to tumor inaccessibility (e.g., Crittenden et al., 2005). To assess the impact of apparent competition on promoting virus spread, we compare the conditions that permit a generalist virus (i.e., one that can infect normal cells as well as tumor cells) to become established when the virus is rare, to conditions allowing a tumor-cell specialist virus to become established when rare. We analyze the local stability of our model when the virus is rare and no host cells are infected (i.e., $C_I, H_I = 0$ and $v(t) \approx 0$), assuming the population sizes of susceptible cancer and normal cells to be approximately constant during the very early stages of virotherapy (so that $dC_S/dt \approx 0$ and $dH_S/dt \approx 0$ when $v(t) \approx 0$). Free virus dynamics can occur on a faster time-scale than host-cell dynamics (e.g., Wu et al., 2001), and thus the assumption that susceptible normal and tumor cell population sizes are approximately constant at the onset of virotherapy may be reasonable if relatively few cells are infected very early in the treatment regime (Wu et al., 2004). Our main conclusions on the parameters governing the ability of the virus population to increase are summarized in Table 1 (for detailed derivations, see Supplementary Information 2).

If the oncolytic virus is a complete tumor cell specialist (i.e., $\lambda_H = 0$ and $\beta_H = 0$), the threshold burst size necessary for virus population expansion rapidly increases as tumor cells become rarer. By contrast, an oncolytic virus capable of infecting both normal cells and tumor cells need not release a large number of propagules; for instance, the threshold burst size b_H for normal cells sufficient for sustaining virus population establishment can be much lower when the normal cell population is large (Table 1).

However, infecting normal cells is not always conducive to facilitating virus population growth. For instance, if the ability of a generalist oncolytic virus to lyse normal cells is poor, then the threshold burst size necessary for a virus population to increase actually exceeds the threshold burst size for a tumor-specialist virus. Moreover, if normal cells are very abundant relative to tumor cells, oncolytic viruses that are poor at lysing normal cells must have a very high infection rate of tumor cells, or a large tumor-cell specific burst size, to compensate for the inability of normal cells to propagate the infection. This characterizes a potential limitation of leveraging apparent competition to facilitate viral establishment: for an oncolytic virus that can encounter and be absorbed into normal cells, non-target cells can become sinks if the virus is unable to propagate effectively in such cells.

Oncolytic virus population growth is also important when the supply of susceptible tumor cells is low even after the virus has become established and is no longer rare (as may happen as the treatment progresses, or in cases where the virus can be injected close to the tumor). We show in Supplementary Information 3 that the conditions characterizing the ability of the virus to increase when rare have a similar effect on the ability of the virus population to continue increasing during any stage of the infection. The key result is that when uninfected normal cells are abundant (H_S large), apparent competition can lower the threshold of the tumor-cell specific infection rate β_C necessary for continued viral propagation.

Table 1
The effect of apparent competition on virus population growth.

Scenario	Conditions for virus population increase	Biological interpretation
Apparent competition very weak ($\lambda_H \ll \lambda_C$ and $\beta_H \ll \beta_C$)	$b_C > \frac{\omega}{\beta_C C_S} + 1$	When uninfected tumor cells are rare, the virus must have a correspondingly large burst size for the virus population to continue increasing
Virus infects normal cells at a lower rate than tumor cells, but is much poorer at lysing tumor cells ($0 < \beta_H < \beta_C$ and $\lambda_H \gg \lambda_C$)	$b_H > \frac{\omega+\beta_H H_S}{\beta_H H_S} + \frac{\beta_C C_S}{\beta_H H_S}$	If uninfected normal cells are very abundant relative to uninfected tumor cells (as could occur, e.g., with early diagnosis or following removal of some fraction of the tumor), even if the infection rate of tumor cells is larger than the infection rate of normal cells ($\beta_H < \beta_C$), the threshold burst size need not be much larger than 1
Virus infects normal cells at a higher rate than tumor cells, but is much poorer at lysing normal cells ($\beta_H > \beta_C > 0$ and $\lambda_H \ll \lambda_C$)	$b_C > \frac{\omega+\beta_C C_S}{\beta_C C_S} + \frac{\beta_H H_S}{\beta_C C_S}$	Normal cells have the potential to become sinks for the virus; in particular, if $\beta_C \ll \beta_H$ or $H_S \gg C_S$, the threshold burst size for viruses infecting tumor cells increases considerably
Virus infects and lyses normal cells and tumor cells at the same rate ($\beta_H = \beta_C = \beta$ and $\lambda_H = \lambda_C = \lambda$)	$b_H > \frac{\omega+\beta C_S}{\beta H_S} + 1$ or $b_C > \frac{\omega+\beta H_S(1-b_H)}{\beta C_S} + 1$	Abundant normal cells can lower the threshold burst size for normal cells b_H required for the virus population to continue increasing

3.2. Comparing the ability of oncolytic viruses to cause tumor elimination in a realistic time frame

An adaptive immune response can substantially reduce the ability of virus particles to be transmitted between cells, for example, by generating large amounts of antibodies that inactivate free virions (e.g., Ferguson et al., 2012). Thus, the transient dynamics prior to the onset of a primary adaptive immune response are especially critical in determining the efficacy of an oncolytic virus. The conditions under which all tumor cells become infected (and thus tumor extinction occurs) in model (1) during this transient stage cannot be derived analytically and must be assessed numerically. We conduct our numerical analyses over a treatment schedule of 7 days, a realistic timeframe given that a strong, primary adaptive immune response will be mounted against the virus (e.g., Janeway et al., 1996). All numerical integrations are carried out using the lsoda routine in R (Soetaert et al., 2010) with the absolute error tolerance set at machine precision ϵ ($\epsilon = 2^{-52}$).

The interaction between viruses and tumor cells is parameterized using data from three biologically distinct oncolytic viruses that have been the subject of earlier modeling work (Wu et al., 2001; Zhu and Yin, 2005; Friedman et al., 2006; Rommelfanger et al., 2012). Tables 2 and 3 summarize the baseline parameter values we use for cell growth and for each virus, Table 3 notes the key biological characteristics that distinguish the interactions of the virus with its tumor cell hosts. We carried out extensive numerical simulations of the tumor-specialist version of the model under a larger range of parameter values (Supplementary Information 4). These simulations illustrate that the burst size b_C and infection rate β_C can have an especially clear effect on the ability of an oncolytic virus to drive the tumor cell population extinct within a short timeframe. Moreover, the infection rate β_C of tumor cells is a particularly difficult parameter to estimate reliably (e.g., Wu et al., 2001). Thus, for all three oncolytic viruses, in addition to varying the ability of the virus to exploit normal cells (i.e., λ_H, b_H and β_H in model (1)), we also systematically vary the tumor cell infection rate β_C across a pre-determined range. To assess whether apparent competition with normal cells can change the outcome of oncolytic virus treatment, we constrain this range with values that permit the persistence of the tumor cell population at the end of the simulated treatment period in the absence of apparent competition (Supplementary Information 4).

For all three viruses, if the ability of oncolytic viruses to exploit normal and tumor cells is comparable, apparent competition shifts the outcome of oncolytic virotherapy from being unable to eradicate the tumor to successfully infecting all tumor cells prior to the onset of an adaptive immune response (Fig. 1). We find that the rate at which apparent competition can facilitate complete infection of the tumor cell population is much faster for oncolytic adenoviruses and HSV than it is for VSV, where the virus' baseline infection rate β_C of tumor cells is much lower.

In practice, the ability of oncolytic viruses to exploit normal cells on the one hand, and their ability to exploit tumor cells on the other, are likely to differ. Thus, we vary the lysing rate λ_H and the burst size b_H of normal cells relative to the corresponding values for tumor cells. To model viruses engineered to reduce losses to normal cell populations, we restrict our numerical analysis of apparent competition to regions of parameter space where the oncolytic viruses are no more efficient at infecting and exploiting normal cells than they are at infecting and exploiting tumor cells (i.e., $\lambda_H \leq \lambda_C$ and $b_H \leq b_C$). For each lysing rate/burst

Table 2
Parameters and units/values governing cell growth.

Parameter	Interpretation	Units	Value/Range	Reference
r_H	The per-capita growth rate of normal cells	hr^{-1}	0.00275	Smalley et al. (2001)
r_C	The per-capita growth rate of tumor cells	hr^{-1}	0.003	Wu et al. (2001)
K_H	The carrying capacity of normal cells	cells	10^{11}	Montaigne (2006)
K_C	The carrying capacity of tumor cells	cells	1.47×10^{12}	Andersen et al. (2000) and Wu et al. (2001)

Table 3
Parameters for different oncolytic viruses.

Virus	Parameter	Interpretation	Default value/Range	Units	Reference
Adenovirus (ONYX-15)	λ_C	Lysing rate of tumor cells	$\frac{1}{48}$	$cell^{-1}\,hr^{-1}$	Wu et al. (2001)
	b_C	Burst size from lysing infected tumor cells	1000	–	Wu et al. (2001)
	ω	Viral clearance rate	1	$Virus^{-1}\,hr^{-1}$	Wu et al. (2001)
	β_C	Uptake/encounter/infection rate of tumor cells	$(5.25 \times 10^{-12}, 5.25 \times 10^{-13.5})$	viruses $cell^{-1}\,hr^{-1}$	Range that permits tumour cell persistence after 7 days
HSV	λ_C	Lysing rate of tumor cells	$\frac{1}{18}$	$cell^{-1}\,hr^{-1}$	Friedman et al. (2006)
	b_C	Burst size from lysing infected tumor cells	50	–	Friedman et al. (2006)
	ω	Viral clearance rate	0.025	$virus^{-1}\,hr^{-1}$	Friedman et al. (2006)
	β_C	Uptake/encounter/infection rate of tumor cells	$(2.5 \times 10^{-12}, 2.5 \times 10^{-13.5})$	viruses $cell^{-1}\,hr^{-1}$	Range that permits tumour cell persistence after 7 days
VSV	λ_C	Lysing rate of tumor cells	$\frac{1}{24}$	$cell^{-1}\,hr^{-1}$	Rescaled from daily rate in Eftimie et al. (2011)
	b_C	Burst size from lysing infected tumor cells	1350	–	Zhu and Yin (2005)
	ω	Viral clearance rate	0.244	$Virus^{-1}\,hr^{-1}$	Based on the half-life reported in Croyle et al. (2004)
	β_C	Uptake/encounter/infection rate of tumor cells	$(5 \times 10^{-12.5}, 5 \times 10^{-14})$	viruses $cell^{-1}\,hr^{-1}$	Range that permits tumor cell persistence after 7 days

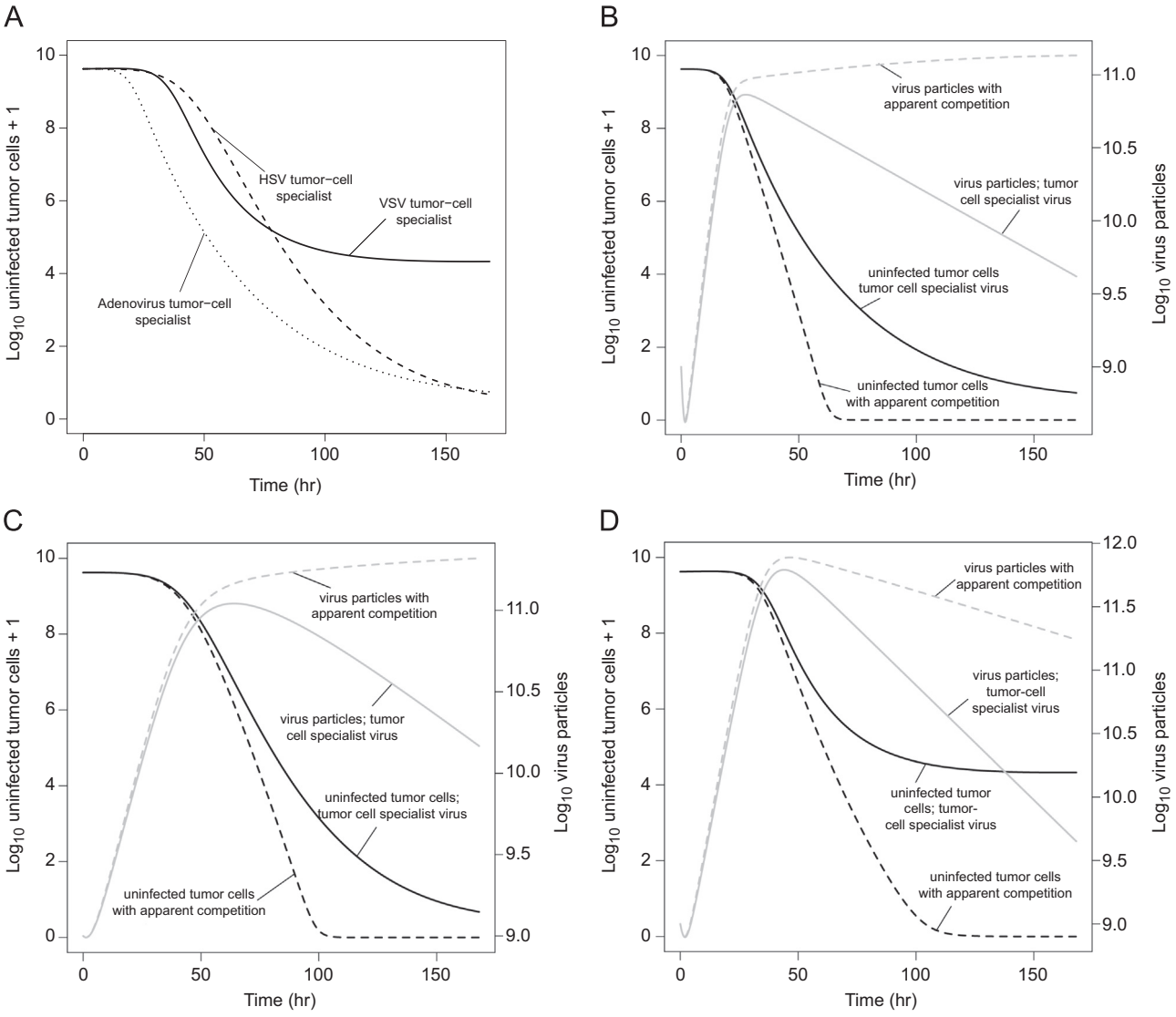

Fig. 1. The population dynamics predicted by Eq. (1) for (a) uninfected tumor cells for each of the three viruses modeled in the absence of apparent competition, (b) uninfected tumor cells with (dashed black line) and without (solid black line) apparent competition and free virus particles with (dashed grey line) and without (solid grey line) apparent competition for an oncolytic adenovirus, (c) uninfected tumor cells with (dashed black line) and without (solid black line) apparent competition and free virus particles with (dashed grey line) and without (solid grey line) apparent competition for an oncolytic HSV, and (d) uninfected tumor cells with (dashed black line) and without (solid black line) apparent competition and free virus particles with (dashed grey line) and without (solid grey line) apparent competition for an oncolytic VSV. The baseline infection rate β_C of tumor cells is $\beta_C = 5.0 \times 10^{-12}$ cell^{-1} pfu^{-1} for the adenovirus, $\beta_C = 2.5 \times 10^{-12}$ cell^{-1} pfu^{-1} for HSV, and $\beta_C = 5.0 \times 10^{-13}$ cell^{-1} pfu^{-1} for VSV. In all panels, the relative lysing rates and burst sizes of normal cells and tumor cells are 1 and the normal cell to tumor cell infection rate ratio is 0.0025. In this, and in subsequent figures, the initial tumor cell population size is 4.2×10^9 cells, which corresponds to the number of cells that could be found in a tumor approximately 2 cm in diameter.

size combination, we also systematically vary the infection rate β_H of normal cells and the baseline tumor cell infection rate β_C to assess the effects of apparent competition on tumor reduction. Although the initial inoculum load (the amount of virus particles injected at the beginning of treatment) is potentially readily manipulated in clinical settings, varying this value across three orders of magnitude (10^8–10^{10}) did not affect our main conclusions, so for brevity we present results only from cases where the initial free virus load $V_0 = 10^9$ pfu.

Fig. 2 illustrates how allowing oncolytic viruses to infect normal cells can affect tumor elimination. When oncolytic viruses are most virulent against normal cells (high λ_H), produce more infectious virions upon infecting normal cells (high b_h), and are able to infect normal cells most readily (high β_h/β_C), then apparent competition can cause tumor eradication, before the onset of an adaptive immune response.

For all oncolytic viruses we model, when the baseline infection rate β_C of tumor cells by oncolytic viruses is low, the infectivity of the virus towards normal cells relative to its infectivity towards tumor cells (β_H/β_C) must be high for apparent competition to cause tumor eradication (Figs. 2–4). As the burst size of oncolytic viruses exploiting normal cells increases, lower infection rates of normal cells suffice to allow the virus to infect all tumor cells. This effect is consistent across a range of lysing rates. Moreover, for moderate and large burst sizes, viruses that are more efficient at lysing normal cells enable tumor eradication under lower normal cell infection rates.

These results also illustrate how normal cells can act as sinks for oncolytic viruses that have high infection (uptake) rates for both tumor and normal cells; even if they have high infection rates, viruses that are less able to exploit normal cells (lower lysing rates or burst sizes) fail to infect all tumor cells within the requisite time frame.

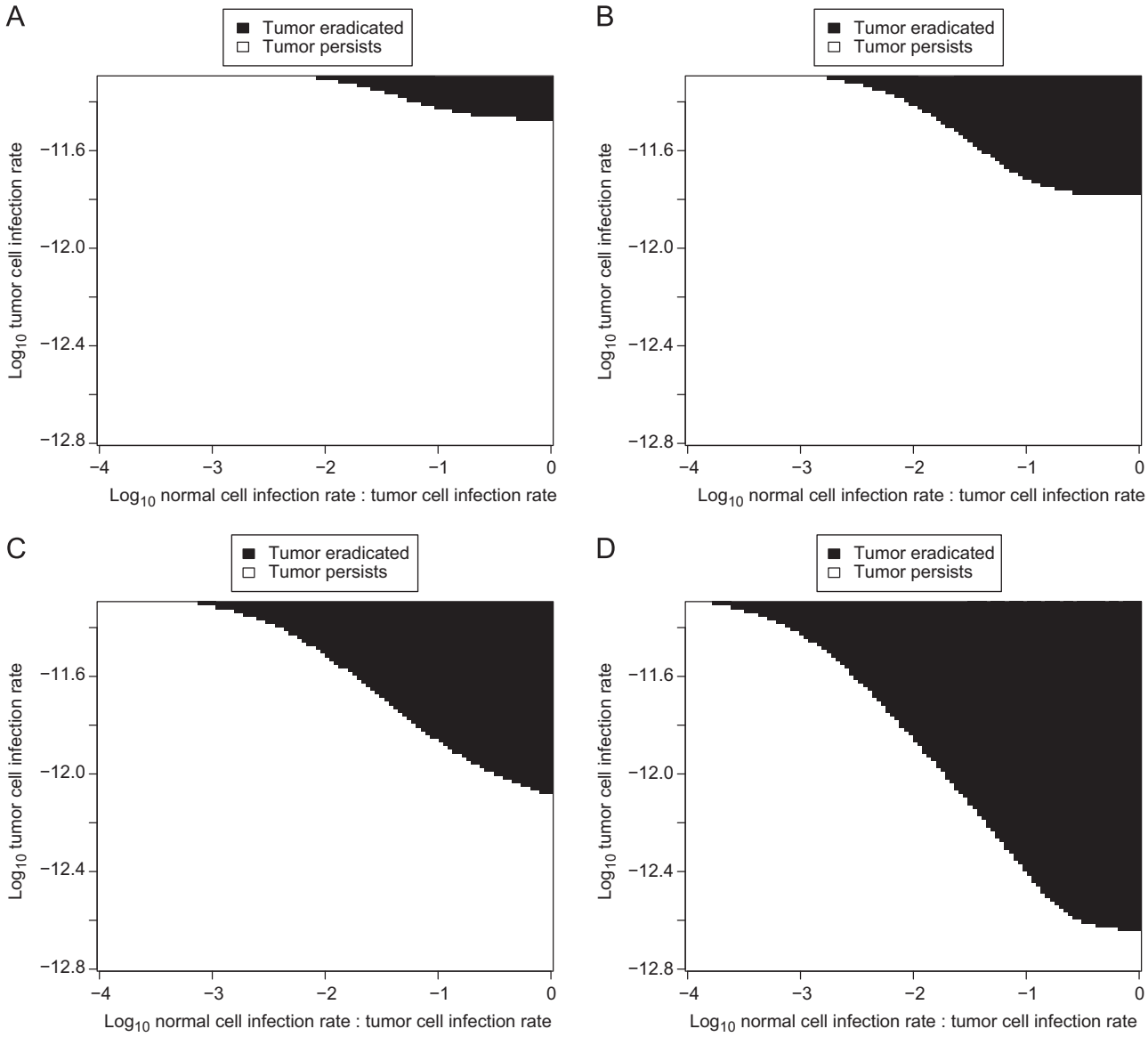

Fig. 2. The effect of the baseline infection rate β_C of tumor cells and the scaled infection rate β_H of normal cells on the ability of an oncolytic adenovirus virus capable of infecting both healthy and tumor cells to eradicate the tumor population within 7 days when (A) the ratio λ_H/λ_C of lysing rates for normal cells to tumor cells = 0.1 and the ratio b_H/b_C of burst sizes for normal cells to tumor cells = 0.1, (B) $\lambda_H/\lambda_C = 0.1$ and $b_H/b_C = 1$, (C) $\lambda_H/\lambda_C = 1$ and $b_H/b_C = 0.1$, and (D) $\lambda_H/\lambda_C = 1$ and $b_H/b_C = 1$. We note that in this, and in Figs. 3 and 4, tumor eradication (black region) occurs when the population of uninfected tumor cells declines below one cell.

We find that these conclusions apply to all three oncolytic viruses modeled. Nevertheless, minor differences exist between different viruses in the quantitative results. For instance, the ability of normal cells to act as sinks is more apparent for oncolytic HSV capable of infecting normal cells. This is because HSV has a relatively lower baseline burst size than the other oncolytic viruses analyzed. Hence, if the burst size of HSV infecting normal cells is also low, then even when HSV is able to infect normal cells at a high rate, most such infections fail to produce large numbers of new virions, mitigating the advantages of apparent competition (Fig. 3). We also find that, because oncolytic VSV has a much lower infection rate of tumor cells than adenovirus or HSV, oncolytic VSV must also infect normal cells at a higher rate for apparent competition to cause tumor eradication (Fig. 4).

3.3. How does apparent competition affect normal cells?

Oncolytic viruses that rely on apparent competition for tumor elimination should ideally still minimize their impact on normal cell populations. Fig. 5 presents the corresponding effects on the population of normal cells caused by different generalist oncolytic viruses. For the parameter ranges we consider, the effect of the generalist virus on normal cells depends strongly on the relative infection rates for tumor and normal cells. Indeed, when the baseline infection rate of tumor cells is high, if the ratio of infection rates of normal cells to the infection rates of tumor cells is modest (so that viruses are much likelier to infect tumor cells), the impact on the population of normal cells also is modest.

For all oncolytic viruses, when the infection rate β_H of normal cells is between $\frac{1}{1000}$th to $\frac{1}{100}$th of the infection rate of tumor cells, the virus often infects a relatively small fraction of normal cells even when the infection rate of tumor cells is high. Increasing the relative burst sizes of each virus in normal cells does not substantially change the region of parameter space where normal cells are infected in large numbers (results not shown). Indeed, for all viruses analyzed, tumor eradication occurs when the baseline infection rate β_C of tumor cells is high, the infection rate β_H of normal cells is modest, and the lysing rates and burst sizes of normal cells is

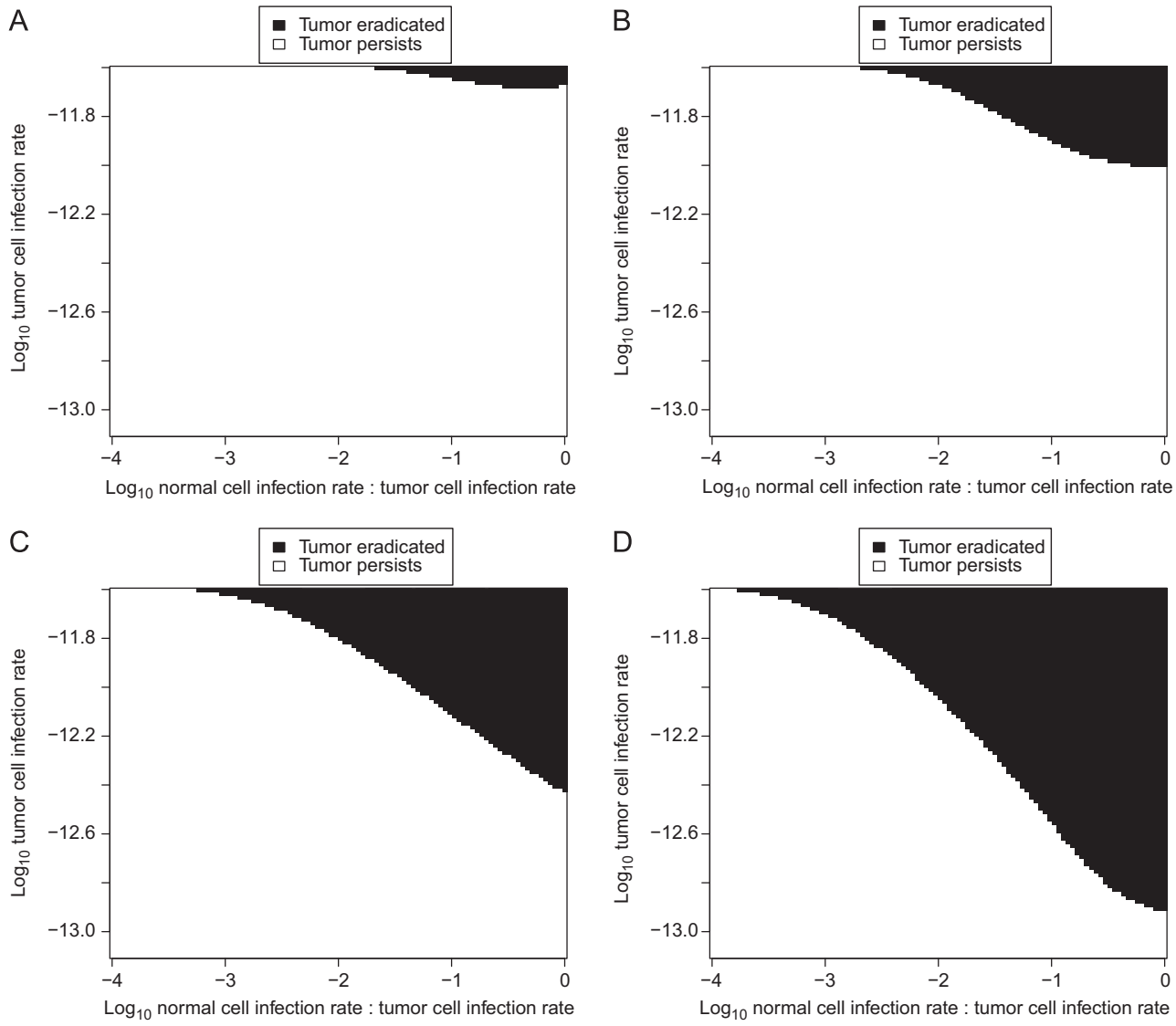

Fig. 3. The effect of the baseline infection rate β_C of tumor cells and the scaled infection rate β_H of normal cells on the ability of an oncolytic HSV capable of infecting both healthy and tumor cells to eradicate the tumor population within 7 days when (A) the ratio λ_H/λ_C of lysing rates for normal cells to tumor cells = 0.1 and the ratio b_H/b_C of burst sizes for normal cells to tumor cells = 0.1, (B) $\lambda_H/\lambda_C = 0.1$ and $b_H/b_C = 1$, (C) $\lambda_H/\lambda_C = 1$ and $b_H/b_C = 0.1$, and (D) $\lambda_H/\lambda_C = 1$ and $b_H/b_C = 1$.

maximal (Figs. 2–4). We highlight two key results. First, reducing only the infection rate β_H for normal cells can mitigate against apparent competition adversely affecting normal cell populations. Second, increasing the lysing rate λ_H for normal cells and/or the burst size b_H of viruses released from normal cells greatly increases the efficacy of apparent competition, but does not always cause substantial numbers of infections among the normal cell population. We note, however, that allowing oncolytic viruses that are completely indiscriminate between normal and tumor cells (so that $\beta_H = \beta_C$) would be undesirable, as they would infect a far larger fraction of normal cells prior to the onset of an adaptive immune response than would be necessary for tumor elimination.

4. Discussion

We show that allowing oncolytic viruses to propagate by infecting a limited number of normal cells can have a profound effect on the trajectory of oncolytic virotherapy. In particular, apparent competition can release virus population growth from being dependent on replication in tumor cells, promoting the control of tumors that may otherwise not be treatable with oncolytic viruses prior to the onset of a primary adaptive immune response. Our results are robust across the biologically distinct oncolytic viruses we examined whose key parameter values can differ by orders of magnitude.

Oncolytic virotherapy is often seen as having two major goals. First, due to concerns regarding the potential toxicity of non-specialist viruses (Kirn et al., 2001) and the possible side-effects arising from oncolytic viruses infecting normal cells (Kuruppu and Tanabe, 2005; Kelly and Russell, 2007), complete tumor-cell tropism has come to be regarded as indispensable for oncolytic virotherapy (Russell et al., 2012). Second, rapid clearance of the virus by an adaptive immune response constrains the timeframe in which virotherapy must eliminate the tumor, and thus therapeutic strategies utilizing oncolytic viruses often aim to infect all tumor cells prior to the onset of an adaptive immune response (reviewed in Prestwich et al., 2009). Consequently, development work on oncolytic viruses has focused on achieving both complete tumor-cell specificity of the oncolytic virus, and the ability to rapidly eliminate tumors *in vivo*. Our work suggests that these two goals may be somewhat at odds, and that a balance can be struck by reducing

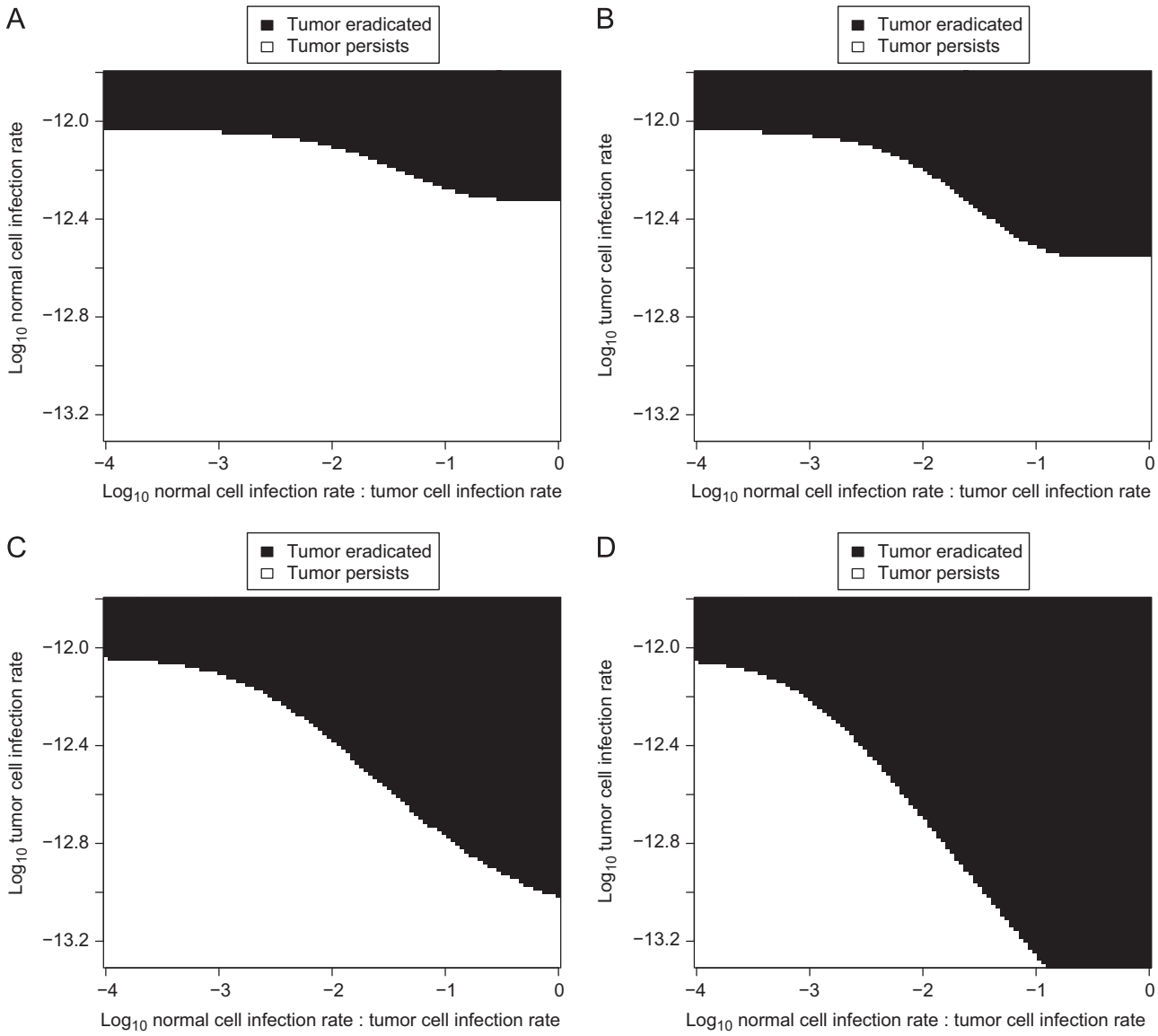

Fig. 4. The effect of the baseline infection rate β_C of tumor cells and the scaled infection rate β_H of normal cells on the ability of an oncolytic VSV capable of infecting both healthy and tumor cells to eradicate the tumor population within 7 days when (A) the ratio λ_H/λ_C of lysing rates for normal cells to tumor cells = 0.1 and the ratio $\frac{b_H}{b_C}$ of burst sizes for normal cells to tumor cells = 0.1, (B) $\lambda_H/\lambda_C = 0.1$ and $b_H/b_C = 1$, (C) $\lambda_H/\lambda_C = 1$ and $b_H/b_C = 0.1$, and (D) $\lambda_H/\lambda_C = 1$ and $b_H/b_C = 1$.

tumor-cell specificity below 100% to facilitate tumor clearance. In our modeling, we also deliberately constrained the timeframe to identify conditions under which an oncolytic virus could infect all tumor cells prior to the onset of the primary adaptive immune response. This permits the immune response to ultimately clear the oncolytic virus, and potentially carry out immune system-mediated killing of any remaining tumor cells. Such post-virotherapy clearing of the virus by an adaptive immune response could also be beneficial for mitigating unintended risks associated with the use of a generalist virus, such as uncontrolled infections (e.g., Kuruppu and Tanabe, 2005) or even possible carcinogenesis.

The most compelling argument advanced in favor of having complete tumor cell specificity in an oncolytic virus is to minimize, or eliminate, off-target effects on normal cells and tissues, and thus prevent side-effects. However, the tolerance, in the broadest sense, for such collateral damage will vary depending on the situation. Patients with life-threatening cancers, and their clinicians, accept the often considerable side-effects of conventional chemotherapy in pursuit of a cure. Collateral damage to normal tissues caused by an oncolytic virus may be expected to be no less tolerable, particularly when the affected normal cells are in organs that have a high potential for regeneration. Such damage appears tolerable in other clinical contexts; for instance, partial hepatectomies to treat metastatic colon cancer can involve the removal of up to half of a patient's liver without compromising basic liver function (Yamanaka et al., 1993). Our analyses show that the beneficial effects of apparent competition in maintaining a high oncolytic virus load during the final stages of tumor clearance are likely to be realized with the removal of a smaller fraction of the normal cell population than occurs in some of these other treatments. Thus, side-effects due to normal tissue being damaged may be comparable to, or even less than, what is common for other cancer therapies. By quantifying the potential effects of oncolytic viruses on normal cells as well as tumor cells, our approach provides a useful point of departure for more sophisticated analyses. For example, patients could base their cost-benefit analyses for undergoing oncolytic virotherapy that takes advantage of apparent competition on our population-dynamical approach. Based on models such as Eq. (1), the likely extent of harm to normal tissue could be quantitatively weighed against the

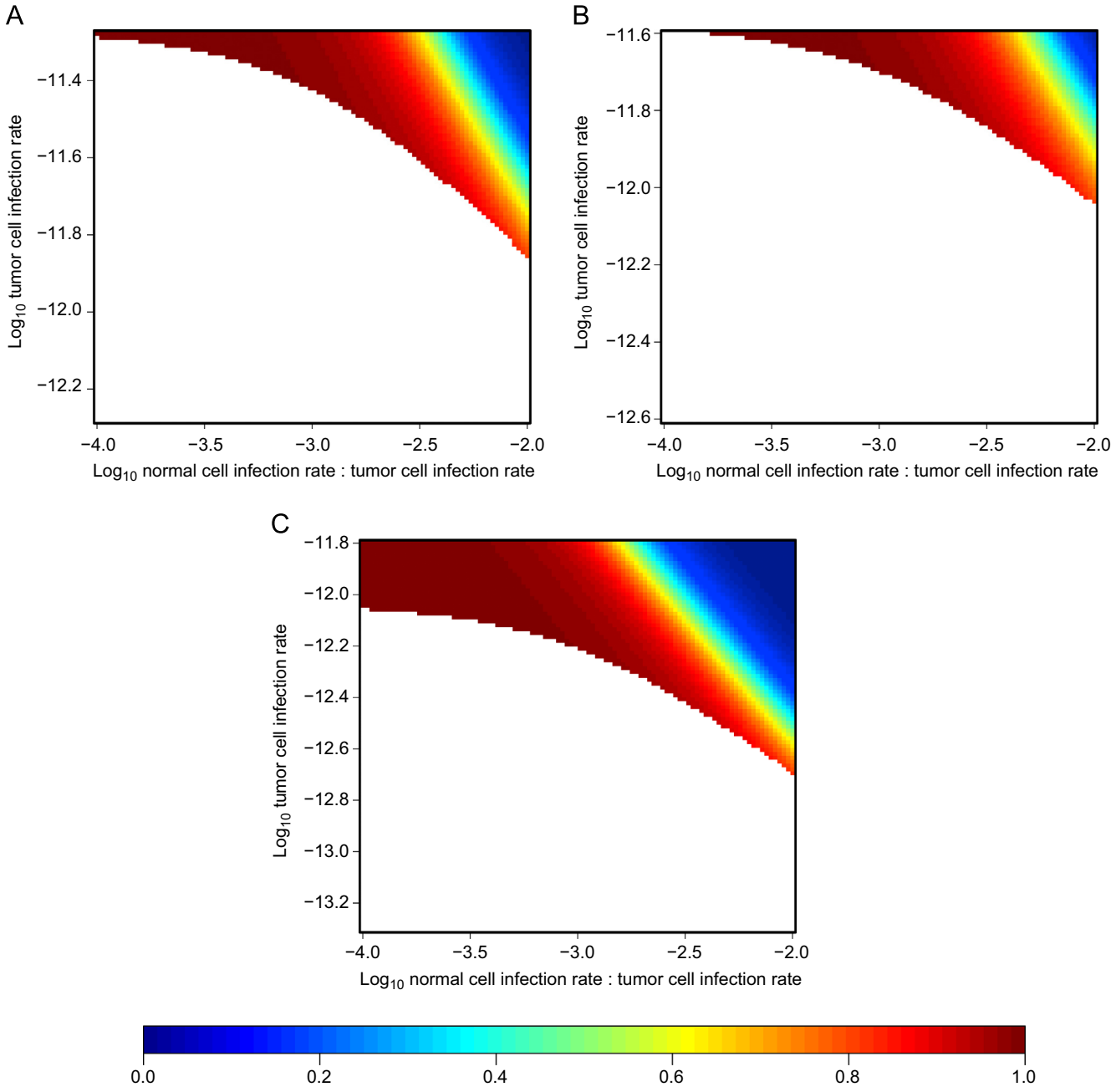

Fig. 5. Diagrams summarizing the joint effects of the baseline infection rate β_C of tumor cells and the scaled infection rate β_H of normal cells on normal cells after 7 days in a region of parameter space permitting apparent-competition mediated tumor eradication. (A) Describes the effects of an oncolytic adenovirus, (B) describes the effects of an oncolytic HSV, and (C) describes the effects of an oncolytic VSV. In all panels, the color scales show the ratio of the number of normal cells that are uninfected 7 days after the initial viral injection to the number of normal cells prior to the initial viral injection, and the white region describes the portion of parameter space that did not result in tumor eradication. In (A)–(C), the ratio λ_H/λ_C of lysing rates for normal cells to tumor cells = 1 and the ratio b_H/b_C of burst sizes for normal cells to tumor cells = 1.

likelihood of effective tumor eradication. Our model therefore provides a systematic foundation for assessing potential consequences in a clinical setting.

Our results may also have utility in the discovery of new virus platforms for oncolytic virotherapy. Estimates of infection rates, lysing rates, and burst sizes for appropriate normal cells and tumor cells can be made *in vitro* for a given virus, and our modeling relates those parameters to the potential for tumor clearance. Such an analysis could be used to narrow-down the choice of candidate viruses, and would provide an intermediate step in oncolytic virus discovery between the demonstration of tumor cell killing *in vitro*, and tumor clearance studies in animal models. With this approach, wild-type viruses would be initially screened to identify those that lie in regions of parameter space where tumor elimination is favored. Although viral life-history parameters obtained from *in-vitro* experiments may fail to reflect *in vivo* dynamics (e.g., Murray et al., 2011), screening a range of wild-type viruses using our model during the *in vitro* stage of development could nevertheless provide a point of departure for proceeding from *in vitro* studies to *in vivo* experiments. Once a suitable virus platform has been identified through screening, it could perhaps be used without modification if the extent of collateral damage to normal tissues is acceptable. Alternatively, it could be subjected to further engineering to refine and optimize its degree of tumor-cell specificity. It is probable that a virus platform could be fine-tuned within the favorable region of parameter space that it

already inhabits, while it would be much more difficult to move a virus into the favorable region from outside it through genetic engineering. For this reason, the discovery strategy we propose may be more efficient than attempting to engineer oncolytic virotherapy agents from viruses that are well-studied for reasons other than their oncolytic potential.

Indeed, while the mechanisms by which cancer-specialist oncolytic viruses either cause, or fail to cause, tumor remission has received attention from mathematical modelers, no study to date provides a similar quantitative approach to understanding how viruses that have less than complete tumor specificity might be able to cause tumor eradication. Such assessments can be critical if potential wild-type viruses continue to be considered for oncolytic virotherapy (e.g., Shafren et al., 2004). For instance, in the last decade, oncolytic virotherapy with wildtype reoviruses has advanced to clinical trials (Comins et al., 2008). Such viruses caused occasional influenza-like symptoms, and managed to infect normal tissue when immune suppressants were administered, suggesting that non-tumor cells contributed to increasing total viral load (Comins et al., 2008). Similar dynamics have been reported with Coxsackie virus A21, which has been used to treat malignant melanoma. Although administration of the Coxsackie virus causes mild upper respiratory infections, its pathogenicity is otherwise limited (Shafren et al., 2004). Elucidating the dynamics of such wild-type or attenuated (but not perfectly tumor-specific) viruses during the course of virotherapy requires integrating the indirect, virus-mediated effects normal cells can have on tumor cells. Our framework begins to fill this gap.

Our results may also be particularly applicable when tumor cell densities are at low numbers. For instance, a generalist oncolytic virus may more readily propagate to levels where it can infect most early-stage metastatic tumor cells enmeshed amid normal cells, especially when compared to a specialist oncolytic virus. Additionally, therapy with generalist viruses could complement surgical tumor debulking, potentially providing an alternative to radiation or chemotherapy to eradicate remnant tumor cells. Finally, apparent competition could be leveraged to mitigate tumor growth during early-stage cancer. As tumor-detection technologies are refined and the detectable tumor size shrinks even further, there may be fewer tumor cells at the onset of treatment and the ability of tumor-specialist, replication-competent oncolytic viruses to grow may be more restricted (but see Rommelfanger et al., 2012). Our analytical results suggest that allowing oncolytic viruses to propagate on normal cells may mitigate some of the challenges to virus propagation posed by low tumor-cell abundance during early-stage cancer.

Our approach lends itself to modifications describing how apparent competition can drive oncolytic-virus-cancer interactions in specific systems. For instance, our model was inspired by epidemiological models describing virus-host cell dynamics (Wu et al., 2001; Nowak and May, 2000) both to enable ready comparison of tumor dynamics with and without apparent competition and to facilitate analytical and numerical tractability. Some previous work has assessed the performance of specific oncolytic viruses in a spatially structured tumor environment (e.g., Wu et al., 2001; Friedman et al., 2006; Wodarz et al., 2012). Modeling such spatial structure may provide an alternative perspective on the efficacy (and potential risks) of apparent competition in particular oncolytic-virus-tumor systems. However, as noted by, e.g., Rommelfanger et al. (2012), such models are considerably more complex and have, in any case, often led to results similar to those obtained by non-spatial models (e.g., Wu et al., 2001 and relevant references in Rommelfanger et al., 2012; for an additional perspective, see Wodarz et al., 2012). Another extension of our model to accommodate specific oncolytic-virus-tumor systems may involve explicitly characterizing the dynamics of a common nutrient/resource of tumor cells and normal cells. We also modeled a potentially more general (but complex) version of Eq. (1) to characterize competition between normal cells and tumor cells for limiting resources (e.g., nutrients or space) as well. Incorporating explicit resource-mediated competition between tumor cells and normal cells had no qualitative effect on our conclusions (Supplementary Information 5). Finally, our model provides a point of departure for comparing the relative efficacies of alternative therapeutic genes. We note that for viruses that leave their host cell through budding or exocytosis, the parameter λ_j in Eq. (1) can be interpreted as the expected per-capita mortality rate of an infected cell of type j, while the parameter b_j describes the expected lifetime production of new virus particles by an infected cell. If a candidate oncolytic virus contains additional therapeutic genes that affect tumor cells by, for instance, sensitizing the cells to chemotherapy or radioisotope killing, then this may accelerate the per-capita mortality rate of cells infected with the oncolytic virus and/or reduce their total virus particle production. Indeed, reduced cell survivorship may also occur when oncolytic viruses facilitate the expression of innate immune effectors by infected cells (e.g., Diaz et al., 2007; Li et al., 2007). Our model can readily accommodate such considerations by modifying the numerical values of b_j and λ_j to account for the inclusion of such genes. The model also provides a useful point of departure for quantitatively comparing the efficacies of oncolytic viruses that directly lyse cells to other therapeutic viruses which, for instance, have been engineered to express transgenes inhibiting the formation of new blood vessels in tumors (e.g., Tysome et al., 2013).

Based on our model, our key empirical prediction is that apparent competition can enhance tumor clearance when there are few surviving tumor cells, and consequently that a tumor-specialist virus would be less effective than a generalist virus under these conditions. Interestingly, a recent paper (Naik et al., 2012) describes a model system that perhaps could be adapted to test this hypothesis experimentally. Otherwise closely matched virus strains that are either generalist or tumor-specialist in their replication were constructed from VSV by engineering them to express interferon-β (INF-β) from either mouse (VSV-mINF) or human (VSV-hINF). These virus strains were tested in a mouse model in which syngeneic tumor cells had been implanted into immunocompetent mice. The tumor cells used were insensitive to INF-β, but INF-β can induce in normal cells an antiviral state that strongly inhibits VSV replication in these cells. Importantly, INF-β is species-specific and human INF-β does not induce an antiviral state in normal mouse cells. Consequently, the expression of mouse INF-β from the viral genome imparts a tumor-specialist replication phenotype on VSV-mINF in the mouse model, while VSV-hINF retains generalist replication characteristics.

Both VSV-mINF and VSV-hINF were shown to be effective for oncolytic virotherapy in the mouse model. Tumor clearance without relapse was observed in 10/10 (VSV-mINF) and 3/10 (VSV-hINF) mice in one experiment. However, the striking success of VSV-mINF in preventing relapse depended in part on a host T-cell response and suppression of this T-cell response resulted in tumor relapse for both VSV strains during oncolytic virotherapy. Although virus-mediated cell killing alone was insufficient for complete clearance of all tumor cells in the published experiments, this model system nevertheless should provide an excellent opportunity to evaluate the effects of apparent competition *in vivo*. The basis of relapse, the outgrowth of tumors from a small number of remaining tumor cells, provides a highly sensitive measure of clearance. Moreover, by initially implanting only small numbers of tumor cells, the relative efficacy of tumor-specialist (VSV-mINF) and generalist (VSV-hINF) viruses in mediating clearance could be determined by recording tumor outgrowth.

Potentially confounding effects of a T-cell response could be controlled by administering anti-CD4 and anti-CD8 antibodies during oncolytic virotherapy (Naik et al., 2012). If an effect of apparent competition is detected, subsequent *in vivo* studies could be carried out to ascertain the interplay between apparent competition and the T-cell response. Our theoretical results suggest that the impact of apparent competition may not be as large for VSV as it would be for other kinds of viruses. Thus, this VSV-based *in vivo* model would provide a stringent test, and any detectable effect of apparent competition in this system would bode well for extrapolating our hypotheses to other therapeutic virus platforms.

In conclusion, our results raise an intriguing possibility: even if feasible, complete attenuation of oncolytic viruses towards normal cells may not be as desirable as is commonly believed. Moderating, rather than seeking to entirely eliminate, their ability to exploit normal cells may provide a viable, alternative route to developing more effective oncolytic viruses.

Acknowledgments

We would like to thank G. F. Grether, R. Vance, V. Savage, S. Pawar, F. Gould and A. L. Lloyd for valuable discussions during the early stages of this work and two anonymous reviewers whose comments greatly improved the article. This research was funded in part from a Chair's Fellowship from the Department of Ecology and Evolutionary Biology at the University of California, Los Angeles, and by the College of Agriculture and Life Sciences, and the College of Sciences, North Carolina State University. P.A. was supported by a Complex Systems Scholar Grant from the James S. McDonnell Foundation.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jtbi.2014.04.030.

References

Andersen, V., Sonne, J., Sletting, S., Prip, A., 2000. The volume of the liver in patients correlates to body weight and alcohol consumption. Alcohol and Alcoholism 35, 531–532.
Anderson, R.M., May, R.M., 1979. Population biology of infectious-diseases: Part I. Nature 280, 361–367.
Anderson, R., May, R., 1981. The population dynamics of microparasites and their invertebrate hosts. Philos. Trans. R Soc. Lond. Ser. B-Biol. Sci. 291, 451–524.
Bajzer, V., Carr, T., Josić, K., Russell, S.J., Dingli, D., 2008. Modeling of cancer virotherapy with recombinant measles viruses. J. Theor. Biol. 252, 109–122.
Chaneton, E.J., Bonsall, M.B., 2000. Enemy-mediated apparent competition: empirical patterns and the evidence. Oikos 2, 380–394.
Comins, C., Heinemann, L., Harrington, K., Melcher, A., De Bono, J., Pandha, H., 2008. Reovirus: viral therapy for cancer 'as nature intended'. Clin. Oncol. R. Coll. Radiol. Gt. Br. 20, 548–554.
Crittenden, M.R., Thanarajasingam, U., Vile, R.G., Gough, M.J., 2005. Intratumoral immunotherapy: using the tumour against itself. Immunology 114, 11–22.
Croyle, M.A., Callahan, S.M, Auricchio, A., Schumer, G., Linse, K.D., Wilson, J.M., Brunner, L.J., Kobinger, G.P., 2004. PEGylation of a vesicular stomatitis virus G pseudotyped lentivirus vector prevents inactivation in serum. J Virol 78, 912–921.
Diaz, R.M., Galivo, F., Kottke, T., Wongthida, P., Qiao, J., Thompson, J., Valdes, M., Barber, G., Vile, R.G., 2007. Oncolytic immunovirotherapy for melanoma using vesicular stomatitis virus. Cancer Res. 67, 2840–2848.
Dingli, D., Offord, C., Myers, R., Peng, K.W., Carr, T.W., Josic, K., Russell, S.J., Bajzer, Z., 2009. Dynamics of multiple myeloma tumor therapy with a recombinant measles virus. Cancer Gene Ther. 16, 873–882.
Dou, J.-W., Zheng, W.-W., 2010. The periodic solutions of impulsive competition system on tumor-normal cell interaction. In: iCBBE 2010 4th International Conference on Bioinformatics and Biomedical Engineering. IEEE, Chengdu, China, pp. 1–4, http://dx.doi.org/10.1109/ICBBE.2010.5516323. (ISBN:9781424447121, ISSN:21517614).
Eftimie, R., Dushoff, J., Bridle, B.W., Bramson, J.L., Earn, D.J.D., 2011. Multi-stability and multi-instability phenomena in a mathematical model of tumor-immune-virus interactions. Bull. Math. Biol. 73, 2932–2961.
Ferguson, M.S., Lemoine, N.R., Wang, Y., 2012. Systemic delivery of oncolytic viruses: hopes and hurdles. Adv. Virol. 2012, 1–14.
Friedman, A., Tian, J.P., Fulci, G., Chiocca, E.A., Wang, J., 2006. Glioma virotherapy: effects of innate immune suppression and increased viral replication capacity. Cancer Res. 66, 2314–2319.
Gatenby, R.A., 1991. Population ecology issues in tumor growth population ecology issues in tumor growth. Cancer Res. 51, 2542–2547.
Gatenby, R.A., 1995. Models of tumor host interaction as competing populations—implications for tumor biology and treatment. J. Theor. Biol. 176, 447–455.
Gatenby, R.A., Gawlinski, E.T., Gmitro, A.F., Kaylor, B., Gillies, R.J., 2006. Acid-mediated tumor invasion: a multidisciplinary study. Cancer Res. 66, 5216–5223.
Guo, Z.S., Parimi, V., O'Malley, M.E., Thirunavukarasu, P., Sathaiah, M., Austin, F., Bartlett, D.L., 2010. The combination of immunosuppression and carrier cells significantly enhances the efficacy of oncolytic poxvirus in the pre-immunized host. Gene Ther. 17, 1465–1475.
Holt, R.D., 1977. Predation, apparent competition, and the structure of prey communities. Theor. Popul. Biol. 12, 197–229.
Holt, R.D., Lawton, J.H., 1994. The ecological consequences of shared natural enemies. Annu. Rev. Ecol. Syst. 25, 495–520.
Hudson, P., Greenman, J., 1998. Competition mediated by parasites: biological and theoretical progress. Trends Ecol. Evol. 13, 387–390.
Janeway, C., Travers, P., Hunt, S., 1996. Immunobiology: the Immune System in Health and Disease. Current Biology, New York.
Kelly, E., Russell, S., 2007. History of oncolytic viruses: genesis to genetic engineering. Mol. Ther. 15, 651–659.
Kirn, D., Martuza, R.L., Zwiebel, J., 2001. Replication-selective virotherapy for cancer: biological principles, risk management and future directions. Nat. Med. 7, 781–787.
Komarova, N.L., Wodarz, D., 2010. ODE models for oncolytic virus dynamics. J. Theor. Biol. 263, 530–543.
Kuang, Y., Nagy, J.D., Elser, J.J., 2004. Biological stoichiometry of tumor dynamics: mathematical models and analysis. Discret. Contin. Dyn. Syst. B 4, 221–240.
Kuruppu, D., Tanabe, K.K., 2005. Viral oncolysis by herpes simplex virus and other viruses. Cancer Biol. Ther. 4, 524–531.
Li, H., Dutuor, A., Fu, X., Zhang, X., 2007. Induction of strong antitumor immunity by an HSV-2-based oncolytic virus in a murine mammary tumor model. JGene Med. 9, 161–169.
Marchuk, G.I., 1997. Mathematical Modelling of Immune Response in Infectious Diseases, vol. 395. Kluwer, Dordrecht.
Montaigne, F., 2006. Medicine by Design: The Practice and Promise of Biomedical Engineering, 1st edition The Johns Hopkins University Press, Baltimore, MD, USA.
Murray, J.M., Kelleher, A.D., Cooper, D.A., 2011. Timing of the components of the HIV life cycle in productively infected CD4+ T cells in a population of HIV-infected individuals. J. Virol. 85, 10798–10805.
Naik, S., Nace, R., Federspiel, M., Barber, G., 2012. Curative one-shot systemic virotherapy in murine myeloma. Leukemia 2012, 1–9.
Novozhilov, A.S., Berezovskaya, F.S., Koonin, E.V., Karev, G.P., 2006. Mathematical modeling of tumor therapy with oncolytic viruses: regimes with complete tumor elimination within the framework of deterministic models. Biol. Direct. 1.
Nowak, M.A., May, R.M., 2000. Virus Dynamics: Mathematical Principles of Immunology and Virology. Oxford University Press, Oxford.
Parato, K.A., Senger, D., Forsyth, P.A.J., Bell, J.C., 2005. Recent progress in the battle between oncolytic viruses and tumours. Nat. Rev. Cancer 5, 965–976.
Perelson, A., Weisbuch, G., 1997. Immunology for Physicists. Rev. Mod. Phys. 69, 1219–1268, http://dx.doi.org/10.1103/RevModPhys.69.1219.
Prestwich, R.J., Errington, F., Diaz, R.M., Pandha, H.S., Harrington, K.J., Melcher, A.A., Vile, R.G., 2009. The case of oncolytic viruses versus the immune system: waiting on the judgment of Solomon. Hum. Gene Ther. 20, 1119–1132.
Roberts, M.S., Lorence, R.M., Groene, W.S., Bamat, M.K., 2006. Naturally oncolytic viruses. Curr. Opin. Mol. Ther. 8, 314–321.
Rommelfanger, D.M., Offord, C.P., Dev, J., Bajzer, Z., Vile, R.G., Dingli, D., 2012. Dynamics of melanoma tumor therapy with vesicular stomatitis virus: explaining the variability in outcomes using mathematical modeling. Gene Ther. 19, 543–549.
Russell, S.J., Peng, K.-W., Bell, J.C., 2012. Oncolytic virotherapy. Nat. Biotechnol. 30, 658–670.
Shafren, D.R., Au, G.G., Nguyen, T., Newcombe, N.G., Haley, E.S., Beagley, L., Johansson, E.S., Hersey, P., Barry, R.D., 2004. Systemic therapy of malignant human melanoma tumors by a common cold-producing enterovirus, Coxsackievirus A21. Clin. Cancer Res. 10, 53–60.
Sinkovics, J.G., Horvath, J.C., 2005. Viral Therapy of Human Cancers. Marcel Dekker, Boca Raton, FL.
Smalley, M., Leiper, K., Tootle, R., McCloskey, P., O'Hare, M.J., Hodgson, H., 2001. Immortalization of human hepatocytes by temperature-sensitive SV40 Large-T antigen. Vitr. Cell Dev. Biol. Anim. 37, 166–168.
Soetaert, K., Petzoldt, T., Setzer, R.W., 2010. Solving differential equations in R: package deSolve. J. Stat. Softw. 33, 1–25.
Spratt, J.A., Vonfournier, D., Spratt, J.S., Weber, E.E., 1993. Decelerating growth and human breast-cancer. Cancer 71, 2013–2019.
Tao, Y., Guo, Q., 2005. The competitive dynamics between tumor cells, a replication-competent virus and an immune response. J. Math. Biol. 51, 37–74.
Tysome, J.R., Lemoine, N.R., Wang, Y., 2013. Update on oncolytic viral therapy—targeting angiogenesis. Onco Targets Ther. 6, 1031–1040.

Vähä-Koskela, M.J.V., Heikkilä, J.E., Hinkkanen, A.E., 2007. Oncolytic viruses in cancer therapy. Cancer Lett. 254, 178–216.
Wodarz, D., 2001. Viruses as antitumor weapons: defining conditions for tumor remission. Cancer Res. 61, 3501–3507.
Wodarz, D., 2009. Use of oncolytic viruses for the eradication of drug-resistant cancer cells. J. R. Soc. Interface R. Soc. 6, 179–186.
Wodarz, D., Komarova, N., 2009. Towards predictive computational models of oncolytic virus therapy: basis for experimental validation and model selection. PLoS One 4.
Wodarz, D., Hofacre, A., Lau, J.W., Sun, Z., Fan, H., Komarova, N.L., 2012. Complex spatial dynamics of oncolytic viruses in vitro: mathematical and experimental approaches. PLoS. Comput. Biol. 8, e1002547.
Wu, J.T., Byrne, H.M., Kirn, D.H., Wein, L.M., 2001. Modeling and analysis of a virus that replicates selectively in tumor cells. Bull. Math. Biol. 63, 731–768.
Wu, J.T., Kirn, D.H., Wein, L.M., 2004. Analysis of a three-way race between tumor growth, a replication-competent virus and an immune response. Bull. Math. Biol. 66, 605–625.
Yamanaka, N., Okamoto, E., Kawamura, E., Kato, T., Oriyama, T., Fujimoto, J., Furukawa, K., Tanaka, T., Tomoda, F., Tanaka, W., 1993. Dynamics of normal and injured human liver regeneration after hepatectomy as assessed on the basis of computed tomography and liver function. Hepatology 18, 79–85.
Zhu, Y., Yin, J., 2005. Burst size distributions from measurements of single cells infected with vesicular stomatitis virus, In: AIChE Annual Meeting. American Institute of Chemical Engineers, Cincinnati, Ohio, p. 432f.