Modeling and Analysis of a Virus that Replicates Selectively in Tumor Cells

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Replication-competent viruses have shown considerable promise in overcoming the inefficient gene transduction experienced by traditional gene therapy approaches to cancer treatment. The viruses infect tumor cells and replicate inside them, eventually causing lysis. Virus particles released during lysis are then able to infect other tumor cells, and, in this way, continuous rounds of infection and lysis allow the virus to spread throughout the tumor. Motivated by this novel cancer treatment, we formulate and analyse a system of partial differential equations that is essentially a radially-symmetric epidemic model embedded in a Stefan problem. We compare three, alternative virus-injection strategies: a fixed fraction of cells pre-infected with the virus are introduced throughout the entire tumor volume, within the tumor core, or within the tumor rim. For all three injection methods, simple and accurate conditions that predict whether the virus will control the tumor are derived.

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1. Introduction

Despite great strides in the understanding of the genetic basis of cancer in the last several decades, the efficacy of gene therapy has not yet lived up to its expectations. The main reason for this disappointing state of affairs is delivery (Jain, 1994): the macromolecules used as gene delivery vehicles, such as monoclonal antibodies and adenoviruses, have great difficulty traveling through highly compressed solid tumors, and cannot be delivered in sufficient quantities to achieve tumor cure. More specifically, these macromolecules are transported by convection and diffusion, but are too big to diffuse effectively within a tumor [Chart 8 in Swabb et al. (1974)]. Moreover, the pressure gradient is nearly constant throughout all but the periphery of a solid tumor, which makes convective transport of macromolecules arduous (Jain, 1994).

One recent approach designed to circumvent this barrier to delivery involves the use of replication-competent viruses, sometimes referred to as ‘smart bomb’ cancer viruses (Lowe, 1997). These viruses do to cancer cells what HIV does to CD4+ T cells: a virus particle attaches to a cancer cell (the virus is engineered to selectively bind to receptors on the tumor cell surface), gains entry and proliferates exponentially, eventually causing cell death (lysis). At lysis, the newly produced virus particles are liberated and become available to infect adjacent cancer cells. In theory, continuous rounds of infection, replication and lysis will lead to a chain reaction that permits the virus to distribute itself throughout the entire tumor. Replication-competent viruses have generated impressive pre-clinical and clinical results (Bischoff et al., 1996; Heise et al., 1997; Rodriguez et al., 1997; Coffey et al., 1998; Yoon et al., 1998), and several are currently in phase III clinical trials.

The only mathematical paper on this topic of which we are aware is by Oelschläger (1992). He constructs a stochastic model that accounts for the spatial spread of virus particles and their propagation through a population of cells. The focus in Oelschläger’s paper is the derivation of a limit theorem that proves the convergence of the stochastic model to a (deterministic) differential equation model as the population size approaches infinity in a particular manner. In contrast, in this paper, we develop a continuum, partial differential equation (PDE) model to describe the growth of a radially-symmetric tumor infected with a replication-competent virus. While our model is, in most respects, considerably simpler than that of Oelschläger (1992) [e.g., the motion of individual virus particles in Oelschläger (1992) is governed by independent Brownian motions in the space between cells], it captures one key feature that is absent from Oelschläger (1992): the generic model in Oelschläger (1992) assumes that cells are distributed throughout multidimensional space, whereas our model—motivated specifically by cancer treatment—takes into account the (moving) tumor boundary. Our simpler model is also amenable to approximate analytical methods, and the goal of this paper is to use such techniques in order to derive necessary and sufficient conditions for virus-induced tumor control.
Our work also relates to the extensive literature on PDE modeling of solid tumor growth [e.g., Greenspan (1972), Adam and Bellomo (1997), Ward and King (1997), Byrne and Chaplain (1997, 1999)]. Tumor growth in this stream of work is typically nutrient-limited and incorporates some detailed spatial structure of avascular spheroids (e.g., a necrotic core). In contrast, we omit these effects (until Section 6) and allow tumor growth to be determined by the manner in which the virus spreads through the tumor.

The remainder of the paper takes the following form. The mathematical model is formulated in Section 2. It is analysed numerically and mathematically in Sections 3–5 for three types of viral injection: uniform injection, where the entire tumor is injected with virus, core injection and rim injection. The model is generalized to include nutrient-limited necrosis in Section 6. The model’s limitations are discussed in Section 7, and the paper concludes with a summary of the key results in Section 8.

2. The Mathematical Model

2.1. Model equations. Our PDE model considers a spherical tumor that has radius \( R(t) \) at time \( t \). Thus, all dependent variables depend on time \( t \) and the radial distance from the center of the tumor, \( r \in (0, R(t)) \). The model tracks the spatial dynamics, within the tumor, of four physical variables: uninfected tumor cells \( x(r, t) \), infected tumor cells \( y(r, t) \), necrotic cells \( n(r, t) \) (it is mathematically convenient to treat the necrotic debris as a collection of cells) and free (i.e., extracellular) virus \( v(r, t) \).

We assume that the cell density is constant throughout the tumor; in contrast, the volume occupied by the virus particles, which are several orders of magnitude smaller than the tumor cells, is neglected. The tumor volume is modeled as an incompressible fluid, through which the cells travel via a convective field whose velocity, \( u(r, t) \), is dictated by spatio-temporal variations in cell proliferation and removal. Because the viruses are highly selective to cancer cells and have not exhibited significant toxicity (Heise et al., 1999), we do not consider the treatment’s impact on normal tissue. The equations that define the evolution of our dependent variables \( (x, y, n, v \text{ and } R) \) are (the space and time indices are included to avoid confusion in the integrals)

\[
\frac{\partial x(r, t)}{\partial t} = \chi x(r, t) - \beta x(r, t) \int_{r-r_c}^{r+r_c} \frac{v(s, t)}{2r_c} \, ds - \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 u(r, t) x(r, t) \right),
\]

or

\[
\text{uninfected cells proliferation infection convection}
\]

(1)
\[
\frac{\partial y(r, t)}{\partial t} = \beta x(r, t) \int_{r-r_c}^{r+r_c} \frac{v(s, t)}{2r_c} ds - \delta y(r, t)
\]
subject to the Stefan, or moving boundary, condition

2.2. Model description. The uninfected tumor cells in (1) proliferate exponentially at rate \( \lambda \). Although we do not model the details of the microenvironment, the implicit assumption is that tumor growth is not limited by a lack of nutrients; this assumption is relaxed in Section 6. The virus infects tumor cells by binding to receptors on cell surfaces and gaining entry by endocytosis. Therefore, we assume that the infection rate of cells centered at \( r \) equals a constant \( \beta \) times the concentration of uninfected cells at \( r \times \bar{v}(r, t) \), which is the spatially-weighted average of virus concentration on the surface of a spherical cell with radius \( r_c \) that is centered at \( r \). Referring to the integrals in equations (1) and (2), we need to show that

\[
\bar{v}(r, t) = \frac{1}{2r_c} \int_{r-r_c}^{r+r_c} v(s, t) ds.
\]
assumption] such that the $\tilde{z}$ axis is parallel to the direction $r$ in the tumor coordinate system, as shown in Fig. 1. The tumor coordinate system and the cell Cartesian coordinate system are related by

$$r = r_s + \tilde{z}, \quad dr = d\tilde{z},$$

whereas the two cell coordinate systems are related via

$$\tilde{z} = r_c \cos \tilde{\phi}, \quad d\tilde{z} = -r_c \sin \tilde{\phi} \, d\tilde{\phi}. \quad (8)$$

For a cell centered at $r_s$, let $A_c$ be its surface area and $V(r_s, t)$ be the total number of viral particles on its surface at time $t$. We make the crucial assumption that $v(r, t)$ is independent of $\tilde{\phi}$; that is, we assume that the local cell coordinate systems are independent of the cell’s orientation within the tumor. This is an accurate
approximation for \( r_s \gg r_c \), and allows for an analytically tractable formulation. Therefore, we have

\[
\tilde{v}(r_s, t) = \frac{V(r_s, t)}{A_c},
\]

where

\[
A_c = \int_0^{2\pi} \int_0^{\pi} r_c^2 \sin \tilde{\phi} \, d\tilde{\phi} \, d\tilde{\theta} = 4\pi r_c^2,
\]

\[
V(r_s, t) = \int_0^{2\pi} \int_0^{\pi} v(r_s + \tilde{z}, t) r_c^2 \sin \tilde{\phi} \, d\tilde{\phi} \, d\tilde{\theta}
\]

\[
= 2\pi r_c^2 \int_0^{\pi} v(r_s + \tilde{z}, t) \sin \tilde{\phi} \, d\tilde{\phi}
\]

\[
= 2\pi r_c \int_{r_c}^{r_c + r_c} v(r_s + \tilde{z}, t) \, d\tilde{z}
\]

\[
= 2\pi r_c \int_{r_s - r_c}^{r_s + r_c} v(r, t) \, dr.
\]

Equation (7) follows from (9)–(11).

More precisely, the upper and lower integration limits in (1) and (2) used in our numerical simulations are, respectively, \( \min\{R(t), r + r_c\} \) and \( \max\{0, r - r_c\} \), but we omit them for notational convenience as they play no role in our subsequent analysis. The convective velocity in (1)–(3) is defined by equation (5) and discussed after explaining the remainder of equations (1)–(4).

All infected cells in (2) undergo lysis (i.e., no lysogenesis occurs) at rate \( \delta \), where \( \delta^{-1} \) represents the mean infected cell lifetime. At the time of lysis, an infected cell becomes necrotic, and this necrotic debris is removed from the tumor at rate \( \mu \) in (3). Notice that, in our model, necrosis occurs as a result of virus-mediated cell death rather than lack of oxygen and other nutrients, which are not included until Section 6 (the inclusion of nutrient-limited necrosis at this stage would obscure the effects of the replication-competent virus, which is the focus of the present study).

When an infected cell dies, we assume that \( N \) virus particles are released, so that \( N\delta \) is the release rate of free virus particles per unit time per infected cell. By using a constant value for the burst size, which is independent of the infected cell lifetime, we are neglecting the effect that multiple viral infections of the same cell might have on the burst size and infected cell lifetime. Because virus particles are present throughout the infected cell at the time of lysis, we assume that the \( N \) virus particles are released uniformly throughout a sphere of radius \( r_c \). Thus, any infected cells undergoing lysis that are located within a sphere of radius \( r_c \) centered at position \( r \) will contribute to the production of free virus there. More specifically, referring to (4), the rate of virus release at location \( r \) at time \( t \) is \( N\delta \) times \( \tilde{y}(r, t) \),
which is the spatially-averaged infected cell density throughout a sphere of radius $r_c$ that is centered at $r$. As before, we derive
\[
\bar{y}(r, t) = \frac{3}{4r_c^3} \int_{r-r_c}^{r+r_c} y(s, t)[r_c^2 - (s - r)^2] \, ds
\]
by constructing local cell coordinate systems, this time in polar $(\tilde{\rho}, \tilde{\theta}, \tilde{z})$ and Cartesian coordinates, that are centered at $r_s$ such that $\tilde{z}$ is parallel to the direction of $r$ in the tumor coordinate system, as shown in Fig. 1(b). Let $V_c$ be the volume of a cell centered at $r_s$ with cell radius $r_c$, and $Y(r_s, t)$ be the total number of infected cells in this spherical cell. Note that this sphere consists of the points located on and enclosed by the surface $\tilde{\rho}^2 = r_c^2 - \tilde{z}^2$ in the polar coordinate system. Analogous to the infection case, we make the key assumption that $y(r, t)$ is independent of $\tilde{\theta}$, which is justified if $r_s \gg r_c$. Therefore, we have
\[
\bar{y}(r_s, t) = \frac{Y(r_s, t)}{V_c},
\]
where
\[
V_c = \int_0^{2\pi} \int_{-r_c}^{r_c} \int_0^{\sqrt{r_c^2 - \tilde{z}^2}} \tilde{\rho} \, d\tilde{\rho} \, d\tilde{z} \, d\tilde{\theta} = \frac{4}{3}\pi r_c^3,
\]
\[
Y(r_s, t) = \int_0^{2\pi} \int_{-r_c}^{r_c} \int_0^{\sqrt{r_c^2 - \tilde{z}^2}} y(r_s + \tilde{z}, t)\tilde{\rho} \, d\tilde{\rho} \, d\tilde{z} \, d\tilde{\theta}
\]
\[
= \pi \int_{-r_c}^{r_c} y(r_s + \tilde{z}, t)(r_c^2 - \tilde{z}^2) \, d\tilde{z}
\]
\[
= \pi \int_{r_s-r_c}^{r_s+r_c} y(r, t)[r_c^2 - (r - r_s)^2] \, dr,
\]
which implies (12).

While the precise mechanism by which the virus is cleared [e.g., an innate immune response (Yang et al., 1994; Worgall et al., 1997), or binding to the extracellular matrix] remains unknown, we assume that it is cleared at a constant rate $\gamma$. We remark that, in our model, the virus does not move by diffusion or convection—it is only transported within and between cells during de novo infection, replication and lysis. In contrast, the three types of cells move via a convection field, as described by the last term in equations (1)–(3). By assuming that the total cell density, $x(r, t) + y(r, t) + n(r, t)$, is constant and equal to $\theta$, we sum equations (1)–(3) to get (5) which defines the velocity $u(r, t)$ (Ward and King, 1997).

As is typical in Stefan problems, we assume that the tumor boundary grows at a rate that is equal to the local velocity at the tumor boundary (Rubensteïn, 1971). Hence, the tumor radius $R(t)$ is governed by the moving boundary condition (6).
We make two further comments before stating the boundary and initial conditions. First, the constant cell density assumption makes the equation for \( n(r, t) \) redundant (\( n(r, t) = \theta - x - y \)), and, therefore, we need not consider equation (3) any further. Second, we introduce the dimensionless parameter

\[
R_0 = \frac{\beta N \theta}{\gamma},
\]

known as the basic reproductive ratio in the epidemic modeling literature (Diekmann et al., 1990), which is the mean number of new virus particles generated by a single virus particle. To follow this interpretation, note that \( \beta \theta \) is the number of cells infected per free virus particle per unit time. The mean lifetime of a free virus particle is \( \gamma^{-1} \), and so \( \beta \theta / \gamma \) is the mean number of cells infected per particle. This quantity is amplified by the factor \( N \) because each infected cell releases \( N \) virus particles upon lysis. We substitute \( R_0 \gamma N \theta \) for \( \beta \) in the model, because \( R_0 \) is easier to estimate from clinical data than \( \beta \), and because it allows us to bypass a nondimensionalization of the entire model.

2.3. Boundary conditions. By radial symmetry, our boundary conditions at the tumor center are

\[
\frac{\partial x(r, t)}{\partial r} = \frac{\partial y(r, t)}{\partial r} = \frac{\partial v(r, t)}{\partial r} = u(r, t) = 0 \quad \text{at} \quad r = 0.
\]  

(17)

As noted later in this section, we numerically compute these equations using a Landau transformation, \( \rho(r, t) = r / R(t) \), \( \tau(r, t) = t \) (Rubenstein, 1971). Under this transformation, the coefficients of \( \frac{\partial x(\rho, \tau)}{\partial \rho} \) and \( \frac{\partial y(\rho, \tau)}{\partial \rho} \) vanish at \( \rho = 1 \). Hence, we do not impose any boundary conditions for \( \frac{\partial x(\rho, \tau)}{\partial \rho} \) and \( \frac{\partial y(\rho, \tau)}{\partial \rho} \) at \( r = R(t) \). Finally, because the virus in our model does not spread by diffusion and convection, and because the coefficient of \( \frac{\partial v(\rho, \tau)}{\partial \rho} \) does not vanish at \( \rho = 1 \), we impose the Neumann condition

\[
\frac{\partial v(r, t)}{\partial r} = 0 \quad \text{at} \quad r = R(t).
\]  

(18)

2.4. Initial conditions. ONX-015 can be administered intravenously or intratumorally (i.e., direct injection), and the latter method results in superior intratumoral viral doses at this time (Kirn et al., 1998). We consider three types of initial conditions that correspond to different injection methods. In all three cases, the cells that are in contact with infectious virus are assumed to become infected immediately. In uniform injection,

\[
x(r, 0) = (1 - p) \theta, \quad y(r, 0) = p \theta, \quad v(r, 0) = 0 \quad \text{for} \quad 0 < r \leq R(0),
\]  

(19)
good approximation to the animal studies of Heise et al. (1999), where a controlled mixture of pre-infected and uninfected tumor cells were injected into a mouse.

The second method is core injection,

\begin{align*}
x(r, 0) &= (1 - p)\theta, \quad y(r, 0) = p\theta, \quad v(r, 0) = 0 \quad \text{for} \quad 0 < r \leq R(0) - w(0); \\
x(r, 0) &= \theta, \quad y(r, 0) = 0, \quad v(r, 0) = 0 \quad \text{for} \quad R(0) - w(0) < r \leq R(0),
\end{align*}

where a fraction \( p \) of the cells in the inner core [with radius \( R(0) - w(0) \), where \( w(0) \) is the uninfected rim width] of the tumor is infected. A single core injection was used in early experiments with ONYX-015 and with hrR3 (Yoon et al., 1998).

The third method is rim injection,

\begin{align*}
x(r, 0) &= \theta, \quad y(r, 0) = 0, \quad v(r, 0) = 0 \quad \text{for} \quad 0 < r \leq r(0); \\
x(r, 0) &= (1 - p)\theta, \quad y(r, 0) = p\theta, \quad v(r, 0) = 0 \quad \text{for} \quad r(0) < r \leq R(0),
\end{align*}

where a fraction \( p \) of cells in the outer rim of the tumor is infected. The rim width of this fraction is \( R(0) - r(0) \), where \( r(0) \) is the uninfected core radius. This mode of injection is akin to fighting a fire by attempting to surround and contain it, and can also be viewed as a crude representation of intravenous administration.

### 2.5. Parameter estimation

The parameter estimates used in our numerical simulations appear in Table 1. The tumor proliferation rate \( \lambda \) is derived from the virus-free control group for uniform injections of ONYX-015 (Heise et al., 1999). Mouse tumors had a volume of 40 mm\(^3\) at time 0 and 2180 mm\(^3\) at 8 weeks, giving \( \lambda = \frac{\ln(2180/40)}{1344} = 0.003 \) h\(^{-1}\), which corresponds to a doubling time of 9.6 days. The values for \( \delta \) and \( N \) are consistent with unpublished laboratory results from Onyx.

The loss rate of necrotic debris is from Fowler (1991), and the tumor cell density and cell radius are typical values in the literature [e.g., O’Donoghue et al. (1995)].

The most difficult parameter to estimate is the viral clearance rate. We used \( \gamma = 1 \) h\(^{-1}\), and have determined (via computational experiments not shown here) that our qualitative results are not altered if the virus is cleared on the order of seconds or minutes.

As noted earlier, we estimated the basic reproductive ratio \( R_0 \) in lieu of the infectivity rate \( \beta \). Unpublished experimental results for Onyx suggest that the percentage of necrotic cells in regions of a tumor where the virus has taken hold is greater than 90%. We use the fact (Mollison, 1977) that the fraction of necrotic cells left in the wake of a classical (i.e., one space dimension, no necrotic removal, no uninfected cell repopulation and no boundary effects) spatial epidemic with reproductive ratio \( R_0 \) is the positive solution \( \tilde{n} \) to

\[ \tilde{n} = 1 - e^{-R_0 \tilde{n}}. \]
Table 1. Values for parameters used in simulations.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Numerical value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda$</td>
<td>Tumor proliferation rate constant</td>
<td>0.003 h$^{-1}$</td>
</tr>
<tr>
<td>$\delta$</td>
<td>Infected cell death rate constant</td>
<td>$\frac{1}{48}$ h$^{-1}$</td>
</tr>
<tr>
<td>$N$</td>
<td>Burst size</td>
<td>1000 pfu cell$^{-1}$</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Debris removal rate constant</td>
<td>$\frac{1}{172}$ h$^{-1}$</td>
</tr>
<tr>
<td>$\theta$</td>
<td>Tumor cell density</td>
<td>$10^6$ cells mm$^{-3}$</td>
</tr>
<tr>
<td>$r_c$</td>
<td>Cell radius</td>
<td>0.01 mm</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>Viral clearance rate constant</td>
<td>1 h$^{-1}$</td>
</tr>
<tr>
<td>$R_0$</td>
<td>Basic reproductive ratio</td>
<td>2.5</td>
</tr>
<tr>
<td>$R(0)$</td>
<td>Initial tumor radius</td>
<td>2 mm</td>
</tr>
<tr>
<td>$p$</td>
<td>Initial fraction infected</td>
<td>0.01</td>
</tr>
</tbody>
</table>

the relationship between our model and the spatial epidemic literature is elucidated further in Section 4. The value of $R_0 = 2.5$ in Table 1 corresponds to $\bar{n} = 0.9$ in (22). However, this value of $R_0$ is rather conservative (i.e., low), because the actual fraction of necrotic cells behind the wavefront in our model is significantly less than 0.9 when $R_0 = 2.5$ (for example, it is about 0.54 in Fig. 5). This discrepancy arises for two reasons: in the PDE model (i) necrotic debris is removed, and (ii) uninfected cells behind the wave proliferate. This leads to the accumulation of a considerable fraction of uninfected (0.27 in Fig. 5) and infected cells (0.19 in Fig. 5) behind the wave. In fact, as we show later, equation (27) implies that in the uniform injection case

$$R_0 = \frac{\delta + \lambda}{\delta(1 - \bar{n})},$$

and hence, $R_0 = 11.44$ if $\bar{n} = 0.9$. Nonetheless, we use $R_0 = 2.5$ in our computational study, mainly because the PDEs in the rim and core injection cases are difficult to simulate when high values of $R_0$ are employed. However, as will be seen in the following sections, our underestimation of $R_0$ in Table 1 has no effect on the qualitative results derived here, and we comment on the more realistic $R_0 = 11.44$ case in Section 7. Finally, the initial tumor size and the fraction infected are chosen to be consistent with the animal studies of Heise et al. (1999).

2.6. Computational details. To facilitate the numerical computations, we used the Landau transformation to map our equations onto a fixed spatial domain. We also nondimensionalized the cell densities by rescaling them with the total cell density $\theta$. The equations were then solved numerically using the MacCormack method and the Runge–Kutta method. Details about the Landau transformation and the computational method are provided in Wu (1999). We do not provide these transformations in the text because these make the subsequent analysis less transparent. For practical and computational purposes, we focused primarily on tumor growth up to 3000 h (125 days) after injection.
3. **Uniform Injection**

3.1. **Numerical results.** Figures 2 and 3 depict numerical results from simulating the PDE model in the uniform injection case. Figure 2 shows that the tumor...
radius $R(t)$ grows initially, attains a maximum at about 1 week after injection, and then shrinks exponentially. The profiles for cells and free virus in Fig. 3 are spatially uniform everywhere, except near the tumor boundary where, after the tumor has started to shrink, uninfected cells predominate. Repeated simulations (not shown here), with different values of $R(0)$ and $p$, show that initial conditions do not affect the long-term behavior of tumor growth; in particular, tumor growth curves similar to those in Fig. 2 were observed for all values of $p$. Guided by these results, we begin our analysis of uniform injection by making two simplifications to the PDE model.

3.2. Model simplifications. Motivated by the small spatial variations in the cell and virus profiles in Fig. 3, we neglect spatial dependence in the case of uniform injection, and seek model solutions of the form $x = x(t)$, $y = y(t)$ and $v = v(t)$.

A nondimensionalization of the nonspatial model, which consists of $\tilde{x} = \frac{x}{\theta}$, $\tilde{y} = \frac{y}{\theta}$ and $\tilde{v} = \frac{v}{N\theta}$, shows that $\frac{dv}{dt} = \frac{y}{\theta} - \gamma \frac{v}{\theta}$. Because $\gamma \gg \delta$, the infected-cell density is relatively constant as the excess free virus is quickly removed. This time-scale separation suggests the quasi-steady-state approximation, $\frac{\partial v}{\partial t} = 0$, which yields $v = \frac{N\delta}{\gamma} y$ in equation (4).

Using the data presented in Table 1, we deduce that $v \sim 20.8 y$, which is in good agreement with the numerical results in Fig. 3, where the profiles of $y$ and $v$ are qualitatively similar.

Adopting these two simplifications, our PDE model for uniform injection reduces to the following system of ordinary differential equations (ODEs) for $x(t)$, $y(t)$ and $R(t)$:

$$
\frac{dx}{dt} = \lambda x - \frac{R_0 \delta}{\theta} x y - \frac{x}{\theta} [\lambda x - \mu (\theta - x - y)] \equiv f(x, y), \tag{24}
$$

$$
\frac{dy}{dt} = \frac{R_0 \delta}{\theta} x y - \delta y - \frac{y}{\theta} [\lambda x - \mu (\theta - x - y)] \equiv g(x, y), \tag{25}
$$

$$
\frac{dR}{dt} = \frac{R}{3 \theta} [\lambda x - \mu (\theta - x - y)]. \tag{26}
$$

We refer to this system as our NQ (nonspatial, quasi-steady-state) model. Figure 4 plots the tumor radius $R(t)$ for the PDE and NQ models. The close agreement between the two curves indicates that the NQ model provides a good approximation to the PDE model in the uniform injection case. Figure 5 depicts the dynamics of $x(t)$ and $y(t)$ for the NQ model, and shows that both the uninfected and infected cell densities undergo damped oscillations before settling to their steady states. Note also that equations (24) and (25), which can be viewed as a Lotka–Volterra competition model (Murray, 1989), are independent of the tumor radius $R(t)$ and that, once $x$ and $y$ reach their steady states, the sign of $\frac{dR}{dt}$ in (26) is invariant. Therefore, the tumor’s long-term behavior can be predicted by simply analysing the steady states of equations (24) and (25).
Modeling of a Replication-competent Virus

3.3. Steady-state analysis. The steady states for $x$ and $y$ are obtained by setting $\frac{dx}{dt} = f(x, y) = 0$ and $\frac{dy}{dt} = g(x, y) = 0$ in equations (24) and (25). There are four possible solutions: $(x, y) = (0, 0), (0, (1 - \delta/\mu)\theta), (\theta, 0)$ and $(x_s, y_s)$ where

$$x_s = \frac{(\mu \lambda - R_0 \delta \mu + R_0 \delta^2 + \mu \delta)\theta}{(R_0 \delta - \lambda)R_0 \delta}, \quad y_s = \frac{(\lambda + \mu)(R_0 \delta - \delta - \lambda)\theta}{(R_0 \delta - \lambda)R_0 \delta}. \quad (27)$$

These four solutions represent, respectively, the elimination of uninfected and infected cells and virus (tumor comprises dead cells only), the elimination of all uninfected cells (viral control), the elimination of the virus, and the coexistence of uninfected and infected tumor cells.

Each solution is stable if and only if the real parts of the eigenvalues of the
linearization matrix  
\[ A = \begin{bmatrix} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial y} \\ \frac{\partial g}{\partial x} & \frac{\partial g}{\partial y} \end{bmatrix}_{x_0, y_0} \]  
are negative. Since a complete stability analysis can be found in Section 4.1.3 of Wu (1999), we merely summarize the results here. Two cases arise, depending upon whether \( \delta > \mu \) or \( \delta < \mu \) (note that \( \delta \) and \( \mu \) are of the same order of magnitude in Table 1). It is possible to show that, in each case, only one steady-state solution is stable and convergence to this steady state is independent of the initial conditions (i.e., the stable steady state is a global attractor).

**Case 1.** (\( \delta > \mu \)).

When \( \delta > \mu \) (as in Table 1) the virus-free solution \((x_0, y_0) = (\theta, 0)\) is stable if \( R_0 < 1 + \frac{\lambda}{\delta} \), whereas the coexistence state \((x_s, y_s)\) defined by (27) is stable if \( R_0 > 1 + \frac{\lambda}{\delta} \). If \( R_0 < 1 + \frac{\lambda}{\delta} \) then the virus is too weak to maintain a positive concentration inside the tumor. Substituting \((x_0, y_0) = (\theta, 0)\) into (26) yields
\[
\frac{dR(t)}{dt} = \frac{\lambda R(t)}{3}; \tag{28}
\]
as expected, the tumor volume eventually grows exponentially at rate \( \lambda \). If \( R_0 > 1 + \frac{\lambda}{\delta} \) then the virus is strong enough to maintain an infection and substituting (27) into (26) yields
\[
\frac{3dR(t)}{R} dt = \left( \frac{\mu}{R_0-\lambda/\delta} \right) \left( 1 + \frac{\lambda}{\delta} + \frac{\lambda}{\mu} - R_0 \right). \tag{29}
\]
The right-hand side of (29) is a decreasing function of the reproductive ratio \( R_0 \), which equals \( \frac{1}{2} \) if \( R_0 = 1 + \frac{\lambda}{\delta} \), and equals zero if \( R_0 = 1 + \lambda \left( \frac{1}{\delta} + \frac{1}{\mu} \right) \).

**Case 2.** (\( \delta < \mu \)).

When \( \delta < \mu \), we find that \((\theta, 0)\) is stable if \( R_0 < 1 + \frac{\lambda}{\delta} \), the coexistence steady-state defined equation (27) is stable if \( R_0 \in \left[ 1 + \frac{\lambda}{\delta}, \frac{\mu (\lambda + \delta)}{\delta (\mu - \delta)} \right] \), and \((0, \frac{(\mu - \delta)\theta}{\mu})\) is stable if \( R_0 \geq \frac{\mu (\lambda + \delta)}{\delta (\mu - \delta)} \). Equation (28) holds if \( R_0 < 1 + \frac{\lambda}{\delta} \), equation (29) holds if \( R_0 \in \left[ 1 + \frac{\lambda}{\delta}, \frac{\mu (\lambda + \delta)}{\delta (\mu - \delta)} \right] \), and \( \frac{dR(t)}{dt} < 0 \) if \( R_0 \geq \frac{\mu (\lambda + \delta)}{\delta (\mu - \delta)} \).

By combining the results for both cases, we derive the following, more general result which relates the tumor’s growth to the virus’ reproduction ratio \( R_0 \):

\[
\begin{align*}
\text{the tumor eventually} & \begin{cases} 
\text{grows exponentially if } R_0 < 1 + \lambda \left( \frac{1}{\delta} + \frac{1}{\mu} \right); \\
\text{ceases to change in size if } R_0 = 1 + \lambda \left( \frac{1}{\delta} + \frac{1}{\mu} \right); \\
\text{shrinks exponentially if } R_0 > 1 + \lambda \left( \frac{1}{\delta} + \frac{1}{\mu} \right).
\end{cases} 
\end{align*} 
\]

For the parameter values in Table 1, \( 1 + \lambda (\delta^{-1} + \mu^{-1}) = 1.36 \). In Fig. 6 we provide simulation results from the PDE model for various values of \( R_0 \). These
tumor growth curves indicate that our approximate analysis accurately predicts the long-term behavior of an injected tumor. Repeated simulations of the PDE model yield a slightly higher threshold of $R_0 = 1.37$. In order to understand why our analysis underestimates this threshold value, we refer to the solution profiles at $t = 2000 \text{ h}$ in Fig. 3: the surge in cell proliferation that occurs near the tumor boundary that is present in the numerical simulations indicates that, in practice, a stronger virus will be needed to control the tumor. Furthermore, log-linear plots (not shown here) of $R(t)$ vs $t$ confirm that the exponential growth and shrinkage rates in (28) and (29) are also very accurate.

In the next two sections, we assume that $R_0 > 1 + \lambda(\delta^{-1} + \mu^{-1})$ (as implied by the values in Table 1), and investigate whether tumor control can be achieved by injecting only a portion of the tumor.

4. **CORE INJECTION**

4.1. **Numerical results.** In the case of core injection, a fixed fraction $p$ of the tumor cells in the inner core of radius $R(0) - w(0)$ is pre-infected with the virus. The tumor growth curves in Fig. 7 show that, in contrast to uniform injection, initial conditions play a decisive role in controlling the tumor. A comparison of the spatial profiles at the four time points in Fig. 8 reveals a race between the outward movement of the traveling wave of viral infection, which is depicted by the spatial profile of the infected cells, and the outward movement of the tumor boundary, which is generated by proliferation in the uninfected rim. More specifically, at times $t = 750, 1500$ and $2250 \text{ h}$, the wave of infected cells extends from the tumor center to 60, 66 and 95% of the corresponding tumor radius, i.e., the infection
Figure 7. Tumor growth curves in the core injection case for various values of $w(0)$.

Figure 8. Spatial profiles of uninfected cells, infected cells, and free virus at four time points in the core injection case [$w(0) = 0.3$ mm].

is spreading faster than the tumor boundary is growing. Indeed, soon after $t = 2250$ h, the wave of infection reaches the tumor boundary, at which point the virus
is distributed throughout the tumor. As predicted by our uniform injection analysis, the tumor shrinks exponentially thereafter (because \( R_0 > 1.36 \)) and displays spatial invariance by \( t = 3000 \) h. Finally, simulations (not shown here) confirm that the eventual fate of the tumor does not depend upon the fraction \( p \) of infected cells.

### 4.2. Model simplifications

In an attempt to derive conditions for virus-induced tumor control in the core injection case, we make two simplifying assumptions, and use them to develop and analyse an approximating ODE model. The first assumption is the quasi-steady-state approximation introduced in Section 3 (Fig. 8 shows that, as for the uniform infection case, this is a reasonable assumption). Setting \( \frac{\partial v}{\partial t} = 0 \) in (4) we eliminate \( v \) from equations (1) and (2) which reduce to give

\[
\begin{align*}
\frac{\partial x(r, t)}{\partial t} &= \lambda x(r) - \frac{R_0 \delta}{\theta} x(r, t) \bar{y}(r, t) - \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 y(r, t) x(r, t) \right), \\
\frac{\partial y(r, t)}{\partial t} &= \frac{R_0 \delta}{\theta} x(r, t) \bar{y}(r, t) - \delta y(r, t) - \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 u(r, t) y(r, t) \right),
\end{align*}
\]  

where

\[ \bar{y}(r, t) = \frac{3}{8r_c} \int_{r-r_c}^{r+r_c} \int_{s-r_c}^{s+r_c} y(w, t) [r^2 - (s - w)^2] \, dw \, ds \]

is a weighted spatial average of \( y(r, t) \) that incorporates the distance traversed by a virus particle during one round of infection and lysis.

Equations (31) and (32) are reminiscent of the classic spatial epidemic problem introduced by Kendall (1965). This similarity motivates our second simplification: we replace (33) with

\[
\bar{y}(r, t) = y(r, t) + d \left( \frac{\partial^2 y(r, t)}{\partial r^2} + \frac{2}{r} \frac{\partial y(r, t)}{\partial r} \right),
\]

which is the diffusion approximation for a sphere \((d \text{ is in units of distance squared})\).

Within the context of the reproduction and dispersal kernel framework for spatial epidemics (Diekmann, 1978; van den Bosch et al., 1990), the diffusion approximation is equivalent to assuming that the duration of one round of infection and lysis is deterministic, and that the corresponding dispersal distance is normally distributed (Mollison, 1991). Making these assumptions, and using the fact [e.g., Rubinow (1975, p. 209)] that the mean square dispersal distance in a sphere with a constant diffusion coefficient \( \bar{d} \) over a period of time \( t \) is \( 6\bar{d}t \), we can determine the diffusion parameter \( d \) that appears in (34) by equating it to the mean square dispersal distance during one round of infection and lysis divided by six.

Now we estimate the mean square dispersal distance for virus particles during one round of infection and lysis by decomposing the total dispersion distance into an infection dispersal distance and a lysis dispersal distance. Because infection
occurs on the cell’s surface, the infection dispersal distance is the distance from the center of a cell of radius $r_c$ to a random point uniformly distributed on the cell’s surface. Similarly, since the virus is released uniformly throughout the spherical cell during lysis, the lysis dispersal distance is the distance from the center of a cell of radius $r_c$ to a random point, uniformly distributed in the cell. By assuming that the two dispersal mechanisms behave independently, we may view the total dispersion distance during one round of infection and lysis as the distance from a given point on the surface of a cell to a random point in the cell. Taking the reference point as the ‘bottom’ of the cell, and letting $z$ index the ‘vertical’ axis and $r$ index the ‘horizontal’ distance from the vertical axis (see Fig. 9), we can compute the mean square dispersal distance as

$$
\int_{-r_c}^{r_c} \int_0^{\sqrt{r_c^2 - z^2}} \left[(z + r_c)^2 + r^2\right] \frac{3r}{2r_c} \, dz \, dr = \frac{8}{5} r_c^2.
$$

Hence, the diffusion parameter in (34) is given by

$$
d = \frac{4}{15} r_c^2.
$$

4.3. Approximating the ODE model. Equations (31), (32), (34) and (3) reduce to Kendall’s spatial epidemic model if we assume a one-dimensional, Cartesian geometry, that there is no cell proliferation ($\lambda = 0$) or removal of necrotic material ($\mu = 0$), and that there is no tumor boundary [$x(r, 0) = \theta$ for all $r > R(0) - w(0)$; i.e., all of one-dimensional space beyond the core is initially fully occupied with uninfected cells]. Kendall derived a minimum wave speed $c_0$ for the traveling wave solutions of his model [i.e., $x(r, t) = x(r - c_0 t)$, $y(r, t) = y(r - c_0 t)$, $n(r, t) = n(r - c_0 t)$]. As noted on p. 280 of Murray (1989), the corresponding spherical problem does not possess traveling wave solutions because of the $\frac{2}{r} \frac{\partial y(r, t)}{\partial r}$ term in (34). However, for large $r$, this term becomes negligible, and so the spherical solution will exhibit wave-like solutions, with speeds that increase monotonically towards the speed in Kendall’s problem. Numerical results (not shown here)
confirm that the wave speed in the spherical problem (with $\lambda = \mu = 0$) converges quickly to Kendall’s one-dimensional wave speed, which in our setting is given by

$$c_0 = 2R_0\sqrt{d(1 - R_0^{-1})} = \frac{4R_0\sqrt{1 - \frac{1}{R_0}}}{\sqrt{15}}r_c \delta. \quad (37)$$

Kendall (1965) also showed that no wave of infection is possible if $R_0 < 1$. Finally, as noted earlier, equation (22) was derived in the context of Kendall’s model.

Our plan is to use Kendall’s results to crudely approximate the PDE model by an ODE model. More specifically, we assume the spherical tumor consists of two regions that vary in size over time: a core, $0 < r \leq r(t)$, that contains free virus and infected, uninfected and necrotic cells, and a rim, $r(t) < r \leq R(t)$, comprised solely of uninfected cells. We refer to the partition $r(t)$ as the wavefront. By our earlier discussion, we assume $r(t) = R(0) - w(0) + c_0 t$; i.e., the wavefront is at the outer edge of the infected region at time zero, and travels outward at velocity $c_0$, which is defined in (37). This definition of the wavefront contains the bold assumption that there is no net proliferation in the core; i.e., the proliferation of uninfected cells in the core is exactly offset by the removal of necrotic debris in the core (without this assumption, the resulting ODE is not analytically solvable). The parameter values of $\lambda$ and $\mu$ in Table 1, together with the evolution of the cells under uniform injection depicted in Fig. 5, suggest that the necrotic removal rate is higher than the cell proliferation rate in the core after the first week. Hence, our assumption that the net proliferation rate in the core is zero should cause us to overestimate the size of the tumor and, consequently, to overestimate the injection volume required to control the tumor. Because the fraction of the tumor volume that is uninfected at time $t$ is given by $1 - \left(\frac{R(0) - w(0) + c_0 t}{R(0)}\right)^3$, we deduce that in this simple two-region model the tumor radius evolves according to the ODE

$$\frac{d R(t)}{dt} = \frac{\lambda R(t)}{3} \left(1 - \frac{(R(0) - w(0) + c_0 t)^3}{R^3(t)}\right). \quad (38)$$

This equation is only valid when $R(0) - w(0) + c_0 t < R(t)$, i.e., until the infection wave reaches the tumor boundary.

The Bernoulli ODE (38) has the solution

$$R(t) = [B + [R^3(0) - B]e^{3t} + C(t)]^{1/3} \quad (39)$$

where

$$B = [R(0) - w(0)]^3 + 3\left(\frac{c_0}{\lambda}\right)[R(0) - w(0)]^2$$

$$+ 6\left(\frac{c_0}{\lambda}\right)^2 [R(0) - w(0)] + 6\left(\frac{c_0}{\lambda}\right)^3. \quad (40)$$
By our uniform injection analysis and by Fig. 8, if the wavefront reaches the tumor boundary then the tumor will be controlled [by our assumption that $R_0 > 1 + \lambda(\delta^{-1} + \mu^{-1})$]. Because $C(t) > 0$ in (41), equation (39) implies that $R^3(0) - B$ must be negative in order for the infection wave to eventually reach the tumor boundary. Although $R(t) \to 0$ as $t \to \infty$ if $R^3(0) < B$, this condition is necessary but not sufficient for tumor control within 3000 h. Numerical solutions of (39) (not shown here) show that $w_0$ has to be less than about 70% of the threshold value that we derive below in order for the wavefront to catch up within 3000 h. Nonetheless, a threshold condition on the initial rim width $w(0)$ can be obtained by solving the cubic equation $0 = R^3(0) - B$, which can be rearranged to give

$$0 = w^3(0) - 3\left(R(0) + \frac{c_0}{\lambda}\right)w^2(0) + 3\left(R^2(0) + 2R(0)\frac{c_0}{\lambda} + 2\frac{c_0^2}{\lambda^2}\right)w(0) - 3\frac{c_0}{\lambda}\left(R^2(0) + 2R(0)\frac{c_0}{\lambda} + 2\frac{c_0^2}{\lambda^2}\right).$$

Under the assumptions $R(0) \gg 1$ and $c_0/\lambda = O(1)$, we let $R(0) = \epsilon^{-1}$ and look for a solution of the form $w(0) = w_0 + \epsilon w_1 + \cdots$. Two of the roots form a conjugate pair and scale with $R(0)$, and the unique, physically realistic (i.e., positive) solution to equation (42) is $w(0) = \frac{c_0}{\lambda} + \frac{c_0^2}{\lambda^2}R(0) + O(R(0)^{-1})$. Because the $O(R(0)^{-1})$ term is negligible compared to the leading term (see Fig. 10), this approximate solution to (42) implies that

the tumor eventually

$$\begin{cases}
grows exponentially if w(0) > \frac{c_0}{\lambda}; \\
achieves a constant size if w(0) = \frac{c_0}{\lambda}; \\
shrinks until eradication if w(0) < \frac{c_0}{\lambda}.
\end{cases}$$

In Fig. 10, we plot the $w(0)$ threshold derived from the PDE model, the cubic equation (42) and the approximation (43). Although the PDE-derived threshold is not independent of the initial tumor size, as predicted by (43), the dependence is quite weak: the threshold varies by only 0.2 mm as the tumor radius varies by 8 mm. As expected, the PDE-derived threshold curve is higher than the curves derived from (42) and (43), because our ODE approximation overestimates the tumor size. From the perspective of the tumor size (2–10 mm), equation (43) is a reasonably accurate (within 0.4 mm) approximation of the PDE-derived threshold.
greater the slack allowed in the volume of tumor injected. As predicted by (43), the PDE-derived threshold appears to be linear in $c_0/\lambda$, although with a slope that is larger than 1.0. The reasonably good absolute accuracy (the difference between the thresholds is less than 0.3 mm, which is negligible for moderate size tumors) suggests that the net loss of cells behind the wave of infection does not have a significant impact on the race between the traveling wave and the tumor boundary, because this cell loss causes both the wave and the tumor boundary to recede.
5. **Rim Injection**

5.1. **Numerical results.** In rim injection, a fraction $p$ of the cells in the outer rim [of width $R(0) - r(0)$] of the tumor are initially infected. As in core injection, Fig. 12 shows that the behavior of tumor growth up until 3000 h is sensitive to $r(0)$. Whereas core injection can be viewed as a race between the wave of infection and the proliferation at the tumor boundary, the spatial profiles in Fig. 13 show that rim injection can be visualized as a competition between the inward movement of the traveling wave of infection from the tumor rim and the radial expansion of the tumor that is caused by cells proliferating within its core. The point at which the two forces collide is not monotonic in time in Fig. 13: the leftmost intersection of the $x(r, t)$ and $v(r, t)$ curves is at 0.87 mm at $t = 7500$ h, 1.14 mm at $t = 1500$ h, 1.39 mm at $t = 2250$ h, and 1.23 mm at $t = 3000$ h. Hence, in this case, tumor proliferation wins the battle initially, but the virus is ultimately victorious.

One unexpected observation from Fig. 13 is that free virus accumulates near the tumor center at $t = 3000$ h, apparently because the inward movement of the wave of infection allows a small amount of virus to penetrate the uninfected core and become trapped (due to the low convective velocity there). To investigate this phenomenon further, we display in Fig. 14 the spatial profiles for the $r(0) = 0.7$ mm case (which appears headed for exponential tumor growth in Fig. 13) between $t = 3000$ and $t = 3500$ h. In this case, the trapped virus generates a secondary wave of infection near the tumor center, and causes the remaining uninfected tumor cells to get sandwiched between two infected regions, as if they were a victim of core and rim injections. This secondary wave of infection reduces the tumor radius from 3.14 mm at $t = 3000$ h to 2.60 mm at $t = 3500$ h, and is sufficient to control the tumor. We discuss the significance of this phenomenon in the Summary section.

5.2. **Approximating the ODE model and analysis.** We follow the approach used to analyse core injection. Thus, we adopt the quasi-steady-state assumption and the diffusion approximation, and view the tumor as having two regions: a core, $0 < r < r(t)$, comprised of uninfected tumor cells and an infected rim, $r(t) < r < R(t)$, consisting of cells and virus. We assume that the wavefront separating the two regions is pushed outward at rate $\lambda r(t)/3$ (this is the growth rate that would arise in the absence of an infected rim) and, by analogy with the core injection case, is pushed inward at constant rate $c_0$ [this is the speed, defined by equation (37), with which the virus spreads through the uninfected cells]. Combining these ideas, we deduce that the wave front in this two-region model is characterized by

$$\frac{dr(t)}{dt} = \frac{\lambda r(t)}{3} - c_0.$$  \hspace{1cm} (44)
Figure 12. Tumor growth curves in the rim injection for various values of \( r(0) \).

\[
\begin{align*}
\text{Figure 13. Spatial profiles of uninfected cells, infected cells, and free virus at four time points for rim injection \( r(0) = 0.6 \text{ mm} \).}
\end{align*}
\]

where \( r(0) \) is the initial uninfected core radius. The solution to (44) is

\[
r(t) = \left( r(0) - \frac{3c_0}{\lambda} \right) e^{\lambda t/3} + \frac{3c_0}{\lambda}.
\]  

(45)
Figure 14. Spatial profiles of uninfected cells, infected cells, and free virus at six time points for rim injection \( r(0) = 0.7 \) mm.

By our assumption that \( R_0 > 1 + \lambda(\delta^{-1} + \mu^{-1}) \), we know from the uniform injection analysis that the infected rim will eventually be eradicated. Hence, \( r(t) \) in (45) determines the long-term behavior of the tumor. However, in light of Fig. 14 and the impermeability of our wavefront \( r(t) \), equation (45) only dictates whether or not the tumor is controlled by the primary wave of infection, not the secondary...
Figure 15. The tumor is controlled by the primary wave of infection if and only if the initial uninfected core radius is below the threshold curve. These curves are derived from the PDE model and equation (46). The value $c_0/\lambda$ is varied in the PDE model by using different values of $R_0$. 

wave. Using (45), we infer that

\[
\begin{align*}
\text{the tumor eventually} & \quad \begin{cases} \\ 
\text{grows exponentially if } r(0) > \frac{3c_0}{\lambda}; \\
\text{achieves a constant size if } r(0) = \frac{3c_0}{\lambda}; \\
\text{shrinks until eradication if } r(0) < \frac{3c_0}{\lambda}.
\end{cases}
\end{align*}
\]

As in the core injection case, our approximate analysis predicts that tumor control caused by the primary wave depends on the absolute—not the relative—initial core size; i.e., it is independent of the initial tumor radius $R(0)$. Simulation results (not shown here) of the PDE model confirm that tumor control by the primary wave of infection is largely independent of $R(0)$ and the fraction infected, $p$. Figure 15 compares the threshold in (46) to the PDE-computed threshold for the primary wave of infection. As in the core injection case, our ODE analysis slightly overestimates the injection volume required to control the tumor, but the absolute difference in the threshold is rather small. Also, the PDE-derived threshold appears to be linear in $c_0/\lambda$, as predicted by (46).

In summary, while our ODE analysis is too crude to capture either the nonmonotonic behavior of the wavefront in Fig. 13 or the secondary wave of infection in Fig. 14, it accurately predicts the tumor’s ability to fight off the primary wave of infection shown in Fig. 12.

5.3. Comparison of core and rim injections. To facilitate a comparison of core and rim injections, we translate the threshold conditions on the core and rim sizes in (43) and (46) into the fraction of total volume infected. The resulting threshold curves in Fig. 16 reveal that a greater tumor volume needs to be infected in rim
Injection than in core injection for any given initial tumor radius. For rim injection to control the tumor via the primary wave of infection, nearly the entire tumor volume has to be infected initially. However, if we also consider the secondary wave of infection generated by rim injection, then rim injection is clearly more efficacious than core injection.

6. Nutrient-Limited Necrosis

Until now, we have assumed that tumor growth is not limited by a lack of nutrients. In contrast, much of the tumor modeling literature focuses on the vital role of nutrients such as oxygen and glucose [e.g., Greenspan (1972), Adam and Bellomo (1997), Ward and King (1997)]. In this section, we superimpose a variant of the simple ‘constant crust’ model [e.g., Conger and Ziskin (1983)] onto our model. In the constant crust model, the tumor consists of a necrotic core and a viable rim, where exponential growth occurs in the outer rim of maximum width $r_0$ and all cells in the core undergo necrosis. If we choose $r_0$ to be the oxygen diffusion limit in tumor tissue, then this model would represent an avascular tumor. For all simulations in this section, we assume $r_0 = 2$ mm, which is about 10 times larger than the oxygen diffusion limit in tumor tissue (Thomlinson and Gray, 1955), to represent a moderately vascularized tumor. In the absence of treatment, such a tumor achieves a finite steady-state size, where the necrotic loss in the tumor core exactly offsets the cell division in the tumor rim.

Because (i) for realistic values of $R_0$, uniform injection controls the tumor without the aid of nutrient-limited necrosis, and (ii) core injection and nutrient-limited necrosis play a similar role in tumor control [while the traveling wave of nutrient-limited necrosis always lags the tumor surface by a radial distance $r_0$, the traveling
wave of tumor-infected cells either reaches the tumor surface or is eventually left far behind by tumor growth, depending upon the relative values of $w(0)$ and $c_0/\lambda$, as approximately given in (43)], the analysis in this section focuses on the rim injection case in the presence of nutrient-limited necrosis. Moreover, for the sake of space and in light of the accuracy of our earlier ODE analyses, we restrict ourselves to an ODE analysis in this section.

We assume that $R_0 \geq 1 + \lambda \left( \frac{1}{3} + \frac{1}{\mu} \right)$, so that the infected rim will eventually be eradicated, and construct an approximating ODE model that generalizes equation (44). Referring to Fig. 17, we let $R(t)$ be the tumor radius, $r(t)$ be the infection wave location that marks the boundary between the infected rim and the uninfected shell, and $l(t)$ denote the location of the boundary between the uninfected shell and the necrotic core. Note that if $r(0) < r_0$, there will be no necrotic core and our previous analysis on rim injection applies. Hence, we assume $r(0) \geq r_0$, so that the uninfected shell is sandwiched between the necrotic core and the infected rim. We refer to the combined mass of the uninfected shell and the necrotic core as the \textit{tumor core}, so that $r(t)$ is the tumor core radius. We also assume that the initial infected rim is very thin, so that $R(t) \approx r(t)$ for all $t$ and $l(0) = r(0) - r_0$; at the end of this section, we comment on the more complicated case, where the thickness of the initial infected rim is larger so that $l(0) > r(0) - r_0$. Because diffusion through necrotic debris is much easier than through live tumor cells (Boucher \textit{et al.}, 1997), we assume that nutrients can sustain cell survival and growth for an inwards distance $r_0$ from the tumor core radius $r(t)$. Finally, we assume that necrosis is irreversible. With these assumptions, the approximating ODE model for rim

Figure 17. The tumor geometry in the case of rim injection and nutrient-limited necrosis.

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injection is

\[ \frac{dr}{dt} = \frac{r}{3} \left[ \lambda - \frac{l^3}{r^3} (\lambda + \mu) \right] - c_0, \]  

(47)

\[ \frac{dl}{dt} = \begin{cases}  
\frac{dr}{dt} & \text{if } l = r - r_0 \text{ and } \frac{dr}{dt} \geq -\frac{\mu}{3}; \\
-\frac{\mu}{3} l & \text{if } l = r - r_0 \text{ and } \frac{dr}{dt} < -\frac{\mu}{3} l; \\
-\frac{\mu}{3} l & \text{if } l > r - r_0 
\end{cases} \]  

(48)

where the dependence of \( r \) and \( l \) on \( t \) is suppressed in this section.

A key role in our analysis is played by the function

\[ g(r, c_0) \equiv \frac{r}{3} \left[ \lambda - \frac{(r - r_0)^3}{r^3} (\lambda + \mu) \right] - c_0, \quad r \geq r_0, \]  

(49)

which is the tumor core growth rate, \( \frac{dr}{dt} \), for times such that \( l = r - r_0 \) and \( \frac{dr}{dt} \geq -\frac{\mu}{3} l \). Differentiating (49) gives \( \frac{dg}{dr} = -\frac{\mu}{3} + \frac{r_0^2}{3r^4} (3r - 2r_0)(\lambda + \mu) \) and \( \frac{d^2g}{dr^2} = -\frac{2}{r^3} r_0^2 (\lambda + \mu)(r - r_0) \), so that \( g \) is strictly concave for \( r > r_0 \). It follows that \( g \) has a unique global maximum, call it \( r_M \) [given in (59)], independent of the value of \( c_0 \). Because \( g(r, c_0) \) is linear in \( c_0 \), there exists a \( c_M \) [given in (60)] such that \( g(r_M, c_0) < 0 \) for all \( c_0 > c_M \). So if \( c_0 > c_M \), \( g(r, c_0) < 0 \) for all \( r \geq r_0 \) and \( g \) has no roots. If \( \frac{\lambda}{2} r_0 \leq c_0 \leq c_M \), \( g \) has two roots, which we denote as \( S_1(c_0) \) and \( S_2(c_0) \), respectively, such that \( r_0 \leq S_1(c_0) \leq S_2(c_0) \). For the special case where \( g(r_M, c_0) = 0 \), we have \( S_1(c_0) = S_2(c_0) = r_M \). Finally, if \( c_0 < \frac{\lambda}{2} r_0 \), then \( g \) has only one root, which is \( S_2(c_0) \). These cases are illustrated in Fig. 18, where the wave speed \( c_0 \) is expressed in terms of \( R_0 \) via (37).

We first consider this tumor in the absence of treatment [i.e., \( c_0 = 0 \) and \( R(t) = r(t) \)]. Let \( r(0) = r_0 \), so that \( \frac{dr(0)}{dt} = g(r_0) = \frac{\lambda}{2} r_0 > 0 \) and \( l = r - r_0 \). Since \( \frac{dl}{dt} \) is
continuous, for small enough \( \tilde{t}, \frac{dr}{d\tilde{t}} > 0 \) and \( l = r - r_0 \) for \( 0 \leq t \leq \tilde{t} \), and so \( \frac{dtr}{d\tilde{t}} = g \) for all \( t \in [0, \tilde{t}] \). Because \( \frac{dtr}{d\tilde{t}} = g \) is positive and strictly concave in \( r \), \( \frac{dtr}{d\tilde{t}} \) eventually becomes strictly decreasing as \( r \) increases. It follows that \( \frac{dtr}{d\tilde{t}} = g \) approaches 0 and the tumor core radius \( r \) approaches the steady-state value

\[ S_2(0) = \left[ 1 + \frac{\lambda + [\lambda(\lambda + \mu)^2]^{1/3}}{\mu} + \frac{\lambda(\lambda + \mu)}{\mu[\lambda(\lambda + \mu)^2]^{1/3}} \right] r_0. \]  

(50)

In Fig. 18, this approach to steady state is depicted by the rightward movement along the top curve. Because the nutrient-limited necrotic core is capable of controlling the growth of the tumor in the absence of treatment, the remaining question is whether or not the tumor will be eradicated by the viral injection.

In the remainder of this section, we derive tumor eradication conditions in terms of the wave speed \( c_0 \), which characterizes the strength of the virus, and the initial tumor core radius \( r(0) \), where \( r_0 \leq r(0) \leq S_2(0) \). The analysis depends on the sign of \( \frac{dr(0)}{dt} \). If \( \frac{dr(0)}{dt} = g(r(0), c_0) \geq 0 \), then our analysis of the no-injection case implies that \( r \) approaches the steady state \( S_2(c_0) \); see Fig. 19(a). If \( \frac{dr(0)}{dt} = 0 \) then \( S_2(c_0) = r(0) \), and the virus halts the growth of the tumor immediately after the injection. In the more complicated case where \( \frac{dr(0)}{dt} < 0 \), there are two possibilities: \( \frac{dr(0)}{dt} \leq -\frac{1}{2} l(0) < 0 \) and \( -\frac{1}{2} l(0) < \frac{dr(0)}{dt} < 0 \), which are referred to as Cases 1 and 2, respectively. Note that \( -\frac{1}{2} l(0) \) is just \( -\frac{\mu}{3} (r(0) - r_0) \). The function \( f(r) = -\frac{\mu}{3} (r - r_0) \) represents the boundary between Cases 1 and 2, as shown in Fig. 19(b)–(d). Starting with Case 1, let us suppose \( \frac{dl}{dt} > \frac{df}{dt} = f = -\frac{\mu}{3} l < 0 \) for some time \( t \). The second derivative of \( r \) is

\[
\frac{d^2r}{dt^2} = \frac{1}{3} \frac{dr}{dt} \left[ \frac{\lambda - \frac{t^3}{r^3}(\lambda + \mu)}{\rho} \right] + \frac{r}{3} \left[ -\frac{(\lambda + \mu)}{\rho} \left( \frac{t^2}{r^3} \frac{dl}{dt} - \frac{t^3}{r^4} \frac{dr}{dt} \right) \right].
\]

(51)

Note that \( \frac{df}{dt} = -\frac{\mu}{3} \frac{dl}{dt} = \frac{\rho^2}{9} l \), and \( f < 0 \) implies \( \rho > 0 \). Using (51), we have

\[
\frac{d^2r}{dt^2} - \frac{df}{dt} = \frac{1}{3} \left( -\frac{\mu}{3} l \right) \left[ \frac{\lambda + 2 \frac{t^3}{r^3}(\lambda + \mu)}{\rho} \right] - \left( \frac{\lambda + \mu}{\rho} \right) \frac{t^2}{r^2} \left( \frac{\mu}{3} l \right) - \frac{\rho^2}{9} l,
\]

\[
= -\frac{\mu}{9} \left[ \frac{\lambda + 2 \frac{t^3}{r^3}(\lambda + \mu)}{\rho} - 3 \frac{t^2}{r^2} \left( \frac{\lambda + \mu}{\rho} \right) \right],
\]

\[
= -\frac{\mu}{9} \frac{r^3}{r^3} \left( \frac{r + \mu}{r^3} \right) (r^3 + 2t^3 - 3t^2 r),
\]

\[
= -\frac{\mu}{9} \frac{r^3}{r^3} \left( \frac{r + \mu}{r^3} \right) (2l + r)(l - r)^2,
\]

< 0.  

(52)
Figure 19. Trajectories for various scenarios. The diamond indicates the point right before
the injection, the triangle indicates the point immediately after the injection, the square rep-
resents the eventual post-treatment result, and the circle represents the steady-state tumor
core radius in the absence of treatment. The line \( f(r) \) delineates the two cases described
above equation (51) of the text. (a) \( \frac{dr}{dt}(0) > 0 \), which results in a reduction of the steady-
state tumor core size. (b) \( \frac{dr}{dt}(0) \leq \frac{dl}{dt}(0) < 0 \), which results in tumor eradication as \( r \)
moves along \( h(r, c_0) \) to 0. (c) \( \frac{dl}{dt}(0) < \frac{dr}{dt}(0) < 0 \) and \( r(0) < S_1(c_0) \), which results in
tumor eradication as \( r \) moves along \( g(r, c_0) \), then switches to \( h(r, c_0) \) after crossing the
line \( f(r) \), and finally goes to 0. (d) \( \frac{dl}{dt}(0) < \frac{dr}{dt}(0) < 0 \) and \( r(0) > S_2(c_0) \), which results
in a reduction of the steady-state tumor core size.

It follows that the gradient of \( \frac{dr}{dt} \) is strictly less than the gradient of \( f \) at times such
that \( \frac{dr}{dt} = f = -\frac{\mu}{r_0}l \). Hence, there exists a time \( \tilde{t} \) such that \( \frac{dr}{dt} < -\frac{\mu}{r_0}l, \frac{dl}{dt} = -\frac{\mu}{r_0}l \)
and \( l > r - r_0 \) for all times in \((t, \tilde{t}]\). Now consider any time point \( t \) such that
\( \frac{dr}{dt} < -\frac{\mu}{r_0}l \) and \( l > r - r_0 \). The tumor core growth rate and the necrotic core growth
rate are described by

\[
\frac{dr}{dt} = \frac{1}{3} \left[ \lambda - \frac{l^3}{r^3(\lambda + \mu)} \right] - c_0, \tag{53}
\]

\[
\frac{dl}{dt} = -\frac{\mu}{3}l. \tag{54}
\]
Using (51) and (52), we obtain
\[
\frac{d^2 r}{dt^2} - \frac{d^2 l}{dt^2} < \frac{1}{3} \left( -\frac{\mu}{3} l \right) \left[ \lambda + 2 l^3 (\lambda + \mu) \right] - (\lambda + \mu) \frac{l^2}{r^3} \left( -\frac{\mu}{3} l \right) - \frac{\mu^2}{9} l,
\]
\[
= -\frac{\mu}{9r^3} l (\lambda + \mu) (2l + r) (l - r)^2,
\]
\[
< 0.
\]
(55)

It follows that the gradient of \( \frac{dr}{dt} \) is always less than the gradient of \( \frac{dl}{dt} \) if \( \frac{dr}{dt} < \frac{dl}{dt} \). Therefore, if \( \frac{dr}{dt} \leq -\frac{\mu}{3} l < 0 \) for some time \( T \), then \( \frac{dr}{dt} < -\frac{\mu}{3} l < 0 \) and \( \frac{dl}{dt} = -\frac{\mu}{3} l \) for all \( t > T \). In particular, if \( \frac{dr(0)}{dt} \leq -\frac{\mu}{3} l(0) < 0 \), the tumor core growth rate and the necrotic core growth rate are described by

\[
\frac{dr}{dt} = \frac{r}{3} \left[ \lambda - \frac{(r(0) - r_0)^3 e^{-\mu t}}{r^3} (\lambda + \mu) \right] - c_0 \equiv h(r, c_0),
\]
\[
(56)
\]
\[
l = l(0)e^{-\frac{\mu}{3} t}.
\]
(57)

respectively. Hence, the tumor shrinks until eradication, as shown in Fig. 19(b). Note that the trajectory starts at \( g(r, c_0) \) but lies on \( h(r, c_0) \) because the growth rate of the tumor core is \( \lambda h(r, c_0) \) and not \( g(r, c_0) \). Now consider Case 2, where \( -\frac{\mu}{3} l(0) < \frac{dr(0)}{dt} < 0 \). Since \( g \) is strictly concave and has two roots, either \( r(0) < S_1(c_0) \) or \( r(0) > S_2(c_0) \). If \( r(0) < S_1(c_0) \) then the strict concavity of \( g \) and \( g(r(0), c_0) < 0 \) imply that \( g \) decreases as \( r \) decreases. It follows that \( \frac{dr}{dt} \) continues to decrease and there exists a time \( T > 0 \) such that \( \frac{dr(T)}{dt} = -\frac{\mu}{3} l(T) \). As shown in Case 1, the growth rate of the tumor changes from \( g(r, c_0) \) to \( h(r, c_0) \) after time \( T \), so the tumor will shrink to eradication; see Fig. 19(c). If \( r(0) > S_2(c_0) \) then \( g \)’s strict concavity and \( g(r(0), c_0) < 0 \) imply that \( g \) increases as \( r \) decreases. It follows that \( \frac{dr}{dt} \) continues to increase until \( \frac{dr}{dt} = 0 \) and \( r = S_2(c_0) \). Therefore, \( r \) approaches the steady-state tumor core size of \( S_2(c_0) \) as time goes to infinity, as shown in Fig. 19(d). In conclusion, we have established the following results. If \( c_0 < \frac{1}{\lambda} r_0 \), the tumor core size approaches \( S_2(c_0) \) in steady state. If \( c_0 > c_M \), the tumor is eradicated. These results hold regardless of initial tumor core size \( r(0) \). If \( \frac{1}{\lambda} r_0 \leq c_0 \leq c_M \), then

the steady-state tumor core size eventually \[
\text{approaches } S_2(c_0) \text{ if } r(0) > S_1(c_0);
\]
\[
\text{stays at } S_1(c_0) \text{ if } r(0) = S_1(c_0);
\]
\[
\text{goes to } 0 \text{ if } r(0) < S_1(c_0).
\]
(58)

We note that for the special case \( c_0 = \frac{1}{\lambda} r_0 \), \( S_1(c_0) = r_0 \leq r(0) \) and so tumor eradication is impossible. Finally, we give the expression for \( c_M \) and \( r_M \):

\[
r_M = \left\{ \left[ \left( 1 + \frac{\lambda}{\mu} \right) \left( i \sqrt{\frac{\lambda}{\mu}} - 1 \right) \right]^{1/3} + \left[ \frac{\left( 1 + \frac{\lambda}{\mu} \right)^2}{i \sqrt{\frac{\lambda}{\mu}} - 1} \right]^{1/3} \right\} r_0,
\]
(59)
Note that for a fixed \( \lambda \) and \( \mu \), \( r_M \) and \( c_M \) are both a constant multiple of \( r_0 \). The expressions for \( S_1(c_0) \) and \( S_2(c_0) \) are too cumbersome to be shown here.

We now briefly comment on controlling the thickness of the uninfected shell at the time of injection. Let \( s(t) = r(t) - l(t) \) denote the thickness of the uninfected shell, where \( s(0) \leq r_0 \). Using our existing results, we know that if \( c_0 < \frac{1}{3} r_0 \), changing the value of \( s(0) \) has no long-term effect and the tumor will always grow to its steady state \( S_2(c_0) \). If \( c_0 > c_M \), the tumor will always be eradicated regardless of the value of \( s(0) \). As before, when \( \frac{1}{3} r_0 \leq c_0 \leq c_M \), there are two cases: \( \frac{dr_0}{dt} < -\frac{\lambda}{3} l(0) < 0 \) and \( -\frac{\mu}{3} l(0) < \frac{dr_0}{dt} < 0 \). In the first case, the tumor will be eradicated as was shown previously. In the second case, because the necrotic core is receding faster than the tumor core, there exists a time \( \tau \) such that \( l(\tau) = r(\tau) - r_0 \). The growth rate of the tumor is described by \( h(r, c_0) \) before time \( \tau \), and by \( g(r, c_0) \) after time \( \tau \). Therefore, using our earlier results, the tumor will be eradicated if and only if \( r(\tau) < S_1(c_0) \). However, to know a priori how thin the uninfected shell should be, we need to know the solution to the differential equation of \( r(t) \) whose rate is \( h(r, c_0) \). While we have been unable to obtain an approximate solution to this equation, a sufficient condition for tumor eradication is \( r(0) \leq \max \{ R(0) - r_0, S_1(c_0) \} \).

Using our best estimate of \( R_0 = 11.44 \) and the data in Table 1, we obtain a traveling wave speed of \( c_0 = 2.35 \times 10^{-3} \) mm h\(^{-1} \). Hence, the tumor is not eradicated by rim injection—not even repeated injections—if the viable rim width \( r_0 \) is greater than \( 3 c_0 / \lambda = 2.35 \) mm, which corresponds [using (50)] to a pre-treatment steady-state tumor radius of 5.37 mm. Numerical computations of the inequality \( c_0 > c_M \) in (59) and (60) show that a single rim injection eradicates the tumor if \( r_0 < 1.93 \) mm, which corresponds to a pre-treatment steady-state tumor radius of 4.41 mm. If \( 1.93 < r_0 < 2.35 \) mm then the eradication condition depends on the initial tumor core size \( r(0) \). In this intermediate region, there are some cases in which repeated injections may eradicate the virus. As can be seen in Fig. 19(b)–(d), an injection eradicates the virus if and only if the tumor begins to recede immediately after the virus is injected and the tumor core growth rate \( \frac{dr(t)}{dt} \) is decreasing.

7. **The Model’s Limitations**

While the numerical and analytical results of Sections 3–6 demonstrate that our model provides a good description of viral infection in solid tumors, nonetheless it ignores several important features. As discussed in detail below, the main limitations relate to our treatment of the tumor microenvironment, the immune response and genetic heterogeneity, and to the introduction of mathematical simplifications.
In terms of the microenvironment, our model does not allow the virus to travel via the traditional modes of diffusion and convection. These modes of transport may be particularly relevant if the virus is injected post-surgically into, or on the periphery of, a fluid-filled cavity. Also, the model does not consider any physical barriers within the tumor (e.g., extracellular matrix, vascular network) that may inhibit virus transport via infection and lysis.

Since viruses are immunogenic, it is possible that the virus elicits a humoral response that could reduce its antitumor efficacy (Worgall et al., 1997; Yang et al., 1994). However, the antibodies may have difficulty penetrating the tumor and coming into contact with the virus (Jain, 1994). Moreover, a cell-mediated immune response may even improve the efficacy of the virus by shortening the lifetime of infected cells.

Viruses are engineered to recognize and attack cells that possess certain genetic characteristics (e.g., ONYX-015 is designed to replicate selectively in p53-deficient cells). While all uninfected tumor cells in our model are potential candidates for viral infection, human tumors are often a heterogeneous collection of cells (Mirchandani et al., 1995; Yang et al., 1996), only a portion of which may be sensitive to the virus. By extending our model to include additional tumor cell populations that are resistant to viral infection [see, for example, Ward and King (1997)], it should be possible to study the efficacy of viral treatments for more realistic, heterogeneous tumors.

Several modeling assumptions were employed in order to derive simple, analytical threshold results. Our model considers a single, radially-symmetric injection into a spherical tumor, whereas the details of actual tumor injections (Ganly et al., 2000) are more complicated and would require an asymmetric model. Finally, our model is deterministic and treats the tumor as a continuum of cells and virus. In practice, tumors contain random elements and consist of discrete collections of cells and virus particles, which may be modeled more realistically by interacting particle systems (Cox and Durrett, 1988; Andjel and Schinazi, 1996). Despite these shortcomings, our model provides a building block for further research in this area.

8. **Summary**

Our paper appears to be the first to construct and analyse a mathematical model of replication-competent viruses for cancer treatment. We derived three main results, one for each injection method, which provide simple conditions for whether or not the primary wave of infection generated by the virus ultimately controls the tumor. While approximate, these results, which are stated in equations (30), (43) and (46), are quite accurate and also very simple: all three thresholds are independent of the initial tumor radius and of the initial fraction of cells, $p$, that are infected in the injected region. Equation (30) states that the tumor will be controlled by uniform injection if and only if the rate of virus infection outstrips the
rate of tumor proliferation. Using our best estimates of $R_0 = 11.44$, $\delta^{-1} = 48 \text{ h}$ and $\mu^{-1} = 72 \text{ h}$, and solving the threshold condition for the breakeven value of $\lambda$, the tumor cell proliferation rate, we obtain a threshold tumor doubling time of eight hours. This result suggests that the virus can eradicate virtually any tumor (i.e., those with doubling times in excess of eight hours). In the case where there is no tumor repopulation, condition (30) reduces to the classic $R_0 = 1$ threshold result for the establishment of a spatial epidemic (Kendall, 1965). This is not surprising, because our problem is essentially a spatial epidemic model embedded in a Stefan problem. Moreover, the basic reproductive ratio $R_0$ can be estimated from the observed fraction of necrotic cells behind the wave via (23).

The threshold condition for tumor control with core injection states that the width of the uninfected tumor rim must be less than a critical threshold. Similarly, the tumor control condition for rim injection requires that the radius of the uninfected tumor core be below a critical value. The core and rim thresholds were derived using an ODE approximation inspired by Kendall’s (1965) traveling wave solutions to the classic one-dimensional spatial epidemic. These thresholds are equal to $\frac{c_0}{\lambda}$ and $\frac{3c_0}{\lambda}$, respectively, where $c_0$ is the minimum wave speed in Kendall’s model and $\lambda$ is the proliferation rate of uninfected tumor cells. Despite the crudeness of the ODE approximation, our derived core and rim thresholds are within 0.2 mm of the exact threshold numerically computed from the PDE model. Using our best estimate of $R_0 = 11.44$ and the data in Table 1 (which includes a proliferation rate calculated from mouse tumors), the derived core radius threshold is 2.35 mm and the rim width threshold is 0.78 mm. Hence, for a 1-cm diameter tumor, our model predicts that tumor control requires 89.6% (60%, respectively) of the tumor volume be injected in the rim (core, respectively) injection case.

The rim injection results described in the last paragraph only pertain to the primary wave of infection. The most surprising computational result that we observed was a secondary wave of infection in the rim injection case. This wave was generated by a few virus particles that penetrated the uninfected core, and became trapped due to the lack of a convection field near the tumor center. The uninfected tumor cells became sandwiched between the primary wave of infection emanating from the tumor rim and the secondary wave emanating from the tumor core, and the tumor was eventually eradicated. However, no secondary infections have been seen with rim injections of ONYX-015. The secondary infection in Fig. 14 is likely a phenomenon of assuming the state is continuous; a similar situation, where a secondary infection of rabies starting from one atto-fox ($10^{-18}$ of a fox) per square millimeter, is discussed on p. 284 of Mollison (1991).

The results in Section 6 suggest that rim injection is more efficacious than core injection, after taking into account necrosis in the tumor core caused by a lack of nutrients. This is because nutrient-limited necrosis complements rim injection by sandwiching the uninfected tumor cells, whereas nutrient-limited necrosis and core injection are highly redundant.

Implications of these results for the design and delivery of replication-competent
viruses can be found in Wu et al. (2000). This companion paper also provides a qualitative comparison of the model’s predictions with laboratory and clinical data. We mention one comparison with the data here, due to its relevance for mathematical modeling. There appears to be a $p$-threshold result for uniform injection in the study of Heise et al. (1999): if the fraction infected is 0.05 then the tumor is controlled, but if the fraction infected is 0.01 then (linear) tumor growth occurs. The absence of a mathematically-constructed $p$-threshold result may be due to the occasional inability of a deterministic, continuous-state model to provide sound predictions in a stochastic, discrete-state world, as pointed out in Mollison (1991), and Durrett and Levin (1994). To derive approximate bounds for a $p$ threshold, one could assume that the pre-infected cells were randomly distributed throughout the tumor initially. In this case, coverage process theory [Chap. 3 in Hall (1988), Chap. 8 in Aldous (1989)] can be used to derive the probability distribution for the largest uninfected sphere in the tumor at time 0. This result could be used in combination with the uninfected core radius threshold in (46) to estimate the $p$ threshold.

Our results suggest a cautious optimism concerning the efficacy of replication-competent viruses for cancer therapy. On the optimistic side, the model predicts that the virus, if injected throughout the tumor, is sufficiently powerful to control a fast-growing tumor. However, our analysis highlights the importance of broad spatial distribution of the virus over high concentration of the virus, and suggests that administration of the virus needs to be extremely aggressive from a geographical viewpoint: a several millimeter diameter region, left uninfected in a fast-growing mouse tumor, may be capable of overcoming the virus. Given that the uninfected tumor radius in (42) is inversely proportional to the tumor growth rate, perhaps larger regions can be successfully left uninfected in slower growing human tumors. Finally, new unpublished data (Ganly et al., 2000) showing a powerful innate immune response to the virus in humans raises new questions (e.g., repeated injections, co-injection with an immune system modulator), and this three-way race between the virus, the tumor and the immune response will be addressed in future research. In any case, our analysis reveals that replication-competent gene therapy pits a linear wave of infection against exponential tumor proliferation, and, to tip the scales in favor of tumor control, the linear infection needs to be administered aggressively and intelligently.

**References**


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