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Analysis of a mathematical model for tumor therapy with a fusogenic oncolytic virus

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ABSTRACT

Oncolytic virotherapy is a tumor treatment which uses viruses to selectively target and destroy cancer cells. Fusogenic viruses, capable of causing cell-to-cell fusion upon infection of a tumor cell, have shown promise in experimental studies. Fusion causes the formation of large, multinucleated syncytia which eventually leads to cell death. We formulate a partial differential equations model with a moving boundary to describe the treatment of a spherical tumor with a fusogenic oncolytic virus. Fusion, lysis, and budding are incorporated as mechanisms of viral spread, resulting in nonlocal integral terms.

A proof is presented for existence and uniqueness of global solutions to the nonlinear hyperbolic–parabolic system. Numerical simulations demonstrate convergence to spatially homogeneous solutions and exponential growth or decay of the tumor radius depending on viral burst size and rate of fusion. Long-term tumor radius is shown to decrease with increasing values of viral burst size while the effect of the rate of fusion on tumor growth is demonstrated to be nonmonotonic.

1. Introduction

Tumor virotherapy uses replication-competent viruses which selectively infect, replicate in, and kill cancer cells. Commonly these viruses cause cell death through lysis; another mode of viral propagation is budding [1,2]. Clinical trials have demonstrated varying degrees of success for the therapy with limitations predominantly due to barriers to viral spread and the immune response to the virus [3].

A particularly interesting mechanism by which some oncolytic viruses act is through the formation of large, multinucleated cells called syncytia. When such a virus infects a tumor cell, the expression of fusogenic membrane glycoproteins on the surface of the cell allow for fusion with neighboring cells. The resulting syncytium will die by proteolytic digestion from within [4]. In this way, a significant bystander effect is created; experiments show that a single transfected cell can kill in excess of 150–200 bystander cells [5]. A measles vaccine strain, modified herpes simplex virus, and recombinant vesicular stomatitis virus have been shown to cause an increased cytopathic effect through the formation of syncytia [2,6,7]. The death of syncytia has also been shown to cause a potent antitumor immune response [2,4,8,9]. Thus, while demonstrating sufficient therapeutic efficacy remains a challenge for virotherapy, fusogenic oncolytic viruses hold promise for future clinical use.

Various mathematical models have been formulated to describe virotherapy treatment of tumors mediated by lysis [10–15]. The only models to our knowledge which consider syncytia formation are those by Bajzer and Dingli et al. [16–19]. Their deterministic models are formulated as ordinary differential equations which assume the law of mass action. However, a well-mixed tumor cell population is not biologically realistic and making this assumption may be obscuring relevant spatial effects. Our aim, therefore, is to develop a model for virotherapy with a fusogenic oncolytic virus which takes into account the inherent spatial dependency of syncytia-forming fusion. We also include lysis and budding, allowing the model to be tailored to a range of oncolytic viruses with differing viral spread mechanisms.

Section 2 describes the formulation of the model. A proof of well-posedness is given in Section 3. Numerical simulations and results are included in Section 4, followed by a brief discussion in Section 5.

2. Formulation of the model

We adapt a similar setup to the partial differential equations models of Wu et al. [10] and Friedman et al. [13] but also incorporate cell-to-cell fusion. We allow for viral budding from infected and syncytia-incorporated cells as well as viral diffusion but neglect necrosis to improve mathematical tractability. We assume that the tumor is spherically symmetric with radius $R(t)$. We let $x(r, t)$ be the density of uninfected tumor cells whose center is a distance r from

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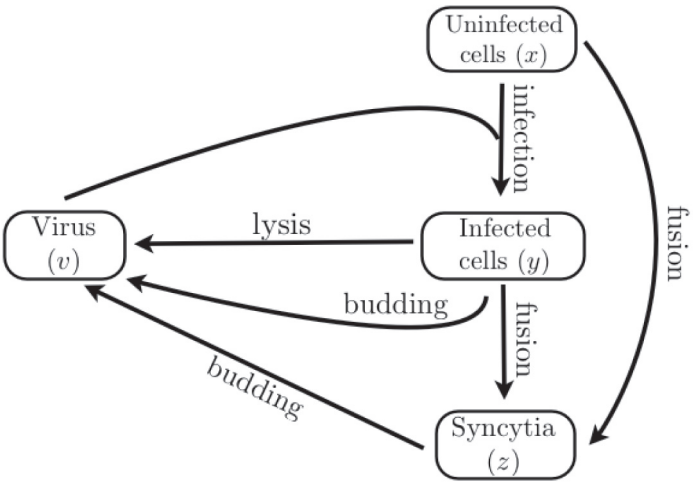

Fig. 1. Model interaction network. Uninfected tumor cells become infected upon entry of a free virus. Infected cells undergo lysis resulting in release of free viruses. Uninfected and infected cells can fuse with neighboring cells to become syncytia. Infected cells and syncytia release free viruses via budding.

the center of the tumor. Similarly, $y(r,t)$ and $z(r,t)$ represent the density of infected tumor cells and syncytia-incorporated cells, respectively. We assume that all tumor cells are spherical with radius r_c. We let $v(r,t)$ be the density of free viral particles which we assume have negligible volume. We model the tumor as an incompressible fluid under an advective field velocity $u(r,t)$.

The dynamics of the tumor cell and virus populations are based on the network shown in Fig. 1. We suppose that only uninfected cells proliferate, at a rate λ. Uninfected cells become infected at a rate that is proportional to the average number of viral particles on the surface of the cell. The coefficient of proportionality, β, takes into the account the probability of success of viral entry. The derivation of the corresponding integral expression in Eqs. (1) and (2) will be discussed in Section 2.2. We make the simplifying assumption that a cell which is syncytia-incorporated is still spherical with radius r_c. An uninfected cell can fuse into a syncytia if it is in contact with either an infected cell or a syncytia-incorporated cell. We assume this fusion occurs at a rate with coefficient ρ and is proportional to the average density of neighboring infected and syncytia-incorporated cells. We will derive in Section 2.2 the exact formulation of the corresponding integral term in Eqs. (1) and (3). A single infected cell can be incorporated into a syncytia through surface contact with a cell of any other type, again at a rate proportional to ρ. Since we neglect necrosis we assume that immediately upon death a cell is removed. For infected cells this process occurs at rate δ and for syncytia at rate μ.

We allow free viral particles to be generated through two mechanisms, budding and lysis. An infected or syncytia-incorporated cell releases viral particles from their surface through budding at a rate α. It is hypothesized that syncytia are removed via a non-apoptotic mechanism that doesn't allow viral release [4]. Therefore we assume that only infected cells undergo lysis upon death, releasing N viral particles. More detail on the corresponding budding and lysis terms in Eq. (4) is discussed in Section 2.2. We further assume that free viral particles are removed at rate γ.

Therefore, for $0 < r \le R(t)$ and $t > 0$, the dynamics of the state variables are determined by

$$\begin{aligned}\frac{Dx}{Dt} &\equiv \frac{\partial x(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u(r,t)x(r,t))\\ &= \lambda x(r,t) - \frac{\beta x(r,t)}{|I_{r_c}(r,t)|}\int_{I_{r_c}(r,t)} v(s,t)\,ds\\ &\quad - \frac{\rho x(r,t)}{|I_{2r_c}(r,t)|}\int_{I_{2r_c}(r,t)} y(s,t)+z(s,t)\,ds, \end{aligned} \tag{1}$$

$$\begin{aligned}\frac{Dy}{Dt} &\equiv \frac{\partial y(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u(r,t)y(r,t))\\ &= \frac{\beta x(r,t)}{|I_{r_c}(r,t)|}\int_{I_{r_c}(r,t)} v(s,t)\,ds - (\rho\theta+\delta)y(r,t), \end{aligned} \tag{2}$$

$$\begin{aligned}\frac{Dz}{Dt} &\equiv \frac{\partial z(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u(r,t)z(r,t))\\ &= \frac{\rho x(r,t)}{|I_{2r_c}(r,t)|}\int_{I_{2r_c}(r,t)} y(s,t)+z(s,t)\,ds + \rho\theta y(r,t) - \mu z(r,t), \end{aligned} \tag{3}$$

$$\begin{aligned}&\frac{\partial v(r,t)}{\partial t} - \kappa\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial v(r,t)}{\partial r}\right)\\ &\quad= \frac{N\delta}{|J_{r_c}(r,t)|}\int_{I_{r_c}(r,t)}\left[r_c^2-(r-s)^2\right]y(s,t)\,ds\\ &\qquad+\frac{\alpha}{|I_{r_c}(r,t)|}\int_{I_{r_c}(r,t)} y(s,t)+z(s,t)\,ds - \gamma v(r,t) \end{aligned} \tag{4}$$

where $I_{r_c}(r,t) = (\max[0, r-r_c], \min[R(t), r+r_c])$ and

$$|J_{r_c}(r,t)| = \int_{I_{r_c}(r,t)}\left[r_c^2-(r-s)^2\right]ds.$$

The last term on the left-hand side in each of Eqs. (1), (2), and (3) corresponds to advection. Note that the viral particles, being of negligible volume, do not undergo advection but do diffuse with diffusion coefficient κ.

Treating the tumor as an incompressible fluid, we assume that the total tumor cell density has a constant value θ. That is,

$$x(r,t)+y(r,t)+z(r,t) = \theta \tag{5}$$

for $0 < r \le R(t)$. Therefore summing Eqs. (1), (2) and (3) gives

$$\frac{\theta}{r^2}\frac{\partial}{\partial r}(r^2 u(r,t)) = \lambda x(r,t) - \delta y(r,t) - \mu z(r,t). \tag{6}$$

Then the advection term, in Eq. (1) for example, by the product rule becomes

$$\begin{aligned}\frac{-1}{r^2}\frac{\partial}{\partial r}(r^2 u(r,t)x(r,t)) &= -u(r,t)\frac{\partial x(r,t)}{\partial r}\\ &\quad - \frac{x(r,t)}{\theta}[\lambda x(r,t) - \delta y(r,t) - \mu z(r,t)].\end{aligned}$$

By Eq. (5) we have $z = \theta - x - y$ and we can reduce the dimension of the system. By integrating Eq. (6) and eliminating z, we present the first complete formulation of our model. For $0 < r \le R(t)$ and $t > 0$,

$$\begin{aligned}&\frac{\partial x(r,t)}{\partial t} + u(r,t)\frac{\partial x(r,t)}{\partial r} = \lambda x(r,t) - \frac{\beta x(r,t)}{|I_{r_c}(r,t)|}\int_{I_{r_c}(r,t)} v(s,t)\,ds\\ &\quad - \frac{\rho x(r,t)}{|I_{2r_c}(r,t)|}\int_{I_{2r_c}(r,t)} \theta - x(s,t)\,ds\\ &\quad - \frac{x(r,t)}{\theta}[\lambda x(r,t) - \delta y(r,t) - \mu(\theta - x(r,t) - y(r,t))], \end{aligned} \tag{7}$$

$$\begin{aligned}&\frac{\partial y(r,t)}{\partial t} + u(r,t)\frac{\partial y(r,t)}{\partial r}\\ &\quad= \frac{\beta x(r,t)}{|I_{r_c}(r,t)|}\int_{I_{r_c}(r,t)} v(s,t)\,ds - (\rho\theta+\delta)y(r,t)\\ &\quad - \frac{y(r,t)}{\theta}[\lambda x(r,t) - \delta y(r,t) - \mu(\theta - x(r,t) - y(r,t))], \end{aligned} \tag{8}$$

$$\begin{aligned}&\frac{\partial v(r,t)}{\partial t} - \kappa\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial v(r,t)}{\partial r}\right)\\ &\quad= \frac{N\delta}{|J_{r_c}(r,t)|}\int_{I_{r_c}(r,t)}\left[r_c^2-(r-s)^2\right]y(s,t)\,ds\\ &\qquad+\frac{\alpha}{|I_{r_c}(r,t)|}\int_{I_{r_c}(r,t)} \theta - x(s,t)\,ds - \gamma v(r,t), \end{aligned} \tag{9}$$