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Analysis of a model of a virus that replicates selectively in tumor cells

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Abstract. We consider a procedure for cancer therapy which consists of injecting replication-competent viruses into the tumor. The viruses infect tumor cells, replicate inside them, and eventually cause their death. As infected cells die, the viruses inside them are released and then proceed to infect adjacent tumor cells. This process is modelled as a free boundary problem for a nonlinear system of hyperbolic-parabolic differential equations, where the free boundary is the surface of the tumor. The unknowns are the densities of uninfected cells, infected cells, necrotic cells and free virus particles, and the velocity of cells within the tumor as well as the free boundary $r = R(t)$. The purpose of this paper is to establish a rigorous mathematical analysis of the model, and to explore the reduction of the tumor size that can be achieved by this therapy.

1. Introduction

A variety of PDE models for tumor growth have been developed in the last three decades. These models are based on mass conservation laws and on reaction-diffusion processes within the tumor. A concentration c of nutrients (such as oxygen or glucose) satisfies a diffusion equation of the form

$$\epsilon_0 \frac{\partial c}{\partial t} = \nabla^2 c - \lambda c \quad (\lambda > 0) \quad (1.1)$$

where ϵ_0 is a small positive coefficient given by the quotient

$$\epsilon_0 = \frac{T_{\text{diffusion}}}{T_{\text{growth}}}$$

where $T_{\text{diffusion}}$ is the diffusion time scale and T_{growth} is the tumor-doubling time scale; typically $\epsilon_0 = 1$ minute/1 day. These models make the following general assumptions:

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The cells within the tumor are in one of three phases: proliferating, quiescent, or necrotic. Living cells die as a result of cell-loss mechanism (apoptosis) and quiescent cells may die also as a result of starvation (necrosis). All living cells undergo mitosis, but proliferating cells undergo mitosis at abnormally large rate. Cells change from quiescent phase to proliferating phase, or vice versa, at rates which depend on the nutrient concentration. Finally, all cells have the same size and density, and the tumor is uniformly packed with cells.

From the above assumptions it is natural to expect that the proliferating cells will be formed mostly near the surface of the tumor, where the nutrient concentration is the largest, and that the dead cells will reside mostly at the inner core of the tumor where the nutrient concentration is the smallest (one speaks of the “necrotic core”). Dead cells are removed from the tumor by large migratory macrophages through a process of phagocytosis. Thus, even though the tumor may grow, the dead core may not necessarily increase.

A unique aspect of cancer modeling arises from the fact that the size and shape of the tumor are changing over time: malignant tumors usually grow in time, whereas non-malignant tumors become stationary (dormant) or may even disappear over a period of time. The tumor’s surface is a free boundary. Free boundary problems are particularly challenging because one has to solve a system of PDEs in a region that is not prescribed in advance. Some physical conditions are usually imposed at the free boundary, and one then seeks to determine simultaneously the unknown free boundary and the solution of differential equations within the domain enclosed by the free boundary.

There are basically two kinds of PDE models:

- (I) The different populations of cells are continuously present everywhere in the tumor, at all times;
- (II) The different populations of cells are separated by interfaces, which themselves are free boundaries. A special case of both (I) and (II) is the following:
- (III) There are only proliferating cells in the tumor.

We shall refer to models of type (I) as *mixed models*, and to models of type (II) as *segregated models*; models such as in (III) will be called *proliferation-only models*.

Although mixed models are more realistic, segregated models may represent a good approximation; this is especially true *in vitro* experiments where multicellular tumors have a nearly spherical shape and the dead core is nearly a concentric ball. If the tumor is spherically symmetric then the (outer) free boundary is a function $r = R(t)$.

The first proliferation-only model was developed by Greenspan [22,23]. Subsequent work mostly in the radially-symmetric case was carried out by Adams [1], Britton and Chaplain [5], Byrne [6] and Byrne and Chaplain [7–9]. The last two authors studied numerically the radially-symmetric segregated model with dead core, and the proliferation-only model in the presence of inhibitors. Rigorous mathematical analysis of these models was carried out by Friedman and Reitich [19] and Cui and Friedman [11, 12]. Articles [6,9] also discuss the possibility of nearby spherical configurations of tumors. Friedman and Reitich [20,21] and Fontelos and

Friedman [17] proved the existence of branches of non-radially symmetric dormant tumors bifurcating from radially symmetric solutions, and Bazaliy and Friedman [3] proved asymptotic stability of radially symmetric stationary solutions, under non-radially symmetric initial conditions, for some range of parameters.

Mixed models were introduced by Sheratt and Chaplain [31], Ward and King [33] and Pettet, Please, Tindall and McElwain [29]; see also the references given in these papers. Rigorous mathematical analysis establishing global existence and asymptotic behavior of solutions were recently established by Cui and Friedman [15] [16] and by Chen, Cui and Friedman [10] for the radially-symmetric case. In the non-radially symmetric case, only local existence is known; see Bazaliy and Friedman [2] and Chen and Friedman [11].

The present paper deals with a model of cancer therapy. Unlike the model of Byrne and Chaplain [7] which introduces a generic inhibitor, the present paper considers a specific therapy which has been undergoing clinical trials in recent years, namely, injection of virus particles into the tumor.

One of the obstacles in developing efficient gene therapy to cancer is in the delivery process. The macromolecules used as gene delivery carriers are too large to be transported into, and diffuse within, the tumor (see Swabb [32] and Jain [25]). A recent approach aimed at bypassing this problem involves the use of virus. The virus is engineered to be replication-competent and to selectively bind to receptors on the tumor cell surface (but not to the surface of normal healthy cells). The virus particles then proceed to proliferate exponentially within the tumor cell, eventually causing death (lysis). Thereupon the newly reproduced virus particles are released and then proceed to infect adjacent cancer cells. This process continues until all the cancer cells are destroyed. Replication-competent virus is currently used in clinical trials; see Bischoff [4], Coffey [12], Heise [24], Rodriguez [30], Yoon [35]. These trials were conducted over a period of at least 30 days and they report on tumor growth reduction by at least 50% at the end of the trials. For example, [35] reports on the efficacy of virus CN706 in treatment of prostate tumor in mice: There was a slight increase in tumor volume for the first two weeks, followed by rapid decrease, and after 42 days from the initial injection, 5 of the 10 mice were visually free of tumor.

A mathematical model which describes the evolution of tumors under viral injection was recently developed by Wu, Byrne, Kirn and Wein [34]. They used simplified versions of their model in order to compute and compare the evolution of the tumor under different initial conditions. In this paper we present a somewhat different model. For the sake of clarity we shall first describe our model (in Section 2), and then (in Section 3) explain the differences between our model and the WKBW model of [34]; we shall also explain in Section 3 the relation of our model to the mixed models mentioned above.

The basic question we would like to pursue is what is the most efficient procedure to administer the viral therapy. The present paper sets up the stage for dealing with this question. First, we give a rigorous mathematical proof that the model has a unique solution for all time (Theorem 2.1, which is proved in Section 11). Next we show (in Section 4) that one can always reduce the size of tumor to an arbitrarily small size by injecting a sufficiently large dose of viral density. Of course

one would like to use small doses if possible. So, in Sections 6-10 we give two examples whereby a tumor of arbitrarily large size can be made to shrink to zero with just a modest density of virus particles. These examples suggest that better therapy can sometimes be achieved by small doses of the drug. Another area for improvement of the therapy process may be achieved by scheduling repeated injections in an optimal fashion. In the concluding section of this paper we list a few open problems along these lines of inquiry.

2. The Model

We introduce the physical variables

$$\begin{aligned}\hat{x} &= \text{density of uninfected tumor cells,} \\ \hat{y} &= \text{density of infected tumor cells,} \\ \hat{n} &= \text{density of necrotic cells,} \\ \hat{v} &= \text{density of free virus, i.e.,} \\ &\quad \text{virus in the extracellular tissue}\end{aligned}$$

and

$$u = \text{the velocity field within the tumor.}$$

The velocity field is a result of the spatio-temporal variation due to the proliferation of uninfected cells and the removal of necrotic cells. We assume that the problem is radially symmetric, so that all the unknown functions depend only on (r, t) where r is the distance from the center of the tumor. As in [29], by mass conservation law for the different phases of the cells,

$$\frac{D\hat{x}}{Dt} \equiv \frac{\partial \hat{x}(r, t)}{\partial t} + \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 u(r, t) \hat{x}(r, t) \right) = \lambda \hat{x}(r, t) - \beta \hat{x}(r, t) \hat{v}(r, t), \quad (2.1)$$

$$\frac{D\hat{y}}{Dt} \equiv \frac{\partial \hat{y}(r, t)}{\partial t} + \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 u(r, t) \hat{y}(r, t) \right) = \beta \hat{x}(r, t) \hat{v}(r, t) - \delta \hat{y}(r, t), \quad (2.2)$$

$$\frac{D\hat{n}}{Dt} \equiv \frac{\partial \hat{n}(r, t)}{\partial t} + \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 u(r, t) \hat{n}(r, t) \right) = \delta \hat{y}(r, t) - \mu \hat{n}(r, t) \quad (2.3)$$

in the tumor region $\{r < R(t)\}$. In (2.1), λ is the proliferation rate of the uninfected cancer cells and β is the infection rate of the uninfected cells; in (2.2), δ is the death rate of the infected cells; in (2.3), μ is the removal rate of the necrotic cells. We have assumed here that infected cells do not proliferate and that all the cells are subjected to the velocity field, but do not undergo diffusion. On the other hand, since the free virus particles are very small relative to the cells, we shall assume that they undergo diffusion within the tumor tissue; see also [28] for a similar assumption. We shall also neglect the effect of the velocity field on the virus. If we denote the diffusion coefficient by κ , then, by combining the mass conservation law with the effect of diffusion, we get

$$\frac{\partial \hat{v}(r, t)}{\partial t} = N \delta \hat{y}(r, t) - \gamma \hat{v}(r, t) + \kappa \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial \hat{v}(r, t)}{\partial r} \right), \quad \frac{\partial \hat{v}(0, t)}{\partial r} = 0; \quad (2.4)$$

here γ is the removal (or clearance) rate of virus ($1/\gamma$ is the mean lifetime of free virus) and $N\delta$ is the virus release rate (N is the burst size of virus at the death of a cell); the last equation in (2.4) is a consequence of the radial symmetry. We finally assume that all cells have the same size and density, and that they are uniformly distributed in the tumor, so that

$$\hat{x} + \hat{y} + \hat{n} \equiv \text{const.} \equiv \theta. \quad (2.5)$$

Since the rates of proliferation and removal of uninfected and necrotic cells are λ and μ , respectively, the conservation law for the total mass can be expressed in the form

$$\frac{\theta}{r^2} \frac{\partial}{\partial r} (r^2 u(r, t)) = \lambda \hat{x}(r, t) - \mu \hat{n}(r, t). \quad (2.6)$$

The boundary conditions, at the moving boundary, are

$$\frac{\partial}{\partial r} \hat{v}(R(t), t) = 0, \quad (2.7)$$

$$\frac{dR(t)}{dt} = u(R(t), t). \quad (2.8)$$

Equation (2.7) means that virus particles do not cross the boundary, for $t > 0$, and (1.8) is the equation of continuity: the velocity of the free surface is the same as the velocity u at the surface.

We note that Equation (2.3) is a consequence of Equations (2.1), (2.2), (2.5) and (2.6), so that in the sequel we may drop this equation and replace $\hat{n}$ by $\theta - \hat{x} - \hat{y}$ in (2.6).

We also note that since the velocity field is radially symmetric,

$$u(0, t) = 0. \quad (2.9)$$

The diffusion coefficient κ in (2.4) is given by

$$\kappa = \frac{T_{\text{diffusion}}}{T_{\text{double}}};$$

T_{double} is the time scale of tumor growth, that is, the time it takes the tumor volume to grow by a factor of 2 or shrink by a factor of $\frac{1}{2}$, and $T_{\text{diffusion}}$ is the time scale for diffusion of the free virus particles. T_{double} depends on how aggressive the specific tumor is. From the experiments conducted, for example, in [4] and [30] one can (very roughly) deduce that κ is proportional to $R^2(t)$ (or $R^{2+\varepsilon}(t)$, for some $0 < \varepsilon < 1$). $T_{\text{diffusion}}$ depends not only on the physical properties of cells and virus but also on their biological affinities (e.g., how fast a free virus adsorbs to the surface of an uninfected cell). We shall make the assumption that

$$\kappa = \kappa_0 R^2(t), \quad \kappa_0 \text{ positive constant.} \quad (2.10)$$

Since T_{double} is of order of magnitude of several weeks whereas $T_{\text{diffusion}}$ is of the order of minutes, κ_0 is small; this fact, however, is not used in this paper. The assumption in (2.10) that κ_0 is a constant will slightly simplify our analysis; however all the results of the paper can easily be extended to the case where κ_0 is a function of $R(t)$.

We introduce the variables

$$x = \frac{\hat{x}}{\theta}, \quad y = \frac{\hat{y}}{\theta}, \quad v = \frac{\hat{v}}{\theta N}$$

and the quantity

$$p_0 = \frac{\beta N \theta}{\gamma}.$$

The parameter p_0 is called the *basic reproductive ratio* in the epidemic modeling. It represents the mean number of virus particles released by one virus.

In terms of the new variables, the system (2.1)–(2.10) takes the following form:

$$\frac{\partial x(r, t)}{\partial t} = \lambda x(r, t) - p_0 \gamma x(r, t) v(r, t) - \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 u(r, t) x(r, t) \right), \quad (2.11)$$

$$\frac{\partial y(r, t)}{\partial t} = p_0 \gamma x(r, t) v(r, t) - \delta y(r, t) - \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 u(r, t) y(r, t) \right), \quad (2.12)$$

$$\frac{\partial v(r, t)}{\partial t} = \delta y(r, t) - \gamma v(r, t) + \kappa_0 R^2(t) \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial v}{\partial r} \right), \quad \frac{\partial v(0, t)}{\partial r} = 0, \quad (2.13)$$

$$\frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 u(r, t) \right) = \lambda x(r, t) - \mu [1 - x(r, t) - y(r, t)] \quad (2.14)$$

in $\{r < R(t), t > 0\}$,

$$\frac{\partial v}{\partial r}(R(t), t) = 0, \quad t > 0, \quad (2.15)$$

$$\frac{dR(t)}{dt} = u(R(t), t), \quad t > 0, \quad (2.16)$$

$$u(0, t) = 0, \quad t > 0 \quad (2.17)$$

with initial conditions

$$R(0) \text{ is prescribed,} \quad (2.18)$$

$$x(r, 0) = x_0(r), \quad y(r, 0) = y_0(r), \quad v(r, 0) = v_0(r)$$

where $x_0(r)$, $y_0(r)$, $v_0(r)$ are nonnegative functions

with $x_0(r) + y_0(r) \leq 1$, for $0 \leq r \leq R(0)$.

It will be convenient to transform the region $\{0 \leq r \leq R(t)\}$ into the fixed region $\{0 \leq \rho \leq 1\}$ by

$$\rho = \rho(r, t) = \frac{r}{R(t)}.$$

Setting

$$\tilde{x}(\rho, t) = x(r, t), \quad \tilde{y}(\rho, t) = y(r, t),$$

$$\tilde{v}(\rho, t) = v(r, t), \quad \tilde{u}(\rho, t) = u(r, t),$$

the differential equations (2.11)–(2.14) combined with (2.17) take the following form in $\{0 < \rho < 1, t > 0\}$:

$$\begin{aligned} \frac{\partial \tilde{x}}{\partial t} + \left[-\rho \frac{\dot{R}(t)}{R(t)} + \frac{\tilde{u}(\rho, t)}{R(t)} \right] \frac{\partial \tilde{x}}{\partial \rho} \\ = \lambda \tilde{x}(\rho, t) - p_0 \gamma \tilde{x}(\rho, t) \tilde{v}(\rho, t) \\ - \left[-\mu + (\lambda + \mu) \tilde{x}(\rho, t) + \mu \tilde{y}(\rho, t) \right] \tilde{x}(\rho, t), \end{aligned} \quad (2.19)$$

$$\begin{aligned} \frac{\partial \tilde{y}}{\partial t} + \left[-\rho \frac{\dot{R}(t)}{R(t)} + \frac{\tilde{u}(\rho, t)}{R(t)} \right] \frac{\partial \tilde{y}}{\partial \rho} \\ = p_0 \gamma \tilde{x}(\rho, t) \tilde{v}(\rho, t) - \delta \tilde{y}(\rho, t) \\ - \left[-\mu + (\lambda + \mu) \tilde{x}(\rho, t) + \mu \tilde{y}(\rho, t) \right] \tilde{y}(\rho, t), \end{aligned} \quad (2.20)$$

$$\frac{\partial \tilde{v}}{\partial t} - \rho \frac{\dot{R}(t)}{R(t)} \frac{\partial \tilde{v}}{\partial \rho} = \delta \tilde{y}(\rho, t) - \gamma \tilde{v}(\rho, t) + \kappa_0 \frac{1}{\rho^2} \frac{\partial}{\partial \rho} \left(\rho^2 \frac{\partial \tilde{v}}{\partial \rho} \right), \quad \frac{\partial \tilde{v}}{\partial \rho}(0, t) = 0, \quad (2.21)$$

$$\tilde{u}(\rho, t) = \frac{R(t)}{\rho^2} \int_0^\rho s^2 \left[-\mu + (\lambda + \mu) \tilde{x}(s, t) + \mu \tilde{y}(s, t) \right] ds. \quad (2.22)$$

The boundary and initial conditions (2.15)–(2.18) become

$$\frac{\partial \tilde{v}}{\partial \rho}(1, t) = 0, \quad (2.23)$$

$$\tilde{u}(0, t) = 0, \quad (2.24)$$

$$\dot{R}(t) = \tilde{u}(1, t), \quad R(0) \text{ is given}, \quad (2.25)$$

$$\tilde{x}(\rho, 0) = \tilde{x}_0(\rho), \quad \tilde{y}(\rho, 0) = \tilde{y}_0(\rho), \quad \tilde{v}(\rho, 0) = \tilde{v}_0(\rho) \quad \text{for } 0 \leq \rho \leq 1 \quad (2.26)$$

and

$$\tilde{x}_0(\rho) \geq 0, \quad \tilde{y}_0(\rho) \geq 0, \quad \tilde{x}_0(\rho) + \tilde{y}_0(\rho) \leq 1. \quad (2.27)$$

We shall also assume that

$$\tilde{x}_0(\rho), \tilde{y}_0(\rho) \text{ and } \tilde{v}_0(\rho) \text{ belong to } C^1[0, 1], \text{ and } \frac{\partial \tilde{v}_0}{\partial \rho}(1) = 0. \quad (2.28)$$

We now state a result on global existence and uniqueness of solutions for the system (2.19)–(2.28).

Theorem 2.1. *The system (2.19)–(2.28) has a unique solution $(\tilde{x}(\rho, t), \tilde{y}(\rho, t), \tilde{v}(\rho, t), \tilde{u}(\rho, t), R(t))$ with $\tilde{x}, \partial \tilde{x} / \partial \rho, \tilde{y}, \partial \tilde{y} / \partial \rho, \tilde{v}, \partial \tilde{v} / \partial \rho$ and $\tilde{u}, \partial \tilde{u} / \partial \rho$ in $C[0 \leq \rho \leq 1, 0 < t < \infty]$, $R(t)$ in $C^1[0, \infty)$, and*

$$R(0)e^{-\beta t} < R(t) < R(0)e^{\beta t}$$

for some $\beta > 0$.

In Sections 6–10 we shall prove other existence theorems (Theorems 9.1 and 10.1) which assert both global existence and uniqueness as well as convergence of $R(t)$ to zero as $t \rightarrow \infty$ under some special initial conditions. Since the proof of Theorem 2.1 can be obtained by slightly modifying a part of the proof of Theorem 9.1, in order to avoid repetition we shall defer the proof of Theorem 2.1 to Section 11.

We conclude this section with the following theorem:

Theorem 2.2. *For any solution of (2.19)–(2.28) there holds:*

$$\tilde{x}(\rho, t) \geq 0, \quad \tilde{y}(\rho, t) \geq 0, \quad \tilde{x}(\rho, t) + \tilde{y}(\rho, t) \leq 1. \quad (2.29)$$

Proof. Introducing the characteristic curves $\xi(\rho_0, t)$ by

$$\frac{d\xi}{dt} = -\rho \frac{\dot{R}(t)}{R(t)} + \frac{\tilde{u}(\rho, t)}{R(t)}, \quad \xi(\rho_0, 0) = \rho_0,$$

we can write (2.19) in the form

$$\frac{d}{dt} \tilde{x}(\xi(\rho_0, t), t) = A(t) \tilde{x}(\xi(\rho_0, t), t)$$

for some function $A(t)$. Hence

$$\tilde{x}(\xi(\rho_0, t), t) \geq \tilde{x}_0(\rho_0) e^{\int_0^t A(s) ds} \geq 0$$

so that $\tilde{x}(\rho, t) \geq 0$. Similarly, from (2.20) we deduce that $\tilde{y}(\rho, t) \geq 0$, and from (2.3) we deduce that $1 - \tilde{x} - \tilde{y} \geq 0$.

3. Comparison with the WKBW model and other models

As mentioned in Section 1, the model introduced in Section 2 is based on the WKBW model [34]. However, there are several differences between the two models. The most important difference is that in the WKBW model there does not appear a diffusion term for virus density. Thus, instead of (2.4) it is assumed that

$$\frac{\partial \hat{v}}{\partial t} = N \delta \hat{y} - \gamma \hat{v}, \quad \frac{\partial \hat{v}(0, t)}{\partial r} = 0 \quad (3.1)$$

and that, at the same time, (2.7) holds. Notice that from (3.1) we get (cf. (2.22))

$$\frac{\partial \tilde{v}}{\partial t} - \rho \frac{\dot{R}(t)}{R(t)} \frac{\partial \tilde{v}}{\partial \rho} = \delta \tilde{y}(\rho, t) - \gamma \tilde{v}(\rho, t). \quad (3.2)$$

A second difference between the two models is in the infection term: Here we take it, for simplicity, to be $N \delta \hat{y}$ where N is the burst size of the virus at the time of death of a cell, whereas in the WKBW model the infection term is more refined as it involves the viral density integrated over the surface of cells (see (4) of [34]). The surface integral can be approximated by a diffusion term (see (34) of [34])

$$\frac{\partial^2 \tilde{y}}{\partial r^2} + \frac{2}{r} \frac{\partial \tilde{y}}{\partial r}.$$

However, this diffusion mechanism is not the same as the diffusion term for $\tilde{v}$ in (2.4).

The WKBW model is, mathematically, not a well posed problem. Indeed, suppose the initial conditions are such that $\dot{R}(0) < 0$. If a solution exists, then $\dot{R}(t) < 0$ for some time interval. By (3.2) the forward characteristic curves for (3.2) which initiate at any point $(\rho_0, 0)$ with $\rho_0 < 1$, $1 - \rho_0$ small, will then intersect the line $\rho = 1$, say at $(1, t_1)$. The value of the function $\tilde{v}$ at $(1, t_1)$ will thus depend on the initial value $\tilde{v}(\rho_0, 0)$. On the other hand, from (2.7) we see that

$$\frac{\partial \tilde{v}(1, t)}{\partial t} = \delta \tilde{y}(1, t) - \gamma \tilde{v}(1, t).$$

Since the functions $\tilde{x}(1, t)$, $\tilde{y}(1, t)$ satisfy similar ODES, $\tilde{v}(1, t_1)$ (and $\tilde{x}(1, t_1)$, $\tilde{y}(1, t_1)$) are determined only by their initial values at $\rho = 1$. Thus $\tilde{v}(1, t_1)$ does not depend on the initial value $\tilde{v}_0(\rho_0, 0)$, which is inconsistent with our previous conclusion. This argument can be extended to the model where $N\delta\hat{y}$ is replaced by the surface integral of (4) in [34].

Suppose next that the initial conditions are such that $\dot{R}(0) > 0$. If a solution exists, then $\dot{R}(t) > 0$ for a small time interval. This implies that the v -characteristic curves initiating at $\rho = 1$, $t = t_0$ (t_0 small) and the v -characteristic curves initiating at $(\rho_0, 0)$ for ρ_0 near 1 may intersect at some point (ρ_1, t_1) ($\rho_0 < \rho_1 < 1$, $t_1 > t_0$). At this point the solution in general will be discontinuous. There are of course exceptional cases where the two sets of v -characteristics will not intersect; for example, when

$$\tilde{x}(\rho, 0) = 1, \tilde{y}(\rho, 0) = 0, \tilde{v}(\rho, 0) = 0$$

(In this case there exists a global solution with $R(t) = R(0)e^{\lambda t/3}$ and the v -characteristics are given by $d\rho/ds = -\lambda\rho/3$).

The above considerations show that without a diffusion term for v the system does not have a mathematical solution, in general. In [34] the authors studied numerically an ODE system which is an approximation of their complete model when no spatial variations are assumed. They compared the efficacy of core injection, whereby, at $t = 0$,

$$\begin{aligned} x &= (1 - p)\theta, y = p\theta, v = 0 \text{ if } 0 < r < R(0) - w_0, \\ x &= 0, y = 0, v = 0 \text{ if } R - w_0 < r < R(0), \end{aligned} \quad (3.3)$$

with rim injection, whereby, at $t = 0$,

$$\begin{aligned} x &= 0, y = 0, v = 0 \text{ if } 0 < r < r_0, \\ x &= (1 - p)\theta, y = p\theta, v = 0 \text{ if } r_0 < r < R(0). \end{aligned} \quad (3.4)$$

As stated in Section 1, our first aim in this paper is to establish the existence of a unique global solution for the model (2.19)–(2.28). Our second aim is to use the model for initial exploration of the question of optimal efficacy of the viral treatment.

The model (2.19)–(2.28) is mathematically somewhat similar to the mixed models considered in [29] [16] [10]. One difference is that instead of diffusion of

nutrients as in (1.1), we here have diffusion of virus particles. Other differences occur in the coupling terms of the PDEs and in the free boundary conditions. Because of these differences, the corresponding proofs of existence for the time-dependent models are substantially different. More importantly, the results on the asymptotic behavior for the present model are completely different from results obtained in [16] [10].

We conclude this section by recalling, from [34], estimates on the size of parameters that appear in the system (2.19)–(2.22).

The parameter λ is typically small; for example, from experiments of injecting adenovirus ONYX-015 into mouse tumors it can be computed that (see [34]) $\lambda = 3 \times 10^{-3} h^{-1}$. The parameters δ and μ are one order of magnitude larger than λ (e.g., $\delta \sim \frac{1}{50} h^{-1}$). The parameter γ is more difficult to estimate, but it is at least one order of magnitude larger than δ and μ ; for definiteness it was taken to be $1 h^{-1}$. Finally, in order to facilitate their numerical studies Wu et al [34] took $p_0 = 2.5$ but, as they noted, the actual value of p_0 may be as large as 11.

We recall that the clinical trials reported in [4], [12], [24], [30], [35] were conducted over a period of 30–42 days, that is, 720–1008 hours. Since the rate parameters in (2.11)–(2.13) do not exceed $1 h^{-1}$, one needs to study the behavior of solutions not only for short or intermediate times, but also for large times.

4. The effect of large doses

Suppose that at the start of the treatment all the cells are uninfected, so that

$$\tilde{x}_0(\rho) = 1, \quad \tilde{y}_0(\rho) = 0. \quad (4.1)$$

We inject

$$\tilde{v}_0(\rho) = A \quad (A \text{ positive constant}) \quad (4.2)$$

and consider its short term effect on the growth of the tumor.

From (2.19), (2.20) we find that

$$\frac{\partial \tilde{x}}{\partial t} = -p_0 \gamma A + O(t),$$

$$\frac{\partial \tilde{y}}{\partial t} = p_0 \gamma A + O(t),$$

so that, by (2.25), (2.22),

$$\dot{R}(t) = R(t) \int_0^1 s^2 [\lambda - \lambda p_0 \gamma A t + O(t^2)] ds$$

or,

$$R(t) = R(0) e^{\frac{1}{3} \lambda t} \beta(t) \quad (4.3)$$

where

$$\beta(t) = \exp\left[-\frac{\lambda}{6} p_0 \gamma A t^2 + O(t^3)\right] \quad (4.4)$$

is the factor by which tumor growth is reduced. Similarly, if initially

$$\tilde{x}_0(\rho) = \text{const.} = x_c, \quad \tilde{y}_0(\rho) = \text{const.} = y_c,$$

then

$$R(t) = R_0(t)\beta_{x_c}(t) \quad (4.5)$$

where $R_0(t)$ is the radius of the untreated tumor and

$$\beta_{x_c}(t) = \exp\left[-\frac{\lambda}{6}p_0\gamma Ax_c t^2 + O(t^3)\right] \quad (4.6)$$

is the reduction factor due to the drug.

We can also quite easily derive estimates on the tumor growth at intermediate times. Taking again, for simplicity, the case (4.1) and setting

$$z = (\lambda + \mu)\tilde{x} + \mu\tilde{y}$$

we have $z(\rho, 0) = \lambda + \mu$ and

$$\frac{Dz}{Dt} = -\lambda p_0 \gamma \tilde{x} \tilde{v} + (\lambda + \mu)\lambda \tilde{x} - \mu \delta \tilde{y} - (-\mu + z)z.$$

Since $\tilde{y} \geq 0$, we deduce from (2.21), (2.23), (4.2) and the parabolic comparison principle (cf. [18, Chapter 2]) that

$$\tilde{v} \geq Ae^{-\gamma t}$$

Given a time $t = T$, let A be so large that

$$Ae^{-\gamma T} \lambda \gamma p_0 > (\lambda + \mu)\delta. \quad (4.7)$$

We then deduce that

$$\frac{Dz}{Dt} < (\lambda + \mu - \delta)z$$

Hence

$$z(\rho, t) < (\lambda + \mu)e^{(\lambda + \mu - \delta)t}$$

and, if $\delta > \lambda + \mu$,

$$\dot{R}(t) < R(t) \int_0^1 s^2 [-\mu + (\lambda + \mu)e^{-(\delta - \lambda - \mu)t}] ds$$

or

$$\log \frac{R(t)}{R(0)} < \frac{1}{3} \left(-\mu t + \frac{\lambda + \mu}{\delta - \lambda - \mu} \right), \quad 0 < t \leq T.$$

We conclude that if T is such that

$$\mu T = \frac{\lambda + \mu}{\delta - \lambda - \mu} \quad (\delta > \lambda + \mu) \quad (4.8)$$

then $R(T) < R(0)$. Thus we can ensure that the tumor radius will have decreased by the time $t = T$, T as in (4.8), provided the dosage A is as large as in (4.7). However, in some special cases we can do much better: we can reduce a tumor of any size to zero by just a modest dose of injection. This will be shown in the following sections.

5. Stationary solutions

The special cases alluded to at the end of the last section are derived from the stationary solutions of (2.11)–(2.14), (2.17) with constant densities. Thus they are determined from the equations

$$u(r)\dot{x}(r) - [(\lambda + \mu) - (\lambda + \mu)x(r) - \mu y(r) - p_0\gamma v(r)]x(r) = 0, \quad (5.1)$$

$$u(r)\dot{y}(r) - [(\mu - \delta) - (\lambda + \mu)x(r) - \mu y(r)]y(r) - p_0\gamma x(r)v(r) = 0, \quad (5.2)$$

$$\delta y(r) - \gamma v(r) + \kappa_0 R^2 \Delta v = 0, \quad (5.3)$$

$$\frac{1}{r^2} \frac{d}{dr} (r^2 u(r)) = -\mu + (\lambda + \mu)x(r) + \mu y(r). \quad (5.4)$$

Since $\dot{x} = \dot{y} = 0$ and $v = \text{const.}$, we easily find that there are precisely four solutions of this type, namely,

$$\begin{aligned} x(r) &\equiv \text{const.} = x_s, & y(r) &\equiv \text{const.} = y_s, \\ v(r) &\equiv \frac{\delta}{\gamma} y_s = v_s \end{aligned} \quad (5.5)$$

and $u_s(r) = \frac{1}{3}(-\mu + (\lambda + \mu)x_s + \mu y_s)r$ where

$$(x_s, y_s) = (0, 0), \quad (5.6)$$

$$(x_s, y_s) = (1, 0), \quad (5.7)$$

$$(x_s, y_s) = (0, 1 - \frac{\delta}{\mu}) \quad \text{provided } \delta < \mu, \quad (5.8)$$

and

$$\begin{aligned} x_s &= \frac{\lambda\mu - p_0\delta\mu + p_0\delta^2 + \mu\delta}{(p_0\delta - \lambda)p_0\delta} \equiv x_*, & y_s &= \frac{(\lambda + \mu)(p_0\delta - \delta - \lambda)}{(p_0\delta - \lambda)p_0\delta} \equiv y_*, \\ &\text{provided } x_* \geq 0, y_* \geq 0. \end{aligned} \quad (5.9)$$

In the following sections we shall prove that if the initial densities are approximately equal to (5.8), then an injection of virus of density approximately equal to $\frac{\delta}{\gamma} y_s$ will make $R(t)$ decrease monotonically to zero as $t \rightarrow \infty$. This result is quite remarkable since it is valid no matter how large the initial radius $R(0)$ is.

We shall also prove a similar result for the case (5.9) provided

$$p_0 > 1 + \frac{\lambda}{\mu} + \frac{\lambda}{\delta}. \quad (5.10)$$

Such a result is obviously not true in the case (5.7) (since $\dot{R}(0) > 0$ in this case). The case (5.6) where almost all cells are necrotic will be considered in Remark 10.2.

6. Local existence and uniqueness (hyperbolic-parabolic system)

Let $(x_s, y_s, v_s) = (0, 1 - \frac{\delta}{\mu}, \frac{\delta}{\gamma}(1 - \frac{\delta}{\mu}))$, where $\delta < \mu$. We shall consider the system (2.19)–(2.28) with $(\tilde{x}_0, \tilde{y}_0, \tilde{v}_0)$ near (x_s, y_s, v_s) . It will be convenient to introduce new variables:

$$\begin{aligned} X(\rho, t) &= \tilde{x}(\rho, t) - x_s, \quad Y(\rho, t) = \tilde{y}(\rho, t) - y_s, \\ V(\rho, t) &= \tilde{v}(\rho, t) - v_s, \quad U(\rho, t) = \tilde{u}(\rho, t). \end{aligned} \quad (6.1)$$

Then the system (2.19)–(2.26) takes the following form in $\{0 < \rho < 1, t > 0\}$:

$$\begin{aligned} \frac{\partial X}{\partial t} + \left[-\rho \frac{\dot{R}(t)}{R(t)} + \frac{U(\rho, t)}{R(t)} \right] \frac{\partial X}{\partial \rho} \\ = [(\lambda + \mu) - (p_0\delta + \mu)y_s - 2(\lambda + \mu)x_s]X - \mu x_s Y - p_0\gamma x_s V \\ - [(\lambda + \mu)X + \mu Y + p_0\gamma V]X + x_s[\lambda + \mu - (p_0\delta + \mu)y_s - (\lambda + \mu)x_s], \end{aligned} \quad (6.2)$$

$$\begin{aligned} \frac{\partial Y}{\partial t} + \left[-\rho \frac{\dot{R}(t)}{R(t)} + \frac{U(\rho, t)}{R(t)} \right] \frac{\partial Y}{\partial \rho} \\ = [p_0\gamma v_s - (\lambda + \mu)y_s]X - [(\delta - \mu) + (\lambda + \mu)x_s + 2\mu y_s]Y \\ + p_0\gamma v_s V + [p_0\gamma X V - (\lambda + \mu)XY - \mu Y^2] \\ + y_s[\mu - \delta - \mu y_s - (p_0\delta - \mu - \lambda)x_s], \end{aligned} \quad (6.3)$$

$$X(\rho, 0) = X_0(\rho), \quad Y(\rho, 0) = Y_0(\rho), \quad (6.4)$$

$$\frac{\partial V}{\partial t} - \rho \frac{\dot{R}(t)}{R(t)} \frac{\partial V}{\partial \rho} - \kappa_0 \frac{1}{\rho^2} \frac{\partial}{\partial \rho} (\rho^2 \frac{\partial V}{\partial \rho}) = \delta Y - \gamma V, \quad \frac{\partial V(0, t)}{\partial \rho} = 0, \quad (6.5)$$

$$V(\rho, 0) = V_0(\rho), \quad \frac{\partial V}{\partial \rho}|_{\rho=1} = 0, \quad (6.6)$$

$$U(\rho, t) = \frac{R(t)}{\rho^2} \int_0^\rho s^2 [3u'_s(0) + (\lambda + \mu)X(s, t) + \mu Y(s, t)] ds, \quad (6.7)$$

$$U(0, t) = 0, \quad (6.8)$$

$$\dot{R}(t) = U(1, t), \quad R(0) \text{ is given}, \quad (6.9)$$

where $X_0(\rho) = \tilde{x}_0(\rho) - x_s$, $Y_0(\rho) = \tilde{y}_0(\rho) - y_s$, $V_0(\rho) = \tilde{v}_0(\rho) - v_s$,

$$u'_s(0) = \frac{1}{3}[\mu + (\lambda + \mu)x_s + \mu y_s]$$

and $\frac{\partial V_0(\rho)}{\partial \rho}|_{\rho=1} = 0$. Note that since $x_s = 0$, several terms on the right-hand sides of (6.2) and (6.3) vanish (in particular, the last terms).

We choose arbitrary positive numbers σ, α satisfying

$$0 < \alpha < \gamma, \quad 0 < \sigma < \frac{\delta}{6}$$

and introduce the following space of functions $U(\rho, t)$:

$$\begin{aligned} E_T &= \{U(\rho, t) \in C^{1,0}([0, 1] \times [0, T]); \quad U(0, t) = 0, \\ U(\rho, 0) &= U_0(\rho) \text{ and } R(t) > 0, \left| \frac{\dot{R}(t)}{R(t)} + \frac{\delta}{3} \right| < \alpha, \\ \left| -\frac{\dot{R}(t)}{R(t)} + \frac{1}{R(t)} \frac{\partial}{\partial \rho} U(\rho, t) \right| &\leq M \|(X_0, Y_0)\|_{C[0,1]} e^{-\alpha t} \end{aligned}$$

where M is a positive constant to be determined later on,

$$U_0(\rho) = \frac{R(0)}{\rho^2} \int_0^\rho s^2 [3u'_s(0) + (\lambda + \mu)X_0(s) + \mu Y_0(s)] ds, \quad (6.10)$$

and $R(t)$ is given in terms of $U(1, \tau)$ by

$$R(t) = R(0) + \int_0^t U(1, \tau) d\tau. \quad (6.11)$$

Here $C^{1,0}([0, 1] \times [0, T])$ is the space of all functions $U(\rho, t)$ which are continuous together with their first ρ derivative $\partial U(\rho, t)/\partial \rho$, and the norm in this space is defined by

$$\|U\|_{C^{1,0}} \equiv \|U\|_{C^0[0 \leq \rho \leq 1, 0 \leq t \leq T]} + \left\| \frac{\partial U}{\partial \rho} \right\|_{C^0[0 \leq \rho \leq 1, 0 \leq t \leq T]}.$$

Since $R(0) > 0$, the space E_T is non-empty if T is sufficiently small.

We shall first solve the system (6.2)–(6.9) for a small time interval $0 \leq t \leq T$, using the contraction mapping principle in the space E_T . Given any $U \in E_T$ we define $R(t)$ by (6.9) and proceed to solve, in this and in the following section, the hyperbolic-parabolic system (6.2)–(6.6) by a fixed-point method. We, then define a mapping

$$\mathcal{F} : U(\rho, t) \rightarrow W(\rho, t)$$

by

$$\begin{aligned} W(\rho, t) &= \frac{R(t)}{\rho^2} \int_0^\rho s^2 [3u'_s(0) + (\lambda + \mu)X(s, t) + \mu Y(s, t)] ds, \\ W(0, t) &= 0. \end{aligned} \quad (6.12)$$

In Section 8 we shall prove that $\mathcal{F}$ is a contraction if T is sufficiently small, and this will complete the proof of local existence and uniqueness for the system (6.2)–(6.9); global existence will be proved in Section 9.

Let us denote by $\xi = \xi(\tau; \rho, t)$ the backward characteristic curve of the equations (6.2) and (6.3), such that $\xi|_{\tau=t} = \rho$. Then, for $0 \leq \tau \leq t$,

$$\begin{cases} \frac{d\xi}{d\tau} = -\xi \frac{\dot{R}(\tau)}{R(\tau)} + \frac{U(\xi, \tau)}{R(\tau)} \equiv h(\xi, \tau), \\ \xi(t; \rho, t) = \rho; \end{cases} \quad (6.13)$$

and

$$\left| \frac{\partial h(\xi, \tau)}{\partial \xi} \right| \leq L \quad (6.14)$$

where the constant L may depend on T . The assumptions on U imply that there exists a unique C^1 solution to (6.13). In view of (6.8), (6.9), the characteristic curves $\xi = \xi(\tau; \rho, t)$ do not exit the interval $0 < \xi < 1$ if $0 < \rho < 1$, and the lines $\xi = 0$ and $\xi = 1$ are characteristic curves.

The above considerations imply that the hyperbolic problem (6.2)–(6.3) in $\{0 \leq \rho \leq 1, t > 0\}$ can be solved as a Cauchy problem (for a given $V(\rho, t) \in C([0, 1] \times [0, T])$); the solution is determined by the initial data $(X_0(\rho), Y_0(\rho))$ for $0 \leq \rho \leq 1$.

To prove the local existence and uniqueness of the hyperbolic-parabolic system (6.2)–(6.6) for a given $U \in E_T$, we shall need two lemmas.

Lemma 6.1. *Suppose $U \in E_T$ and $\tilde{Y}, \frac{\partial \tilde{Y}}{\partial \rho} \in L^\infty([0, 1] \times [0, T])$ and assume that, for some $\varepsilon \in (0, 1)$,*

$$|\tilde{Y}| \leq \varepsilon e^{-\alpha t}, \quad t < T, \quad (6.15)$$

$$\left| \frac{\partial \tilde{Y}}{\partial \rho} \right| \leq \varepsilon e^{-\alpha t}, \quad t < T, \quad (6.16)$$

If $\|V_0(\rho)\|_{C^1([0, 1])} \leq C_ \varepsilon$ where C_* is a constant (independently of ε), then there exists a unique solution of the parabolic problem (6.5)–(6.6) (with Y replaced by $\tilde{Y}$) in $W_p^{2,1}([0, 1] \times [0, T])$ ($p > 1$ arbitrary), and*

$$|V| \leq \max\{C_*, \frac{\delta}{\gamma - \alpha}\} \varepsilon e^{-\alpha t}, \quad t < T, \quad (6.17)$$

$$\left| \frac{\partial V}{\partial \rho} \right| \leq \max\{C_*, \frac{\delta}{\gamma + \sigma - \alpha}\} \varepsilon e^{-\alpha t}, \quad t < T. \quad (6.18)$$

Proof. The existence and uniqueness of the solution to problem (6.5)–(6.6) (with Y replaced by $\tilde{Y}$) follows from the standard parabolic L^p -theory (cf. [26, Chapter 3]). The estimate (6.17) follows from (6.15) and the parabolic comparison principle (cf. [18, Chapter 2]) which implies that $\max\{C_*, \frac{\delta}{\gamma - \alpha}\} \varepsilon e^{-\alpha t}$ majorizes $\pm V$.

Next we prove the estimate (6.18). Differentiating (6.5), (6.6) with respect to ρ and setting $H(\rho, t) \equiv \frac{\partial V}{\partial \rho}$, we get

$$\frac{\partial H}{\partial t} - \kappa_0 \frac{1}{\rho^2} \frac{\partial}{\partial \rho} (\rho^2 \frac{\partial H}{\partial \rho}) - \rho \frac{\dot{R}(t)}{R(t)} \frac{\partial H}{\partial \rho} + (\gamma - \frac{\dot{R}(t)}{R(t)} + \frac{2\kappa_0}{\rho^2}) H = \delta \frac{\partial \tilde{Y}}{\partial \rho}, \quad (6.19)$$

$$H|_{t=0} = V'_0(\rho), \quad H|_{\rho=1} = 0. \quad (6.20)$$

Noting that

$$\gamma - \frac{\dot{R}(t)}{R(t)} \geq \gamma + \sigma > 0 \quad (6.21)$$

and using (6.16) and the parabolic comparison principle, we find that (6.18) holds.

□

Given the V established in Lemma 6.1, we shall now solve the hyperbolic system (6.2)–(6.4).

In the next lemma $U(\rho, t)$ is any function in E_T , $\tilde{Y}$ is any function as in Lemma 6.1, and V is the solution (with $\|V_0\|_{C^1[0,1]} \leq C_*\epsilon$) established in Lemma 6.1.

Lemma 6.2. *Let $(x_s, y_s, v_s) = (0, 1 - \frac{\delta}{\mu}, \frac{\delta}{\gamma}(1 - \frac{\delta}{\mu}))$ where $\delta < \mu$ and assume that*

$$p_0 > \frac{\mu(\lambda + \delta)}{\delta(\mu - \delta)}. \quad (6.22)$$

If $\|(X_0(\rho), Y_0(\rho))\|_{C^1([0,1])}$ is sufficiently small, then, provided T is small enough, there exists a unique solution $(\hat{X}(t), \hat{Y}(t))$ of (6.2)–(6.4) such that

$$(\hat{X}(t), \hat{Y}(t)) \equiv (X(\xi(t; \rho_0, 0), t), Y(\xi(t; \rho_0, 0), t))$$

and

$$\left(\frac{\partial \hat{X}}{\partial \rho}(t), \frac{\partial \hat{Y}}{\partial \rho}(t) \right) \equiv \left(\frac{\partial X}{\partial \rho}(\xi(t; \rho_0, 0), t), \frac{\partial Y}{\partial \rho}(\xi(t; \rho_0, 0), t) \right)$$

are in $C([0, T])$, and

$$|\hat{X}(t)| + |\hat{Y}(t)| \leq M_0 e^{-\alpha t} \|(X_0, Y_0)\|_{C[0,1]}, \quad (6.23)$$

$$\left| \frac{\partial \hat{X}}{\partial \rho}(t) \right| + \left| \frac{\partial \hat{Y}}{\partial \rho}(t) \right| \leq M_1 e^{-\alpha t} \|(X_0, Y_0)\|_{C^1([0,1])} \quad (6.24)$$

where $\xi = \xi(t; \rho_0, 0)$ is the forward characteristic curve of the equations (6.2) and (6.3) initiating at the point $(\rho_0, 0)$ ($0 \leq \rho_0 \leq 1$), and M_0, M_1 are positive constants which depend on C_ but are independent of T .*

Proof. Along the characteristic curve, the system (6.2)–(6.4) takes the following form:

$$\begin{aligned} \frac{d\hat{X}}{dt} &= [(\lambda + \mu) - (p_0\delta + \mu)(1 - \frac{\delta}{\mu})]\hat{X} \\ &\quad - [(\lambda + \mu)\hat{X} + \mu\hat{Y} + p_0\gamma\hat{V}]\hat{X}, \end{aligned} \quad (6.25)$$

$$\begin{aligned} \frac{d\hat{Y}}{dt} &= (p_0\delta - \lambda - \mu)(1 - \frac{\delta}{\mu})\hat{X} - (\mu - \delta)\hat{Y} \\ &\quad + [p_0\gamma\hat{X}\hat{V} - (\lambda + \mu)\hat{X}\hat{Y} - \mu\hat{Y}^2], \end{aligned} \quad (6.26)$$

$$\hat{X}(0) = X_0(\rho_0), \hat{Y}(0) = Y_0(\rho_0). \quad (6.27)$$

Introducing the vector notation

$$Z = (\hat{X}, \hat{Y})^T,$$

$$A = \begin{pmatrix} (\lambda + \mu) - (p_0\delta + \mu)(1 - \frac{\delta}{\mu}) & 0 \\ (p_0\delta - \lambda - \mu)(1 - \frac{\delta}{\mu}) & -(\mu - \delta) \end{pmatrix},$$

$$f(Z) = (- (\lambda + \mu)\hat{X}^2 - \mu\hat{X}\hat{Y}, \quad -(\lambda + \mu)\hat{X}\hat{Y} - \mu\hat{Y}^2)^T,$$

$$g(t, Z) = (-p_0\gamma\hat{V}(t)\hat{X}, \quad p_0\gamma\hat{V}(t)\hat{X})^T,$$

the system (6.25)–(6.27) can be rewritten as follows:

$$\begin{aligned} \frac{dZ}{dt} &= AZ + f(Z) + g(t, Z), \\ Z|_{t=0} &= Z(0) \end{aligned} \quad (6.28)$$

where $f(Z)$, $g(t, Z)$ satisfy:

$$f(Z) = O(Z^2), \quad (6.29)$$

$$|g(t, Z)| \leq C\epsilon e^{-\alpha t}|Z| \quad (\text{by (6.18)}), \quad (6.30)$$

Local existence and uniqueness of a solution to the system (6.28) follows from standard ODE theory. We next proceed to establish some estimates on the solution.

The system (6.28) may be regarded as a perturbation of the linear system

$$\begin{aligned} \frac{d\tilde{Z}}{dt} &= A\tilde{Z}, \\ \tilde{Z}|_{t=0} &= Z(0). \end{aligned} \quad (6.31)$$

Let $\Phi(t)$ denote a fundamental solution of (6.31) with $\Phi(0) = I$. Then, by the variation of constants formula,

$$\begin{aligned} Z(t) &= \Phi(t)\Phi^{-1}(0)Z(0) \\ &\quad + \int_0^t \Phi(t)\Phi^{-1}(s)[f(Z(s)) + g(s, Z(s))]ds \\ &= \Phi(t)Z(0) + \int_0^t \Phi(t-s)[f(Z(s)) + g(s, Z(s))]ds. \end{aligned} \quad (6.32)$$

From the assumptions $\mu > \delta$ and (6.22), it follows that the two characteristic roots λ_1, λ_2 of the matrix A are negative. Therefore there exist positive constants C and η such that

$$\|\Phi(t)\| \leq Ce^{-\eta t}, \quad t \geq 0. \quad (6.33)$$

Hence

$$\begin{aligned} \|Z(t)\| &\leq C \|Z(0)\| e^{-\eta t} \\ &\quad + C \int_0^t e^{-\eta(t-s)} (\|f(Z(s))\| \\ &\quad + \|g(s, Z(s))\|) ds, \end{aligned} \quad (6.34)$$

and, by (6.29), (6.30),

$$\|Z(t)\| \leq C_0 \|Z(0)\| e^{-\alpha t} + C_1 \int_0^t e^{-\alpha(t-s)} \|Z(s)\|^2 ds \quad (6.35)$$

if $0 < \alpha < \eta$ and $\|Z(0)\|$ is smaller than the ε in (6.30) (or in (6.15)–(6.16)).

Setting

$$H(t) = \|Z(t)\| e^{\alpha t}, \quad (6.36)$$

(6.35) can be written as

$$H(t) \leq C_0 \|Z(0)\| + C_1 \int_0^t e^{-\alpha s} H^2(s) ds, \quad (6.37)$$

and, by comparison,

$$H(t) \leq \frac{1}{\frac{1}{C_0 \|Z(0)\|} - \frac{C_1}{\alpha} (1 - e^{-\alpha t})}. \quad (6.38)$$

Therefore, if $\|Z(0)\|$ is so small that

$$\frac{1}{C_0 \|Z(0)\|} > \frac{2C_1}{\alpha}, \quad (6.39)$$

then

$$\|Z(t)\| \leq 2C_0 \|Z(0)\| e^{-\alpha t}, \quad (6.40)$$

so that the estimate (6.23) holds.

Differentiating the system (6.2)–(6.4) with respect to ρ , and using (6.18), (6.23) and the inequality

$$\left| -\frac{\dot{R}(t)}{R(t)} + \frac{U_\rho(\rho, t)}{R(t)} \right| \leq M \|Z_0(\rho)\|_{C[0,1]} e^{-\alpha t} \quad (6.41)$$

which holds for any given $U \in E_T$, we can proceed to establish the estimate (6.24) in the same way as in the derivation of (6.23). $\square$

7. Local existence and uniqueness – continued (hyperbolic-parabolic system)

For any given $U \in E_T$, we shall use a fixed-point method to prove the local existence and uniqueness of the solution of the hyperbolic-parabolic system (6.2)–(6.6). To this end, we introduce the function space

$$S_T = \{Y(\xi(t), t) : Y(\xi(t), t), \frac{\partial Y}{\partial \rho}(\xi(t), t) \in C[0, T],$$

there exists a positive constant C independent of

(X_0, Y_0) and T such that

$$|Y(\xi(t), t)|, \left| \frac{\partial Y}{\partial \rho}(\xi(t), t) \right| \leq C \| (X_0(\rho), Y_0(\rho)) \|_{C^1([0,1])} e^{-\alpha t} \}$$

where $\xi(t)$ is any forward characteristic curve initiating at $t = 0$ of the hyperbolic system (6.2)–(6.3), and the norm

$$\|Y\|_{S_T} \equiv \|Y(\xi(t), t)\|_{C[0, T]} + \left\| \frac{\partial Y}{\partial \rho}(\xi(t), t) \right\|_{C[0, T]}, \quad Y \in S_T.$$

Theorem 7.1. *Let $(x_s, y_s, v_s) = (0, 1 - \frac{\delta}{\mu}, \frac{\delta}{\gamma}(1 - \frac{\delta}{\mu}))$ where $\delta < \mu$ and assume that (6.22) holds. If $\|X_0(\rho), Y_0(\rho), V_0(\rho)\|_{C^1([0, 1])}$ is sufficiently small and T is small enough, then for any $U(\rho, t)$ in E_T there exists a unique solution $(\hat{X}(t), \hat{Y}(t), \hat{V}(t))$ of (6.2)–(6.6) such that*

$$(\hat{X}(t), \hat{Y}(t), \hat{V}(t)) \equiv (X(\xi(t), t), Y(\xi(t), t), V(\xi(t), t))$$

and

$$\left(\frac{\partial \hat{X}}{\partial \rho}(t), \frac{\partial \hat{Y}}{\partial \rho}(t), \frac{\partial \hat{V}}{\partial \rho}(t) \right) \equiv \left(\frac{\partial X}{\partial \rho}(\xi(t), t), \frac{\partial Y}{\partial \rho}(\xi(t), t), \frac{\partial V}{\partial \rho}(\xi(t), t) \right)$$

are in $C([0, T])$, and

$$\begin{aligned} |\hat{X}(t)| + |\hat{Y}(t)| + |\hat{V}(t)| &\leq C_0 e^{-\alpha t} \| (X_0, Y_0) \|_{C[0, 1]}, \\ \left| \frac{\partial \hat{X}}{\partial \rho}(t) \right| + \left| \frac{\partial \hat{Y}}{\partial \rho}(t) \right| + \left| \frac{\partial \hat{V}}{\partial \rho}(t) \right| &\leq C_1 e^{-\alpha t} \| (X_0, Y_0) \|_{C^1([0, 1])} \end{aligned} \quad (7.1)$$

where $\xi = \xi(t)$ is the forward characteristic curve of the equations (6.2) and (6.3) initiating at $t = 0$ and C_0, C_1, α are positive constants independent of T .

Remark 7.1. The appearance of $e^{-\alpha t}$ on the right-hand side of (7.1) (as well as in Theorem 8.1) seems strange, since T is small. We intend however to prove that this factor remains unchanged as we extend the solution to all t , and this will be used to prove that $R(t) \rightarrow 0$ exponentially fast as $t \rightarrow \infty$.

Proof. Given a $\tilde{Y}$ in S_T , let V be the solution of (6.5)–(6.6) with Y replaced by $\tilde{Y}$ and let (X, Y) be the solution of (6.2)–(6.4) with this V . Define the mapping

$$\mathcal{H} : \tilde{Y} \longrightarrow Y \quad (\tilde{Y} \in S_T).$$

From Lemma 6.2 we see that $\mathcal{H}$ maps S_T into itself provided T is sufficiently small. To prove that $\mathcal{H}$ is a contraction, take $\tilde{Y}_1$ and $\tilde{Y}_2$ in S_T , and set

$$Y_1 = \mathcal{H}\tilde{Y}_1, \quad Y_2 = \mathcal{H}\tilde{Y}_2.$$

We wish to prove that

$$\|Y_1 - Y_2\|_{S_T} \leq C(T) \|\tilde{Y}_1 - \tilde{Y}_2\|_{S_T}$$

where $C(T) \rightarrow 0$ as $T \rightarrow 0$.

Let V_i denote the solution of (6.5)–(6.6) with $Y = \tilde{Y}_i$ ($i = 1, 2$). Then

$$\begin{aligned} \frac{\partial(V_1 - V_2)}{\partial t} - \rho \frac{\dot{R}(t)}{R(t)} \frac{\partial(V_1 - V_2)}{\partial \rho} - \kappa_0 \Delta(V_1 - V_2) \\ + \gamma(V_1 - V_2) = \delta(\tilde{Y}_1 - \tilde{Y}_2), \end{aligned} \quad (7.2)$$

$$(V_1 - V_2)(\rho, 0) = 0, \quad \frac{\partial(V_1 - V_2)}{\partial \rho} \Big|_{\rho=1} = 0. \quad (7.3)$$

By the parabolic comparison principle (cf. [18, Chapter 2]),

$$|V_1 - V_2| \leq \frac{\delta}{\gamma} \|\tilde{Y}_1 - \tilde{Y}_2\|_{L^\infty}. \quad (7.4)$$

Set

$$\left(\hat{X}_i(t), \hat{Y}_i(t), \hat{V}_i(t) \right) \equiv \left(X_i(\xi(t), t), Y_i(\xi(t), t), V_i(\xi(t), t) \right). \quad (7.5)$$

From (6.25)–(6.27) we get

$$\begin{aligned} \frac{dZ}{dt} &= AZ + f(t, Z) + g(t), \\ Z|_{t=0} &= 0 \end{aligned} \quad (7.6)$$

where $Z = (\hat{X}_1 - \hat{X}_2, \hat{Y}_1 - \hat{Y}_2)^T$, the matrix A is the same as in Lemma 6.2, and $f(t, Z)$, $g(t)$ satisfy (by (7.4), and Lemmas 6.1, 6.2)

$$|f(t, Z)| \leq C \|(X_0(\rho), Y_0(\rho))\|_{C^1([0,1])} e^{-\alpha t} |Z|, \quad (7.7)$$

$$|g(t)| \leq C \|V_1 - V_2\|_{L^\infty} \leq C \|\tilde{Y}_1 - \tilde{Y}_2\|_{L^\infty}. \quad (7.8)$$

Proceeding as in the proof of Lemma 6.2 and using (7.7) and (7.8), we derive the inequalities

$$\begin{aligned} \|Z(t)\| &\leq C \int_0^t e^{-\eta(t-s)} (\|f(s, Z(s))\| + \|g(s)\|) ds \\ &\leq C_1 \|(X_0(\rho), Y_0(\rho))\|_{C^1([0,1])} e^{-\eta t} \int_0^t e^{(\eta-\alpha)s} \|Z(s)\| ds \\ &\quad + C_2(1 - e^{-\eta t}) \|\tilde{Y}_1 - \tilde{Y}_2\|_{L^\infty}. \end{aligned}$$

The function

$$H(t) = \|Z(t)\| e^{\eta t}$$

then satisfies

$$\begin{aligned} H(t) &\leq C_1 \|(X_0(\rho), Y_0(\rho))\|_{C^1([0,1])} \int_0^t H(s) ds \\ &\quad + C_2(e^{\eta T} - 1) \|\tilde{Y}_1 - \tilde{Y}_2\|_{L^\infty}. \end{aligned}$$

for $0 \leq t \leq T$, and, by Gronwall's inequality,

$$H(t) \leq C_2(e^{\eta T} - 1) \|\tilde{Y}_1 - \tilde{Y}_2\|_{L^\infty} e^{C_1 t \|(X_0(\rho), Y_0(\rho))\|_{C^1([0,1])}},$$

or

$$\|Z(t)\| \leq C_2(e^{\eta T} - 1) \|\tilde{Y}_1 - \tilde{Y}_2\|_{L^\infty} e^{-t(\eta - C_1 \|(X_0(\rho), Y_0(\rho))\|_{C^1([0,1])})} \quad (7.9)$$

for $0 \leq t \leq T$. Taking $\| (X_0(\rho), Y_0(\rho)) \|_{C^1([0,1])}$ such that

$$C_1 \| (X_0(\rho), Y_0(\rho)) \|_{C^1([0,1])} < \eta \quad (7.10)$$

we get

$$\| Z(t) \| \leq C(e^{\eta T} - 1) \| \tilde{Y}_1 - \tilde{Y}_2 \|_{L^\infty}, \quad 0 \leq t \leq T. \quad (7.11)$$

Hence,

$$|\hat{Y}_1(t) - \hat{Y}_2(t)| \leq C(e^{\eta T} - 1) \| \tilde{Y}_1 - \tilde{Y}_2 \|_{L^\infty}, \quad 0 \leq t \leq T, \quad (7.12)$$

or,

$$|Y_1(\xi(t), t) - Y_2(\xi(t), t)| \leq C(e^{\eta T} - 1) \| \tilde{Y}_1 - \tilde{Y}_2 \|_{L^\infty}, \quad 0 \leq t \leq T. \quad (7.13)$$

In the same way we can prove that

$$\left| \frac{\partial Y_1}{\partial \rho}(\xi(t), t) - \frac{\partial Y_2}{\partial \rho}(\xi(t), t) \right| \leq C(e^{\eta T} - 1) \left\| \frac{\partial \tilde{Y}_1}{\partial \rho} - \frac{\partial \tilde{Y}_2}{\partial \rho} \right\|_{L^\infty}, \quad 0 \leq t \leq T. \quad (7.14)$$

Combining (7.13) and (7.14) we conclude that

$$\| Y_1 - Y_2 \|_{S_T} \leq C(e^{\eta T} - 1) \| \tilde{Y}_1 - \tilde{Y}_2 \|_{S_T}. \quad (7.15)$$

This completes the proof that $\mathcal{H}$ is a contraction provided T is sufficiently small. Hence there exists a unique local solution of (6.2)–(6.6) for any given $U \in E_T$. Finally, the estimate (7.1) follows from Lemmas 6.1 and 6.2. $\square$

8. Local existence and uniqueness (free boundary problem)

Theorem 8.1. *Let $(x_s, y_s, v_s) = (0, 1 - \frac{\delta}{\mu}, \frac{\delta}{\gamma}(1 - \frac{\delta}{\mu}))$ where $\delta < \mu$ and assume that (6.22) holds. If $\| (X_0(\rho), Y_0(\rho), V_0(\rho)) \|_{C^1([0,1])}$ is sufficiently small and T is small enough, then the free boundary problem (6.2)–(6.9) admits a unique solution $(X(\rho, t), Y(\rho, t), V(\rho, t), U(\rho, t), R(t))$ with $R \in C^1[0, T]$, (X, Y, V, U) in $C^1([0, 1] \times [0, T])$, and with $R(t) > 0$ for $t \in [0, T]$. Moreover,*

$$|X(\xi(t), t)| + |Y(\xi(t), t)| \leq M_0 e^{-\alpha t} \| (X_0, Y_0) \|_{C([0,1])}, \quad (8.1)$$

$$\left| \frac{\partial X}{\partial \rho}(\xi(t), t) \right| + \left| \frac{\partial Y}{\partial \rho}(\xi(t), t) \right| \leq C e^{-\alpha t} \| (X_0, Y_0) \|_{C^1([0,1])} \quad (8.2)$$

where $\xi = \xi(t)$ is any forward characteristic curve of the equations (6.2) and (6.3) initiating at $t = 0$ and M_0, C are positive constants independent of T .

Proof. Consider the mapping

$$\mathcal{F} : U \rightarrow W \quad (U \in E_T)$$

where W is defined by (6.12). We shall prove that $\mathcal{F}$ maps E_T into itself provided T is sufficiently small.

Define

$$R_W(t) = R(0) + \int_0^t W(1, \tau) d\tau \quad (8.3)$$

By (6.12), (8.3) and Theorem 7.1 we easily see that

$$R_W(t) > \frac{R(0)}{2} > 0, \quad -\frac{\delta}{2} < \frac{\dot{R}_W(t)}{R_W(t)} < -\frac{\delta}{4} \quad t \in [0, T], \quad (8.4)$$

if T is sufficiently small and σ (in the definition of E_T) is chosen small enough.

By (6.12), (6.23), (8.3), (8.4) and direct calculations we have

$$\begin{aligned} & \left| -\frac{\dot{R}_W(t)}{R_W(t)} + \frac{W_\rho(\rho, t)}{R_W(t)} \right| \\ &= \left| \frac{R(t)}{R_W(t)} \right| \cdot \left| -\int_0^1 s^2 [(\lambda + \mu)X(s, t) + \mu Y(s, t)] ds \right. \\ & \quad \left. - \frac{2}{\rho^3} \int_0^\rho s^2 [(\lambda + \mu)X(s, t) + \mu Y(s, t)] ds \right. \\ & \quad \left. + [(\lambda + \mu)X(\rho, t) + \mu Y(\rho, t)] \right| \\ &\leq \frac{2R(0)}{\frac{1}{2}R(0)} \cdot 2[(\lambda + \mu) \|X(\rho, t)\|_{C^0} + \mu \|Y(\rho, t)\|_{C^0}] \\ &\leq 8(\lambda + \mu)M_0 e^{-\alpha t} \| (X_0(\rho), Y_0(\rho)) \|_{C[0,1]}, \end{aligned} \quad (8.5)$$

if T is sufficiently small, where M_0 is a constant independent of M . Taking

$$M = 8(\lambda + \mu)M_0 \quad (8.6)$$

we conclude from (8.5)–(8.6) that $W \in E_T$, so that $\mathcal{F}$ maps E_T into itself provided T is sufficiently small.

To prove that $\mathcal{F}$ is a contraction, take U and $\tilde{U}$ in E_T , define $\tilde{R}(t)$ by (6.11) with $U = \tilde{U}$, and set

$$W = \mathcal{F}U, \quad \tilde{W} = \mathcal{F}\tilde{U}.$$

Then

$$\begin{aligned} & W(\rho, t) - \tilde{W}(\rho, t) \\ &= (R(t) - \tilde{R}(t)) \frac{1}{\rho^2} \int_0^\rho s^2 [3u'_s(0) + (\lambda + \mu)X(s, t) + \mu Y(s, t)] ds \\ & \quad + \frac{\tilde{R}(t)}{\rho^2} \int_0^\rho s^2 [(\lambda + \mu)(X(s, t) - \tilde{X}(s, t)) + \mu(Y(s, t) - \tilde{Y}(s, t))] ds \\ &\equiv I + J. \end{aligned} \quad (8.7)$$

By the definition (6.11) we have

$$R(t) - \tilde{R}(t) = \int_0^t (U(1, \tau) - \tilde{U}(1, \tau)) d\tau$$

and therefore

$$| R(t) - \tilde{R}(t) | \leq T \| U - \tilde{U} \|_{C^0}$$

where $\| U - \tilde{U} \|_{C^0} = \max_{(\rho, t) \in [0, 1] \times [0, T]} | U - \tilde{U} |$, so that, by (6.23),

$$| I | \leq CT \| U - \tilde{U} \|_{C^0}. \quad (8.8)$$

To estimate J , we first need to estimate $(X(s, t) - \tilde{X}(s, t))$. Integrating the equation (6.2) along the backward characteristic curve $\xi = \xi(\tau; s, t)$ which passes through a point (s, t) , we get

$$\begin{aligned} X(s, t) &= X_0(\xi(0; s, t)) + \int_0^t aX(\xi(\tau; s, t), \tau) d\tau \\ &\quad + \int_0^t [b_1 X(\xi(\tau; s, t), \tau) + b_2 Y(\xi(\tau; s, t), \tau) \\ &\quad + b_3 V(\xi(\tau; s, t), \tau)] X(\xi(\tau; s, t), \tau) d\tau \end{aligned} \quad (8.9)$$

where a, b_1, b_2, b_3 are constants. Hence

$$\begin{aligned} X(s, t) - \tilde{X}(s, t) &= X_0(\xi(0; s, t)) - X_0(\tilde{\xi}(0; s, t)) \\ &\quad + a \int_0^t [X(\xi(\tau; s, t), \tau) - \tilde{X}(\tilde{\xi}(\tau; s, t), \tau)] d\tau \\ &\quad + b_1 \int_0^t [X^2(\xi(\tau; s, t), \tau) - \tilde{X}^2(\tilde{\xi}(\tau; s, t), \tau)] d\tau \\ &\quad + b_2 \int_0^t [X(\xi(\tau; s, t), \tau) Y(\xi(\tau; s, t), \tau) \\ &\quad - \tilde{X}(\tilde{\xi}(\tau; s, t), \tau) \tilde{Y}(\tilde{\xi}(\tau; s, t), \tau)] d\tau \\ &\quad + b_3 \int_0^t [X(\xi(\tau; s, t), \tau) V(\xi(\tau; s, t), \tau) \\ &\quad - \tilde{X}(\tilde{\xi}(\tau; s, t), \tau) \tilde{V}(\tilde{\xi}(\tau; s, t), \tau)] d\tau \\ &\equiv I_1 + I_2 + I_3 + I_4 + I_5. \end{aligned} \quad (8.10)$$

In order to estimate the I_k , we first need to estimate $| \xi - \tilde{\xi} | \equiv | \xi(\tau; s, t) - \tilde{\xi}(\tau; s, t) |$. From (6.13) we have

$$\begin{aligned} \frac{d(\xi - \tilde{\xi})}{d\tau} &= \left(-\xi \frac{\dot{R}(\tau)}{R(\tau)} + \frac{U(\xi, \tau)}{R(\tau)} \right) - \left(-\tilde{\xi} \frac{\dot{\tilde{R}}(\tau)}{\tilde{R}(\tau)} + \frac{\tilde{U}(\tilde{\xi}, \tau)}{\tilde{R}(\tau)} \right) \\ &= -\frac{\dot{R}(\tau)}{R(\tau)} (\xi - \tilde{\xi}) - \tilde{\xi} \left(\frac{\dot{R}(\tau)}{R(\tau)} - \frac{\dot{\tilde{R}}(\tau)}{\tilde{R}(\tau)} \right) \\ &\quad + \frac{U(\xi, \tau)}{R(\tau) \tilde{R}(\tau)} (\tilde{R}(\tau) - R(\tau)) + \frac{1}{\tilde{R}(\tau)} (U(\xi, \tau) - U(\tilde{\xi}, \tau)) \\ &\quad + \frac{1}{\tilde{R}(\tau)} (U(\tilde{\xi}, \tau) - \tilde{U}(\tilde{\xi}, \tau)) \end{aligned} \quad (8.11)$$

and each term on the right-hand side is bounded either by $C \|\xi - \tilde{\xi}\|$ or by $C \|U - \tilde{U}\|_{C^0}$.

Integrating (8.11) from τ to t , we then get

$$\begin{aligned} & \|\xi(\tau; s, t) - \tilde{\xi}(\tau; s, t)\| \\ & \leq CT \|U - \tilde{U}\|_{C^0} + C \int_{\tau}^t \|\xi(\bar{\tau}; s, t) - \tilde{\xi}(\bar{\tau}; s, t)\| d\bar{\tau}, \end{aligned}$$

so that, by Gronwall's inequality,

$$\|\xi(\tau; s, t) - \tilde{\xi}(\tau; s, t)\| \leq CT \|U - \tilde{U}\|_{C^0}. \quad (8.12)$$

We now return to (8.10) and set

$$Z(t) = \max_{s \in [0,1]} \|X(s, t) - \tilde{X}(s, t)\|.$$

By (8.12),

$$\begin{aligned} \|I_1\| & \leq \left\| \frac{\partial X_0}{\partial \rho} \right\|_{C^0} \|\xi(0; s, t) - \tilde{\xi}(0; s, t)\| \\ & \leq CT \|U - \tilde{U}\|_{C^0} \end{aligned}$$

and

$$\begin{aligned} \|I_2\| & \leq C \int_0^t \left(\|X(\xi(\tau; s, t), \tau) - \tilde{X}(\xi(\tau; s, t), \tau)\| \right. \\ & \quad \left. + \|\tilde{X}(\xi(\tau; s, t), \tau) - \tilde{X}(\tilde{\xi}(\tau; s, t), \tau)\| \right) d\tau \\ & \leq \int_0^t \left(Z(\tau) + \left\| \frac{\partial \tilde{X}}{\partial \rho} \right\| \|\xi(\tau; s, t) - \tilde{\xi}(\tau; s, t)\| \right) d\tau \\ & \leq C \int_0^t Z(\tau) d\tau + CT \|U - \tilde{U}\|_{C^0}. \end{aligned}$$

Similarly,

$$\|I_3\|, \|I_4\|, \|I_5\| \leq C \int_0^t Z(\tau) d\tau + CT \|U - \tilde{U}\|_{C^0}.$$

Substituting these estimates into (8.10) we find that

$$Z(t) \leq CT \|U - \tilde{U}\|_{C^0} + C \int_0^t Z(\tau) d\tau$$

and, consequently,

$$\max_{s \in [0,1]} \|X(s, t) - \tilde{X}(s, t)\| \leq CT \|U - \tilde{U}\|_{C^0}.$$

Similarly one can prove that

$$\|Y(s, t) - \tilde{Y}(s, t)\| \leq CT \|U - \tilde{U}\|_{C^0},$$

and therefore

$$\|J\| \leq CT \|U - \tilde{U}\|_{C^0}.$$

Substituting this and (8.8) into (8.7), we obtain the estimate

$$\|W - \tilde{W}\|_{C^0} \leq CT \|U - \tilde{U}\|_{C^0}. \quad (8.13)$$

To estimate $\partial(W - \tilde{W})/\partial\rho$ we note that

$$\begin{aligned} \frac{\partial W}{\partial\rho} = & -\frac{2R(t)}{\rho^3} \int_0^\rho s^2 [3u'_s(0) + (\lambda + \mu)X(s, t) + \mu Y(s, t)] ds \\ & + R(t) [3u'_s(0) + (\lambda + \mu)X(\rho, t) + \mu Y(\rho, t)]. \end{aligned}$$

Proceeding as before, one can prove that

$$\left\| \frac{\partial W}{\partial\rho} - \frac{\partial \tilde{W}}{\partial\rho} \right\|_{C^0} \leq CT \|U - \tilde{U}\|_{C^0},$$

and together with (8.13) we get

$$\|W - \tilde{W}\|_{C^{1,0}} \leq CT \|U - \tilde{U}\|_{C^0} \leq CT \|U - \tilde{U}\|_{C^{1,0}}.$$

This completes the proof that $\mathcal{F}$ is a contraction provided T is sufficiently small. We conclude that there exists a unique solution to (6.2)–(6.9) for $0 \leq t \leq T$. Finally, the estimates (8.1), (8.2) follow from Theorem 7.1. $\square$

9. Global existence and convergence of $R(t)$ to zero

Theorem 9.1. *Let $(x_s, y_s, v_s) = (0, 1 - \frac{\delta}{\mu}, \frac{\delta}{\nu}(1 - \frac{\delta}{\mu}))$ where $\delta < \mu$ and assume that*

$$p_0 > \frac{\mu(\lambda + \delta)}{\delta(\mu - \delta)}. \quad (9.1)$$

If

$$\|X_0(\rho), Y_0(\rho), V_0(\rho)\|_{C^1[0,1]} \leq \varepsilon \quad (9.2)$$

where ε is sufficiently small, then there exists a unique global solution $(X(\rho, t), Y(\rho, t), V(\rho, t), U(\rho, t), R(t))$ of (6.2)–(6.9) for all $t > 0$ with $R \in C^1[0, \infty)$, (X, Y, V, U) in $C^1([0, 1] \times [0, \infty))$; furthermore (8.1) and (8.2) hold for all $t > 0$, and

$$\dot{R}(t) < 0 \quad \text{for all } t > 0, \quad (9.3)$$

$$R(0)e^{-\frac{\delta}{2}t} \leq R(t) \leq R(0)e^{-\frac{\delta}{4}t} \quad \text{for all } t > 0. \quad (9.4)$$

Proof. We wish to continue the local solution established in Theorem 8.1 to all $t > 0$. In order to do that we assume that the solution exists for all $t < \tilde{T}$, having

the properties asserted in Theorem 8.1, so that, in particular, (8.1), (8.2) hold for all $t < \tilde{T}$.

Then, by (6.7), (6.9) and the relation $u'_s(0) = -\delta/3$ we have

$$\dot{R}(t) = R(t) \int_0^1 s^2 [-\delta + (\lambda + \mu)X + \mu Y] ds. \quad (9.5)$$

Using (8.1) we find that

$$\dot{R}(t) < 0, \quad (9.6)$$

$$-\frac{\delta}{2} < \frac{\dot{R}(t)}{R(t)} < -\frac{\delta}{4} \quad (9.7)$$

provided ε in (9.2) is sufficiently small. It follows that (9.3) and (9.4) hold. Then, by (6.7), (6.9) and (8.1),

$$\begin{aligned} & \left| -\frac{\dot{R}(t)}{R(t)} + \frac{U_\rho(\rho, t)}{R(t)} \right| \\ &= \left| -\int_0^1 s^2 [(\lambda + \mu)X(s, t) + \mu Y(s, t)] ds \right. \\ &\quad \left. - \frac{2}{\rho^3} \int_0^\rho s^2 [(\lambda + \mu)X(s, t) + \mu Y(s, t)] ds \right. \\ &\quad \left. + [(\lambda + \mu)X(\rho, t) + \mu Y(\rho, t)] \right| \\ &\leq 2[(\lambda + \mu) \|X(\rho, t)\|_{C^0} + \mu \|Y(\rho, t)\|_{C^0}] \\ &\leq 2(\lambda + \mu) M_0 e^{-\alpha t} \| (X_0(\rho), Y_0(\rho)) \|_{C[0,1]} \end{aligned} \quad (9.8)$$

so that

$$\left| -\frac{\dot{R}(t)}{R(t)} + \frac{U_\rho(\rho, t)}{R(t)} \right| \leq M \| (X_0(\rho), Y_0(\rho)) \|_{C[0,1]} e^{-\alpha t} \quad \text{for } t < \tilde{T}, \quad (9.9)$$

where $M = 2(\lambda + \mu)M_0$. Note also (by (9.7)) that $R(t)$ remains uniformly positive for $0 < t < \tilde{T}$. Furthermore, by the argument used in Lemma 6.2 we can deduce from (8.1), (8.2) and (9.9) that

$$X(\cdot, \tilde{T} - \eta_0), \quad Y(\cdot, \tilde{T} - \eta_0), \quad V(\cdot, \tilde{T} - \eta_0)$$

remain uniformly small in the $C^{1,0}[0, 1]$ -norm for all η_0 positive. These facts allow us to apply Theorem 8.1 with initial data at $t = \tilde{T} - \eta_0$ (η_0 arbitrarily small) and thus extend the solution and the estimates (8.1), (8.2) to $0 < t < \tilde{T} + \tilde{\eta}$ for some $\tilde{\eta} > 0$. Since $\tilde{T}$ is arbitrary, the solution can thus be extended to all $t > 0$ together with the desired estimates. $\square$

Remark 9.1. The proof of Theorem 9.1 was based on the fact that the eigenvalues of the matrix A are negative. This condition implies the decay estimate (6.33) which was needed in establishing Lemma 6.2 and Theorems 7.1, 8.1 and 9.1.

Remark 9.2. The assumptions made in Theorem 9.1 on the parameters $\delta, \lambda, \mu, \rho_0$ overlap with the estimated values of these parameters, as given at the end of Section 3. The same remark applies to Theorem 10.1.

10. The case (5.9)

Now consider the stationary solution $(x_s, y_s) = (x_*, y_*)$ given in (5.9), with $v_s = \frac{\delta}{\gamma} y_s$, under the condition (5.10). In this section we prove, for this case, a result similar to Theorem 9.1.

Theorem 10.1. *Let $\mu = s\delta$, $s > 0$ and assume that*

$$(s - 1)p_0 < s \quad (10.1)$$

and

$$\lambda \text{ is sufficiently small.} \quad (10.2)$$

Then the assertion of Theorem 9.1 holds with

$$x_s = x_*, \quad y_s = y_*, \quad v_s = \frac{\delta}{\gamma} y_*$$

and with δ , in (9.5), replaced by the positive number $-(-\mu + (\lambda + \mu)x_s + \mu y_s)$.

Proof. The proof is the same as for Theorem 9.1 provided we can establish that

$$\text{all eigenvalues of the matrix } A \text{ have negative real parts} \quad (10.3)$$

Indeed, as mentioned in Remark 9.1, the condition (10.3) enables us to establish Lemma 6.2 and to extend the proofs of Theorems 7.1, 8.1 and 9.1. In the present case

$$A = \begin{pmatrix} (\lambda + \mu) - (p_0\delta + \mu)y_* - 2(\lambda + \mu)x_* & -\mu x_* \\ (p_0\delta - \lambda - \mu)y_* & -(\delta - \mu) - (\lambda + \mu)x_* - 2\mu y_* \end{pmatrix}.$$

If we take

$$\lambda = 0, \quad \mu = s\delta, \quad s > 0$$

then we get

$$A = \frac{\delta}{p_0^2} \begin{pmatrix} -s(1-s)p_0 - s^2 & -s(1-s)p_0 - s^2 \\ s(p_0 - s)(p_0 - 1) - (1-s)p_0^2 - sp_0 - s^2(p_0 - 1) \end{pmatrix}.$$

This matrix has eigenvalues

$$-\frac{\delta s}{p_0} \text{ and } \frac{\delta}{p_0}(p_0 s - p_0 - s),$$

so that (10.3) is satisfied if (10.1) holds. By the continuity property of the eigenvalues, (10.3) still holds if (10.1) is satisfied and λ is sufficiently small. $\square$

Remark 10.1. If $\mu < \delta$ then $s < 1$ and thus (9.1) is satisfied for any $p_0 > 0$. If $\mu > \delta$ then (9.1) is satisfied provided

$$0 < p_0 < \frac{\mu}{\mu - \delta}.$$

Remark 10.2. In the case (5.6) the matrix A has the form

$$A = \begin{pmatrix} \lambda + \mu & 0 \\ 0 & \mu - \delta \end{pmatrix}.$$

A special solution is $\tilde{x} \equiv \tilde{y} \equiv \tilde{v} \equiv 0$ with $R(t) = R(0)e^{-\mu t}$. Since at least one eigenvalue is positive, the hyperbolic system (6.2)–(6.3) is linearly unstable and we are unable to establish the nonlinear asymptotic stability as in Theorems 9.1 and 10.1.

Remark 10.3. Theorems 9.1 and 10.1 can be extended to the case $\kappa_0 = 0$ provided we drop the boundary condition (2.15). In this case the system for $(\hat{x}, \hat{y}, \hat{v})$ is hyperbolic, and the forward $\hat{v}$ -characteristics go from the free boundary into the tumor region. The proofs exploits [27, Theorem 3.1] on *row diagonally dominant* hyperbolic systems and the fact that the characteristics of the two equations (2.1) and (2.2) coincide.

11. Proof of Theorem 2.1

In proving Theorem 2.1 there is no point in making the transformation (6.1); we work directly with the system (2.19)–(2.28). We replace the spaces E_T and S_T (introduced in Sections 6 and 7) by the following spaces:

$$\begin{aligned} \tilde{E}_T = \{ & \tilde{u}(\rho, t) \in C^{1,0}([0, 1] \times [0, T]); \tilde{u}(0, t) = 0, \tilde{u}(\rho, 0) = \tilde{u}_0(\rho), \\ & R(t) > 0, \quad \left| \frac{\dot{R}(t)}{R(t)} \right| \leq \sigma, \\ & \left| -\frac{\dot{R}(t)}{R(t)} + \frac{\tilde{u}_\rho(\rho, t)}{R(t)} \right| \leq M \} \end{aligned}$$

where $R(t)$ is defined by (6.11) with $U = \tilde{u}$, $\tilde{u}_0(\rho)$ is defined by the right-hand side of (6.10), $\sigma = \frac{1}{2} \min\{\lambda, \mu\}$, and $M = 2(\lambda + 2\mu)$;

$$\begin{aligned} \tilde{S}_T = \{ & \tilde{y}(\xi(t), t) : \tilde{y}(\xi(t), t), \frac{\partial \tilde{y}}{\partial \rho}(\xi(t), t) \in C[0, T], \\ & 0 \leq \tilde{y}(\xi(t), t) \leq 1, \text{ and} \\ & \left| \frac{\partial \tilde{y}}{\partial \rho}(\xi(t), t) \right| \leq Ce^{\eta t} \} \end{aligned}$$

where $\xi(t)$ is any forward characteristic curve, initiating at $t = 0$, of the hyperbolic system (2.19)–(2.20). Here C and η are positive constants to be chosen later on.

The proof of Theorem 2.1 is divided into three steps:

Step 1. Given any $\tilde{u} \in \tilde{E}_T$ we define $R(t)$ by (2.25) and proceed to solve the hyperbolic-parabolic system (2.19)–(2.21), (2.23), (2.26) by a fixed-point method. To this end, we define the mapping

$$\mathcal{H} : \quad \tilde{\tilde{y}} \rightarrow \tilde{y} \quad (\tilde{\tilde{y}} \in \tilde{S}_T)$$

where $(\tilde{x}, \tilde{y})$ is the solution of the hyperbolic system (2.19)–(2.20) (with the initial condition $(\tilde{x}(\rho, 0), \tilde{y}(\rho, 0))$ as in (2.28)) in which $\tilde{v}$ is the solution of the parabolic problem (2.21), (2.23) with the initial condition $\tilde{v}(\rho, 0)$ as in (2.28) and with $\tilde{y}$ replaced by $\tilde{\tilde{y}}$.

Along the characteristic curve $\xi = \xi(t)$, the equation (2.19) has the form

$$\frac{D\tilde{x}}{Dt} = A_1(\xi(t), t)\tilde{x}.$$

We easily conclude that if $\tilde{x}(\rho, 0)$ is non-negative for $0 \leq \rho \leq 1$ then $\tilde{x}(\xi(t), t)$ remains non-negative, i.e.

$$\tilde{x}(\xi(t), t) \geq 0. \quad (11.1)$$

On the other hand, from $\tilde{\tilde{y}} \geq 0$ and the parabolic comparison principle we easily get $\tilde{v} \geq 0$. Combining this and (11.1), we deduce from the equation (2.20) (along the characteristic $\xi = \xi(t)$) the inequality

$$\frac{D\tilde{y}}{Dt} \geq A_2(\xi(t), t)\tilde{y}.$$

It follows that

$$\tilde{y}(\xi(t), t) \geq 0. \quad (11.2)$$

In a similar way we easily get $\tilde{n}(\xi(t), t) \equiv 1 - \tilde{x}(\xi(t), t) - \tilde{y}(\xi(t), t) \geq 0$, i.e.,

$$\tilde{x}(\xi(t), t) + \tilde{y}(\xi(t), t) \leq 1. \quad (11.3)$$

Proceeding as in the proof of Lemma 6.1 we derive estimates

$$|\tilde{v}| \leq C_1 e^{\tilde{\eta}t}, \quad (11.4)$$

$$\left| \frac{\partial \tilde{v}}{\partial \rho} \right| \leq C_2 e^{\tilde{\eta}t}. \quad (11.5)$$

where C_1, C_2 and $\tilde{\eta}$ are positive constants. Here the comparison functions used to estimate $\pm \tilde{v}$ and $\pm \partial \tilde{v} / \partial \rho$ are of the form $\tilde{C} e^{\tilde{\eta}t}$ where $\tilde{\eta}$ is any positive number larger than $\gamma + \sigma$ and $\tilde{C}$ depends on the L^∞ bounds of the initial data of $\tilde{v}$ and $\partial \tilde{v} / \partial \rho$.

Using (11.1)–(11.5) and proceeding as in the proof of Lemma 6.2 we can prove that there exist two positive constants C, η independent of T such that

$$\left| \frac{\partial \tilde{y}}{\partial \rho}(\xi(t), t) \right| \leq C e^{\eta t}. \quad (11.6)$$

If we use these C, η in the definition of the space $\tilde{S}_T$ then we conclude that $\mathcal{H}$ maps $\tilde{S}_T$ into itself. Arguing as in the proof of Theorem 7.1 we can also show that $\mathcal{H}$ is a contraction provided T is sufficiently small. We conclude that there exists a unique local solution of (2.19)–(2.21), (2.23) and (2.26) for a given $\tilde{u} \in \tilde{E}_T$ and $R(t)$ defined by (2.25).

Step 2. We define a mapping

$$\mathcal{F} : \tilde{u}(\rho, t) \rightarrow \tilde{w}(\rho, t) \quad (\tilde{u} \in \tilde{E}_T)$$

by

$$\begin{aligned} \tilde{w}(\rho, t) &= \frac{R(t)}{\rho^2} \int_0^\rho s^2 [-\mu + (\lambda + \mu)\tilde{x}(s, t) + \mu\tilde{y}(s, t)] ds, \\ \tilde{w}(0, t) &= 0 \end{aligned} \quad (11.7)$$

where $(\tilde{x}(\rho, t), \tilde{y}(\rho, t))$ is the solution of the hyperbolic-parabolic system (2.19)–(2.21), (2.23), (2.26) for a given $\tilde{u} \in \tilde{E}_T$ and $R(t)$ defined by (2.25).

Note that from (2.22), (2.25) and (11.1)–(11.3) we get

$$-\frac{\mu}{3}R(t) \leq \dot{R}(t) \leq \frac{\lambda}{3}R(t) \quad (11.8)$$

and, similarly to (8.5), the inequality

$$\left| -\frac{\dot{R}(t)}{R(t)} + \frac{\tilde{w}_\rho(\rho, t)}{R(t)} \right| \leq 2(\lambda + 2\mu) = M \quad (11.9)$$

holds for $0 < t < T$. From (11.9) it follows that

$$R(0)e^{-\mu t/3} \leq R(t) \leq R(0)e^{\lambda t/3} \quad (11.10)$$

and

$$\left| \frac{\dot{R}(t)}{R(t)} \right| \leq \max \left\{ \frac{\lambda}{3}, \frac{\mu}{3} \right\} = \sigma. \quad (11.11)$$

We conclude that $\tilde{w} \in \tilde{E}_T$

Proceeding as in the proof of Theorem 8.1, we can next prove that $\mathcal{F}$ maps $\tilde{E}_T$ into itself provided T is sufficiently small, and

$$\| \tilde{w}_1 - \tilde{w}_2 \|_{C^{1,0}} \leq CT e^{\eta T} \| \tilde{u}_1 - \tilde{u}_2 \|_{C^0} \leq CT e^{\eta T} \| \tilde{u}_1 - \tilde{u}_2 \|_{C^{1,0}} \quad (11.12)$$

where $\tilde{w}_i = \mathcal{F}\tilde{u}_i$, $\tilde{u}_i \in \tilde{E}_T$ ($i = 1, 2$), i.e., $\mathcal{F}$ is a contraction provided T is sufficiently small. We conclude that there exists a unique solution (2.19)–(2.28) for $0 \leq t \leq T$.

Step 3. We wish to continue the local solution established in *Step 2* to all $t > 0$. We assume that the solution has been established for all $t < \tilde{T}$, and we want to extend it to some time $t = \tilde{T} + \tau_1$. In this process we assume that (11.8)–(11.11) and (11.5), (11.6) hold for $t < \tilde{T}$ with constants which are independent of $\tilde{T}$. We can then proceed as in Steps 1, 2, starting from the initial time $t = \tilde{T} - \tau_0$ (τ_0 arbitrarily small) and establishing both the extension of the solution and extension of the same estimates as before to $0 < t < \tilde{T} + \tau_1$, for some $\tau_1 > 0$. We can also proceed somewhat differently by starting with the initial time $t = 0$, but working with the subspaces of $\tilde{E}_{\tilde{T}+\tau_1}$, $\tilde{S}_{\tilde{T}+\tau_1}$ for which the $\tilde{u}$ (in $\tilde{E}_{\tilde{T}+\tau_1}$) coincide the $\tilde{u}$ -component of the solution already constructed in $0 < t < \tilde{T}$, and the $\tilde{y}$ (in $\tilde{S}_{\tilde{T}+\tau_1}$) coincides with the $\tilde{y}$ -component of the solution in $0 < t < \tilde{T}$.

12. Conclusion

We have considered a mathematical model for cancer therapy based on injection of genetically engineered virus into the tumor. The virus selectively infects tumor cells by binding to their surface, replicating inside them, and eventually causing lysis. Thereupon the virus particles burst out and proceed to infect adjacent cells. The mathematical model is formulated as a moving boundary problem for a non-linear hyperbolic-parabolic system of partial differential equations. The unknowns are the radius of the tumor $r = R(t)$, the evolving densities $x(r, t)$, $y(r, t)$, $n(r, t)$ and $v(r, t)$ of the uninfected cells, the infected cells, the necrotic cells and the virus particles, and the velocity field $u(r, t)$. Clinical trials and the size of the rate parameters suggest that one should study the behavior of solutions not only for small and intermediate times but also for large times.

We established the existence of a unique solution to the model, and then considered the problem of determining the effect that the injection of virus has on reducing the growth of the tumor.

We showed that the size of the tumor can be reduced in a very short time if the injected viral density is sufficiently large. However, because of possible adverse side effects, it is desirable to achieve reduction of the tumor with small dosage. The problem then arises: What is the optimal dosage? There is no unique answer to this question since it is difficult to quantify the harm done by side effects.

We have found, however, that for two pairs of initial densities

$$x(r, 0) \sim \text{const.} = x_s, \quad y(r, 0) \sim \text{const.} = y_s$$

the following is true:

Given *any* initial radius $R(0)$, by injecting virus particles of density

$$v(r, 0) \sim \text{const.} \equiv v_s \quad \text{where } v_s = \frac{\delta}{\gamma} y_s,$$

the radius $R(t)$ will decrease monotonically and exponentially to zero as t increase to ∞ .

These two examples suggest that one may reduce tumors with doses of viral densities that are not necessarily large. Thus, searching for "optimal" amounts of doses, as well as determining "optimal" schedules of injections, are promising areas for future research. Here we list several open problems in this direction:

- (1) Given initial tumor's radius $R(0)$ and initial densities $x = \theta$, $y = 0$ (i.e., all living cells are uninfected, and the density of the necrotic cells is $1 - \theta$), what is the smallest amount of viral density V_0 which will reduce the tumor size to $\frac{1}{2}R(0)$ by time T ?
- (2) Is it preferable to administer the viral dosage V_0 in two portions, one at time $t = 0$ with density αV_0 , and another at time $t = t_1$ with density $(1 - \alpha)V_0$? (Take, as terminal time T at which $R(T)$ is to be minimized, $T = n$ weeks, $n = 3, 4, 5, 6$).
- (3) In the clinical trials reported in [4] [24] [25] [30] [32] [35] equal amounts of viral doses were injected once a week. Can one do better by using a different schedule?

One may try to explore these problems using control theory combined with numerical simulations. The global existence and uniqueness theorem that we established in this paper (Theorem 2.1) shows that our model, although based on a number of simplifying assumptions, can be used as a rigorous tool for initial explorations of the above problems.

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