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To our mentor Professor Avner Friedman

and to our parents and families

Preface

(under revision) This book is devoted to the topics of tumor growth and treatment, chemotactic driven cell movement, and cancer invasion. These topics were the focuses of the authors' research work in past decade. Cancers appear with multiscale features: genes, cells, and biological tissues. From the view point of scales, there are basically three types of mathematical models of cancer: microscopic models (at the molecular and the cellular scales), macroscopic models (at the tissue scale), multiscale model (the cancer model is viewed as a system of subsystems with specific scales). However, this book focuses only on macroscopic models which are generally based on partial differential equations.

Chapters 1-5 deal with the mathematical modeling of tumor growth under various therapies, whereas Chapters 6-8 are concerned with typical mathematical problems arising from cancer biology. To explore tumor dynamics and design possible optimal protocols of treatment, the models developed in chapters 1-5 are confined to a spherical geometry.

Chapter 1 deals with a model describing the growth of a prostate tumor under hormone therapy. The model considers the mutation by which androgen-dependent tumor cells mutate into androgen-independent ones. Interestingly, explicit formulae of tumor growth in an androgen-deprived environment are found. The relapse of tumor is a crucial problem in hormonal therapy of prostate cancer. The androgen-independent cells are considered to be responsible for such a recurrence. These cells are not sensitive to androgen suppression but rather apt to proliferate even in an androgen-poor environment. Some experimental and clinical studies suggested that intermittent androgen suppression (IAS) may delay or prevent the relapse when compared with continuous androgen suppression. A mathematical model of prostate tumor growth under the IAS therapy is presented in Chapter 2, and the model suggests an optimal protocol of the IAS therapy.

Replication-competent viruses have been used an alternative therapeutic approach for cancer treatment. However, new clinical data revealed an innate immune response to virus may mitigate the effects of treatment. Chapter 3 is concerned with the competitive dynamics between tumor cells, a replication-competent virus and an immune response. It finds an explicit threshold of the intensity of the immune response for controlling a tumor. Chapter 4 deals with a mathematical model of combined therapy which requires not only injection of viruses but also adminstration of radioiodide. The combination of virotherapy with radiotherapy has recently been experimentally and clinically shown to be significantly more effective than treatment with virotherapy alone. The

mathematical model not only verifies the above observation but also can be used to numerically study an optimal timing for radio-iodine administration and an optimal dose for the radioactive iodide.

Glioblastoma multiforme, a type of glioma, is the most aggressive of brain tumors. The standard treatment for newly diagnosed glioblastoma multiforme is surgical resection followed by radiotherapy and chemotherapy. Chapter 5 gives a mathematical model which could predict the survival time of patients who undergo resection, radiation, and chemotherapy with different protocols.

Chapter 6 qualitatively studies a mathematical model describing the cell cycle dynamics and chemotactic driven cell movement in multicellular tumor spheroids. The model is a free boundary problem for a system of partial differential equations with novel free boundary conditions due to different velocities of cells.

Chapter 7 deals with a chemotaxis-haptotaxis model of cancer invasion. The global existence and uniform-in-time boundedness of solutions to the system is studied. This chapter develops some new a priori estimate techniques for chemotaxis-haptotaxis systems. Chapter 8 is concerned with a density-dependent chemotaxis-haptotaxis model of cancer invasion. The equation for cell density includes two bounded nonlinear density-dependent chemotactic and haptotactic sensitivity functions, which exclude the possibility of blow-up of solutions to the model.

Our work, and this book, would not have been possible without the guidance from Avner Friedman, who introduced the authors to the research field of cancer models.

We would like to express our gratitude to our research collaborators, particularly Kazuyaki Aihara, Qian Guo, Michael Winkler, ... for their helpful and inspiring cooperation in the past decade. Finally, Tao acknowledges the supports of the National Natural Science Foundation of China (NSFC10571023) and the Natural Science Foundation of Shanghai (09ZR1401200); Tian acknowledges the supports of the National Science Foundation of US (DMS-1446139) and the National Natural Science Foundation of China (NNSF-11371048).

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Modeling Prostate Tumor Growth under Androgen Suppression

2.1 Introduction

The prostate cancer is the secondly most common cancer in males after the lung cancer [53]. More than 670,000 men are diagnosed with prostate cancers every year in the world, and that accounts for one in nine of all new cancers in men. The United States and Sweden have the highest incidence rate of prostate cancers, while China and India have the lowest incidence rate [87]. The chestnut-shaped prostate gland under the bladder is a male sexual organ which produces seminal fluid. The proliferation and apoptosis of prostate cells are regulated by androgens. Prostate cancers are characterized as an abnormal and uncontrolled growth of prostate cancer cells. At present, the cause of prostate cancers is not fully understood, although it was found that many factors such as gene mutations, aging, family history, race, and diet may influence the development of prostate cancers [102, 135].

The growth of prostate tumors depends on androgens. Androgens are secreted by the testicles and adrenal glands. In 1941, Huggin and Hodges

[88] pioneered (ADT) for prostate cancers. Since then, ADT has been an important treatment for prostate cancers. Androgen deprivation currently can be achieved by medical castration [83]. ADT stops androgen production from the testes. (TAB) which further combines anti-androgens with ADT is also widely used. However, both ADT and TAB seldom succeed in removing all prostate tumor cells, and relapses of prostate tumors often occur. The so-called androgen-independent (AI) cells are considered to be responsible for tumor relapses. These cells are not sensitive to androgen suppression but rather apt to proliferate even in an androgen-poor environment [16, 90]. Since androgen dependent (AD) cells cannot proliferation under the androgen deprivation condition, a prostate tumor relapse would imply some increase of AI cells. Several mechanisms have been identified for progression of AD cells to AI cells. These include androgen receptor (AR) gene amplification, AR mutation, and bypass of androgenic activation of AR or of AR signaling itself [83, 102, 113]. Hence, the continuous androgen suppression (CAS) therapy with ADT and TAB often results in an AI relapse.

To our knowledge, Jackson [95, 96] developed the first partial differential equation model for the CAS therapy of prostate cancers. The model considers a prostate tumor as a heterogeneous mixture of AD and AI cells, and it is assumed that a relapse of a prostate tumor can possibly result from decreasing the apoptotic rate of the AI cells by androgen-deprivation. Jackson's model well agrees with experimental observations. This model predicts that the CAS therapy is successful only for some small ranges of biological parameters. The

model also suggests that an androgen-independent relapse is associated with decreasing of apoptosis while without increasing of proliferation [95, 96].

In this chapter, we will first extend Jackson's model. Our model will incorporate mutation inhibitors [154]. By the mutation we mean that androgen-dependent (AD) prostate tumor cells mutate into androgen-independent (AI) prostate tumor cells, and by mutation inhibitors we mean inhibition effects to the mutation rates. As afore-mentioned, the relapse of tumors is a crucial problem in hormonal therapy of prostate cancers. Currently we know that there are two possible mechanisms that a prostate tumor can recur [91]. One is mutation or adaptation where AD cells mutate into AI cells under the androgen deprived condition. The other is selection or competition where AI cells are minor but exist from the beginning of the therapy and they will dominate under androgen suppression condition. These two recurrence mechanisms have *different* effects on the prostate tumor relapse, and they may work together. However, we will first consider the mutation mechanism of prostate tumor relapse under continuous androgen suppression.

Qualitative analysis suggests that a tumor relapse cannot be avoided under androgen-deprived therapy. This implication may support a possible strategy of intermittent androgen suppression (IAS). Intermittent androgen suppression is a type of androgen ablative therapy delivered intermittently with off-treatment periods [17]. Actually, there are several mathematical models that study prostate tumor growth under IAS therapy. We will also

review a mathematical model that considers the mutation mechanism of prostate tumor relapse under intermittent androgen suppression.

2.2 Mathematical Model for Continuous Androgen Suppression

Following [95, 96], the prostate tumor is viewed as a densely packed and radially-symmetric sphere. We denote $R(t)$ as the radius of the tumor sphere. The tumor contains both AD and AI cells, and their number densities are denoted by $x_1(r,t)$ and $x_2(r,t)$, respectively. Since the level of androgens within the tissue under consideration can be regulated by medical methods [17, 18, 95, 96], we neglect spatial heterogeneity of androgens within the prostate tumor tissue. The tumor is assumed to be incompressible fluids with a velocity field $\mathbf{v}$ ($v := \mathbf{v}\cdot\mathbf{r}/|\mathbf{r}|$). The velocity field is caused by cell proliferation and death. The cell proliferation depends on the androgen level, $a(t)$. In solid tumor growth modeling, it is usually assumed that cell movement has two components: 1) motion due to the velocity $\mathbf{v}(\mathbf{r},t)$ [93, 94, 168], and 2) random motion [20, 66, 73, 74]. We exploit the spherical symmetry of the problem by assuming henceforth that the variables x_1, x_2, and $\mathbf{v}$ depend only on (r,t) where r is the radial distance from the center of the tumor, and t is time. As an extension of the model [95, 96], the model we consider consists of the following equations:

$$\begin{aligned}
&\frac{\partial x_1}{\partial t}(r,t) + \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 v(r,t)x_1(r,t)\Big) \\
&\quad = \frac{D_1}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial x_1}{\partial r}(r,t)\Big) \\
&\qquad + p_1(a(t))x_1(r,t) - q_1(a(t))x_1(r,t) \\
&\qquad - (1-I)m(a(t))x_1(r,t), \qquad (2.1)\\
&\frac{\partial x_2}{\partial t}(r,t) + \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 v(r,t)x_2(r,t)\Big) \\
&\quad = \frac{D_2}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial x_2}{\partial r}(r,t)\Big) + (1-I)m(a(t))x_1(r,t) \\
&\qquad + p_2(a(t))x_2(r,t) - q_2(a(t))x_2(r,t), \qquad (2.2)
\end{aligned}$$

where D_1 and D_2 are the random motility coefficients of the AD and AI cells; $p_1(a(t))$ and $p_2(a(t))$ are proliferation rates of the AD and AI cells; $q_1(a(t))$, and $q_2(a(t))$ are their apoptosis rates; $m(a(t))$ is the mutation rate by which AD cells mutate to AI ones. The intensity of the inhibitors that reduces the mutation rate is represented by parameter I, which varies from zero to one. $I = 0$ corresponds to no inhibition to the mutation, while $I = 1$ corresponds to the full inhibition to the mutation. So, the rate at which cells mutate from the AD type to AI type is given by $(1-I)m(a(t))$. The cell proliferation rate, apoptotic rate, and mutation rate are assumed to be dependent on the local concentration of androgens, $a(t)$.

It is a fact that within a tumor the total number of cells per unit volume is constant [95, 96, 168]. Hence,

$$x_1 + x_2 = k \equiv \text{constant}. \qquad (2.3)$$

Equations (2.1) and (2.2) with assumption (2.3) yield

$$\frac{k}{r^2}\frac{\partial}{\partial r}\Big(r^2 v(r,t)\Big) = (D_1 - D_2)\frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial x_1}{\partial r}(r,t)\Big) + p_1(a(t))x_1(r,t)$$
$$+p_2(a(t))(k - x_1(r,t)) - q_1(a(t))x_1(r,t)$$
$$-q_2(a(t))(k - x_1(r,t)). \tag{2.4}$$

By the radial symmetry assumption of the problem, we have

$$\frac{\partial x_1}{\partial r}(0,t) = \frac{\partial x_2}{\partial r}(0,t) = v(0,t) = 0. \tag{2.5}$$

To close the system of the equations, we need to impose boundary and initial conditions.

Boundary Conditions: We assume that there is no-flux of cancer cells across the outer boundary of the tumor. This assumption gives the following equations,

$$\begin{cases} \Big[x_1(r,t)\dfrac{dR(t)}{dt} - \Big(x_1(r,t)v(r,t) - D_1\dfrac{\partial x_1}{\partial r}(r,t)\Big)\Big]_{r=R(t)} = 0, \\ \Big[x_2(r,t)\dfrac{dR(t)}{dt} - \Big(x_2(r,t)v(r,t) - D_2\dfrac{\partial x_2}{\partial r}(r,t)\Big)\Big]_{r=R(t)} = 0, \end{cases} \tag{2.6}$$

which, together with (2.3), yield the free boundary conditions:

$$\begin{cases} \dfrac{dR(t)}{dt} - v(R(t),t) = 0, \\ \dfrac{\partial x_1}{\partial r}(R(t),t) = 0. \end{cases} \tag{2.7}$$

Initial Conditions: We prescribe the initial data as follows,

$$R(0) = R_0, \quad x_1(r,0) = x_{10}(r) \quad \text{for } 0 \le r \le R_0. \tag{2.8}$$

Remark 2.1. The *no-flux* boundary condition (2.6) is obtained by considering the *relative* velocities of cells on the outer boundary of the growing tumor. These types of no-flux boundary conditions for diffusion-advection equations in a moving domain $\{r \le R(t)\}$ were firstly clarified by Tao [150].

Since $x_1 + x_2 = k$, it is not necessary to impose any additional initial condition for x_2 in Eq. (2.8). We also note that Eq. (1.2) is a consequence of Eqs. (2.1), (2.3) and (2.4), so in what follows we simply drop this equation.

After adopting the non-dimensional variables and some parameter values given in [95], the model (2.1)-(2.8) can be rewritten as follows:

$$\begin{aligned}
&\frac{\partial x_1}{\partial t}(r,t) + \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 v(r,t)x_1(r,t)\Big) \\
&\quad = \frac{\epsilon_1}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial x_1}{\partial r}(r,t)\Big) + p_1(a(t))x_1(r,t) - q_1(a(t))x_1(r,t) \\
&\qquad -(1-I)m(a(t))x_1(r,t), \qquad (2.9)\\
&\frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 v(r,t)x_1(r,t)\Big) \\
&\quad = p_1(a(t))x_1(r,t) + 1 - x_1(r,t) - q_1(a(t))x_1(r,t) \\
&\qquad -q_2(a(t))(1-x_1(r,t)), \qquad (2.10)\\
&\frac{dR}{dt} = v(R(t),t), \qquad (2.11)\\
&R(0) = 1, \quad x_1(r,0) = x_{10}(r), \qquad (2.12)\\
&\frac{\partial x_1}{\partial r}(0,t) = 0, \quad v(0,t) = 0, \qquad (2.13)\\
&\frac{\partial x_1}{\partial r}(R(t),t) = 0, \qquad (2.14)
\end{aligned}$$

where $0 < \varepsilon_1 \ll 1$ is some constant. The functions $a(t)$, $p_1(a(t))$, $q_1(a(t))$, $q_2(a(t))$, and $m(a(t))$ take the following specific forms (see [95] for details):

$$a(t) = e^{-bt} + a_s, \quad t \geq 0, \tag{2.15}$$

$$p_1(a(t)) = \theta_1 + (1 - \theta_1)\frac{a(t)}{a(t) + K}, \tag{2.16}$$

$$q_1(a(t)) = \delta_1\Big[\omega_1 + (1 - \omega_1)\frac{a(t)}{a(t) + K}\Big], \tag{2.17}$$

$$q_2(a(t)) = \delta_2\Big[\omega_2 + (1 - \omega_2)\frac{a(t)}{a(t) + K}\Big], \tag{2.18}$$

$$m(a(t)) = m_1\Big(1 - \frac{a(t)}{1 + a_s}\Big), \tag{2.19}$$

where b, K, m_1, δ_1, δ_2, ω_1, and ω_2 are some positive constants with the following assumed conditions:

$$0 \leq a_s < 1, \quad 0 \leq \theta_1 < 1, \quad \delta_1 < \delta_2, \quad \omega_1 > 1, \quad \text{and} \quad \omega_2 < 1. \tag{2.20}$$

In Eq. (2.15) we assume that the hormonal treatment is initiated at the time $t = 0$. The parameter $a_s > 0$ corresponds to ADT, while $a_s = 0$ corresponds to TAB. The parameter θ_1 represents the proliferation rate of AD cells in the androgen-deprived state. $0 \leq \theta_1 < 1$ means that the deprivation of androgens will decrease the proliferation rate of the AD cells. The assumption of $\delta_1 < \delta_2$ is due to the fact that the AD cells are dominant in androgen-rich conditions [52, 95, 96]. The assumption of $\omega_1 > 1$ and $\omega_2 < 1$ mean that the deprivation of androgens will increase the apoptosis rate of the AD cells but reduce that of AI cells [95]. Equation (2.19) assumes that the mutation rate $m(a(t))$ is decreasing with increasing the local concentration of androgens $a(t)$.

2.3 Transformation of Continuous Androgen Suppression Model

It is difficult to study free boundary problems, in general. We usually choose various transformations to change free boundary problems to fixed boundary problems. For the model we introduced above, we adopt, as shown in [145], the change of variables $(r,\ t,\ x_1,\ v,\ R) \mapsto (\rho,\ t,\ \tilde{x}_1,\ \tilde{v},\ R)$ as follows:

$$\begin{aligned} &\rho = r/R(t), \quad t = t, \quad R(t) = R(t), \\ &\tilde{x}_1(\rho,t) = x_1(\rho R(t),t), \quad \tilde{v}(\rho,t) = v(\rho R(t),t)/R(t). \end{aligned} \tag{2.21}$$

In terms of the new variables and after dropping the tildes of $\tilde{x}_1(\rho,t)$ and $\tilde{v}(\rho,t)$ for notational convenience, the system (2.9)-(2.14) takes the following form in $\{0<\rho<1,\ t>0\}$:

$$\begin{aligned} &\frac{\partial x_1}{\partial t}(\rho,t) + \big[v(\rho,t) - \rho v(1,t)\big]\frac{\partial x_1}{\partial \rho}(\rho,t) - \frac{\varepsilon_1}{R^2(t)}\frac{1}{\rho^2}\frac{\partial}{\partial \rho}\Big(\rho^2 \frac{\partial x_1}{\partial \rho}(\rho,t)\Big) \\ &= \big[p_1(a(t)) + q_2(a(t)) - 1 - q_1(a(t))\big]x_1(\rho,t)(1-x_1(\rho,t)) \\ &\quad -(1-I)m(a(t))x_1(\rho,t), \end{aligned} \tag{2.22}$$

$$x_1(\rho,0) = x_{10}(\rho), \tag{2.23}$$

$$\frac{\partial x_1}{\partial \rho}(0,t) = \frac{\partial x_1}{\partial \rho}(1,t) = 0, \tag{2.24}$$

$$\begin{aligned} v(\rho,t) = \frac{1}{\rho^2}\int_0^\rho &\big[p_1(a(t))x_1(s,t) + 1 - x_1(s,t) - q_1(a(t))x_1(s,t) \\ &-q_2(a(t))(1-x_1(s,t))\big]s^2 ds, \end{aligned} \tag{2.25}$$

$$\frac{dR(t)}{dt} = R(t)v(1,t), \tag{2.26}$$

$$R(0) = 1, \tag{2.27}$$

where we have used the fact that $v(0,t) = 0$ in deriving Eq. (2.25).

The global existence and uniqueness of solutions to the system (2.22)-(2.27) were prove by Tao et al. [154]. We do not give the results and proofs here, instead, in next section, we will review the dynamic behavior of tumor growth in the androgen-deprived environment.

2.4 Formulae of Prostate Tumor Dynamics under Continuous Androgen Suppression

For the general case where $a = a(t) \neq 0$ given in (2.15), the dynamics of prostate tumor growth can be numerically studied (see Tao et al. [154] for details). In this section, we shall focus on the dynamical behavior of prostate tumor growth in androgen-deprived environment. That is, we consider the case:

$$a = 0, \tag{2.28}$$

and therefore

$$p_1(a) = \theta_1,\ q_1(a) = \delta_1\omega_1,\ q_2(a) = \delta_2\omega_2,\ \text{and } m(a) = \beta_1. \tag{2.29}$$

Under the assumption (2.28), Eqs. (2.22)-(2.27) can be rewritten as follows:

$$\frac{\partial x_1}{\partial t}(\rho,t)+\big[v(\rho,t)-\rho v(1,t)\big]\frac{\partial x_1}{\partial \rho}(\rho,t)-\frac{\varepsilon_1}{R^2(t)}\frac{1}{\rho^2}\frac{\partial}{\partial \rho}\Big(\rho^2\frac{\partial x_1}{\partial \rho}(\rho,t)\Big)$$
$$=\big(\theta_1+\delta_2\omega_2-1-\delta_1\omega_1\big)x_1(\rho,t)(1-x_1(\rho,t))$$
$$-(1-I)m_1x_1(\rho,t), \tag{2.30}$$

$$x_1(\rho,0)=x_{10}(\rho), \tag{2.31}$$

$$\frac{\partial x_1}{\partial \rho}(0,t)=\frac{\partial x_1}{\partial \rho}(1,t)=0, \tag{2.32}$$

$$v(\rho,t)=\frac{1}{\rho^2}\int_0^\rho\big[\theta_1x_1(s,t)+1-x_1(s,t)-\delta_1\omega_1x_1(s,t)$$
$$-\delta_2\omega_2(1-x_1(s,t))\big]s^2ds, \tag{2.33}$$

$$\frac{dR(t)}{dt}=R(t)v(1,t), \tag{2.34}$$

$$R(0)=1. \tag{2.35}$$

Set $x_2(\rho,t):=1-x_1(\rho,t)$, and define

$$V_1(t):=4\pi R^3(t)\int_0^1 x_1(\rho,t)\rho^2d\rho,\quad V_2(t):=4\pi R^3(t)\int_0^1 x_2(\rho,t)\rho^2d\rho,$$

where $V_1(t)$ and $V_2(t)$ are the volumes occupied by AD cells and AI cells at time t, respectively. Then

$$V(t):=V_1(t)+V_2(t)\equiv\frac{4}{3}\pi R^3(t) \tag{2.36}$$

is the tumor volume at time t. In this section we will derive formulae of the tumor volume (or the tumor radius) at time t. The following results were obtained by Tao et al. [154].

Theorem 2.1. *Under various conditions about combined parameters* $\theta_1-\delta_1\omega_1-(1-I)m_1$ *and* $1-\delta_2\omega_2$*, the formulae for prostate tumor volume growth*

over time can be explicitly expressed. Specifically, the tumor volume growth formulae are given under the following 5 different conditions.

(1). If the condition 1, $\theta_1 - \delta_1\omega_1 - (1-I)m_1 = 0$ *and* $1 - \delta_2\omega_2 = 0$*, holds, then we have*

$$V(t) = \frac{4\pi}{3} + V_1(0)(1-I)m_1 t. \tag{2.37}$$

(2). If the condition 2, $\theta_1 - \delta_1\omega_1 - (1-I)m_1 = 0$ *and* $1 - \delta_2\omega_2 \neq 0$*, holds, then we have*

$$V(t) = V_1(0) + V_2(0)e^{(1-\delta_2\omega_2)t} + \frac{(1-I)m_1V_1(0)}{1-\delta_2\omega_2}\Big[e^{(1-\delta_2\omega_2)t} - 1\Big]. \tag{2.38}$$

(3). If the condition 3, $\theta_1 - \delta_1\omega_1 - (1-I)m_1 \neq 0$ *and* $1 - \delta_2\omega_2 = 0$*, holds, then we have*

$$\begin{aligned} V(t) = {} & V_2(0) + V_1(0)e^{[\theta_1 - \delta_1\omega_1 - (1-I)m_1]t} \\ & + \frac{(1-I)m_1V_1(0)}{\theta_1 - \delta_1\omega_1 - (1-I)m_1}\Big\{e^{[\theta_1 - \delta_1\omega_1 - (1-I)m_1]t} - 1\Big\}. \end{aligned} \tag{2.39}$$

(4). If the condition 4, $\theta_1 - \delta_1\omega_1 - (1-I)m_1 \neq 0$*,* $1 - \delta_2\omega_2 \neq 0$*, and* $\theta_1 - \delta_1\omega_1 - (1-I)m_1 = 1 - \delta_2\omega_2$*, holds, then we have*

$$V(t) = \big[V_2(0) + (1-I)m_1V_1(0)t\big]e^{(1-\delta_2\omega_2)t} + V_1(0)e^{[\theta_1 - \delta_1\omega_1 - (1-I)m_1]t}. \tag{2.40}$$

(5). If the condition 5, $\theta_1 - \delta_1\omega_1 - (1-I)m_1 \neq 0$*,* $1 - \delta_2\omega_2 \neq 0$*, and* $\theta_1 - \delta_1\omega_1 - (1-I)m_1 \neq 1 - \delta_2\omega_2$*, holds, then we have*

$$\begin{aligned} V(t) = {} & V_1(0)e^{[\theta_1 - \delta_1\omega_1 - (1-I)m_1]t} + V_2(0)e^{(1-\delta_2\omega_2)t} \\ & + \frac{(1-I)m_1V_1(0)e^{(1-\delta_2\omega_2)t}}{\theta_1 - \delta_1\omega_1 - (1-I)m_1 - 1 + \delta_2\omega_2}\Big\{e^{[\theta_1 - \delta_1\omega_1 - (1-I)m_1 - 1 + \delta_2\omega_2]t} - 1\Big\}. \end{aligned} \tag{2.41}$$

Proof. Combining Eqs. (2.30) and (2.32)-(2.34) and applying integration by parts, we directly calculate,

$$\begin{aligned}
\frac{1}{4\pi}\dot{V}_1(t) &= 3R^2(t)\dot{R}(t)\int_0^1 x_1\rho^2 d\rho + R^3(t)\int_0^1 \frac{\partial x_1}{\partial t}\rho^2 d\rho \\
&= 3R^3(t)v(1,t)\int_0^1 x_1\rho^2 d\rho + R^3(t)\int_0^1 \frac{\partial x_1}{\partial t}\rho^2 d\rho \\
&= 3R^3(t)v(1,t)\int_0^1 x_1\rho^2 d\rho \\
&\quad + R^3(t)\int_0^1 \Big[(\theta_1+\delta_2\omega_2-1-\delta_1\omega_1)x_1(1-x_1)-(1-I)m_1x_1\Big]\rho^2 d\rho \\
&\quad + \varepsilon_1 R(t)\int_0^1 \frac{\partial}{\partial\rho}\Big(\rho^2\frac{\partial x_1}{\partial\rho}\Big)d\rho \\
&\quad - R^3(t)\int_0^1 \Big[\rho^2 v(\rho,t)-\rho^3 v(1,t)\Big]\frac{\partial x_1}{\partial\rho}d\rho \\
&= 3R^3(t)v(1,t)\int_0^1 x_1\rho^2 d\rho \\
&\quad + R^3(t)\int_0^1 \Big[(\theta_1+\delta_2\omega_2-1-\delta_1\omega_1)x_1(1-x_1)-(1-I)m_1x_1\Big]\rho^2 d\rho \\
&\quad + \varepsilon_1 R(t)\Big(\rho^2\frac{\partial x_1}{\partial\rho}\Big)\Big|_{\rho=0}^1 \\
&\quad - R^3(t)\Big\{\Big[\rho^2 v(\rho,t)-\rho^3 v(1,t)\Big]x_1(\rho,t)\Big\}\Big|_{\rho=0}^1 \\
&\quad + R^3(t)\int_0^1 x_1\frac{\partial}{\partial\rho}\Big[\rho^2 v(\rho,t)\Big]d\rho - 3R^3(t)v(1,t)\int_0^1 x_1\rho^2 d\rho \\
&= R^3(t)\int_0^1 \Big[(\theta_1+\delta_2\omega_2-1-\delta_1\omega_1)x_1(1-x_1)-(1-I)m_1x_1\Big]\rho^2 d\rho \\
&\quad + R^3(t)\int_0^1 x_1\Big[\theta_1x_1+1-x_1-\delta_1\omega_1x_1-\delta_2\omega_2(1-x_1)\Big]\rho^2 d\rho \\
&= R^3(t)\int_0^1 \Big[\theta_1-\delta_1\omega_1-(1-I)m_1\Big]x_1\rho^2 d\rho \\
&= \frac{1}{4\pi}\Big[\theta_1-\delta_1\omega_1-(1-I)m_1\Big]V_1(t).
\end{aligned}$$

We obtain an ODE for $V_1(t)$,

$$\dot{V}_1(t) = [\theta_1-\delta_1\omega_1-(1-I)m_1]V_1(t). \tag{2.42}$$

This equation further yields

$$V_1(t) = V_1(0)e^{[\theta_1 - \delta_1\omega_1 - (1-I)m_1]t}. \tag{2.43}$$

Similarly, we combine Eqs. (2.36), (2.33), (2.34), and (2.42), and calculate

$$\begin{aligned}
\dot{V}_2(t) &= 4\pi R^2(t)\dot{R}(t) - \dot{V}_1(t) \\
&= 4\pi R^3(t)V(1,t) - [\theta_1 - \delta_1\omega_1 - (1-I)m_1]V_1(t) \\
&= 4\pi R^3(t)\int_0^1 \Big[\theta_1 x_1 + 1 - x_1 - \delta_1\omega_1 x_1 - \delta_2\omega_2(1-x_1)\Big]\rho^2 d\rho \\
&\quad -4\pi R^3(t)\int_0^1 \Big[\theta_1 - \delta_1\omega_1 - (1-I)m_1\Big]x_1\rho^2 d\rho \\
&= 4\pi R^3(t)\int_0^1 (1-\delta_2\omega_2)x_2\rho^2 d\rho \\
&\quad +4\pi R^3(t)\int_0^1 (1-I)m_1 x_1\rho^2 d\rho \\
&= (1-\delta_2\omega_2)V_2(t) + (1-I)m_1V_1(t).
\end{aligned}$$

This gives us an ODE equation for $V_2(t)$:

$$\dot{V}_2(t) = (1-\delta_2\omega_2)V_2(t) + (1-I)m_1V_1(t). \tag{2.44}$$

Now combining the initial condition(2.35), the tumor volume (2.36), and the expressions (2.43) and (2.44), we easily obtain (2.37)-(2.41). □

Remark 2.2. A necessary condition for successful treatments of prostate tumors was derived in [95]. Our Theorem 2.1 gives the *explicit formulae* of the tumor volume growth over time t in androgen-deprived environment. Therefore, the dynamics of the tumor growth in androgen-deprived environment can be predicted by these formulae. Although the formulae were derived under

the assumption of radial symmetry, it may be useful to predict the long-term behavior of tumor growth qualitatively.

From Theorem 2.1, we can derive some interesting analytical results about androgen deprivation therapy. To demonstrate, we look at several situations in the following.

Case 2.1. In Jackson's article [95], parameter values are given as

$$\delta_1 = \frac{0.3812}{0.4621},\ \delta_2 = \frac{0.4765}{0.4621},\ \theta_1 = 0.8,\ \omega_1 = 1.35,\ \omega_2 = 0.25.$$

For this set of typical paprameter values, we can easily verify that

$$\theta_1 - \delta_1\omega_1 < 0 \quad \text{and} \quad 1 - \delta_2\omega_2 > 0. \tag{2.45}$$

That means that the "*net*" growth rate of AD cells is negative whereas the "*net*" growth rate of AI cells is positive in androgen-deprived environment. It follows from (2.45) that

$$\theta_1 - \delta_1\omega_1 - 1 + \delta_2\omega_2 < 0. \tag{2.46}$$

This is a general case in Theorem 2.1. To explain biological significance, we now rewrite the formula (2.41) as follows:

$$\begin{aligned} V(t) \ = \ & \Big(V_1(0) + \frac{(1-I)m_1V_1(0)}{\theta_1 - \delta_1\omega_1 - (1-I)m_1 - 1 + \delta_2\omega_2}\Big)e^{[\theta_1 - \delta_1\omega_1 - (1-I)m_1]t} \\ & + \Big(V_2(0) - \frac{(1-I)m_1V_1(0)}{\theta_1 - \delta_1\omega_1 - (1-I)m_1 - 1 + \delta_2\omega_2}\Big)e^{(1-\delta_2\omega_2)t} \\ := \ & A(t) + B(t). \end{aligned} \tag{2.47}$$

If we further assume that

$$V_2(0) > 0,$$

namely, the initial volume occupied by AI cells is non-zero, then from (2.45) and (2.46) we have

$$A(t) \to 0 \quad \text{and} \quad B(t) \to +\infty, \qquad \text{as } t \to +\infty.$$

Therefore, from (2.47) we obtain

$$V(t) \to +\infty, \qquad \text{as} \quad t \to +\infty. \tag{2.48}$$

This result implies a prostate tumor relapse under androgen-deprived therapy. We should be aware of that (2.48) holds in a sense of mathematics, and it may not be biologically plausible. In fact, the host will die when the prostate tumor is large enough. However, (2.48) predicts eventual failure of the androgen-deprived therapy.

Case 2.2. Because

$$A(t) \to 0 \quad \text{and} \quad B(t) \to +\infty, \qquad \text{as} \quad t \to +\infty,$$

the term $B(t)$ will dominate the growth of a prostate tumor. We also notice that the factor of $B(t)$,

$$-\frac{(1-I)m_1}{\theta_1 - \delta_1\omega_1 - (1-I)m_1 - 1 + \delta_2\omega_2} \equiv 1 - \frac{(\delta_1\omega_1 - \theta_1) + (1 - \delta_2\omega_2)}{(1-I)m_1 + (\delta_1\omega_1 - \theta_1) + (1 - \delta_2\omega_2)},$$

which is *decreasing* with increasing of $I \in [0, 1]$ under conditions (2.45). This fact suggests that controlling the mutation intensity may delay the relapse of prostate tumors under the androgen-deprived therapy.

Case 2.3. We now explain some biological significance of combined parameters $\theta_1 - \delta_1\omega_1 - (1-I)m_1$ and $1 - \delta_2\omega_2$ in Theorem 2.1. Let's denote

the "*net*" growth rate of AD cells

= the proliferation rate of AD cells − the death rate of AD cells − the mutation rate

$= \theta_1 - \delta_1\omega_1 - (1-I)m_1,$

the "*natural net*" growth rate of AI cells

= the proliferation rate of AI cells −the death rate of AI cells

$= 1 - \delta_2\omega_2,$

the "*net*" growth rate of AI cells

= the mutation rate + the "*natural net*"growth rate of AI cells

$= (1-I)m_1 + (1 - \delta_2\omega_2),$

where the mutation rate $(1-I)m_1$ is defined for AD cells to mutate to AI cells.

The condition 1 means that the "*net*" growth rate of AD cells and the "*natural net*" growth rate of AI cells are both equal to zero. Theorem 2.1 says that under the condition 1 the prostate tumor relapse can not be avoided due to the mutation of AD cells which results in increasing of AI cells as shown in (2.37). However, (2.37) also suggests that controlling the mutation (i.e. increasing the value of I) may delay (for $0 < I < 1$) or prevent (for $I = 1$) the relapse. In fact, from (2.37), as $t \to +\infty$, we see

$$V(t) \to +\infty \text{ if } 0 < I < 1, \quad \text{but } V(t) \equiv \frac{4}{3}\pi \text{ if } I = 1.$$

The condition 2 means that the "*net*" growth rate of AD cells is equal to zero and the "*natural net*" growth rate of AI cells is positive (we assume that $1-\delta_2\omega_2 > 0$ for the typical parameter values as given in [95]). Theorem 2.1 says that under the condition 2 the AI cells will dominate the prostate tumor growth as shown in (2.38) and the tumor relapse can not be avoided. In fact, from (2.38) and $1-\delta_2\omega_2 > 0$, we see that

$$V(t) \to +\infty \quad \text{as } t \to +\infty.$$

The condition 3 means that the "*net*" growth rate of AD cells is non-zero (we assume that it is negative for typical parameter values as given in [95]) and the "*natural net*" growth rate of AI cells is zero. Theorem 2.1 says that under the condition 3 the prostate tumor growth could be controlled as shown in (2.39). In fact, from $\theta_1 - \delta_1\omega_1 - (1-I)m_1 < 0$ and (2.39), we have

$$V(t) \to V_2(0) + \frac{(1-I)m_1V_1(0)}{(1-I)m_1 - (\theta_1 - \delta_1\omega_1)} \quad \text{as } t \to +\infty.$$

The condition 4 means that the "*net*" growth rate of AD cells is equal to the "*natural net*" growth rate of AI cells and they are positive. Theorem 2.1 states that under the condition 4 both AD cells and AI cells contribute to the prostate tumor growth as shown in (2.40) and the tumor relapse can not be avoided. In fact, from (2.40) and $\theta_1 - \delta_1\omega_1 - (1-I)m_1 = 1-\delta_2\omega_2 > 0$, we see

$$V(t) \to +\infty \quad \text{as } t \to +\infty.$$

The condition 5 means that the "*net*" growth rate of AD cells and the "*natural net*" growth rate of AI cells are both non-zero and they are not equal.

For typical parameter values given in [95], we assume that the "*net*" growth rate of AD cells is negative and the "*natural net*" growth rate of AI cells latter is positive (as in (2.45)). Under these assumptions the AI cells will dominate the prostate tumor growth as shown in (2.41) and the tumor relapse can not be avoided as shown in (2.48).

2.5 Mathematical Model for Intermittent Androgen Suppression

The prostate gland is a male sexual organ which produces and secretes seminal fluid. Activities of prostate cells, such as proliferation and apoptosis, are regulated by androgens. Causes of prostate cancer are not fully understood although genes, aging, race, family history, and lifestyle-related factors are regarded as influential factors [135]. The screening, detection, and staging of prostate cancer is currently conducted by using the serum prostate-specific antigen (PSA) test [140].

A prostate tumor as well as the prostate gland itself is influenced by androgens. Androgens are secreted by the testicles and the adrenal glands. Androgens circulate in the blood, diffuse into the prostate tissue, and stimulate the prostate tumor to grow. The androgen suppression therapy for prostate cancers was initially proposed by Huggins and Hodges in 1941 [88]. Androgen suppression can now be realized easily by chemical castration [90]. However, the relapse of a prostate tumor remains a crucial problem for androgen

suppression therapy. The growth of androgen-independent (AI) cells is considered as one of the causes for this relapse. These AI cells are not sensitive to androgen suppression. As a result AI cells can still grow in androgen-deprived environments where androgen-dependent (AD) cells cannot proliferate [16, 17, 18, 90]. Thus continuous androgen suppression (CAS) therapy often results in a tumor relapse due to an emergence of such AI cancer cells, which has already been studied in previous sections.

Recent clinical studies [12, 16, 17, 18] suggest that intermittent androgen suppression (IAS) therapy may prolong or possibly prevent the relapse. In IAS therapies, androgen suppression is stopped when the monitored serum PSA concentration decreases to less than a lower threshold, while androgen suppression is resumed when the PSA concentration exceeds an upper threshold. The clinical results of IAS therapies are reviewed in the article [12]. However, a very important question is how to administer IAS therapy in order to have a maximum efficacy because IAS is dynamical therapy. To answer this question, experimental results about the prostate tumor relapse combining mathematical models for IAS therapy is needed.

There are intensive experimental studies on prostate tumor recurrence [83, 98, 101, 102, 113]. Two possible mechanisms of prostate tumor recurrence [91] are recognized currently. One is mutation or adaptation, where AI cells may emerge from androgen-dependent (AD) cells under the androgen deprived condition. The other is selection or competition, where AI cells are minor but exist from the beginning of the therapy and will be winners of competition

between AD cells and AI cells under the hormonal therapy. Since these two mechanisms may work together and the real situation can be much more complex due to polyclonality of AD cells and AI cells [52, 111, 132], different mathematical models are needed for these mechanisms.

Ideta et al. [89] proposed an ordinary differential equation (ODE) model for prostate cancer IAS therapy, which studies the *mutation mechanism* of prostate tumor relapse. This model simplifies biological reality since spatial heterogeneity is neglected. Incorporating spatial motion of cells, Guo et al. [76] extended this ODE model to a partial differential equation (PDE) model. The main difference between the ODE model [89] and the PDE model [76] is that the subpopulation of AI (or AD) cells in the PDE model is *nonlinearly* related to the subpopulations of AD (or AI) cells due to the spatial movement of tumor cells, while the subpopulation of AI (or AD) cells in the ODE model is *linearly* related to the subpopulations of AD (or AI) cells. Furthermore, the numerical study of the PDE model finds an optimal lower threshold r_0 (when the upper threshold r_1 is fixed), which suggests an optimal protocol for IAS therapy.

As mentioned, mutation and competition are two different mechanisms of the relapse of a prostate tumor. Shimada and Aihara [134] proposed another ODE model for IAS therapy, which studies the *competition mechanism* of a tumor relapse. Tao et al. [152] extended this ODE model to a PDE model by incorporating the spatial motion of cells within the model.

Let's assume that $\Omega \in \mathcal{R}^3$ is the domain of the solid prostate tumor under consideration. To make the model tractable, Ω is assumed to be spherical. Following [95, 96], the tumor is considered as a densely packed, radially-symmetric sphere of radius $R(t)$. We assume that tumor cells move as a result of a convective velocity field $\mathbf{v}$ caused by cell proliferation and death driving local volume changes [95, 168]. We also assume that cells move through random processes such as diffusion processes [73, 74]. Since the growth of a prostate tumor is mainly dependent on androgens [12, 95], we also assume that the growth of a solid prostate tumor is stimulated by androgens (here we neglect other nutrients or inhibitors). Androgen deprivation now can be easily performed by chemical castration [12, 90], for instance, by administration of pharmacological agents such as luteinizing hormone releasing hormone (LHRH) analogs that inhibit the production of androgens from its primary source, the testes. The remaining androgens that are produced by the adrenal glands can also be eliminated by additional treatment with androgen-receptor antagonists (anti-androgens). Thus, the level of androgens within the tissue under consideration can be controlled by medical means, and we can neglect spatial heterogeneity of androgens within the tissue. As mentioned before, prostate cancer cells are divided into two groups: androgen-dependent (AD) cells and androgen-independent (AI) cells. AI cells are not sensitive to androgen suppression but rather apt to increase even in an androgen deprivation condition in which AD cells cannot proliferate. Therefore, we assume that their proliferation rate

and apoptosis rate only depend on the androgen concentration within the tissue. The serum PSA is secreted by prostate cancer cells, and its level can be observed by medical blood examination. We can consider the PSA concentration is a function of time only. The PSA is a good bio-marker for estimating the progression for prostate cancer [16, 140], and IAS therapy is based on monitoring of the concentration of PSA.

We introduce the following physical variables:

- the androgen concentration a
- the number density of the AD cells x_1
- the number density of the AI cells x_2
- the serum PSA concentration y
- the velocity field within the tumor v.

Since IAS therapy is a dynamical therapy, we use a binary variable $u(t)$ to describe IAS therapy of a prostate tumor: the medication is alternatively either present ($u = 1$) or absent ($u = 0$). The switch on/off of the medication is based on the monitored level $y(t)$ of the serum PSA. Hence, the androgen concentration level $a(t)$ (nmol/l) satisfies the following equation [89]:

$$\frac{da(t)}{dt} = -\gamma\big(a(t) - a_0\big) - \gamma a_0 u(t), \tag{2.49}$$

where a_0 (nmol/l) denotes the steady-state value of the normal androgen concentration, which takes a value between 15 and 30 for usual adult males. The rate of the recovery and decay of the androgen concentration is governed by the parameter γ.

Under the assumptions mentioned above, the mass balance equations for the AD cell population and the AI cell population are given:

$$\begin{aligned}
&\frac{\partial x_1}{\partial t}(r,t) + \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 v(r,t)x_1(r,t)\Big) \\
&\quad = \frac{D}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial x_1}{\partial r}(r,t)\Big) \\
&\qquad + \big[\alpha_1 p_1(a(t)) - \beta_1 q_1(a(t)) - m(a(t))\big]x_1(r,t), \qquad (2.50)\\
&\frac{\partial x_2}{\partial t}(r,t) + \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 v(r,t)x_2(r,t)\Big) \\
&\quad = \frac{D}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial x_2}{\partial r}(r,t)\Big) + m(a(t))x_1(r,t) \\
&\qquad + \big[\alpha_2 p_2(a(t)) - \beta_2 q_2(a(t))\big]x_2(r,t), \qquad (2.51)
\end{aligned}$$

where D is the random motility coefficient of the AD and AI cells, $\alpha_1 p_1(a(t))$ and $\beta_1 q_1(a(t))$ are proliferation rate and apoptosis rate of AD cells respectively, $\alpha_2 p_2(a(t))$ and $\beta_2 q_2(a(t))$ are proliferation rate and apoptosis rate of IA cells, $m(a(t))$ is the mutation rate by which AD cells mutate to AI cells. The cell proliferation rate, apoptotic rate, and mutation rate are assumed to be dependent on the androgen concentration $a(t)$ as assumed. These androgen-dependent functions are given as follows [89]:

$$p_1(a(t)) = k_1 + (1-k_1)\frac{a(t)}{a(t)+k_2}, \qquad (2.52)$$

$$q_1(a(t)) = k_3 + (1-k_3)\frac{a(t)}{a(t)+k_4}, \qquad (2.53)$$

$$p_2(a(t)) = \begin{cases} (i) & 1, \\ (ii) & 1 - \left(1 - \frac{\beta_2}{\alpha_2}\right)\frac{a(t)}{a_0}\ , \\ (iii) & 1 - \frac{a(t)}{a_0}, \end{cases} \tag{2.54}$$

$$q_2(a(t)) = 1, \tag{2.55}$$

$$m(a(t)) = m_1\Big(1 - \frac{a(t)}{a_0}\Big). \tag{2.56}$$

As shown in Eqs. (2.52)-(2.53), the proliferation rate of AD cells is an increasing function of the androgen concentration a while the apoptosis rate of AD cells is a decreasing function of the androgen concentration a, where $0 \leq k_1 \leq 1$ and $k_3 > 1$. The proliferation rate and apoptosis rate of AI cells also depends on the androgen concentration [100], although details of their androgen dependence remain unclear. We assume three possibilities on the net growth rate of the AI cells, as given in Eqs. (2.54) and (2.55), which are characterized by whether the net growth rate is positive, zero, or negative in androgen-rich environments.

The fact that the number density of cells is constant within a solid tumor [95, 168] gives,

$$x_1(r,t) + x_2(r,t) \equiv 1. \tag{2.57}$$

Further, we assume that the serum PSA concentration $y(t)$ is monitored as a bio-marker for the prostate tumor growth. Since a large amount of PSA is secreted by cancer cells, the PSA concentration is assumed to be linearly dependent on the densities of the AD and AI cell populations as follows [89]:

$$y(t) = \int_0^{2\pi} d\theta \int_0^{\pi} d\varphi \int_0^{R(t)} \big(c_1 x_1(r,t) + c_2 x_2(r,t)\big) r^2 \sin\varphi \; dr, \tag{2.58}$$

where c_1 and c_2 are some constants. The PSA concentration $y(t)$ can be used as a basis for intermittent administration in the IAS therapy model.

We switch the medication when the serum PSA marker level $y(t)$ crosses the upper and lower thresholds [89]:

$$u(t) = \begin{cases} 0 \to 1 & \text{when } y(t) = r_1 \text{ and } dy(t)/dt > 0 \\ 1 \to 0 & \text{when } y(t) = r_0 \text{ and } dy(t)/dt < 0 \end{cases}, \tag{2.59}$$

where r_1 and r_0 are the upper and lower thresholds, respectively. However, how to administer IAS therapy, or how to appropriately set adjustable parameters r_1 and r_0 under the condition of $r_1 > r_0 > 0$, is a very important question for clinical practice [12].

By the radial symmetry assumption of the problem, we have

$$\frac{\partial x_1}{\partial r}(0,t) = \frac{\partial x_2}{\partial r}(0,t) = 0, \quad v(0,t) = 0. \tag{2.60}$$

To complete the system, we impose the following initial and boundary conditions:

$$R(0) = R_0, \quad x_1(r,0) = x_{10}(r) \text{ with } 0 \le x_{10}(r) \le 1, \tag{2.61}$$

$$\Big[x_1(r,t)\frac{dR(t)}{dt} - \Big(x_1(r,t)v(r,t) - D\frac{\partial x_1}{\partial r}(r,t)\Big)\Big]_{r=R(t)} = 0, \tag{2.62}$$

$$\Big[x_2(r,t)\frac{dR(t)}{dt} - \Big(x_2(r,t)v(r,t) - D\frac{\partial x_2}{\partial r}(r,t)\Big)\Big]_{r=R(t)} = 0, \tag{2.63}$$

where Eqs. (2.62) and (2.63) are no-flux boundary conditions for AD and AI cells respectively, as explained in Chapter 2.2.

The system (2.49)-(2.63) is the mathematical problem of prostate tumor growth under intermittent androgen suppression. In order to solve this problem, we need some more conditions or equations.

By adding Eqs. (2.50) and (2.51) and using the fact (2.57), we obtain an equation for the velocity field within the tumor,

$$\frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 v(r,t)\Big) = \big[\alpha_1 p_1(a(t)) - \beta_1 q_1(a(t))\big]x_1(r,t) + \big[\alpha_2 p_2(a(t)) - \beta_2 q_2(a(t))\big](1 - x_1(r,t)). \quad (2.64)$$

By adding Eqs. (2.62) and (2.63) and using (2.57), we obtain an equation for the velocity of the outer boundary of the tumor,

$$\frac{dR(t)}{dt} = v(R(t),t). \quad (2.65)$$

This equation, together with Eq. (2.62), yields the following boundary condition for AD cells

$$\frac{\partial x_1}{\partial r}(R(t),t) = 0. \quad (2.66)$$

We notice that Eq. (2.51) is a consequence of Eqs. (2.50), (2.57), and the expression (2.64). Therefore, in what follows we may drop this equation and replace x_2 by $1 - x_1$ in Eqs. (2.50) and (2.58).

We also notice that the no-flux boundary conditions (2.62)-(2.63) are equivalent to the boundary conditions (2.65)-(2.66) under the condition (2.57). So shall replace Eqs. (2.62)-(2.63) with Eqs. (2.65)-(2.66).

In next section we will transform the problem (2.49)-(2.66) in the moving domain $\{r \le R(t)\}$ into a new system in a fixed domain.

2.6 Transformation of Intermittent Androgen Suppression Model

To transform the moving domain $\{r \le R(t)\}$ into a fixed domain, as done in Chapter 2.2, we introduce a change of variables $(r,\ t,\ a,\ x_1,\ v,\ R,\ y,\ u) \mapsto (\rho,\ t,\ a,\ \tilde{x}_1,\ \tilde{v},\ R,\ y,\ u)$ as follows:

$$\rho = r/R(t), \quad \tilde{x}_1(\rho,t) = x_1(\rho R(t),t), \quad \tilde{v}(\rho,t) = v(\rho R(t),t)/R(t). \tag{2.67}$$

For notational convenience, we drop the tildes of $\tilde{x}_1(\rho,t)$ and $\tilde{v}(\rho,t)$, in terms of the new variables, the system (2.49)-(2.66) takes the following form in $\{0<\rho<1,\ 0<t<T\}$:

$$\frac{da(t)}{dt} = -\gamma\big(a(t)-a_0\big) - \gamma a_0 u(t), \quad a(0)=a_0, \tag{2.68}$$

$$\begin{aligned}&\frac{\partial x_1}{\partial t}(\rho,t) + \big[v(\rho,t) - \rho v(1,t)\big]\frac{\partial x_1}{\partial \rho}(\rho,t) - \frac{D}{R^2(t)}\frac{1}{\rho^2}\frac{\partial}{\partial\rho}\Big(\rho^2\frac{\partial x_1}{\partial\rho}(\rho,t)\Big)\\ &= \big[\alpha_1 p_1(a(t)) - \beta_1 q_1(a(t)) - \alpha_2 p_2(a(t)) + \beta_2 q_2(a(t))\big]x_1(\rho,t)(1-x_1(\rho,t))\\ &\quad -m(a(t))x_1(\rho,t),\end{aligned} \tag{2.69}$$

$$x_1(\rho,0) = x_{10}(\rho), \tag{2.70}$$

$$\frac{\partial x_1}{\partial\rho}(0,t) = \frac{\partial x_1}{\partial\rho}(1,t) = 0, \tag{2.71}$$

$$\begin{aligned}v(\rho,t) = \frac{1}{\rho^2}\int_0^\rho \Big\{&\big[\alpha_1 p_1(a(t)) - \beta_1 q_1(a(t))\big]x_1(s,t)\\ &+\big[\alpha_2 p_2(a(t)) - \beta_2 q_2(a(t))\big](1-x_1(s,t))\Big\}s^2 ds,\end{aligned} \tag{2.72}$$

$$\frac{dR(t)}{dt} = R(t)v(1,t), \quad R(0)=R_0, \tag{2.73}$$

$$y(t) = c_0 R^3(t), \tag{2.74}$$

$$u(t) = \begin{cases} 0 \to 1 & \text{when } y(t) = r_1 \text{ and } dy(t)/dt > 0 \\ \\ 1 \to 0 & \text{when } y(t) = r_0 \text{ and } dy(t)/dt < 0 \end{cases}, \tag{2.75}$$

where we have used the fact that $v(0,t) = 0$ in deriving Eq. (2.72), and we have used the assumptions $c_1 = c_2$ and (2.57) in deriving Eq. (2.74) ($c_0 := 4\pi c_1/3$). The model dynamics will be examined using numerical simulation in next section.

2.7 Numerical Study of Intermittent Androgen Suppression Model

In this section we will perform numerical simulations of the model (2.68)-(2.75) to study the effects of IAS therapy in the three cases (i)-(iii) of the proliferation rate of the AI cells in (2.54). The model describes IAS therapy for $0 < r_0 < r_1$, while the model can be viewed to describe CAS therapy if $r_0 = 0$. The typical parameter values and the initial conditions for the numerical simulations are given[76, 89, 95]:

$$k_1 = 0, \quad k_2 = 2, \quad k_3 = 8, \quad k_4 = 0.5, \quad \alpha_1 = 0.0204, \quad \alpha_2 = 0.0242,$$

$$\beta_1 = 0.0076, \quad \beta_2 = 0.0168, \quad \gamma = 0.08, \quad a_0 = 30, \quad m_1 = 0.00005$$

$$a(0) = 30, \quad u(0) = 1, \quad D = 0 \quad \text{and} \quad R(0) = 2 \text{ mm}.$$

In the simulations, the initial condition for x_{10} is taken as follows:

$$x_{10} = 0.95.$$

This initial condition implies that AI cells are minor at the beginning of the therapy. The parameters r_0 and r_1 are the adjustable parameters in our model.

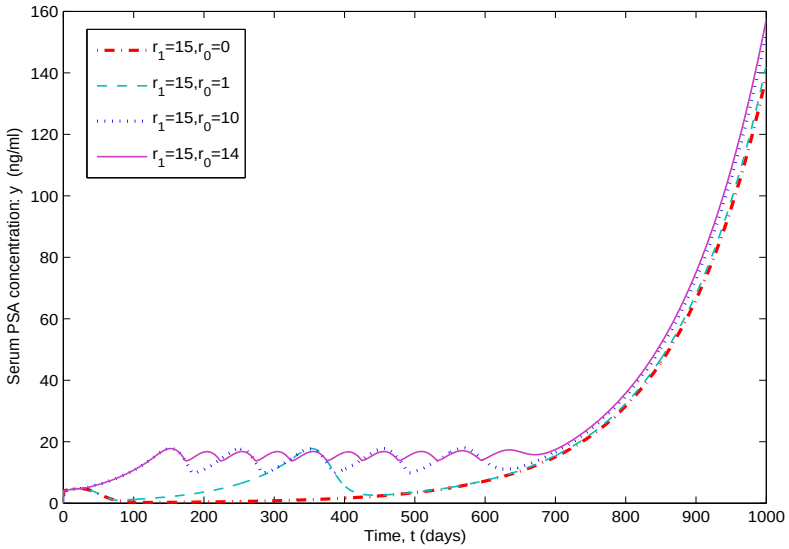

Fig. 2.1. The dynamics of the serum PSA concentration $y(t)$ in case (i), where $c_0 = 0.5$.

Figure 2.1 shows the dynamics of the serum PSA concentration $y(t)$ in case (i). It indicates that IAS seems to be more ineffective than CAS in prolonging a relapse, which is similar to the dynamics of the ODE model [89]. We notice that the net growth rate (the proliferation rate − the apoptosis rate) of AI cells is always positive due to $\alpha_2 p_2 - \beta_2 q_2 = \alpha_2 - \beta_2 > 0$ in case (i), and therefore AI cells will be rapidly dominant within a prostate tumor. On the other hand, Figure 2.1 also shows that a relapse occurs within approximately

three years in all the trials with different values of r_0 similarly with the CAS. Therefore, the IAS therapy may be worthy to be adopted in the sense that the periods of off-adminstration introduced by this therapy can reduce side effects of androgen deprivation and improve the quality of life for patients.

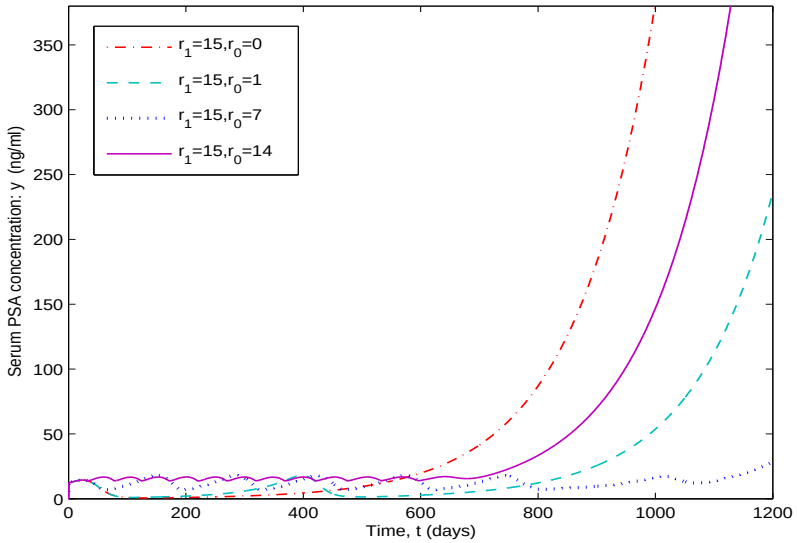

Fig. 2.2. The dynamics of the serum PSA concentration $y(t)$ in case (ii), where $c_0 = 1.5$. $r_0 = 7$ is a nearly *optimal* lower threshold for IAS therapy if we fix the upper threshold at $r_1 = 15$.

The dynamics of the serum PSA concentration $y(t)$ in case (ii) of Eq. (2.54) is presented in Figure 2.2. Unlike the previous case, all the trials with IAS therapy prolong the relapse time when compared with the CAS therapy. Figure 2.2 shows that the relapse time is *not* monotonously decreasing in the lower threshold $r_0 \in [1, 14]$ if $c_0 = 1.5$. Then, to achieve better effects of

IAS therapy, the lower threshold r_0 should be carefully selected. In fact, to maximally delay the relapse time, a nearly *optimal* lower threshold $r_0 = 7$ is numerically found if the upper threshold is fixed at $r_1 = 15$ as shown in Figure 2.2. It is impossible, however, to avoid an eventually relapse in case (ii) due to $\alpha_2 p_2(a) - \beta_2 q_2(a) > 0$ for $0 \le a < a_0$ and $\alpha_2 p_2(a_0) - \beta_2 q_2(a_0) = 0$. This implies that the population of AI cells increases in androgen-poor environments, and does not decrease even in environments that have the normal androgen concentration a_0.

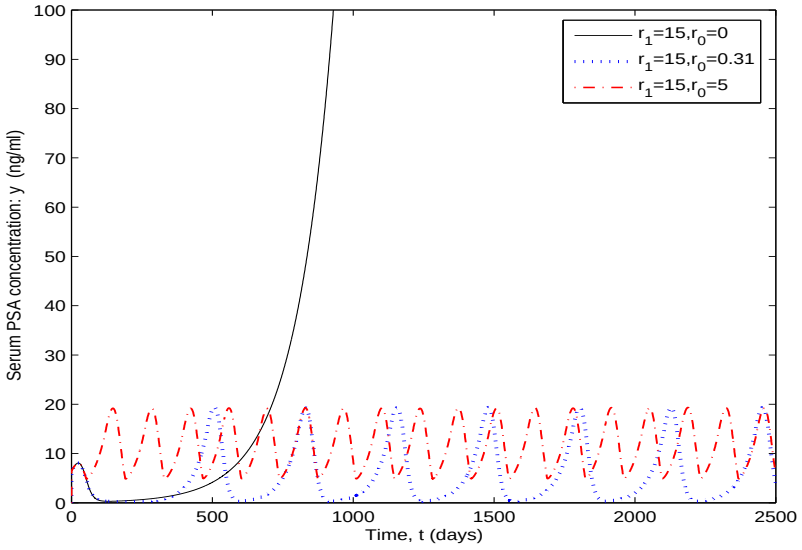

Fig. 2.3. The dynamics of the serum PSA concentration $y(t)$ in case (iii), where $c_0 = 0.8$ and $r_1 = 15.0$. $y(t)$ will be periodically oscillatory for $0.31 \le r_0 < r_1$, where $r_0 = 0.31$ is the *critical* lower threshold for the existence of a stable periodic solution which corresponds to successful IAS.

Figure 2.3 shows the dynamics of the serum PSA concentration $y(t)$ in case (iii) with $c_0 = 0.8$ and $r_1 = 15.0$. The CAS therapy leads to a relapse due to $\alpha_2 p_2(0) - \beta_2 q_2(0) = \alpha_2 - \beta_2 > 0$. This implies that the population of AI cells continues to increase in an androgen-deprived state. However, IAS therapy can realize cyclic growth and regression of the tumor without a relapse due to $\alpha_2 p_2(a_0) - \beta_2 q_2(a_0) = -\beta_2 < 0$, which implies that the population of AI cells decreases in an androgen-rich environment. In fact, the biological evidence that proliferation of AI cancer cells is repressed by androgen [102].

2.8 Summary

This chapter reviews mathematical models for prostate tumor growth under hormone therapy with mutation inhibitors. The prostate tumors have two types of cancerous cells, androgen-dependent (AD) cells and androgen-independent (AI) cells. AI cells are undetectable prior to treatments, but they grow even in androgen-poor conditions during continuous hormone therapy. The models are formulated as free boundary problems of nonlinear parabolic systems, and describe the evolution of cancerous cell populations within a prostate tumor and the dynamics of the tumor radius (volume).

We found explicit formulae of the tumor volume at any time t in continuously androgen-deprived environment. The long-term behavior of tumor growth can be predicted by these formulae. Qualitative analysis suggests that a tumor relapse cannot be avoided under androgen-deprived therapy. This implication

may support a possible strategy of intermittent androgen suppression (IAS). Intermittent androgen suppression is a type of androgen ablative therapy delivered intermittently with off-treatment periods [17].

In fact, a crucial problem of the CAS therapy on prostate cancer is the relapse of a prostate tumor, which has been shown by a number of experimental and clinical studies [12, 16, 17, 18, 83, 90, 95, 102]. This forces us to look for alternative method to treat prostate tumor, which is intermittent androgen suppression. We then reviews the PDE model [76] for IAS therapy. The numerical results show that the IAS therapy may be more effective than the CAS therapy in delaying a relapse in some cases (see Figs. 2.2 and 2.3). To achieve a better effect of the IAS therapy, we need to optimally administer the intermittent treatment. That is, we need to optimally choose the lower threshold r_0 (see Fig. 2.2), which depends on the parameters r_1 and c_0.

We should mention that the nonlinear competitive effects between AD and AI cancer cells has been recently considered by Shimada and Aihara [134]. In the same way as presented in this chapter, Tao et al. [152] extended this ODE model to a PDE model and performed some qualitative and numerical analysis of the extended PDE model.

3

Modeling the Competition between Tumor Cells, Oncolytic Viruses and Immune Response

3.1 Introduction

In this chapter, we will review mathematical models for tumor virotherapy [144, 170, 65]. Unlike the model of Byrne and Chaplain [19] which introduces a genetic inhibitor, the present chapter considers a tumor therapy by oncolytic viruses, called virotherapy. Virotherapy has been and is continues to be actively tested in clinical trials for variety of malignant cancers [14, 34, 38, 77, 128, 181].

One of the obstacles in developing efficient gene therapies for cancers is in the delivery process. The macromolecules used as gene delivery carriers are too large to be transported into, and diffuse within, the tumor [92, 141]. A recent approach aimed at bypassing this problem involves the use of viruses. Viruses are engineered to selectively bind to receptors on the tumor cell surface (but not to the surface of normal healthy cells). The virus particles then gain entry by endocytosis and proceed to reproduce within the tumor cell, eventually causing death (lysis). On lysis of an infected cell, a swarm of new

viruses burst out of the dead cell, and then infect neighboring tumor cells. This process continue until all cancer cells are destroyed.

However, most virus species are unable to eradicate the majority of tumor modules. There are increasing evidences that the host immune response to active viral infections. Indeed, it has been manifested that the innate immune system destroys infected cells as well as free virus particles, thus enabling the tumor to grow [33].

A mathematical model that describes the evolution of a solid tumor under viral injection was initially developed by Wu, Byrne, Kirn and Wein [178]. They computed and compared the evolution of the tumor under different initial conditions using the 'simplified' version of their model. Friedman and Tao [61] presented a somewhat different model, and made a rigorous mathematical analysis on their model. The main difference between the FT model and the WBKW model is a PDE for viruses. The WBKW model does not include the diffusion term and their mathematical system is not well posed.

Later on, Wein, Wu and Kirn [170] incorporated the immune response into their earlier model [178]. They used some preclinical and clinical data to validate their model and estimate several key parameter values. They also discussed some design of oncolytic viruses. The viruses should be designed for rapid intratumoral spread and immune avoidance, in addition to tumor-selectively and safety. Tao and Guo [144] made a rigorous mathematical analysis of the WWK model. A very interesting point of the analysis is to theoretically find

an explicit threshold of the intensity of the immune response for controlling a tumor, which is the focus of the present chapter.

We also review a mathematical model proposed by Friedman and Tian et al [65]. This model is formulated for spherical glioma under virotherapy. The model studies administration of oncolytic virus hrR3 into the tumor center. HrR3 is a mutant of herpes simplex virus (HSV) [34]. Importantly, this model includes the effects of the immunosuppression drug cyclophosphamide. We used this mathematical model to determine how different protocols of cyclophosphamide treatment and how the burst size of mutated viruses will affect the growth of gliomas. It is showed that with the current burst size of oncolytic virus hrR3 the glioma tumor cannot be eradicated even with administration of cyclophosphamide. If, however, the viruses can be further altered to yield a burst size $b \geq 150$, then the glioma tumor will shrink to very small size even with no cyclophosphamide treatment.

In this chapter, we will mainly review the model [170] initially proposed by Wein et al. and present some analytical mathematical results [144] on this model. Section 3.2 gives the model. Section 3.3 re-formulates the model. Section 3.4 states the analytical results. Section 3.5 numerically studies a mathematical model with a time-delay of the immune response. Section 3.6 review the mathematical model for glioma virotherapy. Finally, this chapter is closed with a summary section.

3.2 Mathematical Model

Consider a radially symmetrical tumor, and denote its boundary by $R(t)$. We use symbol r for the distance from a point to the center of the tumor, and r will be a variable. We also introduce the following physical variables

the number density of uninfected tumor cells : $\hat{x}(r,t)$

the number density of infected tumor cells : $\hat{y}(r,t)$

the number density of dead cells : $\hat{n}(r,t)$

the number density of free virus particles : $\hat{v}(r,t)$

the number density of the immune molecules : $\hat{z}(r,t)$

the velocity field within the tumor : $u(r,t)$.

As that in Chapter 2.2, the proliferation and removal of cells cause movements of cells with the radial velocity field $u(r,t)$, where $u(0,t)=0$.

There is some biological evidences that many types of tumor cells secrete a variety of growth-promoting factors, for example, epidermal growth factor (EGF) and transforming growth factor-α (TGF-α) [182]. So, we usually consider that tumor cells proliferate. Following Wu *et al* [178], we assume that the uninfected cells proliferate exponentially at rate λ. Viruses infect tumor cells by binding to receptors on cell surfaces and gaining entry by endocytosis. Therefore, as in [178] we assume that the infection rate of cells centered at r equals a constant β times the density of uninfected cells at r times $\bar{v}(r,t)$, which is the spatially-weighted average of virus density on the surface of a

spherical cell with radius r_c that is centered at r . In [178], Wu *et al* showed that

$$\bar{v}(r,t) = \frac{1}{2r_c}\int_{r-r_c}^{r+r_c} \hat{v}(s,t)ds. \tag{3.1}$$

Since the diffusion coefficient of tumor cells is much smaller than the diffusion coefficient of the motile virus particles, we assume that the tumor cells are subjected to the convection with velocity field $u(r,t)$, and the diffusion of tumor cells is neglected. for a similar assumption, we refer to articles [175, 178, 179]. By the conservation law of mass for the uninfected tumor cells,

$$\begin{aligned}\frac{D\hat{x}}{Dt} &\equiv \frac{\partial \hat{x}(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 u(r,t)\hat{x}(r,t)\Big) \\ &= \lambda\hat{x}(r,t) - \beta\hat{x}(r,t)\bar{v}(r,t).\end{aligned} \tag{3.2}$$

As in papers [178, 179], we assume that the infected cells do not proliferate and that all infected cells undergo lysis at rate δ, where δ^{-1} represents the mean infected cell lifetime. Clinical results suggest that the immune response is cytokine-mediated. The expression of viruses in tumor cells sensitizes cells to lysis by the TNF (tumor necrosis factor) cytokine [130]. The binding of TNF to death receptors on the tumor cell surface preferentially induces apoptosis of viral-infected tumor cells, whereas the uninfected tumor cells are generally resistant to TNF-induced killing. Based on the ability of TNF to selectively kill viral-infected cells, we postulate that the immune response kills only the infected tumor cells. The immune response is assumed to kill the infected tumor cells at a rate (with proportionality constant k) proportional to the product of the densities of the infected tumor cells and the immune response.

We assumed that these killed cells do not release any free viruses. By the conservation law of mass for infected cells,

$$\begin{aligned}\frac{D\hat{y}}{Dt} &\equiv \frac{\partial \hat{y}(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 u(r,t)\hat{y}(r,t)\Big) \\ &= \beta \hat{x}(r,t)\bar{v}(r,t) - \delta \hat{y}(r,t) - k\hat{y}(r,t)\hat{z}(r,t). \end{aligned} \tag{3.3}$$

At the time of lysis, an infected cell becomes necrotic. We also regard the infected cells which have been killed by the immune response as necrotic cells. The necrotic debris is removed from the tumor at rate μ. By the conservation law of mass for the necrotic cells,

$$\begin{aligned}\frac{D\hat{n}}{Dt} &\equiv \frac{\partial \hat{n}(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 u(r,t)\hat{n}(r,t)\Big) \\ &= \delta \hat{y}(r,t) + k\hat{y}(r,t)\hat{z}(r,t) - \mu \hat{n}(r,t). \end{aligned} \tag{3.4}$$

Since the free virus particles are very small relative to the cells, we assume that they undergo diffusion within the tumor tissue. The viruses addressed in this chapter play a role similar to an anti-tumor drug. The major difference between viruses and anti-tumor drugs is that viruses have replicating ability once they infect tumor cells and newly replicated viruses can infect neighboring tumor cell when infected tumor cell lysis. The drugs usually undergo diffusion within the tumor tissue [168]. There are some experimental evidences that the diffusion coefficient of drugs is lowest near the center of the tumor, and it is increasing to maximal levels at the tumor periphery [92]. However, for simplicity, one usually assume that the diffusion coefficient of a drug is constant, see [168]. In this chapter we shall also confine ourselves to

consider the situation in which the virus diffusion coefficient (denoted by D_1) is constant. When an infected tumor cell dies, we assume that N new virus particles are released, and this number is call the burst size of the viruses. The combined parameter $N\delta$ is the release rate of free virus particles per unit time per infected cell. Because virus particles are present throughout a sphere of radius r_c (where r_c is the tumor cell radius), the rate of virus release at location r is $N\delta$ times $\bar{y}(r,t)$, which is the spatially-averaged infected cell density throughout a sphere of radius r_c that is centered at r. In [178], Wu *et al* derived that

$$\bar{y}(r,t) = \frac{1}{4{r_c}^3}\int_{r-r_c}^{r+r_c} \hat{y}(s,t)[r_c^2 - (s-r)^2]ds. \tag{3.5}$$

As in [178, 179], we assume that the infected cells killed by the immune cells do not release any free virus. The precise mechanism by which the viruses are cleared remains unknown. We assume that it is cleared at a constant rate γ, where $1/\gamma$ is the mean lifetime of free viruses. We shall also neglect the effect of the velocity field on the virus, as in [178, 179]. By combining the conservation law of mass with the effect of diffusion, we obtain

$$\frac{\partial \hat{v}(r,t)}{\partial t} = N\delta\bar{y}(r,t) - \gamma\hat{v}(r,t) + D_1\frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial \hat{v}(r,t)}{\partial r}\Big), \quad \frac{\partial \hat{v}(0,t)}{\partial r} = 0, \tag{3.6}$$

where the last equation in (3.6) is a consequence of the radial symmetry.

Since the immune response (several innate immune cell populations) under consideration in this chapter mainly consists of molecules with very small size, we assume that it undergoes diffusion. Also, we will confine ourselves to consider the situation in which the diffusion coefficient of immune response

(denoted by D_2) is constant. Typically, $D_2 = 10^{-2}\ cm^2 day^{-1} \gg D_c = 1.3 \times 10^{-6}\ cm^2 day^{-1}$ (the diffusion coefficient of tumor cells) [27]. We assume that the immune response is produced at an unsaturated rate that is proportional (with constant l) to the product of the density of infected tumor cells and the immune response, and incurs second-order clearance with rate constant ω. We assume second-order clearance because first-order clearance was inconsistent with the clinical data [170]. By the conservation law of mass, we have

$$\frac{\partial \hat{z}(r,t)}{\partial t} = l\hat{z}(r,t)\hat{y}(r,t) - \omega[\hat{z}(r,t)]^2 + D_2 \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 \frac{\partial \hat{z}(r,t)}{\partial r}\Big), \quad \frac{\partial \hat{z}(0,t)}{\partial r} = 0, \tag{3.7}$$

where the last equation in (3.7) is a consequence of the radial symmetry.

We finally assume that all tumor cells have the same size, and that they are uniformly distributed in the tumor [178], so that

$$\hat{x} + \hat{y} + \hat{n} \equiv \text{const.} \equiv \theta. \tag{3.8}$$

Adding equations (3.2)-(3.4) and using (3.8), we get the equation for velocity field,

$$\frac{\theta}{r^2}\frac{\partial}{\partial r}\Big(r^2 u(r,t)\Big) = \lambda \hat{x}(r,t) - \mu \hat{n}(r,t). \tag{3.9}$$

The boundary conditions, at the outer boundary of the tumor, are

$$\frac{\partial}{\partial r}\hat{v}(R(t),t) = 0, \tag{3.10}$$

$$\frac{\partial}{\partial r}\hat{z}(R(t),t) = 0, \tag{3.11}$$

$$\frac{dR(t)}{dt} = u(R(t),t). \tag{3.12}$$

Remark 3.1. We assume that there is no-flux of tumor cells, virus particles and the immune response across the outer boundary of the tumor, that is, they remain within the tumor. Then, we have boundary conditions,

$$\left[\hat{x}(r,t)\frac{dR(t)}{dt} - \hat{x}(r,t)u(r,t)\right]_{r=R(t)} = 0, \tag{3.13}$$

$$\left[\hat{y}(r,t)\frac{dR(t)}{dt} - \hat{y}(r,t)u(r,t)\right]_{r=R(t)} = 0, \tag{3.14}$$

$$\left[\hat{n}(r,t)\frac{dR(t)}{dt} - \hat{n}(r,t)u(r,t)\right]_{r=R(t)} = 0, \tag{3.15}$$

$$\left[\hat{v}(r,t)\frac{dR(t)}{dt} - \left(\hat{v}(r,t)u(r,t) - D_1\frac{\partial \hat{v}}{\partial r}(r,t)\right)\right]_{r=R(t)} = 0, \tag{3.16}$$

$$\left[\hat{z}(r,t)\frac{dR(t)}{dt} - \left(\hat{z}(r,t)u(r,t) - D_2\frac{\partial \hat{z}}{\partial r}(r,t)\right)\right]_{r=R(t)} = 0. \tag{3.17}$$

Adding Eqs. (3.13)-(3.15) and using Eq. (3.8), we derived the free boundary condition (3.12). This, along with Eqs. (3.16) and (3.17), further yields the boundary conditions (3.10) and (3.11). In Eqs. (3.6) and (3.7) we neglected the effects of the velocity field on the virus and the immune response. However, we need to consider the velocity field in deriving appropriate and tractable boundary conditions for the viruses and immune response at the moving outer boundary of the tumor. We further notice that, as addressed in Remark 2.1, Eqs. (3.13)-(3.17) are obtained by considering the *relative* velocity of cells on the outer boundary of the growing tumor.

We notice that Equation (3.4) is a consequence of Eqs. (3.2), (3.3), (3.8) and (3.9). Therefore, in what follows we simply drop this equation and replace $\hat{n}$ by $\theta - \hat{x} - \hat{y}$ in Eq. (3.9).

3.3 Transformation

For the typical parameters $r_c = 0.01\ mm, \quad R(0) = 2\ mm$ given in [178], we have $r_c \ll R(0)$. By (3.1) and (3.5) we get

$$\bar{v}(r,t) \approx \hat{v}(r,t), \quad \bar{y}(r,t) \approx \hat{y}(r,t). \tag{3.18}$$

We introduce the new variables

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

and the quantity

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

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

In terms of the new variables, the system (3.1)-(3.12) takes the following form:

$$\frac{\partial \tilde{x}(r,t)}{\partial t} = \lambda \tilde{x} - p_0 \gamma \tilde{x} \tilde{v} - \frac{1}{r^2} \frac{\partial}{\partial r} \Big(r^2 \tilde{u} \tilde{x} \Big), \tag{3.19}$$

$$\frac{\partial \tilde{y}(r,t)}{\partial t} = p_0 \gamma \tilde{x} \tilde{v} - \delta \tilde{y} - k \tilde{y} \tilde{z} - \frac{1}{r^2} \frac{\partial}{\partial r} \Big(r^2 \tilde{u} \tilde{y} \Big), \tag{3.20}$$

$$\frac{\partial \tilde{v}(r,t)}{\partial t} = \delta \tilde{y} - \gamma \tilde{v} + D_1 \frac{1}{r^2} \frac{\partial}{\partial r} \Big(r^2 \frac{\partial \tilde{v}}{\partial r} \Big), \quad \frac{\partial \tilde{v}(0,t)}{\partial r} = 0, \tag{3.21}$$

$$\frac{\partial \tilde{z}(r,t)}{\partial t} = l \theta \tilde{z} \tilde{y} - \omega \tilde{z}^2 + D_2 \frac{1}{r^2} \frac{\partial}{\partial r} \Big(r^2 \frac{\partial \tilde{z}}{\partial r} \Big), \quad \frac{\partial \tilde{z}(0,t)}{\partial r} = 0, \tag{3.22}$$

$$\frac{1}{r^2} \frac{\partial}{\partial r} \Big(r^2 \tilde{u}(r,t) \Big) = \lambda \tilde{x} - \mu (1 - \tilde{x} - \tilde{y}) \tag{3.23}$$

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

$$\frac{\partial \tilde{v}}{\partial r}(R(t),t) = 0, \quad t > 0, \tag{3.24}$$

$$\frac{\partial \tilde{z}}{\partial r}(R(t),t) = 0, \quad t > 0, \tag{3.25}$$

$$\frac{dR(t)}{dt} = \tilde{u}(R(t),t), \quad t > 0, \tag{3.26}$$

$$\tilde{u}(0,t) = 0, \quad t > 0 \tag{3.27}$$

with initial conditions

$$\begin{aligned} &R(0) \quad \text{is prescribed,} \\ &\tilde{x}(r,0) = \tilde{x}_0(r), \tilde{y}(r,0) = \tilde{y}_0(r), \tilde{v}(r,0) = \tilde{v}_0(r), \tilde{z}(r,0) = \tilde{z}_0(r) \\ &\text{where } \tilde{z}_0(r) > 0 \text{ and } \tilde{x}_0(r), \tilde{y}_0(r), \tilde{v}_0(r) \text{ are nonnegative} \\ &\text{functions with } x_0(r) + y_0(r) \leq 1, \text{ for } 0 \leq r \leq R(0). \end{aligned} \tag{3.28}$$

It is convenient to transform the moving region $\{0 \leq r \leq R(t)\}$ to the fixed region $\{0 \leq \rho \leq 1\}$. So, we use Landau transformation

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

and setting

$$\begin{aligned} &x(\rho,t) = \tilde{x}(r,t), \quad y(\rho,t) = \tilde{y}(r,t), \quad z(\rho,t) = \tilde{z}(r,t), \\ &v(\rho,t) = \tilde{v}(r,t), \quad u(\rho,t) = \tilde{u}(r,t)/R(t), \end{aligned}$$

Eqs. (3.19)-(3.23) combined with (3.27) take the following form in $\{0 < \rho < 1, t > 0\}$:

$$\begin{aligned} &\frac{\partial x}{\partial t} + \Big[u(\rho,t) - \rho u(1,t)\Big]\frac{\partial x}{\partial \rho} \\ &= \lambda x - p_0 \gamma x v - \big[-\mu + (\lambda+\mu)x + \mu y\big]x, \end{aligned} \tag{3.29}$$

$$\frac{\partial y}{\partial t} + \Big[u(\rho,t) - \rho u(1,t)\Big]\frac{\partial y}{\partial \rho}$$
$$= p_0\gamma x v - \delta y - kyz - \big[-\mu + (\lambda+\mu)x + \mu y\big]y, \tag{3.30}$$

$$\frac{\partial v}{\partial t} - \rho u(1,t)\frac{\partial v}{\partial \rho} = \delta y - \gamma v + \frac{D_1}{R^2(t)}\ \frac{1}{\rho^2}\ \frac{\partial}{\partial \rho}\Big(\rho^2\frac{\partial v}{\partial \rho}\Big), \quad \frac{\partial v}{\partial \rho}(0,t) = 0, \tag{3.31}$$

$$\frac{\partial z}{\partial t} - \rho u(1,t)\frac{\partial z}{\partial \rho} = l\theta zy - \omega z^2 + \frac{D_2}{R^2(t)}\ \frac{1}{\rho^2}\ \frac{\partial}{\partial \rho}\Big(\rho^2\frac{\partial z}{\partial \rho}\Big), \quad \frac{\partial z}{\partial \rho}(0,t) = 0, \tag{3.32}$$

$$u(\rho,t) = \frac{1}{\rho^2}\int_0^\rho s^2\big[-\mu + (\lambda+\mu)x(s,t) + \mu y(s,t)\big]ds. \tag{3.33}$$

The boundary and initial conditions (3.24)-(3.3) become

$$\dot{R}(t) = R(t)u(1,t), \quad R(0) \text{ is given}, \tag{3.34}$$

$$\frac{\partial v}{\partial \rho}(1,t) = 0, \tag{3.35}$$

$$\frac{\partial z}{\partial \rho}(1,t) = 0, \tag{3.36}$$

$$x(\rho,0) = x_0(\rho), y(\rho,0) = y_0(\rho), v(\rho,0) = v_0(\rho), z(\rho,0) = z_0(\rho) \tag{3.37}$$

$$x_0(\rho) \geq 0, y_0(\rho) \geq 0, \quad x_0(\rho) + y_0(\rho) \leq 1, \quad z_0(\rho) > 0. \tag{3.38}$$

We also assume that

$$x_0(\rho), y_0(\rho), v_0(\rho) \text{ and } z_0(\rho) \text{ belong to } C^1[0,1], \text{ and } \frac{\partial v_0}{\partial \rho}(1) = \frac{\partial z_0}{\partial \rho}(1) = 0. \tag{3.39}$$

We now state a result on the global existence and uniqueness of solutions to the system (3.29)-(3.39) (see [144]).

Theorem 3.1. *The system (3.29)-(3.39) has a unique solution* $(x(\rho,t), y(\rho,t), v(\rho,t), z(\rho,t), u(\rho,t), R(t))$ *with* $x, \partial x/\partial\rho, y, \partial y/\partial\rho, v, \partial v/\partial\rho, z, \partial z/\partial\rho$ *and* $u, \partial u/\partial\rho$ *in* $C[0 \leq \rho \leq 1, 0 < t < \infty]$, $R(t)$ *in* $C^1[0,\infty)$, *and*

$$x(\rho,t) \geq 0, \quad y(\rho,t) \geq 0, \quad x(\rho,t) + y(\rho,t) \leq 1. \tag{3.40}$$

$$R(0)e^{-\beta t} < R(t) < R(0)e^{\beta t} \qquad \textit{for some } \beta > 0. \tag{3.41}$$

Furthermore, if $z_0(\rho) = const. = z_0$, *then*

$$\frac{z_0}{1+z_0\omega t} \leq z(\rho,t) \leq \frac{1}{\frac{\omega}{l\theta} + \left(\frac{1}{z_0} - \frac{\omega}{l\theta}\right)e^{-l\theta t}} \leq \max\left(z_0, \frac{l\theta}{\omega}\right). \tag{3.42}$$

We conclude this section by recalling, from [170], estimates on the size of parameters that appear in the system (3.29)-(3.32).

The parameter λ is typically small. For example, $\lambda = 3.2 \times 10^{-4}\ hr^{-1}$, which corresponds to a tumor doubling time of three months, typical for head and neck tumors [118]. The parameters δ and μ are one order of magnitude larger than λ. Laboratory results from Onyx suggest that the mean infected cell lifetime is about two days, and so we set $\delta = \frac{1}{48}\ hr^{-1}$. Typical necrotic removal rate $\mu = \frac{1}{72}\ hr^{-1}$. The tumor cell density $\theta = 10^6\ cells/mm^3$. The parameter γ is at least one order of magnitude larger than δ and μ, and some laboratory data suggests that γ is about 1 hr^{-1} [178]. Typical value of the clearance rate ω of the immune response is 1.6 $ml/ng\text{-}hr$. The three parameters, the immune stimulation rate l, the immune killing rate k, and the basic reproductive ration p_0, are more difficult to estimate. In [170], the authors use new clinical data to estimate that $p_0 = 3.73,\ k = 15.3\ mm^3/ng\text{-}hr,\ l = 0.048\ mm^3/cells\text{-}hr$.

The diffusion coefficients of several drugs given in [168] lay in the range $10^{-6} \sim 10^{-5}\ cm^2/s = 0.0864 \sim 0.864\ cm^2/day$. The drug diffusion coefficient given in [93] is 1.7 cm^2/day. For clarity and definiteness, we will take $D_1 =$

1 cm^2/day in (3.31). The immune response diffusion coefficient $D_2 = 7.0 \times 10^{-5} \sim 10^{-2}\ cm^2/day$ in (3.32), see [27] and the references therein.

3.4 Threshold of the Immune Response

In this section we study the effect of the immune response to cancer treatment. We will explore the threshold of the intensity of the immune response for controlling the tumor. We begin with the constant equilibrium solutions (x_s, y_s, v_s, z_s) to equations (3.29)-(3.32). We easily find there are precisely following six solutions of this type:

$$E_1 = (0,\ 0,\ 0,\ 0),$$

$$E_2 = (1,\ 0,\ 0,\ 0),$$

$$E_3 = \big(0,\ 1-\frac{\delta}{\mu},\ \frac{\delta}{\gamma}(1-\frac{\delta}{\mu}),\ 0\big),$$

$$E_4 = \Big(\frac{p_0\delta^2 - \mu(p_0\delta-\delta-\lambda)}{p_0\delta(p_0\delta-\lambda)},\ \frac{(\lambda+\mu)(p_0\delta-\delta-\lambda)}{p_0\delta(p_0\delta-\lambda)},\ \frac{\delta}{\gamma}\cdot\frac{(\lambda+\mu)(p_0\delta-\delta-\lambda)}{p_0\delta(p_0\delta-\lambda)},\ 0\Big),$$

$$E_5 = \Big(0,\ \frac{\omega(\mu-\delta)}{kl\theta+\mu\omega},\ \frac{\delta}{\gamma}\cdot\frac{\omega(\mu-\delta)}{kl\theta+\mu\omega},\ \frac{l\theta(\mu-\delta)}{kl\theta+\mu\omega}\Big),$$

$$E_6 = \Big(\frac{kl\theta(\lambda+\mu)+\omega[p_0\delta^2-\mu(p_0\delta-\delta-\lambda)]}{kl\theta(\lambda+\mu)+p_0\delta\omega(p_0\delta-\lambda)},\ \frac{\omega(\lambda+\mu)(p_0\delta-\delta-\lambda)}{kl\theta(\lambda+\mu)+p_0\delta\omega(p_0\delta-\lambda)},\ \frac{\delta}{\gamma}\cdot\frac{\omega(\lambda+\mu)(p_0\delta-\delta-\lambda)}{kl\theta(\lambda+\mu)+p_0\delta\omega(p_0\delta-\lambda)},\ \frac{l\theta(\lambda+\mu)(p_0\delta-\delta-\lambda)}{kl\theta(\lambda+\mu)+p_0\delta\omega(p_0\delta-\lambda)}\Big).$$

From (3.42) in Theorem 3.1 we have that $z(t)$ is nonnegative for all $t > 0$ if $z_0(\rho) = const. = z_0 > 0$. As a result, we are only interested in the stability of the equilibrium solutions in which $z_s > 0$. Hence, the equilibrium solutions $E_1,\ E_2,\ E_3$ and E_4 can be discarded. In the process of our analysis, we also

assume

$$\delta > \mu, \tag{3.43}$$

$$p_0 > 1 + \frac{\lambda}{\mu} + \frac{\lambda}{\delta} \tag{3.44}$$

which hold for the typical parameter values given in previous section. Since $\mu < \delta$ by (3.43), we see that $z_s < 0$ in E_5, and hence this equilibrium solution can also be discarded. So, we are only interested in the equilibrium solution E_6. In the following we shall prove that if the initial densities are approximately equal to E_6, then the evolution of the tumor radius $R(t)$ will *strongly* depend on the intensity ($m = \frac{lk\theta}{\omega}$) of the immune response.

Let $(x_s, y_s, v_s, z_s) = E_6$. We look at the system (3.29)-(3.39) with (x_0, y_0, v_0, z_0) near (x_s, y_s, v_s, z_s). It is convenient to introduce new variables:

$$\begin{aligned} &X(\rho,t) = x(\rho,t) - x_s,\ Y(\rho,t) = y(\rho,t) - y_s, \\ &V(\rho,t) = v(\rho,t) - v_s,\ \ Z(\rho,t) = z(\rho,t) - z_s, \\ &U(\rho,t) = u(\rho,t). \end{aligned} \tag{3.45}$$

Then the system (3.29)-(3.39) takes the following form in $\{0 < \rho < 1, t > 0\}$:

$$\begin{aligned} &\frac{\partial X}{\partial t} + \Big[U(\rho,t) - \rho U(1,t)\Big]\frac{\partial X}{\partial \rho} \\ &= \big[(\lambda+\mu) - (p_0\delta+\mu)y_s - 2(\lambda+\mu)x_s\big]X \\ &\quad -\mu x_s Y - p_0\gamma x_s V - \big[(\lambda+\mu)X + \mu Y + p_0\gamma V\big]X \\ &\quad +x_s[\lambda+\mu-(p_0\delta+\mu)y_s - (\lambda+\mu)x_s], \end{aligned} \tag{3.46}$$

$$\frac{\partial Y}{\partial t}+\Big[U(\rho,t)-\rho U(1,t)\Big]\frac{\partial Y}{\partial \rho}$$
$$=\big[p_0\gamma v_s-(\lambda+\mu)y_s\big]X-\big[(\delta-\mu)+(\lambda+\mu)x_s+2\mu y_s+kz_s\big]Y$$
$$+p_0\gamma x_s V-ky_sZ+\big[p_0\gamma XV-(\lambda+\mu)XY-\mu Y^2-kYZ\big]$$
$$+y_s[\mu-\delta-\mu y_s+(p_0\delta-\mu-\lambda)x_s-kz_s], \tag{3.47}$$

$$X(\rho,0)=X_0(\rho),\quad Y(\rho,0)=Y_0(\rho), \tag{3.48}$$

$$\frac{\partial V}{\partial t}-\rho U(1,t)\frac{\partial V}{\partial \rho}-\frac{D_1}{R^2(t)}\frac{1}{\rho^2}\frac{\partial}{\partial \rho}(\rho^2\frac{\partial V}{\partial \rho})=\delta Y-\gamma V, \tag{3.49}$$

$$V(\rho,0)=V_0(\rho),\quad \frac{\partial V}{\partial \rho}\Big|_{\rho=0}=\frac{\partial V}{\partial \rho}\Big|_{\rho=1}=0, \tag{3.50}$$

$$\frac{\partial Z}{\partial t}-\rho U(1,t)\frac{\partial Z}{\partial \rho}-\frac{D_2}{R^2(t)}\frac{1}{\rho^2}\frac{\partial}{\partial \rho}(\rho^2\frac{\partial Z}{\partial \rho})=(l\theta y_s-2\omega z_s)Z-\omega Z^2$$
$$+l\theta ZY+l\theta z_sY+z_s(l\theta y_s-\omega z_s), \tag{3.51}$$

$$Z(\rho,0)=Z_0(\rho),\quad \frac{\partial z}{\partial \rho}\Big|_{\rho=0}=\frac{\partial Z}{\partial \rho}\Big|_{\rho=1}=0, \tag{3.52}$$

$$U(\rho,t)=\frac{1}{\rho^2}\int_0^\rho s^2\big[Q+(\lambda+\mu)X(s,t)+\mu Y(s,t)\big]ds, \tag{3.53}$$

$$\dot{R}(t)=R(t)U(1,t),\quad R(0)\quad \text{is given}, \tag{3.54}$$

where $X_0(\rho)=x_0(\rho)-x_s, Y_0(\rho)=y_0(\rho)-y_s, V_0(\rho)=v_0(\rho)-v_s, Z_0(\rho)=z_0(\rho)-z_s$,

$$Q\equiv-\mu+(\lambda+\mu)x_s+\mu y_s$$
$$=\frac{m\lambda(\lambda+\mu)-p_0\delta[\mu(p_0\delta-\delta-\lambda)-\lambda\delta]}{m(\lambda+\mu)+p_0\delta(p_0\delta-\lambda)}$$
$$(\text{where } m=\frac{lk\theta}{\omega})$$

and $\frac{\partial V_0(\rho)}{\partial \rho}|_{\rho=1} = \frac{\partial Z_0(\rho)}{\partial \rho}|_{\rho=1} = 0$. Since (x_s, y_s, v_s, z_s) is an equilibrium solution, the last terms on the right-hand sides of (3.46), (3.47) and (3.51) vanish.

As in [178] we combine the immune response parameters l, k and ω into the single parameter $m = \frac{lk\theta}{\omega}$, which indicates the intensity of the immune response against the virus. That is, the immune response is strong when the value of l (the immune stimulation rate) and k (the immune killing rate) is large relative to ω (the immune response clearance rate).

In the following we shall assume

$$Q \neq 0. \tag{3.55}$$

Let us first consider the two eigenvalues (denoted by λ_1 and λ_2) of the linear coefficient matrix A of the hyperbolic system (3.46)-(3.47). Here

$$A = \begin{pmatrix} (\lambda+\mu) - (p_0\delta+\mu)y_s - 2(\lambda+\mu)x_s & -\mu x_s \\ (p_0\delta - \lambda - \mu)y_s & -(\delta-\mu) - (\lambda+\mu)x_s - 2\mu y_s - kz_s \end{pmatrix}. \tag{3.56}$$

Notice that

$$l\theta y_s = \omega z_s, \quad \lambda + \mu - (p_0\delta+\mu)y_s - (\lambda+\mu)x_s = 0,$$

then the matrix A can be rewritten as

$$\begin{aligned} A &= \begin{pmatrix} -(\lambda+\mu)x_s & -\mu x_s \\ (p_0\delta - \lambda - \mu)y_s & -(\delta-\mu) - (\lambda+\mu)x_s - (2\mu+m)y_s \end{pmatrix} \\ &=: \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}. \end{aligned} \tag{3.57}$$

By the assumptions (3.43) and (3.44) we easily find that

$$\lambda_1 + \lambda_2 \equiv a_{11} + a_{22} < 0,$$

$$\lambda_1 \cdot \lambda_2 \equiv |A| = a_{11}a_{22} - a_{12}a_{21} > 0.$$

Therefore, λ_1 and λ_2 have negative real parts,

$$Re\lambda_1 < 0, \quad Re\lambda_2 < 0. \tag{3.58}$$

Thus, we may expect that the constant equilibrium solution $(x_s, y_s, v_s, z_s) = E_6$ to Eqs. (3.29)-(3.33) is locally asymptomatically stable.

In fact, we have the following results [144].

Theorem 3.2. *Denote*

$$m = \frac{lk\theta}{\omega}$$

and assume that

$$Q =: \frac{m\lambda(\lambda+\mu) - p_0\delta[\mu(p_0\delta - \delta - \lambda) - \lambda\delta]}{m(\lambda+\mu) + p_0\delta(p_0\delta - \lambda)} \neq 0, \tag{3.59}$$

$$\delta > \mu \text{ and } p_0 > 1 + \frac{\lambda}{\mu} + \frac{\lambda}{\delta}. \tag{3.60}$$

If

$$\| X_0(\rho), Y_0(\rho), V_0(\rho), Z_0(\rho)\|_{C^1[0,1]} \leq \varepsilon \tag{3.61}$$

where ε is sufficiently small, then there exists a unique global solution $(X(\rho,t)$, $Y(\rho,t)$, $V(\rho,t)$, $Z(\rho,t)$, $U(\rho,t)$, $R(t))$ of (3.46)-(3.54) for all $t > 0$ with $R \in C^1[0,\infty)$, (X, Y, V, Z, U) in $C^1([0,1] \times [0,\infty))$ and the following estimates:

$$|X(\xi(t),t)| + |Y(\xi(t),t)| \leq Ce^{-\alpha t} \| (X_0, Y_0)\|_{C[0,1]}, \tag{3.62}$$

$$|\frac{\partial X}{\partial \rho}(\xi(t),t)| + |\frac{\partial Y}{\partial \rho}(\xi(t),t)| \leq Ce^{-\alpha t} \parallel (X_0, Y_0)\|_{C^1([0,1])}, \tag{3.63}$$

which hold for all $t > 0$*, where* $\xi(t) = \xi(t; \rho_0)$ *is any forward characteristic curve of the equations (3.46) and (3.47) satisfying* $\rho_0 = \xi(0; \rho_0)$ *and* C *is some positive constants independent of* T*. Furthermore, if*

$$0 \leq m < \frac{p_0\delta[\mu(p_0\delta - \delta - \lambda) - \lambda\delta]}{\lambda(\lambda + \mu)} =: m_0, \tag{3.64}$$

then

$$\dot{R}(t) < 0 \quad \textit{for all} \quad t > 0, \tag{3.65}$$

$$R(0)e^{-\frac{|Q|}{2}t} \leq R(t) \leq R(0)e^{-\frac{|Q|}{6}t} \quad \textit{for all} \quad t > 0; \tag{3.66}$$

if

$$m > m_0, \tag{3.67}$$

then

$$\dot{R}(t) > 0 \quad \textit{for all} \quad t > 0, \tag{3.68}$$

$$R(t) \geq R(0)e^{\frac{|Q|}{6}t} \quad \textit{for all} \quad t > 0. \tag{3.69}$$

Remark 3.2. In order to perform (3.1) and (3.5) mathematically, we need the following assumption

$$R(t) > r_c.$$

In fact, if the tumor radius $R(t) < r_c$ (here r_c is the radius of a tumor cell), then the tumor cannot contain a single live tumor cell and therefore the tumor is controlled. Actually, the models in [170, 178, 179] are valid only for $R(t) > r_c$. From $r_c = 0.01\ mm$, $R(0) = 2\ mm$ [178] we find that the tumor

nodule with a size of 2 mm in radius contains around 8×10^6 cells. So, the assumption $R(t) > r_c$ is minor, and the approximation (3.18) is reasonable.

Remark 3.3. In the absence of an immune response, the viruses (if uniformly injected throughout the tumor) may be powerful enough to eradicate the tumor. For example, if no immune response occurs (i.e., $m = 0$), then by Theorem 3.2 and the parameter values, $\lambda = 3.2 \times 10^{-4},\ \delta = \frac{1}{48},\ \mu = \frac{1}{72},\ p_0 = 3.73$, given in Section 3.3, we easily find that

$$R(t) \to 0 \qquad \text{monotonously and exponentially as } t \to +\infty.$$

Further, we see that without immune response (i.e., $m = 0$), the viruses can eradicate tumors with

$$\lambda \leq \big(\frac{1}{\delta} + \frac{1}{\mu}\big)^{-1}(p_0 - 1) = 0.0225\ hr^{-1}. \tag{3.70}$$

This means that any tumor with a doubling time more than 31 hours will be eradicated.

However, the strength of the immune-mediated clearance displayed in the human clinical data changes the entire picture. The viruses cannot control the tumor in the presence of the effective immune response. For example, by the clinical data given in [170], we have

$$m = \frac{lk\theta}{\omega} = 459\ hr^{-1},$$
$$m_0 = \frac{p_0\delta[\mu(p_0\delta - \delta - \lambda) - \lambda\delta]}{\lambda(\lambda + \mu)} \approx 13.81\ hr^{-1}.$$

Therefore

$$m \gg m_0.$$

So, from Theorem 3.2 we get

$$R(t) \to +\infty \qquad \text{monotonously and exponentially as } t \to +\infty.$$

Because of the relative low of p_0 we see that only the slowest-growing tumors might be eradicated by the viruses in presence of immune-mediated clearance. By Theorem 3.2, in order to control tumor, we need the following condition:

$$m < m_0.$$

that is,

$$\lambda < \frac{p_0(p_0-1)\delta^2}{m} \approx 0.0963 \times 10^{-7}\ hr^{-1},\ \text{approximately.} \tag{3.71}$$

Remark 3.4. The *critical* immune response intensity m_0 found in Theorem 3.2 is biologically interesting. In order to improve the efficacy of the oncolytic adenovirus, the immune-mediated viral clearance must be suppressed. One possible strategy to combat the effect of the immune response is to administer an immune suppressor, which would decrease the stimulation rate l in our model. For example, if

$$l < 1.4441 \times 10^{-3}\ mm^3/cells - hr, \tag{3.72}$$

then, the tumor can be controlled from Theorem 3.2 for the typical parameter values given in Section 3.3. In fact, Friedman et al [65] proposed a mathematical model considering the effects of an immune suppressor.

Remark 3.5. Currently, biopharmaceutical companies and academic investigators working in the area of cancer viral therapies have made hundreds of viruses that are potential candidates for cancer therapy (see [170], for instance).

3.5 A Time-Delay Model

The data in [170] suggests that the immune system responds to the virus infection with a time delay of about 42 hours.

Using the quasi-steady-state approximation, $V = \frac{\delta}{\gamma}Y$, a simplified version of the system (3.46)-(3.54) with a time delay τ for the immune response takes the following form:

$$\begin{aligned}
&\frac{\partial X}{\partial t} + \Big[U(\rho,t) - \rho U(1,t)\Big]\frac{\partial X}{\partial \rho} \\
&= \big[(\lambda+\mu) - (p_0\delta+\mu)y_s - 2(\lambda+\mu)x_s\big]X \\
&\quad -\mu x_s Y - p_0\gamma x_s V - \big[(\lambda+\mu)X + \mu Y + p_0\gamma V\big]X, \qquad (3.73)
\end{aligned}$$

$$\begin{aligned}
&\frac{\partial Y}{\partial t} + \Big[U(\rho,t) - \rho U(1,t)\Big]\frac{\partial Y}{\partial \rho} \\
&= \big[p_0\gamma v_s - (\lambda+\mu)y_s\big]X - \big[(\delta-\mu) + (\lambda+\mu)x_s + 2\mu y_s + k z_s\big]Y \\
&\quad + p_0\gamma x_s V - k y_s Z + \big[p_0\gamma XV - (\lambda+\mu)XY - \mu Y^2 - kYZ\big], \qquad (3.74)
\end{aligned}$$

$$X(\rho,0) = X_0(\rho), \quad Y(\rho,0) = Y_0(\rho), \qquad (3.75)$$

$$\begin{aligned}
&\frac{\partial Z}{\partial t} - \rho U(1,t)\frac{\partial Z}{\partial \rho} - \frac{D_2}{R^2(t)}\frac{1}{\rho^2}\frac{\partial}{\partial \rho}(\rho^2\frac{\partial Z}{\partial \rho}) = (l\theta y_s - 2\omega z_s)Z - \omega Z^2 \\
&\qquad + l\theta ZY(\cdot, t-\tau) + l\theta z_s Y(\cdot, t-\tau), \qquad (3.76)
\end{aligned}$$

$$Z(\rho,0)=Z_0(\rho),\quad \frac{\partial Z}{\partial \rho}\Big|_{\rho=0}=\frac{\partial Z}{\partial \rho}\Big|_{\rho=1}=0, \tag{3.77}$$

$$U(\rho,t)=\frac{1}{\rho^2}\int_0^\rho s^2\big[Q+(\lambda+\mu)X(s,t)+\mu Y(s,t)\big]ds, \tag{3.78}$$

$$\dot{R}(t)=R(t)U(1,t),\quad R(0)\quad \text{is given.} \tag{3.79}$$

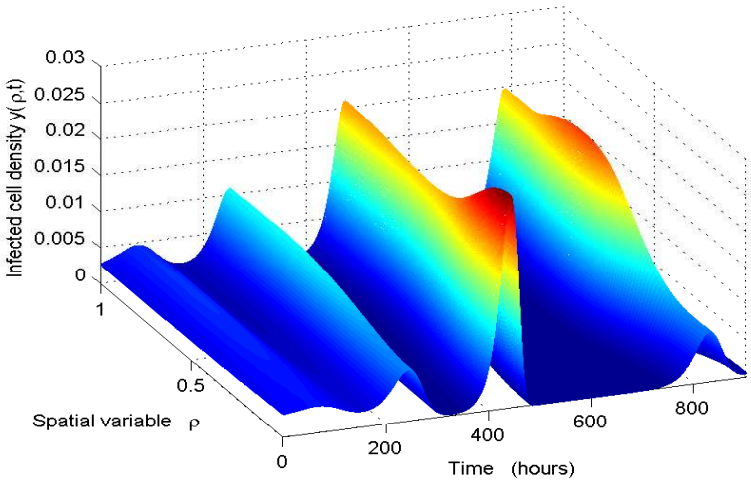

Fig. 3.1. The spatio-temporal dynamics of the density $y(\rho,t)$ of the infected cells for $D_2=0.015,\ l=1.8\times10^{-3},\ \tau=50,\ (x_s,y_s,z_s)=(0.97933,0.00321,0.00361)$. Take $(x_0(\rho),y_0(\rho),z_0(\rho))\sim(x_s,y_s,z_s)$.

Figure 3.1 shows the spatio-temporal dynamics of the infected cells. Clearly, if the immune system responds to the virus with a time delay $\tau>\tau_0$ (where $\tau_0\approx 28.6$ is the critical value for the stability of the steady state E_6, see [144]), then the density of the infected cells will have an oscillation. This oscillation may become strong. Figure 3.1 also indicates the spatially heterogeneous distribution of the infected cells.

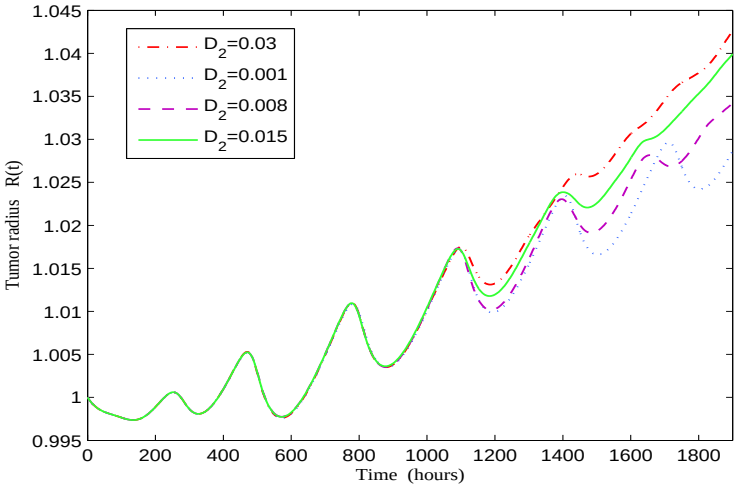

Fig. 3.2. The effects of the diffusivity D_2 of the immune response on tumor growth for $l = 1.8 \times 10^{-3}$, $\tau = 50$, $(x_s, y_s, z_s) = (0.97933, 0.00321, 0.00361)$. Take $(x_0(\rho), y_0(\rho), z_0(\rho)) \sim (x_s, y_s, z_s)$.

Figure 3.2 shows that the diffusivity D_2 of the immune response has little effects on the tumor growth when the time $t \leq 1100$ (hours) and the immune system responds to the virus with a time-delay $\tau > \tau_0$. However, the tumor growth will heavily influenced by the diffusivity D_2 when the time is large ($t > 1100$ hours ≈ 46 days). Furthermore, we find that the tumor growth is monotonously increasing if the time t is sufficiently large. This phenomenon may be biologically explained as follows. The faster the immune response diffuses, the more quickly the viruses may be killed, which may mitigate the effects of the treatment.

3.6 Glioma Virotherapy

In this section, we review a mathematical model about glioma virotherapy proposed by Friedman and Tian et al [65]. This model is similar to a model introduced by Wu et al [178, 179]. However, there are several important differences. First, this model has included the effects of immunosuppressive agent Cyclophosphamide (CPA), and we used our model to determine the effect of administering CPA under different protocols on the progress of glioma. A second difference is that our model includes the presence of innate immune cells in the tumor tissue, whereas [178] includes only the immune response (tumor necrotic factor TNF) which consists of molecules with negligible volume. This difference is important, since the immune cells make up to 50% of the total number of cells at some stages of the tumor progression. We have also added a term which accounts for the destruction of virus particles by the immune cells [5]. Finally, in the mathematical model of [178], the parameters are estimated by using data from head and neck cancer. In our model, the parameters are estimated so as to conform with experimental results for glioma in article by Fulci G et al, *Cyclophospharnide enhances glioma virotherapy by inhibiting innate immune response* [68]. There is a substantial difference in the values of some of the parameters due to the fact that glioma is much more aggressive cancer.

3.6.1 Mathematical model and parameter values

Our model includes infected tumor cells (y), uninfected tumor cells (x), necrotic cells (n), immune cells (z) and free virus particles (v). The model is given as follows.

$$\frac{\partial x(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u(r,t)x(r,t)) = \lambda x(r,t) - \beta x(r,t)v(r,t), \tag{3.80}$$

$$\frac{\partial y(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u(r,t)y(r,t)) = \beta x(r,t)v(r,t) - ky(r,t)z(r,t) - \delta y(r,t), \tag{3.81}$$

$$\frac{\partial n(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 n(r,t)u(r,t)) = ky(r,t)z(r,t) + \delta y(r,t) - \mu n(r,t), \tag{3.82}$$

$$\frac{\partial z(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 z(r,t)u(r,t)) = sy(r,t)z(r,t) - c(z(r,t))z(r,t) - P(r,t)z(r,t) \tag{3.83}$$

$$\frac{\partial v(r,t)}{\partial t} - D\frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial v}{\partial r} = b\delta y(r,t) - k_0 v(r,t)z(r,t) - \gamma v(r,t), \tag{3.84}$$

We assume that all the cells have the same size and that they are uniformly distributed in the tumor. Then

$$x(r,t) + y(r,t) + n(r,t) + z(r,t) = \text{const.} = \theta \tag{3.85}$$

and, by [122], $\theta \approx 10^6 \text{cells}/mm^3$.

Combining the equations (3.80)-(3.83) and using (3.85), we obtain

$$\begin{aligned} &\frac{\theta}{r^2}\frac{\partial}{\partial r}(r^2 u(r,t)) \\ &= \lambda x(r,t) - \mu n(r,t) + sy(r,t)z(r,t) - c(z(r,t))z(r,t) - P(r,t)z(r,t). \end{aligned} \tag{3.86}$$

We also have

$$\frac{\partial v}{\partial r}(0,t) = 0, \qquad \text{for} t > 0. \tag{3.87}$$

Since the free viruses remain in the tumor,

$$\frac{\partial v}{\partial r}(R(t),t) = 0, \text{ for } t > 0. \tag{3.88}$$

Finally, the free boundary is subject to the kinematic condition

$$\frac{dR(t)}{dt} = u(R(t),t). \tag{3.89}$$

In our simulation, we will take R(0)=2 mm and

$$x(r,0) = 0.84 \times 10^6, y(r,0) = 0.1 \times 10^6,$$

$$z(r,0) = 0.06 \times 10^6, v(r,0) = Ae^{-\frac{r^2}{2^2}}, 0 \leq r \leq 2$$

$$5.2\pi \times 10^8 \leq 4\pi \int_0^2 Ae^{-\frac{r^2}{2^2}} r dr \leq 11.2\pi \times 10^8.$$

The way immune cells are cleared is typically by membrane protein Fas and FasL which, when combined on the cell surface, signal to caspase protein to execute the cell. The percentage of immune cells in the brain is typically 1-2%. When stimulated by infected cells in glioma, this percentage arises sharply. As the number of infected cells drops, the need for immune cells diminishes, so they undergo apoptosis, either by killing themselves (using their own Fas and FasL to activate caspase) or by killing each other (Fas from one cell ligands to FasL from another cell)[5] [121]. The first process occurs when z is small, and yields a linear clearance; the second process occurs when z is large, and it yields a quadratic clearance. Hence,

$$c(z)z = \begin{cases} cz & \text{if } z < z_0, \\ \frac{c}{z_0} z^2 & \text{if } z \geq z_0. \end{cases}$$

From [121] one can infer the value of z_0, and combining this with the linear clearance rate, we arrive at the number $\omega = \frac{c}{z_0} \approx 20 \times 10^{-8} mm^3/hour \cdot cell$. For simplicity we will assume only quadratic clearance with a rate ω as above.

After CPA is administered to the rats, the level of CPA arises and reaches a plateau after 2 days. This level is maintained for approximately 3 days and then begins to drop off to zero in the next two days. We simulate the CPA level in the tumor by a piecewise linear function

$$P(t) = \begin{cases} 8.5 \times 10^{-2} & \text{if } 0 \leq t \leq 72, \\ \frac{8.5 \times 10^{-2}}{48}(120 - t) & \text{if } 72 \leq t \leq 120, \end{cases}$$

and $P(t) = 0$ if $t \geq 120$, where the unit of $P(t)$ is 1/hour.

The model parameters are based on experimental results of Fulci et al **??**. In these experiments D74/HveC Rat Glioma cell lines were implanted into the brain of rats. After 7 days, the tumor reached the size of 4mm in diameter, and then the oncolytic virus hrR3 (which is a mutant of Herpes Simplex virus 1 (HSV)) was injected into the center of the tumor. This mutant attacks tumor cells, but does not attack healthy normal cells. Six hours after injection, some rats were sacrificed, the tumor was stained and the JPEG pictures were taken, and then the infected area of the tumor was measured. This procedure was repeated after 72-76 hours from the time of virus injection, and then once more, one week after virus injection. Five different stains were used: one for

each of four innate immune cells, and one for the infected cells. The immune cells are CD11b (dendritic cells), CD68+ (main monocytes, also called ED1 in rats), CD163+ (also called ED2 in rats) and CD169 (also called ED3 in rats). Different immune cells may participate in the inflammatory response at different time points and may be cleared at different time points. Rapid up-regulation was observed for certain immune cells, and depletion of some macrophages alone has also been produced. However, the CPA effects on the different immune cells were only partially reproduced. For this reason, we shall take in our model the average response of all the immune cells, rather than the response of each population of immune cells. The immunosuppression drug CPA was pre-administered to rats on the fifth day after tumor cell implantation, that is, 2 days before virus injection. Most of the parameter values we obtained from experimental results or literature. We provide them here: Proliferation rate of tumor cells $\lambda = 2 \times 10^{-2}$ per hour, Infected cell lysis rate $\delta = \frac{1}{18}$ per hour, Removal rate of necrotic cells $\mu = \frac{1}{48}$ per hour, Burst size of infected cells $b = 50$ viruses per cell, Density of tumor cells $\theta = 10^6$ cells per mm^3, Diffusion coefficient of viruses $D = 3.6 \times 10^{-2}$ mm^2 per hour, Infection rate $\beta = \frac{7}{10} \times 10^{-9}$ mm^3 per hour per virus, Immune killing rate $k = 2 \times 10^{-8} mm^3$ per hour per immune cell, Take-up rate of viruses $k_0 = 10^{-8} mm^3$ per hour immune cell, Stimulation rate by infected cells $s = 5.6 \times 10^{-7} mm^3$ per hour per infected cell, Clearance rate of immune cells $\omega = 20 \times 10^{-8} mm^3$ per hour per cell, Clearance rate of viruses $\gamma = 2.5 \times 10^{-2}$ per hour.

3.6.2 Comparing with data

In order to compare our numerical simulation with the experimental results of article [68] we take, as in article [68], the initial radius of the tumor to be 2mm, and the number of particle forming units (pfu) of virus injected at the center to be 10^8-10^9. The initial time is the seventh day after tumor implantation in the rat's brain.

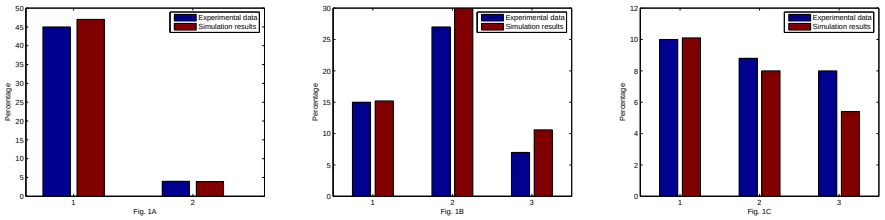

Fig. 3.3. Experimental data vs simulation results. Figure 1A is for infected tumor cells without CPA; Figure 1B is for immune cells without CPA; Figure 1C is for innate immune cells with CPA. In each picture, data group 1 is after 6 hours, data group 2 is after 72 hours and data group 3 is before the rat dies.

Fig.3.3 1A compares the experimental measurements with our numerical simulation of the percentage of infected tumor cells (relative to the total number of all cells) without pretreatment of CPA. Fig.3.3 1B compares the experimental measurement data with the numerical simulation of the percentage of the innate immune cells without pretreatment of CPA. Fig.3.3 1C compares the experimental measurements of immune cells, when CPA was administered, with our numerical simulation. The discrepancy between

measurements and simulation develops only after a relatively long time both in Fig.3.3 1B and 1C.

Fig.3.3 shows that our model fits quite well with experiments. We next proceed to compare the cancer progression with and without CPA.

3.6.3 Comparing studies

Fig.3.4 shows simulation results based on our model. Fig.3.4 A shows the

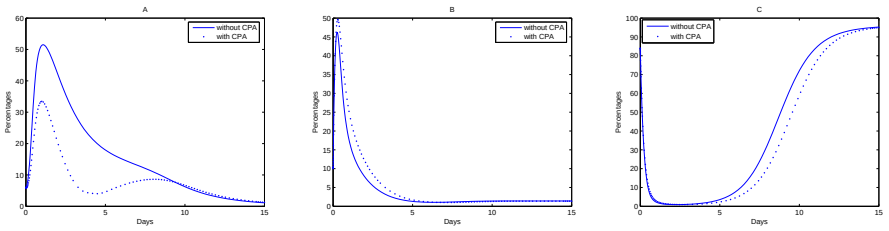

Fig. 3.4. Profiles of the percentages of cell populations within the tumor with and without CPA. Figure A is for innate immune cells, B is for infected tumor cells, and C is for uninfected tumor cells.

profiles of the averages over space, of immune cell densities with and without CPA pre-treatments. Without CPA, the immune cells reach the maximum 52% at 26th hour after virus injection; with CPA, the immune cells reach the maximum 34% at 24th hour after virus injection. Thus, CPA suppresses the maximum level of innate immune cells and shortens the time that the immune system reaches its peak. Since the effect of CPA disappears after 120 hours, the percentage of the immune cells climbs up after 120 hours, thus forming a bimodal profile.

Fig.3.4 B shows the profiles of the percentage of infected tumor cell with and without CPA. Clearly with CPA we expect to have more infected cells. As the simulation shows, without CPA, the infected cells reach the maximum 46% at 5th hour; with CPA, the infected cells reach the maximum 50% at 7th hour approximately.

Fig.3.4 C shows the profiles of the percentage of uninfected tumor cells with and without CPA. The first thing to notice is that there is a time delay in the effect of CPA; the immune suppression does not begin right away; in fact, there is a 3 days delay. The effect of CPA becomes negligible after approximately 17 days. However, during the intermediate period, it is significant.

3.6.4 Burst size of viruses

Suppose we inject into the tumor OV which replicates at a faster rate than hrR3. A large burst size b of virus will increase the stimulation of the immune system, which will then attack the infected cells and the free viruses. As a result, the population of viruses will decrease and this will be followed by a decrease in the population of immune cells. The population of virus and infected cells will then be able to increase, and it will follow by a re-stimulation of the immune system, etc. Thus, we may expect a "feedback mechanism" which will cause an oscillatory behavior of the percentages of infected cells, immune cells, and uninfected cells, with slight time-shift of the corresponding maxima. This is indeed demonstrated in Fig.3.5 for burst size $b = 400$ and

1000. For smaller values of b such as $b = 200$, oscillations occur only in the first 20-30 days. For $b = 50$ (not shown here), we do not see any oscillation.

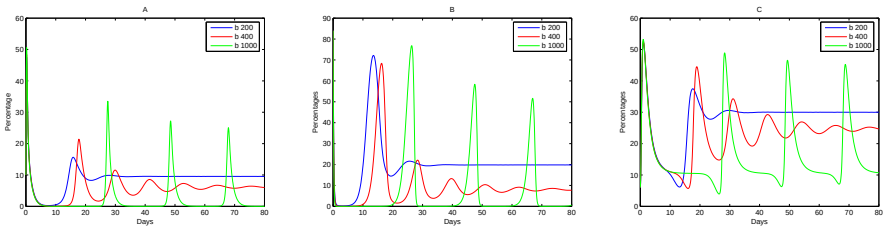

Fig. 3.5. Profiles of cell populations within the tumor with different burst sizes. Figure A is for infected tumor cells, B is for uninfected tumor cells, and C is for innate immune cells.

3.6.5 CPA treatments

We compare two different protocols for administering CPA. The first protocol is to administer a "normal" amount of CPA weekly, and the second protocol is to administer twice the normal amount every two weeks. The simulation results of the percentage of uninfected tumor cells for burst sizes $b = 100, 200$ and 400 is shown in Fig.3.6.

These figures show that there is little difference between the weekly and bi-weekly treatments, especially when we consider weekly averages.

It is instructive to compare these treatments with the "traditional" treatment, where we pre-administer normal amount CPA just once. The weekly treatment reduces the weekly averages of the uninfected cells, but due to oscillations

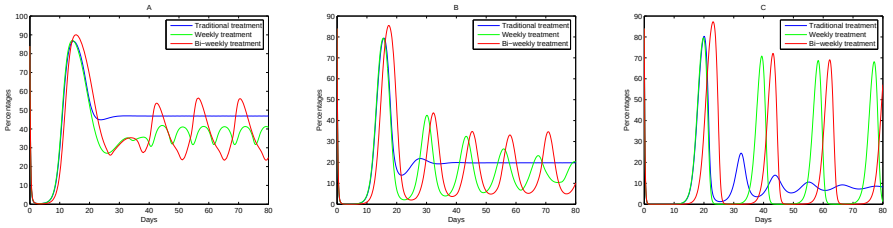

Fig. 3.6. Profiles of uninfected tumor cell populations with different treatments and different burst sizes. Figure A is for burst size 100, B is for burst size 200, and C is for burst size 400.

there are periods of time when this traditional treatment yields a small percentage of uninfected cells.

3.6.6 The tumor radius

All the preceding numerical results are based on solving the partial differential equations (PDEs) of the model given in the Appendix and then taking averages over the tumor region. We have obtained approximately the same numerical results using the much simpler ordinary differential equations (ODEs) obtained by neglecting spatial variations.

There is however one important quantity that we have not yet taken into account, namely, the radius of the tumor, and in order to compute it we need to work directly with the PDE system.

As the simulations presented above show, uninfected tumor cells will persist even with large burst sizes and with repeated CPA treatments. However, if the radius of the tumor can be kept small enough then long term

survival of the animals can be assured, unless cell invasion and metastasis will occur as a result of cell shedding and migration.

Fig.3.7 simulates the growth of the tumor radius for $b = 50$ without CPA and with one pre-treatment of CPA.

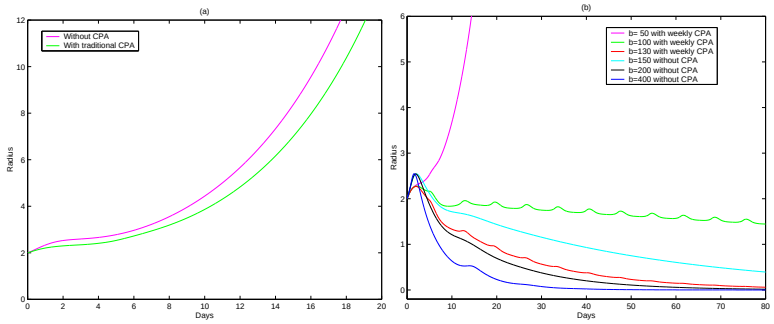

Fig. 3.7. Tumor radius with different burst sizes and CPA treatments.

According to Fulci et al [68], without CPA the rats die after 8-10 days after the injection of viruses, and with one CPA pretreatment the rats die after 11-13 days after the injection of viruses; at death, the radius of the tumor is approximately 6 mm. These experimental results roughly fit with the simulations in Fig.3.7a.

Fig.3.7b simulates the growth of the tumor's radius without CPA and with weekly CPA treatment for different burst sizes.

We see that with weekly CPA treatment, the radius of the tumor will decrease as long as the burst size is bigger than 100; without any CPA treatment and with burst size b already as high as 150, the radius of the tumor will decrease to 1 mm. If the burst size could be increased to 400, the

tumor will shrink to an extremely small size. Finally, the weekly treatment by CPA helps in decreasing the radius of the tumor, as can by seen by comparing the profiles in Fig.3.7b for burst size $b = 130$ and $b = 150$: For $b = 130$ with CPA we achieve a smaller radius than for $b = 150$ without CPA.

3.6.7 Conclusion of glioma virotherapy

We have shown that with the current burst size of oncolytic virus hrR3 the tumor cannot be eradicated with CPA treatment. In fact, its radius will grow, and the rats will die within several weeks. If, however, the virus can be further altered to yield a burst size $b \geq 150$, then the tumor will shrink to a very small size, even with no CPA treatment. It is well known that tumor cells in glioma may shed and migrate into other areas in the brain. We did consider this infiltration/invasion problem. Thus even when the tumor size can be kept very small, there is still a chance of developing a secondary tumor. In this respect, a repeated treatment of the tumor by CPA is important, for it decreases the percentage of uninfected tumor cells, and thus reduces the risk of secondary tumors.

As was shown, by our model, that there is little difference between the weekly and bi-weekly CPA treatments. The protocol of choice should therefore depend on the side effects to this chemotherapy.

Finally, our model considers only spherical gliomas with oncolytic virus injection at the center. But we expect that conclusions here will hold also for non-spherical gliomas.

Based on this mathematical model, there are several studies on particular aspect of the glioma virotherapy. For example, an analysis [157] shows the replicability of oncolytic virus is a critical parameter, [158, 159] show rich and complex dynamical behavior involved in virotherapy.

3.7 Summary

Replication-selective viruses as a novel therapeutic approach for cancer treatment have now been used in clinical trials. The immune response to anti-tumor virus can cause early elimination of viruses but also possibly be beneficial because it causes the immune-mediated killing of tumor cells. So, the competitive dynamics between tumor cells, a replication virus and the immune response is complex. To figure out the complex dynamics and help to design optimal protocols of tumor treatment, mathematical models may be needed. Wein, Wu and Kirn [170] have formulated a model describing the complex interplay between tumor cells, a replication-competent virus that kill tumor cells, and an immune response that kills the virus-infected tumor cells (and hence the virus itself). The mathematical model is a free boundary problem for a nonlinear system of partial differential equations. The variables are the radius of the tumor $r = R(t)$, the evolving densities $x(r,t), y(r,t), n(r,t), v(r,t)$ and $z(r,t)$ of the uninfected cells, the infected cells, the dead cells, the free viruses and the immune response, and the velocity field $u(r,t)$.

Importantly, an explicit and theoretical threshold m_0 of the intensity m of the immune response for controlling the tumor was found by Tao and Guo [144] in the following sense:

(i) If $0 \leq m < m_0$, then for the initial densities

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

$$v(r,0) \sim \text{const.} = v_s,\ z(r,0) \sim \text{const.} = z_s,$$

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

(ii) If $m > m_0$, then for the same initial densities $(x(r,0), y(r,0), v(r,0), z(0)) \sim (x_s, y_s, v_s, z_s)$ as in (i), the radius $R(t)$ will *increase* monotonically and exponentially to ∞ as t increase to ∞.

The above result suggests that the efficacy of the replication-competent viruses for treatment of tumors *strongly* depends on the intensity of an innate immune response against virus-infected tumor cells. Therefore, the viruses should be designed to immune avoidance, in addition to tumor-selectivity and safety. One possible strategy to combat the effect of the immune response is to co-administer an immune suppressor, which have been considered by Friedman et al. [65]. It is reported that hundreds of viruses have now been tested preclinically, and at least ten have already initiated testing in humans [65, 179].

We have found that for one pair of initial densities

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

the following is true:

Given *any* initial radius $R(0)$, if the intensity m of the immune response against the virus is weaker than the threshold m_0, by injecting virus particles of density

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

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

This example suggests that one may reduce tumors with doses of viral densities that are not necessarily large, which is quite different from the traditional chemotherapy in the sense that the doses of drugs of chemotherapy are usually large [92]. The above difference may be due to the replicating ability of virus within the tumor tissue.

We also review a similar mathematical model for glioma virotherapy in Section 3.6. This model includes the effects of immunosuppressive agent Cyclophosphamide (CPA). This model has a new term which accounts for the destruction of virus particles by the immune cells. This model explicitly includes the biological parameter virus burst size b. As a concrete study, the parameter values are estimated so as to conform with experimental results for glioma in article [68]. We used this model to determine the effect of administering CPA under different protocols on the progress of glioma. We showed that with the current burst size of oncolytic virus hrR3 the tumor cannot be eradicated with CPA treatment. In fact, the gliomas will grow, and

the rats will die within several weeks. But, if the virus can be further altered to yield a burst size $b \geq 150$, then the tumor will shrink to a very small size, even with no CPA treatment. There is a difference between CPA pre-treatment and repeated treatment, although there is little difference between the weekly and bi-weekly CPA treatments.

This chapter also reviews the spatio-temporal heterogeneity of cancer cells caused by the time-delay of the immune response. In fact, spatial heterogeneity is an important topic in mathematical biology; see [28, 41], for instance.

4

Modeling Cancer Radiovirotherapy

4.1 Introduction

Traditional therapy for tumors is chemotherapy. Mathematicians have developed some mathematical models to study and improve chemotherapy, for example, models presented in articles [93, 168] and rigorously analysis presented in articles [143, 145]. However, one of the obstacles in developing efficient chemotherapy to cancers is in the delivery process. The macromolecules used as drug delivery carriers are too large to be transported into, and diffuse within, the tumor [92]. Recently, replication-competent viruses have been proposed as an approach to bypass the delivery problem. The advantage of replicating viruses for cancer therapy is the establishment of the persistent infection with ongoing viral proliferation. The virus is engineered to selectively bind to receptors on the tumor cell surface (but not to the surface of normal healthy cells). The virus particles then gain entry by endocytosis and 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. Mathematical models of virotherapy have recently been developed [178] and studied [61]. However, a major factor influencing the efficacy of virus agents is immune response. New clinical data [117, 118] revealed an innate immune response to viruses that may mitigate the effects of treatments. The interaction between tumor cells, a replication-competent virus and the potential immune response is a complex biological process [170, 175, 176, 179].

The study in [175] suggests that a fast growth rate of the tumor decreases the efficacy of treatments with viruses, the success of therapies can be promoted by using a combination of viral therapy and conventional chemotherapy or radiotherapy. These suggestions are supported by experimental data [56, 77, 129]. The studies in [49, 50, 51] show that while some cell lines are sensitive in vitro to the oncolytic effect of the virus, tumor xenografts in animal models can persist despite repeated doses of the virus. In order to circumvent this problem, Dingli *et al* [49, 50] engineered the virus to induce expression of the human sodium iodide symporter that allows infected tumor cells to concentrate on iodide isotopes. This virus retains the natural oncolytic activity of the parent virus but has the advantage that it can eliminate tumors resistant to the virus when it is combined with radioiodide [49]. The ODE model developed by Dingli *et al* in [51], is the first mathematical model for radiovirotherapy.

Radiovirotherapy requires not only injection of viruses but also administration of radioiodide. Radioiodide is in a continuous state of flux between the tumor and the remaining part and continuously lost from the system due to both

physical decay as well as losses to the environment due to excretion [49]. The experimental data in [49, 50] were obtained for immunocompromised mice and these mice do not mount an immune response to either the virus or tumor. On the other hand, the model in [51] focuses on multiple myeloma and patients with multiple myeloma, the disease for which the virus was designed, have profound defects in the immune system. So, the model in [51] does not explicitly include the immune system.

Tao and Guo [146] developed a PDE model for cancer radiovirotherapy, which is a generalization of Dingli *et al*'s ODE model [51]. The ODE model in [51] provides a simplified description of cancer radiovirotherapy as homogeneity assumption is imposed. However, more effective therapy requires a deep understanding of non homogeneity of tumor spatial structures. In this chapter, we review the PDE model for radiovirotherapy proposed by Tao and Guo (2007). Modeling method in this article is a combination of that in [51, 61] and [178]. The tumor volume is modeled as an incompressible fluid, through which cells move via a convective field. Local changes in cell numbers lead to variations of the internal pressure, which in turn induce motion of tumor cells.

((The structure of this chapter is as follows. Section 4.2 presents the model. Section 4.3 scales the system of equations by non-dimensionalization and reduces the free boundary problem into a problem in a fixed region. Section 4.4 discusses constant equilibrium solutions. Section 4.5 is devoted to study the stability of equilibrium solutions and to find an explicit parameter condition

for tumor eradication by this novel therapy. Section 4.6 numerically studies the model to explore possible optimal therapy strategies. Finally, this chapter is closed with a summary and discussion section.))

4.2 Mathematical Model

In order to model the effects of radiation on tumor cells, we introduced a population of cells that is irreparably damaged by radiation, in addition to populations of virus particles, uninfected cells, infected cells and necrotic cells. These damaged cells do not proliferate, and are destined to die. But they still occupy space and compete for nutrients, and therefore should contribute to the self-regulation of tumor growth. We then introduce the following physical variables,

$\hat{x}$ = density of uninfected tumor cells,

$\hat{y}$ = density of infected tumor cells,

$\hat{z}$ = density of tumor cells irreparably damaged by radiation,

$\hat{n}$ = density of necrotic cells,

$\hat{v}$ = density of free viruses in the extracellular tissues,

u = the velocity field within the tumor.

The velocity field is a result of the spatio-temporal variation due to the proliferation of uninfected tumor cells and the removal of necrotic cells. Local changes in cell population lead to variations in the internal pressure, which

in turn, induce motion of tumor cells. We assume that the tumor is radially symmetric, so that all unknown variables or functions depend only on (r,t), where r is the distance from the tumor center and t is time. The model was derived by applying the principle of mass conservation to each of the cell population. The model consists of the following system of equations:

$$\begin{aligned}\frac{D\hat{x}}{Dt} &\equiv \frac{\partial \hat{x}}{\partial t}(r,t) + \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 u(r,t)\hat{x}(r,t)\Big) \\ &= \lambda\hat{x}(r,t) - \beta\hat{x}(r,t)\hat{v}(r,t) - \kappa D(t)\hat{x}(r,t), \end{aligned} \tag{4.1}$$

$$\begin{aligned}\frac{D\hat{y}}{Dt} &\equiv \frac{\partial \hat{y}}{\partial t}(r,t) + \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 u(r,t)\hat{y}(r,t)\Big) \\ &= \beta\hat{x}(r,t)\hat{v}(r,t) - \delta\hat{y}(r,t) - \kappa D(t)\hat{y}(r,t), \end{aligned} \tag{4.2}$$

$$\begin{aligned}\frac{D\hat{z}}{Dt} &\equiv \frac{\partial \hat{z}}{\partial t}(r,t) + \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 u(r,t)\hat{z}(r,t)\Big) \\ &= \kappa D(t)\big(\hat{x}(r,t) + \hat{y}(r,t)\big) - \sigma\big(\hat{z}(r,t)\big)^{\nu}, \end{aligned} \tag{4.3}$$

$$\begin{aligned}\frac{D\hat{n}}{Dt} &\equiv \frac{\partial \hat{n}}{\partial t}(r,t) + \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 u(r,t)\hat{n}(r,t)\Big) \\ &= \delta\hat{y}(r,t) + \sigma\big(\hat{z}(r,t)\big)^{\nu} - \mu\hat{n}(r,t), \end{aligned} \tag{4.4}$$

$$\frac{\partial \hat{v}}{\partial t}(r,t) = N\delta\hat{y}(r,t) - \gamma\hat{v}(r,t) + d\frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial \hat{v}}{\partial r}(r,t)\Big), \quad \frac{\partial \hat{v}}{\partial r}(0,t) = 0. \tag{4.5}$$

Although we do not consider the microenvironment within the tumor, we implicitly assume that tumor cells have ample nutrients, and allow them to experience first-order growth with a rate constant λ in (4.1) [178]. β is the infection rate of the uninfected cells. The rate κ by which tumor cells (both virus infected and uninfected) become irreparably damaged by radiation is

assumed to be proportional to the radiation dose $D(t)$ absorbed by these cells and to their densities [51, 164]. Parameter κ is taken to be the constant for simplicity.

In (4.2), δ is the death rate of the infected cells from lysis. This parameter measures viral cytotoxicity.

In (4.3), the term $\sigma\big(\hat{z}(r,t)\big)^{\nu}$ represents the effective death rate of damaged cells. Power-law dependence of rates is known to represent general behavior of biological systems [131]. The data in [51] suggests that $0 < \nu \leq 1$.

In (4.4), μ is the removal rate of the necrotic cells.

In (4.5), γ is the removal (or clearance) rate of viruses ($1/\gamma$ is the mean lifetime of free viruses), $N\delta$ is the virus release rate (N is the burst size of virus at the death of an infected cell), and d is the diffusion coefficient of viruses.

Radioiodide is in a continuous state of flux between the tumor and the remaining part. Iodide undergoes beta particle decay. The emitted beta particles have a path length of 0.8 mm with a significant effect on tumor cells [49, 50]. In model (4.1)-(4.5), we assume that after injection, radioactive iodine is rapidly distributed within the tumor, and that only the radioactivity at tumor site contributes to the absorbed dose [51]. The absorbed radiation dose $D(t)$ is proportional to the cumulative activity [49, 82].

We finally assume that all tumor cells have the same size, and that they are uniformly distributed in the tumor. Then,

$$\hat{x} + \hat{y} + \hat{z} + \hat{n} \equiv \text{const.} \equiv \theta. \tag{4.6}$$

Summing equations (4.1)-(4.4) together and using (4.6) yield

$$\frac{\theta}{r^2}\frac{\partial}{\partial r}\Big(r^2 u(r,t)\Big) = \lambda \hat{x}(r,t) - \mu \hat{n}(r,t). \tag{4.7}$$

The boundary conditions, at the outer boundary of the tumor, are

$$\frac{\partial}{\partial r}\hat{v}(R(t),t) = 0, \tag{4.8}$$

$$\frac{dR(t)}{dt} = u(R(t),t), \tag{4.9}$$

which can be biologically explained as in Chapter 2.

We notice that Eq. (4.4) is a consequence of Equations (4.1)-(4.3), (4.6) and (4.7). So, in what follows we may drop this equation and replace $\hat{n}$ by $\theta - \hat{x} - \hat{y} - \hat{z}$ in (4.7).

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

$$u(0,t) = 0. \tag{4.10}$$

To completely pose this free boundary problem, we impose the following initial conditions,

$$\begin{aligned} &R(0) \quad \text{is prescribed,} \\ &\hat{x}(r,0) = \hat{x}_0(r), \hat{y}(r,0) = \hat{y}_0(r), \hat{z}(r,0) = \hat{z}_0(r), \hat{v}(r,0) = \hat{v}_0(r), \\ &\text{where } \hat{x}_0(r), \hat{y}_0(r), \hat{z}_0(r) \text{ and } \hat{v}_0(r) \text{ and are nonnegative} \\ &\text{functions with } \hat{x}_0(r) + \hat{y}_0(r) + \hat{z}_0(r) \le \theta, \text{ for } 0 \le r \le R(0). \end{aligned} \tag{4.11}$$

In next section, we will transform free boundary problem (4.1)-(4.2) into a problem in a fixed region.

4.3 Model transformation

We first introduce the variables

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

and the quantity

$$p_0 = \frac{\beta N \theta}{\gamma}, \quad \sigma_0 = \frac{\sigma}{\theta^{1-\nu}}.$$

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

Then, we introduce the change of variables:

$$\begin{aligned} \rho &= \rho(r,t) = r/R(t), \\ x(\rho,t) &= \tilde{x}(r,t), \quad y(\rho,t) = \tilde{y}(r,t), \quad z(\rho,t) = \tilde{z}(r,t), \\ v(\rho,t) &= \tilde{v}(r,t), \quad u(\rho,t) = \tilde{u}(r,t)/R(t), \end{aligned}$$

In terms of new variables, Eqs. (4.1)-(4.3), (4.5) and (4.7) take the following form in $\{0 < \rho < 1, t > 0\}$:

$$\begin{aligned} &\frac{\partial x}{\partial t} + \big[u(\rho,t) - \rho u(1,t)\big]\frac{\partial x}{\partial \rho} \\ &= \lambda x - p_0 \gamma x v - \kappa D(t) x - \big[-\mu + (\lambda+\mu)x + \mu y + \mu z\big]x, \end{aligned} \tag{4.12}$$

$$\begin{aligned} &\frac{\partial y}{\partial t} + \big[u(\rho,t) - \rho u(1,t)\big]\frac{\partial y}{\partial \rho} \\ &= p_0 \gamma x v - \delta y - \kappa D(t) y - \big[-\mu + (\lambda+\mu)x + \mu y + \mu z\big]y, \end{aligned} \tag{4.13}$$

$$\begin{aligned} &\frac{\partial z}{\partial t} + \big[u(\rho,t) - \rho u(1,t)\big]\frac{\partial z}{\partial \rho} \\ &= \kappa D(t)(x+y) - \sigma_0 z^{\nu} - \big[-\mu + (\lambda+\mu)x + \mu y + \mu z\big]z, \end{aligned} \tag{4.14}$$

$$\frac{\partial v}{\partial t} - \frac{d}{R^2(t)}\frac{1}{\rho^2}\frac{\partial}{\partial \rho}\Big(\rho^2 \frac{\partial v}{\partial \rho}\Big) - \rho u(1,t)\frac{\partial v}{\partial \rho} = \delta y - \gamma v, \tag{4.15}$$

$$u(\rho,t) = \frac{1}{\rho^2}\int_0^\rho s^2\big[-\mu + (\lambda+\mu)x(s,t) + \mu y(s,t) + \mu z(s,t)\big]ds. \tag{4.16}$$

The boundary and initial conditions (4.8)-(4.9) and (4.2) become

$$\dot{R}(t) = R(t)u(1,t), \quad R(0) \text{ is given}, \tag{4.17}$$

$$v_\rho(0,t) = v_\rho(1,t) = 0, \tag{4.18}$$

$$x(\rho,0) = x_0(\rho),\ y(\rho,0) = y_0(\rho),\ z(\rho,0) = z_0(\rho),\ v(\rho,0) = v_0(\rho), \tag{4.19}$$

$$x_0(\rho),\ y_0(\rho),\ z_0(\rho) \geq 0, \qquad x_0(\rho) + y_0(\rho) + z_0(\rho) \leq 1. \tag{4.20}$$

We also assume that,

$$x_0(\rho),\ y_0(\rho),\ z_0(\rho) \text{ and } v_0(\rho) \text{ belong to } C^1[0,1], \text{ and } \frac{\partial v_0}{\partial \rho}(1) = 0, \tag{4.21}$$

$$D(t) \in C[0,\infty),\ D(t) \geq 0,\ \overline{D} = \lim_{t\to\infty} D(t). \tag{4.22}$$

Here the absorbed radiation dose $D(t)$ is proportional to the cumulative activity (so we assume that it is increasing in t), and we assume that it has a maximum value $\overline{D}$.

The global existence and uniqueness of the solutions to the system (4.12)-(4.22) was proved by Tao and Guo [146]. We do not present the proof here, instead, we will focus our attention on finding an explicit parameter condition for success of therapy (i.e., $R(t) \to 0$ as $t \to \infty$).

4.4 Constant Equilibrium Solutions

To find a parameter condition for $R(t) \to 0$, we first discuss the constant equilibrium solutions of (4.12)-(4.15). These solutions are determined by the

equations,

$$\big[(\lambda+\mu-\kappa\overline{D})-(\lambda+\mu)x-(p_0\delta+\mu)y-\mu z\big]x=0, \tag{4.23}$$

$$\big[(\delta+\kappa\overline{D}-\mu)+(\lambda+\mu-p_0\delta)x+\mu y+\mu z\big]y=0, \tag{4.24}$$

$$\kappa\overline{D}(x+y)-\sigma_0 z^{\nu}-\big[-\mu+(\lambda+\mu)x+\mu y+\mu z\big]z=0, \tag{4.25}$$

$$\delta y-\gamma v=0. \tag{4.26}$$

Clearly, $(x_s,y_s,z_s,v_s)=(0,0,0,0):=E^0$ is a trivial equilibrium solution. In the following we try to find non-zero equilibrium solutions. Throughout this section, we assume

$$\kappa\overline{D}>\lambda+\mu, \tag{4.27}$$

which is the maximal rate condition for radiation damage.

Theorem 4.1. *Under the assumption (4.27), we have*

(i) if

$$\frac{(1-\nu)^{1-\nu}}{(2-\nu)^{2-\nu}}<\frac{\sigma_0}{\mu}, \tag{4.28}$$

there is no *non-zero equilibrium solutions;*

(ii) if

$$\frac{(1-\nu)^{1-\nu}}{(2-\nu)^{2-\nu}}=\frac{\sigma_0}{\mu}, \tag{4.29}$$

there exists unique non-zero equilibrium solution $(x_s,y_s,z_s,v_s)=(0,0,z_s^{(0)},0):=E_0$ *where* $z_s^{(0)}=\frac{1-\nu}{2-\nu}$*;*

(iii) if

$$\frac{(1-\nu)^{1-\nu}}{(2-\nu)^{2-\nu}}>\frac{\sigma_0}{\mu}, \tag{4.30}$$

there exist two non-zero equilibrium solutions $(x_s^{(1)}, y_s^{(1)}, z_s^{(1)}, v_s^{(1)}) = (0, 0, z_s^{(1)}, 0) := E_1$ *and* $(x_s^{(2)}, y_s^{(2)}, z_s^{(2)}, v_s^{(2)}) = (0, 0, z_s^{(2)}, 0) := E_2$ *where* $0 < z_s^{(1)} < z_s^{(0)} < z_s^{(2)} < 1$.

Proof. The proof was given by Tao and Guo [146]. We distinguish four cases.

Case 1: $x = 0, y = 0$.

From (4.25), the equilibrium solutions satisfy

$$\sigma_0 z^\nu + (-\mu + \mu z)z = 0.$$

Noting $z \neq 0$ in this case for non-zero equilibrium solutions, this equation can be rewritten as

$$\frac{\sigma_0}{\mu} + (-1 + z)z^{1-\nu} = 0. \tag{4.31}$$

Define

$$f(z) = \frac{\sigma_0}{\mu} + (-1 + z)z^{1-\nu}, \quad 0 \leq z \leq 1. \tag{4.32}$$

We easily check that

$$\begin{aligned}
&f(0) = f(1) = \frac{\sigma_0}{\mu} > 0, \\
&f'(z) = (2 - \nu)z^{-\nu}\big(z - \frac{1 - \nu}{2 - \nu}\big), \\
&f'(z_s^{(0)}) = 0 \quad \text{where } z_s^{(0)} = \frac{1 - \nu}{2 - \nu}, \qquad (4.33) \\
&f'(z) < 0 \quad \text{for } 0 < z < z_s^{(0)}, \qquad (4.34) \\
&f'(z) > 0 \quad \text{for } z_s^{(0)} < z \leq 1, \qquad (4.35) \\
&f(z_s^{(0)}) = \min_{0 \leq z \leq 1} f(z) = \frac{\sigma_0}{\mu} - \frac{(1 - \nu)^{1-\nu}}{(2 - \nu)^{2-\nu}}.
\end{aligned}$$

From these facts we easily get the conclusions in Theorem 4.1.

Case 2: $x = 0, y \neq 0$.

From (4.24) we have that the non-zero equilibrium solutions must satisfy

$$(\delta + \kappa\overline{D} - \mu) + \mu y + \mu z = 0,$$

which does *not* exist non-negative solution (y_s, z_s) by assumption (4.27).

Case 3: $x \neq 0, y = 0$.

This case can be discussed similarly to Case 2.

Case 4: $x \neq 0, y \neq 0$.

From (4.23) and (4.27), we easily check that there do *not* exist non-zero equilibrium solutions in this case. □

4.5 Stability of Equilibrium Solutions

For simplicity, throughout this section we assume that $D(t) \equiv \overline{D}$. We denote the right-hand sides of Eqs. (4.12)-(4.14) by $g_1(x, y, z, v)$, $g_2(x, y, z, v)$ and $g_3(x, y, z, v)$, respectively.

We begin with considering the trivial equilibrium solution $E^0 = (x_s, y_s, z_s, v_s) = (0, 0, 0, 0)$. By simple calculation, the linearized coefficient matrix A^0 of the right-hand terms of hyperbolic system (4.12)-(4.14) with $\nu = 1$ at equilibrium point E^0 has the form:

$$A^0 = \begin{pmatrix} \frac{\partial g_1}{\partial x} & \frac{\partial g_1}{\partial y} & \frac{\partial g_1}{\partial z} \\ \frac{\partial g_2}{\partial x} & \frac{\partial g_2}{\partial y} & \frac{\partial g_2}{\partial z} \\ \frac{\partial g_3}{\partial x} & \frac{\partial g_3}{\partial y} & \frac{\partial g_3}{\partial z} \end{pmatrix}_{E^0} = \begin{pmatrix} -(\kappa\overline{D} - \lambda - \mu) & 0 & 0 \\ 0 & -(\kappa\overline{D} + \delta - \mu) & 0 \\ 0 & 0 & -\sigma_0 + \mu \end{pmatrix}.$$

We have

Theorem 4.2. *In addition to the assumption (4.27), we also assume that*

$$\sigma_0 > \mu. \tag{4.36}$$

Then, the trivial equilibrium solution E^0 of the system (4.12)-(4.22) with $\nu = 1$ is locally stable.

Proof. Under the assumptions (4.27) and (4.36), the three eigenvalues of matrix A^0 are negative. Therefore, the equilibrium solution E^0 to system (4.12)-(4.22) with $\nu = 1$ is *linearly* stable. Furthermore, proceeding as in the proofs of Lemma 6.2, Theorem 7.1 and Theorem 8.1 in [61], we can obtain the locally *nonlinear* stability of equilibrium solution E^0 to the system (4.12)-(4.22) with $\nu = 1$. □

Remark 4.1. The stability of the trivial equilibrium solution E^0 of the system (4.12)-(4.22) for general $0 < \nu < 1$ remains open, because the function $\partial g_3/\partial z$ has *singularity* at E^0 ($\frac{\partial g_3}{\partial z}\big|_{E^0} = \infty$). The stability of the equilibrium solution E^0 corresponds to success of the therapies. However, the instability of the equilibrium solution E^0 may imply the recurrence of a tumor.

We next turn to study the stability of the non-zero equilibrium solutions E_i $(i = 0,\ 1,\ 2)$. It is easy to check that

$$\frac{\partial g_1}{\partial x}\big|_{E_i} = \lambda + \mu - \kappa\overline{D} - \mu z_s^{(i)}, \quad \frac{\partial g_1}{\partial y}\big|_{E_i} = 0, \quad \frac{\partial g_1}{\partial z}\big|_{E_i} = 0,$$
$$\frac{\partial g_2}{\partial x}\big|_{E_i} = 0, \quad \frac{\partial g_2}{\partial y}\big|_{E_i} = \mu - \delta - \kappa\overline{D} - \mu z_s^{(i)}, \quad \frac{\partial g_2}{\partial z}\big|_{E_i} = 0,$$
$$\frac{\partial g_3}{\partial x}\big|_{E_i} = \kappa\overline{D} - (\lambda + \mu) z_s^{(i)}, \quad \frac{\partial g_3}{\partial y}\big|_{E_i} = \kappa\overline{D} - \mu z_s^{(i)},$$
$$\frac{\partial g_3}{\partial z}\big|_{E_i} = -\sigma_0 \nu \big(z_s^{(i)}\big)^{\nu-1} + \mu - 2\mu z_s^{(i)}.$$

Hence, the linearized coefficient matrix A_i $(i = 0,\ 1,\ 2)$ of the right-hand sides of the hyperbolic system (4.12)-(4.14) at corresponding equilibrium point E_i has the form:

$$A_i = \begin{pmatrix} \lambda + \mu - \kappa\overline{D} - \mu z_s^{(i)} & 0 & 0 \\ 0 & \mu - \delta - \kappa\overline{D} - \mu z_s^{(i)} & 0 \\ \kappa\overline{D} - (\lambda + \mu) z_s^{(i)} & \kappa\overline{D} - \mu z_s^{(i)} & -\sigma_0 \nu \big(z_s^{(i)}\big)^{\nu-1} + \mu - 2\mu z_s^{(i)} \end{pmatrix}. \tag{4.37}$$

Using the assumption (4.27) and noting $z_s^{(i)} > 0$ $(i = 0, 1, 2)$, we easily find that

$$\lambda + \mu - \kappa\overline{D} - \mu z_s^{(i)} < 0, \tag{4.38}$$

$$\mu - \delta - \kappa\overline{D} - \mu z_s^{(i)} < 0. \tag{4.39}$$

Define

$$h(z) \equiv g_3(0, 0, z, 0) = -\sigma_0 z^\nu + (\mu - \mu z) z. \tag{4.40}$$

That is,

$$h(z) = -\mu z^\nu f(z), \tag{4.41}$$

where $f(z)$ is defined by (4.32). Clearly, by (4.40) we have

$$h'(z) = -\sigma_0 \nu z^{\nu-1} + \mu - 2\mu z. \tag{4.42}$$

On the other hand, by (4.41) we get

$$h'(z) = -\mu\nu z^{1-\nu} f(z) - \mu z^{\nu} f'(z). \tag{4.43}$$

In the following we assume that condition (4.30) holds. Using (4.34), (4.35), (4.43) and Theorem 4.1 and noting $f(z_s^{(1)}) = f(z_s^{(2)}) = 0$, we have

$$h'(z_s^{(1)}) = -\mu\big(z_s^{(1)}\big)^{\nu} f'(z_s^{(1)}) > 0, \tag{4.44}$$

$$h'(z_s^{(2)}) = -\mu\big(z_s^{(2)}\big)^{\nu} f'(z_s^{(2)}) < 0. \tag{4.45}$$

From (4.37), (4.43) and (4.44) we find that matrix A_1 has a *positive* eigenvalue. Therefore, arrive at the following theorem.

Theorem 4.3. *Under assumptions (4.27) and (4.44), the non-zero equilibrium solution E_1 is linearized* unstable.

By (4.37)-(4.39), (4.43) and (4.45) we find that under the assumptions (4.27) and (4.30), all eigenvalues of matrix A_2 are negative, and therefore the non-zero equilibrium solution E_2 is *linearly* stable. Furthermore, proceeding as in the proofs of Lemma 6.2, Theorem 7.1 and Theorem 8.1 in [61], we can get the locally *nonlinear* stability of the non-zero equilibrium solution E_2. More precisely, we have

Theorem 4.4. *Assume that (4.27) and (4.30) hold. If*

$$\|x_0(\rho),\ y_0(\rho),\ z_0(\rho) - z_s^{(2)},\ v_0(\rho)\|_{C^1[0,1]} \le \varepsilon$$

where ε is sufficiently small, then the global solution $(x(\rho,t),\ y(\rho,t),\ z(\rho,t),$ $v(\rho,t),\ u(\rho,t),\ R(t))$ satisfies

$$|x(\xi(t),t)|,\ |y(\xi(t),t)|,\ |z(\xi(t),t)-z_s^{(2)}|,\ |v(\xi(t),t)|\le C\varepsilon e^{-\eta t}\quad \textit{for all } t>0$$

where C and η are some positive constants, and $\xi(t)=\xi(t;\rho_0)$ is the forward characteristic curve of the first-order hyperbolic equation (4.12) satisfying $\rho_0=\xi(0;\rho_0)$.

We are now in a position to study the convergence of the tumor radius $R(t)$ to zero, which corresponds to the success of therapies. In fact, we have

Theorem 4.5. *Assume that (4.27) and (4.30) hold. If*

$$\|x_0(\rho),\ y_0(\rho),\ z_0(\rho)-z_s^{(2)},\ v_0(\rho)\|_{C^1[0,1]}\le\varepsilon$$

where $\varepsilon<\mu(1-z_s^{(2)})/2$, then we have

$$R(t)\to 0\quad \textit{exponentially.}$$

Proof. (4.16) and (4.17) yield

$$\frac{\dot R(t)}{R(t)}=\int_0^1 s^2\big[-\mu+(\lambda+\mu)x(s,t)+\mu y(s,t)+\mu z(s,t)\big]ds.$$

This, together with Theorem 4.4, yields

$$\begin{aligned}\frac{\dot R(t)}{R(t)}&<\int_0^1 s^2\big(-\mu+\mu z_s^{(2)}+\varepsilon\big)ds\\&=\frac{1}{3}\big[-\mu(1-z_s^{(2)})+\varepsilon\big]\\&<-\frac{1}{6}\mu(1-z_s^{(2)})\quad\text{for sufficiently large } t.\end{aligned}$$

Thus,

$$R(t)<R(0)e^{-\frac{1}{6}\mu(1-z_s^{(2)})t}\to 0\quad\text{exponentially.}$$

□

Remark 4.2. We conclude from Theorems 4.4 and 4.5 that the non-zero equilibrium point E_2 corresponds to a successful therapy, which has *not* been found in [51]. Hence, the condition (4.27) and (4.30) is a *new* explicit parameter condition for successful eradication of a tumor.

4.6 Possible Optimal Protocols

In this section we will numerically explore possible optimal therapy strategies. The typical parameter values for the numerical simulation are $\lambda = 0.0086,\ \delta = 0.0293,\ \gamma = 0.0119,\ \nu = 0.176,\ \sigma = 18.57/24,\ d = 25/6,\ \mu = 1/72,\ p_0 = 3.73,\ \theta = 10^6$ given in [146, 179, 117].

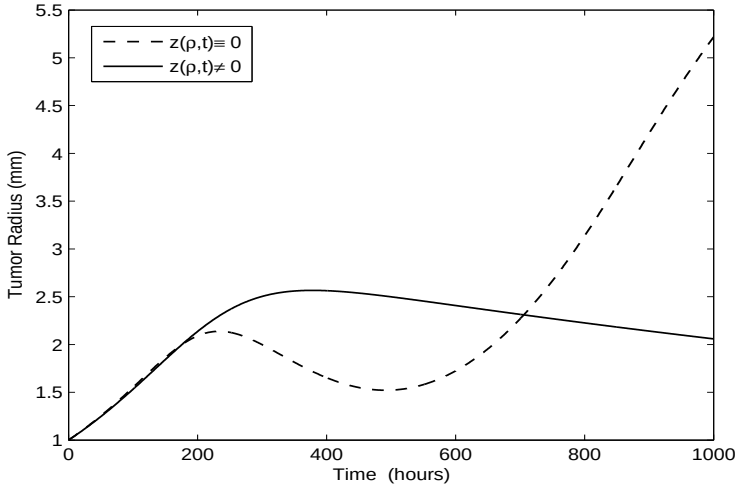

Fig. 4.1. The comparison between the effect of radiovirotherapy with $(x_0, y_0, v_0, z_0) = (0.01, 0.001, 0.1, 0.02),\ D = 0.01$ and the effect of virotherapy alone with $(x_0, y_0, v_0) = (0.01, 0.001, 0.1),\ D = 0,\ z(t) \equiv 0$.

Fig.4.1 shows that radiovirotherapy is more effective than virotherapy alone. Fig.4.1 clearly indicates that the combination of virotherapy with radiation (radiovirotherapy) may reduce tumors when virotherapy alone failed. This has been verified by experimental research [50]. The mathematical model and numerical simulation in [146] give us a deeper understanding of the design of radiovirotherapy strategy.

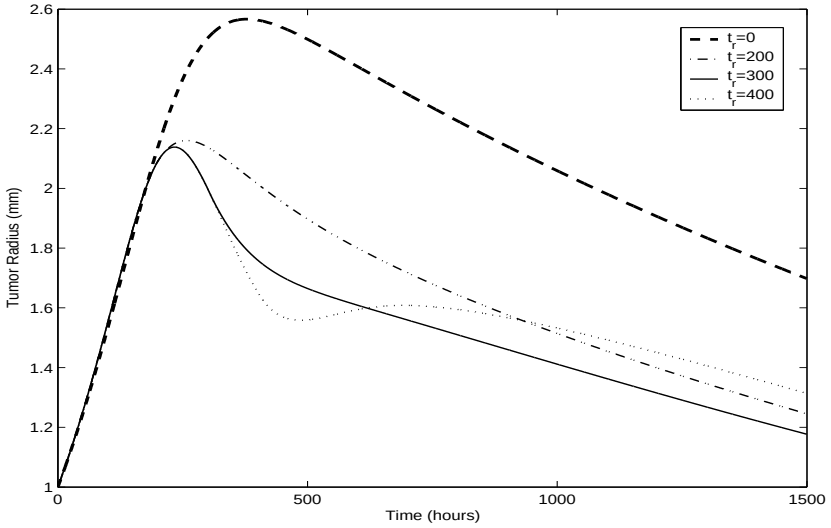

Fig. 4.2. The effects of the different timing of radio-iodine administration on tumor growth. Take $(x_0, y_0, v_0) = (0.01, 0.001, 0.1)$, $D = 0.01$ $(t > t_r)$, $z|_{t=t_r} = 0.02$, $z(t) \equiv 0$ and $D = 0$ for $0 \leq t < t_r$.

Fig.4.2 shows the effects of the different timing of radio-iodine administration on tumor growth. If we take $(x_0, y_0, v_0) = (0.01, 0.001, 0.1)$, $D = 0.01$ $(t > t_r)$, $z|_{t=t_r} = 0.02$, $z(t) \equiv 0$ and $D = 0$ for $0 \leq t < t_r$ (where t_r is the start timing of radio-iodine administration), then Fig.4.2 shows that there

exists an optimal timing $t_r^{opt} \approx 300$ (hours) for radio-iodine administration. Earlier or later administrations of iodine result in a larger size of the tumor. Furthermore, our numerical simulations (not presented here) also show that the optimal timing t_r^{opt} depends on the dose D of the radioactive iodide. The optimal timing $t_r^{opt} = 0$ for small D and large D.

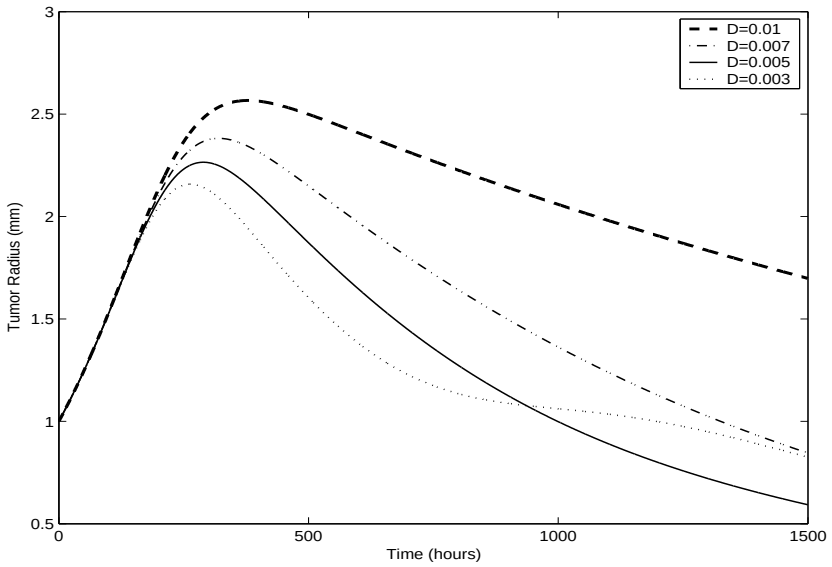

Fig. 4.3. The effects of the different doses of radioactive iodide on tumor growth. Take $(x_0, y_0, v_0, z_0) = (0.01, 0.001, 0.1, 0.02),\ t_r = 0.$

Fig.4.3 shows the effects of the different doses of radioactive iodide on tumor growth. If we take $(x_0, y_0, v_0, z_0) = (0.01, 0.001, 0.1, 0.02)$ and $t_r = 0$, then Fig.4.3 shows that there exists an optimal dose $D^{opt} \approx 0.005$ of the radioactive iodide. Fig.4.3 shows that the dose of radio-iodine administration is another important issue for radiovirotherapy. It suggests

that given *intermediate* dose of radioactive iodide for treatment may be an optimal therapy strategy. Another reason why the dose of radioactive iodide given for treatment is important is that radiation damages the health tissue. Therefore, the optimal dose of iodine for treatments still needs to be further experimentally investigated.

The numerical simulations lead to the design of possible optimal therapeutic strategies. The timing of radio-iodine administration and the dose of iodine are two critical factors for the efficacy of a combined treatment of viral and radio therapy. The numerical results of this section may be helpful for experimental research.

4.7 Summary and Discussion

The combination of virotherapy with radiotherapy (radiovirotherapy) is more effective than treatments with virotherapy alone, which has been supported by experimental data. Radiovirotherapy is a very complex and sensitive dynamical system. To better understand its outcome, mathematical modeling may play a role. The PDE model [146] reviewed in this chapter is a generalization of the previously existing ODE model [51]. And it is also a generalization of the previously existing PDE model [61], which is a model of virotherapy. This chapter reviews the modeling of a combined action of viral and radio therapy, which allows us to study the optimal strategies for treatments.

Under some appropriate assumptions on model parameters, we found that there are two non-zero equilibrium solutions $E_1 = (x_s^{(1)}, y_s^{(1)}, z_s^{(1)}, v_s^{(1)}) = (0, 0, z_s^{(1)}, 0)$ and $E_2 = (x_s^{(2)}, y_s^{(2)}, z_s^{(2)}, v_s^{(2)}) = (0, 0, z_s^{(2)}, 0)$ with $0 < z_s^{(1)} < z_s^{(2)} < 1$. The non-zero equilibrium solution E_1 is linearly *unstable*. However, we proved the locally *nonlinear stability* of the non-zero equilibrium solution E_2, which corresponds to a successful therapy of a tumor.

The numerical simulations in Section 4.6 verify that radiovirotherapy is more effective than treatments with virotherapy alone. These simulations also suggest that there is an optimal timing of radio-iodine administration and an optimal dose of the radioactive iodide, which need to be further experimentally tested.

ONYX-015, a genetically modified adenovirus, is one of oncolytic viruses that have been tested in clinical trials. Studies in clinical trials have shown that the expression of the coxsackie-adenovirus receptor (CAR) strongly influences the entry of virus into cancer cells (for example, see [10]). Mitogen-activated protein kinase kinase (MEK, also known as MAP-kinase kinase) inhibitors have been shown to promote CAR expression, and could result in increased ONYX-015 entry into target cells (see [183] and references therein). This could lead to a novel combined therapeutic approach to cancer, using ONYX-015 and MEK inhibitors. However, MEK inhibitors can cause temporary cell-cycle arrest, which inhibits the life-cycle of ONYX-015 (the cell cycle is generally considered to consist of four phases of proliferate growth: the growth phase (G_1), a phase of DNA synthesis (S), a period before cell division (G_2) and

mitosis (M); and a single phase of quiescent behavior (G_0). ONYX-015 needs to lock the cell in S-phase to replicate and lyse the cell). So, MEK inhibitors may limit the replication of viruses. To design an effective protocol of combined therapies against cancer using ONYX-015 and MEK inhibitors, the positive effect of MEK inhibitors should be optimally balanced with the negative effect of MEK inhibitors. This complicates the dynamics of MEK inhibitors, viruses and tumor cells. Zurakowski and Wodarz [183] initially introduced an ODE model to study the effects of MEK inhibitors and viruses on tumor cells. They used their model to explore the reduction of the tumor size, and the tumor size reduction can be achieved by the combined therapies. Tao and Guo [148] extended Zurakowski and Wodarz's model to a PDE model and used the PDE model to analytically and numerically explore a possible optimal dose and the optimal timing of MEK inhibitors.

5

Modeling of Resection, Radiation, and Chemotherapy in Glioblastoma

5.1 Introduction

Glioblastoma multiforme, a type of glioma, is the most aggressive of brain tumors. The life expectancy from the time when it is diagnosed is typically one year. The current treatment is surgical resection followed by radiotherapy and chemotherapy. There are only a few consistent clinical studies which compare life expectancies of patients who underwent different resections (residual or complete) and different protocols of radiotherapy and chemotherapy. Among the most consistent studies are those of Albert et al. [3], Lacroix et al. [107], and Stupp et al. [137].

A detailed study of 135 patient data by Albert et al. [3] showed that patients who underwent subtotal surgery postoperatively had 6.6 times higher risk of death in comparison to patients who underwent complete resection, and patients treated by radiotherapy had 0.26 times lower risk of death in comparison to patients who were not treated with radiation. Lacroix et al. [107] analyzed 416 patients data and showed that a significant survival

advantage was associated with resection of 98% or more of the tumor volume, and generally, gross total tumor resection led to longer life expectancy.

The efficacy of chemotherapy has been steadily improved with the development of new cancer drugs. Stupp et al. [137] analyzed the data of 573 patients and showed that the median survival time (MST) was 14.6 months for patients who underwent radiotherapy plus chemotherapy with temozolomide, but only 12.1 months for those with radiotherapy alone.

All these clinical data analysis are retrospective. They have value for reference, but they are likely quite biased in nature, and cannot give any perspective prediction. Tian et al. [160] developed a mathematical model which integrates the treatment of patients by surgery, radiotherapy and chemotherapy. The model parameters were chosen in Tian et al. [160] so that the simulation results fit with the patient data analysis reported in [3, 107, 137]. The Study of the model in [160] suggested a combination of treatment protocols that can give patients maximal survival time. This chapter reviews the mathematical model proposed by Tian et al [160].

5.2 Mathematical Model and Clinical Data

The mathematical model describes a spherical tumor regrowing after surgical resection. The tumor contains tumor stem cells x and necrotic cells y. The quantity x represents the number density of tumor cells (i.e., the number of tumor cells in 1 mm^3), the quantity y represents the number density of

necrotic cells. It is assumed that the number density of cells in a tumor is a constant [178], that is, $x + y =$ number of cells in 1 mm^3, which is 10^6 [119]. New tumor cells are produced by proliferation, and they transit to necrotic cells by lysis.

Tumor cells that are near to the expanding surface of the solid tumor receive more nutrients and proliferate faster than tumor cells that are near the core of the tumor. Indeed, as mentioned in [127], the proportion of proliferating cells varies considerably from the outer region to the inner region of the tumor. For simplicity we assume that the proliferation rate, λ, is constant. According to [68], $\lambda = 2 \times 10^{-2}\ h^{-1}$. We shall also assume the rate of cells become necrotic, δ, is constant. We take δ to be slightly smaller that λ, namely, $\delta = 1.89 \times 10^{-2}\ h^{-1}$. According to [67], necrotic cells are removed on the average of 2–3 days. We shall take the removal rate μ to be $1/72\ h^{-1}$.

According to [107], the median preoperative tumor volume was 34 cm^3. If we assume that the tumor is spherical, then this corresponds to radius at resection time of $R_0 = 20\ mm$. In the partial resection case, a smaller ball of radius R_* is removed, and residual tumor cells remain in the region between the two concentric balls. After surgery the ball of radius R_* fills with cerebro-spinal fluid, and the residual tumor begins to grow outward, as illustrated schematically in Fig. 5.1. From the rate λ of tumor cell proliferation and the reported life expectancy, we estimate that the patient dies at the time when the tumor radius reaches 40 mm. This estimate is confirmed in [107].

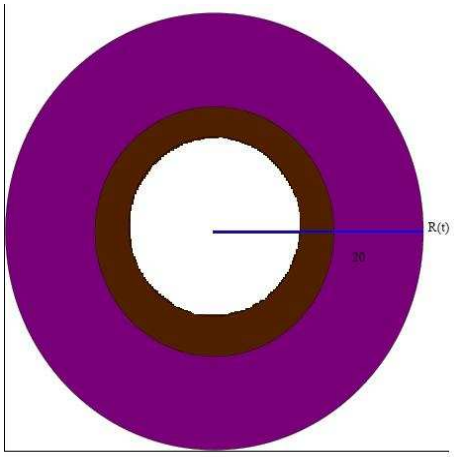

Fig. 5.1. The inner ball is the surgically removed part of the tumor, the dark concentric ball is the residual tumor, and the outer shell is the regrowth part of the tumor.

Consider a radially symmetrical tumor and denoted by r the distance from a point to the origin. We denote the boundary of the tumor by $r = R(t)$.

The proliferation and removal of cells cause a movement of cells within the tumor, with a convection term, for tumor cells x, in the form $\frac{1}{r}\frac{\partial}{\partial r}\left[r^2 u(r,t)x(r,t)\right]$, where $u(r,t)$ is the radial velocity field, and $u(R_*,t) = 0$ since the tumor does not grow inward. By the conservation law of mass, we have the equation for tumor cell population,

$$\frac{\partial x(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 u(r,t)x(r,t)\Big) = \lambda x(r,t) - \delta x(r,t). \tag{5.1}$$

Similarly, we have the for necrotic cell population,

$$\frac{\partial y(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 u(r,t)y(r,t)\Big) = \delta x(r,t) - \mu y(r,t). \tag{5.2}$$

As mentioned before, the total number density of tumor cells is constant, that is, $x(r,t) + y(r,t) = const. = \theta$, and $\theta = 10^6/mm^3$ [119]. Adding Eqs. (5.1) and (5.2) together, we obtain the equation for the radial velocity field:

$$\frac{\theta}{r^2}\frac{\partial}{\partial r}\big(r^2 u\big) = (\lambda + \mu)x(r,t) - \mu\theta. \tag{5.3}$$

The tumor radius evolves according to

$$\frac{dR}{dt} = u(R(t),t). \tag{5.4}$$

We assume that,

$$x(r,0) = \frac{9}{10}\theta, \qquad \text{for } R_* \le r \le R_0. \tag{5.5}$$

That is, initially 90% of cells are tumor (stem) cells, and 10% are necrotic cells.

We need to solve Eqs. (5.1), (5.3) in $R_* \le r \le R(t)$ with the initial condition (5.5) and with the tumor growth condition (5.4). The above model does not include radiotherapy and chemotherapy yet. According to [137], within 6 weeks after the histologic diagnosis of glioblastoma, patients were assigned to receive standard focal radiotherapy alone or standard radiotherapy plus concomitant daily temozolomide followed by adjuvant temozolomide, whether or not they had previously undergone debulking surgery. The standard radiotherapy consists of fractionated focal irradiation at a dose of 2 Gy per fraction given daily, 5 days per week (Monday through Friday), over a period of 6 weeks, for a total dose of 60 Gy. Accordingly, we take the radiation activity function to be

$$\rho(t) = \begin{cases} 1 & \text{if } 6 \le t \le 12, \\ 0 & \text{otherwise.} \end{cases}$$

We assume that the radiation kills tumor cells at a rate A, so that the death rate by radiotherapy is $A\rho(t)$. For simplicity, we lump together the cells killed by radiation with necrotic cells.

Chemotherapy we consider is administration of temozolomide at a dose of 75 mg per square meter of body surface per day, given 7 days a week from the first day of radiation until the last day of radiation. Then, after a 4-week break, chemotherapy continues, and patients receive a double dose of temozolomide daily for 28 days. After the end of this period, another cycle of temozolomide dosing is administered at $\frac{8}{3}$ level of the original dose, that is 200 mg per square meter. We therefore introduce the temozolomide dosing function as

$$\tau(t) = \begin{cases} 1 & \text{if } 6 \le t \le 12, \\ 2 & \text{if } 16 \le t \le 20, \\ \frac{8}{3} & \text{if } 20 \le t \le 40, \\ 0 & \text{otherwise.} \end{cases}$$

If chemotherapy with 75 mg dose kills tumor cells at a rate B, then the killing rate by chemotherapy treatment is $B\tau(t)$.

If the standard radiotherapy is administered over a period of 6 weeks during the time period $6 \le t \le 12$ and the temozolomide is given for 40 weeks. Eqs. (5.1) and (5.2) are replaced by

$$\frac{\partial x(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 u(r,t)x(r,t)\Big)$$
$$= \lambda x(r,t) - \delta x(r,t) - A\rho(t)x(r,t) - B\tau(t)x(r,t), \tag{5.6}$$
$$\frac{\partial y(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 u(r,t)y(r,t)\Big)$$
$$= \delta x(r,t) + A\rho(t)x(r,t) + B\tau(t)x(r,t) - \mu y(r,t). \tag{5.7}$$

By adding this two equations together, we obtain the same Eq. (5.3), as before, for the velocity field $u(r,t)$.

In next section we will numerically solve Eqs. (5.6), (5.3) in $R_* \le r \le R(t)$ together with (5.4) and (5.5).

Albert et al. [3] provide the median survival time (MST) for various age groups of patients. For definiteness we consider the group of patients between the age of 20 and 39. This group is further divided into three subgroups [3]:

(a) Patients had complete resection (no residual tumor) and undergone radiotherapy; their MST was 92 weeks.

(b) Patients had partial resection (with residual tumor) and undergone radiotherapy; their MST was 46 weeks.

(c) Patients had partial resection (with residual tumor) without radiotherapy; their MST was 15 weeks.

A recent study by Stummer et al. [136] of 243 patients compares the MST of patients who underwent complete resection versus subtotal (partial) resection while both groups received radiation therapy. Repeat surgery and /or initiation of chemotherapy were applied to some patients after tumor progression. The MST was 71 weeks for the first group and 49 weeks for

the second group. By contrast with the data in [3] quoted above (in (a) and (b)) the study in [136] lumps together all ages$\leq$ 60; these data may indicate that older patients may not do as well as younger patients undergoing complete resection. Studies on the effect of different modes of radiation (without distinguishing between complete and subtotal resection) are reported in [25, 54, 139, 171].

It is commonly believed that by the time glioblastoma is diagnosed, some cancer cells have already migrated from the main body of the tumor. Thus, even when resection is complete there are residual tumor cells in the vicinity of the tumor. The model [160] accounts for these cells by defining complete resection to be the removal of not all the ball of radius R_0, but of a slightly smaller ball of radius $R_0 - \varepsilon$. We take $\varepsilon = 5\ \mu m$, half the size of a typical cell, thereby making implicit assumption that glioma cells in the thin shell $R_0 - \varepsilon \leq r \leq R_0$ are in 'migration mode' from the solid tumor.

In the next section we use data from [3, 107, 137] to determine the parameter R_* corresponding to partial resection and the parameters A and ε.

5.3 Parameter Estimation

In all the numerical simulations discussed below we assume that the initial density of tumor cells in the shell $R_* \leq r \leq R_0$, in nine times higher than the density of the necrotic cells. We first use numerical simulations to determine what the partial resection means mathematically. That is, in order to call

a surgery is partial resection, how much should the tumor be removed? or what is R_*? Second, we determine the radiotherapy killing rate A. Third, we determine what the complete resection means, $R(0) = R_0 - \varepsilon$, what is ε? After we obtain these parameter values, we can use our model to study some treatment protocols.

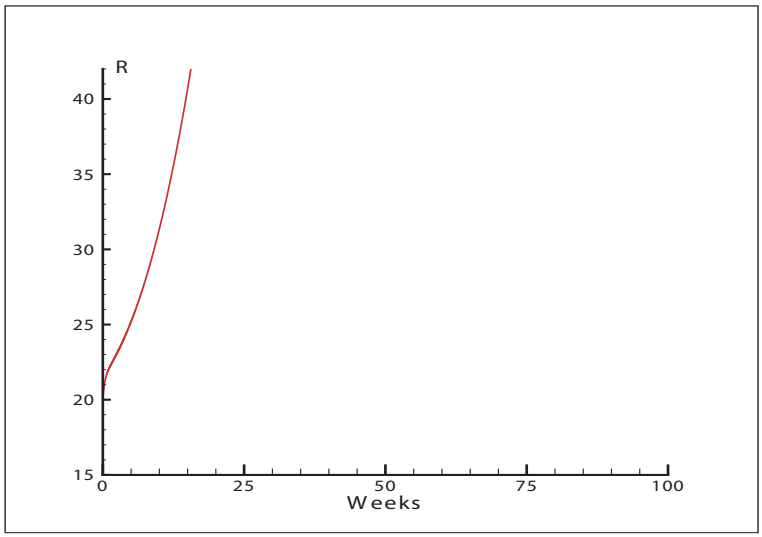

Fig. 5.2. Partial resection $R_* = 18$ mm: residual tumor regrowth without radiotherapy and chemotherapy

Fig. 5.2 shows the growth of the tumor radius $R(t)$ without any therapy if $R_* = 18\ mm$ (partial resection). The time T at which $R(T)$ becomes 40 mm, that is the survival time, is approximately 15 weeks, as reported for the subgroup (c) above. This agreement validates our choice of R_*. We notice that the initial growth of the tumor is extremely fast. Thus although

the simulation begins with tumor radius of 18 mm, the radius very quickly arises to over 20 mm. The same holds for the subsequent figures.

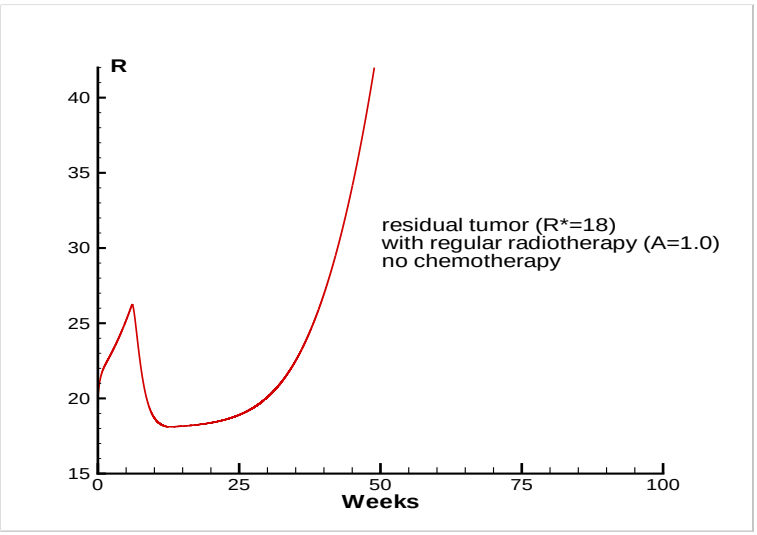

Fig. 5.3. Partial resection $R_* = 18$ mm: residual tumor regrowth with radiotherapy only, at regular strength (A = 1.0)

Fig. 5.3 shows the growth of the tumor radius $R(t)$ if we take in the model the radiation killing rate $A = 1.0$ and partial resection $R_* = 18$ mm. We see that $R(T) = 40$ mm at approximately $T = 46$, as reported for the subgroup (b) above. This validates the choice of the parameter value $A = 1.0$. Note that the tumor radius begins growing until the start of radiation. Radiation treatment decreases the radius, but as soon as radiation is stopped, the tumor begins to grow again.

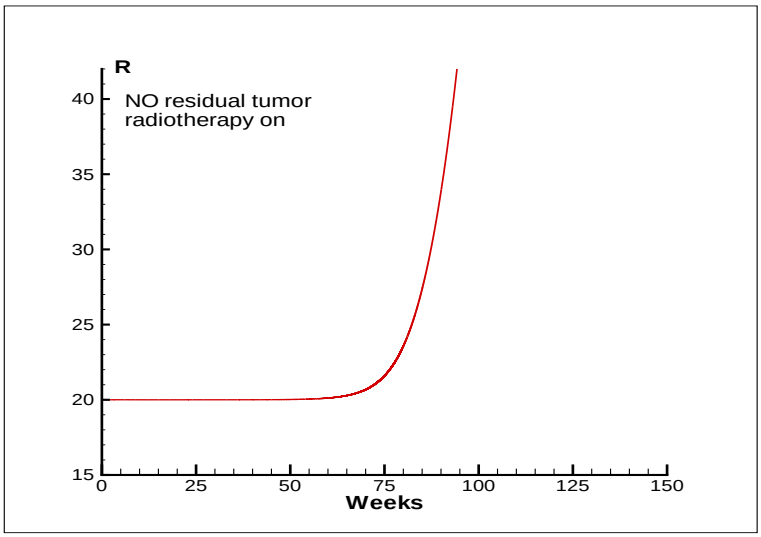

Fig. 5.4. Complete resection $R(0) = R_0 - \varepsilon$, $\varepsilon = 5\mu m$, with radiotherapy only, at regular strength (A = 1.0)

Fig. 5.4 shows the growth of $R(t)$ after the complete resection (that is, $R(0) = R_0 - \varepsilon$, where $\varepsilon = 5\mu m$) and radiotherapy. We see that $R(T) = 40\ mm$ at $T = 92$ weeks which is in agreement with the MST reported for the subgroup (a). This agreement validates the choice of the parameter ε.

5.4 Mathematical Protocols

The mathematical model can be used to explore the effect of different radiation protocols and resections. The standard radiation is given for a period of 6 weeks. In Fig. 5.5 we see the result of giving the same total amount 60 Gy of radiation within 3 weeks instead of 6 weeks, and of giving the same total amount distributed over 12 weeks; both profiles are computed for the

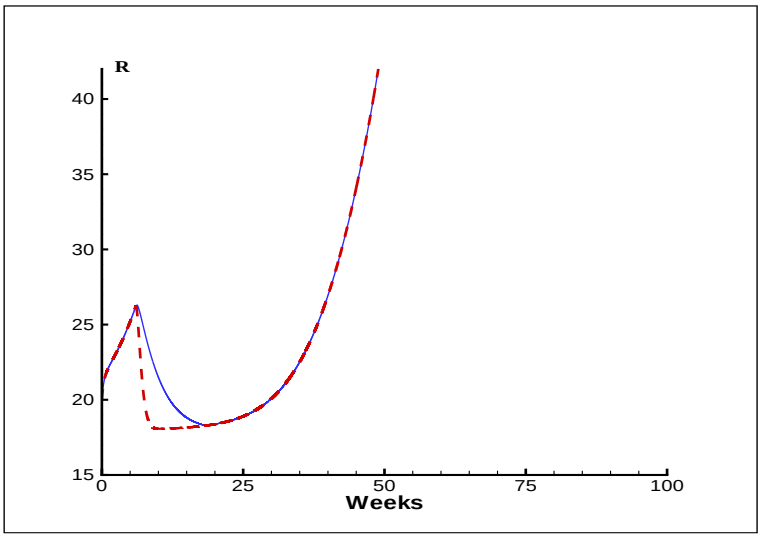

Fig. 5.5. Radiation with $R_* = 18$mm. Protocol 1 (dashed line): radiotherapy only, at double strength, half time. Protocol 2 (solid line): radiotherapy only, at half strength, double time

residual case. The survival time increases in the first case from 46 weeks to 50 weeks, and in the second case from 46 weeks to 49.5 weeks. Thus both procedure of 6 weeks. It should be pointed out that the use of 60 Gy is actually radiobiologically impertinent as it ignores overriding issues of normal cerebral toxicity and radioresistance, but is interesting to consider in the abstract.

The model can also be extended to explore the effect of chemotherapy. As in the case of radiotherapy, chemotherapy kills tumor cells at some rate B. Fig. 5.6 profiles $R(t)$ in the residual tumor case. By choosing $B = 0.03$ we achieve survival time of 60 weeks as given in [137]. We see that chemotherapy has

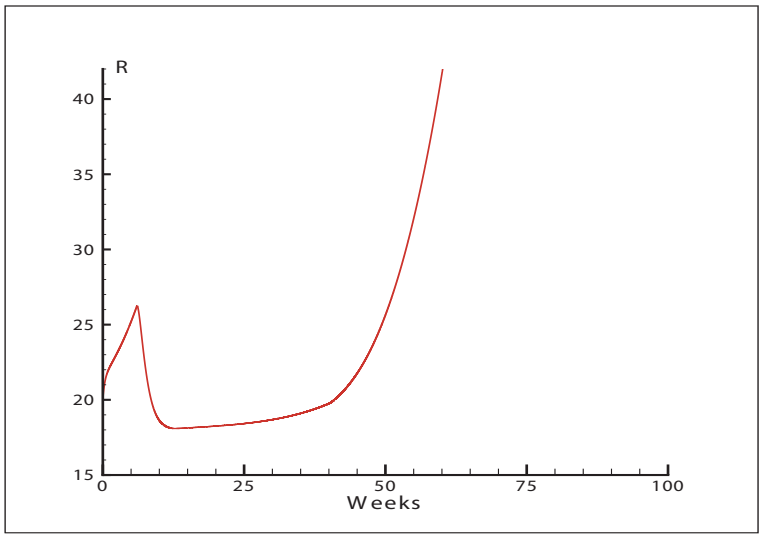

Fig. 5.6. Residual tumor, $R_* = 18$mm, regrowth with radiotherapy at regular strength ($A = 1$) and chemotherapy $B = 0.03$

very little benefits compared to radiotherapy (i.e., $B = 0.03$ is much smaller than $A = 1.0$).

Our model can predict the benefits that will occur if the resection will be more complete, or if the radiation dose is increased. For example, Fig. 5.7 shows that resection with $R_* = 19$ mm followed by radiotherapy yields survival time of 52 weeks as compared to 46 weeks when $R_* = 18$ mm, and 92 weeks when resection is complete. Fig. 5.8 shows, in the case of residual resection ($R_* = 18$mm), that if in the standard radiation treatment the amount of dose is doubled, then the MST will increase from 46 weeks to 80 weeks. But this of course does not take into account toxic side effects due to increased radiation.

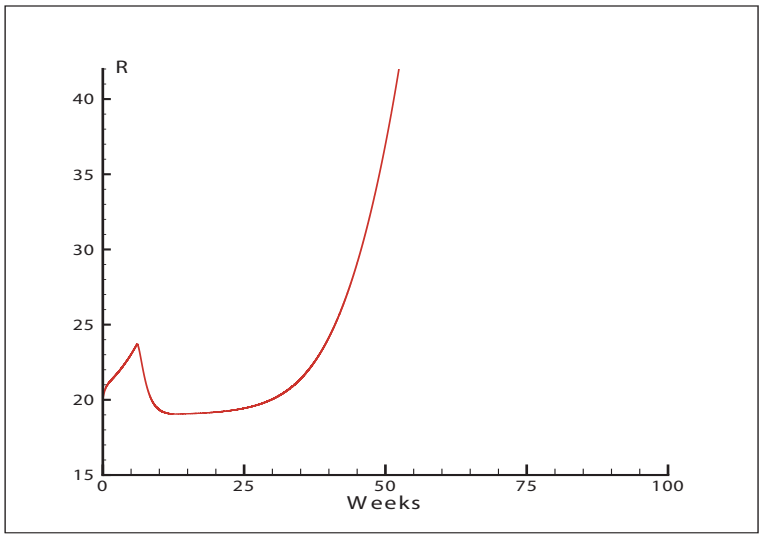

Fig. 5.7. Residual tumor, $R_* = 19$mm, regrowth with radiotherapy at regular strength ($A = 1$) but no chemotherapy

5.5 Explicit solutions

It is well known that most nonlinear free boundary problems are impossible to solve in terms of explicit analytical solutions. In contrast, the hyperbolic free boundary problem 5.1 – 5.7 is solvable, and the explicit solution is found by using the backward characteristic curve method [180]. An interesting finding is that the original free boundary problem can be reformulated as a fixed boundary problem defined on an infinite domain with discontinuous initial condition. To our knowledge, this analytical treatment of nonlinear free boundary problems is new, and was published in [180] recently. These solutions will not only confirm the numerical prediction in the previous sections, but

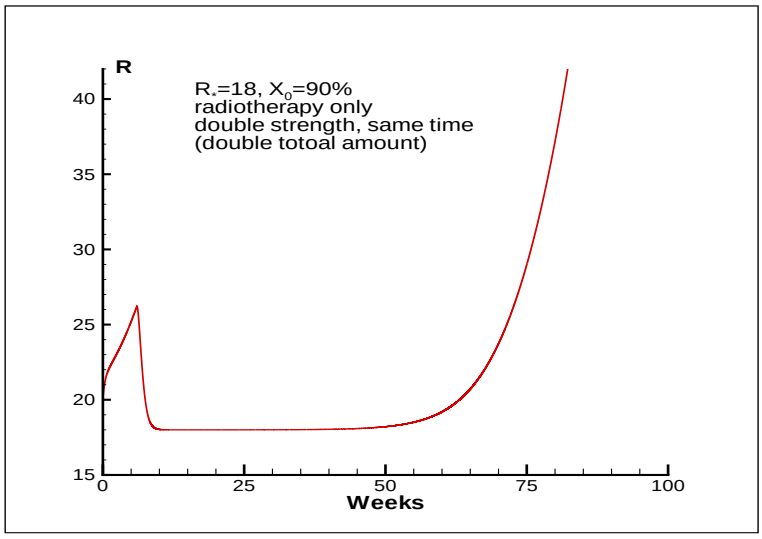

Fig. 5.8. Radiation protocol 3: $R_* = 18$mm with radiotherapy only as standard treatment, but with double stength dosage

also shed light on further analysis for problems of this type towards better understanding the complicated phenomena of tumor growth.

Below we first transform this model for ease of analysis.

Notice $\alpha(t) := \lambda - \delta - A\rho(t) - B\tau(t)$. We will treat $\alpha(t)$ as step function or constant. We apply the following minor change of notations:

$$\tilde{x}(r,t) = x(r,t)/\theta \quad \beta = \lambda + \mu,$$

and the system becomes:

$$\begin{cases} \dfrac{\partial \tilde{x}(r,t)}{\partial t} + \dfrac{1}{r^2}\dfrac{\partial}{\partial t}(r^2 u(r,t)\tilde{x}(r,t)) = \alpha \tilde{x}(r,t), \quad R_* \le r \le R(t), t \ge 0, \\ \dfrac{1}{r^2}\dfrac{\partial}{\partial t}(r^2 u(r,t)) = \beta \tilde{x}(r,t) - \mu, \quad R_* \le r \le R(t), t \ge 0, \\ u(R_*,t) = 0, \quad t \ge 0, \\ \dfrac{dR(t)}{dt} = u(R(t),t), \quad t \ge 0, \end{cases}$$

with the initial conditions: $R(0) = R_0$, $\tilde{x}(r,0) = c$, for $R_* \le r \le R(0)$. Here the second equation is also replaced by the sum of the first two equations.

To get rid of all r^2 or r terms, we introduce the "volume velocity":

$$v(r,t) := r^2 u(r,t)$$

The system then becomes:

$$\begin{cases} \dfrac{\partial \tilde{x}(r,t)}{\partial t} + \dfrac{1}{r^2}\dfrac{\partial}{\partial t}(v(r,t)\tilde{x}(r,t)) = \alpha \tilde{x}(r,t), \quad R_* \le r \le R(t), t \ge 0, \\ \dfrac{1}{r^2}\dfrac{\partial v(r,t)}{\partial t} = \beta \tilde{x}(r,t) - \mu, \quad R_* \le r \le R(t), t \ge 0, \\ v(R_*,t) = 0, \quad t \ge 0, \\ R(t)^2 \dfrac{dR(t)}{dt} = v(R(t),t), \quad t \ge 0, \end{cases}$$

with the initial conditions: $R(0) = R_0$, $\tilde{x}(r,0) = c$, for $R_* \le r \le R(0)$.

Then we apply the following change of variables:

$$s := r^3,$$

$$V(t) := R(t)^3,$$

$$V_* := R_*^3,$$

$$V_0 := R_0^3,$$

$$\omega(s,t) := 3v(\sqrt[3]{s},t).$$

By abusing notations, we redefine "x" as function $\tilde{x}$ in terms of variable s:

$$x(s,t) := \tilde{x}(\sqrt[3]{s}, t).$$

Then we have:

$$\begin{aligned}
&\frac{\partial \omega(s,t)}{\partial s} = 3\frac{\partial}{\partial s} v(\sqrt[3]{s}, t) = \frac{\partial v(r,t)}{\partial r} s^{-\frac{2}{3}} = v_r(r,t) r^{-2},\\
&\frac{\partial x(s,t)}{\partial s} = \frac{1}{3}\frac{\partial \tilde{x}(r,t)}{\partial r} s^{-\frac{2}{3}} = \frac{1}{3}\frac{\partial \tilde{x}(r,t)}{\partial r} r^{-2},\\
&\frac{dV(t)}{dt} = \frac{d}{dt}(R(t)^3) = 3R(t)^2 \frac{dR(t)}{dt} = 3v(R(t),t) = \omega(V(t),t).
\end{aligned}$$

After the change of variables, the system becomes:

$$\begin{cases}
\dfrac{\partial x(s,t)}{\partial t} + \dfrac{\partial}{\partial s}(\omega(s,t)x(s,t)) = \alpha x(s,t), \quad V_* \le s \le V(t), t \ge 0,\\
\dfrac{\partial \omega(s,t)}{\partial s} = \beta x(s,t) - \mu, \quad V_* \le s \le V(t), t \ge 0,\\
\omega(V_*, t) = 0, \quad t \ge 0,\\
\dfrac{dV(t)}{dt} = \omega(V(t),t), \quad t \ge 0,
\end{cases}$$

with the initial conditions: $V(0) = V_0$, $x(s,0) = c$, for $V_* \le s \le V(0)$.

Substitute the second equation into the first one to obtain:

$$\frac{\partial x(s,t)}{\partial t} + \omega(s,t)\frac{\partial x(s,t)}{\partial s} = \beta x(s,t)\left(K - x(s,t)\right),$$

where $K := \frac{\alpha+\mu}{\beta}$, and $K < 1$.

Thus, we have transformed the original system into the following system:

$$\begin{cases}
\dfrac{\partial x(s,t)}{\partial t} + \omega(s,t)\dfrac{\partial x(s,t)}{\partial s} = \beta x(s,t)\left(K - x(s,t)\right), \quad V_* \le s \le V(t), t \ge 0,\\
\dfrac{\partial \omega(s,t)}{\partial s} = \beta x(s,t) - \mu, \quad V_* \le s \le V(t), t \ge 0,\\
\omega(V_*, t) = 0, \quad t \ge 0,\\
\dfrac{dV(t)}{dt} = \omega(V(t),t), \quad t \ge 0,
\end{cases} \tag{5.8}$$

with the initial conditions: $V(0) = V_0$, $x(s,0) = \varphi(s)$, for $V_* \le s \le V(0)$. Here a more general initial condition $\varphi(s)$ will be considered.

We define the "characteristic" curve of the first equation in the system (5.8) as follows,

$$\gamma = \gamma(s,t), \quad V_* \le s \le V_0, t \ge 0, \tag{5.9}$$

which satisfies:

$$\begin{cases} \dfrac{d\gamma(s,t)}{dt} = \omega(\gamma(s,t),t), \quad V_* \le s \le V_0, t \ge 0, \\ \gamma(s,0) = s, \quad V_* \le s \le V_0. \end{cases} \tag{5.10}$$

Since $\omega(s,t)$ is continuous in (s,t) and continuously differentiable in γ, these curves are uniquely defined, satisfying $V_* < \gamma(s,t) < V(t)$ for $V_* < s < V_0$, $t \ge 0$, and $\gamma(V_*,t) = V_*$, $\gamma(V_0,t) = V(t)$ for $t \ge 0$. Setting $\hat{x}(s,t) := x(\gamma(s,t),t)$, $\hat{\omega}(s,t) := \omega(\gamma(s,t),t)$, the system (5.8) reduces to:

$$\begin{cases} \dfrac{\partial \hat{x}(s,t)}{\partial t} = \beta \hat{x}(s,t)\left(K - \hat{x}(s,t)\right), \quad V_* \le s \le V_0, t \ge 0, \\ \dfrac{\partial \hat{\omega}(s,t)}{\partial s} = (\beta \hat{x}(s,t) - \mu)\dfrac{\partial \gamma(s,t)}{\partial s}, \quad V_* \le s \le V_0, t \ge 0, \\ \dfrac{d\gamma(s,t)}{dt} = \hat{\omega}(s,t), \quad V_* \le s \le V_0, t \ge 0, \end{cases} \tag{5.11}$$

with the initial conditions $\hat{x}(s,0) = x(s,0) = \varphi(s)$ for $V_* \le s \le V_0$.

The first equation of the system (5.11) is a logistic equation, which has a standard solution

$$\hat{x}(s,t) = \begin{cases} \dfrac{K\varphi(s)e^{\beta K t}}{K + \varphi(s)(e^{\beta K t} - 1)}, & \text{if } K \ne 0\,; \\ \dfrac{\varphi(s)}{\varphi(s)\beta t + 1}, & \text{if } K = 0\,. \end{cases} \tag{5.12}$$

Combine the second and the third equations in the system (5.11), we get an ordinary differential equation of $\frac{\partial \gamma}{\partial s}(s,t)$,

$$\begin{cases} \dfrac{\partial}{\partial t}\left(\dfrac{\partial \gamma(s,t)}{\partial s}\right) = (\beta \hat{x}(s,t) - \mu)\dfrac{\partial \gamma(s,t)}{\partial s}, \\ \dfrac{\partial \gamma(s,0)}{\partial s} = 1, \end{cases}$$

which has the solution:

$$\frac{\partial \gamma(s,t)}{\partial s} = \exp\left(\int_0^t (\beta \hat{x}(s,\rho) - \mu)d\rho\right).$$

Hence

$$\gamma(s,t) = V_* + \int_{V_*}^{s} \exp\left(\int_0^t (\beta \hat{x}(\sigma,\rho) - \mu)d\rho\right)d\sigma, \tag{5.13}$$

where $\hat{x}(s,t)$ is given by the formula (5.12). Since $\frac{\partial \gamma(s,t)}{\partial s} = \exp\left(\int_0^t (\beta \hat{x}(s,\rho) - \mu)d\rho\right) > 0$, we can solve for the inverse of $\gamma(s,t)$ for fixed t. Denote the inverse of $\gamma(s,t)$ by $\eta(s,t)$. It follows that

$$\begin{cases} x(s,t) = \hat{x}(\eta(s,t),t), \\ \omega(s,t) = \displaystyle\int_{V_*}^{s} (\beta x(\sigma,t) - \mu)d\sigma. \end{cases}$$

The free boundary is given by:

$$\begin{aligned} V(t) &= \gamma(V_0,t) = V_* + \int_{V_*}^{V_0} \exp\left(\int_0^t (\beta \hat{x}(\sigma,\rho) - \mu)d\rho\right)d\sigma, \\ R(t) &= \sqrt[3]{V(t)} = \sqrt[3]{R_*^3 + \int_{R_*^3}^{R_0^3} \exp\left(\int_0^t (\beta \hat{x}(\sigma,\rho) - \mu)d\rho\right)d\sigma}, \end{aligned} \tag{5.14}$$

where $\hat{x}(s,t)$ is calculated by formula (5.12).

In order to solve the system we assumed α to be a constant. If α is a step function, the solution can be given piece-wise by applying the formula (5.12) piece by piece. Let $\alpha(t) = \alpha_i$, $t \in [t_{i-1}, t_i)$, $i = 1, 2, \ldots, n$, $\hat{x}_0(s,0) := \varphi(s)$, $K_i := \frac{\alpha_i + \mu}{\beta}$, then the solution in (5.12) changes to $\hat{x}(s,t) = \hat{x}_i(s,t)$, $t \in [t_{i-1}, t_i)$, $i = 1, 2, \ldots, n$, where

$$\hat{x}_i(s,t) = \begin{cases} \dfrac{K_i \hat{x}_{i-1}(s,t_{i-1}) e^{\beta K_i (t-t_{i-1})}}{K_i + \hat{x}_{i-1}(s,t_{i-1})(e^{\beta K_i (t-t_{i-1})} - 1)}, & \text{if } K_i \neq 0\,; \\ \dfrac{\hat{x}_{i-1}(s,t_{i-1})}{\hat{x}_{i-1}(s,t_{i-1})\beta(t-t_{i-1}) + 1}, & \text{if } K_i = 0\,, \end{cases} \tag{5.15}$$

whereas the formula (5.14) will also be given piece by piece.

Here we look at several interesting cases or applications of this explicit solution. First, we look at how tumor regrows after the surgical resection without any treatment. In this case, $K = \frac{\lambda+\mu-\delta}{\lambda+\mu}$, where λ is the tumor cell proliferation rate, δ is death rate of tumor cells (the rate at which the tumor cells becomes necrotic), μ is the removal rate of necrotic cells.

When $K = 0$, that is, $\delta = \lambda + \mu$, the growth of the tumor radius $R(t)$, or scaled volume $V(t) = R^3(t)$ will follow the following curve,

$$V(t) = (\beta \int_{V_*}^{V_0} \varphi(s)ds)e^{-\mu t}t + V_0 e^{-\mu t} + V_*(1 - e^{-\mu t}).$$

From this expression, we find there is a time T, approximately $T = \frac{1}{\mu}$, such that the tumor radius will increase before T and decrease after it. When time goes to infinity, the tumor shrinks to the size V_*.

When $K \neq 0$, we have

$$V(t) = V_0 + \frac{(e^{\beta K t} - 1)e^{-\mu t}}{K} \int_{V_*}^{V_0} \varphi(s)ds. \tag{5.16}$$

Since $\int_{V_*}^{V_0} \varphi(s)ds$ is a constant, the growth of the radius depends on $\frac{(e^{\beta K t}-1)e^{-\mu t}}{K}$. Substituting original parameters, we have $(e^{\beta K t} - 1)e^{-\mu t} = e^{(\beta K - \mu)t} - e^{-\mu t} = e^{(\lambda-\delta)t} - e^{-\mu t}$. Hence, if $\lambda > \delta$, the tumor will grow infinitely. If $\lambda < \delta$, the tumor will shrink to the size V_0. If $\lambda = \delta$, the tumor radius will reach a stationary solution

$$V_s = V_0 + \frac{\lambda+\mu}{\mu}\int_{V_*}^{V_0} \varphi(s)ds.$$

Second, we consider radiotherapy and chemotherapy. After the surgical resection, the patient has to rest for a period of time, usually six weeks, and then is treated by radiotherapy and chemotherapy. Set the rest period to be $0 \le t \le t_1$. Then, the tumor grows from V_0 to $V(t_1)$, where $V(t_1)$ is given by (5.16) at $t = t_1$, or explicitly

$$V(t_1) = V_0 + \frac{(\lambda+\mu)(e^{(\lambda-\delta)t_1} - e^{-\mu t_1})}{\lambda+\mu-\delta}\int_{V_*}^{V_0} \varphi(s)ds.$$

Let the treatment period of radiotherapy with chemotherapy be $t_1 \le t \le t_2$, then the tumor growth follows

$$V(t) = V_0 + \frac{(\lambda+\mu)(e^{(\lambda-\delta-A-B)t} - e^{-\mu t})}{\lambda+\mu-\delta-A-B}\int_{V_*}^{V_0} \varphi(s)ds, \quad t_1 \le t \le t_2. \quad (5.17)$$

Let the treatment period of chemotherapy be $t_2 \le t \le t_3$, then the tumor growth follows

$$V(t) = V_0 + \frac{(\lambda+\mu)(e^{(\lambda-\delta-B)t} - e^{-\mu t})}{\lambda+\mu-\delta-B}\int_{V_*}^{V_0} \varphi(s)ds, \quad t_2 \le t \le t_3. \quad (5.18)$$

These solutions clearly give the tumor growth pattern in any finite period of time. They provide some information for treatments. We will discuss this issue in next section.

5.6 Summary and Discussion

We have reviewed a mathematical model of glioblastoma treatment by radiotherapy and chemotherapy, which also incorporates the size of the tumor which is

removed by surgery. The model can be used to explore the benefits of different protocols of treatment. In particular we have shown that somewhat greater benefits incur if the same total amount of radiation is given over a period of 12 weeks instead of over 6 weeks.

We have also shown that the benefits of chemotherapy are very little for patients already undergoing radiotherapy. Subtotal resection occurs either by design (if the tumor borders a critically essential part of the brain) or because of failure of the surgeon to determine the precise boundary of the tumor. We have estimated the average diameter for the residual tumor at $R_* = 18$mm, when the tumor size is $R_0 = 20$mm. Our model can predict the benefits that will occur if the resection will be more complete, or if the radiation dose is increased.

If instead of using the data of the group of patients between the age of 20 and 39 in Albert et al. [3] we use the patients data of different age groups in [3] or the patients data of Stummer et al. [136] for the age group B60, we obtain slightly different parameters A, B, ε, but this does not affect the qualitative conclusions as described in Figs. 5.2 – 5.8.

The present chapter is based on data from [3, 107, 137]. A recent article by Gorlia et al. [72] provides similar data which agree with those of [3, 107, 137] in the case of patients who undergone partial resection with radiotherapy and with or without chemotherapy. However it gives a shorter MST for patients who undergone complete resection with radiotherapy. This inconsistency may be the result of how one interprets complete resection. Our model parameters

can be adjusted to the data in [72], but the qualitative results described in Figs. 5.2 – 5.8 will not be affected.

We conclude this chapter with some comments and discussion about explicit solutions we obtained in the previous section.

There is an interesting feature of the explicit solution. Observing the solution formula, we see the dependent domain of $\hat{x}(s,t)$ is one point $\{s\}$ and the dependent domain of $\gamma(s,t)$, as calculated by the formula (5.13), is the interval $[V_*, s]$, hence the dependent domain of the tumor radius $R(t)$, or $V(t)$, is the interval $[V_*, V_0]$. Therefore, if we extend the domain of $\varphi(s)$ from $[V_*, V_0]$ to $[V_*, +\infty)$ by assigning arbitrary values to the extended part of $\varphi(s)$, the solution will not be affected.

Due to this property of the solution, the original free boundary problem can be reformulated as a fixed boundary problem defined on an infinite domain $[V_*, +\infty)\times[0, +\infty)$ with a discontinuous initial condition. That is, the solution of the system (5.8) on its domain coincides with that of the following system:

$$\begin{cases} \dfrac{\partial x(s,t)}{\partial t} + \omega(s,t)\dfrac{\partial x(s,t)}{\partial s} = \beta x(s,t)\left(K - x(s,t)\right), \quad V_* \le s, t \ge 0, \\ \dfrac{\partial \omega(s,t)}{\partial s} = \beta x(s,t) - \mu, \quad V_* \le s, t \ge 0, \\ \omega(V_*, t) = 0, \quad t \ge 0, \\ \dfrac{dV(t)}{dt} = \omega(V(t), t), \quad t \ge 0, \end{cases} \tag{5.19}$$

with the initial conditions: $V(0) = V_0$, $x(s,0) = \psi(s)$, for $V_* \le s$, where

$$\psi(s) = \begin{cases} \varphi(s)\,, & s \le V_0\,; \\ 0\,, & s > V_0\,. \end{cases} \tag{5.20}$$

For the hyperbolic free boundary problem obtained by the mass conversation law where the free boundary moves only because of the expansion of the inside mass, this property of the solution seems true. Conceptually, we can change this type of free boundary problem to a fixed boundary problem. Moreover, the methods developed in this paper can be used in analysis of more general free boundary problems.

We now discuss some biological significance of our explicit solutions. Based on the solution (5.16) where there is no treatment after the surgical resection, if the tumor cell proliferation rate λ is greater than the tumor cell death rate δ, the tumor will grow until the patient dies. If the the tumor cell proliferation rate λ is smaller than the tumor cell death rate δ, the tumor will shrink, and the patient survives. If the the tumor cell proliferation rate λ is equal to the tumor cell death rate δ, the tumor will grow to a certain size and then stop growing, so that it reaches a stationary state. This threshold phenomenon is biologically reasonable. Unfortunately, the tumor cell proliferation rate λ is always greater than the tumor cell death rate δ in reality; otherwise, there will be no tumor. By the solution (5.17), the tumor is treated by the combined radiotherapy and chemotherapy after the tumor regrows to a size of $V(t_1)$. Theoretically, we can make the combined parameter $\lambda-\delta-A-B$ as small as we want by increasing A and B. This means, we need to increase the strength of the radiotherapy and chemotherapy. Within the tolerable toxicity of these therapies, $\lambda - \delta - A - B$ may be negative. It is obvious that the longer the tumor is treated by the combined radiotherapy and chemotherapy, the more

the tumor cells are killed. However, the radiotherapy cannot be applied too long because of its side effects and toxicity. Then, the chemotherapy has to be applied individually as the solution (5.18) shows. It may be the case where the density of tumor cells drops to such a low level that is beyond the detection after these treatments. A condition on which the tumor could be eradicated is $\lambda < \delta + B$, and then it is automatically true that $\lambda < \delta + A + B$. Since these are parameters of exponential functions, there is no guarantee that all tumor cells are killed with a period of finite time. However, these solutions can be used to compute the survival times when different protocols of radiotherapy and chemotherapy are applied.

6

Tumor Modeling with Different Cell Velocities

6.1 Introduction

Cancers appear with multiscale features: genes, cells, and biological tissues, corresponding to the molecular, cellular, and tissue scales. Hence, selecting the proper modeling scale from the multiple scales is an important issue. Bellomo *et al.* [8, 9] discussed the multiscale aspects of cancer modeling. According to the classification of scales, there are basically three types of mathematical models of cancers: microscopic models (at the molecular and the cellular scales), macroscopic models (at the tissue scale), multiscale models (the overall system is viewed as a system of subsystems with specific scales). Microscopic models usually refer to the early stage of cancer onset and developments, and they are derived in the framework of the kinetic theory for active interactions (see [7, 9, 47], for instance). After a suitable maturation time, tumor cells may start to condense and aggregate into a solid form. At this stage, various space phenomena, such as cell motion and tumor size, play a relevant role in the overall dynamics, and macroscopic models may be

needed for understanding of tumor growth. Macroscopic models are usually based on mass conservation laws and on reaction-diffusion processes within tumor (see [1, 11, 26, 63, 73, 74, 93, 94, 143, 145, 147, 168], for instance). Multiscale models illustrate that the molecular and cellular events continue to play a crucial role in macroscopic tumor progression (see [23], for instance). Microscopic models often consist of nonlinear integro-differential equations (IDEs), macroscopic models lead to systems of nonlinear partial differential equations (PDEs), and multiscale models are usually hybrid systems. For more detailed descriptions of microscopic models, macroscopic models and multiscale models, the reader is refer to two recent review articles [9, 112].

Multiscale models are good approximations of biological realities, although they can become analytically intractable. On the other hand, microscopic models are often complex and abstract, and they can also become analytically intractable. So, the present chapter and the next two chapters will focus on the mathematical analysis of macroscopic models.

In this chapter, we reviews a mathematical model describing the cell cycle dynamics and chemotactic driven cell movement in a multicellular tumor spheroid. Tumor cells consist of two types of cells: proliferating cells and quiescent cells, which have different chemotactic responses to an extracellular nutrient supply.

((This chapter is organized as follows. Section 6.2 presents the model. Section 6.3 transforms the problem in a moving-domain into a new problem in a fixed domain. Section 6.4 establishes some useful *a priori* bounds. Section

6.5 gives the main ideas of the proof. Section 6.6 studies a parabolic problem with a *nonlinear* boundary condition. Section 6.7 proves the local existence and uniqueness of solutions of the problem. Section 6.8 extends the above local solution to all $t > 0$. Finally, this chapter is closed with a summary section.))

6.2 Mathematical Model

Multicellular tumor spheroids (MCTSs) are three-dimensional cell cultures which have structural similarity to in vivo tumors, and MCTSs are routinely used as in vitro models of tumor growth. A number of mathematical models of partial differential equations (PDEs) have been developed to describe the growth of MCTSs (see [19, 20, 46, 73, 125, 133, 163, 166, 167, 168], for instance). Rigorous mathematical analysis of these models, such as global existence, uniqueness and stability of a solution are interesting (see [43, 44, 58, 62, 63, 143, 145], for instance).

In this chapter, we review a mathematical model describing the cell cycle and cell movement in a MCTS. This model was proposed by Tindall and Please [163]. One novelty of this model is that the model includes an explicit description of proliferating and quiescent cells within a MCTS. A common feature of most continuum mathematical models of avascular tumor growth is the assumption that all cells within a tumor have a common spatial velocity profile. However, in the model [163], Tindall and Please have considered the possibility of differing cell velocities, which is another novelty of their model.

The different cell velocities are created when proliferating and quiescent cells have different chemotactic responses to an extracellular nutrient supply. Considering a spherically symmetric MCTS, Tindall and Please's model reads as follows:

$$\frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial c}{\partial r}\Big) = \lambda(c)c, \qquad \text{for } 0 < r < R(t),\ t > 0, \tag{6.1}$$

$$p + q = N, \qquad \text{for } 0 \le r \le R(t),\ t \ge 0, \tag{6.2}$$

$$u_q(r,t) = u_p(r,t) + \chi\frac{\partial c}{\partial r}, \qquad \text{for } 0 \le r \le R(t),\ t > 0, \tag{6.3}$$

$$\begin{aligned}&\frac{\partial p}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2(u_p p)\Big)\\ &\quad = D\frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial p}{\partial r}\Big) + \big(K_b(c) - K_q(c) - K_a(c)\big)p\\ &\qquad + K_p(c)q, \qquad \text{for } 0 < r < R(t),\ t > 0,\end{aligned} \tag{6.4}$$

$$\begin{aligned}&\frac{\partial q}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2(u_q q)\Big)\\ &\quad = D\frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial q}{\partial r}\Big) + K_q(c)p\\ &\qquad - \big(K_d(c) + K_p(c)\big)q, \qquad \text{for } 0 < r < R(t),\ t > 0,\end{aligned} \tag{6.5}$$

$$\frac{\partial c}{\partial r}(r,t) = 0 \text{ at } r = 0, \quad \text{for } t > 0, \tag{6.6}$$

$$c(r,t) = c_\infty \text{ at } r = R(t), \quad \text{for } t > 0, \tag{6.7}$$

$$p(r,0) = p_0(r), \text{ for } 0 \le r \le R(0),\ t > 0, \tag{6.8}$$

$$\frac{\partial p}{\partial r}(r,t) = \frac{\partial q}{\partial r}(r,t) = u_p(r,t) = u_q(r,t) = 0 \text{ at } r = 0, \text{ for } t > 0, \tag{6.9}$$

$$p\frac{dR(t)}{dt} - \Big(pu_p - D\frac{\partial p}{\partial r}\Big) = 0 \quad \text{at } r = R(t), \tag{6.10}$$

$$q\frac{dR(t)}{dt} - \Big(qu_q - D\frac{\partial q}{\partial r}\Big) = 0 \quad \text{at } r = R(t), \tag{6.11}$$

$$R(0) = R_0 > 0 \quad \text{is prescribed.} \tag{6.12}$$

Here $R(t),\ c,\ p,\ q,\ u_p$ and u_q are unknown functions, which will be explained in the following. $R(t)$ represents the spheroid radius. In (6.1), $c(r,t)$ is the concentration of nutrient, $\lambda(c)$ is any positive smooth function, and $\lambda(c)c$ is a consumption rate of nutrient which is zero when $c = 0$. In (6.2), N is the total number of live cells per unit volume, and we assume that tumor cells consist of two types of cells: proliferating and quiescent cells. $p(r,t)$ and $q(r,t)$ are the proliferating and quiescent cell densities, respectively. The cells are taken to fill any region within the tumor. In addition, for simplicity, we shall neglect the space taken by any dead cell material [163, 168]. In (6.3), $u_p = u_p(r,t)$ is the velocity of proliferating cells, $u_q = u_q(r,t)$ is the velocity of quiescent cells, and χ is a parameter introduced to describe the relative strength of the chemotactic response of the two cell phases [163]: proliferating cells move up the chemotactic gradient relative to quiescent cells when $\chi < 0$; proliferating cells move at the same velocity as quiescent cells when $\chi = 0$; and proliferating cells move down the chemotactic gradient relative to quiescent cells if $\chi > 0$. In (6.4) and (6.5), cell motion is described by both random motion of the cells (diffusion) and directed motion stimulated by nutrient gradients (chemotaxis). D is a positive constant, which is the random diffusion coefficient of the cells. $K_b(c)$ is the rate of cell birth, $K_p(c)$ is the rate at which cells return to the proliferative compartment from quiescence, $K_q(c)$ is the rate at which proliferating cells become quiescent, $K_a(c)$ is the death rate of proliferating cells, and $K_d(c)$ is the death rate of quiescent cells. $K_a(c)p$ in (6.4) is the death of proliferating cells due to apoptosis, while $K_d(c)q$ in (6.5) is the death

of quiescent cells due to necrosis. (6.6) is a result of the radial symmetry assumption of the problem, and (6.7) assumes that the spheroid is supported in a nutrient-rich medium. (6.8) is an initial condition for the cell distribution. (6.9) is also a result of the radial symmetry assumption of the problem. On the outer boundary of the spheroid we impose no-flux conditions as given in (6.10) and (**??**) for proliferating cells and quiescent cells, respectively; see Remark 6.2 below for further explanation. (6.12) is an initial condition for tumor radius.

By adding Eqs. (6.4) and (6.5) and invoking assumptions (6.2) and (6.3) an equation for the velocity of the proliferating cells is obtained

$$\frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 u_p\Big) = \frac{1}{N}\Big(K_b(c)p - K_a(c)p - K_d(c)(N-p)\Big) + \frac{\chi}{N}\frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2(p-N)\frac{\partial c}{\partial r}\Big). \tag{6.13}$$

By adding Eqs. (6.10) and (6.11) and using assumptions (6.2) and (6.3) an equation for the velocity of the outer boundary of the spheroid is obtained

$$\frac{dR(t)}{dt} = u_p + \frac{\chi}{N} q \frac{\partial c}{\partial r} \quad \text{at } r = R(t). \tag{6.14}$$

This, together with (6.10), yields a boundary condition for proliferating cells

$$D\frac{\partial p}{\partial r} + \Big(\frac{\chi}{N} q \frac{\partial c}{\partial r}\Big)p = 0 \quad \text{at } r = R(t). \tag{6.15}$$

We note that Eq. (6.5) is a consequence of Eqs. (6.2)-(6.4) and (6.13), so that in the sequel we may drop this equation and replace q by $N - p$ in (6.4), (6.14) and (6.15).

We also notice that the no-flux boundary conditions (6.10)-(6.11) are equivalent to the boundary conditions (6.14)-(6.15) under the assumptions (6.2) and (6.3), so that in what follows we shall replace (6.10)-(6.11) with (6.14)-(6.15).

We further note that the empirical rules used for the functional dependence of K_a, K_b, K_d, K_p and K_q on c are *not* critical to our analytical result. For the global existence of a solution to the model, we only need the following simple,

$$K_a(c) \geq 0, K_b(c) \geq 0, K_d(c) \geq 0, K_p(c) \geq 0, K_q(c) \geq 0$$
$$\text{and these functions are } C^1\text{-smooth functions,} \tag{6.16}$$

This assumption is physically realistic. The requirement of the C^1-smoothness will be explained in Section 6.7.

Remark 6.1. In Tindall and Please's model [163], they neglected the random cell motion term in Eqs. (6.4) and (6.5). Their numerical results clearly indicate the formation of *shocks* in the proliferating cell distributions. Mathematically, by dropping the diffusion terms in Eqs. (6.4) and (6.5), the solution of corresponding first-order hyperbolic equations may evolve shocks due to the dominant cell motion directed by chemotaxis. Here we retain random cell motion in Eqs. (6.4) and (6.5), and prove that afore-mentioned shocks can be smoothed by this random cell motion. Indeed, we will prove the global existence and uniqueness of a $C^{1+\lambda,(1+\lambda)/2}$-smooth $(0 < \lambda < 1)$ solution of the model (6.1)-(6.16). Furthermore, in section 6.8 we will give some indication

where the analysis might break down if the diffusion of the cell types is sent to zero.

Remark 6.2. If $\chi = 0$, the global existence and uniqueness of a solution to the model (6.1)-(6.16) can be proved using the methods of [145, 169]. So, throughout the remainder of this chapter, we assume that $\chi \neq 0$. On the outer boundary of the spheroid, the flux of proliferating cells has two components, One is the diffusion flux $-D\frac{\partial p}{\partial r}(R(t), t)$, and the other is the flux, $pu_p(R(t), t)$, due to proliferation and death of cells. Since the spheroid changes at the rate $\dot{R}(t)$, the *no-flux* boundary condition for p should be $p\dot{R} - \left(pu_p - D\frac{\partial p}{\partial r}\right) = 0$ as shown in (6.10). The no-flux boundary condition (6.11) can be similarly explained.

Remark 6.3. Once diffusion is introduced, the analysis in this chapter will be independent of the sign of χ. However, for definiteness and clarity of the statement, we will assume that $\chi > 0$ throughout the remainder of this chapter.

Tindall and Please [163] numerically studied the model (6.1)-(6.16) with $D = 0$ and empirical linear functions $K_a(c), K_b(c), K_d(c), K_p(c)$ and $K_q(c)$. In particular, they investigated the different distributions of quiescent and proliferating cells that can occur within a MCTS. Tao [150] proved the global existence and uniqueness of a solution to the model (6.1)-(6.16). This chapter will mainly review Tao's results [150]. The main difficulties of the proof are due to the *chemotactic* term in (6.13), to the *nonlinear* boundary condition

(6.15), and to possible singularity at tumor center if we regard Eqs. (6.4) and (6.5) as two 1-dimension parabolic equations with a radial spatial variable r (Note that $\frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial p}{\partial r}) = \frac{\partial^2 p}{\partial r^2} + \frac{2}{r}\frac{\partial p}{\partial r}$). To overcome these difficulties, we establish some necessary estimates, employ the Leray-Schauder fixed point theorem, and use the three-dimensional Cartesian coordinate.

6.3 Transformation and Main Results

After re-scalings (see Appendix in [163]), the system (6.1)-(6.16) takes the following form in $\{0 < \bar{r} < \bar{R}(\bar{t}),\ \bar{t} > 0\}$:

$$\triangle_{\bar{r}}\bar{c} = \bar{\lambda}(\bar{c})\bar{c}, \tag{6.17}$$

$$\frac{\partial \bar{c}}{\partial \bar{r}}(0,\bar{t}) = 0, \tag{6.18}$$

$$\bar{c}(\bar{R}(\bar{t}),\bar{t}) = 1, \tag{6.19}$$

$$\begin{aligned}&\frac{\partial \bar{p}}{\partial \bar{t}} + \frac{1}{\bar{r}^2}\frac{\partial}{\partial \bar{r}}\Big(\bar{r}^2(\bar{u}_p\bar{p})\Big)\\ &= \bar{D}\triangle_{\bar{r}}\bar{p} + \big(\bar{K}_b(\bar{c}) - \bar{K}_q(\bar{c}) - \bar{K}_a(\bar{c})\big)\bar{p} + \bar{K}_p(\bar{c})(1-\bar{p}),\end{aligned} \tag{6.20}$$

$$\bar{p}(r,0) = \bar{p}_0(r), \tag{6.21}$$

$$\frac{\partial \bar{p}}{\partial \bar{r}}(0,\bar{t}) = 0, \quad D\frac{\partial \bar{p}}{\partial \bar{r}} + \Big(\bar{\chi}(1-\bar{p})\frac{\partial \bar{c}}{\partial \bar{r}}\Big)\bar{p} = 0 \quad \text{at } \bar{r} = \bar{R}(\bar{t}), \tag{6.22}$$

$$\begin{aligned}&\frac{1}{\bar{r}^2}\frac{\partial}{\partial \bar{r}}\Big(\bar{r}^2\bar{u}_p\Big)\\ &= \bar{K}_b(\bar{c})\bar{p} - \bar{K}_a(\bar{c})\bar{p} - \bar{K}_d(\bar{c})(1-\bar{p}) - \frac{\bar{\chi}}{\bar{r}^2}\frac{\partial}{\partial \bar{r}}\Big(\bar{r}^2(1-\bar{p})\frac{\partial \bar{c}}{\partial \bar{r}}\Big),\end{aligned} \tag{6.23}$$

$$\bar{u}_p(0,\bar{t}) = 0, \tag{6.24}$$

$$\frac{d\bar{R}(\bar{t})}{d\bar{t}} = \bar{u}_p + \bar{\chi}\big(1-\bar{p}\big)\frac{\partial \bar{c}}{\partial \bar{r}} \quad \text{at } \bar{r} = \bar{R}(\bar{t}), \tag{6.25}$$

$$\bar{R}(0) = \bar{R}_0, \tag{6.26}$$

where

$$0 \le \bar{K}_a(\bar{c}), \bar{K}_b(\bar{c}), \bar{K}_d(\bar{c}), \bar{K}_p(\bar{c}), \bar{K}_q(\bar{c}) \in C^1 \tag{6.27}$$

and

$$\triangle_{\bar{r}} = \frac{1}{\bar{r}^2}\frac{\partial}{\partial \bar{r}}\Big(\bar{r}^2 \frac{\partial}{\partial \bar{r}}\Big).$$

To transform the moving domain $\{\bar{r} < \bar{R}(\bar{t})\}$ into a fixed domain, as shonw in [145], we introduce a change of variables $(\bar{r}, \bar{t}, \bar{c}, \bar{p}, \bar{u}_p, \bar{R}) \mapsto (\rho, \bar{t}, \tilde{c}, \tilde{p}, \tilde{u}, \bar{R})$ as follows:

$$\begin{aligned}
&\rho = \bar{r}/\bar{R}(\bar{t}), \quad \bar{t} = \bar{t},\\
&\tilde{c}(\rho, \bar{t}) = \bar{c}(\rho\bar{R}(\bar{t}), \bar{t}), \quad \tilde{p}(\rho, \bar{t}) = \bar{p}(\rho\bar{R}(\bar{t}), \bar{t}),\\
&\tilde{u}(\rho, \bar{t}) = \bar{u}_p(\rho\bar{R}(\bar{t}), \bar{t})/\bar{R}(\bar{t}), \quad \bar{R}(\bar{t}) = \bar{R}(\bar{t}).
\end{aligned} \tag{6.28}$$

In terms of the new variables and after dropping the tildes of $\tilde{c},\ \tilde{p}$ and $\tilde{u}$ and the bars of $\bar{t},\ \bar{R},\ \bar{D},\ \bar{K}_a,\ \bar{K}_b,\ \bar{K}_d,\ \bar{K}_p,\ \bar{K}_q,\ \bar{\chi}$ and $\bar{R}_0$ for notational convenience, the system (6.17)-(6.27) takes the following form in $\{0 < \rho < 1,\ t > 0\}$:

$$\triangle_\rho c = R^2(t)\lambda(c)c, \tag{6.29}$$

$$\frac{\partial c}{\partial \rho}(0,t) = 0, \quad c(1,t) = 1, \tag{6.30}$$

$$\begin{aligned}
&\frac{\partial p}{\partial t} + \big[u(\rho,t) - \rho u(1,t)\big]\frac{\partial p}{\partial \rho}\\
&\quad + \Big[\frac{\chi}{R^2(t)}\frac{\partial c}{\partial \rho}p - \chi\rho\frac{1}{R^2(t)}\frac{\partial c(1,t)}{\partial \rho}\big(1 - p(1,t)\big)\Big]\frac{\partial p}{\partial \rho} - \frac{D}{R^2(t)}\triangle_\rho p\\
&= \big[-K_q(c) + \big(K_b(c) + K_d(c) - K_a(c) + \chi\lambda(c)c\big)(1-p)\big]p\\
&\quad + K_p(c)(1-p),
\end{aligned} \tag{6.31}$$

$$p(\rho,0)=p_0(\rho), \tag{6.32}$$

$$\frac{\partial p}{\partial \rho}(0,t)=0, \quad \Big[D\frac{\partial p}{\partial \rho}+\Big(\chi(1-p)\frac{\partial c}{\partial \rho}\Big)p\Big]\Big|_{\rho=1}=0, \tag{6.33}$$

$$u(\rho,t)=\frac{1}{\rho^2}\int_0^\rho \big[K_b(c)p-K_a(c)p-K_d(c)(1-p)\big]s^2ds \\ -\chi(1-p)\frac{1}{R^2(t)}\frac{\partial c}{\partial \rho}, \tag{6.34}$$

$$\frac{dR(t)}{dt}=R(t)\int_0^1 \big[K_b(c)p-K_a(c)p-K_d(c)(1-p)\big]s^2ds, \tag{6.35}$$

$$R(0)=R_0, \quad R_0 \text{ is given}, \tag{6.36}$$

$$0\le K_a(c),K_b(c),K_d(c),K_p(c),K_q(c)\in C^1, \tag{6.37}$$

where we have used the fact that $\triangle_\rho c=R^2(t)\lambda(c)c$ in deriving Eq. (6.31). We shall also assume that

$$0\le p_0(\rho)\le 1,$$

$$p_0(\rho)\in W_k^2(B_1(0)), \tag{6.38}$$

$$\frac{\partial p_0}{\partial \rho}(0)=\Big(D\frac{\partial p_0}{\partial \rho}+\chi p_0(1-p_0)\frac{\partial c}{\partial \rho}\Big|_{t=0}\Big)\Big|_{\rho=1}=0,$$

here $B_1(0)=\{y\in\mathcal{R}^3:\ |y|\le 1\}$ and $W_k^2(B_1(0)):=\big\{\varphi(\rho)\big|\varphi,\ \varphi_{y_i},\ \varphi_{y_iy_j}\in L^k(B_1(0)\big\}$, in which $k>5,\ i,j=1,2,3$, and the derivatives are in the weak sense. We note that (6.38) is physically realistic as it ensures that both of the cell populations, p and q, are initially non-negative. Throughout this chapter, we also assume that

$$\lambda(c) \text{ is any positive } C^1\text{-smooth function}, \tag{6.39}$$

which is physically realistic as it ensures that the consumption rate of nutrient, $\lambda(c)c$, is non-negative smooth function of c which is zero when $c = 0$. The requirement of the C^1-smoothness of $\lambda(c)$ will be explained in next section.

Remark 6.4. Tindall and Please's model [163] empirically assumed that $\lambda(c) = 1$. However, physically any positive smooth function should be adequate for global existence of a solution to the model.

We shall use the following notation:

$$Q_T = B_1(0) \times [0,T], \quad W_k^{2,1}(Q_T) = \left\{p(\rho,t)|p,\ p_{y_i},\ p_{y_iy_j},\ p_t \in L^k(Q_T)\right\}$$

where $1 \le k \le \infty$, $i,j = 1,2,3$, and the derivatives are in the weak sense.

The main result of this chapter is as follows:

Theorem 6.1. *Under the assumptions (6.37)-(6.39), there exists a unique solution $(R(t), c(\rho,t), u(\rho,t), p(\rho,t))$ of the problem (6.29)-(6.36) for all $t > 0$; furthermore, $R(t) \in C^1[0,\infty)$, $u(\rho,t) \in C^1([0,1] \times [0,\infty))$, $c(\rho,t) \in C^{2,1}([0,1] \times [0,\infty))$, $p(\rho,t) \in W_k^{2,1}(Q_T)$ for some $k > 5$ and any $T > 0$, and*

$$0 < c(\rho,t) \le 1, \tag{6.40}$$

$$0 \le p(\rho,t) \le 1, \tag{6.41}$$

$$|u(\rho,t)| \le \beta, \tag{6.42}$$

$$R_0 e^{-\beta t} \le R(t) \le R_0 e^{\beta t} \tag{6.43}$$

for some $\beta > 0$.

6.4 A Priori Bounds

In this section we establish several *a priori* bounds which will be used later.

Lemma 6.1. *Under the assumptions (6.37)-(6.39), for any solution of (6.29)-(6.36) there hold:*

$$0 \le c(\rho,t) \le 1, \quad \textit{for } 0 \le \rho \le 1,\ t > 0, \tag{6.44}$$

$$0 \le \frac{1}{\rho R^2(t)} \frac{\partial c}{\partial \rho} \le M_0, \quad \textit{for } 0 \le \rho \le 1,\ t > 0, \tag{6.45}$$

where $M_0 := \frac{1}{3} \max_{0 \le c \le 1} \lambda(c) > 0$.

Proof. Set $r := \rho R(t)$. Then Eqs. (6.29)-(6.30) can be rewritten as follows:

$$\triangle_r c = \lambda(c)c, \quad \text{for } 0 < r < R(t),\ t > 0, \tag{6.46}$$

$$\frac{\partial c}{\partial r}(0,t) = 0, \quad c(R(t),t) = 1. \tag{6.47}$$

By $\lambda(c) > 0$ and the maximum principle for elliptic equations, we have

$$c(r,t) \ge 0 \tag{6.48}$$

and

$$c(r,t) \le 1. \tag{6.49}$$

Hence, the proof of (6.44) is completed.

We now turn to prove (6.45). We derive from (6.46), the first equation in (6.47), (6.39), (6.48) and (6.49) that

$$0 \le r^2 \frac{\partial c}{\partial r}(r,t) = \int_0^r \lambda(c(s,t))c(s,t)s^2 ds \le \frac{1}{3}\lambda_1 r^3$$

and therefore

$$0 \le \frac{1}{r}\frac{\partial c}{\partial r}(r,t) \le \frac{1}{3}\lambda_1, \tag{6.50}$$

where $\lambda_1 = \max_{0\le c\le 1} \lambda(c) > 0$. This completes of the proof of (6.45). □

Remark 6.5. We note that the C^1-smoothness of function $\lambda(c)$ as assumed in (6.39) is used for deriving the C^2-regularity of the solution to problem (6.46)-(6.47) by Schauder theory.

Lemma 6.2. *For any solution of (6.29)-(6.39) with $p \in C(Q_T)$ and $R(t) \in C[0,T]$, there holds:*

$$0 \le p(\rho,t) \le 1. \tag{6.51}$$

Proof. We first assert that

$$\begin{aligned} &\text{if the minimum of } p \text{ in } Q_T \text{ is negative, then it } \textit{cannot} \\ &\text{be attained at the boundary } \rho = 1. \end{aligned} \tag{6.52}$$

Suppose, to the contrary, that there exists a point (y_0,t_0) ($|y_0| = 1$, $0 < t_0 \le T$) such that

$$p(y_0,t_0) = \min_{0\le t\le T} p(y,t) < 0. \tag{6.53}$$

Then we have

$$\frac{\partial p}{\partial \rho}\Big|_{(y_0,t_0)} \le 0. \tag{6.54}$$

We note that

$$\frac{\partial c}{\partial \rho}(1,t) > 0 \tag{6.55}$$

by (6.29)-(6.30) and the strong maximum principle of elliptic equations. The inequality (6.55), together with (6.53)-(6.54) and $\chi > 0$, further yields

$$\Big(D\frac{\partial p}{\partial \rho}+\chi p(1-p)\frac{\partial c}{\partial \rho}\Big)\Big|_{(y_0,t_0)}<0$$

which contradicts the boundary condition of p at the boundary $\rho=1$ in (6.33). So, (6.52) holds.

On the other hand, by $K_p(c)\geq 0$, Eq. (6.31) can be written as follows:

$$\frac{\partial p}{\partial t}-\frac{D}{R^2(t)}\triangle_\rho\, p+a(p,u,c)\frac{\partial p}{\partial \rho}+b_1(p,u,c)p\geq 0, \tag{6.56}$$

where

$$a(p,u,c)=u(\rho,t)-\rho u(1,t)+\frac{\chi}{R^2(t)}\frac{\partial c}{\partial \rho}p-\chi\rho\frac{1}{R^2(t)}\frac{\partial c(1,t)}{\partial \rho}\big(1-p(1,t)\big),$$

$$b_1(p,u,c)=K_p(c)+K_q(c)$$

$$-\big(K_b(c)+K_d(c)-K_a(c)+\chi\lambda(c)c\big)(1-p).$$

Without loss of generality, we may assume that $b_1\geq 0$ due to the standard exponential transform (i.e. $p=e^{k_0t}\bar{p}$ for large $k_0>0$). Therefore, we derive from $b_1\geq 0$ and (6.56) that

$$\begin{aligned}&\text{if the minimum of } p \text{ in } Q_T \text{ is negative, then it } \textit{cannot}\\ &\text{be attained in the interior of } Q_T.\end{aligned} \tag{6.57}$$

This, together with (6.52), (6.32) and (6.38), that

$$p(\rho,t)\geq 0. \tag{6.58}$$

Next we shall prove that $p(\rho,t)\leq 1$. To this end, we set $q=:1-p$. We easily derive from (6.31)-(6.33), (6.38), (6.58) and $K_q(c)\geq 0$ that

$$\frac{\partial q}{\partial t} - \frac{D}{R^2(t)} \triangle_\rho q + a(p,u,c)\frac{\partial q}{\partial \rho} + b_2(p,u,c)q \geq 0 \quad \text{in } Q_T, \tag{6.59}$$

$$q(\rho,0) = 1 - p_0(\rho) \geq 0, \quad \frac{\partial q}{\partial \rho}(0,t) = 0, \tag{6.60}$$

$$\Big[D\frac{\partial q}{\partial \rho} + \Big(-\chi p \frac{\partial c}{\partial \rho}\Big)q\Big]_{\rho=1} = 0, \tag{6.61}$$

here

$$b_2(p,u,c) = K_p(c) + \big(K_b(c) + K_d(c) - K_a(c) + \chi\lambda(c)c\big)p$$

and $\frac{\partial}{\partial \rho} \equiv \frac{\partial}{\partial \nu}$, in which ν is the *outward* vector of the domain $B_1(0)$. By (6.45), $p \in C(Q_T)$ and $R(t) \in C[0,T]$, we also have

$$-\chi p\frac{\partial c}{\partial \rho} \geq -A(T) \Leftrightarrow -\chi p\frac{\partial c}{\partial \rho} \text{ is bounded from below,}$$

where $A(T) > 0$ is some constant possibly depending on T. Therefore, the comparison principle holds for problem (6.59)-(6.61) with the third boundary condition (cf. [109, Theorem 2.10] and the remarks following that). Hence

$$q(\rho,t) \geq 0.$$

This completes the proof of Lemma 6.2. □

From (6.34)-(6.35) and Lemmas 6.1 and 6.2, we easily deduce that

Lemma 6.3. *For any solution of (6.29)-(6.39) with $p \in C(Q_T)$ and $R(t) \in C[0,T]$, there hold:*

$$-\beta \leq \frac{u(\rho,t)}{\rho} \leq \beta, \tag{6.62}$$

$$R_0 e^{-\beta t} \leq R(t) \leq R_0 e^{\beta t}, \tag{6.63}$$

where $\beta > 0$ is some positive constant.

If we regard Eq. (6.31) as a 1-dimensional parabolic equation with the spatial variable ρ, then the coefficient of $\partial p/\partial\rho$ has *singularity* at tumor center $\rho = 0$ due to

$$\triangle_\rho p \equiv \frac{\partial^2 p}{\partial \rho^2} + \frac{2}{\rho}\frac{\partial p}{\partial \rho}.$$

However, this singularity can be eliminated by using the estimates (6.45) and (6.62) and employing the three-dimensional Cartesian coordinate.

It is easily checked that

$$\rho p_\rho \equiv y \cdot \bigtriangledown p, \quad \triangle_\rho p \equiv \triangle p, \tag{6.64}$$

where $y = (y_1, y_2, y_3)$, $\rho = \sqrt{y_1^2 + y_2^2 + y_3^2}$, $\nabla = (\frac{\partial}{\partial y_1}, \frac{\partial}{\partial y_2}, \frac{\partial}{\partial y_3})$, $\triangle = \frac{\partial^2}{\partial y_1^2} + \frac{\partial^2}{\partial y_2^2} + \frac{\partial^2}{\partial y_3^2}$. Then the system (6.29)-(6.36) can be rewritten in the following form in Q_T:

$$\triangle_\rho c = R^2(t)\lambda(c)c, \tag{6.65}$$

$$\frac{\partial c}{\partial \rho}(0,t) = 0, \quad c(1,t) = 1, \tag{6.66}$$

$$\begin{aligned}&\frac{\partial p}{\partial t} - \frac{D}{R^2(t)} \triangle p \\ &\quad + \Big[\frac{u(\rho,t)}{\rho} - u(1,t) + \frac{\chi}{\rho R^2(t)}\frac{\partial c}{\partial \rho}p - \frac{\chi}{R^2(t)}\frac{\partial c(1,t)}{\partial \rho}\big(1 - p(1,t)\big)\Big] y \cdot \bigtriangledown p \\ &\quad = \big[- K_q(c) + K(c)(1-p)\big]p + K_p(c)(1-p),\end{aligned} \tag{6.67}$$

$$p(\rho, 0) = p_0(\rho), \tag{6.68}$$

$$\frac{\partial p}{\partial \rho}(0,t) = 0, \quad \Big[D\frac{\partial p}{\partial \rho} + \Big(\chi(1-p)\frac{\partial c}{\partial \rho}\Big)p\Big]\Big|_{\rho=1} = 0, \tag{6.69}$$

$$\begin{aligned}u(\rho,t) = \frac{1}{\rho^2}\int_0^\rho &\big[K_b(c)p - K_a(c)p - K_d(c)(1-p)\big]s^2\, ds \\ &-\chi(1-p)\frac{1}{R^2(t)}\frac{\partial c}{\partial \rho},\end{aligned} \tag{6.70}$$

$$\frac{dR(t)}{dt} = R(t)\int_0^1 \big[K_b(c)p - K_a(c)p - K_d(c)(1-p)\big]s^2\ ds, \tag{6.71}$$

$$R(0) = R_0, \quad R_0 \text{ is given}, \tag{6.72}$$

$$0 \le K_a(c), K_b(c), K_d(c), K_p(c), K_q(c) \in C^1, \tag{6.73}$$

where

$$K(c) = K_b(c) + K_d(c) - K_a(c) + \chi\lambda(c)c. \tag{6.74}$$

Lemma 6.4. *Let T be any finite positive number. Then, for any solution of (6.29)-(6.39) with $p \in C^{\gamma,\gamma/2}(Q_T)$ and $R(t) \in C^1[0,T]$, there holds $p \in W_k^{2,1}(Q_T)$ with $k(1-\gamma) < 1$. Furthermore,*

$$\|p\|_{W_k^{2,1}(Q_T)} \le M(T), \tag{6.75}$$

where $M(T) > 0$ is some constant which may depend on T.

Proof. By (6.37), Lemmas 6.6, 6.8 and 6.9, and the assumption $R(t) \in C[0,T]$, Eq. (6.67) can be rewritten in the following form:

$$\frac{\partial p}{\partial t} - \frac{D}{R^2(t)}\triangle p + a_0\ y\cdot\bigtriangledown p + b_0\ p = h \tag{6.76}$$

with

$$\frac{D}{R^2(t)} \in C(Q_T), \quad \frac{D}{R_0^2}e^{-2\beta T} \le \frac{D}{R^2(t)} \le \frac{D}{R_0^2}e^{2\beta T}, \tag{6.77}$$

$$\|a_0\|_{L^\infty},\ \|b_0\|_{L^\infty},\ \|h\|_{L^\infty} \le M_1, \tag{6.78}$$

where M_1 is some positive constant. We easily derive from (6.65)-(6.66) and $R(t) \in C^1[0,T]$ that

$$\frac{\partial c}{\partial \rho} \in C^{1,1}(Q_T).$$

This, together with $p \in C^{\gamma,\gamma/2}(Q_T)$, yields

$$\chi(1-p)\frac{\partial c}{\partial \rho} \in C^{\gamma,\gamma/2}(Q_T). \tag{6.79}$$

Hence, by (6.76)-(6.79), (6.68)-(6.69), (6.38) and the parabolic L^p-theory (cf. [109, Theorem 7.20]) we see that $\hat{p} \in W_k^{2,1}(Q_T)$ with $k(1-\gamma) < 1$ and

$$\|p\|_{W_k^{2,1}(Q_T)} \leq A(T)\Big(\|p_0(\rho)\|_{W^{2,k}(B_1(0))} + \|h\|_{L^k(Q_T)}\Big), \tag{6.80}$$

where $A(T)$ is some constant which may depend on T. This, combined with $\|h\|_{L^\infty} \leq M_1$, further yields

$$\|p\|_{W_k^{2,1}(Q_T)} \leq A(T)\Big(\|p_0(\rho)\|_{W^{2,k}(B_1(0))} + M_1\big|B_1(0)\big|T^{\frac{1}{k}}\Big) := M(T).$$

This completes the proof of Lemma 6.4. □

6.5 Main Ideas

For clarity, in this section we will give the sketch of the proof of Theorem **??**. The detailed proof will be left in the next three sections. We shall use the contraction mapping principle to prove that (6.65)-(6.74) has a unique local solution. For given $T > 0$, we introduce a metric space (X_T, d) as follows:

$$
\begin{aligned}
X_T = \big\{\ & (R,p) = (R(t), p(\rho,t)) \quad (0 \le \rho \le 1,\ 0 \le t \le T): \\
& R(t) \in C^1[0,T],\ R(0) = R_0,\ \frac{1}{2}R_0 \le R(t) \le 2R_0; \\
& p(\rho,t) \in C^{\gamma,\gamma/2}(Q_T) \text{ with } \gamma \in (\frac{4}{5}, 1),\ 0 \le p(\rho,t) \le 1, \\
& \frac{\partial p}{\partial \rho}(0,t) = 0,\ p(\rho,0) = p_0(\rho), \\
& \Big[D\frac{\partial p}{\partial \rho} + \Big(\chi(1-p)\frac{\partial c}{\partial \rho}\Big)p\Big]\Big|_{\rho=1} = 0 \quad \text{where } c \text{ is} \\
& \text{the solution to problem (6.65)-(6.66) for given } R(t) \quad \big\}.
\end{aligned}
$$

The metric d in X_T is defined by

$$
d\big((R_1,p_1),(R_2,p_2)\big) = \|R_1 - R_2\|_{C^1[0,T]} + \|p_1 - p_2\|_{C^{\gamma,\gamma/2}(Q_T)}.
$$

For any given $(R(t), p(\rho,t)) \in X_T$ we define $c(\rho,t)$ being the solution of (6.65)-(6.66) and define $u(\rho,t)$ by (6.70). Let $\hat{R}(t)$ and $\hat{p}(\rho,t)$ solve the following two decoupled problems in $\{0 \le \rho \le 1,\ t \ge 0\}$:

$$
\frac{d\hat{R}(t)}{dt} = \hat{R}(t)\int_0^1 \big[K_b(c)p - K_a(c)p - K_d(c)(1-p)\big]s^2\ ds, \tag{6.81}
$$

$$
\hat{R}(0) = R_0, \tag{6.82}
$$

$$
\begin{aligned}
& \frac{\partial \hat{p}}{\partial t} - \frac{D}{R^2(t)} \triangle \hat{p} \\
& \quad + \Big[\frac{u(\rho,t)}{\rho} - u(1,t) + \frac{\chi}{\rho R^2(t)}\frac{\partial c}{\partial \rho}p - \frac{\chi}{R^2(t)}\frac{\partial c(1,t)}{\partial \rho}\big(1 - p(1,t)\big)\Big] y \cdot \bigtriangledown \hat{p} \\
& \quad = \big[-K_q(c) + K(c)(1-\hat{p})\big]\hat{p} + K_p(c)(1-\hat{p}),
\end{aligned} \tag{6.83}
$$

$$
\hat{p}(\rho,0) = p_0(\rho), \tag{6.84}
$$

$$
\frac{\partial \hat{p}}{\partial \rho}(0,t) = 0, \quad \Big[D\frac{\partial \hat{p}}{\partial \rho} + \Big(\chi(1-\hat{p})\frac{\partial c}{\partial \rho}\Big)\hat{p}\Big]\Big|_{\rho=1} = 0. \tag{6.85}
$$

Then, we define a mapping

$$
F:\ (R(t),\ p(\rho,t)) \longrightarrow (\hat{R}(t),\ \hat{p}(\rho,t)).
$$

In next two sections we will prove that F is contractive if T is sufficiently small, and this will complete the proof of the local existence and uniqueness of a solution of the system (6.65)-(6.74). The global existence will be proved in Section 6.8.

We first consider the problem (6.81)-(6.82). Clearly,

$$\hat{R}(t) = R_0 e^{\int_0^t \left(\int_0^1 \left[K_b(c)p - K_a(c)p - K_d(c)(1-p) \right] s^2 \, ds \right) d\tau} \in C^1[0,T], \tag{6.86}$$

$$\frac{R_0}{2} \le \hat{R}(t) \le 2R_0, \quad \text{for } 0 \le t \le T, \tag{6.87}$$

where $T > 0$ is sufficiently small.

Since the problem (6.83)-(6.85) is a *new* nonlinear parabolic problem, the solvability of it will be left in next section.

6.6 Problem with Nonlinear Boundary Condition

In this section we shall solve the problem (6.83)-(6.85). For notational convenience, in what follows we shall denote various constants which are independent of T by A_0. The main result of this section is as follows.

Theorem 6.2. *Under the assumptions (6.37)-(6.39), for any $(R,p) \in X_T$, the problem (6.83)-(6.85) has a unique solution $\hat{p} \in C^{\gamma,\gamma/2}(Q_T)$ for $0 < T < 1$. Furthermore,*

$$0 \le \hat{p}(\rho,t) \le 1, \tag{6.88}$$

$$\|\hat{p}(\rho,t)\|_{W_k^{2,1}(Q_T)} \le A_0, \tag{6.89}$$

where $A_0 > 0$ is some constant being independent of T.

Proof. Existence: We will use the Leray-Schauder fixed point theorem (cf. [71, Theorem 11.6]) to prove the existence of a solution $\hat{p} \in C^{\gamma,\gamma/2}(Q_T)$ to the problem (6.83)-(6.85). To this end, we set $P =: \{p \mid p(\rho,t) \in C^{\gamma,\gamma/2}(Q_T)\}$, which is a Banach space. For any $w \in P$ and $\sigma \in [0,1]$, we let $\hat{p}$ solve the following *linear* parabolic problem:

$$\begin{aligned}
&\frac{\partial \hat{p}}{\partial t} - \frac{D}{R^2(t)} \triangle \hat{p} \\
&\quad + \Big[\frac{u(\rho,t)}{\rho} - u(1,t) + \frac{\chi}{\rho R^2(t)} \frac{\partial c}{\partial \rho} p - \frac{\chi}{R^2(t)} \frac{\partial c(1,t)}{\partial \rho} \big(1 - p(1,t)\big)\Big] y \cdot \bigtriangledown \hat{p} \\
&\quad = \sigma \big[- K_q(c) + K(c)(1-w)\big]\hat{p} + \sigma K_p(c)(1-\hat{p}), \qquad (6.90)
\end{aligned}$$

$$\hat{p}(\rho,0) = \sigma p_0(\rho), \qquad (6.91)$$

$$\frac{\partial \hat{p}}{\partial \rho}(0,t) = 0, \qquad (6.92)$$

$$\Big[D \frac{\partial \hat{p}}{\partial \rho} + \sigma \Big(\chi(1-w) \frac{\partial c}{\partial \rho}\Big)\hat{p}\Big]\Big|_{\rho=1} = 0. \qquad (6.93)$$

Using $(R,p) \in X_T$, Lemmas 6.1 and 6.3, the assumptions (6.37)-(6.39), and the parabolic L^p-theory (cf. [109, Theorem 7.20]), we find that problem (6.90)-(6.93) has a unique solution $\hat{p}(\rho,t) \in W_k^{2,1}(Q_T)$ with $k(1-\gamma) < 1$. Furthermore, as before,

$$\|\hat{p}(\rho,t)\|_{W_k^{2,1}(Q_T)} \le A_0 \qquad (6.94)$$

provided $0 < T < 1$. We then can take some $k > 5$ satisfying $k(1-\gamma) < 1$ due to $\gamma \in (\frac{4}{5}, 1)$. Using the Sobolev embedding $W_k^{2,1}(Q_T) \hookrightarrow C^{1+\lambda,(1+\lambda)/2}(Q_T)$ ($k > 5$, $\lambda = 1 - \frac{5}{k}$; cf. [108]) and therefore by (6.94), we have

$$\|\hat{p}(\rho,t)\|_{C^{1+\lambda,(1+\lambda)/2}(Q_T)} \le A_0. \qquad (6.95)$$

We now can define a mapping

$$S: \quad P \times [0,1] \mapsto P$$

$$\hat{p} = S(w, \sigma).$$

By $C^{1+\lambda,(1+\lambda)/2}(Q_T) \hookrightarrow C^{\gamma,\gamma/2}(Q_T)$ compactly,

the mapping S is well defined and it is a compact mapping. (6.96)

Clearly, by the maximum principle,

$$S(w,0) = 0 \quad \text{for all } w \in P. \tag{6.97}$$

If $\hat{p} = S(\hat{p}, \sigma)$ for some $\sigma \in [0,1]$, then by the define of the mapping S, $\hat{p}$ satisfies

$$\begin{aligned} &\frac{\partial \hat{p}}{\partial t} - \frac{D}{R^2(t)} \triangle \hat{p} \\ &\quad + \Big[\frac{u(\rho,t)}{\rho} - u(1,t) + \frac{\chi}{\rho R^2(t)} \frac{\partial c}{\partial \rho} p - \frac{\chi}{R^2(t)} \frac{\partial c(1,t)}{\partial \rho} \big(1 - p(1,t)\big) \Big] y \cdot \bigtriangledown \hat{p} \\ &\quad = \sigma \big[- K_q(c) + K(c)(1-\hat{p}) \big] \hat{p} + \sigma K_p(c)(1-\hat{p}), \end{aligned} \tag{6.98}$$

$$\hat{p}(\rho, 0) = \sigma p_0(\rho), \tag{6.99}$$

$$\frac{\partial \hat{p}}{\partial \rho}(0,t) = 0, \tag{6.100}$$

$$\Big[D \frac{\partial \hat{p}}{\partial \rho} + \sigma \Big(\chi (1-\hat{p}) \frac{\partial c}{\partial \rho} \Big) \hat{p} \Big] \Big|_{\rho=1} = 0. \tag{6.101}$$

Proceeding as in the proof of Lemma 6.2, we can prove that

$$0 \le \hat{p} \le 1. \tag{6.102}$$

Then, by Lemma 6.4, we have

$$\|\hat{p}(\rho,t)\|_{W_k^{2,1}(Q_T)} \le A_0 \tag{6.103}$$

for $0 < T < 1$, and therefore by the Sobolev embedding $W_k^{2,1}(Q_T) \hookrightarrow C^{1+\lambda,(1+\lambda)/2}(Q_T)$ ($k > 5$, $\lambda = 1 - \frac{5}{k}$) again

$$\|\hat{p}(\rho,t)\|_{C^{1+\lambda,(1+\lambda)/2}(Q_T)} \leq A_0.$$

This further yields

$$\begin{aligned}
&\|\hat{p}(\rho,t)\|_{C^{\gamma,\gamma/2}(Q_T)} \\
=\ &\|\hat{p}(\rho,t)\|_{C^0(Q_T)} + \|\hat{p}(\rho,t)\|_{C^{\gamma,0}(Q_T)} + \|\hat{p}(\rho,t)\|_{C^{0,\gamma/2}(Q_T)} \\
\leq\ &\|\hat{p}(\rho,t) - \hat{p}(\rho,0)\|_{C^0(Q_T)} + \|\hat{p}(\rho,0)\|_{C^0(Q_T)} \\
&+\|\hat{p}(\rho,t)\|_{C^{1,0}(Q_T)} + \|\hat{p}(\rho,t)\|_{C^{0,\gamma/2}(Q_T)} \\
\leq\ &T^{\frac{1+\lambda}{2}}\|\hat{p}(\rho,t)\|_{C^{0,(1+\lambda)/2}(Q_T)} + \|\hat{p}(\rho,0)\|_{C^0(Q_T)} \\
&+\|\hat{p}(\rho,t) - \hat{p}(\rho,0)\|_{C^{1,0}(Q_T)} + \|\hat{p}(\rho,0)\|_{C^1(Q_T)} \\
&+T^{\frac{1+\lambda-\gamma}{2}}\|\hat{p}(\rho,t)\|_{C^{0,(1+\lambda)/2}(Q_T)} \\
\leq\ &\left(T^{\frac{1+\lambda}{2}} + T^{\frac{1+\lambda-\gamma}{2}}\right)\|\hat{p}(\rho,t)\|_{C^{0,(1+\lambda)/2}(Q_T)} \\
&+T^{\frac{1+\lambda}{2}}\|\hat{p}(\rho,t)\|_{C^{1,(1+\lambda)/2}(Q_T)} + 2\|\hat{p}_0(\rho)\|_{C^1(B_1(0))} \\
\leq\ &\left(2T^{\frac{1+\lambda}{2}} + T^{\frac{1+\lambda-\gamma}{2}}\right)A_0 + 2\|\hat{p}_0(\rho)\|_{C^1(B_1(0))} \\
\leq\ &3A_0 + \|\hat{p}_0(\rho)\|_{C^1(B_1(0)))} \quad \text{provided } 0 < T < 1 \\
:=\ &M, \qquad (6.104)
\end{aligned}$$

where $M > 0$ is a constant. Summarizing (6.98)-(6.102) and (6.104), we have that there exists a constant $M > 0$ such that

$$\|\hat{p}(\rho,t)\|_{C^{\gamma,\gamma/2}(Q_T)} \leq M \qquad (6.105)$$

for all $(\hat{p}, \sigma) \in P \times [0, T]$ satisfying $\hat{p} = S(\hat{p}, \sigma)$. We then conclude from (6.96), (6.97), (6.105), and the Leray-Schauder fixed point theorem that $S(\hat{p}, 1)$ has a fixed point in P for $0 < T < 1$. That is, (6.83)-(6.85) has a solution $\hat{p}(\rho, t) \in C^{\gamma, \gamma/2}(Q_T)$ for $0 < T < 1$.

Uniqueness: By the maximum principle for parabolic equations with the third boundary condition as afore-mentioned, we easily prove the uniqueness of a solution to problem (6.83)-(6.85) with given $(R, p) \in X_T$.

Estimates: The estimates (6.88) and (6.89) follow from Lemmas 6.2 and 6.4. □

Now, we conclude from (6.82), (6.84)-(6.87), (6.88) and (6.105), that $(\hat{R}(t), \hat{p}(\rho, t)) \in X_T$ for small $T > 0$. Thus, the mapping F is well defined and it maps X_T into itself for small $T > 0$.

In next section we shall prove that F is contractive provided T is sufficiently small.

6.7 Local Existence and Uniqueness

To complete the proof of the local existence and uniqueness of a solution to problem (6.65)-(6.74), we still need to prove that F is contractive provided T is sufficiently small.

Take (R_1, p_1) and (R_2, p_2) in X_T, denote $(\hat{R}_i, \hat{p}_i) = F(R_i, p_i),\ i = 1, 2,$ and set $R^* = \hat{R}_1 - \hat{R}_2,\ p^* = \hat{p}_1 - \hat{p}_2$. Then, by direct calculations we see that $R^*(t)$ and $p^*(\rho, t)$ satisfy the following two decoupled problems:

$$\frac{dR^*(t)}{dt} = R^*(t)g_1(t) + g_2(t), \quad \text{for } t > 0, \tag{6.106}$$

$$R^*(0) = 0, \tag{6.107}$$

where

$$g_1(t) = \int_0^1 \big[K_b(c_1)p_1 - K_a(c_1)p_1 - K_d(c_1)(1-p_1)\big]s^2\ ds, \tag{6.108}$$

$$\begin{aligned} g_2(t) &= \hat{R}_2(t)\int_0^1 \big[K_b(c_1)p_1 - K_a(c_1)p_1 - K_d(c_1)(1-p_1)\big]s^2\ ds \\ &\quad -\hat{R}_2(t)\int_0^1 \big[K_b(c_2)p_2 - K_a(c_2)p_2 - K_d(c_2)(1-p_2)\big]s^2\ ds, \end{aligned} \tag{6.109}$$

$$\begin{aligned} &\frac{\partial p^*}{\partial t} - \frac{D}{R_1^2(t)} \triangle p^* \\ &\quad + \Big[\frac{u_1(\rho,t)}{\rho} - u_1(1,t) + \frac{\chi}{\rho R_1^2(t)}\frac{\partial c_1}{\partial \rho}p_1 - \frac{\chi}{R_1^2(t)}\frac{\partial c_1(1,t)}{\partial \rho}\big(1-p_1(1,t)\big)\Big] y\cdot \bigtriangledown p^* \\ &\quad - \big[-K_q(c_1) - K_p(c_1) + K(c_1)(1-\hat{p}_1)\big]p^* = f(\rho,t) \quad \text{in } Q_T, \end{aligned} \tag{6.110}$$

$$p^*(\rho,0) = 0, \tag{6.111}$$

$$\frac{\partial p^*}{\partial \rho}(0,t) = 0, \tag{6.112}$$

$$D\frac{\partial p^*}{\partial \rho} + \Big(\chi(1-\hat{p}_1-\hat{p}_2)\frac{\partial c_1}{\partial \rho}\Big)p^* = g(\rho,t) \quad \text{at } \rho = 1, \tag{6.113}$$

where

$$\begin{aligned} &f(\rho,t) = D\Big(\frac{1}{R_1^2(t)} - \frac{1}{R_2^2(t)}\Big) \triangle \hat{p}_2 \\ &-\Big[\Big(\frac{u_1(\rho,t)}{\rho} - u_1(1,t) + \frac{\chi}{\rho R_1^2(t)}\frac{\partial c_1}{\partial \rho}p_1 - \frac{\chi}{R_1^2(t)}\frac{\partial c_1(1,t)}{\partial \rho}\big(1-p_1(1,t)\big)\Big) \\ &-\Big(\frac{u_2(\rho,t)}{\rho} - u_2(1,t) + \frac{\chi}{\rho R_2^2(t)}\frac{\partial c_2}{\partial \rho}p_2 - \frac{\chi}{R_2^2(t)}\frac{\partial c_2(1,t)}{\partial \rho}\big(1-p_2(1,t)\big)\Big)\Big] y\cdot \bigtriangledown \hat{p}_2 \\ &+\big[\big(-K_q(c_1) + K(c_1)(1-\hat{p}_1)\big) - \big(-K_q(c_2) + K(c_2)(1-\hat{p}_2)\big)\big]\hat{p}_2 \\ &+\big(K_p(c_1) - K_p(c_2)\big)(1-\hat{p}_2), \\ &g(\rho,t) = -\chi\hat{p}_2(1-\hat{p}_2)\Big(\frac{\partial c_1}{\partial \rho} - \frac{\partial c_2}{\partial \rho}\Big). \end{aligned}$$

We first consider the problem (6.106)-(6.107). By (6.65)-(6.66), (6.37), (6.44), (6.45), (6.87) and $(R_i, p_i) \in X_T$ $(i = 1, 2)$, we get

$$\|g_1(t),\ g_2(t)\|_{L^\infty[0,\ T]} \le A_0\big(\|R_1 - R_2\|_{C[0,\ T]} + \|p_1 - p_2\|_{C(Q_T)}\big). \quad (6.114)$$

We easily derive from (6.106) and (6.107) that

$$R^*(t) = \int_0^t g_2(\tau) e^{\int_\tau^t g_1(\tilde{\tau})d\tilde{\tau}}\ d\tau. \quad (6.115)$$

This, along with (6.114), yields

$$\begin{aligned} &\|R^*(t)\|_{C^1[0,\ T]} \\ &\le T e^{A_0 T}\|g_2(t)\|_{L^\infty[0,\ T]} + T^{\frac{\gamma}{2}}\|g_2(t)\|_{C^{\gamma/2}[0,T]} \\ &\le A_0\big(T + T^{\frac{\gamma}{2}}\big)\big(\|R_1 - R_2\|_{C^1[0,\ T]} + \|p_1 - p_2\|_{C^{\gamma,\gamma/2}(Q_T)}\big), \end{aligned} \quad (6.116)$$

here we have used $R_1(0) - R_2(0) = p_1(0) - p_2(0) = c_1(\rho, 0) - c_2(\rho, 0) = 0$ and we have assumed that $0 < T < 1$.

Next, we turn to consider the parabolic problem (6.110)-(6.113). By $(R_i, p_i) \in X_T$ $(i = 1, 2)$, (6.88), (6.103), and the parabolic L^p-estimate as before, we have

$$\begin{aligned} &\|p^*\|_{W_k^{2,1}(Q_T)} \\ &\le A_0\big(\|f\|_{L^k(Q_T)} + \|g\|_{W_k^{1,1}(Q_T)}\big) \\ &\le A_0\big(\|R_1 - R_2\|_{C^1[0,\ T]} + \|p_1 - p_2\|_{C(Q_T)}\big)\big(1 + \|\hat{p}_2\|_{W_k^{2,1}(Q_T)}\big). \end{aligned} \quad (6.117)$$

However, by (6.103), we have

$$\|\hat{p}_2\|_{W_k^{2,1}(Q_T)} \le A_0\big(1 + \|p_0(\rho)\|_{W^{2,k}(B_1(0))}\big). \quad (6.118)$$

Combining (6.117) and (6.118) we have

$$\|p^*\|_{W_k^{2,1}(Q_T)} \le A_0\big(\|R_1 - R_2\|_{C^1[0,\ T]} + \|p_1 - p_2\|_{C(Q_T)}\big), \tag{6.119}$$

where the constant A_0 depends on $\|p_0(\rho)\|_{W^{2,k}(B_1(0))}$. Using the embedding $W_k^{2,1}(Q_T) \hookrightarrow C^{1+\lambda,\frac{1+\lambda}{2}}(Q_T)$ $(k > 5,\ \lambda = 1 - \frac{5}{k})$, we find that

$$\|p^*\|_{C^{1+\lambda,\frac{1+\lambda}{2}}(Q_T)} \le A_0\big(\|R_1 - R_2\|_{C^1[0,\ T]} + \|p_1 - p_2\|_{C^{\gamma,\gamma/2}(Q_T)}\big). \tag{6.120}$$

Hence, proceeding as in (6.104) and using (6.111), we have

$$\begin{aligned}
&\|p^*(\rho,t)\|_{C^{\gamma,\gamma/2}(Q_T)} \qquad (6.121)\\
&\le \Big(2T^{\frac{1+\lambda}{2}} + T^{\frac{1+\lambda-\gamma}{2}}\Big)\|p^*\|_{C^{1+\lambda,\frac{1+\lambda}{2}}(Q_T)} + 2\|p_0^*(\rho)\|_{C^1(B_1(0))}\\
&= \Big(2T^{\frac{1+\lambda}{2}} + T^{\frac{1+\lambda-\gamma}{2}}\Big)\|p^*\|_{C^{1+\lambda,\frac{1+\lambda}{2}}(Q_T)}\\
&\le A_0\Big(2T^{\frac{1+\lambda}{2}} + T^{\frac{1+\lambda-\gamma}{2}}\Big)\big(\|R_1 - R_2\|_{C^1[0,\ T]} + \|p_1 - p_2\|_{C^{\gamma,\gamma/2}(Q_T)}\big).
\end{aligned}$$

Finally, we derive from (6.116) and (6.121) that

$$d\big((\hat{R}_1,\hat{p}_1),\ (\hat{R}_2,\hat{p}_2)\big) \le A_0\Big(2T^{\frac{1+\lambda}{2}} + T^{\frac{1+\lambda-\gamma}{2}}\Big)d\big((R_1,p_1),\ (R_2,p_2)\big). \tag{6.122}$$

This yields that the mapping F is contractive provided T is sufficiently small such that $A_0\big(2T^{\frac{1+\lambda}{2}} + T^{\frac{1+\lambda-\gamma}{2}}\big) < 1$. Hence, F has a unique fixed point (R,p) in X_T. That is, (R,p) together with (c,u) defined by (6.65)-(6.66) and (6.70), is the unique solution of the problem (6.65)-(6.74) for $0 \le t \le T$. Summarizing above results, we obtain

Theorem 6.3. *Under the assumptions (6.37)-(6.39), there exists a $T > 0$ which only depends on $\|p_0(\rho)\|_{W^{2,k}(B_1(0))}$, such that the problem (6.65)-(6.72)*

has a unique solution $(R(t),\ c(\rho,t),\ u(\rho,t),p(\rho,t))$ *with* $R(t)\in C^1[0,\ T],\ c(\rho,t)\in C^{2,1}(Q_T),\ u(\rho,t)\in C^1(Q_T)$ *and* $p(\rho,t)\in W_k^{2,1}(Q_T)$ *(*$k>5$*).*

Remark 6.6. The C^1-smoothness of functions $K_a(c), K_b(c), K_d(c), K_p(c)$ and $K_q(c)$ assumed in (6.37) is used for deriving the estimates (6.114) and (6.117).

6.8 Global Existence

Theorem 6.4. *Under the assumptions (6.37)-(6.39), there exists a unique solution* $(R(t),\ c(\rho,t),\ u(\rho,t),p(\rho,t))$ *of the problem (6.65)-(6.72) for all* $t>0$*; furthermore,* $R(t)\in C^1[0,\ \infty),\ c(\rho,t)\in C^{2,1}([0,\ 1]\times[0,\ \infty)),\ u(\rho,t)\in C^1([0,\ 1]\times[0,\ \infty))$*,* $p(\rho,t)\in W_k^{2,1}(Q_T)$ *for* $k>5$ *and any* $T>0$*, and*

$$0\le c(\rho,t)\le 1, \tag{6.123}$$

$$0\le p(\rho,t)\le 1, \tag{6.124}$$

$$|u(\rho,t)|\le \beta, \tag{6.125}$$

$$R_0e^{-\beta t}\le R(t)\le R_0e^{\beta t} \tag{6.126}$$

for some $\beta>0$*.*

Proof. Suppose to the contrary that $[0,\tilde{T})$ is the maximum time interval for the existence of the solution. By *a priori* estimates established in Section 6.4, we find that (6.44),(6.45), (6.51), (6.62), (6.63) and (6.77) hold for all $t<\tilde{T}$. Therefore, we have

$$0 \le c(\rho,t) \le 1,\ 0 \le p(\rho,t) \le 1,\ \text{for all } t < \tilde{T} \text{ and } 0 \le \rho \le 1, \quad (6.127)$$

$$R_0 e^{-A_0 \tilde{T}} \le R(t) \le R_0 e^{A_0 \tilde{T}}, \quad \text{for all } t < \tilde{T}\ , \quad (6.128)$$

$$\|\frac{u(\rho,t)}{\rho}\|_{L^\infty},\ \|\frac{1}{\rho R^2(t)}\frac{\partial c}{\partial \rho}\|_{L^\infty} \le A_0, \quad \text{for all } t < \tilde{T}\ , \quad (6.129)$$

$$\|p\ |_{W_k^{2,1}(Q_{\tilde{T}})} \le M(\tilde{T}), \quad (6.130)$$

where $M(\tilde{T})$ is some constant which may depend on $\tilde{T}$.

We take $p(\rho, \tilde{T} - \varepsilon)$ (where $0 < \varepsilon < \tilde{T}$ is arbitrary) as a *new initial data*, then we can extend the solution to $Q_{(\tilde{T}-\varepsilon)+\delta}$ for small $\delta > 0$ proceeding as in the proof of Theorem 6.3. Furthermore, the proof of Theorem 6.3 shows that δ depends only on an upper bound on $\| p(\rho, \tilde{T} - \varepsilon) \|_{W^{2,k}(B_1(0))}$. By *a priori* estimate (6.130) we find that δ depends on $A(\tilde{T})$ (but δ is independent of ε), i.e., $\delta = \delta(\tilde{T})$. If we take $\varepsilon < \delta(\tilde{T})$, then we get

$$(\tilde{T} - \varepsilon) + \delta > \tilde{T},$$

which contradicts the assumption that $[0, \tilde{T})$ is the maximum time interval for the existence of the solution. Therefore, the maximum time interval for the existence of the solution is $[0, \infty)$. □

Remark 6.7. The estimate (6.130) may break down if the diffusion of the cell types is sent to zero (i.e., $D = 0$ in (6.67)). To prove that the mapping F defined in Section 6.5 is contractive, we need to establish some necessary bound $\frac{\partial p}{\partial \rho}$ (see the estimate (6.117)). However, the hyperbolic equation (6.67) with $D = 0$ has the feature that the characteristic curves come from the region

$\{0 < \rho < 1\}$ at the outer boundary $\rho = 1$. So difficulties will arise on this boundary. This is why the diffusion is so central to our results.

6.9 Summary

In this chapter, we reviewed Tindall and Please's model [163] and Tao's analytical results [150]. The model describs the cell cycle dynamics and chemotactic driven cell movement in a multicellular tumor spheroid which consists of proliferating and quiescent cells. The two types of cells are assumed to move with *different* velocity whereas most partial differential equation models of tumor growth assume that all cells within a tumor have a common spatial velocity profile. This chapter extended Tindall and Please's model to a new one with diffusion of the two cell types. The extended model [150] assumes that cell movement is affected by not only chemotaxis but also diffusion. Noting the *relative* velocity of cells on the outer boundary of the spheroid, we clarified how to impose appropriate no-flux boundary condition for reaction-diffusion-advection equations in a moving-domain. By including the diffusion terms the formation of possible shock should be avoided. Indeed, we have proven the global existence and uniqueness of a solution to the newly extended model. The methods of the proof include a fixed point argument and L^p-theory for parabolic equations with the third boundary condition.

In Tindall and Please's model, as well as the PDE models studied in previous chapters, is confined to a spherical geometry. However, the morphological

instability of a tumor, such as fingering and fragmentation, provides a mechanism for invasion. So, the stability of spherical tumors to asymmetric perturbations and the symmetry-breaking bifurcation from stability to instability are biologically and mathematically interesting topics (see [6, 21, 22, 28, 42, 45, 59, 62, 64], for instance), which are not included in this book.

7

Chemotaxis-Haptotaxis Modeling for Cancer Invasion

7.1 Introduction

Cancer invasion is a very complex process which involves many various biological mechanisms. In fact, a variety of mathematical models have been proposed for various aspects of cancer invasion, and various attempts of including more relevant biology into models have been made by different researchers. Gatenby and Gawlinski [69] used a reaction-diffusion population competition model to examine how the tumor invades the surrounding normal tissue or extracellular matrix (ECM). They suggested that tumor cells produce lactic acid toxic to normal tissue, and the high acidity leads to the death of the normal tissue, which creates space for tumor cells to proliferate and invade into the surrounding tissue. In contrast to the acid-invasion mechanism, Perumpanani and Byrne [124] found that ECM heterogeneity affects invasion. They proposed a model under the assumptions that ECM is degraded by proteases; in addition to random diffusion, the movement of tumor cells is biased towards a gradient of the non-diffusible ECM, which is referred to

as *haptotaxis*; the protease production is proportional to the product of the tumor cell density and the collagen gel concentration. Chaplain and Anderson [29] also developed a haptotaxis model to describe the interactions between the tumor and surrounding tissue. They made assumptions that the tumor cells produce MDEs to degrade the ECM; the degradation gives rise to the haptotactic movement of the tumor cells. Later on, Chaplain and Lolas [30] suggested that, in addition to random diffusion and haptotactic movement, the migration of cancer cells is biased towards a gradient of the diffusible MDEs, which is referred to as *chemotaxis*. Besides, the proliferation of tumor cells and the re-modeling of ECM are taken into account. Recently, Gerisch and Chaplain [70] developed a novel non-local model which incorporates cell-cell adhesion and cell-matrix adhesion, playing important roles in the tumor invasion process. We note that Szymańska et al. [142] proposed another non-local model which focuses on the role of nonlocal kinetic terms modeling competition for space and degradation. We also mention that Lachowicz [105, 106] constructed some microscopic models for tumor invasion and bridged the microscopic model [106] with the macroscopic model [29].

The qualitative analysis of various models of cancer invasion is mathematically interesting. Walker and Webb [165] examined the issues of global existence and uniqueness for Chaplain and Andersons's model [29]. Tao and Wang [149] and Tao [151] studied the global existence of solutions to the Chaplain and Lolas model [30] for large logistic growth rate of cells in dimension 3 and for any positive logistic growth rate in dimension 2, respectively. Tao and

Wang [153] also proved the global existence and boundedness of solutions to a simplified version of the Chaplain and Lolas model. Marciniak-Czochra and Ptashnyk recently [114] proved the uniform boundedness of solutions to the haptotaxis model [29]. Szymańska et al. [142] studied the global existence and uniqueness of solutions to their non-local model. Very recently, Lit̨canu and Morales-Rodrigo [110] established the asymptotic behavior of solutions to a simplified haptotaxis model of cancer invasion. We should note that the global existence for the chemotaxis-haptotaxis model [30] is still open for small positive logistic growth rate of cells in dimension 3.

This chapter mainly reviews a chemotaxis-haptotaxis model [30] and its mathematical analysis [153]. Actually, Chaplain and Lolas' model can be regarded as an extension of the classical chemotaxis model which may be first proposed in 1970 by Keller and Segel [99].

The 2×2 Keller-Segel model takes into account the density of cells and the concentration of the chemical substance which is assumed to influence the movement of the cell population, and the total mass of cells is formally conserved. The Keller-Segel model has now been greatly extended and studied in the last two decades (see [24, 35, 36, 39, 40, 55, 60, 79, 81, 84, 85, 97, 103, 104, 120, 147, 161, 162, 172] and the references cited therein). The interesting feature of Keller-Segel types of models is the possibility of blow-up of solutions in finite time, which strongly depends on the space dimension and initial mass (see [15, 36, 37, 79, 97, 115, 116, 123, 126, 173], for instance). Jäger and Luckhaus [97], to our knowledge, initiated the technique of L^p estimates in

the analysis of the Keller-Segel system and proved the blow-up of solutions for small initial mass. Blanchet, Dolbeault and Perthame [15] found the critical mass for the blow-up of solutions in the two-dimensional case. Some recent studies show that the nonlinear chemotactic sensitivity function (see [24, 80, 81, 86, 177]), the nonlinear porous medium diffusion (see [104, 138]) and the logistic growth term (see [162, 172, 174]) may prevent the blow-up of solutions. However, Chaplain and Lolas' model under consideration in this paper is a 3×3 system which considers the competition between chemotaxis, haptotaxis and logistic cell growth, and the total mass of cells is *not* conserved.

Chaplain and Lolas' model [30] consists of a parabolic chemotaxis-haptotaxis PDE describing the evolution of tumor cell density, a parabolic PDE governing the evolution of proteolytic enzyme concentration, and an ODE modeling the proteolysis of ECM. Since the proteolytic enzyme diffuses much faster than cancer cells do, in this chapter we will consider a simplified version of Chaplain and Lolas' model in which an elliptic PDE, instead of the above-mentioned parabolic PDE, governs the evolution of proteolytic enzyme concentration. The above quasi-stationary simplification was initially proposed by Jäger and Luckhaus [97], and it was mostly considered in the study of the blow-up of smooth solutions to the classical chemotaxis model (see [97, 115, 123], for instance).

We should note that there exists an important technical difference between a 2×2 parabolic-elliptic chemotaxis system and a 3×3 parabolic-ODE-elliptic chemotaxis-haptotaxis system. For a 2×2 parabolic-elliptic chemotaxis system,

one may easily estimate the chemotaxis-related integral term $\int_\Omega c^{s-1} \bigtriangledown c \cdot \bigtriangledown u dx$ by directly multiplying the elliptic equation for the chemoattractant concentration by c^s and integrating the product in Ω. However, for a 3×3 parabolic-ODE-elliptic chemotaxis-haptotaxis system, we need to develop new techniques to estimate the chemotaxis-related integral term $\int_\Omega c^{s-1} | \bigtriangledown c \cdot \bigtriangledown u | dx$. Here, we should emphasize that we must estimate the term $\int_\Omega c^{s-1} | \bigtriangledown c \cdot \bigtriangledown u | dx$ rather than the term $\int_\Omega c^{s-1} \bigtriangledown c \cdot \bigtriangledown u dx$.

This chapter is organized as follows. Section 7.2 describes the mathematical model. Section 7.3 proves the local existence and uniqueness of smooth solutions to the model. Finally, Sections 7.4 and 7.5 study the global existence and uniform-in-time boundedness of solutions in three dimensional space for large logistic growth rate of cells and in two dimensional space for any positive logistic growth rate of cells, respectively.

7.2 Mathematical Model

The mathematical model of cancer invasion is involved in the following three key physical variables: the cancer cell density c, the extracellular matrix density v, and the matrix degrading enzyme (MDE) concentration u.

The migration of cancer cells is assumed to undergo random motion, chemotaxis, and haptotaxis. In the absence of any extracellular matrix (ECM), cancer cell proliferation is assumed to follow a logistic growth law. The presence of ECM leads to competition for space between the cancer cells and

the ECM. Hence, the equation describing the evolution of cancer cell density is given as follows [30]:

$$\frac{\partial c}{\partial t} = \underbrace{D_c \triangle c}_{\text{random motion}} - \underbrace{\bigtriangledown \cdot (\chi c \bigtriangledown u)}_{\text{chemotaxis}} - \underbrace{\bigtriangledown \cdot (\xi c \bigtriangledown v)}_{\text{haptotaxis}} + \underbrace{\mu c(1-c-v)}_{\text{proliferation}}, \tag{7.1}$$

where D_c is the random motility coefficient, χ and ξ are the chemotactic and haptotactic coefficients, respectively, μ is the logistic proliferation rate of the cells.

Since ECM is "static", we neglect any diffusion and focus solely on its degradation by MDEs upon contact. For simplicity, we assume that no remodeling of the ECM takes place. The equation modeling the proteolysis of the ECM is therefore given by [30]:

$$\frac{\partial v}{\partial t} = - \underbrace{\delta u v}_{\text{proteolysis}}, \tag{7.2}$$

where $\delta > 0$ is a rate parameter of degradation.

The MDE concentration is assumed to be influenced by diffusion, production, and decay. Specifically, MDE is produced by cancer cells, diffuses throughout ECM, and undergoes decay through a simple degradation. Hence, we have the following equation for the MDE concentration [30]:

$$\frac{\partial u}{\partial t} = \underbrace{D_u \triangle u}_{\text{diffusion}} + \underbrace{\alpha c}_{\text{production}} - \underbrace{\beta u}_{\text{decay}}, \tag{7.3}$$

where D_u, α, and β are assumed to be positive constants.

We define a non-dimensional variable:

$$\tilde{t} = D_c t$$

and new parameters via the following scaling:

$$\tilde{\chi} = \frac{\chi}{D_c},\ \tilde{\xi} = \frac{\xi}{D_c},\ \tilde{\mu} = \frac{\mu}{D_c},\ \tilde{\delta} = \frac{\delta}{D_c},\ \epsilon = \frac{D_c}{D_u},\ \tilde{\alpha} = \frac{\alpha}{D_u},\ \tilde{\beta} = \frac{\beta}{D_u}.$$

Henceforth, we omit the tildes for notational simplicity. The dimensionless governing equations can then be written as follows:

$$\frac{\partial c}{\partial t} = \Delta c - \nabla \cdot (\chi c \nabla u) - \nabla \cdot (\xi c \nabla v) + \mu c(1 - c - v), \tag{7.4}$$

$$\frac{\partial v}{\partial t} = -\delta u v, \tag{7.5}$$

$$\epsilon \frac{\partial u}{\partial t} = \Delta u + \alpha c - \beta u. \tag{7.6}$$

For the parameter values given in [30], ϵ is typically very small compared with other parameters: α, β, δ, χ, ξ, and μ.

In this chapter we will consider the limit $\epsilon \to 0$ and fix the positive parameters $\alpha, \beta, \delta, \chi, \xi$, and μ (this approach of quasi-steady-state approximation was mostly used to study the classical chemotaxis model; see [97, 123] and references cited therein). Finally, we obtain ($\epsilon = 0$ in (7.6))

$$\frac{\partial c}{\partial t} = \Delta c - \nabla \cdot (\chi c \nabla u) - \nabla \cdot (\xi c \nabla v) + \mu c(1 - c - v), \tag{7.7}$$

$$\frac{\partial v}{\partial t} = -\delta u v, \tag{7.8}$$

$$0 = \Delta u + \alpha c - \beta u. \tag{7.9}$$

The equations (7.7)-(7.9) are considered on some bounded domain $\Omega \subset \mathcal{R}^d$ ($d = 2$ or 3) with boundary $\partial\Omega$. To close the system of equations, we need to impose boundary and initial conditions.

Boundary conditions: Guided by the *in vitro* experimental protocol in

which invasion takes place within an isolated system [124], we assume that there is no-flux of cancer cells or MDEs across the boundary of the domain,

$$-\frac{\partial c}{\partial \nu}+\chi c\frac{\partial u}{\partial \nu}+\xi c\frac{\partial v}{\partial \nu}=0 \quad \text{on } \partial\Omega\times(0,T), \tag{7.10}$$

$$\frac{\partial u}{\partial \nu}=0 \quad \text{on } \partial\Omega\times(0,T), \tag{7.11}$$

where ν is the outward normal vector to $\partial\Omega$. We note that the choice of the boundary conditions (7.10) and (7.11) is rather mathematically than biologically motivated. This chapter does not consider possible boundary effects. The boundary conditions (7.10) and (7.11), however, may be justified by the fact that the tumor is far from the boundary of the domain containing the tissue under consideration [31].

Initial conditions: We prescribe the initial data

$$c(x,0)=c_0(x), \quad v(x,0)=v_0(x), \quad x\in\Omega. \tag{7.12}$$

For any $0<T\leq\infty$, we set

$$Q_T=\Omega\times\{0<t<T\}, \quad \Gamma_T=\partial\Omega\times\{0<t<T\}.$$

For consistency, we shall use the following notations:

$$W_p^2(\Omega)=\{u|\ u, D_xu, D_x^2u\in L^p(\Omega)\},$$

$$W_p^{2,1}(Q_T)=\{u|\ u, D_xu, D_x^2u, D_tu\in L^p(Q_T)\}$$

with norm

$$\| u \|_{W_p^2(\Omega)}=\| u \|_{L^p(\Omega)}+\| D_xu \|_{L^p(\Omega)}+\| D_x^2u \|_{L^p(\Omega)},$$

$$\| u \|_{W_p^{2,1}(Q_T)}=\| u \|_{L^p(Q_T)}+\| D_xu \|_{L^p(Q_T)}+\| D_x^2u \|_{L^p(Q_T)}+\| D_tu \|_{L^p(Q_T)}$$

in which $p \geq 1$ is integer, $T > 0$, and the derivatives are in the weak sense.

We denote by $C^{k+\lambda,\theta}(Q_T)$ ($k \geq 0$ integer, $0 < \lambda < 1$, $0 < \theta < 1$) the space of function $u(x,t)$ with finite norm

$$\| u \|_{C^{k+\lambda,\theta}(Q_T)} = \sum_{|j|=0}^{k} \left[\sup_{Q_T} |D_x^j u| + < D_x^j u >_{x,\ Q_T}^{(\lambda)} + < D_x^j u >_{t,\ Q_T}^{(\theta)} \right]$$

where

$$< u >_{x,\ Q_T}^{(\lambda)} = \sup_{(x,t),\ (y,t) \in Q_T} \frac{|u(x,t) - u(y,t)|}{|x-y|^{\lambda}},$$

$$< u >_{t,\ Q_T}^{(\theta)} = \sup_{(x,t),\ (x,\tau) \in Q_T} \frac{|u(x,t) - u(x,\tau)|}{|t-\tau|^{\theta}}.$$

We denote by $C^{2+\lambda,1+\theta}(Q_T)$ the space of functions $u(x,t)$ with norm

$$\| u \|_{C^{2+\lambda,\theta}(Q_T)} + \| u_t \|_{C^{\lambda,\theta}(Q_T)}.$$

We introduce the following variable change:

$$a = ce^{-\xi v}. \tag{7.13}$$

In terms of the variables $a,\ v$, and u, the system (7.7)-(7.12) takes the following form:

$$\frac{\partial a}{\partial t} = e^{-\xi v} \bigtriangledown \cdot (e^{\xi v} \bigtriangledown a) - e^{-\xi v} \bigtriangledown \cdot (\chi e^{\xi v} a \bigtriangledown u)$$

$$+ \xi \delta a u v + \mu a (1 - e^{\xi v} a - v) \quad \text{in } Q_T, \tag{7.14}$$

$$\frac{\partial v}{\partial t} = -\delta u v \quad \text{in } Q_T, \tag{7.15}$$

$$0 = \triangle u + \alpha e^{\xi v} a - \beta u \quad \text{in } Q_T, \tag{7.16}$$

$$\frac{\partial a}{\partial \nu} = \frac{\partial u}{\partial \nu} = 0 \quad \text{on } \Gamma_T, \tag{7.17}$$

$$a(x,0) = a_0(x),\ v(x,0) = v_0(x) \quad \text{in } \Omega. \tag{7.18}$$

Remark 7.1. The L^p estimate techniques for the hapotactic term and the chemotactic term in Eq. (7.7) are quite *different* in three space dimensions, since the ECM density v satisfies the first-order ODE (7.8) whereas the proteolytic enzyme concentration u solves the elliptic equation (7.9). We note that there appears the second-order spatial derivative of v in Eq. (7.7), but this second-order spatial derivative term $\triangle v$ can be transformed into the time derivative term $\partial v/\partial t$ (i.e., $-\delta uv$ by Eq. (7.8)) under the transformation (7.13). However, it doesn't make sense to transform the second-order spatial derivative term $\triangle u$ in Eq. (7.7) into the time derivative term $\partial u/\partial t$, since u solves the second-order elliptic equation (7.9). We also note that the *divergence* form of Eq. (7.14) on a is favorable for L^p estimates in three space dimensions (see Section 7.4 below). The transformation (7.13) has already been performed in [39, 55, 60] in order to prove the existence of classical solutions. Here, we should further note that, in order to guarantee that (7.14)-(7.16) and (7.7)-(7.9) are equivalent, we need $(a, v, u) \in C^{2,1}(Q_T)\times C^{2,1}(Q_T)\times C^{2,0}(Q_T)$. Hence, we will study the existence of $C^{2,1}(Q_T)\times C^{2,1}(Q_T)\times C^{2,0}(Q_T)$-smooth solutions to the system (7.14)-(7.18).

Throughout this chapter we assume that

$$\begin{cases} a_0(x) \geq 0,\ 0 \leq v_0(x) \leq 1, \\ \partial\Omega \in C^{2+\sigma}, a_0(x) \in C^{2+\sigma}(\overline{\Omega}),\ v_0(x) \in C^3(\overline{\Omega}), \\ \frac{\partial a_0(x)}{\partial \nu} = \frac{\partial u_0(x)}{\partial \nu} = \frac{\partial v_0(x)}{\partial \nu} = 0 \quad \text{on } \partial\Omega, \end{cases} \tag{7.19}$$

where $\sigma = 3/4$.

In next section we will prove that the system (7.14)-(7.2) has a unique local (in time) classical solution.

7.3 Local Existence and Uniqueness

For notational convenience , in what follows we denote various constants which depend on T by A, while we denote various constants which are independent of T by A_0.

Theorem 7.1. *Under the assumption (7.2), there exists a unique solution* $(a(x,t), v(x,t), u(x,t)) \in C^{2+\sigma,1+\sigma/2}(Q_T) \times C^{2+\sigma,1+\sigma/2}(Q_T) \times C^{2+\sigma,\sigma/2}(Q_T)$ *to the system (7.14)-(7.18) for small* $T > 0$ *which depends on*

$$M := \| c_0(x) \|_{C^{2+\sigma}(\Omega)} + \| v_0(x) \|_{C^{2+\sigma}(\Omega)} + 1$$

.

Proof. We shall prove the local existence by a fixed point argument. We introduce the Banach space $\mathcal{X}$ of the function c with norms

$$\| c \|_{C^{\sigma,\frac{\sigma}{2}}(\bar{Q}_T)} \quad (0 < T < 1)$$

and a subset

$$\mathcal{X}_M = \{c \in \mathcal{X} : \ c \geq 0, \ \ \| c \|_{C^{\sigma,\frac{\sigma}{2}}(\bar{Q}_T)} \leq M\}.$$

Given any $\tilde{c} \in \mathcal{X}_M$, we define a corresponding function $c = F\tilde{c}$ by

$$c = e^{\xi v} a,$$

where $(a,\ v)$, together with u, satisfies the following system:

$$-\triangle u+\beta u=\alpha\tilde{c}\quad \text{in } Q_T, \tag{7.20}$$

$$\frac{\partial u}{\partial \nu}=0\quad \text{on } \Gamma_T, \tag{7.21}$$

$$\frac{\partial v}{\partial t}=-\delta uv\quad \text{in } Q_T, \tag{7.22}$$

$$v(x,0)=v_0(x)\quad \text{in } \Omega, \tag{7.23}$$

$$\begin{aligned}&\frac{\partial a}{\partial t}-\triangle a+(\chi\bigtriangledown u-\xi\bigtriangledown v)\cdot\bigtriangledown a\\&\quad+\big[\chi\triangle u+\chi\xi\bigtriangledown v\cdot\bigtriangledown u-\xi\delta uv-\mu(1-\tilde{c}-v)\big]a=0\quad \text{in } Q_T,\end{aligned} \tag{7.24}$$

$$\frac{\partial a}{\partial \nu}=0\quad \text{on } \Gamma_T,\quad a(x,0)=a_0(x)\quad \text{in } \Omega. \tag{7.25}$$

By (7.20)-(7.21) and the standard elliptic Schauder theory [71], we have

$$\parallel u\parallel_{C^{2+\sigma,0}(\bar{Q}_T)}\leq A_0\parallel\tilde{c}\parallel_{C^{\sigma,0}(\bar{Q}_T)}\leq A_0M. \tag{7.26}$$

By $\tilde{c}\geq 0$ and the maximum principle [71], we also have

$$u\geq 0\quad \text{in } Q_T. \tag{7.27}$$

Note that for any $x\in\Omega$ and $0<t_1<t_2<T<1$,

$$\begin{aligned}&-\triangle\Big(\frac{u(x,\ t_1)-u(x,\ t_2)}{\mid t_1-t_2\mid^{\sigma/2}}\Big)+\beta\frac{u(x,\ t_1)-u(x,\ t_2)}{\mid t_1-t_2\mid^{\sigma/2}}\\&\quad=\alpha\frac{\tilde{c}(x,\ t_1)-\tilde{c}(x,\ t_2)}{\mid t_1-t_2\mid^{\sigma/2}}\qquad \text{in } Q_T,\end{aligned} \tag{7.28}$$

$$\frac{\partial}{\partial\nu}\Big(\frac{u(x,\ t_1)-u(x,\ t_2)}{\mid t_1-t_2\mid^{\sigma/2}}\Big)=0\quad \text{on } \Gamma_T. \tag{7.29}$$

By (7.28)-(7.29) and the maximum principle, we further have

$$\begin{aligned}&\max_{\Omega}\frac{\mid u(x,\ t_1)-u(x,\ t_2)\mid}{\mid t_1-t_2\mid^{\sigma/2}}\leq A_0\parallel\frac{\tilde{c}(x,\ t_1)-\tilde{c}(x,\ t_2)}{\mid t_1-t_2\mid^{\sigma/2}}\parallel_{L^\infty(\Omega)}\\&\leq A_0\parallel\tilde{c}(x,t)\parallel_{C^{0,\sigma/2}(Q_T)}\leq A_0\parallel\tilde{c}(x,t)\parallel_{C^{\sigma,\sigma/2}(Q_T)}\leq A_0M,\end{aligned}$$

so

$$\| u \|_{C^{0,\sigma/2}(\bar{Q}_T)} \leq A_0 M. \tag{7.30}$$

We easily conclude from (7.2), (7.22)-(7.23), (7.3)-(7.27), (7.30), and $0 < T < 1$ that

$$\| u \|_{C^{2+\sigma,\sigma/2}(\bar{Q}_T)} \leq A_0 M, \quad \| v \|_{C^{2+\sigma,\sigma/2}(\bar{Q}_T)} \leq A_0 M. \tag{7.31}$$

This, together with Eq. (7.22), yields

$$\| v \|_{C^{2+\sigma,1+\sigma/2}(\bar{Q}_T)} \leq A_0 M. \tag{7.32}$$

Furthermore, by (7.2), (7.22)-(7.23), and (7.27), we easily get

$$0 \leq v \leq 1. \tag{7.33}$$

We now turn to Eq. (7.24). Note that Eq. (7.24) can be rewritten as

$$\frac{\partial a}{\partial t} - \triangle a + (\chi \bigtriangledown u - \xi \bigtriangledown v) \cdot \bigtriangledown a + ha = 0 \tag{7.34}$$

with

$$\| \chi \bigtriangledown u - \xi \bigtriangledown v \|_{C^{\sigma,\sigma/2}(\bar{Q}_T)} \leq B_1, \tag{7.35}$$

$$\begin{aligned} &\| h \|_{C^{\sigma,\sigma/2}(\bar{Q}_T)} \\ &= \| \chi \triangle u + \chi\xi \bigtriangledown v \cdot \bigtriangledown u - \xi\delta uv - \mu(1 - \tilde{c} - v) \|_{C^{\sigma,\sigma/2}(\bar{Q}_T)} \leq B_2 \end{aligned} \tag{7.36}$$

by the estimates (7.3), (7.30), (7.32) and $\tilde{c} \in \mathcal{X}_M$; here and in the following we shall denote various constants which depend only on M by B_k $(k = 1, 2, ...)$. Hence, Eq. (7.3) is a *linear* parabolic equation with $C^{\sigma,\sigma/2}(\bar{Q}_T)$ coefficients

and, by the Schauder theory, the parabolic problem (7.3) and (7.25) has a unique solution satisfying

$$\begin{aligned} \| a \|_{C^{2+\sigma,1+\sigma/2}(\bar{Q}_T)} &\leq \| a \|_{t=0}\|_{C^{2+\sigma}(\Omega)} + B_3 \\ &\leq M + B_3 := B_4. \end{aligned} \tag{7.37}$$

By (7.2), (7.24)-(7.25), and the maximum principle [108], we easily get

$$a \geq 0. \tag{7.38}$$

We conclude from (7.32)-(7.33) and (7.37)-(7.38) that

$$c \geq 0, \quad \| c \|_{C^{2+\sigma,1+\sigma/2}(\bar{Q}_T)} \leq B_5. \tag{7.39}$$

For any function $c(x,t)$, it is easy to check that

$$\| c(x,t) - c(x,0) \|_{C^{\sigma,\sigma/2}(\bar{Q}_T)} \leq A_0 \max(T^{\sigma/2}, T^{1-(\sigma/2)}) \| c \|_{C^{2+\sigma,1+\sigma/2}(\bar{Q}_T)} . \tag{7.40}$$

Combining (7.39) and (7.40), we conclude that if T is sufficiently small (T depends only on M), then

$$\begin{aligned} \| c(x,t) \|_{C^{\sigma,\sigma/2}(\bar{Q}_T)} &\leq \| c(x,0) \|_{C^{\sigma,\sigma/2}(Q_T)} + A_0 \max(T^{\sigma/2}, T^{1-(\sigma/2)}) B_5 \\ &\leq \| c_0(x) \|_{C^{\sigma}(\Omega)} + 1 \leq M. \end{aligned} \tag{7.41}$$

This, together with $c \geq 0$, yields $c \in \mathcal{X}_M$. Hence, F maps $\mathcal{X}_M$ into itself.

Next, proceeding as in the proof of the contraction in Theorem 3.1 in [149], we can prove that F is contractive in $\mathcal{X}_M$ if we take T sufficiently small. By the contraction mapping principle F has a unique fixed point c. Furthermore,

we can raise the regularity of c to $C^{2+\sigma,1+\sigma/2}(Q_T)$ by using the parabolic Schauder estimates. □

7.4 Global Existence and Boundedness in Dimension 3

We shall need the following Gagliardo-Nirenberg interpolation inequality [57, 75]: Assume that $\Omega \subset R^d$ is a bounded domain, $\partial\Omega \in C^k$, $u(x) \in W_q^k(\Omega) \bigcap L^r(\Omega)$, and $0 \le l \le k$. Then,

$$\| D^l u \|_{L^p(\Omega)} \le A_0 \| u \|^{\theta}_{W_q^k(\Omega)} \| u \|^{1-\theta}_{L^r(\Omega)}, \tag{7.42}$$

where

$$\frac{l}{k} \le \theta \le 1,\ 1 \le q,\ r \le \infty,\ \frac{d}{p} - l = \theta\Big(\frac{d}{q} - k\Big) + \Big(1 - \theta\Big)\frac{d}{r}$$

when $k - l - \frac{d}{q}$ is not a nonnegative integer;

$$\theta = \frac{l}{k} < 1,\ 1 < q < \infty,\ 1 < r < \infty$$

when $k - l - \frac{d}{q}$ is a nonnegative integer.

We shall also need the following Sobolev imbedding Theorem (see [32, Theorem 3.5]): Assume that $u \in W_p^{2l,l}(Q_T)$, $\partial\Omega \in C^{2l}$, where l is a positive integer. Then, for $0 \le r + 2s = \mu < 2l$, $p > \frac{d+2}{2l-\mu}$ (where $\frac{d+2}{p}$ is not an integer), we have

$$\| D_t^s D_x^r u \|_{C^{\alpha,\alpha/2}(Q_T)} \le A \| u \|_{W_p^{2l,l}(Q_T)}, \tag{7.43}$$

where $\alpha = 2l - \mu - (d+2)/p$.

To continue the local solution established in the above section to all $t > 0$, we need to establish some a priori estimates.

Lemma 7.1. *There holds*

$$a \geq 0, \quad u \geq 0, \quad 0 \leq v \leq 1. \tag{7.44}$$

Proof. The inequality $a \geq 0$ follows from the parabolic maximum principle, and the inequality $u \geq 0$ follows from $a \geq 0$ and the elliptic maximum principle. The inequalities $0 \leq v \leq 1$ follow from $u \geq 0$ and the maximum principle. This completes the proof of Lemma 7.1. □

Lemma 7.2. *There holds*

$$\| a \|_{L^1(\Omega)} \leq \| c \|_{L^1(\Omega)} \leq \max(\| c_0 \|_{L^1(\Omega)}, |\Omega|), \tag{7.45}$$

$$\| u \|_{L^1(\Omega)} \leq \alpha\beta^{-1} \max(\| c_0 \|_{L^1(\Omega)}, |\Omega|). \tag{7.46}$$

Proof. Integrating (7.7) in Ω and noting (7.10) and (7.1), we have

$$\begin{aligned} \frac{d}{dt} \| c \|_{L^1(\Omega)} &\leq \mu \| c \|_{L^1(\Omega)} - \mu \int_\Omega c^2 \, dx \\ &\leq \mu \| c \|_{L^1(\Omega)} - \frac{\mu}{|\Omega|} \| c \|^2_{L^1(\Omega)}, \end{aligned} \tag{7.47}$$

where we have used the Hölder's inequality:

$$\Big(\int_\Omega c dx \Big)^2 \leq \int_\Omega 1^2 dx \cdot \int_\Omega c^2 dx = |\Omega| \int_\Omega c^2 dx.$$

We derive from (7.47) that

$$\| c \|_{L^1(\Omega)} \leq \frac{1}{\frac{1}{|\Omega|} + \big(\frac{1}{\| c_0 \|_{L^1(\Omega)}} - \frac{1}{|\Omega|} \big) e^{-\mu t}} \leq \max(\| c_0 \|_{L^1(\Omega)}, |\Omega|). \tag{7.48}$$

This, along with (7.13) and (7.1), yields (7.45).

Integrating (7.9) in Ω and noting (7.11), we have

$$\frac{d}{dt} \parallel u \parallel_{L_1(\Omega)} \leq \parallel c \parallel_{L_1(\Omega)} - \parallel u \parallel_{L_1(\Omega)} .$$

This, along with (7.48), yields (7.46). □

Up to now we have had the $L^1(\Omega)$-estimate on a. In the following we shall raise the a priori estimate of a from $L^1(\Omega)$ to $L^2(\Omega)$ and then to $L^4(\Omega)$.

Theorem 7.2. *There exists some positive constant*

$$\mu^* = \mu^*(\chi,\ \xi,\ \alpha,\ \beta,\ \delta,\ |\Omega|,\ \parallel a_0(x) \parallel_{L^2(\Omega)})$$

such that

$$\parallel a \parallel_{L^4(\Omega)} \leq A_0 \tag{7.49}$$

for all $t \in (0, T]$ *and* $\mu \geq \mu^*$.

Proof. For $s \geq 2$, we will perform the $L^s(\Omega)$-estimate of a. To this end, we need to consider the integral $\int_\Omega a^s dx$, which is equivalent to $\int_\Omega e^{\xi v} a^s dx$ by the estimate $0 \leq v \leq 1$ in (7.1). There is a *strong difference* between the cases $\xi > 0$ and $\xi = 0$ when we proceed to estimate the integral $\int_\Omega e^{\xi v} a^s dx$ (this point will be addressed more clearly later on). We also note that the quantities a and c are almost equivalent by the transformation (7.13) and $0 \leq v \leq 1$. It should be pointed out that there are *bad* influences of the haptotaxis contribution ($\xi > 0$) and chemotaxis contribution ($\chi > 0$) in the following computations for getting a priori estimates, whereas there is a *good* influence of the logistic damping ($\mu > 0$).

We derive from (7.14), (7.15), (7.17) and (7.1) that

$$\begin{aligned}
\frac{d}{dt}\int_\Omega e^{\xi v}a^s dx &= \int_\Omega \xi e^{\xi v}\frac{\partial v}{\partial t}a^s dx + \int_\Omega e^{\xi v} s a^{s-1}\frac{\partial a}{\partial t}dx \\
&= -\xi\delta\int_\Omega e^{\xi v}a^s uv dx + \int_\Omega s a^{s-1}\bigtriangledown\cdot(e^{\xi v}\bigtriangledown a)dx \\
&\quad -\chi\int_\Omega s a^{s-1}\bigtriangledown\cdot(e^{\xi v}a\bigtriangledown u)dx + \xi\delta\int_\Omega e^{\xi v}s a^{s-1}auv dx \\
&\quad +\mu\int_\Omega e^{\xi v}s a^{s-1}a(1-e^{\xi v}a-v)dx \\
&\le -\int_\Omega s(s-1)a^{s-2}|\bigtriangledown a|^2 e^{\xi v}dx \\
&\quad +\chi\int_\Omega s(s-1)a^{s-1}e^{\xi v}\bigtriangledown a\cdot\bigtriangledown u dx \\
&\quad +\xi\delta s\int_\Omega e^{\xi v}a^s u dx + \mu s\int_\Omega e^{\xi v}a^s dx - \mu s\int_\Omega e^{2\xi v}a^{s+1}dx \\
&\le -\frac{4(s-1)}{s}\int_\Omega |\bigtriangledown a^{s/2}|^2 dx \\
&\quad +\mu e^{\xi}s\int_\Omega a^s dx - \mu s\int_\Omega a^{s+1}dx \\
&\quad +\xi\delta e^{\xi}s\int_\Omega u a^s dx \\
&\quad +\chi e^{\xi}s(s-1)\int_\Omega a^{s-1}|\bigtriangledown a\cdot\bigtriangledown u|dx. \qquad (7.50)
\end{aligned}$$

We note that the integral $\int_\Omega ua^s dx$ in (7.50) comes from the haptotaxis term in Eq. (7.7), whereas the integral $\int_\Omega a^{s-1}|\bigtriangledown a\cdot\bigtriangledown u|dx$ in (7.50) comes from the chemotaxis term in Eq. (7.7). From the derivation of the inequality (7.50), we find that we need only to estimate the integral $\int_\Omega a^{s-1}\bigtriangledown a\cdot\bigtriangledown u dx$ in order to deal with the chemotaxis term in Eq. (7.7) for the case $\xi = 0$. However, we must estimate the integral $\int_\Omega a^{s-1}|\bigtriangledown a\cdot\bigtriangledown u|dx$ for the case $\xi > 0$. Multiplying Eq. (7.16) by a^s, integrating the product in Ω, and using the no-flux boundary condition $\frac{\partial u}{\partial\nu}|_{\Gamma_T} = 0$ in (7.17), one may easily estimate the integral $\int_\Omega a^{s-1}\bigtriangledown a\cdot\bigtriangledown u dx$ for the case $\xi = 0$. However, it needs many more techniques to estimate

the integral $\int_\Omega a^{s-1}|\bigtriangledown a \cdot \bigtriangledown u|dx$ for the case $\xi > 0$ (see the remainder of the proof of Lemma 7.2).

The proof of the estimate (7.49) is divided into the following two steps.

Step 1: Estimate $\| a \|_{L^2(\Omega)}$. Taking $s = 2$ in (7.50), one finds

$$\frac{d}{dt}\int_\Omega e^{\xi v}a^2dx = -2\int_\Omega |\bigtriangledown a|^2dx + 2\mu e^\xi \int_\Omega a^2dx - 2\mu\int_\Omega a^3dx \\ +2\xi\delta e^\xi\int_\Omega ua^2dx + 2\chi e^\xi\int_\Omega a|\bigtriangledown a\cdot\bigtriangledown u|dx. \quad (7.51)$$

We first note that, by the Young inequality

$$yz \le \epsilon y^p + A_0\epsilon^{-\frac{q}{p}}z^q \quad (y,\ z \ge 0,\ \epsilon > 0,\ p,\ q > 0,\ \frac{1}{p}+\frac{1}{q} = 1), \quad (7.52)$$

one may estimate

$$\int_\Omega a^2dx \le \varepsilon\int_\Omega a^3dx + A_0(\varepsilon), \quad (7.53)$$

with $\varepsilon > 0$ arbitrary.

We next estimate the integral $\int_\Omega ua^2dx$. Applying the Young inequality (7.52), one obtains

$$\int_\Omega ua^2dx \le \int_\Omega a^3dx + A_0\int_\Omega u^3dx. \quad (7.54)$$

Using Eq. (7.16), the estimate $0 \le v \le 1$ and the elliptic L^p-estimate [71], one finds

$$\| u \|_{W^{2,3}(\Omega)} \le A_0 \| a \|_{L^3(\Omega)}. \quad (7.55)$$

Combining (7.54) and (7.55), one has

$$\int_\Omega ua^2dx \le A_0\int_\Omega a^3dx. \quad (7.56)$$

We now consider the integral $\int_\Omega a|\bigtriangledown a\cdot\bigtriangledown u|dx$. Using the Young inequality (7.52), one finds

$$\begin{aligned}&\int_\Omega a|\bigtriangledown a\cdot\bigtriangledown u|dx\\ &\leq\epsilon\int_\Omega|\bigtriangledown a|^2dx+A_0(\epsilon)\int_\Omega a^2|\bigtriangledown u|^2dx\\ &\leq\epsilon\int_\Omega|\bigtriangledown a|^2dx+A_0(\epsilon)\int_\Omega a^3dx+A_0(\epsilon)\int_\Omega|\bigtriangledown u|^6dx.\end{aligned}\tag{7.57}$$

Applying the interpolation inequality (7.42) with $l=1$, $p=6$, $k=2$, $q=3$, $r=1$, $d=3$, $\theta=1/2$ and using the estimates (7.46) and (7.55), one obtains

$$\|\bigtriangledown u\|_{L^6(\Omega)}\leq A_0\|u\|^{1/2}_{W^2_3(\Omega)}\|u\|^{1/2}_{L^1(\Omega)}\leq A_0\|u\|^{1/2}_{W^2_3(\Omega)}\leq A_0\|a\|^{1/2}_{L^3(\Omega)},$$

and therefore

$$\|\bigtriangledown u\|^6_{L^6(\Omega)}\leq A_0\|a\|^3_{L^3(\Omega)}\,.\tag{7.58}$$

One derives from (7.57) and (7.58) that

$$\int_\Omega a|\bigtriangledown a\cdot\bigtriangledown u|dx\leq\epsilon\int_\Omega|\bigtriangledown a|^2dx+A_0(\epsilon)\int_\Omega a^3dx.\tag{7.59}$$

Inserting (7.53), (7.56), and (7.59) into (7.51), and taking ϵ sufficiently small, one finds

$$\frac{d}{dt}\int_\Omega e^{\xi v}a^2dx\leq-\int_\Omega|\bigtriangledown a|^2dx-(\mu-A_0\xi\delta e^\xi-A_0\chi e^\xi)\int_\Omega a^3dx+A_0\mu e^\xi.\tag{7.60}$$

Note that

$$\mu-A_0\xi\delta e^\xi-A_0\chi e^\xi\geq1\quad\text{if }\mu\geq A_0(\xi\delta+\chi)e^\xi+1.\tag{7.61}$$

Clearly, it follows from the fully explicit bound of μ from below in (7.61) that this bound is worse than for the haptotaxis system without chemotaxis.

Also, this bound is worse than for the Fisher-Kolmogorov-Petrovski-Piskunov equation without chemotaxis/haptotaxis. We further find from the explicit bound of μ from below in (7.61) that this bound becomes worse for faster degradation of the ECM (i.e., for larger δ).

By (7.60), (7.61), the estimate $0 \le v \le 1$, and the Hölder inequality, one obtains

$$\begin{aligned}
&\frac{d}{dt}\int_\Omega e^{\xi v}a^2dx \le -\int_\Omega a^3dx + A_0\mu e^\xi\\
&\le -\frac{1}{|\Omega|^{\frac{1}{2}}}\Big(\int_\Omega a^2dx\Big)^{\frac{3}{2}} + A_0\mu e^\xi\\
&\le -\frac{1}{e^{\frac{3}{2}\xi}|\Omega|^{\frac{1}{2}}}\Big(\int_\Omega e^{\xi v}a^2dx\Big)^{\frac{3}{2}} + A_0\mu e^\xi. \qquad (7.62)
\end{aligned}$$

Denote $\tilde{A}_0 := e^{-\frac{3}{2}\xi}|\Omega|^{-\frac{1}{2}}$, $h(t) := \int_\Omega e^{\xi v}a^2dx$. Then, $h(t)$ satisfies

$$h'(t) \le -\tilde{A}_0 h(t)^{\frac{3}{2}} + A_0\mu e^\xi, \qquad (7.63)$$

implying (see [162], for instance)

$$h(t) \le \max\Big\{h(0),\ \Big(\frac{A_0\mu e^\xi}{\tilde{A}_0}\Big)^{\frac{2}{3}}\Big\}. \qquad (7.64)$$

Hence,

$$\int_\Omega a^2dx \le A_0, \qquad (7.65)$$

where A_0 may depend on $\| a_0 \|_{L^2(\Omega)}$. From the fully explicit bound of $\| a \|_{L^2(\Omega)}$ from above in (7.64), we find that the bound is worse than for the chemotaxis system without haptotaxis ($\xi = 0$) and that this bound is also worse than for the haptotaxis system without chemotaxis ($\chi = 0$) (note that we can choose a smaller μ for the haptotaxis system without chemotaxis ($\chi = 0$) by (7.61)).

Step 2: Estimate $\| a \|_{L^4(\Omega)}$. Taking $s = 4$ in (7.50), one finds

$$\frac{d}{dt}\int_\Omega e^{\xi v}a^4dx \le -3\int_\Omega |\bigtriangledown a^2|^2dx + 4\mu e^\xi\int_\Omega a^4dx - 4\mu\int_\Omega a^5dx \\ +4\xi\delta e^\xi\int_\Omega ua^4dx + 12\chi e^\xi\int_\Omega a^3|\bigtriangledown a\cdot\bigtriangledown u|dx. \quad (7.66)$$

First, employing the Young inequality and proceeding as in Step 1, one has, for $\varepsilon > 0$ arbitrary,

$$\int_\Omega a^4dx \le \varepsilon\int_\Omega a^5dx + A_0(\varepsilon), \quad (7.67)$$

$$\int_\Omega ua^4dx \le A_0\int_\Omega a^5dx. \quad (7.68)$$

We now focus on estimating the integral $\int_\Omega a^3|\bigtriangledown a\cdot\bigtriangledown u|dx$ in (7.66). Applying the Young inequality (7.52), one finds

$$\begin{aligned}&\int_\Omega a^3|\bigtriangledown a\cdot\bigtriangledown u|dx\\ &\le \int_\Omega (a^3|\bigtriangledown a|)^{\frac{10}{9}}dx + A_0\int_\Omega |\bigtriangledown u|^{10}dx\\ &= \int_\Omega (a^2\cdot a|\bigtriangledown a|)^{\frac{10}{9}}dx + A_0\int_\Omega |\bigtriangledown u|^{10}dx\\ &\le \epsilon\int_\Omega (a|\bigtriangledown a|)^{\frac{10}{9}\cdot\frac{9}{5}}dx + A_0(\epsilon)\int_\Omega a^{\frac{20}{9}\cdot\frac{9}{4}}dx + A_0\int_\Omega |\bigtriangledown u|^{10}dx\\ &= \frac{\epsilon}{4}\int_\Omega |\bigtriangledown a^2|^2dx + A_0(\epsilon)\int_\Omega a^5dx + A_0\int_\Omega |\bigtriangledown u|^{10}dx. \end{aligned} \quad (7.69)$$

Using Eq. (7.16), the estimates (7.65), $0 \le v \le 1$, and the elliptic L^p-estimate [71], one finds

$$\| u \|_{W_2^2(\Omega)} \le A_0 \| a \|_{L^2(\Omega)} \le A_0.$$

This, together with the Sobolev imbedding theorem [71], yields

$$\| \bigtriangledown u \|_{L^6(\Omega)} \le A_0 \| u \|_{W_2^2(\Omega)} \le A_0. \quad (7.70)$$

Again, by the elliptic L^p-estimate [71], one has

$$\| u \|_{W_5^2(\Omega)} \leq A_0 \| a \|_{L^5(\Omega)} . \tag{7.71}$$

Applying the interpolation inequality (7.42) with $l = 0$, $p = 10$, $k = 1$, $q = 5$, $r = 6$, $d = 3$, $\theta = 2/9$ and using the estimates (7.70) and (7.71), one obtains

$$\begin{aligned} \| \bigtriangledown u \|_{L^{10}(\Omega)} &\leq A_0 \| u \|^{2/9}_{W_5^2(\Omega)} \| \bigtriangledown u \|^{7/9}_{L^6(\Omega)} \\ &\leq A_0 \| u \|^{2/9}_{W_5^2(\Omega)} \\ &\leq A_0 \| a \|^{2/9}_{L^5(\Omega)} . \end{aligned}$$

This, together with the Young inequality, yields

$$\| \bigtriangledown u \|^{10}_{L^{10}(\Omega)} \leq A_0 \| a \|^{20/9}_{L^5(\Omega)} \leq A_0 \| a \|^5_{L^5(\Omega)} + A_0. \tag{7.72}$$

Combining (7.69) and (7.72), one has

$$\int_\Omega a^3 | \bigtriangledown a \cdot \bigtriangledown u | dx \leq \frac{\epsilon}{4} \int_\Omega | \bigtriangledown a^2 |^2 dx + A_0(\epsilon) \int_\Omega a^5 dx + A_0. \tag{7.73}$$

Inserting (7.67), (7.68), and (7.73) into (7.66) and taking ϵ sufficiently small, one obtains if $\mu \geq A_0 + 1/4$, then

$$\begin{aligned} \frac{d}{dt} \int_\Omega e^{\xi v} a^4 dx &\leq - \int_\Omega | \bigtriangledown a^2 |^2 dx - 4(\mu - A_0) \int_\Omega a^5 dx + A_0 \\ &\leq -4(\mu - A_0) \int_\Omega a^5 dx + A_0 \\ &\leq - \int_\Omega a^5 dx + A_0 \\ &\leq - \frac{1}{|\Omega|^{\frac{1}{4}}} \Big(\int_\Omega a^4 dx \Big)^{\frac{5}{4}} + A_0 \\ &\leq - \frac{1}{e^{\frac{5}{4}\xi} |\Omega|^{\frac{1}{4}}} \Big(\int_\Omega e^{\xi v} a^4 dx \Big)^{\frac{5}{4}} + A_0. \end{aligned} \tag{7.74}$$

As before, the inequality (7.74) implies

$$\int_{\Omega} e^{\xi v} a^4 dx \leq A_0.$$

This completes the proof of Theorem 7.2. □

Theorem 7.3. *Assume that $\mu \geq \mu^*$, where μ^* is defined in Theorem 7.2. Then, there holds*

$$\| u \|_{C^{\gamma}(\Omega)} \leq A_0, \quad \| v \|_{C^{\gamma}(\Omega)} \leq A \tag{7.75}$$

for any $0 \leq \gamma < \frac{5}{4}$.

Proof. It follows from Eq. (7.16), the estimates (7.1) and (7.49), and the elliptic L^p-theory that

$$\| u \|_{W_4^2(\Omega)} \leq A_0. \tag{7.76}$$

This, together with the Sobolev imbedding theorem, yields

$$\| u \|_{C^{\gamma}(\Omega)} \leq A_0 \quad \text{for any } 0 \leq \gamma < \frac{5}{4}. \tag{7.77}$$

One derives from Eq. (7.15) that

$$v(x,t) = v_0(x) e^{-\delta \int_0^t u(x,s) ds}, \tag{7.78}$$

$$\bigtriangledown v = e^{-\delta \int_0^t u(x,s) ds} \bigtriangledown v_0 - \delta v_0(x) e^{-\delta \int_0^t u(x,s) ds} \int_0^t \bigtriangledown u ds. \tag{7.79}$$

Combining (7.77)-(7.79), (7.1), and (7.2), one obtains

$$\| v \|_{C^{\gamma}(\Omega)} \leq A \quad \text{for any } 0 \leq \gamma < \frac{5}{4}. \tag{7.80}$$

This completes the proof of Theorem 7.3. □

Theorem 7.4. *Assume that $\mu \geq \mu^*$, where μ^* is defined in Theorem 7.2. Then, there holds*

$$\| a(x,t),\ v(x,t) \|_{C^{2+\sigma,1+\sigma/2}(Q_T)} \leq A, \quad \| u(x,t) \|_{C^{2+\sigma,\sigma/2}(Q_T)} \leq A, \tag{7.81}$$

where $\sigma = 3/4$.

Proof. Eq. (7.14) can be rewritten as in the following nondivergence form:

$$a_t - \triangle a - (\xi \bigtriangledown v - \chi \bigtriangledown u) \cdot \bigtriangledown a + [\chi\xi \bigtriangledown u \cdot \bigtriangledown v + \chi \triangle u - \xi\delta uv - \mu(1-c-v)]a = 0, \tag{7.82}$$

where

$$\| \xi \bigtriangledown v - \chi \bigtriangledown u \|_{L^\infty(Q_T)} \leq A, \tag{7.83}$$

$$\| \chi\xi \bigtriangledown u \cdot \bigtriangledown v + \chi \triangle u - \xi\delta uv - \mu(1-c-v) \|_{L^4(Q_T)} \leq A \tag{7.84}$$

by the estimates (7.1), (7.75), and (7.76). By (7.82)-(7.84) and the parabolic L^p-estimates [108], one obtains

$$\| a \|_{W_4^{2,1}(Q_T)} \leq A.$$

Applying the Sobolev imbedding theorem (7.43) with $l = 1,\ p = 4,\ d = 3,\ r = s = \mu = 0$, one finds

$$\| a \|_{C^{\sigma,\sigma/2}(Q_T)} \leq A, \tag{7.85}$$

where $\sigma = 3/4$.

One may derive from (7.78), (7.2) and (7.77) that, for any $0 < t_1 < t_2 < T$,

$$\begin{aligned}
&\frac{|v(x,\ t_1) - v(x,\ t_2)|}{|t_1 - t_2|^{\sigma/2}} \\
&= |v_0(x)| \frac{|e^{-\delta \int_0^{t_1} u(x,\ s)ds} - e^{-\delta \int_0^{t_2} u(x,\ s)ds}|}{|t_1 - t_2|^{\sigma/2}} \\
&= |v_0(x)||\delta u(x,\ \eta) e^{-\delta \int_0^{\eta} u(x,\ s)ds}| \cdot |t_1 - t_2|^{1-\sigma/2} \quad \text{(for some } t_1 < \eta < t_2\text{)} \\
&\leq A.
\end{aligned}$$

This, together with (7.80), yields

$$\| v \|_{C^{\sigma,\sigma/2}(Q_T)} \leq A. \tag{7.86}$$

Proceeding as in the proof of Theorem 7.1, one obtains from Eq. (7.16), the estimates (7.85) and (7.86), and the elliptic Schauder estimates that

$$\| u \|_{C^{2+\sigma,\sigma/2}(Q_T)} \leq A. \tag{7.87}$$

Again, proceeding as in the proof of Theorem 7.1, one can get

$$\| v \|_{C^{2+\sigma,1+\sigma/2}(Q_T)} \leq A. \tag{7.88}$$

Finally, one derives from Eq. (7.82), the estimates (7.87) and (7.88), and the parabolic Schauder estimates that

$$\| a \|_{C^{2+\sigma,1+\sigma/2}(Q_T)} \leq A.$$

This completes the proof of Theorem 7.4. □

The a priori estimate (7.81) allows us to continue the local solution in Theorem 7.1 step-by-step to all $t > 0$, as done in Chapter 6. Thus, we have the following result of global existence of solutions.

Theorem 7.5. *Under the assumption (7.2), there exists some constant*

$$\mu^* = \mu^*(\chi,\ \xi,\ \alpha,\ \beta,\ \delta,\ |\Omega|,\ \ \| a_0(x) \|_{L^2(\Omega)}) > 0$$

such that, for any $\mu > \mu^*$, the system (7.14)-(7.18) admits a unique global solution $(a,\ v,\ u) \in C^{2+\sigma,1+\sigma/2}(Q_T) \times C^{2+\sigma,1+\sigma/2}(Q_T) \times C^{2+\sigma,\sigma/2}(Q_T)$ for any $T > 0$. Furthermore,

$$a \geq 0,\ u \geq 0,\ 0 \leq v \leq 1, \tag{7.89}$$

$$\| u \|_{L^\infty(Q_T)} \leq A_0, \quad \| \bigtriangledown u \|_{L^\infty(Q_T)} \leq A_0. \tag{7.90}$$

Remark 7.2. If $\mu = 0$, $v \equiv 0$ in (7.7)-(7.9), then blow-up of smooth solutions occurs for large initial mass as aforementioned in Section 7.1 in three dimensions and two dimensions. In next section, we shall prove that global existence holds true for $\mu > 0$ in two dimensions. However, it remains open whether blow-up of classical solutions occurs for *small* $\mu > 0$ in three dimensions

Furthermore, in the following we will derive the uniform-in-time boundedness of $a(x,t)$ of the global solution.

Theorem 7.6. *Let $(a,\ v,\ u)$ be the unique global solution of the system (7.14)-(7.18) in Theorem 7.5. Then, there holds*

$$\|a\|_{L^\infty(Q_T)} \leq A_0 \|a_0\|_{L^\infty(\Omega)}, \tag{7.91}$$

where A_0 depends on $\chi,\ \xi,\ \alpha,\ \beta,\ \delta,\ \mu$, and $|\Omega|$.

Proof. We go back to the differential inequality (7.50).

We first estimate the integral $\int_\Omega ua^s dx$. By the estimate $u \geq 0$ in (7.89) and the estimate $\|u\|_{L^\infty(Q_T)} \leq A_0$ in (7.90), one obtains

$$\int_\Omega ua^s dx \leq A_0 \int_\Omega a^s dx. \tag{7.92}$$

We next consider the integral $\int_\Omega a^{s-1} | \bigtriangledown a \cdot \bigtriangledown u| dx$. By the estimate $\| \bigtriangledown u\|_{L^\infty(Q_T)} \leq A_0$ in (7.90) and the Cauchy inequality, one has

$$\begin{aligned}
\int_\Omega a^{s-1} | \bigtriangledown a \cdot \bigtriangledown u| dx &\leq A_0 \int_\Omega a^{s-1} | \bigtriangledown a| dx \\
&= A_0 \int_\Omega a^{\frac{s}{2}} \cdot a^{\frac{s}{2}-1} | \bigtriangledown a| dx \\
&\leq A_0 \epsilon \int_\Omega a^{s-2} | \bigtriangledown a|^2 dx + \frac{A_0}{\epsilon} \int_\Omega a^s dx \\
&= \frac{4A_0\epsilon}{s^2} \int_\Omega | \bigtriangledown a^{\frac{s}{2}}|^2 dx + \frac{A_0}{\epsilon} \int_\Omega a^s dx.
\end{aligned} \tag{7.93}$$

Inserting (7.92) and (7.93) into (7.50) and taking ϵ sufficiently small, one finds

$$\frac{d}{dt} \int_\Omega e^{\xi v} a^s dx + \frac{2(s-1)}{s} \int_\Omega | \bigtriangledown a^{s/2}|^2 dx \leq A_0 s(s-1) \int_\Omega a^s dx \quad \text{for all } s \geq 2. \tag{7.94}$$

Noting $0 \leq v \leq 1$ and using the iterative technique of Alikakos [4], one obtains from (7.94) that

$$\sup_{t \geq 0} \|e^{\xi v(x,\ t)} a(x,\ t)\|_{L^\infty(\Omega)} \leq A_0 \|e^{\xi v_0(x)} a_0(x)\|_{L^\infty(\Omega)}. \tag{7.95}$$

We also refer to recent references [40, 103] for a detailed derivation of the estimate (7.95). Hence, the proof of Theorem 7.6 is completed. □

7.5 Global Existence and Boundedness in dimension 2

Throughout this section, we assume that $d = 2$. We first note that Lemmas 7.1 and 7.2 are also true for $d = 2$. Up to now we have had the $L^1(\Omega)$-estimate on c. In the following we shall raise the a priori estimate of c in the following way: $L^1(\Omega) \to L^3(Q_T) \to L^2(\Omega) \to L^4(Q_T) \to L^3(\Omega)$.

From Eq. (7.7), we have the following two lemmas [151].

Lemma 7.3. *There holds*

$$\begin{aligned}
&\frac{d}{dt}\int_\Omega \big[(c+1)\log(c+1)-c\big]dx + \int_\Omega \frac{1}{c+1}|\bigtriangledown c|^2 dx \\
&\le \mu\int_\Omega \big[(c+1)\log(c+1)-c\big]dx \\
&\quad +A_0(\chi+\xi)\Big(\parallel \triangle u(t)\parallel^2_{L^2(\Omega)} + \parallel \triangle v(t)\parallel^2_{L^2(\Omega)} + \parallel c(t)\parallel^2_{L^2(\Omega)}\Big) + A_0\mu.
\end{aligned} \tag{7.96}$$

Proof. We easily derive from (7.8), the boundary condition (7.11), and the assumption $\frac{\partial v_0(x)}{\partial \nu}\Big|_{\partial\Omega} = 0$ in (7.2) that

$$\frac{\partial v}{\partial \nu}\Big|_{\partial\Omega_T} = 0. \tag{7.97}$$

Multiplying Eq. (7.7) by $\log(c+1)$, integrating the product in Ω, and using the no-flux boundary condition (7.10), one obtains

$$\begin{aligned}
&\frac{d}{dt}\int_\Omega \Big[(c+1)\log(c+1)-c\Big]\,dx + \int_\Omega \frac{1}{c+1}|\bigtriangledown c|^2\,dx \\
&= \chi\int_\Omega \frac{c}{c+1}\bigtriangledown c\cdot\bigtriangledown u\,dx + \xi\int_\Omega \frac{c}{c+1}\bigtriangledown c\cdot\bigtriangledown v\,dx \\
&\quad +\mu\int_\Omega c(1-c-v)\log(c+1)\,dx.
\end{aligned} \tag{7.98}$$

Here, one observes that

$$\int_\Omega \frac{c}{c+1} \bigtriangledown c \cdot \bigtriangledown u \; dx = \int_\Omega \Big[\log(c+1) - c \Big] \bigtriangleup u \; dx, \tag{7.99}$$

$$\int_\Omega \frac{c}{c+1} \bigtriangledown c \cdot \bigtriangledown v \; dx = \int_\Omega \Big[\log(c+1) - c \Big] \bigtriangleup v \; dx, \tag{7.100}$$

in which we have used the boundary condition (7.11) and (7.97). On the other hand, one observes that

$$\int_\Omega \Big[\log(c+1) - c \Big] \bigtriangleup u \; dx \leq A_0(\| \bigtriangleup u(t) \|^2_{L^2} + \| c(t) \|^2_{L^2}), \tag{7.101}$$

$$\int_\Omega \Big[\log(c+1) - c \Big] \bigtriangleup v \; dx \leq A_0(\| \bigtriangleup v(t) \|^2_{L^2} + \| c(t) \|^2_{L^2}), \tag{7.102}$$

$$\begin{aligned} &\int_\Omega c(1-c-v)\log(c+1) \; dx \leq \int_\Omega c\log(c+1) \; dx \\ &\leq \int_\Omega \Big[(c+1)\log(c+1) - c \Big] \; dx + \|c\|_{L^1(\Omega)} \\ &\leq \int_\Omega \Big[(c+1)\log(c+1) - c \Big] \; dx + A_0, \end{aligned} \tag{7.103}$$

in which we have used the basic inequality: $\log(1+c) \leq c$ for any $c \geq 0$ in derivation of estimates (7.101) and (7.102), and we have used estimates (7.1) and (7.45) in derivation of estimate (7.103). Taking into account all above estimates, one obtains from (7.96) from (7.98). □

Lemma 7.4. *Assume that $\mu > 0$ and that the following estimate*

$$\| (c+1)\log(c+1) \|_{L^1(\Omega)} \leq A \tag{7.104}$$

is true; then there holds

$$\begin{aligned} &\frac{d}{dt}\int_\Omega c^2 dx + \int_\Omega |\bigtriangledown c|^2 dx \\ &\leq \epsilon\Big(\| \bigtriangledown \bigtriangleup u(t) \|^2_{L^2(\Omega)} + \| \bigtriangledown \bigtriangleup v(t) \|^2_{L^2(\Omega)} \Big) \\ &\quad + A\epsilon^{-1/2} g(\epsilon^{-1}) + A, \end{aligned} \tag{7.105}$$

where $\epsilon > 0$ is any number and $g(\cdot)$ is some increasing function.

Proof. This lemma is the core of the argument concerning global existence in the two-dimensional case.

Multiply Eq. (7.7) by c, integrate the product in Ω, and use the no-flux boundary condition (7.10). One obtains

$$\frac{1}{2}\frac{d}{dt}\int_\Omega c^2 dx + \int_\Omega |\bigtriangledown c|^2 dx = \chi \int_\Omega c \bigtriangledown c \cdot \bigtriangledown u dx + \xi \int_\Omega c \bigtriangledown c \cdot \bigtriangledown v dx + \mu \int_\Omega c^2(1-c-v)dx. \tag{7.106}$$

Note that

$$\int_\Omega c \bigtriangledown c \cdot \bigtriangledown u \; dx = -\frac{1}{2}\int_\Omega c^2 \bigtriangleup u \; dx, \tag{7.107}$$

$$\int_\Omega c \bigtriangledown c \cdot \bigtriangledown v \; dx = -\frac{1}{2}\int_\Omega c^2 \bigtriangleup v \; dx \tag{7.108}$$

by the boundary conditions (7.11) and (7.97).

Applying the Gagliardo–Nirenberg interpolation inequality (7.42) with $l = 1, p = 3, k = q = r = d = 2$, and $\theta = 2/3$, one obtains

$$\| \bigtriangleup u\|_{L^3(\Omega)} \le A_0 \|u\|^{2/3}_{H^3(\Omega)} \|u\|^{1/3}_{H^1(\Omega)} \quad \text{for } u \in H^3(\Omega), \tag{7.109}$$

where $H^q(\Omega) := W_2^q(\Omega)$.

We shall also need the following interpolation inequality proved by Biler, Hebisch, and Nadzieja [13]:

$$\|c\|^3_{L^3(\Omega)} \le \varepsilon \|c\|^2_{H^1(\Omega)} \| (c+1)\log(c+1) \|_{L^1(\Omega)} + g(\varepsilon^{-1})\|c\|_{L^1(\Omega)} \tag{7.110}$$

for $c \ge 0$ and $c \in H^1(\Omega)$, where $\varepsilon > 0$ is any number and $g(\cdot)$ is some increasing function.

By (7.45), Eq. (7.9) and the regularity theory for elliptic equations in two dimensions, one has

$$\| \bigtriangledown u\|_{L^2(\Omega)} \leq A_0 \| c\|_{L^1(\Omega)} \leq A_0. \tag{7.111}$$

Applying the interpolation inequality (7.42) and using the estimates (7.46) and (7.11), one obtains

$$\| u\|_{L^2(\Omega)} \leq A_0 \| u\|_{W_1^1\Omega)} \| u\|_{L^1(\Omega)} \leq A_0. \tag{7.112}$$

Now we estimate $\Big| \int_\Omega c^2 \bigtriangleup u \ dx\Big|$:

$$\begin{aligned}
&\Big| \int_\Omega c^2 \bigtriangleup u \ dx\Big| \leq A_0 \|c\|^2_{L^3(\Omega)} \| \bigtriangleup u\|_{L^3(\Omega)} \quad \text{(by Hölder's inequality)} \\
&\leq A_0 \|c\|^2_{L^3(\Omega)} \|u\|^{2/3}_{H^3(\Omega)} \|u\|^{1/3}_{H^1(\Omega)} \quad \text{(by (7.109))} \\
&\leq A_0 \|c\|^2_{L^3(\Omega)} \|u\|^{2/3}_{H^3(\Omega)} \quad \text{(by (7.111) and (7.112))} \\
&\leq A_0 \Big[\varepsilon \|c\|^2_{H^1(\Omega)} \| \ (c+1)\log(c+1) \ \|_{L^1(\Omega)} + g(\varepsilon^{-1}) \|c\|_{L^1(\Omega)}\Big]^{2/3} \|u\|^{2/3}_{H^3(\Omega)} \\
&\qquad\qquad \text{(by Biler, Hebisch, and Nadzieja's interpolation inequality (7.110))} \\
&\leq A \Big[\varepsilon \|c\|^2_{H^1(\Omega)} + g(\varepsilon^{-1})\Big]^{2/3} \|u\|^{2/3}_{H^3(\Omega)} \quad \text{(by (7.45) and (7.104))} \\
&\leq \varepsilon \|u\|^2_{H^3(\Omega)} + A\varepsilon^{-1/2} \Big[\varepsilon \|c\|^2_{H^1(\Omega)} + g(\varepsilon^{-1})\Big] \quad \text{(by Young's inequality)} \\
&= \varepsilon \|u\|^2_{H^3(\Omega)} + A\varepsilon^{1/2} \|c\|^2_{H^1(\Omega)} + A\varepsilon^{-1/2} g(\varepsilon^{-1}).
\end{aligned} \tag{7.113}$$

Similarly, one has

$$\Big| \int_\Omega c^2 \bigtriangleup v \ dx\Big| \leq \varepsilon \|v\|^2_{H^3(\Omega)} + A\varepsilon^{1/2} \|c\|^2_{H^1(\Omega)} + A\varepsilon^{-1/2} g(\varepsilon^{-1}). \tag{7.114}$$

On the other hand, by Young's inequality,

$$\int_\Omega c^2 \ dx \leq \varepsilon \int_\Omega c^3 \ dx + A_0(\varepsilon)|\Omega|. \tag{7.115}$$

Taking into account above estimates (7.106)-(7.108), (7.113)-(7.115), and using assumption $\mu > 0$, one has

$$\begin{aligned}
&\frac{1}{2}\frac{d}{dt}\int_\Omega c^2 dx + \int_\Omega |\bigtriangledown c|^2 dx \\
&\leq \varepsilon\Big(\|u\|^2_{H^3(\Omega)} + \|v\|^2_{H^3(\Omega)}\Big) + A\varepsilon^{-1/2} g(\varepsilon^{-1}) + A_0 \\
&\leq \varepsilon\Big(\|\bigtriangledown \triangle u\|^2_{L^2(\Omega)} + \|\bigtriangledown \triangle v\|^2_{L^2(\Omega)}\Big) + A\varepsilon^{-1/2} g(\varepsilon^{-1}) + A
\end{aligned}$$

for sufficiently small $\varepsilon > 0$, where we have used the facts that

$$\begin{aligned}
\|u\|_{H^3(\Omega)} &\leq A_0\Big(\|\bigtriangledown \triangle u\|_{L^2(\Omega)} + \|u\|_{H^1(\Omega)}\Big) \quad (\text{for } u \in H^3(\Omega) \text{ with } \frac{\partial u}{\partial \nu}\Big|_{\partial\Omega} = 0) \\
&\leq A_0\|\bigtriangledown \triangle u\|_{L^2(\Omega)} + A \qquad (\text{by (7.111) and (7.112)})
\end{aligned}$$

and that

$$\|v\|_{H^3(\Omega)} \leq A_0\|\bigtriangledown \triangle v\|_{L^2(\Omega)} + A \quad (\text{for } v \in H^3(\Omega) \text{ with } \frac{\partial v}{\partial \nu}\Big|_{\partial\Omega} = 0).$$

This completes the proof of Lemma 7.4. □

Lemma 7.5. *Assume that $d = 2$ and $\mu > 0$. Then there holds*

$$\| c \|_{L^3(Q_T)} \leq A. \tag{7.116}$$

Proof. The proof is divided into the following eight steps. In Steps 1-6, we will give attention to the dependency of the bounds of some estimates on the parameters μ, χ and ξ. From (7.45) and its proof, we find that the bound from above of $\|c\|_{L^1(\Omega)}$ is independent of the parameters μ, χ, and ξ. In the following we may assume that $\mu > 0$ is *small*, say, $0 < \mu < 1$, since we can proceed the estimates for large $\mu > 0$ in two dimensions as in three dimensions in Section 7.4.

Step 1: Estimate $\| c \|^2_{L^2(Q_T)}$. Integrating Eq. (7.7) in $\Omega \times [0,\ t]$ $(t \leq T)$, noting the no-flux boundary condition (7.10), and using the assumption that

$\mu > 0$ and the estimates (7.1) and (7.45), one obtains

$$\int_0^t \int_\Omega c^2 dxds \leq A\mu^{-1}. \tag{7.117}$$

Step 2: Estimate $\| \triangle u \|^2_{L^2(Q_T)}$. Multiply Eq. (7.9) by $\triangle u$, integrate the product in Ω, and use the no-flux boundary condition (7.11). Then

$$\int_\Omega | \triangle u|^2 dx + \beta \int_\Omega | \bigtriangledown u|^2 dx = -\alpha \int_\Omega c \triangle u dx.$$

Cauchy's inequality allows us to write

$$\frac{1}{2} \int_\Omega | \triangle u|^2 dx + \beta \int_\Omega | \bigtriangledown u|^2 dx \leq \frac{\alpha^2}{2} \int_\Omega c^2 dx,$$

which gives

$$\int_\Omega | \triangle u|^2 dx \leq \alpha^2 \int_\Omega c^2 dx.$$

This, together with the estimate (7.117), yields

$$\int_0^t \int_\Omega | \triangle u|^2 dxds \leq A\mu^{-1}. \tag{7.118}$$

Step 3: Estimate $\| \bigtriangledown u \|^2_{L^2(\Omega)}$. We notice by the standard results in the regularity theory for elliptic equations that from Eq. (7.9) and the L^1-estimate (7.45) of c we have

$$\sup_{t\in[0,T]} \| \bigtriangledown u(\cdot, t)\|_{L^q(\Omega)} \leq A_0 \sup_{t\in[0,T]} \|c(\cdot, t)\|_{L^1(\Omega)} \leq A_0 \tag{7.119}$$

where

$$q = \frac{d}{d-1},$$

which gives

$$\| \bigtriangledown u(\cdot, t)\|_{L^2(\Omega)} \leq A_0. \tag{7.120}$$

Step 4: Estimate $\| \bigtriangledown v\|^2_{L^2(\Omega)}$. Note that Eq. (7.8) can be rewritten as

$$v(x,\ t) = v_0(x)e^{-\delta \int_0^t u(x,\ s)ds}, \tag{7.121}$$

and therefore

$$\bigtriangledown v = e^{-\delta \int_0^t u(x,\ s)ds} \bigtriangledown v_0 - \delta v_0(x)e^{-\delta \int_0^t u(x,\ s)ds} \int_0^t \bigtriangledown u ds. \tag{7.122}$$

Using the estimates (7.1) and (7.120), one obtains from (7.122) that

$$\int_\Omega | \bigtriangledown v|^2 dx \leq A. \tag{7.123}$$

Step 5: Estimate $\| \bigtriangleup v\|^2_{L^2(Q_T)}$. One derives from (7.122) that

$$\begin{aligned} \bigtriangleup v = {} & e^{-\delta \int_0^t u(x,\ s)ds} \bigtriangleup v_0 - 2\delta e^{-\delta \int_0^t u(x,\ s)ds} \int_0^t \bigtriangledown u \cdot \bigtriangledown v_0 ds \\ & + \delta^2 v_0(x)e^{-\delta \int_0^t u(x,\ s)ds} \Big(\int_0^t \bigtriangledown u ds \Big)^2 \\ & - \delta v_0(x)e^{-\delta \int_0^t u(x,\ s)ds} \int_0^t \bigtriangleup u ds. \end{aligned} \tag{7.124}$$

By Eq. (7.9) and the elliptic L^p-theory, one finds

$$\|u\|_{H^2(\Omega)} \leq A_0 \|c\|_{L^2(\Omega)}. \tag{7.125}$$

This, together with the estimate (7.117), yields

$$\int_0^t \|u\|^2_{H^2(\Omega)} ds \leq A_0 \int_0^t \|c\|^2_{L^2(\Omega)} ds \leq A\mu^{-1}. \tag{7.126}$$

Applying the Gagliardo–Nirenberg interpolation inequality (7.42) with $l = 0,\ p = 4,\ k = 1,\ q = r = d = 2,\ \theta = 1/2$ and using the estimate (7.120), one obtains

$$\| \bigtriangledown u\|_{L^4(\Omega)} \leq A_0 \|u\|^{1/2}_{H^2(\Omega)} \| \bigtriangledown u\|^{1/2}_{L^2(\Omega)} \leq A_0 \|u\|^{1/2}_{H^2(\Omega)}.$$

This, together with the estimate (7.126), yields

$$\int_0^t \| \bigtriangledown u\|^4_{L^4(\Omega)} ds \leq A_0 \int_0^t \|u\|^2_{H^2(\Omega)} ds \leq A\mu^{-1}. \tag{7.127}$$

Finally, using the estimates (7.1), (7.118), (7.120) and (7.127), one derives from (7.124) that

$$\int_0^t \int_\Omega | \bigtriangleup v|^2 dxds \leq A\mu^{-1}. \tag{7.128}$$

Step 6: Estimate $\|(c+1)\log(c+1)\|_{L^1(\Omega)}$. Lemma 7.3, together with Gronwall's lemma and the estimates (7.117), (7.118), and (7.128), yields

$$\int_\Omega \big[(c+1)\log(c+1) - c\big] dx \leq A(\chi + \xi + 1)\mu^{-1}. \tag{7.129}$$

Here we should note that $(c+1)\log(c+1) - c \geq 0$ for any $c \geq 0$. Combining (7.45) and (7.129), one has

$$\int_\Omega (c+1)\log(c+1) dx \leq A(\chi + \xi + 1)\mu^{-1}. \tag{7.130}$$

Clearly, the bound from above of $\|(c+1)\log(c+1)\|_{L^1(\Omega)}$ in (7.130) strongly depends on μ, and it becomes unbounded as $\mu \to 0^+$. This is why the assumption that $\mu > 0$ is so crucial to our results of global existence in two dimensions.

Step 7: Estimate $\| \bigtriangledown c\|_{L^2(Q_T)}$. By Lemma 7.4 and the estimate (7.130), one has

$$\begin{aligned} &\frac{d}{dt}\int_\Omega c^2 dx + \int_\Omega | \bigtriangledown c|^2 dx \\ &\leq \epsilon\Big(\| \bigtriangledown \bigtriangleup u\|^2_{L^2(\Omega)} + \| \bigtriangledown \bigtriangleup v\|^2_{L^2(\Omega)} \Big) + A\epsilon^{-1/2} g(\epsilon^{-1}) + A. \end{aligned} \tag{7.131}$$

We first estimate $\| \bigtriangledown \triangle u\|_{L^2(\Omega)}$. We derive from (7.122), the boundary condition (7.11), and the assumption $\frac{\partial v_0(x)}{\partial \nu} \mid_{\partial\Omega} = 0$ in (7.2) that

$$\frac{\partial v}{\partial \nu}\Big|_{\Gamma_T} = 0. \tag{7.132}$$

This, together with the boundary conditions (7.10) and (7.11), further yields

$$\frac{\partial c}{\partial \nu}\Big|_{\Gamma_T} = 0. \tag{7.133}$$

Next, multiply Eq. (7.9) by $\triangle^2 u$ and integrate the products. Using integration by parts, one obtains

$$\begin{aligned} &\int_\Omega | \bigtriangledown \triangle u|^2 dx + \beta \int_\Omega | \triangle u|^2 dx \\ &= -\alpha \int_\Omega \bigtriangledown c \cdot \bigtriangledown \triangle u dx \\ &\leq \frac{1}{2} \int_\Omega | \bigtriangledown \triangle u|^2 dx + \frac{\alpha^2}{2} \int_\Omega | \bigtriangledown c|^2 dx, \end{aligned} \tag{7.134}$$

where we have used the following compatibility condition

$$\frac{\partial \triangle u}{\partial \nu}\Big|_{\Gamma_T} = \beta \frac{\partial u}{\partial \nu}\Big|_{\Gamma_T} - \alpha \frac{\partial c}{\partial \nu}\Big|_{\Gamma_T} = 0 \tag{7.135}$$

by (7.9), (7.11), and (7.133). One further derives from (7.134) that

$$\int_\Omega | \bigtriangledown \triangle u|^2 dx \leq \alpha^2 \int_\Omega | \bigtriangledown c|^2 dx. \tag{7.136}$$

We are now in a position to consider $\| \bigtriangledown \triangle v\|^2_{L^2(\Omega)}$. One can derive from (7.124), the assumption $v_0(x) \in C^3(\overline{\Omega})$ in (7.2), the estimate $u \geq 0$, and the estimates (7.118), (7.120), and (7.127) that

$$\| \bigtriangledown \triangle v\|^2_{L^2(\Omega)} \leq A + A \int_0^t \int_\Omega | \bigtriangledown \triangle u|^2 dx ds. \tag{7.137}$$

Inserting (7.136) and (7.137) into (7.131), one obtains

$$\frac{d}{dt}\int_\Omega c^2 dx + (1-\alpha^2\epsilon)\int_\Omega |\bigtriangledown c|^2 dx \le A\epsilon\int_0^t\int_\Omega |\bigtriangledown c|^2 dxds + A(\epsilon).$$

Integrating with respect to the variable t in both sides of the above inequality and taking $\epsilon > 0$ sufficiently small, one finds

$$\int_0^T\int_\Omega |\bigtriangledown c|^2 dxdt \le A. \tag{7.138}$$

Step 8: Estimate $\|c\|_{L^3(Q_T)}$. Applying the Gagliardo–Nirenberg inequality (7.42) with $l = 0,\ k = 1,\ p = 3,\ q = d = 2,\ r = 1,\ \theta = 2/3$ and using the estimate (7.45), one obtains

$$\begin{aligned}\|c(t)\|_{L^3(\Omega)} &\le A_0\|c(t)\|^{2/3}_{W^1_2(\Omega)}\|c(t)\|^{1/3}_{L^1(\Omega)}\\ &\le A_0\|c(t)\|^{2/3}_{W^1_2(\Omega)}.\end{aligned}$$

This, together with the estimate (7.117) and (7.138), yields

$$\int_0^t \|c(s)\|^3_{L^3(\Omega)}ds \le A_0\int_0^t \|c(s)\|^2_{W^1_2(\Omega)}ds \le A.$$

This completes the proof of Lemma 7.5. □

Lemma 7.6. *Assume that $d = 2$ and $\mu > 0$. Then there holds*

$$\|\bigtriangledown u\|_{L^6(Q_T)} \le A. \tag{7.139}$$

Proof. Applying the interpolation inequality (7.42) with $l = 0,\ p = d = 2,\ k = q = r = 1,\ \theta = 1$ and using the estimates (7.46) and (7.120), one obtains

$$\|u\|_{L^2(\Omega)} \le A_0\|u\|_{W^1_1(\Omega)}\|u\|_{L^1(\Omega)} \le A_0. \tag{7.140}$$

Combining (7.136) and (7.138), one also has

$$\int_0^T \int_\Omega |\bigtriangledown \triangle u|^2 dxdt \leq A. \tag{7.141}$$

Note the fact that

$$\|u\|_{H^3(\Omega)} \leq A_0\Big(\|\bigtriangledown \triangle u\|_{L^2(\Omega)} + \|u\|_{H^1(\Omega)}\Big) \quad \text{for } u \in H^3(\Omega) \text{ with } \frac{\partial u}{\partial \nu}\Big|_{\partial\Omega} = 0.$$

This, together with (7.120), (7.140) and (7.41), yields

$$\int_0^T \|u(t)\|^2_{H^3(\Omega)} \leq A. \tag{7.142}$$

Applying the interpolation inequality (7.42) with $l = 0,\ p = 6,\ k = q = r = d = 2,\ \theta = 1/3$ and using the estimate (7.120), one obtains

$$\|\bigtriangledown u\|_{L^6(\Omega)} \leq A_0 \|\bigtriangledown u\|^{1/3}_{H^2(\Omega)} \|\bigtriangledown u\|^{2/3}_{L^2(\Omega)} \leq A_0 \|u\|^{1/3}_{H^3(\Omega)}. \tag{7.143}$$

Combining (7.142) and (7.143), one finds

$$\int_0^T \|\bigtriangledown u(t)\|^6_{L^6(\Omega)} dt \leq A \int_0^T \|u(t)\|^2_{H^3(\Omega)} dt \leq A.$$

This completes the proof of Lemma 7.6. □

Lemma 7.7. *Assume that $d = 2$ and $\mu > 0$. Then there holds*

$$\|a\|_{L^2(\Omega)} \leq A. \tag{7.144}$$

Proof. Setting $s = 2$ in the inequality (7.50), one finds

$$\begin{aligned}\frac{d}{dt}\int_\Omega e^{\xi v} a^2 dx \leq & -2\int_\Omega |\bigtriangledown a|^2 dx + 2\mu e^\xi \int_\Omega a^2 dx \\ & + 2\delta\xi e^\xi \int_\Omega u a^2 dx + 2\chi e^\xi \int_\Omega a |\bigtriangledown a \cdot \bigtriangledown u| dx. \end{aligned} \tag{7.145}$$

We first estimate the integral $\int_\Omega ua^2dx$. Using the Young inequality and the elliptic L^p-theory as before, one has

$$\int_\Omega ua^2dx \le \frac{1}{3}\int_\Omega u^3dx + \frac{2}{3}\int_\Omega a^3dx \le A_0\int_\Omega a^3dx. \tag{7.146}$$

We now consider the integral $\int_\Omega a|\bigtriangledown a\cdot\bigtriangledown u|dx$ in (7.145). Applying the Young inequality (7.52), one finds

$$\begin{aligned}
&\int_\Omega a|\bigtriangledown a\cdot\bigtriangledown u|dx\\
&\le \epsilon\int_\Omega (a|\bigtriangledown a|)^{\frac{6}{5}}dx + A_0(\epsilon)\int_\Omega |\bigtriangledown u|^6dx\\
&\le \epsilon\int_\Omega |\bigtriangledown a|^{\frac{6}{5}\cdot\frac{5}{3}} + A_0(\epsilon)\int_\Omega a^{\frac{6}{5}\cdot\frac{5}{2}}dx + A_0(\epsilon)\int_\Omega |\bigtriangledown u|^6dx\\
&= \epsilon\int_\Omega |\bigtriangledown a|^2dx + A_0(\epsilon)\int_\Omega a^3dx + A_0(\epsilon)\int_\Omega |\bigtriangledown u|^6dx.
\end{aligned} \tag{7.147}$$

Inserting (7.146) and (7.147) into (7.145), taking ϵ sufficiently small, using $1 \le e^{\xi v} \le e^{\xi}$, and noting $\int_\Omega a^2dx \le A_0 + A_0\int_\Omega a^3dx$, one obtains

$$\frac{d}{dt}\int_\Omega e^{\xi v}a^2dx \le A_0 + A_0\int_\Omega a^3dx + A_0\int_\Omega |\bigtriangledown u|^6dx.$$

This, together with Lemmas 7.5 and 7.6, yields

$$\begin{aligned}
\int_\Omega e^{\xi v}a^2dx &\le \int_\Omega e^{\xi v_0(x)}a_0^2(x)dx + A_0T\\
&\quad + A_0\int_0^T\int_\Omega a^3dxdt + A_0\int_0^T\int_\Omega |\bigtriangledown u|^6dxdt\\
&\le A.
\end{aligned}$$

This completes the proof of Lemma 7.7. □

Lemma 7.8. *Assume that $d = 2$ and $\mu > 0$. Then there hold*

$$\|c\|_{L^4(Q_T)} \leq A, \tag{7.148}$$

$$\| \bigtriangledown u\|_{L^q(\Omega)} \leq A \quad \textit{for any } 1 < q < \infty. \tag{7.149}$$

Proof. Applying the interpolation inequality (7.42) with $l = 0,\ p = 4,\ q = r = d = 2$, $\theta = 1/2$ and using Lemma 7.7 and the estimate (7.1), one finds

$$\|c\|_{L^4(\Omega)} \leq A_0 \|c\|^{1/2}_{H^1(\Omega)} \|c\|^{1/2}_{L^2(\Omega)} \leq A\|c\|^{1/2}_{H^1(\Omega)}.$$

Hence, using the estimates (7.138) and (7.144), one obtains

$$\begin{aligned}\int_0^T \|c(t)\|^4_{L^4(\Omega)} dt &\leq A \int_0^t \|c(t)\|^2_{H^1(\Omega)} dt \\ &\leq A \int_0^T \| \bigtriangledown c(t)\|^2_{L^2(\Omega)} dt + A \int_0^T \|c(t)\|^2_{L^2(\Omega)} dt \\ &\leq A.\end{aligned}$$

So, the estimate (7.148) holds.

We now turn to prove the estimate (7.149). Note that Eq. (7.9) can be rewritten as follows:

$$-\bigtriangleup u + \beta u = \alpha c \in L^2(\Omega) \tag{7.150}$$

by Lemma 7.7. We conclude from (7.150), (7.11), and the standard elliptic L^p-theory [71] that $u \in W^2_2(\Omega)$. This, together with Sobolev imbedding theorem, yields the estimate (7.149). Hence, Lemma 7.8 is proved. □

Lemma 7.9. *Assume that $d = 2$ and $\mu > 0$. Then there holds*

$$\|a\|_{L^3(\Omega)} \leq A. \tag{7.151}$$

Proof. Setting $s = 3$ in the inequality (7.50), one finds

$$\frac{d}{dt}\int_\Omega e^{\xi v}a^3dx \le -\frac{8}{3}\int_\Omega |\bigtriangledown a^{3/2}|^2dx + 3\mu e^\xi\int_\Omega a^3dx$$
$$+3\xi\delta e^\xi\int_\Omega ua^3dx + 6\chi e^\xi\int_\Omega a^2|\bigtriangledown a\cdot\bigtriangledown u|dx. \quad (7.152)$$

We first estimate the integral $\int_\Omega ua^3dx$. Applying the Young inequality and using the the elliptic L^p-theory as before, one finds

$$\int_\Omega ua^3dx \le \frac{1}{4}\int_\Omega u^4dx + \frac{3}{4}\int_\Omega a^4dx \le A_0\int_\Omega a^4dx. \quad (7.153)$$

We now turn to the integral $\int_\Omega a^2|\bigtriangledown a\cdot\bigtriangledown u|dx$ in (7.152). Applying the Young inequality and using the estimate (7.149), one finds

$$\begin{aligned}\int_\Omega a^2|\bigtriangledown a\cdot\bigtriangledown u|dx &\le \epsilon\int_\Omega (a^2|\bigtriangledown a|)^{\frac{12}{11}}dx + A(\epsilon)\int_\Omega |\bigtriangledown u|^{12}dx\\ &\le \epsilon\int_\Omega (a^{\frac{3}{2}}\cdot a^{\frac{1}{2}}|\bigtriangledown a|)^{\frac{12}{11}}dx + A(\epsilon)\\ &\le \epsilon\int_\Omega (a^{\frac{1}{2}}|\bigtriangledown a|)^{\frac{12}{11}\cdot\frac{11}{6}}dx + A(\epsilon)\int_\Omega a^{\frac{3}{2}\cdot\frac{12}{11}\cdot\frac{11}{5}}dx + A(\epsilon)\\ &= \frac{4\epsilon}{9}\int_\Omega |\bigtriangledown a^{\frac{3}{2}}|^2dx + A(\epsilon)\int_\Omega a^{\frac{18}{5}}dx\\ &\le \epsilon\int_\Omega |\bigtriangledown a^{\frac{3}{2}}|^2dx + A(\epsilon)\int_\Omega a^4dx + A(\epsilon). \quad (7.154)\end{aligned}$$

Finally, inserting (7.153) and (7.154) into the inequality (7.152), noting $\int_\Omega a^3dx \le A_0 + A_0\int_\Omega a^4dx$, and taking ϵ sufficiently small, one obtains

$$\frac{d}{dt}\int_\Omega e^{\xi v}a^3dx \le A + \int_\Omega a^4dx.$$

Integrating with respect to t in both sides of above inequality and using the estimate (7.148), one finds

$$\int_\Omega e^{\xi v}a^3dx \le \int_\Omega e^{\xi v_0(x)}a_0^3(x)dx + \int_0^T\int_\Omega a^4dxdt \le A.$$

This completes the proof of Lemma 7.9. □

Remark 7.3. It is almost impossible to find an explicit bound from above in terms of μ, χ, and ξ in the estimate (7.151), since this bound is involved in all the bounds appeared in the estimates (7.104)-(7.149) and it concerns many complicated computations. However, the bound from above of $\|(c+1)\log(c+1)\|_{L^1(\Omega)}$ in (7.130) has already given us a good understanding of the above-mentioned dependency on the parameters μ, χ and ξ. Roughly speaking, the bound from above in the estimate (7.151) will probably be directly proportional to the following quantity: $(\chi+\xi)\mu^{-1}$. Therefore, we conclude that the assumption that $\mu > 0$ is central to our results of global existence in two dimensions.

Using the estimate (7.151) and proceeding as in the proof of Theorem 7.3 - 7.4 and Theorems 7.5 - 7.6, one has the following main results of this section.

Theorem 7.7. *Under the assumptions (7.2) and that $d = 2$ and $\mu > 0$, there exists a unique global solution*

$$(a,\ v,\ u) \in C^{2+\widetilde{\sigma},\ 1+\widetilde{\sigma}/2}(Q_T) \times C^{2+\widetilde{\sigma},\ 1+\widetilde{\sigma}/2}(Q_T) \times C^{2+\widetilde{\sigma},\ \widetilde{\sigma}/2}(Q_T) \quad (\widetilde{\sigma} := \frac{2}{3})$$

of the system (7.14)-(7.18) for any $T > 0$. Furthermore,

$$a \geq 0, \quad u \geq 0, \quad 0 \leq v \leq 1, \tag{7.155}$$

$$\|u\|_{L^\infty(Q_T)} \leq A_0, \quad \| \bigtriangledown u\|_{L^\infty(Q_T)} \leq A_0, \tag{7.156}$$

$$\|a\|_{L^\infty(Q_T)} \leq A_0 \|a_0\|_{L^\infty(\Omega)}. \tag{7.157}$$

8

Density-Dependent Chemotaxis-Haptotaxis Model of Cancer Invasion

8.1 Introduction

In Chapter 7, we reviewed a simplified version of the Chaplain and Lolas' model [30]. However, the original model is a 3×3 parabolic-ODE-parabolic chemotaxis-haptotaxis system. The global existence and uniqueness of classical solutions to this model has been proved for any $\mu \geq 0$ (where μ is the logistic growth rate of cancer cells) in one space dimension (see [149]), for any $\mu > 0$ in two space dimensions (see [151]) and for large μ in three space dimensions (see [149]). In addition to global existence and uniqueness, the uniform-in-time boundedness of solutions to a simplified 3×3 parabolic-ODE-elliptic chemotaxis-haptotaxis system has been proved for any $\mu > 0$ in two space dimensions and for large μ in three space dimensions (see [153]), which has been reviewed in last chapter. We should note that the global existence is still open for *small* $\mu > 0$ in three space dimensions for the parabolic-ODE-parabolic chemotaxis-haptotaxis system and the parabolic-ODE-elliptic chemotaxis-haptotaxis system. When $\mu = 0$, the solution of Chaplain and Lolas' model may blow up

in finite time (see [149, Section 6]). However, it is obvious that the blow-up of cancer cell density in a finite time is biologically irrelevant. Hence, we need to deal with the following problem, how can we reasonably modify the Chaplain and Lolas model [30] to obtain the global existence? This is the concern of the present chapter.

Recently, Tao and Cui [155] extended the Chaplain and Lolas' model to a new one with nonlinear density-dependent chemotaxis and haptotaxis, and studied the global existence and boundedness of solutions to this newly extended model.

This chapter will review the extended model and its mathematical analysis. This chapter is organized into five sections. Section 8.2 presents the mathematical model. Section 8.3 proves the local existence and uniqueness of solutions. Section 8.4 completes the proof of global existence. Finally, Section **??** shows the boundedness of solutions to a chemotaxis-haptotaxis model with volume-filling.

8.2 Mathematical Model

The mathematical model of cancer invasion is involved in the following three physical variables: cancer cell density $c(x,t)$, ECM density $v(x,t)$, and MDE concentration $u(x,t)$.

The migration of cancer cells is assumed to be governed by random motion, chemotaxis and haptotaxis. In the absence of any ECM, cancer cell

proliferation is assumed to be typically logistic. The presence of ECM leads to competition for space between the cancer cells and the ECM. Hence, the equation describing the evolution of cancer cell density reads (see [30])

$$\frac{\partial c}{\partial t} = \underbrace{D_c \triangle c}_{\text{random motion}} - \underbrace{\bigtriangledown \cdot (V_1(c) \bigtriangledown u)}_{\text{chemotaxis}} - \underbrace{\bigtriangledown \cdot (V_2(c) \bigtriangledown v)}_{\text{haptotaxis}} + \underbrace{\mu c(1-c-v)}_{\text{proliferation}}, \quad (8.1)$$

where D_c is the random diffusion coefficient, $V_1(c)$ and $V_2(c)$ are the density-dependent chemotactic and haptotactic sensitivity functions, respectively, and μ is the logistic proliferation rate of the cells.

Since ECM is "static,"we neglect any diffusion and focus solely on its degradation by MDEs upon contact; for simplicity, we assume that no remodeling of the ECM takes palce. Hence, the equation modeling the proteolysis of ECM is therefore given by (see [30])

$$\frac{\partial v}{\partial t} = - \underbrace{\delta u v}_{\text{proteolysis}}, \quad (8.2)$$

where $\delta > 0$ is a rate parameter of degradation.

MDE is produced by cancer cells, diffuses throughout ECM, and undergoes decay through simple degradation. Hence, the equation for MDE concentration is (see [30])

$$\frac{\partial u}{\partial t} = \underbrace{D_u \triangle u}_{\text{diffusion}} + \underbrace{\alpha c}_{\text{production}} - \underbrace{\beta u}_{\text{decay}}, \quad (8.3)$$

where D_u, α and β are assumed to be positive constants.

Throughout this paper we will assume that

$$V_i(c) \in C^1([0,+\infty)),\ V_i(c) \geq 0,\ V_i(0) = 0, \text{ and } V_i'(c) \text{ is Lipschitz continuous,} \quad (8.4)$$

where $i = 1, 2$. Here we should note that it is necessary for the global existence of C^2-smooth solutions of Eqs. (8.1)-(8.3) to assume that $V_1'(c)$ and $V_2'(c)$ are Lipschitz continuous (see [156]).

In Chaplain and Lolas' original model [30], it is assumed that $V_1(c) = \chi c$ and $V_2(c) = \xi c$ ($\chi,\ \xi > 0$ are some constants). For this choice of $V_1(c)$ and $V_2(c)$, although the assumption (8.4) is satisfied, the solution of the model may blow up in finite time as afore-mentioned. However, the blow-up of cancer density in finite time is biologically irrelevant. Hence, we would like to slightly modify the choice of $V_1(c)$ and $V_2(c)$ such that the modified model has a unique global solution, which excludes the possibility of a blow-up in finite time. To this end, in addition to the assumption (8.4), we will assume that

$$V_1(c) \text{ and } V_2(c) \text{ are bounded for any } c \geq 0. \tag{8.5}$$

For example, we may take $V_1(c) = \frac{\chi c}{1+\varepsilon_1 c}$ and $V_2(c) = \frac{\xi c}{1+\varepsilon_2 c}$ ($\varepsilon_1, \varepsilon_2 > 0$ are small constants; see [81], for instance). Clearly $V_1(c) \to \chi c$ as $\varepsilon_1 \to 0$ and $V_2(c) \to \xi c$ as $\varepsilon_2 \to 0$. For this choice of $V_1(c)$ and $V_2(c)$, the assumptions (8.4) and (8.5) are both satisfied. Another choice of $V_1(c)$ and $V_2(c)$ satisfying (8.5) is that $V_1(c) \equiv 0$ and $V_2(c) \equiv 0$ for $c \geq c_m$, which has a clear biologically relevant interpretation: the cancer cells stop to accumulate at a given point of the tumor tissue after their density attains a maximal density c_m. A similar assumption for a prey-taxis sensitivity function was made in [2].

However, for typical volume-filling chemotactic-haptotactic functions $V_1(c) = \chi c(1 - c/\gamma)$ and $V_2(c) = \xi c(1 - c/\gamma)$ ($\gamma \geq 1$ denotes the maximal cell density;

see [81]), the assumption (8.5) is not satisfied. However, these specific forms of $V_1(c)$ and $V_2(c)$ will be in favor of the proofs of global existence and boundedness of solutions to the model (see Section **??** below).

The Eqs. (8.1)-(8.3) are considered on some bounded domain $\Omega \subset \mathcal{R}^3$ with boundary $\partial\Omega$. To close the system of equations, we need to impose boundary and initial conditions.

Boundary conditions: Guided by the in vitro experimental protocol in which invasion takes place within an isolated system [124], we assume that there is no-flux of cancer cells or MDEs across the boundary of the domain

$$-D_c\frac{\partial c}{\partial \nu} + V_1(c)\frac{\partial u}{\partial \nu} + V_2(c)\frac{\partial v}{\partial \nu} = 0 \quad \text{on } \partial\Omega \times (0,\infty), \tag{8.6}$$

$$\frac{\partial u}{\partial \nu} = 0 \quad \text{on } \partial\Omega \times (0,\infty), \tag{8.7}$$

where ν is the outward normal vector to $\partial\Omega$.

Initial conditions: We prescribe the initial data

$$c(x,0) = c_0(x), \quad v(x,0) = v_0(x), \quad u(x,0) = u_0(x), \quad x \in \Omega. \tag{8.8}$$

For any $0 < T < \infty$ we set

$$\Omega_T = \Omega \times \{0 < t < T\}, \qquad \partial\Omega_T = \partial\Omega \times \{0 < t < T\}.$$

To simplify the formulae, throughout this chapter we suppose that

$$D_c = \delta = D_u = \alpha = \beta = 1. \tag{8.9}$$

However, we will keep the key model parameter μ, since our result on global existence will depend on the presence of logistic damping.

Throughout this chapter we assume that

$$\begin{cases} c_0(x) \geq 0, \quad 0 \leq v_0(x) \leq 1, \quad u_0(x) \geq 0, \\ \partial\Omega \in C^{2+\sigma}, \quad 0 < \sigma < 1, \\ c_0(x),\ v_0(x),\ u_0(x) \in C^{2+\sigma}(\overline{\Omega}), \\ \frac{\partial c_0(x)}{\partial \nu} = \frac{\partial v_0(x)}{\partial \nu} = \frac{\partial u_0(x)}{\partial \nu} = 0 \quad \text{on } \partial\Omega. \end{cases} \tag{8.10}$$

Note that Eq. (8.2) can be rewritten as

$$v = v_0(x) e^{-\int_0^t u(x,s)ds}$$

and therefore

$$\bigtriangledown v = e^{-\int_0^t u(x,s)ds} \bigtriangledown v_0 - v_0(x) e^{-\int_0^t u(x,s)ds} \int_0^t \bigtriangledown u \, ds.$$

This, along with (8.7) and $\frac{\partial v_0(x)}{\partial \nu} = 0$ on $\partial\Omega$ in (8.10), yields

$$\frac{\partial v}{\partial \nu} = 0 \qquad \text{on } \partial\Omega_T. \tag{8.11}$$

We then conclude from (8.6), (8.7), and (8.11) that

$$\frac{\partial c}{\partial \nu} = 0 \qquad \text{on } \partial\Omega_T. \tag{8.12}$$

8.3 Local Existence and Uniqueness

Using the assumptions (8.9) and the boundary conditions (8.11) and (8.12), the problem (8.1)-(8.3) and (8.6)-(8.2) takes the following form:

$$c_t = \triangle c - \bigtriangledown \cdot (V_1(c) \bigtriangledown u) - \bigtriangledown \cdot (V_2(c) \bigtriangledown v) + \mu c(1 - c - v) \quad \text{in } \Omega_T, \tag{8.13}$$

$$v_t = -uv \quad \text{in } \Omega_T, \tag{8.14}$$

$$u_t = \triangle u + c - u \quad \text{in } \Omega_T, \tag{8.15}$$

$$\frac{\partial c}{\partial \nu} = \frac{\partial v}{\partial \nu} = \frac{\partial u}{\partial \nu} = 0 \quad \text{on } \partial\Omega_T, \tag{8.16}$$

$$c(x,0) = c_0(x),\ v(x,0) = v_0(x),\ u(x,0) = u_0(x) \quad \text{in } \Omega. \tag{8.17}$$

For notational convenience, in what follows we denote various constants which are independent of T by A_0, whereas we denote various constants which depend on T by A.

In the following, under the assumptions (8.4) and (8.10), we shall prove that the system (8.13)-(8.17) has a unique local (in time) smooth solution for any $\mu \geq 0$.

Theorem 8.1. *For any $\mu \geq 0$, under the assumptions (8.4) and (8.10), there exists a unique solution $(c,\ v,\ u) \in \left(C^{2+\sigma,\ 1+\sigma/2}(\Omega_T)\right)^3$ of the system (8.13)-(8.17) for some small $T > 0$ which depends on $\| (c_0(x),\ v_0(x),\ u_0(x)) \|_{C^{2+\sigma}(\overline{\Omega})}$.*

Proof. We shall prove the local existence by a fixed point argument. We introduce the Banach space X of function c with norm

$$\|c\|_X = \|c\|_{C^{1+\sigma,\sigma/2}(\bar{\Omega}_T)} \qquad (0 < T < 1)$$

and a subset

$$X_M = \Big\{ c \in X :\ \|c\|_{C^{1+\sigma,\sigma/2}(\bar{\Omega}_T)} \leq M \Big\},$$

where

$$M := \| c_0(x) \|_{C^{2+\sigma}(\overline{\Omega})} + \| v_0(x) \|_{C^{2+\sigma}(\overline{\Omega})} + \| u_0(x) \|_{C^{2+\sigma}(\overline{\Omega})} + 1.$$

Given any $c \in X_M$, we define a corresponding function $\tilde{c} = Fc$, where $\tilde{c}$, together with u and v, satisfies the following system:

$$u_t - \triangle u + u = c \qquad \text{in } \Omega_T, \tag{8.18}$$

$$\frac{\partial u}{\partial \nu} = 0 \qquad \text{on } \partial\Omega_T, \tag{8.19}$$

$$u(x,0) = u_0(x) \qquad \text{in } \Omega, \tag{8.20}$$

$$v = v_0(x) e^{-\int_0^t u(x,s)ds} \qquad \text{in } \Omega_T, \tag{8.21}$$

$$\tilde{c}_t - \triangle \tilde{c} - \mu(1 - c - v)\tilde{c} = f(c,u,v) \qquad \text{in } \Omega_T, \tag{8.22}$$

$$\frac{\partial \tilde{c}}{\partial \nu} = 0 \qquad \text{on } \partial\Omega_T, \tag{8.23}$$

$$\tilde{c}(x,0) = c_0(x) \qquad \text{in } \Omega. \tag{8.24}$$

where

$$\begin{aligned} f(c,u,v) :&= - \bigtriangledown \cdot (V_1(c) \bigtriangledown u) - \bigtriangledown \cdot (V_2(c) \bigtriangledown v) \\ &= -V_1(c) \triangle u - V_2(c) \triangle v \\ &\quad -(V_1'(c) \bigtriangledown u + V_2'(c) \bigtriangledown v) \cdot \bigtriangledown c. \end{aligned} \tag{8.25}$$

We first consider the linear parabolic problem (8.18)-(8.20). By $c \in X_M, 0 < T < 1$, (8.10), the maximum principle, and the Schauder theory (see [108], for instance), the problem (8.18)-(8.20) has a unique solution u satisfying

$$\begin{aligned}\|u\|_{C^{2+\sigma,1+\sigma/2}(\bar{\Omega}_T)} &\le A_0\Big(\|u\|_{C^0(\bar{\Omega}_T)} + \|u_0\|_{C^{2+\sigma}(\bar{\Omega})} + \|c\|_{C^{\sigma,\sigma/2}(\bar{\Omega}_T)}\Big)\\ &\le A_0\Big(\|u_0\|_{C^0(\bar{\Omega})} + A_0T\|c\|_{C^0(\bar{\Omega}_T)}\\ &\qquad +\|u_0\|_{C^{2+\sigma}(\bar{\Omega})} + \|c\|_{C^{\sigma,\sigma/2}(\bar{\Omega}_T)}\Big)\\ &\le A_0M. \end{aligned} \tag{8.26}$$

We easily derive from (8.21) that

$$\bigtriangledown v = e^{-\int_0^t u(x,s)ds} \bigtriangledown v_0 - v_0(x)e^{-\int_0^t u(x,s)ds}\int_0^t \bigtriangledown u\, ds, \tag{8.27}$$

$$\begin{aligned}\triangle v = {} & e^{-\int_0^t u(x,s)ds} \triangle v_0\\ & -2e^{-\int_0^t u(x,s)ds}\int_0^t \bigtriangledown u\cdot\bigtriangledown v_0 ds + v_0(x)e^{-\int_0^t u(x,s)ds}\Big(\int_0^t \bigtriangledown u ds\Big)^2\\ & -v_0(x)e^{-\int_0^t u(x,s)ds}\int_0^t \triangle u\, ds. \end{aligned} \tag{8.28}$$

Using $v_0(x) \in C^{2+\sigma}(\overline{\Omega})$, (8.26), and $0 < T < 1$, we obtain from (8.21), (8.27), and (8.28) that

$$\|v\|_{C^{2+\sigma,1+\sigma/2}(\bar{\Omega}_T)} \le A_0M. \tag{8.29}$$

We now turn to the linear parabolic problem (8.22)-(8.24). Using $c \in X_M$, (8.25), (8.26), and (8.29) and noting $V_1'(c)$ and $V_2'(c)$ are Lipschitz continuous, we have

$$\|f\|_{C^{\sigma,\sigma/2}(\bar{\Omega}_T)} \le A_0M, \tag{8.30}$$

$$\|1 - c - v\|_{C^{\sigma,\sigma/2}(\bar{\Omega}_T)} \le A_0M. \tag{8.31}$$

Hence, by $0 < T < 1$ and the parabolic Schauder theory as before, the problem (8.22)-(8.24) admits a unique solution $\tilde{c}$ satisfying

$$\|\tilde{c}\|_{C^{2+\sigma,1+\sigma/2}(\bar{\Omega}_T)} \le A_0\Big(\|c_0\|_{C^{2+\sigma}(\bar{\Omega})} + \|f\|_{C^{\sigma,\sigma/2}(\bar{\Omega}_T)}\Big)$$
$$\le A_0 M. \tag{8.32}$$

By direct calculations, we find that for any function $\tilde{c}$,

$$\|\tilde{c}(x,t) - \tilde{c}(x,0)\|_{C^{1+\sigma,\sigma/2}(\bar{\Omega}_T)} \le A_0 \max(T^{\sigma/2}, T^{1/2})\|\tilde{c}\|_{C^{2+\sigma,1+\sigma/2}(\bar{\Omega}_T)}.$$

If we further take $T = T(M)$ sufficiently small, then by (8.32)

$$\|\tilde{c}(x,t)\|_{C^{1+\sigma,\sigma/2}(\bar{\Omega}_T)} \le \|\tilde{c}(x,0)\|_{C^{1+\sigma}(\bar{\Omega})} + A_0 \max(T^{\sigma/2}, T^{1/2})M$$
$$\le \|\tilde{c}(x,0)\|_{C^{1+\sigma}(\bar{\Omega})} + 1$$
$$\le M.$$

Hence, $\tilde{c} \in X_M$, i.e. F maps X_M into itself.

We are now in a position to show that F is contractive. Take c_1, c_2 in X_M and set $\tilde{c}_1 \equiv Fc_1, \tilde{c}_2 \equiv Fc_2$. We derive from (8.18)-(8.20) that

$$\partial_t(u_1 - u_2) - \triangle(u_1 - u_2) + (u_1 - u_2) = c_1 - c_2 \qquad \text{in } \Omega_T, \tag{8.33}$$
$$\frac{\partial(u_1 - u_2)}{\partial \nu} = 0 \qquad \text{on } \partial\Omega_T, \tag{8.34}$$
$$(u_1 - u_2)(x,0) = 0 \qquad \text{in } \Omega. \tag{8.35}$$

Proceeding as in the proof of (8.26), we have

$$\|u_1 - u_2\|_{C^{2+\sigma,1+\sigma/2}(\bar{\Omega}_T)} \le A_0\|c_1 - c_2\|_{C^{\sigma,\sigma/2}(\bar{\Omega}_T)}. \tag{8.36}$$

This, along with (8.21), (8.27), (8.28), and $0 < T < 1$, yields

$$\|v_1 - v_2\|_{C^{2+\sigma,1+\sigma/2}(\bar{\Omega}_T)} \le A_0\|u_1 - u_2\|_{C^{2+\sigma,1+\sigma/2}(\bar{\Omega}_T)} \le A_0\|c_1 - c_2\|_{C^{\sigma,\sigma/2}(\bar{\Omega}_T)}. \tag{8.37}$$

Next, we derive from (8.22)-(8.25) that

$$\partial_t(\tilde{c}_1-\tilde{c}_2)-\triangle(\tilde{c}_1-\tilde{c}_2)-\mu(1-c_1-v_1)(\tilde{c}_1-\tilde{c}_2)=h \quad \text{in } \Omega_T, \tag{8.38}$$

$$\frac{\partial(\tilde{c}_1-\tilde{c}_2)}{\partial\nu}=0 \quad \text{on } \partial\Omega_T, \tag{8.39}$$

$$(\tilde{c}_1-\tilde{c}_2)(x,0)=0 \quad \text{in } \Omega, \tag{8.40}$$

where

$$\begin{aligned} h:=&-\mu\tilde{c}_2[(c_1-c_2)+(v_1-v_2)]\\ &-V_1(c_1)\triangle(u_1-u_2)+\big(V_1(c_2)-V_1(c_1)\big)\triangle u_2\\ &-V_2(c_1)\triangle(v_1-v_2)+\big(V_2(c_2)-V_2(c_1)\big)\triangle v_2\\ &-V_1'(c_1)\bigtriangledown c_1\cdot\bigtriangledown(u_1-u_2)+\big(V_1'(c_2)\bigtriangledown c_2-V_1'(c_1)\bigtriangledown c_1\big)\cdot\bigtriangledown u_2\\ &-V_2'(c_1)\bigtriangledown c_1\cdot\bigtriangledown(v_1-v_2)+\big(V_2'(c_2)\bigtriangledown c_2-V_1'(c_1)\bigtriangledown c_1\big)\cdot\bigtriangledown v_2. \end{aligned}$$

Noting $V_1'(c)$ and $V_2'(c)$ are Lipschitz continuous and using (8.4), (8.26), (8.29), (8.32), (8.36), and (8.37), we find that

$$\begin{aligned} &\|h\|_{C^{\sigma,\sigma/2}(\bar{\Omega}_T)}\\ &\le A_0\Big(\|c_1-c_2\|_{C^{\sigma,\sigma/2}(\bar{\Omega}_T)}+\|u_1-u_2\|_{C^{2+\sigma,1+\sigma/2}(\bar{\Omega}_T)}+\|v_1-v_2\|_{C^{2+\sigma,1+\sigma/2}(\bar{\Omega}_T)}\Big)\\ &\le A_0\|c_1-c_2\|_{C^{\sigma,\sigma/2}(\bar{\Omega}_T)}. \end{aligned} \tag{8.41}$$

This, along with (8.38)-(8.40) and the parabolic Schauder theory, yields

$$\|\tilde{c}_1-\tilde{c}_2\|_{C^{2+\sigma,1+\sigma/2}(\bar{\Omega}_T)}\le A_0\|c_1-c_2\|_{C^{\sigma,\sigma/2}(\bar{\Omega}_T)}. \tag{8.42}$$

Noting $(\tilde{c}_1-\tilde{c}_2)(x,0)\equiv 0$ and proceeding as before, we have

$$\begin{aligned}\|\tilde{c}_1-\tilde{c}_2\|_{C^{1+\sigma,\sigma/2}(\bar{\Omega}_T)} &\equiv \|(\tilde{c}_1-\tilde{c}_2)(x,t)-(\tilde{c}_1-\tilde{c}_2)(x,0)\|_{C^{1+\sigma,\sigma/2}(\bar{\Omega}_T)}\\ &\le A_0\max(T^{\sigma/2},T^{1/2})\|\tilde{c}_1-\tilde{c}_2\|_{C^{2+\sigma,1+\sigma/2}(\bar{\Omega}_T)}\\ &\le A_0\max(T^{\sigma/2},T^{1/2})\|c_1-c_2\|_{C^{\sigma,\sigma/2}(\bar{\Omega}_T)}. \qquad (8.43)\end{aligned}$$

Finally, taking T sufficiently small such that

$$A_0\max(T^{\sigma/2},T^{1/2})\le 1/2,$$

we conclude from (8.43) that F is contractive in X_M. By the contraction mapping theorem, F has a unique fixed point c in X_M. This completes the proof of Theorem 8.1. □

8.4 A Priori Estimates and Global Existence

To continue the local solution in Theorem 8.1 to all $t > 0$, we need to establish some *a priori* estimates. Throughout this section, in addition to the assumptions (8.4) and (8.10), we assume that the assumption (8.5) holds.

Noting $V_1(0)=V_2(0)=0,\ c_0(x)\ge 0,\ 0\le v_0(x)\le 1$, and $u_0(x)\ge 0$, and using the maximum principle, we easily prove the following lemma.

Lemma 8.1. *Assume that $(c,v,u)\in C^{2,1}(\Omega_T)$ is a solution to (8.13)-(8.17), then there holds*

$$c\ge 0,\quad 0\le v\le 1,\quad u\ge 0. \qquad (8.44)$$

Lemma 8.2. *Assume that $(c,v,u)\in C^{2,1}(\Omega_T)$ is a solution to (8.13)-(8.17) and that*

$$\mu > 0, \tag{8.45}$$

then there hold

$$\|c\|_{L^1(\Omega)} \le A_0, \tag{8.46}$$

$$\|u\|_{L^1(\Omega)} \le A_0, \tag{8.47}$$

$$\| \bigtriangledown u\|_{L^2(\Omega)} \le A_0, \tag{8.48}$$

$$\| \bigtriangledown v\|_{L^2(\Omega)} \le A. \tag{8.49}$$

Proof. Integrating Eqs. (8.13) and (8.11) over Ω and proceeding as in the proof of Lemma 7.2 in Chapter 7, we easily prove the estimates (8.46) and (8.47).

We next turn to prove the estimate (8.48). Integrating Eq. (8.13) over Ω and using (8.16) and (8.44), we have

$$\frac{d}{dt}\|c\|_{L^1(\Omega)} \le \mu\|c\|_{L^1(\Omega)} - \mu\int_\Omega c^2 dx. \tag{8.50}$$

Multiplying Eq. (8.11) by $-\bigtriangleup u$ and integrating over Ω, we find that

$$\begin{aligned}&\frac{1}{2}\frac{d}{dt}\int_\Omega |\bigtriangledown u|^2 dx + \int_\Omega |\bigtriangleup u|^2 dx + \int_\Omega |\bigtriangledown u|^2 dx\\ &= -\int_\Omega c\bigtriangleup u dx \le \frac{1}{4}\int_\Omega c^2 dx + \int_\Omega |\bigtriangleup u|^2 dx.\end{aligned}$$

So,

$$\frac{1}{2}\frac{d}{dt}\int_\Omega |\bigtriangledown u|^2 dx + \int_\Omega |\bigtriangledown u|^2 dx \le \frac{1}{4}\int_\Omega c^2 dx.$$

Combining this with (8.50), we get

$$\begin{aligned}&\frac{d}{dt}\Big(\frac{1}{2}\int_\Omega |\bigtriangledown u|^2 dx + \frac{1}{4\mu}\int_\Omega c\, dx\Big) + 2\Big(\frac{1}{2}\int_\Omega |\bigtriangledown u|^2 dx + \frac{1}{4\mu}\int_\Omega c\, dx\Big)\\ &\le \Big(\frac{1}{4} + \frac{1}{2\mu}\Big)\|c\|_{L^1(\Omega)}.\end{aligned}$$

This, along with Gronwall's lemma and the estimate (8.46), yields

$$\frac{1}{2}\int_\Omega |\bigtriangledown u|^2 dx + \frac{1}{4\mu}\int_\Omega c\, dx \le A_0.$$

Hence, the estimate (8.48) holds.

Finally, we prove the estimate (8.49). We derive from (8.10), (8.27), (8.48), $u \ge 0$ and Hölder's inequality that

$$\int_\Omega |\bigtriangledown v|^2 dx \le A_0 + A_0 T\int_0^T\int_\Omega |\bigtriangledown u|^2 dxds \le A.$$

This completes the proof of Lemma 8.2. □

Lemma 8.3. *Assume that $(c, v, u) \in C^{2,1}(\Omega_T)$ is a solution to (8.13)-(8.17) and that the assumption (8.45) holds, then there hold*

$$\|c\|_{L^2(\Omega)} \le A. \tag{8.51}$$

Proof. For any $s \ge 2$, we derive from (8.13), (8.16), (8.44), and the assumption (8.5) that

$$\begin{aligned}
\frac{d}{dt}\int_\Omega c^s dx &= s\int_\Omega c^{s-1}c_t dx \\
&= s\int_\Omega c^{s-1}\big[\triangle c - \bigtriangledown\cdot(V_1(c)\bigtriangledown u) - \bigtriangledown\cdot(V_2(c)\bigtriangledown v) + \mu c(1-c-v)\big]dx \\
&\le -\frac{4(s-1)}{s}\int_\Omega \big|\bigtriangledown c^{s/2}\big|^2 dx + \mu s\int_\Omega c^s dx \\
&\quad + A_0 s(s-1)\int_\Omega c^{s-2}\big(|\bigtriangledown c|\cdot|\bigtriangledown u| + |\bigtriangledown c|\cdot|\bigtriangledown v|\big)dx.
\end{aligned} \tag{8.52}$$

Taking $s = 2$ in (8.52) and using Cauchy's inequality and the estimates (8.48) and (8.49), we obtain

$$\begin{aligned}\frac{d}{dt}\int_\Omega c^2dx &\le -2\int_\Omega \big|\bigtriangledown c\big|^2dx + 2\mu\int_\Omega c^2dx\\ &\quad +A_0\int_\Omega \big(|\bigtriangledown c|\cdot|\bigtriangledown u| + |\bigtriangledown c|\cdot|\bigtriangledown v|\big)dx\\ &\le -2\int_\Omega \big|\bigtriangledown c\big|^2dx + 2\mu\int_\Omega c^2dx\\ &\quad +2\varepsilon\int_\Omega |\bigtriangledown c|^2dx + A_0(\varepsilon)\int_\Omega \big(|\bigtriangledown u|^2 + |\bigtriangledown v|^2\big)dx\\ &\le A + 2\mu\int_\Omega c^2dx.\end{aligned}$$

This, together with Gronwall's lemma, yields the estimate (8.51). □

Up to now we have had the $L^2(\Omega)$-estimate. To raise the a priori estimate to $L^s(\Omega)$-estimate ($s > 3$), we need the following lemma [104, Lemma 1], which is an extension of Lemma 4.1 in [86].

Lemma 8.4. *Consider the following linear parabolic problem*

$$u_t - \triangle u + u = c \qquad \text{in } \Omega_T, \tag{8.53}$$

$$\frac{\partial u}{\partial \nu} = 0 \qquad \text{on } \partial\Omega_T, \tag{8.54}$$

$$u(x,0) = u_0(x) \qquad \text{in } \Omega. \tag{8.55}$$

Assume that $u_0 \in W^1_\infty(\Omega)$ and that (u,c) satisfies (8.53)-(8.55). Moreover,

$$\| c \|_{L^\rho(\Omega)} \le A_0$$

for all $t \in (0,T)$. Then for every $1 \le \rho < d$ (where $d :=$ the space dimension) we have

$$\| u(t) \|_{W^1_q(\Omega)} \le A_0(q), \tag{8.56}$$

where

$$q < \frac{d\rho}{d-\rho}. \tag{8.57}$$

If $\rho = d$, then (8.56) is true with every $q < +\infty$ and if $\rho > d$, then (8.56) is true with $q = +\infty$.

Lemma 8.5. *Assume that $(c, v, u) \in C^{2,1}(\Omega_T)$ is a solution to (8.13)-(8.17) and that the assumption (8.45) holds, then there holds*

$$\|c\|_{L^4(\Omega)} \leq A. \tag{8.58}$$

Proof. Going back to (8.52) and taking $s = 4$, we have

$$\begin{aligned}\frac{d}{dt}\int_\Omega c^4 dx \leq -3\int_\Omega \big|\bigtriangledown c^2\big|^2 dx + 4\mu\int_\Omega c^4 dx \\ + A_0\int_\Omega c^2\big(|\bigtriangledown c|\cdot|\bigtriangledown u| + |\bigtriangledown c|\cdot|\bigtriangledown v|\big)dx.\end{aligned} \tag{8.59}$$

By the estimate (8.51) and Lemma 8.4, we have

$$\| u(t) \|_{W^1_q(\Omega)} \leq A \qquad \text{for any } 1 < q < 6;$$

in particular,

$$\| \bigtriangledown u(t) \|_{L^5(\Omega)} \leq A. \tag{8.60}$$

This, along with (8.27) and Hölder's inequality, yields

$$\int_\Omega |\bigtriangledown v|^5 dx \leq A_0 + A_0 T^4 \int_0^T \int_\Omega |\bigtriangledown u|^5 dxdt \leq A. \tag{8.61}$$

By Young's inequality and the estimate (8.60), we have that for any sufficiently small $\varepsilon > 0$,

$$
\begin{aligned}
&\int_\Omega c^2|\bigtriangledown c|\cdot|\bigtriangledown u|dx\\
&\le \varepsilon\int_\Omega c^2|\bigtriangledown c|^2dx + A_0(\varepsilon)\int_\Omega c^2|\bigtriangledown u|^2dx\\
&\le \frac{\varepsilon}{4}\int_\Omega |\bigtriangledown c^2|^2dx + A_0(\varepsilon)\int_\Omega \left(c^2\right)^{\frac{5}{3}}dx + A_0(\varepsilon)\int_\Omega \left(|\bigtriangledown u|^2\right)^{\frac{5}{2}}dx\\
&\le \frac{\varepsilon}{4}\int_\Omega |\bigtriangledown c^2|^2dx + A_0(\varepsilon)\int_\Omega c^{\frac{10}{3}}dx + A(\varepsilon)\\
&\le \frac{\varepsilon}{4}\int_\Omega |\bigtriangledown c^2|^2dx + A_0(\varepsilon)\int_\Omega c^4dx + A(\varepsilon). \qquad (8.62)
\end{aligned}
$$

Similarly,

$$
\int_\Omega c^2|\bigtriangledown c|\cdot|\bigtriangledown v|dx \le \frac{\varepsilon}{4}\int_\Omega |\bigtriangledown c^2|^2dx + A_0(\varepsilon)\int_\Omega c^4dx + A(\varepsilon). \qquad (8.63)
$$

Inserting (8.62) and (8.63) into (8.59) and taking ε sufficiently small, we get

$$
\frac{d}{dt}\int_\Omega c^4dx \le A_0\int_\Omega c^4dx + A.
$$

This, together with Gronwall's lemma, yields the estimate (**??**). □

Lemma 8.6. *Assume that $(c, v, u) \in C^{2,1}(\Omega_T)$ is a solution to (8.13)-(8.17) and that the assumption (8.45) holds, then there hold*

$$
\|u\|_{W^1_\infty(\Omega)} \le A, \qquad (8.64)
$$

$$
\|\bigtriangledown v\|_{L^\infty(\Omega)} \le A, \qquad (8.65)
$$

$$
\|c\|_{L^p(\Omega)} \le A \qquad \text{for any } p > 5. \qquad (8.66)
$$

Proof. By the estimate (**??**) and Lemma 8.4, we find that the estimate (8.64) holds. This, along with (8.27), yields the estimate (8.65).

We now turn to prove the estimate (8.66). Going back to (8.52), taking $s = p > 5$ and using (8.64), (8.65), and Young's inequality, we have

$$\begin{aligned}\frac{d}{dt}\int_\Omega c^p dx &\le -\frac{4(p-1)}{p}\int_\Omega \left|\bigtriangledown c^{p/2}\right|^2 dx + p\mu\int_\Omega c^p dx\\ &\quad + A(p)\int_\Omega c^{p-2}|\bigtriangledown c|dx\\ &\le -\frac{4(p-1)}{p}\int_\Omega \left|\bigtriangledown c^{p/2}\right|^2 dx + p\mu\int_\Omega c^p dx\\ &\quad + \varepsilon\int_\Omega \left|\bigtriangledown c^{p/2}\right|^2 dx + A(p,\varepsilon)\int_\Omega c^{p-2}dx\\ &\le A\int_\Omega c^p dx + A.\end{aligned}$$

So,

$$\frac{d}{dt}\int_\Omega c^p dx \le A\int_\Omega c^p dx + A.$$

This, along with Gronwall's lemma, yields the estimate (8.66). □

Lemma 8.7. *Assume that $(c, v, u) \in C^{2,1}(\Omega_T)$ is a solution to (8.13)-(8.17) and that the assumption (8.45) holds, then, for any $p > 5$ there hold*

$$\|u\|_{W_p^{2,1}(\Omega_T)} \le A, \tag{8.67}$$

$$\|\bigtriangleup v\|_{L^p(\Omega)} \le A. \tag{8.68}$$

Proof. By (8.53)-(8.55), (8.66), and the parabolic L^p-theory, we get the estimate (8.67).

By (8.28), (8.44), (8.64), (8.67), and Hölder's inequality, we have

$$\int_\Omega |\bigtriangleup v|^p dx \le A + A_0 T^{p-1}\int_0^T\int_\Omega |\bigtriangleup u|^p dxdt \le A.$$

So, the estimate (8.68) holds. □

In the following we will establish a priori $W_p^{2,1}(\Omega_T)$-estimate on c. We derive from (8.13), (8.16), and (8.17) that

$$c_t - \triangle c + \mathbf{b} \cdot \bigtriangledown c = g \qquad \text{in } \Omega_T, \tag{8.69}$$

$$\frac{\partial c}{\partial \nu} = 0 \qquad \text{on } \partial\Omega_T, \tag{8.70}$$

$$c(x,0) = c_0(x) \qquad \text{in } \Omega, \tag{8.71}$$

where

$$\mathbf{b} := V_1'(c) \bigtriangledown u + V_2'(c) \bigtriangledown v, \tag{8.72}$$

$$g := \mu c(1 - c - v) - V_1(c) \triangle u - V_2(c) \triangle v. \tag{8.73}$$

To apply the L^p-theory to the problem (8.69)-(8.71), we need to prove $\|\mathbf{b}\|_{L^\infty(\Omega)} \le A$. To this end, by (8.64) and (8.65), we need only $\|V_1'(c)\|_{L^\infty(\Omega)} \le A$ and $\|V_2'(c)\|_{L^\infty(\Omega)} \le A$, which in turn need to prove $\|c\|_{L^\infty(\Omega)} \le A$.

In Chapter 7 we used the iterative technique of Alikakos [4] to establish the uniform-in-time boundedness of solutions. However, in the present chapter we cannot get the unifrom-in-time boundedness of c since the $L^2(\Omega)$-bound of $\bigtriangledown v$ depends on the time T (see (8.49)). Unlike Chapter 7, this chapter will employ Horstmann and Winkler's method (see [48, 86]), along with the estimates (8.64)-(8.66) and the assumption (8.5), to establish a $L^\infty(\Omega)$-bound of c, which depends on the time T.

Let $p > 1$ and define

$$B := - \triangle + I$$

with domain

$$D(B) := \Big\{ c \in W_p^2(\Omega) : \ \frac{\partial c}{\partial \nu} = 0 \quad \text{on } \partial\Omega \Big\}.$$

For each $\eta \geq 0$, define the sectorial operator B^η (see [78]) and

$$X_\eta := D(B^\eta) \text{ with the norm } \|c\|_{X_\eta} := \|B^\eta c\|_{L^p(\Omega)}.$$

Lemma 8.8. *Assume that $(c, v, u) \in C^{2,1}(\Omega_T)$ is a solution to (8.13)-(8.17) and that the assumption (8.45) holds, then there hold*

$$\|c(t)\|_{X_\eta} \leq A(t_0) \quad \text{for } 2\eta < 1 \text{ and } t \in [t_0, T) \ (0 < t_0 < T), \tag{8.74}$$

$$\|c(t)\|_{L^\infty(\Omega)} \leq A \qquad \text{for all } t \in [0, T). \tag{8.75}$$

Proof. We first prove the estimate (8.74). By (8.13) and $c(x, 0) = c_0(x)$, we have

$$c(t) = e^{-tB}c_0 + \int_0^t e^{-(t-\tau)B}\big[-\bigtriangledown\cdot(V_1(c)\bigtriangledown u) - \bigtriangledown\cdot(V_2(c)\bigtriangledown v) + (\mu+1)c - \mu c^2 - \mu cv\big]d\tau$$

and therefore

$$\begin{aligned}\|c(t)\|_{X_\eta} \leq \|e^{-tB}c_0\|_{X_\eta} + \int_0^t \|e^{-(t-\tau)B}\big[&- \bigtriangledown\cdot(V_1(c)\bigtriangledown u) - \bigtriangledown\cdot(V_2(c)\bigtriangledown v) \\ &+(\mu+1)c - \mu c^2 - \mu cv\big]\|_{X_\eta} d\tau.\end{aligned} \tag{8.76}$$

By [78, Theorem 1.4.3] and (8.10)

$$\|e^{-tB}c_0\|_{X_\eta} \leq A_0 t^{-\eta} e^{-\delta t}\|c_0\|_{L^p(\Omega)} \leq A_0 t^{-\eta} e^{-\delta t} \tag{8.77}$$

and, by $0 \leq v \leq 1$ and (8.66),

$$\begin{aligned}&\|e^{-(t-\tau)B}\big((\mu+1)c - \mu c^2 - \mu cv\big)\|_{X_\eta} \\ &\leq (t-\tau)^{-\eta} e^{-\delta(t-\tau)}\Big((2\mu+1)\|c\|_{L^p(\Omega)} + \mu\|c^2\|_{L^p(\Omega)}\Big) \\ &\leq A(t-\tau)^{-\eta} e^{-\delta(t-\tau)}\end{aligned} \tag{8.78}$$

where $\delta \in (0,1)$ and $p > 5$. By [86, Lemma 2.1], (8.5), (8.64), and (8.65), we have

$$\begin{aligned}
&\|e^{-(t-\tau)B}\big[-\bigtriangledown\cdot(V_1(c)\bigtriangledown u)-\bigtriangledown\cdot(V_2(c)\bigtriangledown v)\big]\|_{X_\eta}\\
&\le A_0\|e^{-(t-\tau)\triangle}\big[-\bigtriangledown\cdot(V_1(c)\bigtriangledown u)-\bigtriangledown\cdot(V_2(c)\bigtriangledown v)\big]\|_{X_\eta}\\
&\le A_0(\varepsilon)(t-\tau)^{-1/2-\eta-\varepsilon}e^{-\delta(t-\tau)}\|V_1(c)\bigtriangledown u - V_2(c)\bigtriangledown v\|_{L^p(\Omega)}\\
&\le A(t-\tau)^{-1/2-\eta-\varepsilon}e^{-\delta(t-\tau)} \qquad (8.79)
\end{aligned}$$

where $\varepsilon > 0$ such that $-1/2-\eta-\varepsilon > -1$.

Inserting (8.77)-(8.79) into (8.76) and noting $1/2+\eta+\varepsilon < 1$ and $\eta < 1$, we obtain

$$\begin{aligned}
\|c(t)\|_{X_\eta} &\le A_0 t^{-\eta}e^{-\delta t} + A(\varepsilon)\int_0^t \big[(t-\tau)^{-1/2-\eta-\varepsilon}e^{-\delta(t-\tau)} + (t-\tau)^{-\eta}e^{-\delta(t-\tau)}\big]d\tau\\
&\le A(t_0)
\end{aligned}$$

for all $t \in [t_0, T)$ $(0 < t_0 < T)$. Hence, the estimate (8.74) is proved.

We are now in a position to prove the estimate (8.75). Note $p > 5$ and let $2\eta \in (\frac{3}{p}, 1)$. Since $2\eta > d/p$ ($d :=$ the space dimension), by [78, Theorem 1.6.1] we have that

$$X_\eta \hookrightarrow C(\overline{\Omega}).$$

Hence, by (8.74) we have that

$$\|c(t)\|_{L^\infty(\Omega)} \le A(t_0) \qquad \text{for } t > t_0 > 0.$$

Furthermore, the local existence Theorem 8.1 yields that there exists some $t_0 \in (0,1)$ such that

$$\|c(t)\|_{L^\infty(\Omega)} \le A_0 \qquad \text{for } t \le t_0.$$

Therefore,

$$\|c(t)\|_{L^\infty(\Omega)} \le A \qquad \text{for all } t \in [0, T).$$

This completes the proof of the estimate (8.75). □

Lemma 8.9. *Assume that $(c, v, u) \in C^{2,1}(\Omega_T)$ is a solution to (8.13)-(8.17) and that the assumption (8.45) holds, then, for any $p > 5$ there hold*

$$\|c\|_{W_p^{2,1}(\Omega_T)} \le A. \tag{8.80}$$

Proof. Returning to (8.69)-(8.73), noting (8.4) and (8.44), and using Lemmas 8.6 - 8.8, we have

$$\|\mathbf{b}\|_{L^\infty(\Omega)} \le A, \tag{8.81}$$

$$\|g\|_{L^p(\Omega_T)} \le A. \tag{8.82}$$

These, along with (8.10) and the parabolic L^p-theory, yields the estimate (8.80). □

Lemma 8.10. *Assume that $(c, v, u) \in C^{2,1}(\Omega_T)$ is a solution to (8.13)-(8.17) and that the assumption (8.45) holds, then there hold*

$$\|u\|_{C^{2+\sigma,1+\sigma/2}(\Omega_T)} \le A, \tag{8.83}$$

$$\|v\|_{C^{2+\sigma,1+\sigma/2}(\Omega_T)} \le A, \tag{8.84}$$

$$\|c\|_{C^{2+\sigma,1+\sigma/2}(\Omega_T)} \le A. \tag{8.85}$$

Proof. By (8.80) and the Sobolev embedding theorem (see [108], taking p sufficiently large),

$$\|c\|_{C^{\sigma,\sigma/2}(\Omega_T)} \le A.$$

This, together with (8.53)-(8.55) and the parabolic Schauder theory, yields (8.83).

Moreover, by (8.10), (8.21), (8.27), (8.28), and (8.83), we get the estimate (8.84).

We next turn to prove the estimate (8.85). Returning to (8.69)-(8.73) and noting (8.4), (8.83), and (8.84), we have

$$\|\mathbf{b}\|_{C^{\sigma,\sigma/2}(\Omega_T)} \le A, \qquad \|g\|_{C^{\sigma,\sigma/2}(\Omega_T)} \le A.$$

Hence, by the Schauder theory again, we obtain the estimate (8.85). □

With a priori estimates (8.83)-(8.85), we can extend the local classical solution established in Theorem 8.1 to all $t > 0$, as done in Chapters 6 and 7. Namely, we have

Theorem 8.2. *In addition to the assumption (8.4), (8.5), and (8.10), we assume that*

$$\mu > 0.$$

Then, there exists a unique solution $(c,\ v,\ u) \in \left(C^{2+\sigma,\ 1+\sigma/2}(\Omega_T)\right)^3$ *of the system (8.13)-(8.17) for any given* $T > 0$. *Furthermore*

$$c \ge 0, \quad 0 \le v \le 1, \quad u \ge 0.$$

Remark 8.1. The uniform-in-time boundedness of c remains open due to the bound of $\| \bigtriangledown v\|_{L^2(\Omega)}$ depends on the time T (see the estimate (8.49) and its

proof). Moreover, our global existence result strongly depends on the presence of the logistic damping (i.e. $\mu > 0$). In other word, the global existence remains open for $\mu = 0$.

8.5 Boundedness for A Volume-Filling Model

Assuming that cancer cells carry a nonzero finite volume and that occupation of an area limits other cells from penetrating it, typical density-dependent chemotactic and haptotactic sensitivity functions reads as follows (see[70, 81]): for $i = 1, 2$,

$$V_i(c) = \chi_i c\Big(1 - \frac{c}{\gamma}\Big), \quad \text{where } \gamma \geq 1 \text{ denotes the maximum cell density.} \tag{8.86}$$

In (8.86), χ_1 and χ_2 are assumed to be two positive constants. Clearly, $V_i(c) \to \chi_i c$ as $\gamma \to +\infty$. For this choice of $V_1(c)$ and $V_2(c)$, the assumption (8.4) holds, but the assumption (8.5) is not satisfied (since $V_1(c), V_2(c) \to -\infty$ as $c \to +\infty$). However, these specific forms of $V_1(c)$ and $V_2(c)$ are in favor of the proofs of global existence and boundedness. In fact, we have

Theorem 8.3. *In addition to the assumption (8.10) and (8.86), we assume that*

$$0 \leq c_0(x) \leq \gamma. \tag{8.87}$$

Then, there exists a unique solution $(c,\ v,\ u) \in \Big(C^{2+\sigma,\ 1+\sigma/2}(\Omega_T)\Big)^3$ *of the system (8.13)-(8.17) for any given* $T > 0$. *Furthermore*

$$0 \le c \le \gamma, \tag{8.88}$$

$$0 \le v \le 1, \tag{8.89}$$

$$u \ge 0. \tag{8.90}$$

Proceeding as in the proof of Theorem 8.1, we can first establish the local existence and uniqueness of solutions. To extend the local solution to all $t > 0$, as done in Section **??**8.4, we need to establish a priori $C^{2+\sigma,\ 1+\sigma/2}(\Omega_T)$-estimate of (c, v, u), which strongly depends on a priori $L^\infty \Omega)$-estimate of c.

Lemma 8.11. *Assume that $(c, v, u) \in C^{2,1}(\Omega_T)$ is a solution to (8.13)-(8.17) and that the assumptions (8.86) and (8.87) hold, then there holds*

$$0 \le c \le \gamma. \tag{8.91}$$

Proof. By $V_1(0) = V_2(0) = 0$ and $c_0(x) \ge 0$, we easily find that $\underline{c} := 0$ is a sub-solution of the problem (8.69)-(8.71). On the other hand, by (8.87), $v \ge 0$, and $V_1(\gamma) = V_2(\gamma) = 0$, we easily find that $\overline{c} := \gamma$ is a sup-solution of the problem (8.69)-(8.71). Hence, by the maximum principle, we have the estimate (8.91). □

With the a priori estimate (8.91), we can prove Theorem 8.3 in the same way of the proof of Theorem 8.2.

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