



# A free boundary problem modeling tumor growth with different chemotactic responses and random motions for various cell types

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## ABSTRACT

This paper deals with a mathematical model describing the growth of an avascular tumor. Tumor cells are assumed to consist of two cell types: the proliferative cells and the quiescent non-dividing cells, which might have different chemotactic responses to gradients of extracellular nutrients (oxygen, glucose, etc.). The model is a free boundary problem for a coupled system of nonlinear convection–diffusion–reaction equations, where the diffusion rates of the two cell types might be different and the free boundary is the outer boundary of the tumor. We prove the global solvability of this model by a fixed point argument and some a priori estimate techniques. This work extends a recent result by the second author [Y. Tao, A free boundary problem modeling the cell cycle and cell movement in multicellular tumor spheroids, J. Differential Equations 247 (2009), 49–68] on a model with the same diffusion rate for two cell types to a new one on a model with different cell diffusion rates.

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## 1. The model

Generally speaking, the formulation of mathematical models for the growth of *in vivo* avascular tumors was based on the available experimental data for *in vitro* multicellular spheroids (MCS), since the latter can mimic the former to a great extent. In order to describe cell cycle, cell movement, cellular heterogeneity, mechanical effects, therapeutic effects, chemotactic phenomena and other interactions between tumor cells and their micro-environment, a number of mathematical models of avascular tumor growth have been proposed and studied (cf. a review article [1] for more details).

This work will focus on studying a new model recently proposed by Tindall and Please in [2] and Mahmood et al. in [3]. Considering a spherically symmetric geometry and assuming that tumor cells consist of proliferative cells and quiescent cells, the model includes the following six unknown variables:  $p$ ,  $q$ ,  $u_p$ ,  $u_q$ ,  $c$  and  $R(t)$ . Here,  $p$  and  $q$  denote the proliferative and quiescent cell densities respectively,  $u_p$  and  $u_q$  reflect the proliferative and quiescent cell velocities respectively,  $c$  is the concentration of nutrient (oxygen, glucose, etc.) and  $R(t)$  represents the tumor radius. The cell velocities are created by the local volume changes due to cell death and birth [4] or by a chemotactic response to gradients of nutrients [2,3]. The above-mentioned directed movement of cells towards gradients of chemicals (nutrient, growth factor, etc.) is referred to as *chemotaxis* (cf. [5]). Following [2,3] (cell diffusion was neglected in [2], whereas cell diffusion was retained in [3]), the evolution of the proliferative and quiescent cell densities are given by

$$\frac{\partial p}{\partial t} + \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 (u_p p) \right) = D_p \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial p}{\partial r} \right) + (K_b(c) - K_q(c) - K_a(c))p + K_p(c)q, \quad (1.1)$$

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$$\frac{\partial q}{\partial t} + \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 (u_q q) \right) = D_q \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial q}{\partial r} \right) + K_q(c)p - (K_d(c) + K_p(c))q. \quad (1.2)$$

Here,  $D_p$  and  $D_q$  are the random motility coefficients of the proliferative and quiescent cell respectively,  $K_b(c)$  is the rate of cell birth,  $K_q(c)$  is the rate at which proliferative cells become quiescent whereas  $K_p(c)$  is the rate at which cells return to the proliferative compartment from quiescent,  $K_a(c)$  is the death rate of proliferative cells, and  $K_d(c)$  is the death rate of quiescent cells.  $K_a(c)p$  in (1.1) is the death of proliferative cells due to apoptosis, whereas  $K_d(c)q$  in (1.2) is the death of quiescent cells due to necrosis.

Since the diffusion rate of the nutrient is much greater than that of cells (cf. [3]), we shall use the approach of quasi-steady-state approximation for the nutrient equation (cf. [1,6] or [7], for instance). Hence, the equation for the nutrient concentration reads as [3,6]

$$\frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial c}{\partial r} \right) = \lambda(c)c \cdot N \quad (1.3)$$

where  $\lambda(c)$  is any positive smooth function,  $\lambda(c)c$  is a consumption rate of nutrient which is equal to zero at  $c = 0$ , and  $N$  is the number of viable cells per unit volume [8].

We also assume that the volume fraction being occupied by the living cells (proliferating and quiescent cells) is a constant [4], namely  $N$  is a constant. Therefore,

$$p + q = N. \quad (1.4)$$

Based on the chemotactic phenomenon and experimental observation, the proliferating and quiescent cells might have different chemotactic responses to gradients of the nutrient [2,3,8]. Hence, we assume that

$$u_q(r, t) = u_p(r, t) + \chi \frac{\partial c}{\partial r}, \quad (1.5)$$

where  $\chi$  is a parameter to measure the relative strength of the chemotactic responses of the two types of cells: proliferating cells move up the nutrient gradients relative quiescent cells if  $\chi < 0$ ; quiescent cells move more actively in response to the nutrient gradient than the proliferating cells if  $\chi > 0$ ; the proliferating and quiescent cells have the identical velocity if  $\chi = 0$ .

Eqs. (1.1)–(1.5) are considered on a spherically symmetric domain  $\{r | r < R(t)\} \subset \mathbb{R}^3$  with a free boundary  $r = R(t)$ . To close the system, we impose the Dirichlet boundary condition for  $c$  and zero-flux boundary conditions for  $p$  and  $q$  at the free boundary  $r = R(t)$  (cf. [2,6]):

$$c(r, t) = c_\infty \quad \text{at } r = R(t), \quad (1.6)$$

$$p \frac{dR(t)}{dt} - \left( pu_p - D_p \frac{\partial p}{\partial r} \right) = 0 \quad \text{at } r = R(t), \quad (1.7)$$

$$q \frac{dR(t)}{dt} - \left( qu_q - D_q \frac{\partial q}{\partial r} \right) = 0 \quad \text{at } r = R(t), \quad (1.8)$$

where  $c_\infty > 0$  is a constant. The boundary condition (1.6) presupposes that the tumor is supported in a nutrient-rich medium, and the no-flux boundary conditions (1.7) and (1.8) are based on the facts that the tumor changes at the rate  $\dot{R}(t)$  and that every cell type has two velocity components: one is the random motion velocity and the other is the velocity due to chemotaxis and local volumes changes caused by the death and birth of cells (cf. [6, Remark 1.2] for more details of the explanation of (1.7) and (1.8)).

To close the system, we also need to prescribe the initial conditions:

$$R(0) = R_0, \quad (1.9)$$

$$p(r, 0) = p_0(r) \quad \text{for } 0 \leq r \leq R(0), \quad (1.10)$$

where  $R_0 > 0$  is a constant and  $0 \leq p_0(r) \leq N$ .

Finally, by the radial symmetry assumption of the problem, we have

$$\frac{\partial c}{\partial r}(0, t) = \frac{\partial p}{\partial r}(0, t) = \frac{\partial q}{\partial r}(0, t) = u_p(0, t) = u_q(0, t) = 0, \quad t > 0. \quad (1.11)$$

The present work aims at studying the global well-posedness of the full model (1.1)–(1.11). To this end, we first need to derive a basic relation for  $u_p$  and some familiar free boundary conditions. Adding (1.1) to (1.2) and invoking (1.4) and (1.5)

yield an equation for  $u_p$

$$\begin{aligned} \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 u_p \right) &= \frac{D_p - D_q}{N} \cdot \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial p}{\partial r} \right) + \frac{1}{N} \cdot (K_b(c)p - K_a(c)p - K_d(c)(N - p)) \\ &\quad - \frac{\chi}{N} \cdot \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 (N - p) \frac{\partial c}{\partial r} \right), \quad 0 < r \leq R(t), \quad t > 0. \end{aligned} \quad (1.12)$$

Adding (1.7) to (1.8) and using (1.4) and (1.5) we obtain an equation for the velocity of the free boundary  $r = R(t)$

$$\frac{dR(t)}{dt} = u_p + \chi \left( 1 - \frac{p}{N} \right) \frac{\partial c}{\partial r} - \frac{D_p - D_q}{N} \cdot \frac{\partial p}{\partial r} \quad \text{at } r = R(t). \quad (1.13)$$

This in conjunction with (1.7) yields a nonlinear third boundary condition for  $p$

$$\frac{\partial p}{\partial r} + \left[ \frac{\chi(N - p)}{(N - p)D_p + pD_q} \cdot \frac{\partial c}{\partial r} \right] p = 0 \quad \text{at } r = R(t). \quad (1.14)$$

We note that (1.2) is a consequence of (1.1), (1.4), (1.5) and (1.12), so that in the sequel we may drop this equation and replace  $q$  by  $N - p$  in (1.1).

We also note that the no-flux boundary conditions (1.7) and (1.8) are equivalent to the boundary conditions (1.13) and (1.14) under assumptions (1.4) and (1.5), so that in the sequel we shall replace (1.7) and (1.8) with (1.13) and (1.14).

We further note that the empirical rules used for the functional dependence of  $\lambda$ ,  $K_a$ ,  $K_b$ ,  $K_d$ ,  $K_p$  and  $K_q$  on  $c$  are not critical to our analysis. For the existence of solutions to the model, we need only a very simple assumption

$$\lambda(c), K_a(c), K_b(c), K_d(c), K_p(c) \text{ and } K_q(c) \text{ are nonnegative } C^1\text{-smooth function}, \quad (1.15)$$

which is physically realistic. The requirement of the  $C^1$ -regularity is due to a technical reason (cf. [6, Remark 6.1] for details). The analysis in this paper will also be independent of the sign of  $\chi$ ; however, for definiteness and simplicity of the statement, we will assume that  $\chi > 0$  throughout the remainder of this paper.

After re-scalings (cf. [2,3] or [6]), without loss of generality, we may assume that

$$N = 1, \quad c_\infty = 1 \quad \text{and} \quad R_0 = 1. \quad (1.16)$$

Under a special assumption that  $D_p = D_q$ , the author in [6] proved global solvability of problem (1.1), (1.3), (1.5), (1.6) and (1.9)–(1.16). The present work aims at extending the above result to a new one for the general case  $D_p \neq D_q$ . To deal with the highly coupling of  $u_p$  with  $p$  in (1.12) and the strong nonlinearity in the resulting equation for  $p$  (see Section 2) due to  $D_p \neq D_q$ , we need to delicately choose a suitable mapping on an appropriate closed convex set in a Banach space for a fixed point argument and improve some a priori estimates in [6] (see Section 4). This is the main novel point of the present paper.

The plan of this paper goes as follows. In Section 2, we reformulate the problem by straightening the free boundary and state our main results. In Section 3, we give some preliminary observations. Finally, in Section 4, we prove our main result.

## 2. Reformulation of the problem

It might be convenient to transform the moving domain  $\{r < R(t)\}$  into a fixed domain, we introduce a transformation of variables  $(r, t, c, p, u_p, R) \mapsto (\rho, t, \tilde{c}, \tilde{p}, \tilde{u}, R)$  as follows

$$\rho = \frac{r}{R(t)}, \quad \tilde{c}(\rho, t) = c(\rho R(t), t), \quad \tilde{p}(\rho, t) = p(\rho R(t), t) \quad \tilde{u}(\rho, t) = \frac{u_p(\rho R(t), t)}{R(t)}. \quad (2.1)$$

For simplicity, we denote the operator

$$\Delta_\rho := \frac{1}{\rho^2} \frac{\partial}{\partial \rho} \left( \rho^2 \frac{\partial}{\partial \rho} \right).$$

In terms of the new variables by dropping the tildes of  $\tilde{c}$ ,  $\tilde{p}$  and  $\tilde{u}$  for notational convenience and in view of (1.12)–(1.16), the problem (1.1)–(1.11) takes the following form:

$$\Delta_\rho c = R^2(t) \lambda(c) c, \quad 0 < \rho < 1, \quad t > 0, \quad (2.2)$$

$$\frac{\partial c}{\partial \rho}(0, t) = 0, \quad c(1, t) = 1, \quad t > 0, \quad (2.3)$$

$$\begin{aligned} \frac{\partial p}{\partial t} + \left[ u(\rho, t) - \rho \frac{\dot{R}(t)}{R(t)} + \frac{\chi}{R^2(t)} \frac{\partial c}{\partial \rho} p \right] \frac{\partial p}{\partial \rho} - \frac{(1-p)D_p + pD_q}{R^2(t)} \Delta_\rho p \\ = [-K_q(c) + (K_b(c) - K_a(c) + K_d(c) + \chi \lambda(c)c)(1-p)]p + K_p(c)(1-p), \quad 0 < \rho < 1, t > 0, \end{aligned} \quad (2.4)$$

$$\frac{\partial p}{\partial \rho}(0, t) = 0, \quad \left\{ \frac{\partial p}{\partial \rho} + \left[ \frac{\chi(1-p)}{(1-p)D_p + pD_q} \cdot \frac{\partial c}{\partial \rho} \right] p \right\} \Big|_{\rho=1} = 0, \quad t > 0, \quad (2.5)$$

$$p(\rho, 0) = p_0(\rho), \quad 0 \leq \rho \leq 1, \quad (2.6)$$

$$\begin{aligned} u(\rho, t) = \frac{1}{\rho^2} \int_0^\rho [K_b(c)p - K_a(c)p - K_d(c)(1-p)] s^2 ds + (D_p - D_q) \cdot \frac{1}{R^2(t)} \frac{\partial p}{\partial \rho} \\ - \chi(1-p) \frac{1}{R^2(t)} \frac{\partial c}{\partial \rho}, \quad 0 < \rho < 1, t > 0, \end{aligned} \quad (2.7)$$

$$\frac{dR(t)}{dt} = R(t) \int_0^1 [K_b(c)p - K_a(c)p - K_d(c)(1-p)] s^2 ds, \quad R(0) = 1. \quad (2.8)$$

We shall use the following notations:

$$B_1 := \{y \in \mathbb{R}^3 : |y| = \sqrt{y_1^2 + y_2^2 + y_3^2} < 1\}, \quad Q_T := B_1 \times [0, T],$$

$$W_k^2(B_1) := \{\varphi(\rho)|\varphi, \varphi_{y_i}, \varphi_{y_i y_j} \in L^k(B_1)\},$$

$$W_k^{2,1}(Q_T) := \{p(\rho, t)|p, p_{y_i}, p_{y_i y_j}, p_t \in L^k(Q_T)\},$$

where  $1 \leq k \leq \infty$ ,  $i, j = 1, 2, 3$ ,  $T > 0$  is an arbitrary constant, and the derivatives are in the weak sense.

The main result of this paper can be stated as follows:

**Theorem 2.1.** Assume that

$$0 \leq p_0(\rho) \leq 1 \quad \text{and} \quad p_0(\rho) \in W_k^2(B_1) \quad \text{with some } k > 5 \quad (2.9)$$

and that

$$0 < \lambda(c) \in C^1 \quad \text{and} \quad 0 \leq K_a(c), K_b(c), K_d(c), K_p(c) \text{ and } K_q(c) \in C^1. \quad (2.10)$$

Then there exists a unique solution  $(R(t), u(\rho, t), c(\rho, t), p(\rho, t))$  of problem (2.2)–(2.8) for all  $t > 0$ , which possesses the following regularity properties:

$$\begin{aligned} R(t) \in C^1([0, \infty)), \quad u(\rho, t) \in C^0([0, 1] \times [0, \infty)), \\ c(\rho, t) \in C^{2,1}([0, 1] \times [0, \infty)) \quad \text{and} \quad p(\rho, t) \in W_k^{2,1}(Q_T). \end{aligned}$$

Furthermore, for any  $0 \leq \rho \leq 1$ ,  $t > 0$  there hold

$$0 \leq c(\rho, t) \leq 1, \quad (2.11)$$

$$0 \leq p(\rho, t) \leq 1 \quad (2.12)$$

and

$$e^{-\beta t} \leq R(t) \leq e^{\beta t} \quad \text{for some } \beta > 0. \quad (2.13)$$

### 3. Preliminary observations

If  $p(\rho, t) \in C^{2,0}((0, 1) \times (0, T)) \cap C^{1,0}([0, 1] \times (0, T))$ , then the Lagrange mean-value theorem in conjunction with the boundary condition  $\frac{\partial p}{\partial \rho}(0, t) = 0$  in (2.5) yields some  $\xi(\rho, t) \in (0, \rho)$  such that

$$\frac{2}{\rho} \cdot \frac{\partial p}{\partial \rho}(\rho, t) = \frac{2}{\rho} \cdot \left[ \frac{\partial p}{\partial \rho}(\rho, t) - \frac{\partial p}{\partial \rho}(0, t) \right] = 2 \frac{\partial^2 p}{\partial \rho^2}(\xi(\rho, t), t).$$

Therefore,  $\Delta_\rho p \equiv \frac{\partial^2 p}{\partial \rho^2} + \frac{2}{\rho} \cdot \frac{\partial p}{\partial \rho}$  does not have singularity at  $\rho = 0$ . However, since the coefficient  $\frac{2}{\rho}$  of  $\frac{\partial p}{\partial \rho}$  in the expression of  $\Delta_\rho p$  is unbounded near  $\rho = 0$ , we cannot apply the  $L^p$  theory to  $p$ -Eq. (2.4) whenever we regard it as an one-dimensional parabolic equation with the spatial variable  $\rho$ . This obstacle can be overcome by using the three-dimensional Cartesian coordinate (cf. [9]) and some a priori estimates (see Lemma 3.1 and Section 4).

It is easily checked that

$$\rho p_\rho \equiv y \cdot \nabla p, \quad \Delta_\rho p \equiv \Delta p,$$

where  $y = (y_1, y_2, y_3)$ ,  $\rho = \sqrt{y_1^2 + y_2^2 + y_3^2}$ ,  $\nabla = (\frac{\partial}{\partial y_1}, \frac{\partial}{\partial y_2}, \frac{\partial}{\partial y_3})$ ,  $\Delta = \frac{\partial^2}{\partial y_1^2} + \frac{\partial^2}{\partial y_2^2} + \frac{\partial^2}{\partial y_3^2}$ . Then  $p$ -Eq. (2.4) can be rewritten in the following form:

$$\begin{aligned} & \frac{\partial p}{\partial t} - \frac{(1-p)D_p + pD_q}{R^2(t)} \Delta p + \left[ u(\rho, t) - \rho \frac{\dot{R}(t)}{R(t)} + \chi \cdot \frac{1}{R^2(t)} \frac{\partial c}{\partial \rho} \cdot p \right] \frac{y}{\rho} \cdot \nabla p \\ & = [-K_q(c) + K(c)(1-p)]p + K_p(c)(1-p), \quad 0 < |y| < 1, \quad t > 0, \end{aligned} \quad (3.1)$$

where

$$K(c) := K_b(c) - K_a(c) + K_d(c) + \chi \lambda(c)c. \quad (3.2)$$

The following observation is simple but important:

$$\min(D_p, D_q) \leq (1-p)D_p + pD_q \leq \max(D_p, D_q) \quad \text{if } 0 \leq p \leq 1. \quad (3.3)$$

To assert the coefficient of  $\nabla p$  in (3.1) has no singularity at  $\rho = 0$ , we need only to prove the boundedness of  $u(\rho, t)$  and  $\frac{1}{R^2(t)} \frac{\partial c}{\partial \rho}$  due to  $|\frac{y}{\rho}| \equiv 1$ . Since  $u(\rho, t)$  is coupled with  $\frac{\partial p}{\partial \rho}$  in (2.7) for the general case  $D_p \neq D_q$ , the boundedness of  $u(\rho, t)$  will be addressed later.

We begin with proving the boundedness of  $\frac{1}{R^2(t)} \frac{\partial c}{\partial \rho}$ .

**Lemma 3.1.** For any given  $R(t) \in C^1([0, T])$  with  $R(t) > 0$ , (2.2)–(2.3) admits a unique solution  $c(\rho, t) \in C^{2,1}(\bar{Q}_T)$  satisfying

$$0 \leq c(\rho, t) \leq 1 \quad (3.4)$$

and

$$0 \leq \frac{1}{R^2(t)} \frac{\partial c}{\partial \rho} \leq \frac{1}{3} \max_{0 \leq c \leq 1} \lambda(c) \quad (3.5)$$

for all  $0 \leq \rho \leq 1$  and  $t \in [0, T]$ .

**Proof.** The proof is similar to [6, Lemma 3.1], so we omit the details.  $\square$

#### 4. Proof of the main results

We prove the existence and uniqueness of solutions to (2.2)–(2.8) by a fixed point argument inspired by [10] (cf. also [6,11]).

**Lemma 4.1.** Let (2.9) and (2.10) hold. Then there exists a small  $T$  which depends only on  $\|p_0(\rho)\|_{W_k^2(B_1)}$ , such that (2.2)–(2.8) has a unique solution  $(R(t), u(\rho, t), c(\rho, t), p(\rho, t))$  satisfying  $R(t) \in C^1([0, T])$ ,  $u(\rho, t) \in C^0(\bar{Q}_T)$ ,  $c(\rho, t) \in C^{2,1}(\bar{Q}_T)$  and  $p(\rho, t) \in W_k^{2,1}(\bar{Q}_T)$ . Moreover, for any  $0 \leq \rho \leq 1$  and  $t > 0$  there hold

$$0 \leq c(\rho, t) \leq 1 \quad (4.1)$$

and

$$0 \leq p(\rho, t) \leq 1. \quad (4.2)$$

**Proof.** We divide the proof into five steps.

*Step 1.* Choosing of the mapping on a closed convex set in a Banach space.

We shall use the contraction mapping principle to prove the existence and uniqueness of solutions to (2.2)–(2.8). To this end, for any given  $0 < T < 1$  we introduce a Banach space  $X_T$  as follows

$$X_T := \left\{ (R, p) = (R(t), p(\rho, t)) \mid (0 \leq \rho \leq 1, 0 \leq t \leq T) : R(t) \in C^1([0, T]), p(\rho, t) \in C^{1,1/2}(\bar{Q}_T) \right\}.$$

The norm in  $X_T$  is defined by

$$\|(R, p)\|_{X_T} := \|R\|_{C^1([0, T])} + \|p\|_{C^{1,1/2}(\bar{Q}_T)} \quad \text{for any } (R, p) \in X_T.$$

We further introduce a closed convex set  $X_{T,M}$  in  $X_T$  by defining

$$X_{T,M} := \left\{ (R, p) \in X_T : \frac{1}{2} \leq R(t) \leq 2, \|R(t)\|_{C^1([0, T])} \leq M; 0 \leq p(\rho, t) \leq 1, \|p(\rho, t)\|_{C^{1,1/2}(\bar{Q}_T)} \leq M \right\},$$

where

$$M := 2 + \frac{2}{3} \max_{0 \leq c \leq 1} (K_a(c) + K_b(c) + K_d(c)) + 2\|p_0(\rho)\|_{C^1(\bar{B}_1)} + \|p_0(\rho)\|_{W_k^2(B_1)}.$$

For any given  $(R(t), p(\rho, t)) \in X_{T,M}$ , by Lemma 3.1 we can define  $c(\rho, t)$  being the solution of (2.2)–(2.3). For this  $c(\rho, t)$ , along with the given  $(R(t), p(\rho, t)) \in X_{T,M}$ , we then define  $u(\rho, t)$  by (2.7). Hence, by (3.4), (3.5) and the define of  $X_{T,M}$  we find that there exists some constant  $C_1(M) > 0$  such that

$$|u(\rho, t)| \leq C_1(M) \quad \text{for all } 0 \leq \rho \leq 1 \text{ and } 0 \leq t \leq T. \quad (4.3)$$

We now define a mapping

$$F : (R(t), p(\rho, t)) \in X_{T,M} \longmapsto (\hat{R}(t), \hat{p}(\rho, t)),$$

where  $\hat{R}(t)$  and  $\hat{p}(\rho, t)$  solve the following two decoupled problems:

$$\frac{d\hat{R}(t)}{dt} = \hat{R}(t) \int_0^1 [K_b(c)p - K_a(c)p - K_d(c)(1-p)] s^2 ds, \quad \hat{R}(0) = 1 \quad (4.4)$$

and

$$\begin{cases} \frac{\partial \hat{p}}{\partial t} - \frac{(1-p)D_p + pD_q}{R^2(t)} \Delta \hat{p} + \left[ u(\rho, t) - \rho \frac{\dot{R}(t)}{R(t)} + \frac{\chi}{R^2(t)} \frac{\partial c}{\partial \rho} p \right] \frac{y}{\rho} \cdot \nabla \hat{p} \\ = [-K_q(c) + K(c)(1-\hat{p})] \hat{p} + K_p(c)(1-\hat{p}), \quad 0 < \rho < 1, \quad t > 0, \\ \frac{\partial \hat{p}}{\partial \rho}(0, t) = 0, \quad \left\{ \frac{\partial \hat{p}}{\partial \rho} + \left[ \frac{\chi(1-p)}{(1-p)D_p + pD_q} \cdot \frac{\partial c}{\partial \rho} \right] \hat{p} \right\} \Big|_{\rho=1} = 0, \quad t > 0, \\ \hat{p}(\rho, 0) = p_0(\rho), \quad 0 \leq \rho \leq 1. \end{cases} \quad (4.5)$$

Here we note that to guarantee  $0 \leq \hat{p} \leq 1$  (see Step 3 below), it is necessary to choose  $K(c)(1-\hat{p})$  rather than  $K(c)(1-p)$  in the first equation in (4.5).

*Step 2. Estimate on  $\hat{R}(t)$ .*

For given  $(R, p) \in X_{T,M}$ , by (2.10) and Lemma 3.1 we find that  $(\int_0^1 [K_b(c)p - K_a(c)p - K_d(c)(1-p)] s^2 ds)$  is continuous and bounded function in  $t$ , and therefore (4.4) admits a unique solution

$$\hat{R}(t) = \exp \left( \int_0^t \int_0^1 [K_b(c)p - K_a(c)p - K_d(c)(1-p)] s^2 ds d\tau \right) \in C^1([0, T]). \quad (4.6)$$

This in conjunction with (2.10),  $0 \leq c \leq 1$  and  $0 \leq p \leq 1$  yields that

$$\frac{1}{2} \leq \hat{R}(t) \leq 2 \quad \text{for all } t \in [0, T], \text{ if } T \text{ is sufficiently small} \quad (4.7)$$

and

$$\|\hat{R}(t)\|_{C^1([0, T])} \leq 2 + \frac{2}{3} \max_{0 \leq c \leq 1} (K_a(c) + K_b(c) + K_d(c)) \leq M, \quad \text{if } T \text{ is sufficiently small.} \quad (4.8)$$

*Step 3. Estimate on  $\hat{p}(\rho, t)$ .*

By  $(R, p) \in X_{T,M}$  and (3.3), we observe that

$$\frac{(1-p)D_p + pD_q}{R^2(t)} \in C(\bar{Q}_T) \quad \text{and} \quad \frac{\min(D_p, D_q)}{4} \leq \frac{(1-p)D_p + pD_q}{R^2(t)} \leq 4 \max(D_p, D_q). \quad (4.9)$$

So, the first equation in (4.5) is uniformly parabolic. By  $(R, p) \in X_{T,M}$ , (3.5) and (4.3), we obtain

$$\left\| u(\rho, t) - \rho \frac{\dot{R}(t)}{R(t)} + \frac{\chi}{R^2(t)} \frac{\partial c}{\partial \rho} p \right\|_{L^\infty(\bar{Q}_T)} \leq C_2(M) \quad (4.10)$$

for some  $C_2(M) > 0$ . Using  $(R, p) \in X_{T,M}$  and (3.5) once again, we find

$$\frac{\chi(1-p)}{(1-p)D_p + pD_q} \cdot \frac{\partial c}{\partial \rho} \geq 0 \quad \text{in } \bar{Q}_T. \quad (4.11)$$

From this, (4.9), (4.10), (2.9), (2.10) and the comparison principle for parabolic equations with the third boundary condition (cf. [12, Theorem 2.10] and the remarks following that) we infer that  $\hat{p}_* \equiv 0$  and  $\hat{p}^* \equiv 1$  are sub- and sup-solutions of (4.5), respectively. Hence, the standard sub- and sup-solution method [13, Chapter 2, Theorem 5.1] entails that (4.5) admits a unique solution  $\hat{p}(\rho, t)$  satisfying

$$0 = \hat{p}_* \leq \hat{p}(\rho, t) \leq \hat{p}^* = 1 \quad \text{in } \bar{Q}_T. \quad (4.12)$$

By  $(R, p) \in X_{T,M}$  and Lemma 3.1 we also have

$$\frac{\chi(1-p)}{(1-p)D_p + pD_q} \cdot \frac{\partial c}{\partial \rho} \in C^{1,1/2}(\bar{Q}_T). \quad (4.13)$$

From this, (4.9)–(4.11), (2.9), (2.10), (3.4) and the  $L^p$ -theory for parabolic equations with the third boundary condition (cf. [12, Theorem 7.20]) we infer that

$$\|\hat{p}(\rho, t)\|_{W_k^{2,1}(\bar{Q}_T)} \leq C_3(M) \quad (4.14)$$

for some  $C_3(M) > 0$  due to  $0 < T < 1$ .

**Step 4.** We prove that  $F$  maps  $X_{T,M}$  into itself provided that  $T$  is sufficiently small.

From (4.14) and the Sobolev embedding  $W_k^{2,1}(\bar{Q}_T) \hookrightarrow C^{1+\lambda, (1+\lambda)/2}(\bar{Q}_T)$  for  $k > 5$  and  $\lambda = 1 - \frac{5}{k}$  (cf. [14, Lemma 3.3]) we infer that there exists some  $C_4(M) > 0$  such that

$$\|\hat{p}(\rho, t)\|_{C^{1+\lambda, (1+\lambda)/2}(\bar{Q}_T)} \leq C_4(M). \quad (4.15)$$

This yields

$$\begin{aligned} \|\hat{p}(\rho, t)\|_{C^{1,1/2}(\bar{Q}_T)} &= \|\hat{p}(\rho, t)\|_{C^0(\bar{Q}_T)} + \|\hat{p}(\rho, t)\|_{C^{1,0}(\bar{Q}_T)} + \|\hat{p}(\rho, t)\|_{C^{0,1/2}(\bar{Q}_T)} \\ &\leq \|\hat{p}(\rho, t) - \hat{p}(\rho, 0)\|_{C^0(\bar{Q}_T)} + \|\hat{p}(\rho, 0)\|_{C^0(\bar{Q}_T)} \\ &\quad + \|\hat{p}(\rho, t) - \hat{p}(\rho, 0)\|_{C^{1,0}(\bar{Q}_T)} + \|\hat{p}(\rho, 0)\|_{C^{1,0}(\bar{Q}_T)} + \|\hat{p}(\rho, t)\|_{C^{0,1/2}(\bar{Q}_T)} \\ &\leq T^{\frac{1+\lambda}{2}} \|\hat{p}(\rho, t)\|_{C^{0, (1+\lambda)/2}(\bar{Q}_T)} + T^{\frac{1+\lambda}{2}} \|\hat{p}(\rho, t)\|_{C^{1, (1+\lambda)/2}(\bar{Q}_T)} \\ &\quad + T^{\frac{\lambda}{2}} \|\hat{p}(\rho, t)\|_{C^{0, (1+\lambda)/2}(\bar{Q}_T)} + 2\|p_0(\rho)\|_{C^1(\bar{B}_1)} \\ &\leq \left( 2T^{\frac{1+\lambda}{2}} + T^{\frac{\lambda}{2}} \right) \|\hat{p}(\rho, t)\|_{C^{1+\lambda, (1+\lambda)/2}(\bar{Q}_T)} + 2\|p_0(\rho)\|_{C^1(\bar{B}_1)} \\ &\leq 3T^{\frac{\lambda}{2}} C_4(M) + 2\|p_0(\rho)\|_{C^1(\bar{B}_1)} \end{aligned} \quad (4.16)$$

due to  $T < 1$ . If we take  $T$  sufficiently small such that

$$T \leq \left( \frac{2}{3C_4(M)} \right)^{\frac{2}{\lambda}}, \quad (4.17)$$

then (4.16) entails that

$$\|\hat{p}(\rho, t)\|_{C^{1,1/2}(\bar{Q}_T)} \leq 2 + 2\|p_0(\rho)\|_{C^1(\bar{B}_1)} \leq M. \quad (4.18)$$

From (4.6)–(4.8), (4.12) and (4.18) we conclude that  $(\hat{R}, \hat{p}) \in X_{T,M}$  for sufficient small  $T$ . Hence, the mapping  $F$  is well defined and it maps  $X_{T,M}$  into itself provided  $T$  is small.

**Step 5.** We prove that  $F$  is contractive provided  $T$  is sufficiently small.

By a straightforward adaptation of the above reasoning (cf. [6, Section 6] for details), we can deduce that if  $T$  is further diminished then  $F$  is contractive on  $X_{T,M}$ . Therefore, by the contraction mapping principle [15, Theorem 5.1],  $F$  has a unique fixed point  $(R, p)$  in  $X_{T,M}$ . This in conjunction with (4.17), the definition of  $M$  and the embedding  $W_k^2(B_1) \hookrightarrow C^1(\bar{B}_1)$  for  $k > 5$  completes the proof of Lemma 4.1.  $\square$

We are now in the position to prove our main result.

**Proof of Theorem 2.1.** Suppose to the contrary that  $[0, \tilde{T})$  with  $\tilde{T} < +\infty$  is the maximum time interval for the existence of the solution. Then, by a similar reasoning in the proof of Lemma 4.1, we can establish the following *a priori* estimates:

$$0 \leq c(\rho, t) \leq 1 \quad \text{for all } t < \tilde{T} \text{ and } 0 \leq \rho \leq 1, \quad (4.19)$$

$$0 \leq p(\rho, t) \leq 1 \quad \text{for all } t < \tilde{T} \text{ and } 0 \leq \rho \leq 1, \quad (4.20)$$

$$e^{-\beta \tilde{T}} \leq R(t) \leq e^{\beta \tilde{T}} \quad \text{for all } t < \tilde{T}, \quad \text{and} \quad (4.21)$$

$$\|p(\rho, t)\|_{W_k^{2,1}(Q_{\tilde{T}})} \leq C(\tilde{T}), \quad (4.22)$$

where  $\beta := \frac{1}{3} \max_{0 \leq c \leq 1} (K_a(c) + K_b(c) + K_d(c)) > 0$  and  $C(\tilde{T})$  is some constant which may depend on  $\tilde{T}$ .

By Lemma 4.1 and (4.22) we can extend the solution on  $[0, \tilde{T})$  to a new one on  $[0, \tilde{\tilde{T}})$  with  $\tilde{\tilde{T}} > \tilde{T}$  (cf. [6, The proof of Theorem 7.1] for details). This contradicts the definition of  $\tilde{T}$ . Hence  $\tilde{T} = +\infty$ . This completes the proof.  $\square$

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