

癌症疫苗和抑制剂治疗模型整体解的存在唯一性^{*}

刘春燕¹, 卫雪梅¹, 冯兆永², 刘成霞³
(1. 广东工业大学应用数学学院, 广东 广州 510520;
2. 中山大学数学学院, 广东 广州 510275;
3. 南方医科大学口腔医院, 广东 广州 510280)

摘 要: 研究癌症疫苗和检查点抑制剂联合治疗的数学模型, 该模型为包含九个相互耦合反应扩散方程的方程组。先通过运用 Banach 不动点定理、抛物型方程的 L^p 估计证明了模型的局部解的存在唯一性, 然后利用延拓方法得到了整体解的存在唯一性。

关键词: 癌症疫苗; 检查点抑制剂; 联合治疗; 局部解; 整体解; 存在唯一性

中图分类号: O175 **文献标志码:** A **文章编号:** 0529-6579 (2019) 03-0094-09

Existence and uniqueness of global solution for the treatment model of cancer vaccine and checkpoint inhibitor

LIU Chunyan¹, WEI Xuemei¹, FENG Zhaoyong², LIU Chengxia³

(1. School of Applied Mathematics, Guangdong University of Technology, Guangzhou 510520, China;
2. School of Mathematics, Sun Yat-sen University, Guangzhou 510275, China;
3. Stomatological Hospital, Southern Medical University, Guangzhou 510280, China)

Abstract: A combined treatment model of cancer vaccine and checkpoint inhibitor, which contains nine coupled reaction diffusion equations, is studied. By using the Banach fixed point theorem and L^p -theory of parabolic equation, the existence and uniqueness of the model in the local solution is proved. And then the existence and uniqueness of the global solution is obtained by using the extension method.

Key words: cancer vaccine; checkpoint inhibitor; combined treatment; local solution; global solution; existence and uniqueness

当癌细胞发生坏死时, 它们释放高活性组蛋白-1 (HMGB-1) 激活树突细胞, 树突细胞便产生 IL-12 来激活效应 T 细胞 CD4⁺ Th1 和 CD8⁺ T。CD4⁺ Th1 和 CD8⁺ T 细胞都能杀死癌细胞^[1-3]。CD8⁺ T 细胞在杀死癌细胞方面更有效, 但 CD4⁺ Th1 细胞的辅助功能可提高肿瘤反应性 CD8⁺ T 细

胞的能效^[4]。癌症疫苗可以扩大肿瘤特异性 T 细胞的储备, 也可以激活休眠的肿瘤特异性 T 细胞^[5]。由于缺乏肿瘤浸润效应 T 细胞, 临床试验中的许多患者对检查点抑制剂治疗没有反应; 另一方面, 癌症疫苗可以诱导效应 T 细胞浸润到肿瘤

^{*} 收稿日期: 2018-10-11

基金项目: 国家自然科学基金 (11101095); 广东省高校特色创新类项目 (2016KTSCX028); 广东省高层次人才项目 (2014011); 研究生教育创新项目 (2014QTLXXM17); 广东省医学科研基金 (A2018339); 南方医科大学口腔医院科研培育计划 (PY2017017)

作者简介: 刘春燕 (1994 年生), 女; 研究方向: 偏微分方程; E-mail: 2460298996@qq.com

通信作者: 卫雪梅 (1972 年生), 女; 研究方向: 偏微分方程; E-mail: wxm_gdut@163.com

刘成霞 (1981 年生), 女; 研究方向: 口腔临床医学; E-mail: 349471214@qq.com

中,而且癌症疫苗和免疫检查点抑制剂的组合可以协同作用以诱导更有效的抗肿瘤免疫反应^[6-8]。

早期在文献[9-10]中提出了用常微分方程系统描述癌症疫苗免疫治疗的数学模型,但这些模型没有考虑检查点抑制剂。2017年,Lai等^[11]认为疫苗增加T细胞库,检查点抑制剂使T细胞保持完全活性,杀死癌细胞,从而提出了一种将癌症疫苗与检查点抑制剂结合起来的数学模型。在该模型中Lai等进行了数值模拟,对数值解进行渐近分析^[11]。具体模型如下:

$$\begin{aligned} \frac{\partial D}{\partial t} + \nabla \cdot (\vec{u}D) - \delta_1 \nabla^2 D = \\ \lambda_1 D_0 \frac{C}{K_1 + C} + \lambda_2 \frac{G}{K_2 + G} - d_1 D, \\ 0 \leq r \leq R(t), \quad t > 0; \end{aligned} \quad (1)$$

$$\begin{aligned} \frac{\partial T_1}{\partial t} + \nabla \cdot (\vec{u}T_1) - \delta_2 \nabla^2 T_1 = \\ (\lambda_3 T_{10} \frac{I_1}{K_3 + I_1} + \lambda_4 T_1 \frac{I_2}{K_4 + I_2}) \times \\ \frac{1}{1 + \frac{Q}{K_5}} - d_2 T_1, 0 \leq r \leq R(t), t > 0; \quad (2) \\ \frac{\partial T_2}{\partial t} + \nabla \cdot (\vec{u}T_2) - \delta_2 \nabla^2 T_2 = \\ \left(\lambda_5 T_{20} \frac{I_1}{K_3 + I_1} + \lambda_6 T_2 \frac{I_2}{K_4 + I_2} \right) \times \\ \frac{1}{1 + \frac{Q}{K_5}} - d_3 T_2, 0 \leq r \leq R(t), t > 0; \quad (3) \end{aligned}$$

$$\begin{aligned} \frac{\partial C}{\partial t} + \nabla \cdot (\vec{u}C) - \delta_3 \nabla^2 C = \\ \lambda_7 C \left(1 - \frac{C}{C_M} \right) - (\theta_1 T_1 C + \theta_2 T_2 C) - d_4 C, \\ 0 \leq r \leq R(t), \quad t > 0; \end{aligned} \quad (4)$$

$$\begin{aligned} \frac{\partial G}{\partial t} - \delta_4 \nabla^2 G = \lambda_8 + \hat{G}(t) - d_5 G, \\ 0 \leq r \leq R(t), \quad t > 0; \end{aligned} \quad (5)$$

$$\begin{aligned} \frac{\partial I_1}{\partial t} - \delta_5 \nabla^2 I_1 = \lambda_9 D - d_6 I_1, \\ 0 \leq r \leq R(t), \quad t > 0; \end{aligned} \quad (6)$$

$$\begin{aligned} \frac{\partial I_2}{\partial t} - \delta_6 \nabla^2 I_2 = \lambda_{10} T_1 - d_7 I_2, \\ 0 \leq r \leq R(t), \quad t > 0; \end{aligned} \quad (7)$$

$$\begin{aligned} \frac{\partial P}{\partial t} + \nabla \cdot (\vec{u}P) - \delta_2 \nabla^2 P = \frac{P}{T_1 + T_2} \cdot \\ \left[(\lambda_3 T_{10} + \lambda_5 T_{20}) \frac{I_1}{K_3 + I_1} + \right. \\ \left. (\lambda_4 T_1 + \lambda_6 T_2) \frac{I_2}{K_4 + I_2} \right] \times \frac{1}{1 + \frac{Q}{K_5}} - \\ \frac{P}{T_1 + T_2} (d_2 T_1 + d_3 T_2) - \mu P A, \\ 0 \leq r \leq R(t), \quad t > 0; \end{aligned} \quad (8)$$

$$\begin{aligned} \frac{\partial A}{\partial t} - \delta_7 \nabla^2 A = \hat{A}(t) - \mu P A - d_8 A, \\ 0 \leq r \leq R(t), \quad t > 0; \end{aligned} \quad (9)$$

$$\begin{aligned} \nabla \cdot \vec{u} = h(D, T_1, T_2, C, G, I_1, I_2, Q), \\ 0 \leq r \leq R(t), \quad t > 0; \end{aligned} \quad (10)$$

$$\frac{dR(t)}{dt} = u(R(t), t), \quad t > 0; \quad (11)$$

$$u(0, t) = 0; \quad (12)$$

$$\begin{aligned} \frac{\partial D}{\partial r} \Big|_{r=0} = \frac{\partial D}{\partial r} \Big|_{r=R(t)} = 0, \\ D(r, 0) = D_0(r); \end{aligned} \quad (13)$$

$$\frac{\partial T_1}{\partial r} \Big|_{r=0} = 0, \quad \frac{\partial T_1}{\partial r} \Big|_{r=R(t)} +$$

$$\begin{aligned} \sigma_0 \frac{I_1}{I_1 + K_3} (T_1 - \hat{T}_1) \Big|_{r=R(t)} = 0, \\ T_1(r, 0) = T_{10}(r); \end{aligned} \quad (14)$$

$$\frac{\partial T_2}{\partial r} \Big|_{r=0} = 0, \quad \frac{\partial T_2}{\partial r} \Big|_{r=R(t)} +$$

$$\begin{aligned} \sigma_0 \frac{I_1}{I_1 + K_3} (T_2 - \hat{T}_2) \Big|_{r=R(t)} = 0, \\ T_2(r, 0) = T_{20}(r); \end{aligned} \quad (15)$$

$$\begin{aligned} \frac{\partial C}{\partial r} \Big|_{r=0} = \frac{\partial C}{\partial r} \Big|_{r=R(t)} = 0, \\ C(r, 0) = C_0(r); \end{aligned} \quad (16)$$

$$\begin{aligned} \frac{\partial G}{\partial r} \Big|_{r=0} = \frac{\partial G}{\partial r} \Big|_{r=R(t)} = 0, \\ G(r, 0) = G_0(r); \end{aligned} \quad (17)$$

$$\frac{\partial I_1}{\partial r} \Big|_{r=0} = \frac{\partial I_1}{\partial r} \Big|_{r=R(t)} = 0,$$

$$I_1(r, 0) = I_{10}(r); \quad (18)$$

$$\left. \frac{\partial I_2}{\partial r} \right|_{r=0} = \left. \frac{\partial I_2}{\partial r} \right|_{r=R(t)} = 0,$$

$$I_2(r, 0) = I_{20}(r); \quad (19)$$

$$\left. \frac{\partial P}{\partial r} \right|_{r=0} = \left. \frac{\partial P}{\partial r} \right|_{r=R(t)} = 0,$$

$$P(r, 0) = P_0(r); \quad (20)$$

$$\left. \frac{\partial A}{\partial r} \right|_{r=0} = \left. \frac{\partial A}{\partial r} \right|_{r=R(t)} = 0,$$

$$A(r, 0) = A_0(r); \quad (21)$$

$$R(0) = R_0 \quad (22)$$

$$h(D, T_1, T_2, C, G, I_1, I_2, Q) =$$

$$c \left[\lambda_1 D_0 \frac{C}{K_1 + C} + \lambda_2 \frac{G}{K_2 + G} + \frac{1}{1 + \frac{Q}{K_5}} \left((\lambda_3 T_{10} + \lambda_5 T_{20}) \frac{I_1}{K_3 + I_1} + \right. \right.$$

$$\left. (\lambda_4 T_1 + \lambda_6 T_2) \frac{I_2}{K_4 + I_2} \right) +$$

$$\lambda_7 C \left(1 - \frac{C}{C_M} \right) - (\theta_1 T_1 C + \theta_2 T_2 C) - (d_1 D + d_2 T_1 + d_3 T_2 + d_4 C) \quad (23)$$

$$C + D + T_1 + T_2 = N_0 \quad (24)$$

其中 $D, T_1, T_2, C, G, I_1, I_2, P, A$ 分别为树突细胞 (DC) 的密度, 活化的 $CD4^+$ T 细胞的密度, 活化的 $CD8^+$ T 细胞的密度, 癌细胞密度, GM-CSF 浓度, IL-12 浓度, IL-2 浓度, PD-1 浓度, 抗 PD-1 浓度; $\delta_n (n = 1, 2, \dots, 7), K_i (i = 1, 2, \dots, 5), d_j (j = 1, 2, \dots, 8), \lambda_k (k = 1, 2, \dots, 10), \theta_1, \theta_2, \mu, D_0, T_{10}, T_{20}, C_M, N_0$ 为正常数。 $\hat{G}(t)$ 是 GM-CSF 的来源, 表达式如下:

$$\hat{G}(t) = \begin{cases} \gamma_G, & t \leq 30 \\ \gamma_G \times \frac{33-t}{3}, & 30 < t \leq 33 \\ 0, & t > 33 \end{cases}$$

γ_G 是正常数, 表示药物的有效水平, 显然 $\hat{G}(t)$ 是有界且连续的。

另外, $P = \rho_P (T_1 + T_2), L = \rho_L (T_1 + T_2 + \varepsilon C), Q = \sigma PL$, 则 $Q = \sigma P \rho_L (T_1 + T_2 + \varepsilon C)$ 且 ρ_P, ρ_L 与 ε 均为正常数; 而 $\hat{A}(t)$ 是抗 PD-1 的来源且表达式为:

$$\hat{A}(t) = \begin{cases} \gamma_A, & t \leq 30; \\ \gamma_A \times \frac{33-t}{3}, & 30 < t \leq 33; \\ 0, & t > 33 \end{cases}$$

γ_A 是正常数, 表示药物的有效水平, 显然

$\hat{A}(t)$ 也是有界且连续的。

1999 年 Friedman 及其合作者考虑了肿瘤生长的自由边界问题^[14], 得到了模型整体解的存在唯一性、稳态解以及解的渐近性态。之后, 大量数学工作者对肿瘤生长的自由边界问题进行了一系列研究^[15-18]。

根据生物学和医学原理, 我们有以下假设:

(A) $D_0(r), T_{10}(r), T_{20}(r), C_0(r), I_{10}(r), I_{20}(r), P_0(r), A_0(r) \in D_p(0, 1), D_0(r), T_{10}(r), T_{20}(r), C_0(r), I_{10}(r), I_{20}(r), P_0(r), A_0(r) \geq 0$ 。

本文的主要结论如下:

定理 1 假设条件 (A) 满足, 则对任意的 $T > 0$, 系统 (1) ~ (22) 的整体解存在且唯一。

1 预备引理

下面我们将介绍一些引理, 首先引入一些记号。

(i) 记 $\Omega_T = \{(r, t) : 0 < r < L, 0 < t < T\}, T > 0$ 。 $\bar{\Omega}_T$ 是 Ω_T 的闭包。 $W_p^{2,1}(\Omega_T)$ 定义如下

$$W_p^{2,1}(\Omega_T) = \{u, v \in L^p(\Omega_T) \mid u_t, v_t, \nabla u, \nabla v, \Delta u, \Delta v \in L^p(\Omega_T)\}$$

且规定

$$\|u\|_{W_p^{2,1}(\Omega_T)} = \sum_{|m|+2k \leq 2} \|\partial_x^m \partial_t^k u\|_{L^p}$$

(ii) 对 $p > \frac{5}{2}$, 记 $D_p(0, 1)$ 为 $t = 0$ 时 $W_p^{2,1}(\Omega_T)$ 的迹空间, i. e. $\varphi \in D_p(0, 1)$ 当且仅当 $\exists u \in W_p^{2,1}(\Omega_T)$ 使得 $u(\cdot, 0) = \varphi$ 。定义 $D_p(0, 1)$ 中的范数如下:

$$\|\varphi\|_{D_p(0,1)} =$$

$$\{T_p^{-1} \|u\|_{W_p^{2,1}(\Omega_T)} \mid u \in W_p^{2,1}(\Omega_T), u(\cdot, x) = \varphi(x)\}$$

由于 $p > \frac{5}{2}$, $W_p^{2,1}(\Omega_T)$ 连续嵌入到 $C(\Omega_T)$ (见文献 [13]), 上面的定义是有意义的。而且, 显然如果 $\varphi \in W^{2,p}(0, 1)$, 则 $\varphi \in D_p(0, 1)$ 且 $\|\varphi\|_{D_p(0,1)} \leq \|\varphi\|_{W^{2,p}(0,1)}$ 。

引理 1^[12] 假设 D 是一个正常数, $a(z, \tau), b(z, \tau)$ 是定义在区间 $\bar{\Omega}_T$ 上的有界连续函数, $f(z, \tau) \in L^p(\Omega_T), \varphi \in C^1[0, T]$, 且对任意的 $1 < p < \infty, c_0 \in D_p(0, L)$ 。令 $Bu = \alpha \frac{\partial u}{\partial n} + \beta(x, \tau)u$, 其中

(i) $\alpha = 0, \beta = 1$, (ii) $\alpha = 1, \beta \geq 0$, 则初边值问题

$$\frac{\partial c}{\partial \tau} = D \frac{\partial^2 c}{\partial z^2} + a(z, \tau) \frac{\partial c}{\partial z} + b(z, \tau)c + f(z, \tau),$$

$$0 \leq z \leq 1, 0 \leq \tau \leq T; \quad (25)$$

$$z = 0, 1; Bc = \varphi, 0 \leq \tau \leq T; \quad (26)$$

$$c(z, 0) = c_0(z), 0 \leq z \leq 1 \quad (27)$$

有唯一解 $c(z, \tau) \in W_p^{2,1}(\Omega_T)$, 且

$$\|c\|_{W_p^{2,1}(\Omega_T)} \leq$$

$$C_p(T) (\|c_0\|_{D_p(0,L)} + \|\varphi\|_{W^{1,p}(0,T)} + \|f\|_{L^p})$$

其中 $C_p(T)$ 是一个依赖于 $p, T, \|a\|_\infty, \|b\|_\infty$ 的常数, 且对任意有界的 $T, C_p(T)$ 是有界的。

2 模型的等价形式

考虑到直接解决自由边界问题 (1) ~ (22) 的困难性, 我们将该自由边界问题变换为固定区域 $\{(z, \tau), 0 \leq z \leq 1, \tau \geq 0\}$ 上的初边值问题, 以利于讨论其解的适定性。

作变换 $(D, T_1, T_2, C, G, I_1, I_2, P, A, R(t)) \rightarrow (D', T'_1, T'_2, C', G', I'_1, I'_2, P', A', \eta(\tau))$ 如下

$$z = \frac{r}{R(t)}, \tau = \int_0^t \frac{ds}{R^2(s)}, \eta(\tau) = R(t),$$

$$D'(z, \tau) = D(r, t), C'(z, \tau) = C(r, t),$$

$$G'(z, \tau) = G(r, t), T'_1(z, \tau) = T_1(r, t),$$

$$T'_2(z, \tau) = T_2(r, t), I'_1(z, \tau) = I_1(r, t),$$

$$I'_2(z, \tau) = I_2(r, t); \quad (28)$$

$$P'(z, \tau) = P(r, t), A'(z, \tau) = A(r, t),$$

$$u'(z, \tau) = R(t)u(r, t),$$

$$Q'(z, \tau) = Q(r, t)$$

又由于 $P' = \rho_p(T'_1 + T'_2)$, 于是问题 (1) ~ (22) 变换为

$$\begin{aligned} \frac{\partial D'}{\partial \tau} + v(z, \tau) \frac{\partial D'}{\partial z} - \delta_1 \frac{1}{z^2} \frac{\partial}{\partial z} \left(z^2 \frac{\partial D'}{\partial z} \right) = \\ \eta^2 \left(\lambda_1 D_0 \frac{C'}{K_1 + C'} + \lambda_2 \frac{G'}{K_2 + G'} - d_1 D' - h' D' \right), \\ 0 \leq z \leq 1, \quad \tau > 0; \end{aligned} \quad (29)$$

$$\frac{\partial D'}{\partial z} \Big|_{z=0} = \frac{\partial D'}{\partial z} \Big|_{z=1} = 0, \quad D'(z, 0) = D'_0(z); \quad (30)$$

$$\begin{aligned} \frac{\partial T'_1}{\partial \tau} + v(z, \tau) \frac{\partial T'_1}{\partial z} - \delta_2 \frac{1}{z^2} \frac{\partial}{\partial z} \left(z^2 \frac{\partial T'_1}{\partial z} \right) = \\ \eta^2 \left[\left(\lambda_3 T_{10} \frac{I'_1}{K_3 + I'_1} + \lambda_4 T'_1 \frac{I'_2}{K_4 + I'_2} \right) \times \right. \\ \left. \frac{1}{1 + \frac{Q'}{K_5}} - d_2 T'_1 - h' T'_1 \right], \end{aligned}$$

$$0 \leq z \leq 1, \tau > 0; \quad (31)$$

$$\frac{\partial T'_1}{\partial z} \Big|_{z=0} = 0, \quad \frac{\partial T'_1}{\partial z} \Big|_{z=1} +$$

$$\begin{aligned} \sigma_0 \frac{I'_1}{I'_1 + K_3} (T'_1 - \hat{T}_1) \Big|_{z=1} = 0, \\ T'_1(z, 0) = T'_{10}(z); \end{aligned} \quad (32)$$

$$\frac{\partial T'_2}{\partial \tau} + v(z, \tau) \frac{\partial T'_2}{\partial z} - \delta_2 \frac{1}{z^2} \frac{\partial}{\partial z} \left(z^2 \frac{\partial T'_2}{\partial z} \right) =$$

$$\begin{aligned} \eta^2 \left[\left(\lambda_5 T_{20} \frac{I'_1}{K_3 + I'_1} + \lambda_6 T'_2 \frac{I'_2}{K_4 + I'_2} \right) \times \right. \\ \left. \frac{1}{1 + \frac{Q'}{K_5}} - d_3 T'_2 - h' T'_2 \right], \end{aligned}$$

$$0 \leq z \leq 1, \tau > 0; \quad (33)$$

$$\begin{aligned} \frac{\partial T'_2}{\partial z} \Big|_{z=0} = 0, \\ \frac{\partial T'_2}{\partial z} \Big|_{z=1} + \sigma_0 \frac{I'_1}{I'_1 + K_3} (T'_2 - \hat{T}_2) \Big|_{z=1} = 0, \end{aligned}$$

$$T'_2(z, 0) = T'_{20}(z); \quad (34)$$

$$\frac{\partial C'}{\partial \tau} + v(z, \tau) \frac{\partial C'}{\partial z} - \delta_3 \frac{1}{z^2} \frac{\partial}{\partial z} \left(z^2 \frac{\partial C'}{\partial z} \right) =$$

$$\eta^2 \left[\lambda_7 C' \left(1 - \frac{C'}{C_M} \right) - \right.$$

$$\left. (\theta_1 T'_1 C' + \theta_2 T'_2 C') - d_4 C' - h' C' \right],$$

$$0 \leq z \leq 1, \quad \tau > 0; \quad (35)$$

$$\frac{\partial C'}{\partial z} \Big|_{z=0} = \frac{\partial C'}{\partial z} \Big|_{z=1} = 0, \quad C'(z, 0) = C'_0(z); \quad (36)$$

$$\frac{\partial G'}{\partial \tau} + u'(1, \tau) z \frac{\partial G'}{\partial z} - \delta_4 \frac{1}{z^2} \frac{\partial}{\partial z} \left(z^2 \frac{\partial G'}{\partial z} \right) =$$

$$\eta^2 (\lambda_8 + \hat{G}(t) - d_5 G'), 0 \leq z \leq 1, \quad \tau > 0; \quad (37)$$

$$\frac{\partial G'}{\partial z} \Big|_{z=0} = \frac{\partial G'}{\partial z} \Big|_{z=1} = 0, \quad G'(z, 0) = G'_0(z); \quad (38)$$

$$\frac{\partial I'_1}{\partial \tau} + u'(1, \tau) z \frac{\partial I'_1}{\partial z} - \delta_5 \frac{1}{z^2} \frac{\partial}{\partial z} \left(z^2 \frac{\partial I'_1}{\partial z} \right) =$$

$$\eta^2 (\lambda_9 D' - d_6 I'_1), \quad 0 \leq z \leq 1, \quad \tau > 0; \quad (39)$$

$$\left. \frac{\partial I'_1}{\partial z} \right|_{z=0} = \left. \frac{\partial I'_1}{\partial z} \right|_{z=1} = 0,$$

$$I'_1(z, 0) = I'_{10}(z); \quad (40)$$

$$\begin{aligned} \frac{\partial I'_2}{\partial \tau} - u'(1, \tau)z \frac{\partial I'_2}{\partial z} - \delta_6 \frac{1}{z^2} \frac{\partial}{\partial z} \left(z^2 \frac{\partial I'_2}{\partial z} \right) = \\ \eta^2 (\lambda_{10} T'_{11} - d_7 I'_2), \\ 0 \leq z \leq 1, \quad \tau > 0; \end{aligned} \quad (41)$$

$$\left. \frac{\partial I'_2}{\partial z} \right|_{z=0} = \left. \frac{\partial I'_2}{\partial z} \right|_{z=1} = 0, I'_2(z, 0) = I'_{20}(z); \quad (42)$$

$$\begin{aligned} \frac{\partial A'}{\partial \tau} - u'(1, \tau)z \frac{\partial A'}{\partial z} - \delta_7 \frac{1}{z^2} \frac{\partial}{\partial z} \left(z^2 \frac{\partial A'}{\partial z} \right) = \\ \eta^2 (\hat{A}(t) - \mu P' A' - d_8 A'), \\ 0 \leq z \leq 1, \quad \tau > 0; \end{aligned} \quad (43)$$

$$\begin{aligned} \left. \frac{\partial A'}{\partial z} \right|_{z=0} = \left. \frac{\partial A'}{\partial z} \right|_{z=1} = 0, \\ A'(z, 0) = A'_0(z); \quad (44) \\ v(z, \tau) = u'(z, \tau) - zu'(1, \tau), \\ 0 \leq z \leq 1, \quad \tau > 0; \end{aligned} \quad (45)$$

$$\begin{aligned} \frac{1}{z^2} \frac{\partial}{\partial z} (z^2 u') = \\ \eta(\tau)^2 h(D', T'_{11}, T'_{22}, C', G', I'_{11}, I'_{22}, Q') = \eta^2 h', \\ 0 \leq z \leq 1, \quad \tau > 0; \end{aligned} \quad (46)$$

$$\begin{aligned} \frac{d\eta(\tau)}{dt} = \eta(\tau)u'(1, \tau), \quad \tau > 0; \quad (47) \\ u'(0, \tau) = 0; \quad (48) \\ \eta(0) = R_0 \quad (49) \end{aligned}$$

根据以上变换过程, 可以得出如下结论:

引理 2 在变量替换 (28) 下, 自由边界问题 (1) ~ (22) 与初边值问题 (29) ~ (49) 等价。

3 局部解的存在唯一性

这部分将证明系统 (29) ~ (49) 有唯一的整体解。先通过运用 Banach 不动点定理证明系统 (29) ~ (49) 有唯一的局部解。记

$$U = (D', T'_{11}, T'_{22}, C', G', I'_{11}, I'_{22}, P', A'),$$

$$\tilde{U} = (\tilde{D}', \tilde{T}'_{11}, \tilde{T}'_{22}, \tilde{C}', \tilde{G}', \tilde{I}'_{11}, \tilde{I}'_{22}, \tilde{P}', \tilde{A}');$$

$$U_1 = (D'_{11}, T'_{11}, T'_{21}, C'_{11}, G'_{11}, I'_{11}, I'_{21}, P'_{11}, A'_{11}),$$

$$U_2 = (D'_{22}, T'_{12}, T'_{22}, C'_{22}, G'_{22}, I'_{12}, I'_{22}, P'_{22}, A'_{22})$$

对给定的 $T > 0$ 和正常数 M , 引进度量空间 (X_T, d) 如下: X_T 由向量函数 $(U, \eta) = (U, \eta(\tau))$ ($0 \leq z \leq 1, 0 \leq \tau \leq T$) 组成, 满足如下条件:

$$(i) \quad \eta(\tau) \in C[0, T], \eta(0) = R_0, \frac{1}{2}R_0 \leq$$

$$\eta(\tau) \leq 2R_0;$$

$$(ii) \quad D', T'_{11}, T'_{22}, C', G', I'_{11}, I'_{22}, P', A' \in C(\bar{\Omega}_T), \\ 0 \leq D', T'_{11}, T'_{22}, C', G', I'_{11}, I'_{22}, P', A' \leq M;$$

$$(iii) \quad |h(D', T'_{11}, T'_{22}, C', G', I'_{11}, I'_{22}, Q')| \leq B \\ (B \text{ 为正常数}), \text{ 即 } |h'| \leq B.$$

定义空间 X_T 上的度量为

$$d((U_1, \eta_1), (U_2, \eta_2)) =$$

$$\|U_1 - U_2\| + \|\eta_1 - \eta_2\| (0 \leq z \leq 1, 0 \leq \tau \leq T)$$

显然 (X_T, d) 是一个完备度量空间。由式 (46)、式 (48) 得

$$u'(z, \tau) = \frac{\eta^2(\tau)}{z^2} \int_0^z h's^2 ds \quad (50)$$

对任意 $(U, \eta) \in X_T$, 定义一个空间 X_T 上的映射 $F: (U, \eta) \rightarrow (\tilde{U}, \tilde{\eta}): (\tilde{U}, \tilde{\eta}) = F(U, \eta)$ 满足如下问题:

$$\frac{d\tilde{\eta}(\tau)}{d\tau} = \tilde{\eta}(\tau)u'(1, \tau); \quad (51)$$

$$\tilde{\eta}(0) = R_0; \quad (52)$$

$$\begin{aligned} \frac{\partial \tilde{D}'}{\partial \tau} + v(z, \tau) \frac{\partial \tilde{D}'}{\partial z} - \delta_1 \frac{1}{z^2} \frac{\partial}{\partial z} \left(z^2 \frac{\partial \tilde{D}'}{\partial z} \right) = \\ \eta^2 \left(\lambda_1 D_0 \frac{C'}{K_1 + C'} + \lambda_2 \frac{G'}{K_2 + G'} - d_1 \tilde{D}' - h' \tilde{D}' \right), \\ 0 \leq z \leq 1, \quad \tau > 0; \end{aligned} \quad (53)$$

$$\left. \frac{\partial \tilde{D}'}{\partial z} \right|_{z=0} = \left. \frac{\partial \tilde{D}'}{\partial z} \right|_{z=1} = 0,$$

$$\tilde{D}'(z, 0) = D'_0(z); \quad (54)$$

$$\begin{aligned} \frac{\partial \tilde{T}'_1}{\partial \tau} + v(z, \tau) \frac{\partial \tilde{T}'_1}{\partial z} - \delta_2 \frac{1}{z^2} \frac{\partial}{\partial z} \left(z^2 \frac{\partial \tilde{T}'_1}{\partial z} \right) = \\ \eta^2 \left[\left(\lambda_3 T_{10} \frac{I'_1}{K_3 + I'_1} + \lambda_4 \tilde{T}'_1 \frac{I'_2}{K_4 + I'_2} \right) \times \right. \\ \left. \frac{1}{1 + \frac{Q'}{K_5}} - d_2 \tilde{T}'_1 - h' \tilde{T}'_1 \right], \end{aligned}$$

$$0 \leq z \leq 1, \tau > 0; \quad (55)$$

$$\begin{aligned} \frac{\partial \tilde{T}'_1}{\partial z} \Big|_{z=0} &= 0, \frac{\partial \tilde{T}'_1}{\partial z} \Big|_{z=1} + \\ \sigma_0 \frac{I'_1}{I'_1 + K_3} (\tilde{T}'_1 - \hat{T}_1) \Big|_{z=1} &= 0, \\ \tilde{T}'_1(z, 0) &= T'_{10}(z); \end{aligned} \quad (56)$$

$$\begin{aligned} \frac{\partial \tilde{T}'_2}{\partial \tau} + v(z, \tau) \frac{\partial \tilde{T}'_2}{\partial z} - \delta_2 \frac{1}{z^2} \frac{\partial}{\partial z} \left(z^2 \frac{\partial \tilde{T}'_2}{\partial z} \right) = \\ \eta^2 \left[\left(\lambda_5 T_{20} \frac{I'_1}{K_3 + I'_1} + \lambda_6 \tilde{T}'_2 \frac{I'_2}{K_4 + I'_2} \right) \cdot \right. \\ \left. \frac{1}{1 + \frac{Q'}{K_5}} - d_3 \tilde{T}'_2 - h'_2 \tilde{T}'_2 \right], \end{aligned}$$

$$0 \leq z \leq 1, \tau > 0; \quad (57)$$

$$\begin{aligned} \frac{\partial \tilde{T}'_2}{\partial z} \Big|_{z=0} &= 0, \\ \frac{\partial \tilde{T}'_2}{\partial z} \Big|_{z=1} + \sigma_0 \frac{I'_1}{I'_1 + K_3} (\tilde{T}'_2 - \hat{T}_2) \Big|_{z=1} &= 0, \end{aligned}$$

$$\tilde{T}'_2(z, 0) = T'_{20}(z); \quad (58)$$

$$\begin{aligned} \frac{\partial \tilde{C}'}{\partial \tau} + v(z, \tau) \frac{\partial \tilde{C}'}{\partial z} - \delta_3 \frac{1}{z^2} \frac{\partial}{\partial z} \left(z^2 \frac{\partial \tilde{C}'}{\partial z} \right) = \\ \eta^2 \left[\lambda_7 \tilde{C}' \left(1 - \frac{C'}{C_M} \right) - (\theta_1 T'_{11} \tilde{C}' + \theta_2 T'_{12} \tilde{C}') - \right. \\ \left. d_4 \tilde{C}' - h' \tilde{C}' \right], 0 \leq z \leq 1, \tau > 0; \quad (59) \\ \frac{\partial \tilde{C}'}{\partial z} \Big|_{z=0} = \frac{\partial \tilde{C}'}{\partial z} \Big|_{z=1} = 0, \quad \tilde{C}'(z, 0) = C'_0(z); \end{aligned} \quad (60)$$

$$\begin{aligned} \frac{\partial \tilde{G}'}{\partial \tau} + u'(1, \tau) z \frac{\partial \tilde{G}'}{\partial z} - \delta_4 \frac{1}{z^2} \frac{\partial}{\partial z} \left(z^2 \frac{\partial \tilde{G}'}{\partial z} \right) = \\ \eta^2 (\lambda_8 + \hat{G}(t) - d_5 \tilde{G}'), 0 \leq z \leq 1, \tau > 0; \end{aligned} \quad (61)$$

$$\frac{\partial \tilde{G}'}{\partial z} \Big|_{z=0} = \frac{\partial \tilde{G}'}{\partial z} \Big|_{z=1} = 0,$$

$$\tilde{G}'(z, 0) = G'_0(z); \quad (62)$$

$$\begin{aligned} \frac{\partial \tilde{I}'_1}{\partial \tau} + u'(1, \tau) z \frac{\partial \tilde{I}'_1}{\partial z} - \delta_5 \frac{1}{z^2} \frac{\partial}{\partial z} \left(z^2 \frac{\partial \tilde{I}'_1}{\partial z} \right) = \\ \eta^2 (\lambda_9 D' - d_6 \tilde{I}'_1), 0 \leq z \leq 1, \tau > 0; \end{aligned} \quad (63)$$

$$\begin{aligned} \frac{\partial \tilde{I}'_1}{\partial z} \Big|_{z=0} = \frac{\partial \tilde{I}'_1}{\partial z} \Big|_{z=1} = 0, \tilde{I}'_1(z, 0) = I'_{10}(z); \end{aligned} \quad (64)$$

$$\begin{aligned} \frac{\partial \tilde{I}'_2}{\partial \tau} - u'(1, \tau) z \frac{\partial \tilde{I}'_2}{\partial z} - \delta_6 \frac{1}{z^2} \frac{\partial}{\partial z} \left(z^2 \frac{\partial \tilde{I}'_2}{\partial z} \right) = \\ \eta^2 (\lambda_{10} T'_{11} - d_7 \tilde{I}'_2), \\ 0 \leq z \leq 1, \tau > 0; \end{aligned} \quad (65)$$

$$\begin{aligned} \frac{\partial \tilde{I}'_2}{\partial z} \Big|_{z=0} = \frac{\partial \tilde{I}'_2}{\partial z} \Big|_{z=1} = 0, \tilde{I}'_2(z, 0) = I'_{20}(z); \end{aligned} \quad (66)$$

$$\begin{aligned} \frac{\partial \tilde{A}'}{\partial \tau} - u'(1, \tau) z \frac{\partial \tilde{A}'}{\partial z} - \delta_7 \frac{1}{z^2} \frac{\partial}{\partial z} \left(z^2 \frac{\partial \tilde{A}'}{\partial z} \right) = \\ \eta^2 (\hat{A}(t) - \mu P' \tilde{A}' - d_8 \tilde{A}'), 0 \leq z \leq 1, \tau > 0; \end{aligned} \quad (67)$$

$$\begin{aligned} \frac{\partial \tilde{A}'}{\partial z} \Big|_{z=0} = \frac{\partial \tilde{A}'}{\partial z} \Big|_{z=1} = 0, \tilde{A}'(z, 0) = A'_0(z) \end{aligned} \quad (68)$$

首先证 F 是映射空间 X_T 到自身的映射。

(I₁) 若 $(U, \eta) \in X_T$, 考虑问题 (51) ~ (52), 显然有唯一解 $\tilde{\eta}(\tau) \in C^1[0, T]$:

$$\tilde{\eta}(\tau) = R_0 e^{\int_0^\tau u'(1, s) ds} \quad (69)$$

考虑问题 (51), 利用条件 (i) 和 (iii), 可得

$$|u'(1, \tau)| \leq \frac{4}{3} B_0 R_0^2 \quad (70)$$

结合式 (69) 得

$$R_0 e^{-\frac{4}{3} B_0 R_0^2 T} \leq \tilde{\eta}(\tau) \leq R_0 e^{\frac{4}{3} B_0 R_0^2 T}, 0 \leq \tau \leq T$$

当 T 且足够小时, 满足 $e^{\frac{4}{3} B_0 R_0^2 T} \leq 2$, 此时 $\frac{1}{2} R_0 \leq$

$\eta(\tau) \leq 2R_0$, 因此满足条件 (i)。

(I₂) 考虑问题 (53) ~ (54),

$$\eta^2 \left(\lambda_1 D_0 \frac{C'}{K_1 + C'} + \lambda_2 \frac{G'}{K_2 + G'} \right) \in L^p(\Omega_T)$$

由引理 1 知它有唯一解 $\tilde{D}' \in W_p^{2,1}(\Omega_T)$, 且满足

$$\|\tilde{D}'\|_{W_p^{2,1}(\Omega_T)} \leq C(T) \left(\|D'_0(z)\|_{D_p(0,L)} + \left\| \eta^2 \left(\lambda_1 D_0 \frac{C'}{K_1 + C'} + \lambda_2 \frac{G'}{K_2 + G'} \right) \right\|_{L^p} \right) \leq C(T)K$$

K 为依赖于 $D'_0(z)$ 和 M 的正常数。

(I₃) 同理, 由引理 1 知问题 (55) ~ (68) 有唯一解 $\tilde{T}'_1, \tilde{T}'_2, \tilde{C}', \tilde{G}', \tilde{I}'_1, \tilde{I}'_2, \tilde{A}' \in W_p^{2,1}(\Omega_T)$, 且满足

$$\|\tilde{T}'_1, \tilde{T}'_2, \tilde{C}', \tilde{G}', \tilde{I}'_1, \tilde{I}'_2, \tilde{A}'\|_{W_p^{2,1}(\Omega_T)} \leq C(T)K$$

由于

$$\tilde{P}' = \rho_p(\tilde{T}'_1 + \tilde{T}'_2)$$

则有 $\|\tilde{P}'\|_{W_p^{2,1}(\Omega_T)} \leq C(T)K$, 因此

$$\|\tilde{T}'_1, \tilde{T}'_2, \tilde{C}', \tilde{G}', \tilde{I}'_1, \tilde{I}'_2, \tilde{P}', \tilde{A}'\|_{W_p^{2,1}(\Omega_T)} \leq C(T)K$$

综上所述, 若取 $K > 0$, 则当 $T > 0$ 充分小时, $C(T)$ 是有界的, $C(T)K \leq M$, 有

$$\|\tilde{T}'_1, \tilde{T}'_2, \tilde{C}', \tilde{G}', \tilde{I}'_1, \tilde{I}'_2, \tilde{P}', \tilde{A}'\|_{W_p^{2,1}(\Omega_T)} \leq M$$

利用嵌入定理

$$W_p^{2,1}(\Omega_T) \subset C^{\lambda, \frac{\lambda}{2}}(\Omega_T) \left(p > \frac{5}{2}, \lambda = 2 - \frac{5}{p} \right)$$

得

$$\|\tilde{T}'_1, \tilde{T}'_2, \tilde{C}', \tilde{G}', \tilde{I}'_1, \tilde{I}'_2, \tilde{P}', \tilde{A}'\|_{\infty} \leq M$$

因此 $\tilde{T}'_1, \tilde{T}'_2, \tilde{C}', \tilde{G}', \tilde{I}'_1, \tilde{I}'_2, \tilde{P}', \tilde{A}'$ 满足条件 (ii)。而且

$$\left\| \left(\frac{\partial \tilde{D}'}{\partial z}, \frac{\partial \tilde{T}'_1}{\partial z}, \frac{\partial \tilde{T}'_2}{\partial z}, \frac{\partial \tilde{C}'}{\partial z}, \frac{\partial \tilde{G}'}{\partial z}, \frac{\partial \tilde{I}'_1}{\partial z}, \frac{\partial \tilde{I}'_2}{\partial z}, \frac{\partial \tilde{P}'}{\partial z}, \frac{\partial \tilde{A}'}{\partial z} \right) \right\|_{\infty} \leq C(T)$$

这就证明了 $(\tilde{U}, \tilde{\eta}) \in X_T$, 所以 F 是 X_T 到 X_T 上的映射。

其次要证当 T 充分小时, 映射 F 压缩。

(II₁) 显然, 通过计算可得

$$|u'_1(z, \tau) - u'_2(z, \tau)| \leq C(T)d$$

因此由式 (69) 可得

$$\|\tilde{\eta}_1 - \tilde{\eta}_2\|_{\infty} \leq TC(T)d$$

(II₂) 记 $\tilde{D}^* = \tilde{D}'_1 - \tilde{D}'_2$, 则由问题 (53) ~ (54) 可得

$$\frac{\partial \tilde{D}^*}{\partial \tau} = \delta_1 \frac{1}{z^2} \frac{\partial}{\partial z} \left(z^2 \frac{\partial \tilde{D}^*}{\partial z} \right) -$$

$$v_1(z, \tau) \frac{\partial \tilde{D}^*}{\partial z} - \eta_1^2(d_1 + h'_1) \tilde{D}^* + f_D,$$

$$\frac{\partial \tilde{D}^*}{\partial z} \Big|_{z=0} = \frac{\partial \tilde{D}^*}{\partial z} \Big|_{z=1} = 0, \quad \tilde{D}^*(z, 0) = 0$$

其中

$$f_D = \lambda_1 D_0 \left(\eta_1^2 \frac{C'_1}{K_1 + C'_1} - \eta_2^2 \frac{C'_2}{K_1 + C'_2} \right) +$$

$$\lambda_2 \left(\eta_1^2 \frac{G'_1}{K_2 + G'_1} - \eta_2^2 \frac{G'_2}{K_2 + G'_2} \right) - (v_1 - v_2) \frac{\partial \tilde{D}'_2}{\partial z} -$$

$$(\eta_1^2 - \eta_2^2) d_1 \tilde{D}'_2 - (\eta_1^2 h'_1 - \eta_2^2 h'_2) \tilde{D}'_2$$

易知 $v_1(z, \tau), \eta_1^2(d_1 + h'_1)$ 均为有界连续函数以及 $f_D \in L^p(\Omega_T)$, 由解的最大模估计^[14], 有

$$\|\tilde{D}^*\|_{\infty} \leq T\|f\|_{\infty} =$$

$$T \left\| \lambda_1 D_0 \left(\eta_1^2 \frac{C'_1}{K_1 + C'_1} - \eta_2^2 \frac{C'_2}{K_1 + C'_2} \right) + \right.$$

$$\lambda_2 \left(\eta_1^2 \frac{G'_1}{K_2 + G'_1} - \eta_2^2 \frac{G'_2}{K_2 + G'_2} \right) - (v_1 - v_2) \frac{\partial \tilde{D}'_2}{\partial z} -$$

$$(\eta_1^2 - \eta_2^2) d_1 \tilde{D}'_2 - (\eta_1^2 h'_1 - \eta_2^2 h'_2) \tilde{D}'_2 \|_{\infty} \leq$$

$$T \left(\lambda_1 D_0 \left\| \eta_1^2 \frac{C'_1}{K_1 + C'_1} - \eta_2^2 \frac{C'_2}{K_1 + C'_2} \right\|_{\infty} + \right.$$

$$\lambda_2 \left\| \eta_1^2 \frac{G'_1}{K_2 + G'_1} - \eta_2^2 \frac{G'_2}{K_2 + G'_2} \right\|_{\infty} +$$

$$\|v_1 - v_2\|_{\infty} \left\| \frac{\partial \tilde{D}'_2}{\partial z} \right\|_{\infty} \Big) + (d_1 \|\eta_1^2 - \eta_2^2\|_{\infty} +$$

$$\|\eta_1^2 h'_1 - \eta_2^2 h'_2\|_{\infty}) \|\tilde{D}'_2\|_{\infty} \leq TC(T)Md$$

(II₃) 同理, 记

$$\tilde{T}_1^* = \tilde{T}'_{11} - \tilde{T}'_{12}, \quad \tilde{T}_2^* = \tilde{T}'_{21} - \tilde{T}'_{22},$$

$$\tilde{C}^* = \tilde{C}'_1 - \tilde{C}'_2, \quad \tilde{G}^* = \tilde{G}'_1 - \tilde{G}'_2,$$

$$\tilde{I}_1^* = \tilde{I}'_{11} - \tilde{I}'_{12}, \quad \tilde{I}_2^* = \tilde{I}'_{21} - \tilde{I}'_{22},$$

$$\tilde{A}^* = \tilde{A}'_1 - \tilde{A}'_2$$

则有

$$\|\tilde{T}_1^*\|_{\infty} \leq C(T)Md, \quad \|\tilde{T}_2^*\|_{\infty} \leq C(T)Md,$$

$$\|\tilde{C}^*\|_{\infty} \leq TC(T)Md, \quad \|\tilde{G}^*\|_{\infty} \leq TC(T)Md,$$

$$\|\tilde{I}_1^*\|_{\infty} \leq TC(T)Md, \quad \|\tilde{I}_2^*\|_{\infty} \leq$$

$$TC(T)Md, \|\tilde{A}^*\|_\infty \leq TC(T)Md$$

(II₄) 由于 $\|\tilde{T}_1^*\|_\infty \leq C(T)Md$, $\|\tilde{T}_2^*\|_\infty \leq C(T)Md$, 又因为 $P' = \rho_P(T'_1 + T'_2)$, 因此

$$\|\tilde{P}^*\|_\infty \leq C(T)Md$$

则由情形 (II₂) ~ (II₄) 可得

$$\|\tilde{U}_1 - \tilde{U}_2\|_\infty \leq C(T)Md$$

结合情形 (II₁) ~ (II₄), 可推出

$$d((\tilde{U}_1, \tilde{\eta}_1), (\tilde{U}_2, \tilde{\eta}_2)) =$$

$$\|\tilde{U}_1 - \tilde{U}_2\|_\infty + \|\tilde{\eta}_1 - \tilde{\eta}_2\|_\infty \leq C(T)Md$$

因此, 当 T 足够小时满足 $C(T)M < 1$, 此时 F 为压缩映射。

应用 Banach 不动点定理, 可知当 T 足够小时

F 在 X_T 中有唯一的不动点 $(\tilde{U}, \tilde{\eta})$, 它是问题 (51) ~ (68) 的局部唯一解, 其中 $0 \leq \tau \leq T$ 。

由上述分析可得如下结果:

定理 2 若条件 (A) 满足, 当 $0 \leq t \leq T$ 时, 系统 (1) ~ (22) 存在唯一解。

4 整体解的存在唯一性

由上下解原理得

引理 3 问题 (1) ~ (25) 的解有如下结论

$$D, T_1, T_2, C, G, I_1, I_2, P, A \geq 0$$

由式 (24) 知 $C + D + T_1 + T_2 = N_0$, 即 $C' + D' + T'_1 + T'_2 = N_0$, 则 $0 \leq C', D', T'_1, T'_2 \leq N_0$, 由 h 的表达式 (23) 可知, h' 为有界连续函数, 记

$$B = \max\{h' | 0 \leq C', D', T'_1, T'_2 \leq N_0\}$$

将式 (10) 变换为

$$\frac{1}{r^2} \frac{\partial}{\partial r}(r^2 u) = h$$

对上式关于 r 积分可得

$$u(r, t) = \frac{1}{r^2} \int_0^r h s^2 ds$$

则

$$-\frac{1}{3}Br \leq u(r, t) \leq \frac{1}{3}Br,$$

$$0 \leq r \leq R(t), \quad 0 \leq t \leq T$$

将上式代入式 (11) 得

$$-\frac{1}{3}BR(t) \leq \dot{R}(t) \leq \frac{1}{3}BR(t), \quad 0 \leq t \leq T$$

因此

$$R_0 e^{-\frac{1}{3}Bt} \leq R(t) \leq R_0 e^{\frac{1}{3}Bt}, \quad 0 \leq t \leq T$$

由此可得

$$R_0 e^{-\frac{1}{3}BT} \leq R(t) \leq R_0 e^{\frac{1}{3}BT}, \quad 0 \leq t \leq T$$

即

$$R_0 e^{-\frac{1}{3}BT} \leq \eta(\tau) \leq R_0 e^{\frac{1}{3}BT}, \quad 0 \leq \tau \leq T \quad (71)$$

引理 4 对任意的 $1 < p < \infty$, 存在一个依赖于时间 T 的常数 $C(T)$, 满足

$$\|(D, T_1, T_2, C, G, I_1, I_2, P, A)\|_\infty \leq C(T)$$

证明 显然, $v(z, \tau)$ 为连续函数, $|h'| \leq B$ 为有界连续函数, 则由式 (45)、式 (50) 与式 (71) 可得

$$|u'(z, \tau)| \leq \frac{1}{3}BR_0^2 e^{\frac{2}{3}BT},$$

$$|u'(1, \tau)| \leq \frac{1}{3}BR_0^2 e^{\frac{2}{3}BT}$$

且

$$|v(z, \tau)| \leq \frac{2}{3}BR_0^2 e^{\frac{2}{3}BT}$$

因此 $u'(z, \tau)$ 与 $v(z, \tau)$ 均为有界连续函数。

(a) 考虑问题 (29) ~ (30), 由 $v(z, \tau)$, h' 以及 $\eta(\tau)$ 均为有界连续函数可知方程 (28) 的系数项和非齐次项均满足引理 1 的条件, 故方程组 (28) ~ (29) 有唯一解 $D' \in W_p^{2,1}(\Omega_T)$, 且有

$$\|D'\|_{W_p^{2,1}(\Omega_T)} \leq C(T)$$

(b) 考虑问题 (31) ~ (32), 因为 $Q = \sigma P \rho_L(T_1 + T_2 + \varepsilon C) \geq 0$, 所以 $\frac{1}{1 + \frac{Q'}{K_5}}$ 有界且连续,

又由 $v(z, \tau)$, h' 以及 $\eta(\tau)$ 均为有界连续函数可知方程 (30) 的系数项和非齐次项均满足引理 1 的条件, 故方程组 (31) ~ (32) 有唯一解 $T'_1 \in W_p^{2,1}(\Omega_T)$, 且有

$$\|T'_1\|_{W_p^{2,1}(\Omega_T)} \leq C(T)$$

同理有

$$\|T'_2\|_{W_p^{2,1}(\Omega_T)} \leq C(T)$$

由

$$P' = \rho_P(T'_1 + T'_2)$$

可得

$$\|P'\|_{W_p^{2,1}(\Omega_T)} \leq C(T)$$

(c) 考虑问题 (35) ~ (40) 和 (43) ~ (44), 因为 $\|T'_1\|_\infty \leq C(T)$, $\|T'_2\|_\infty \leq C(T)$, 而且显然 $\hat{A}(t)$, $\hat{G}(t)$ 均有界且连续, 因此同理可得

$$\|C'\|_{W_p^{2,1}(\Omega_T)} \leq C(T), \|G'\|_{W_p^{2,1}(\Omega_T)} \leq C(T),$$

$$\|I'_1\|_{W^{2,1}_p(\Omega_T)} \leq C(T), \|A'\|_{W^{2,1}_p(\Omega_T)} \leq C(T)$$

则有

$$\|I'_2\|_{W^{2,1}_p(\Omega_T)} \leq C(T)$$

由情形 (a) ~ (c) 可得

$$\|(D', T'_1, T'_2, C', G', I'_1, I'_2, P', A')\|_{W^{2,1}_p(\Omega_T)} \leq C(T)$$

继而由

$$W^{2,1}_p(\Omega_T) \subset C^{\lambda, \frac{\lambda}{2}}(\Omega_T) \left(p > \frac{5}{2}, \lambda = 2 - \frac{5}{p} \right)$$

参考文献:

- [1] FERNANDEZ N C, LOZIER A, FLAMENT C, et al. Dendritic cells directly trigger NK cell functions: cross-talk relevant in innate anti-tumor immune responses in vivo [J]. Nat Med, 1999, 5(4): 405-411.
- [2] GONG J, AVIGAN D, CHEN D, et al. Activation of antitumor cytotoxic T lymphocytes by fusions of human dendritic cells and breast carcinoma cells [J]. J Cancer, 2000, 97(6): 2715-2718.
- [3] MAILLIARD R B, EGAWA S, CAI Q, et al. Complementary dendritic cell-activating function of CD8+ and CD4+ T cells: helper role of CD8+ T cells in the development of T helper type 1 responses [J]. J Exp Med, 2002, 195(4): 473-483.
- [4] HAABETH O A, TVEITA A A, FAUSKANGER M, et al. How do CD4(+) T cells Detect and eliminate tumor cells that either lack or express MHC class II molecules? [J]. Front Immunol, 2014, 5: 174. doi: 10.3389/fimmu.2014.00174.
- [5] van der BURG S H, ARENS R, OSSENDORP F, et al. Vaccines for established cancer: overcoming the challenges posed by immune evasion [J]. Nature Reviews Cancer, 2016, 16: 219-233.
- [6] KLEPONIS J, SKELTON R, ZHENG L. Fueling the engine and releasing the break: combinational therapy of cancer vaccines and immune checkpoint inhibitors [J]. Cancer Biol Med, 2015, 12(3): 201-208.
- [7] GUO C, MANJILI M H, SUBJECK J R, et al. Therapeutic cancer vaccines: past, present and future [J]. Adv Cancer Res, 2013, 119: 421-475.
- [8] BUROTTO M, SINGH N, HEERY C R, et al. Exploiting synergy: immune-based combinations in the treatment of prostate cancer [J]. Front Oncol, 2014, 4: 351. doi: 10.3389/fonc.2014.00351.
- [9] JOSHI B, WANG X, BANERJEE S, et al. On immunotherapies and cancer vaccination protocols: a mathematical modelling approach [J]. J Theor Biol, 2009, 259(4): 820-827.
- [10] de PILLIS L, GU W, RADUNSKAYA A E. Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations [J]. J Theor Biol, 2006, 238(4): 841-862.
- [11] LAI X, FRIEDMAN A. Combination therapy of cancer with cancer vaccine and immune checkpoint inhibitors: A mathematical model [J]. PLOS One. 2017, 12(5): 1-24.
- [12] LADYZENSKAJA O A, SOLONNIKOV V A, URALTSEVA N N. Linear and quasilinear partial differential equations of parabolic type [M]. Rhode Island: Amer Math Soc, 1968.
- [13] 崔尚斌. 偏微分方程现代理论引论[M]. 北京: 科学出版社, 2015.
- [14] FRIEDMAN A, REITICH F. Analysis of a mathematical model for the growth of tumors [J]. Math Biol, 1999, 38: 262-284.
- [15] 高帅帅, 卫雪梅, 冯兆永. 一个肿瘤化学治疗空间结构模型的定性分析[J]. 中山大学学报(自然科学版), 2012, 51(2): 30-34.
GAO S S, WEI X M, FENG Z Y. Analysis of a mathematical model of the response of spatially structured tumors to chemotherapy model [J]. Acta Scientiarum Naturalium Universitatis Sunyatseni, 2012, 51(2): 30-34.
- [16] WEI X, CUI S. Existence and uniqueness of the global solution for a mathematical model of the use of macrophages in tumor medicine [J]. Nonlinear Analysis: Real World Applications, 2007, 8(3): 922-938.
- [17] WEI X, CUI S. Existence and uniqueness of global solutions for a mathematical model of antiangiogenesis in tumor growth [J]. Nonlinear Analysis: Real World Applications, 2008, 9(5): 1827-1836.
- [18] WEI X, CUI S. Global existence for a mathematical model of the immune response to cancer [J]. Nonlinear Analysis: Real World Applications, 2010, 11(5): 3903-3911.