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Existence analysis of solutions of a class of cross diffusion equations on the mechanism of drug resistance of melanoma*

CHEN Wei[1], *WEI Xuemei*[1]✉, *FENG Zhaoyong*[2]✉, *LIU Chengxia*[3]

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 mathematical model of checkpoint inhibitor targeted therapy for human melanoma is investigated. The model consists of twelve coupled reaction-diffusion equations, which includes free boundary conditions and discontinuous terms. By transforming the free boundary problem into the fixed boundary problem, using the L^p theory of the parabolic equation and the Schauder fixed point theorem, and combining with the method of function approximation, the existence of the global weak solution of the mathematical model is obtained.

Key words: melanoma; reaction-diffusion equations; weak solution; existence
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Human melanoma originates from melanocytes, and it is a malignant tumor of the skin. *B-raf* gene is one of the most common mutations in metastatic melanoma. Combining with the influence of drug resistance, Ascierto et al. obtained data from clinical trials, which showed that *BRAF*-targeted therapy by *BRAF*-inhibitor would first show obvious positive reaction, but usually relapses and becomes negative after half a year (Ascierto et al. ,2012; Menzies et al. ,2013;Sanchez-Laorden et al. ,2014). Considering the factors of cell cycle parameters and age structure, Gaffney (2004) proposed a PDE model of the circulatory dynamics system, which mainly analyzed the effect of chemotherapy when drugs were used alternately. Steinberg et al. (2017) adjusted the chemotherapy regimen and medication strategy, and proposed different combination schemes for *BRAFi*, anti-*CCL*2 and checkpoint inhibitors. The purpose is to explore how to reduce drug resistance by combining drugs. Friedman et al. (2020) established a mathematical model corresponding to the experimental setup based on the existing experimental data (Steinberg et al. ,2017) .

The model comprises four cell equations, four chemokine equations and four drug equations(Friedman et al. , 2020). Their concentrations are respectively denoted by $C = C(r,t), M = M(r,t)$, etc. , where r is a radial space variable satisfies $0 \leqslant r \leqslant R(t)$, and the tumor radius $R(t)$ satisfies a differential equation. Besides, $t \geqslant 0$ is a time variable. We assume that the density of apoptotic or necrotic cell debris is constant. Then we consider the following free boundary problem:

$$\frac{\partial C}{\partial t} + \nabla \cdot (\vec{u}C) - \delta_1 \nabla^2 C = \lambda_1 C\left(1 - \frac{C}{C_M}\right)\frac{1}{1 + B/k_3} - \mu_{15} T_8 C - \mu_1 C, \tag{1}$$

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✉ **Corresponding authors**: WEI Xuemei (*wxm_gdut@163.com*), FENG Zhaoyong (*fzhaoy@mail.sysu.edu.cn*)
CHEN Wei (*2801978117@qq.com*) , LIU Chengxia (*349471214@qq.com*)

$$\frac{\partial M}{\partial t}+\nabla\cdot\left(\vec{u}M\right)-\delta_2\nabla^2 M=\lambda_2\frac{P}{k_5+P}\frac{1}{1+A_2/k_9}H\left(M_0-M\right)-\nabla\cdot\left(\chi M\nabla P\right)-\mu_2 M,\tag{2}$$

$$\frac{\partial D}{\partial t}+\nabla\cdot\left(\vec{u}D\right)-\delta_3\nabla^2 D=\lambda_3 D_0\frac{C}{k_1+C}\cdot\frac{1}{1+N/k_2}\Re_D(t)-\mu_3 D,\tag{3}$$

$$\frac{\partial T_8}{\partial t}+\nabla\cdot\left(\vec{u}T_8\right)-\delta_4\nabla^2 T_8=\lambda_4 T_{80}\frac{I_2}{k_7+I_2}\cdot\frac{1}{1+I_1/k_6}\cdot\frac{1}{1+P_1P_3/k_4}\cdot\frac{1}{1+P_2B_7/k_8}-\mu_4 T_8,\tag{4}$$

$$\frac{\partial P}{\partial t}-\delta_5\nabla^2 P=\lambda_5 C\left(1-\Re_P(t)\frac{B}{k_{10}+B}\right)-\mu_5 P,\tag{5}$$

$$\frac{\partial I_1}{\partial t}-\delta_6\nabla^2 I_1=\lambda_6 C+\lambda_{10}M-\mu_6 I_1,\tag{6}$$

$$\frac{\partial I_2}{\partial t}-\delta_7\nabla^2 I_2=\lambda_7 D\left(1+\theta_1\frac{B}{k_{10}+B}\right)-\mu_7 I_2,\tag{7}$$

$$\frac{\partial N}{\partial t}-\delta_8\nabla^2 N=\lambda_8 M-\mu_8 N,\tag{8}$$

$$\frac{\partial B}{\partial t}-\delta_9\nabla^2 B=\Phi_B(t)-\mu_{16}C\frac{B}{k_{10}+B}-\mu_9 B,\tag{9}$$

$$\frac{\partial A_1}{\partial t}-\delta_{10}\nabla^2 A_1=\Phi_{A_1}(t)-\mu_{13}P_1A_1-\mu_{10}A_1,\tag{10}$$

$$\frac{\partial A_2}{\partial t}-\delta_{11}\nabla^2 A_2=\Phi_{A_2}(t)-\mu_{17}MA_2-\mu_{11}A_2,\tag{11}$$

$$\frac{\partial A_4}{\partial t}-\delta_{12}\nabla^2 A_4=\Phi_{A_4}(t)-\mu_{14}P_2A_4-\mu_{12}A_4,\tag{12}$$

$$\dot{R}(t)=u\left(R(t),t\right),\quad t>0,\tag{13}$$

where C is the density of cancer cells, M is the density of macrophages ($MDSCs$), D is the density of dendritic cells (DC), T_8 is the density of cells ($CD8^+T$), P is the density of catalytic factors ($CCL2$), I_1 is the density of interleukin-10, I_2 is the density of interleukin-12, N is the density of nitric oxide (NO), B is the density of anti-$BRAF$, A_1 is the density of anti-PD-1, A_2 is the density of anti-PD-2, A_4 is the density of anti-PD-4. Moreover the coefficients are non-negative constants, $\Re_D(t)$ and $\Re_P(t)$ are nonnegative decreasing bounded continuous functions (p. 14 (Friedman et al. ,2020)). We can assume that some other variables express the following four dynamic equations in this paper, i. e. , $P_1=\rho_1T_8$, $P_2=\rho_2T_8$, $P_3=\rho_3(T_8+M+\varepsilon_C C)$, $B_7=\rho_7 D$, so that P_1, P_2 are proportional to T_8 (p. 4 (Cui,2005)), P_3 is expressed on activated T_8, M and C, B_7 is proportional to D. Therefore, we do not need to deal with these four variables directly in this paper.

According to Friedman et al. (2020), the boundary conditions of the model is no flow boundary as follows :

$$\frac{\partial C}{\partial r}=\frac{\partial M}{\partial r}=\frac{\partial D}{\partial r}=\frac{\partial P}{\partial r}=\frac{\partial I_1}{\partial r}=\frac{\partial I_2}{\partial r}=\frac{\partial N}{\partial r}=\frac{\partial B}{\partial r}=\frac{\partial A_1}{\partial r}=\frac{\partial A_2}{\partial r}=\frac{\partial A_4}{\partial r}=0,\qquad r=0,\tag{14}$$

$$\frac{\partial C}{\partial r}=\frac{\partial M}{\partial r}=\frac{\partial D}{\partial r}=\frac{\partial P}{\partial r}=\frac{\partial I_1}{\partial r}=\frac{\partial I_2}{\partial r}=\frac{\partial N}{\partial r}=\frac{\partial B}{\partial r}=\frac{\partial A_1}{\partial r}=\frac{\partial A_2}{\partial r}=\frac{\partial A_4}{\partial r}=0,\qquad r=R(t).\tag{15}$$

We assumed that inactive T_8 cells have a constant density $\hat{T}_8$ at the free boundary of the tumor, they are activated by I_2 when they enter the tumor environment (Friedman et al. ,2020). Then we have the following boundary flux conditions

$$\begin{aligned}&\frac{\partial T_8}{\partial r}=0, && r=0;\\ &\frac{\partial T_8}{\partial r}+\sigma_0\frac{I_2}{k+I_2}(T_8-\hat{T}_8)=0, && r=R(t).\end{aligned}\tag{16}$$

Let U_0 indicate the initial condition of these variables, a. e. ,

$$U_0=(C_0,M_0,D_0,T_{80},P_0,I_{10},I_{20},N_0,B_0,A_{10},A_{20},A_{40}),\tag{17}$$

it is clear that U_0 is a nonnegative array (p. 11 (Friedman et al. ,2020)). In addition, we denote $R_0=R(0)$.

In this paper, H is an approximated Heaviside function (Friedman et al. ,2020)

$$H(M_0 - M) = \begin{cases} \dfrac{(M_0 - M)^6}{10^{-6} + (M_0 - M)^6}, & M_0 \geqslant M, \\ 0, & M_0 < M. \end{cases}$$

Obviously, it can be checked easily that $H(M - M_0)$ is Lipschitz continuous. We assume a logistic growth for C with carrying capacity C_M, such that $0 \leqslant C \leqslant C_M$ and Δ_r represents the radial Laplacian, i. e. ,

$$\Delta_r := \nabla^2 = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial}{\partial r}\right).$$

We assume the total density of cells in the tumor remains constant in space and time (Friedman et al. ,2020):

$$C + M + D + T_8 = 1, \tag{18}$$

and we assume that all cells have approximately the same diffusion coefficients. Adding Eqs. (1)-(4) and using Eq. (18), we get

$$\nabla \cdot \vec{u} = h(C, B, T_8, P, A_2, M, D, N, I_1, I_2), \quad 0 < r < R(t),\ t > 0, \tag{19}$$

where

$$\begin{aligned} & h\left(C, B, T_8, P, A_2, M, D, N, I_1, I_2\right) \\ = {} & \lambda_1 C\left(1 - \frac{C}{C_M}\right)\frac{1}{1 + B/k_3} + \lambda_2 \frac{P}{k_5 + P} \cdot \frac{1}{1 + A_2/k_9} \cdot H\left(M_0 - M\right) + \lambda_3 D_0 \frac{C}{k_1 + C} \cdot \frac{1}{1 + N/k_2}\Re_D(t) \\ & + \lambda_4 T_{80} \cdot \frac{I_2}{k_7 + I_2} \cdot \frac{1}{1 + I_1/k_6} \cdot \frac{1}{1 + P_1 P_3/k_4} \cdot \frac{1}{1 + P_2 B_7/k_8} \\ & - \left[\mu_{15} T_8 C + \nabla \cdot \left(\chi M \nabla P\right)\right] - \left(\mu_1 C + \mu_2 M + \mu_3 D + \mu_4 T_8\right), \end{aligned}$$

and $u(0, t) = 0$. According to Friedman et al. (2020), there are some discontinuous items in this model, which indicate the source of the drug:

$$\Phi_B(t) = \begin{cases} \gamma_B, & t \leqslant 120, \\ 0, & \text{otherwise}, \end{cases} \qquad \Phi_{A_1}(t) = \begin{cases} \gamma_{A_1}, & 60 < t \leqslant 120, \\ 0, & \text{otherwise}, \end{cases}$$

$$\Phi_{A_2}(t) = \begin{cases} \gamma_{A_2}, & 60 < t \leqslant 120, \\ 0, & \text{otherwise}, \end{cases} \qquad \Phi_{A_4}(t) = \begin{cases} \gamma_{A_4}, & 60 < t \leqslant 120, \\ 0, & \text{otherwise}, \end{cases}$$

where $\gamma_B, \gamma_{A_1}, \gamma_{A_2}$ and γ_{A_4} are positive constants, indicating the level of drug efficacy. Obviously Φ_B, Φ_{A_1}, Φ_{A_2} and Φ_{A_4} are bounded. It is not easy to deal with these discontinuous terms directly. Therefore, this paper draws lessons from the treatment method of parabolic equations with discontinuous terms in references (Cui, 2005; Wei, 2006; Wei et al. ,2010; Xu et al. ,2014), and intends to make a rigorous mathematical analysis of the model.

According to the biological principles, we have the following assumption:

(A) $U_0 := (C_0, M_0, D_0, T_{80}, P_0, I_{10}, I_{20}, N_0, B_0, A_{10}, A_{20}, A_{40}) \in D_p(0,1)$, the definition of $D_p(0,1)$ is given in the following preliminary lemma. Besides, $U_0 \geqslant 0$.

Under the assumption (A), we obtain our main result as follows:

Theorem 1 The problem (1)-(17) has global weak solutions.

The structure of this paper is following. In section 1, we will present some preliminary lemmas which will be used in the following proofs. In section 2, we will transform the free boundary problem (1)-(17) into an equivalent problem on a fixed domain, which have some discontinuous terms in the model. We will focus on proving the existence of a fixed boundary problem after smoothing. And we prove that the initial-boundary value problem has global weak solutions in the last section.

1 Preliminary lemmas

In this section, we will present some preliminary lemmas. We first introduce some notations:

(i) $Q_T = \left\{(r,t) : 0 \leqslant r \leqslant 1, 0 \leqslant t \leqslant T\right\}, T > 0$. $\bar{Q}_T$ is the closure of Q_T.

(ii) $W_p^{2,1}(Q_T)=\{u\in L^p(Q_T): u_t,\nabla u,\nabla^2 u\in L^p\}$, and stipulate $\|u\|_{W_p^{2,1}}=\sum_{|m|+2k\le 2}\|\partial_x^m\partial_t^k\|_{L^p}$.

(iii) For a number $p>5/2$, we denote by $D_p(0,1)$, the trace space of $W_p^{2,1}(Q_T)$ at $t=0$, i. e. , $\varphi\in D_p(0,1)$, if and only if there exists a function $u\in W_p^{2,1}(Q_T)$ such that $u(\cdot,0)=\varphi$. The norm in $D_p(0,1)$ is defined as follows:

$$\|\varphi\|_{D_p(0,1)}=\left\{T^{-\frac{1}{p}}\|u\|_{W_p^{2,1}(Q_T)}: u\in W_p^{2,1}(Q_T),\ u(x,0)=\varphi(x)\right\},$$

since for $p>5/2$, $W_p^{2,1}(Q_T)$ is continuously embedded in $C(\bar{Q}_T)$, the above definition makes sense. Besides, it is clear that if $\varphi\in W^{2,p}(0,1)$, then $\varphi\in D_p(0,1)$ and $\|\varphi\|_{D_p(0,1)}\le\|\varphi\|_{W^{2,p}(0,1)}$.

Lemma 1 (Ladyzenskaja et al. ,1968) Suppose D is a positive constant, and let $a(z,\tau)$, $b(z,\tau)$ be bounded continuous functions defined on $\bar{Q}_T$. Let $f(z,\tau)\in L^p(Q_T)$, $q(\tau)\in C^1[0,T]$ and $c_0\in D_p(0,1)$ for some $1<p<+\infty$, let $Bu=\alpha\frac{\partial u}{\partial n}+\beta(z,\tau)u$, where either (i) $\alpha=0$, $\beta(z,\tau)=1$, or (ii) $\alpha=1$, $\beta(z,\tau)\ge 0$. Then the initial-boundary value problem

$$\begin{aligned}
\frac{\partial c}{\partial\tau}&=D\frac{\partial^2 c}{\partial z^2}+a(z,\tau)\frac{\partial c}{\partial z}+b(z,\tau)c+f(z,\tau), && 0\le z\le 1,\ 0\le\tau\le T,\\
Bc&=q, && z=0,1,0\le\tau\le T,\\
c(z,0)&=c_0(z), && 0\le z\le 1,
\end{aligned}$$

has a unique solution $c(z,\tau)\in W_p^{2,1}(Q_T)$. Moreover,

$$\|c\|_{W_p^{2,1}(Q_T)}\le C_p(T)\left(\|c_0\|_{D_p(0,1)}+\|q\|_{W^{1,p}(0,T)}+\|f\|_{L^p}\right).$$

Here $C_p(T)$ are constants depending only on $p,T,\|a\|_\infty,\|b\|_\infty$ and $C_p(T)$ are bounded for T in a bounded set.

2 Existence of approximate solutions

In order to solve the free boundary problem (1)−(17), we firstly transform it into an initial-boundary value problem in the fixed domain (z,τ), $0\le z\le 1$, $0\le\tau\le T$. Therefore, we introduce a transformation of variables $(C,M,D,T_8,P,I_1,I_2,N,B,A_1,A_2,A_4)\to(C',M',D',T_8',P',I_1',I_2',N',B',A_1',A_2',A_4')$,

$$z=\frac{r}{R(t)},\quad \tau=\int_0^t\frac{\mathrm{d}s}{R^2(s)},\quad \eta(\tau)=R(t),\quad \omega(z,\tau)=R(t)u(r,t),\quad \eta_0=R_0. \tag{20}$$

Then the new initial boundary value problem is as follows:

$$\begin{cases}
\frac{\partial C'}{\partial\tau}+v(z,\tau)\frac{\partial C'}{\partial z}-\delta_1\frac{1}{z^2}\frac{\partial}{\partial z}\left(z^2\frac{\partial C'}{\partial z}\right)=\eta^2\left[\lambda_1\left(1-\frac{C'}{C_M}\right)\frac{1}{1+B'/k_3}-\mu_{15}T_8'-\mu_1-h'\right]C',\\
\frac{\partial C'(0,\tau)}{\partial z}=\frac{\partial C'(1,\tau)}{\partial z}=0,\\
C'(z,0)=C_0,
\end{cases} \tag{21}$$

$$\begin{cases}
\frac{\partial M'}{\partial\tau}+\left[v(z,\tau)+\chi\frac{\partial P'}{\partial z}\right]\frac{\partial M'}{\partial z}-\delta_2\frac{1}{z^2}\frac{\partial}{\partial z}\left(z^2\frac{\partial M'}{\partial z}\right)\\
\qquad=\eta^2\left[\frac{\lambda_2 P'}{k_5+P'}\frac{H(M_0-M')}{1+A_2'/k_9}-\left(\chi\frac{1}{\eta^2}\frac{1}{z^2}\frac{\partial}{\partial z}(z^2\frac{\partial P'}{\partial z})+\mu_2+h'\right)M'\right],\\
\frac{\partial M'(0,\tau)}{\partial z}=\frac{\partial M'(1,\tau)}{\partial z}=0,\\
M'(z,0)=M_0,
\end{cases} \tag{22}$$

$$\begin{cases} \dfrac{\partial D'}{\partial \tau} + v(z,\tau)\dfrac{\partial D'}{\partial z} - \delta_3 \dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2 \dfrac{\partial D'}{\partial z}\right) = \eta^2\left[\lambda_3 D_0 \dfrac{C'}{k_1 + C'} \cdot \dfrac{1}{1 + N'/k_2}\Re_D(t) - \mu_3 D' - h'D'\right], \\ \dfrac{\partial D'(0,\tau)}{\partial z} = \dfrac{\partial D'(1,\tau)}{\partial z} = 0, \\ D'(z,0) = D_0, \end{cases} \tag{23}$$

$$\begin{cases} \dfrac{\partial T_8'}{\partial \tau} + v(z,\tau)\dfrac{\partial T_8'}{\partial z} - \delta_4 \dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2 \dfrac{\partial T_8'}{\partial z}\right) \\ \qquad = \eta^2\left(\lambda_4 T_{80}\dfrac{I_2'}{k_7 + I_2'} \cdot \dfrac{1}{1 + I_1'/k_6} \cdot \dfrac{1}{1 + P_1'P_3'/k_4} \cdot \dfrac{1}{1 + P_2'B_7'/k_8} - \mu_4 T_8' - h'T_8'\right), \\ \dfrac{\partial T_8'(0,\tau)}{\partial z} = \dfrac{\partial T_8'(1,\tau)}{\partial z} + \sigma_0 \dfrac{I_2'}{k - I_2'}(T_8' - \hat{T}_8)\Big|_{z=1} = 0, \\ T_8'(z,0) = T_{80}, \end{cases} \tag{24}$$

$$\begin{cases} \dfrac{\partial P'}{\partial \tau} - \omega(1,\tau) z\dfrac{\partial P'}{\partial z} - \delta_5 \dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2 \dfrac{\partial P'}{\partial z}\right) = \eta^2\left[\lambda_5 C'\left(1 - \Re_P(\tau)\dfrac{B'}{k_{10} + B'}\right) - \mu_5 P'\right], \\ \dfrac{\partial P'(0,\tau)}{\partial z} = \dfrac{\partial P'(1,\tau)}{\partial z} = 0, \\ P'(z,0) = P_0, \end{cases} \tag{25}$$

$$\begin{cases} \dfrac{\partial I_1'}{\partial \tau} - \omega(1,\tau) z\dfrac{\partial I_1'}{\partial z} - \delta_6 \dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2 \dfrac{\partial I_1'}{\partial z}\right) = \eta^2(\lambda_6 C' + \lambda_{10} M' - \mu_6 I_1'), \\ \dfrac{\partial I_1'(0,\tau)}{\partial z} = \dfrac{\partial I_1'(1,\tau)}{\partial z} = 0, \\ I_1'(z,0) = I_{10}, \end{cases} \tag{26}$$

$$\begin{cases} \dfrac{\partial I_2'}{\partial \tau} - \omega(1,\tau) z\dfrac{\partial I_2'}{\partial z} - \delta_7 \dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2 \dfrac{\partial I_2'}{\partial z}\right) = \eta^2\left[\lambda_7 D'\left(1 + \theta_1\dfrac{B'}{k_{10} + B'}\right) - \mu_7 I_2'\right], \\ \dfrac{\partial I_2'(0,\tau)}{\partial z} = \dfrac{\partial I_2'(1,\tau)}{\partial z} = 0, \\ I_2'(z,0) = I_{20}, \end{cases} \tag{27}$$

$$\begin{cases} \dfrac{\partial N'}{\partial \tau} - \omega(1,\tau) z\dfrac{\partial N'}{\partial z} - \delta_8 \dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2 \dfrac{\partial N'}{\partial z}\right) = \eta^2(\lambda_8 M' - \mu_8 N'), \\ \dfrac{\partial N'(0,\tau)}{\partial z} = \dfrac{\partial N'(1,\tau)}{\partial z} = 0, \\ N'(z,0) = N_0, \end{cases} \tag{28}$$

$$\begin{cases} \dfrac{\partial B'}{\partial \tau} - \omega(1,\tau) z\dfrac{\partial B'}{\partial z} - \delta_9 \dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2 \dfrac{\partial B'}{\partial z}\right) = \eta^2\left[\Phi_B(\tau) - \mu_{16} C'\dfrac{B'}{k_{10} + B'} - \mu_9 B'\right], \\ \dfrac{\partial B'(0,\tau)}{\partial z} = \dfrac{\partial B'(1,\tau)}{\partial z} = 0, \\ B'(z,0) = B_0, \end{cases} \tag{29}$$

$$\begin{cases} \dfrac{\partial A_1'}{\partial \tau} - \omega(1,\tau) z\dfrac{\partial A_1'}{\partial z} - \delta_{10} \dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2 \dfrac{\partial A_1'}{\partial z}\right) = \eta^2\left[\Phi_{A_1}(\tau) - \mu_{13} P_1' A_1' - \mu_{10} A_1'\right], \\ \dfrac{\partial A_1'(0,\tau)}{\partial z} = \dfrac{\partial A_1'(1,\tau)}{\partial z} = 0, \\ A_1'(z,0) = A_{10}, \end{cases} \tag{30}$$

$$\begin{cases}\dfrac{\partial A_2'}{\partial \tau}-\omega(1,\tau)z\dfrac{\partial A_2'}{\partial z}-\delta_{11}\dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2\dfrac{\partial A_2'}{\partial z}\right)=\eta^2\left[\Phi_{A_2}(\tau)-\mu_{17}M'A_2'-\mu_{11}A_2'\right],\\ \dfrac{\partial A_2'(0,\tau)}{\partial z}=\dfrac{\partial A_2'(1,\tau)}{\partial z}=0,\\ A_2'(z,0)=A_{20},\end{cases} \tag{31}$$

$$\begin{cases}\dfrac{\partial A_4'}{\partial \tau}-\omega(1,\tau)z\dfrac{\partial A_4'}{\partial z}-\delta_{12}\dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2\dfrac{\partial A_4'}{\partial z}\right)=\eta^2\left[\Phi_{A_4}(\tau)-\mu_{14}P_2'A_4'-\mu_{12}A_4'\right],\\ \dfrac{\partial A_4'(0,\tau)}{\partial z}=\dfrac{\partial A_4'(1,\tau)}{\partial z}=0,\\ A_4'(z,0)=A_{40},\end{cases} \tag{32}$$

$$\frac{\mathrm{d}\eta(\tau)}{\mathrm{d}\tau}=\eta(\tau)\omega(1,\tau),\quad 0\leqslant\tau\leqslant T, \tag{33}$$

$$\eta(0)=R_0, \tag{34}$$

$$\frac{1}{z^2}\frac{\partial}{\partial z}\left(z^2\omega\right)=\eta^2 h\left(C',\ M',\ D',\ T_8{}',\ P',\ I_1{}',\ I_2{}',\ N',\ B',\ A_2{}'\right), \tag{35}$$

$$v(z,\tau)=\omega(z,\tau)-z\omega(1,\tau). \tag{36}$$

We summarize the above result in the following lemma.

Lemma 2 Under the variable substitution of (20), the problem (21)–(36) is equivalent to the problem (1)–(17).

Considering the discontinuous terms in problem (29)–(32), we can use smooth functions to approximate the discontinuous terms. In this case, these smooth functions $(\Phi_B)_\varepsilon,(\Phi_{A_1})_\varepsilon,(\Phi_{A_2})_\varepsilon$ and $(\Phi_{A_4})_\varepsilon$ are the approximations of discontinuous terms $\Phi_B,\Phi_{A_1},\Phi_{A_2}$ and Φ_{A_4}, respectively in $C(0,T)$. The selection functions are as follows

$$(\Phi_B)_\varepsilon(\tau)=\begin{cases}0, & \tau\in[0,120],\\ \dfrac{\gamma_B}{\varepsilon}(\tau-120), & \tau\in(120,120+\varepsilon),\\ \gamma_B, & \tau\in[120+\varepsilon,+\infty),\end{cases}\qquad (\Phi_{A_1})_\varepsilon(\tau)=\begin{cases}0, & \tau\in[0,60]\cup(120,+\infty),\\ \dfrac{\gamma_{A_1}}{\varepsilon}(\tau-60), & \tau\in(60,60+\varepsilon],\\ \gamma_{A_1}, & \tau\in(60+\varepsilon,120-\varepsilon),\\ -\dfrac{\gamma_{A_1}}{\varepsilon}(\tau-120), & \tau\in[120-\varepsilon,120],\end{cases}$$

$$(\Phi_{A_2})_\varepsilon(\tau)=\begin{cases}0, & \tau\in[0,60]\cup(120,+\infty),\\ \dfrac{\gamma_{A_2}}{\varepsilon}(\tau-60), & \tau\in(60,60+\varepsilon],\\ \gamma_{A_2}, & \tau\in(60+\varepsilon,120-\varepsilon),\\ -\dfrac{\gamma_{A_2}}{\varepsilon}(\tau-120), & \tau\in[120-\varepsilon,120],\end{cases}\qquad (\Phi_{A_4})_\varepsilon(\tau)=\begin{cases}0, & \tau\in[0,60]\cup(120,+\infty),\\ \dfrac{\gamma_{A_4}}{\varepsilon}(\tau-60), & \tau\in(60,60+\varepsilon],\\ \gamma_{A_4}, & \tau\in(60+\varepsilon,120-\varepsilon),\\ -\dfrac{\gamma_{A_4}}{\varepsilon}(\tau-120), & \tau\in[120-\varepsilon,120].\end{cases}$$

Clearly, $(\Phi_B)_\varepsilon,(\Phi_{A_1})_\varepsilon,(\Phi_{A_2})_\varepsilon,(\Phi_{A_4})_\varepsilon$ are Lipschitz continuous in $\bar{Q}_T$. Therefore, variables $(C',M',D',T_8',P',I_1',I_2',N',B',A_1',A_2',A_4')$ can be approximated by $U=(C_\varepsilon',M_\varepsilon',D_\varepsilon',(T_8')_\varepsilon,P_\varepsilon',(I_1')_\varepsilon,(I_2')_\varepsilon,N_\varepsilon',B_\varepsilon',(A_1')_\varepsilon,(A_2')_\varepsilon,(A_4')_\varepsilon)$.

Lemma 3 For any $T>0$, the problem (21)–(34) has solutions $(U_\varepsilon(z,\tau),\eta(\tau))$ under the approximation. For convenience, we denote $U=(C_\varepsilon',M_\varepsilon',D_\varepsilon',(T_8')_\varepsilon,P_\varepsilon',(I_1')_\varepsilon,(I_2')_\varepsilon,N_\varepsilon',B_\varepsilon',(A_1')_\varepsilon,(A_2')_\varepsilon,(A_4')_\varepsilon)$, where $U_\varepsilon(z,\tau)\in W_p^{2,1}(Q_T)$, $\eta(\tau)\in C[0,T]$.

Proof For a given $T>0$ and a positive constant G to be specified later, G is independent of the values of z and τ. We introduce a metric space (X_T,d) as follows: the set X_T consists of a vector function $(U(z,\tau),\eta(\tau)),(0\leqslant z\leqslant 1,0\leqslant\tau\leqslant T)$ satisfying the following condition:

(i) $\eta(\tau)\in C[0,T]$, $\eta(0)=R_0$, $\dfrac{1}{2}R_0\leqslant\eta(\tau)\leqslant 2R_0$.

(ii) $U(z,\tau)\in C(\bar{Q}_T)$, $0\leqslant\left\|U(z,\tau)\right\|_\infty\leqslant G$.

The metric d is defined $d((U_1,\eta_1),(U_2,\eta_2)) = \|U_1 - U_2\|_\infty + \|\eta_1 - \eta_2\|_\infty, (0 \leqslant z \leqslant 1, 0 \leqslant \tau \leqslant T)$, it is obvious that (X_T,d) is a complete metric space. Noting that by (35), we get

$$\omega(z,\tau) = \frac{\eta^2(\tau)}{z^2}\int_0^z h(C,\ M,\ D,\ T_8,\ P,\ I_1,\ I_2,\ N,\ B,\ A_2)\cdot s^2\,\mathrm{d}s, \tag{37}$$

and

$$\left|h(C,\ M,\ D,\ T_8,\ P,\ I_1,\ I_2,\ N,\ B,\ A_2)\right| \leqslant C_p(T). \tag{38}$$

Here $C_p(T)$ is a positive constant depending on $T, p, \lambda_1, \lambda_2, \lambda_3, D_0, T_{80}$ and C_0.

In the following, for $(C,M,D,T_8,P,I_1,I_2,N,B,A_1,A_2,A_4) \in X_T$, we define a mapping $F:(U(z,\tau),\eta(\tau)) \mapsto (\tilde{U}(z,\tau),\tilde{\eta}(\tau))$. Given $(U(z,\tau),\eta(\tau)) \in X_T$, we define $(\tilde{U}(z,\tau),\tilde{\eta}(\tau))$ to be the solutions of the following problems:

$$\begin{cases} \dfrac{\partial\tilde{C}}{\partial\tau} + v(z,\tau)\dfrac{\partial\tilde{C}}{\partial z} - \delta_1\dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2\dfrac{\partial\tilde{C}}{\partial z}\right) = \eta^2\left[\lambda_1\left(1 - \dfrac{C}{C_M}\right)\dfrac{1}{1 + B/k_3} - \mu_{15}T_8 - \mu_1 - h\right]\tilde{C}, \\ \dfrac{\partial\tilde{C}(0,\tau)}{\partial z} = \dfrac{\partial\tilde{C}(1,\tau)}{\partial z} = 0, \\ \tilde{C}(z,0) = C_0, \end{cases} \tag{39}$$

$$\begin{cases} \dfrac{\partial\tilde{M}}{\partial\tau} + \left[v(z,\tau) + \chi\dfrac{\partial P}{\partial z}\right]\dfrac{\partial\tilde{M}}{\partial z} - \delta_2\dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2\dfrac{\partial\tilde{M}}{\partial z}\right) \\ \qquad = \eta^2\left[\dfrac{\lambda_2 P}{k_5 + P}\dfrac{H(M_0 - M)}{1 + A_2/k_9} - \left(\dfrac{\chi}{\eta^2}\dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2\dfrac{\partial P}{\partial z}\right) + \mu_2 + h\right)\tilde{M}\right], \\ \dfrac{\partial\tilde{M}(0,\tau)}{\partial z} = \dfrac{\partial\tilde{M}(1,\tau)}{\partial z} = 0, \\ \tilde{M}(z,0) = M_0, \end{cases} \tag{40}$$

$$\begin{cases} \dfrac{\partial\tilde{D}}{\partial\tau} + v(z,\tau)\dfrac{\partial\tilde{D}}{\partial z} - \delta_3\dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2\dfrac{\partial\tilde{D}}{\partial z}\right) = \eta^2\left[\dfrac{\lambda_3 D_0 C}{k_1 + C}\cdot\dfrac{1}{1 + N/k_2}\Re_D(t) - \mu_3\tilde{D} - h\tilde{D}\right], \\ \dfrac{\partial\tilde{D}(0,\tau)}{\partial z} = \dfrac{\partial\tilde{D}(1,\tau)}{\partial z} = 0, \\ \tilde{D}(z,0) = D_0, \end{cases} \tag{41}$$

$$\begin{cases} \dfrac{\partial\tilde{T}_8}{\partial\tau} + v(z,\tau)\dfrac{\partial\tilde{T}_8}{\partial z} - \delta_4\dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2\dfrac{\partial\tilde{T}_8}{\partial z}\right) \\ \qquad = \eta^2\left(\dfrac{\lambda_4 T_8^0 I_2}{k_7 + I_2}\cdot\dfrac{1}{1 + I_1/k_6}\cdot\dfrac{1}{1 + P_1P_3/k_4}\cdot\dfrac{1}{1 + P_2B_7/k_8} - \mu_4\tilde{T}_8 - h\tilde{T}_8\right), \\ \dfrac{\partial\tilde{T}_8(0,\tau)}{\partial z} = \dfrac{\partial\tilde{T}_8(1,\tau)}{\partial z} + \sigma_0\dfrac{I_2'}{k - I_2'}(\tilde{T}_8 - \hat{T}_8)\Big|_{z=1} = 0, \\ \tilde{T}_8(z,0) = T_{80}, \end{cases} \tag{42}$$

$$\begin{cases} \dfrac{\partial\tilde{P}}{\partial\tau} - \omega(1,\tau)z\dfrac{\partial\tilde{P}}{\partial z} - \delta_5\dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2\dfrac{\partial\tilde{P}}{\partial z}\right) = \eta^2\left[\lambda_5 C\left(1 - \Re_P(\tau)\dfrac{B}{k_{10} + B}\right) - \mu_5\tilde{P}\right], \\ \dfrac{\partial\tilde{P}(0,\tau)}{\partial z} = \dfrac{\partial\tilde{P}(1,\tau)}{\partial z} = 0, \\ \tilde{P}(z,0) = P_0, \end{cases} \tag{43}$$

$$\begin{cases}\dfrac{\partial \tilde{I}_1}{\partial \tau}-\omega(1,\tau)z\dfrac{\partial \tilde{I}_1}{\partial z}-\delta_6\dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2\dfrac{\partial \tilde{I}_1}{\partial z}\right)=\eta^2(\lambda_6 C+\lambda_{10}M-\mu_6\tilde{I}_1),\\ \dfrac{\partial \tilde{I}_1(0,\tau)}{\partial z}=\dfrac{\partial \tilde{I}_1(1,\tau)}{\partial z}=0,\\ \tilde{I}_1(z,0)=I_{10},\end{cases}\tag{44}$$

$$\begin{cases}\dfrac{\partial \tilde{I}_2}{\partial \tau}-\omega(1,\tau)z\dfrac{\partial \tilde{I}_2}{\partial z}-\delta_7\dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2\dfrac{\partial \tilde{I}_2}{\partial z}\right)=\eta^2\left[\lambda_7 D\left(1+\theta_1\dfrac{B}{k_{10}+B}\right)-\mu_7\tilde{I}_2\right],\\ \dfrac{\partial \tilde{I}_2(0,\tau)}{\partial z}=\dfrac{\partial \tilde{I}_2(1,\tau)}{\partial z}=0,\\ \tilde{I}_2(z,0)=I_{20},\end{cases}\tag{45}$$

$$\begin{cases}\dfrac{\partial \tilde{N}}{\partial \tau}-\omega(1,\tau)z\dfrac{\partial \tilde{N}}{\partial z}-\delta_8\dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2\dfrac{\partial \tilde{N}}{\partial z}\right)=\eta^2\left[\lambda_8 M-\mu_8\tilde{N}\right],\\ \dfrac{\partial \tilde{N}(0,\tau)}{\partial z}=\dfrac{\partial \tilde{N}(1,\tau)}{\partial z}=0,\\ \tilde{N}(z,0)=N_0,\end{cases}\tag{46}$$

$$\begin{cases}\dfrac{\partial \tilde{B}}{\partial \tau}-\omega(1,\tau)z\dfrac{\partial \tilde{B}}{\partial z}-\delta_9\dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2\dfrac{\partial \tilde{B}}{\partial z}\right)=\eta^2\left[(\Phi_B)_\varepsilon(\tau)-\mu_{16}C\dfrac{B}{k_{10}+B}-\mu_9\tilde{B}\right],\\ \dfrac{\partial \tilde{B}(0,\tau)}{\partial z}=\dfrac{\partial \tilde{B}(1,\tau)}{\partial z}=0,\\ \tilde{B}(z,0)=B_0,\end{cases}\tag{47}$$

$$\begin{cases}\dfrac{\partial \tilde{A}_1}{\partial \tau}-\omega(1,\tau)z\dfrac{\partial \tilde{A}_1}{\partial z}-\delta_{10}\dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2\dfrac{\partial \tilde{A}_1}{\partial z}\right)=\eta^2\left[(\Phi_{A_1})_\varepsilon(\tau)-\mu_{13}P_1\tilde{A}_1-\mu_{10}\tilde{A}_1\right],\\ \dfrac{\partial \tilde{A}_1(0,\tau)}{\partial z}=\dfrac{\partial \tilde{A}_1(1,\tau)}{\partial z}=0,\\ \tilde{A}_1(z,0)=A_{10},\end{cases}\tag{48}$$

$$\begin{cases}\dfrac{\partial \tilde{A}_2}{\partial \tau}-\omega(1,\tau)z\dfrac{\partial \tilde{A}_2}{\partial z}-\delta_{11}\dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2\dfrac{\partial \tilde{A}_2}{\partial z}\right)=\eta^2\left[(\Phi_{A_2})_\varepsilon(\tau)-\mu_{17}M\tilde{A}_2-\mu_{11}\tilde{A}_2\right],\\ \dfrac{\partial \tilde{A}_2(0,\tau)}{\partial z}=\dfrac{\partial \tilde{A}_2(1,\tau)}{\partial z}=0,\\ \tilde{A}_2(z,0)=A_{20},\end{cases}\tag{49}$$

$$\begin{cases}\dfrac{\partial \tilde{A}_4}{\partial \tau}-\omega(1,\tau)z\dfrac{\partial \tilde{A}_4}{\partial z}-\delta_{12}\dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2\dfrac{\partial \tilde{A}_4}{\partial z}\right)=\eta^2\left[(\Phi_{A_4})_\varepsilon(\tau)-\mu_{14}P_2\tilde{A}_4-\mu_{12}\tilde{A}_4\right],\\ \dfrac{\partial \tilde{A}_4(0,\tau)}{\partial z}=\dfrac{\partial \tilde{A}_4(1,\tau)}{\partial z}=0,\\ \tilde{A}_4(z,0)=A_{40},\end{cases}\tag{50}$$

$$\frac{d\tilde{\eta}(\tau)}{d\tau}=\tilde{\eta}(\tau)\omega(1,\tau),\qquad 0\leqslant\tau\leqslant T,\tag{51}$$

$$\tilde{\eta}(0)=R_0,\tag{52}$$

$$\frac{1}{z^2}\frac{\partial}{\partial z}\left(z^2\omega\right)=\eta^2 h\left(\tilde{C},\tilde{B},\tilde{T}_8,\tilde{P},\tilde{A}_2,\tilde{M},\tilde{D},\tilde{N},\tilde{I}_1,\tilde{I}_2\right).\tag{53}$$

In the sequel, we will prove that (39)–(52) have global solutions by using Schauder fixed point theorem.

Step 1 First, we need to prove that F is a mapping from X_T to X_T. If $(U,\eta)\in X_T$, it is clear that (51)–(52) has a unique solution $\tilde{\eta}\in C[0,T]$, and

$$\tilde{\eta}(\tau) = R_0 \exp\left(\int_0^\tau u'(1,s)\mathrm{d}s\right). \tag{54}$$

Noting that (37), applying (i) and (38), we get

$$\left|\omega(1,\tau)\right| \leqslant \frac{4}{3}C_p(T)R_0^2. \tag{55}$$

Combining problem (54), we obtain

$$R_0 \exp\left(-\frac{4}{3}C_p(T)R_0^2 T\right) \leqslant \tilde{\eta}_\varepsilon(\tau) \leqslant R_0 \exp\left(\frac{4}{3}C_p(T)R_0^2 T\right), \quad 0 \leqslant \tau \leqslant T. \tag{56}$$

Since (39) satisfies the conditions of Lemma 1, we know that it has local solution $\tilde{C} \in W_p^{2,1}(Q_T)$, and

$$\left\|\tilde{C}\right\|_{W_p^{2,1}(Q_T)} \leqslant C(T)\left\|C_0\right\|_{D_p(0,1)} \leqslant C(T, C_0). \tag{57}$$

Similarly, we have

$$\left\|\tilde{M}, \tilde{D}, \tilde{T}_8, \tilde{P}, \tilde{I}_1, \tilde{I}_2, \tilde{N}, \tilde{B}, \tilde{A}_1, \tilde{A}_2, \tilde{A}_4\right\|_{W_p^{2,1}(Q_T)} \leqslant C(T, R_0, \psi), \tag{58}$$

where ψ depends on the initial values of variables and related coefficients. In summary, we let $T \geqslant 0$ be small enough, then $C(T,\psi) \leqslant G$. Using the embedding theorem, we have

$$W_p^{2,1}(Q_T) \subset\subset C^{\alpha,\frac{\alpha}{2}}(\bar{Q}_T), \left(0 < \alpha < 2 - \frac{5}{p}, p > 5\right).$$

Therefore $\left\|\tilde{U}\right\|_\infty \leqslant G$, i. e.

$$\left\|\tilde{C}, \tilde{M}, \tilde{D}, \tilde{T}_8, \tilde{P}, \tilde{I}_1, \tilde{I}_2, \tilde{N}, \tilde{B}, \tilde{A}_1, \tilde{A}_2, \tilde{A}_4\right\|_\infty \leqslant G. \tag{59}$$

We can see that $\tilde{U}$ satisfy the condition (ii), such that $\left(\tilde{U}_\varepsilon, \tilde{\eta}\right) \in X_T$. It proves that F is a mapping from X_T to X_T.

Step 2 Here we will show that E is a closed convex subset of X_T. The set E is defined by

$$E = \left\{\left(\tilde{U}_\varepsilon, \tilde{\eta}\right)\middle| 0 \leqslant z \leqslant 1, 0 \leqslant \tau \leqslant T, \tilde{U}_\varepsilon \in C\left(\overline{Q}_T\right), \eta_\varepsilon \in C[0,T]\right\},$$

and $\tilde{U}_\varepsilon, \tilde{\eta}$ satisfy (39)–(52). Obviously, E is a closed convex subset of X_T.

Step 3 In the following, we prove $F(E)$ is a compact mapping,i. e. , $F(E)$ is precompact on X_T. Applying Lemma 1, we have $\tilde{C}, \tilde{M}, \tilde{D}, \tilde{T}_8, \tilde{P}, \tilde{I}_1, \tilde{I}_2, \tilde{N}, \tilde{B}, \tilde{A}_1, \tilde{A}_2, \tilde{A}_4 \in W_p^{2,1}(Q_T)$, and then according to the Sobolev compact embedding theorem (Cui,2015), we obtain $W_p^{2,1}(Q_T) \subset\subset C^{\alpha,\frac{\alpha}{2}}(\bar{Q}_T), (0 < \alpha < 2 - 5/p, p > 5)$. Clearly, $F(E)$ is precompact on X_T.

Step 4 Finally, we devote to proving that F is a continuous mapping. Combining (37) and (38), we deduce that

$$\left\|\omega_1(z,\tau) - \omega_2(z,\tau)\right\| \leqslant C(T)d.$$

Considering (54), applying the differential mean value theorem of one variable function, we have

$$\left\|\tilde{\eta}_1 - \tilde{\eta}_2\right\| \leqslant C(T)d.$$

Denote $U^* = U_1 - U_2$, $\eta^* = \eta_1 - \eta_2$, then C^* satisfies:

$$\begin{cases} \dfrac{\partial C^*}{\partial \tau} + v_1(z,\tau)\dfrac{\partial C^*}{\partial z} - \delta_1 \dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2 \dfrac{\partial C^*}{\partial z}\right) = \eta_1^2\left[\lambda_1 \dfrac{f(C_1)}{1 + B_1/k_3} - \mu_{15}T_{81} - \mu_1 - h_2\right]C^* + g(z,\tau), \\ \dfrac{\partial C^*(0,\tau)}{\partial z} = \dfrac{\partial C^*(1,\tau)}{\partial z} = 0, \\ C^*(z,0) = 0, \end{cases} \tag{60}$$

where $f\left(C_j\right) = 1 - \dfrac{C_j}{C_M}\left(j = 1,2\right)$, and $0 \leqslant f\left(C_j\right) \leqslant 1$. Obviously, $f\left(C_j\right)$ is a bounded continuous function. And

$$g(z,\tau)=\left[\left(\eta_1^2\lambda_1\frac{f(C_1)}{1+B_1/k_3}-\eta_2^2\lambda_1\frac{f(C_2)}{1+B_2/k_3}\right)-\left(\eta_1^2\mu_{15}T_{81}-\eta_2^2\mu_{15}T_{82}\right)\right.$$
$$\left.-\left(\eta_1^2\mu_1-\eta_2^2\mu_1\right)-\left(\eta_1^2h_1-\eta_2^2h_2\right)\right]C_2-\left(v_1-v_2\right)\frac{\partial C_2}{\partial z}.$$

We see that $v_1(z,\tau)$, $\eta_1\left[\lambda_1\frac{1}{1+B/k_3}\cdot f(C_1)-\mu_{15}T_{81}-\mu_1-h_2\right]$ are bounded continuous functions, and $g(z,\tau)\in L^p(Q_T)$. According to the maximum norm estimation of solution, we get

$$\begin{aligned}\|C^*\|_\infty &\leqslant C_1(T)\|g(z,\tau)\|_\infty\\
&=C_1(T)\cdot\left\|\left[\left(\eta_1^2\lambda_1\frac{f(C_1)}{1+B_1/k_3}-\eta_2^2\lambda_1\frac{f(C_2)}{1+B_2/k_3}\right)-\left(\eta_1^2\mu_{15}T_{81}-\eta_2^2\mu_{15}T_{82}\right)\right.\right.\\
&\qquad\left.\left.-(\eta_1^2\mu_1-\eta_2^2\mu_1)-(\eta_1^2h_1-\eta_2^2h_2)\right]\cdot C_2-(v_1-v_2)\cdot\frac{\partial C_2}{\partial z}\right\|_\infty\\
&\leqslant C_1(T)\cdot\left\{\left[\eta_1^2\lambda_1\frac{1}{1+B_1/k_3}\left\|f(C_1)-f(C_2)\right\|_\infty+\eta_1^2\lambda_1\cdot f(C_2)\cdot\left\|\frac{1}{1+B_1/k_3}-\frac{1}{1+B_2/k_3}\right\|_\infty\right.\right.\\
&\qquad+\frac{\lambda_1f(C_2)}{1+B_2/k_3}(\eta_1+\eta_2)\cdot\left\|(\eta_1-\eta_2)\right\|_\infty-\mu_{15}T_{81}\cdot\|\eta_1-\eta_2\|_\infty\\
&\qquad-\eta_2\mu_{15}\cdot\|T_{81}-T_{82}\|_\infty-\mu_1(\eta_1+\eta_2)\|\eta_1-\eta_2\|_\infty\\
&\qquad\left.\left.-\eta_1^2\cdot\|h_1-h_2\|_\infty-h_2\cdot(\eta_1+\eta_2)\|\eta_1-\eta_2\|_\infty\right]\cdot\|C_2\|_\infty+\left\|(v_1-v_2)\right\|_\infty\left\|\frac{\partial C_2}{\partial z}\right\|_\infty\right\}\\
&\leqslant C_2(T)d.\end{aligned}$$

In the same way, we shall also get

$$\|M^*\|\leqslant C_3(T)d,\ \|D^*\|\leqslant C_4(T)d,\ \|T_8^*\|\leqslant C_5(T)d,\ \|P^*\|\leqslant C_6(T)d,\ \|I_1^*\|\leqslant C_7(T)d,\ \|A_1^*\|\leqslant C_{11}(T)d,$$
$$\|I_2^*\|\leqslant C_8(T)d,\ \|N^*\|\leqslant C_9(T)d,\ \|B^*\|\leqslant C_{10}(T)d,\ \|A_2^*\|\leqslant C_{12}(T)d,\ \|A_4^*\|\leqslant C_{13}(T)d.$$

Thus we conclude that $d((U_1,\eta_1),(U_2,\eta_2))=\|U_1-U_2\|_\infty+\|\eta_1-\eta_2\|_\infty\leqslant C(T)d$, i. e. , F is continuous mapping.

In summary, we can prove that the mapping F has a fixed point on E by using the Schauder fixed point theorem, and the global solution can be obtained from the arbitrariness of T. So Lemma 3 is proved.

3 The existence of solutions to original problem

In this section, we will use the function approximation method to prove the original problem has weak solutions.

Lemma 4 For each $T>0$, (1)–(17) has weak solutions $(U,\eta)=(U_\varepsilon,\eta_\varepsilon)$ on X_T.

Proof Applying Lemma 3, we obtain that (21)–(32) exist weak solutions U_ε under the approximation, which satisfy $U_\varepsilon\in W_p^{2,1}(Q_T)$. Therefore, by Sobolev's compact embedding theorem, we see that

$$W_p^{\,2,1}(\tilde{Q}_T)\subset\subset C^{\alpha,\alpha/2}(\tilde{Q}_T),\ (0<\alpha<2-\frac{5}{p},p>5).$$

Then for any sequence $\left\{\left(C_{\varepsilon_k},M_{\varepsilon_k},D_{\varepsilon_k},T_{8\varepsilon_k},P_{\varepsilon_k},I_{1\varepsilon_k},I_{2\varepsilon_k},N_{\varepsilon_k},B_{\varepsilon_k},A_{1\varepsilon_k},A_{2\varepsilon_k},A_{4\varepsilon_k}\right)\right\}_{k=1}^\infty$, it follows that we can find a subsequence

$$\left\{\left(C_k,M_k,D_k,T_{8k},P_k,I_{1k},I_{2k},N_k,B_k,A_{1k},A_{2k},A_{4k}\right)\right\}_{k=1}^\infty,$$

and a vector function $U=(C,M,D,T_8,P,I_1,I_2,N,B,A_1,A_2,A_4)$ satisfy

$$U\in C^{\alpha,\alpha/2}(\bar{Q}_T).$$

For each $(z,\tau)\in Q_T$, $\varepsilon_k\to 0$, as $k\to\infty$, if we denote $U_k=U_{\varepsilon_k}$, then

$$U_k\to U,\ \nabla U_k\to\nabla U,\ v_k\to v,\ \omega_k(1,\tau)\to\omega(1,\tau)\ \text{uniformly for}\ (z,\tau)\in\bar{Q}_T,$$
$$(U_k)_\tau\rightharpoonup U_\tau\left(L^p(Q_T)\right),\quad \Delta U_k\rightharpoonup\Delta U\left(L^p(Q_T)\right).$$

Since $(\Phi_{A_1})_k(\tau)$ is a bounded function on $[0,T]$. We can find a weakly convergent subsequence of it, denoted by $\{(\Phi_{A_1})_k(\tau)\}$ as well as a function $y_1(\tau)$. Taking $k\to\infty$, we obtain

$$(\Phi_{A_1})_k(\tau)\rightharpoonup y_1(\tau),\ \ \tau\in[0,T].$$

Consider (30) and take $\varepsilon=\varepsilon_k$, then $(A_1)_\varepsilon=(A_1)_{\varepsilon_k}$. We get $\nabla(A_1)_\varepsilon\to\nabla A_1$, $(\Phi_{A_1})_\varepsilon\rightharpoonup\Phi_{A_1}$, $(A_1)_\varepsilon\to A_1$, $\Delta(A_1)_\varepsilon\rightharpoonup\Delta A_1$, and $\dfrac{\partial(A_1)_\varepsilon}{\partial\tau}\rightharpoonup\dfrac{\partial A_1}{\partial\tau}$ as $\varepsilon\to 0$. Hence, when $k\to\infty$, we have

$$\begin{cases}\dfrac{\partial A_1}{\partial\tau}-u'(1,\tau)z\dfrac{\partial A_1}{\partial z}-\delta_{10}\dfrac{1}{z^2}\dfrac{\partial}{\partial z}\left(z^2\dfrac{\partial A_1}{\partial z}\right)=\eta^2\left[y_{A_1}(\tau)-\mu_{13}P_1'A_1-\mu_{10}A_1\right],\\ \dfrac{\partial A_1(0,\tau)}{\partial z}=\dfrac{\partial A_1(1,\tau)}{\partial z}=0,\\ A_1(z,0)=A_{10}.\end{cases}\tag{61}$$

We assert that

$$y_1(\tau)\overset{a.e.}{=\!=}\begin{cases}\gamma_{A_1}, & \tau\in(60,120),\\ 0, & \text{otherwise.}\end{cases}$$

Indeed, it is clear that for any $\delta>0$, $y_1(\tau)\overset{a.e.}{=\!=}0$ in the set $\{\tau\in(0,T)\,|\,\tau\in[0,60-\delta]\cup[120+\delta,+\infty)\}$.

By the arbitrariness of δ, we infer that $y_1(\tau)\overset{a.e.}{=\!=}0$ in the set $\{\tau\in(0,T)\,|\,\tau\in[0,60)\cup(120,+\infty)\}$. Similarly, we can also prove that $y_1(\tau)\overset{a.e}{=\!=}\gamma_A$ in the set $\{\tau\in(0,T)\,|\,\tau\in(60,120)\}$, the assertion holds. Since $A_1=0$ as $\tau=60$ (p. 4 (Cui, 2005)), then

$$\frac{\partial A_1}{\partial\tau}=0,\ \Delta A_1=0,\ \nabla A_1=0,\ \text{a. e. on the set}\ \{\tau\in(0,T)\,|\,\tau=60\}.$$

Furthermore, the drug A_1 is depleted in the process of blocking $PD-1$ (p. 9 (Friedman et al. ,2020)), so once the drug injection is stopped, there is $A_1=0$ instantly. By (61) it follows that

$$y_1(\tau)\overset{a.e.}{=\!=}0,\ \{\tau\in(0,T)\,|\,\tau=60\cup\tau=120\}.$$

Hence

$$y_1(\tau)\overset{a.e.}{=\!=}\Phi_{A_1}(\tau),\ \ \tau\in[0,T].$$

In the same way, we can also obtain

$$y_2(\tau)\overset{a.e.}{=\!=}\Phi_B(\tau),\ \ y_{A_2}(\tau)\overset{a.e.}{=\!=}\Phi_B(\tau),\ y_4(\tau)\overset{a.e.}{=\!=}\Phi_{A_4}(\tau),\ \ \tau\in[0,T].$$

By the above analysis, Lemma 4 is proved.

In summary, by Lemma 2–4 and the arbitrariness of time T, we see that Theorem 1 immediately follows.

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一类黑色素瘤耐药机制交叉扩散方程组模型解的存在性

陈为[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：研究了检查点抑制剂靶向治疗人类黑色素瘤的数学模型。该模型由12个耦合的反应扩散方程组成，模型具有不连续项且包含自由边界条件。将自由边界问题转化为固定边界问题，并利用抛物方程的L^p理论和Schauder不动点定理，结合函数逼近的方法，得到了该数学模型全局弱解的存在性。

关键词：黑色素瘤；反应扩散方程；弱解；存在性

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