数理解析研究所講究録
第 1792 巻 2012 年 82-98

The existence of solutions for tumor invasion problem equipped by the unknown diffusion

RISEI KANO
Center for the Advancement of Higher Education,
Faculty of Engineering, Kinki University,
Takayaumenobe 1, Higashihiroshimashi, Hiroshima 739-2116 Japan
(E-mail: kano@hiro.kindai.ac.jp)

Abstract. We consider a tumor invasion model with constraint. The original model was proposed by M.A.J.Chaplain and A.R.A. Anderson in [1]. In the paper, the diffusion of tumor cells is given by the function, because there is the effect of heat shock proteins. Moreover, we consider that the diffusion is affected by the extracellular matrix which is the unknown function for tumor invasion model. Then, our problem has the given function of diffusion depending upon time, place and the unknown function. We show the exsitence of solution for above problem.

1 Introduction

In this paper, we consider the following parabolic systems with a constraint condition;

$$(P)\begin{cases} \frac{\partial n}{\partial t}=\nabla\cdot\{k_n(t,x,f)\nabla n-\lambda(t,x)n\nabla f\}+\mu(t,x)n(1-n-f) & \text{in } Q_T,\\ n+f\leq 1, & \text{in } Q_T,\\ \frac{\partial f}{\partial t}=-\delta mf & \text{in } Q_T,\\ \frac{\partial m}{\partial t}=k_m\Delta m+C_1n-C_2m & \text{in } Q_T,\\ n=0,\quad \frac{\partial m}{\partial \mathbf{n}}=0 & \text{in } \Sigma_T,\\ n(0)=n_0,\ f(0)=f_0,\ m(0)=m_0 & \text{in } \Omega. \end{cases}$$

where, T is a any positive number, Ω is a bounded domain in $\mathbb{R}^N, (1 \leq N \leq 3)$ having the smooth boundary $\Gamma := \partial\Omega$, $Q_T = (0,T) \times \Omega$, $\Sigma_T = (0,T) \times \Gamma$, k_n is a positive function in $(0,T) \times \Omega\mathbb{R}$, λ and μ are positive functions in Q_T, δ, k_m, C_1 and C_2 are positive constants and n_0, f_0 and m_0 is a function in Ω.

This system which is a mathematical modelling for the tumor invasion phenomena with some constraints , is well-known by [1],[2]. The unknown functions n, f and m mean density of solid tumor cells, the extracellular matrix(ECM) and the matrix degrading enzymes(MDEs) concentration, respectively. The first equation contains the three teams that mean the diffusions, moving to the place of destroyed ECM by MDEs(hapotaxis) and the growth. The second equation describes the ECM destroyed by MDEs. The third equation consists of three terms that mean diffusion of MDEs, production by tumor cell and natural decay.

In the paper [1] (Chaplain and Anderson), All given functions, k_n, λ and μ, are positive constants for simplicity. However, in the paper [2] (Szymańska, Urbański and Marciniak-Czochra), they are given by the above functions to functions depending the parameters, because they pick on the act of the heat shock protein (HSP). The heat shock protein has the following three acts:(1) The HSP affects the 1-D protein which is a freshly generated, a kind of strap, then, the one is made over a general protein. (2) The HSP affects the destroyed protein by some stress, then, the one is restored. (3) By the strong stress, the HSP leads a protein to the apoptosis (Self-induced cell death). Since these properties, they thought that the heat shock protein acts on the material of forming the cytoskeleton. Hence, they assume that the diffusion of tumor cell is determined by the amount of the heat shock protein, namely, they give the diffusion coefficient function to $k_n = k_n(t)$.

On the models of [2], we get the time local and time global solution of that problem, in the paper [3] and [4], respectively. Impose the same conditions $n + f \leq 1$ as (P), we proved the existence of solutions by the approach for quasi-variational inequalities (QVI). Quasi-variational inequalities is to find a function which satisfies a variational inequality in which the constraint depend upon the unknown function. In 1973, Bensoussan and Lions proposed quasi-variational inequalities in [5], firstly.

Later, quasi-variational inequalities were studied by many mathematician. It was well known that there are two methods for analysis of quasi-variational inequalities. The first method is called by "Monotonicity Method" that is proved the solutions by the order relation. There are many results of this method, for example, [6], [7] and [8]. The other is called by "Compactness Method" that is proved the solutions by compact operator defined in the Banach spaces. There are many results of this method, too. For example, [9], [10], [11] and [12].

It was used in [3],[4] that this is the existence theorem of solutions for parabolic quasi-variational inequalities in [12]. Moreover, for the case which the distribution of the heat shock protein is not uniformity in the domain (namely $k_n = k_n(t,x)$), we proved the existence of solutions as the same method of quasi-variational inequalities. (cf.[13])

In this paper, we consider that the diffusion of tumor is affected by the heat shock proteins and the extracellular matrix which is a basis of cells. Namely, $k_n = k_n(t,x,f)$.

2 The approach by QVI

We define the following three operators.

Definition 2.1.

(1) For each $t \in [0,T]$ and $\tilde{n} \in L^2(0,t;L^2(\Omega))$, we consider the following parabolic problem (P1):

$$
(\mathrm{P1}) \begin{cases} \frac{\partial \tilde{m}}{\partial t} = k_m \Delta \tilde{m} + C_1 \tilde{n} - C_2 \tilde{m} & \text{a.e. in } Q_t, \\ \frac{\partial \tilde{m}}{\partial n} = 0 \quad \text{a.e. in } \Sigma_t, \\ \tilde{m}(0) = m_0 \quad \text{a.e. in } \Omega. \end{cases}
$$

This problem has a unique solution $\tilde{n}$ as well known. Then, we define the solution operator $\Lambda_1(t) : L^2(0,t;L^2(\Omega)) \to W^{1,2}(0,t;L^2(\Omega)) \cap L^\infty(0,t;H^1(\Omega)) \cap L^2(0,t;H^2(\Omega))$ for $\tilde{n}$. i.e.$\Lambda_1(t)\tilde{n} = \tilde{m}$.

(2) For each $t \in [0,T]$ and $\tilde{m} \in L^2(0,t;L^2(\Omega))$, we define the operator $\Lambda_2(t)\tilde{m} := \tilde{f} \in W^{1,2}(0,t;L^2(\Omega))$ by the following formulation;

$$\tilde{f}(x,s) := f_0(x)\exp\left(-\delta\int_0^s \tilde{m}(x,\tau)d\tau\right), \quad \forall(x,s) \in Q_t.$$

Namely, for each $\tilde{m}$, $\Lambda_2(t)$ is the solution operator of the following initial value problem (P2):

$$\text{(P2)} \begin{cases} \frac{d\tilde{f}}{dt} = -\delta\tilde{m}\tilde{f} & \text{a.e. in } Q_t, \\ \tilde{f}(0) = f_0 & \text{a.e. in } \Omega. \end{cases}$$

(3) For each $t \in [0,T]$, we define the composite operator $\Lambda(t) := \Lambda_2(t) \circ \Lambda_1(t)$.

We define the solution of our problem (P) using the above operators.

Definition 2.2.

For each $t \in [0,T]$, we say that the triplet $\{n,f,m\}$ is a solution of the our problem (P) on $[0,t]$, if $\{n,f,m\}$ satisfies that the following conditions (S1)-(S4);

(S1) $n \in W^{1,2}(0,t;L^2(\Omega)) \cap L^\infty(0,t;H_0^1(\Omega))$

(S2) $n \le 1-f \quad$ a.e. in Q_t,

$$\int_0^t\int_\Omega\left(\frac{\partial n}{\partial t} - \mu n(1-n-f)\right)(n-v)dxds$$
$$+\int_0^t\int_\Omega\Big(\lambda(s)\{n\nabla f\}+k_n(t,x,f)\nabla n\Big)\cdot\nabla(n-v)dxds \le 0,$$

for $\forall v \in L^2(0,t;H_0^1(\Omega))$ with $v \le 1-f$ a.e. in Q_t,

(S3) $n(0) = n_0 \quad$ a.e. in Ω,

(S4) $m = \Lambda_1(t)n,\ f = \Lambda(t)n,\ $ in $L^2(\Omega)$.

We assume that the following condition (A1)-(A6) are satisfied for we discuss our problem (P).

(A1) k_n which is a positive function in $(0,T)\times\Omega\times\mathbb{R}$, is satisfied the following three condition (i)(ii)(iii):

(i) For each $r \in \mathbb{R}$, there is a positive number $p > 1$ such that

$$k_n(\cdot, \cdot, r) \in W^{1,p}(0, T; L^\infty(\Omega)).$$

(ii) There are positive numbers K_0 and $K_1 > 0$ such that

$$K_0 \leq K_n(t, x, r) \leq K_1,$$

for all $(t, x, r) \in (0, T) \times \Omega \times \mathbb{R}$.

(iii) For each $(t, x) \in (0, T) \times \Omega$, $k_n(t, x, \cdot)$ is Lipschitz continuous in $\mathbb{R}$. Namely, there exists positive number $K_2 > 0$ such that

$$|k_n(t, x, r_1) - k_n(t, x, r_2)| \leq K_2 |r_1 - r_2|$$

for all $r_1, r_2 \in \mathbb{R}$.

(A2) λ is non-negative function in $L^\infty(Q_T)$,

(A3) μ is non-negative function in $L^2(Q_T) \cap L^1(0, T; L^\infty(\Omega))$,

(A4) $n_0 \in H^1(\Omega)$, $0 \leq n_0 \leq 1$ a.e. in Ω,

(A5) $f_0 \in W^{1,\infty}(\Omega) \cap H^2(\Omega)$, $0 \leq f_0 \leq 1 - n_0$ a.e. in Ω,

(A6) $m_0 \in H^2(\Omega)$, $0 \leq m_0$ a.e. in Ω.

Theorem 2.1.
We assume that the condition (A1)-(A6) are satisfied. Then, our problem (P) has at least one solution $\{n, f, m\}$ in $[0, T_0]$, $(0 < T_0 \leq T)$.

3 Convex functions

We show the proof of our main result by the method of quasi-variational inequalities. Firstly, we define some notations to use the approach by quasi-variational inequalities. We introduce a time-dependent, non-negative, proper, l.s.c. and convex function φ_0 on $L^2(\Omega)$ such that

$$\varphi_0(z) = \begin{cases} \dfrac{K_0}{2} \displaystyle\int_\Omega |\nabla z|^2 dx & \text{if } z \in L^2(\Omega),\ z \in K, \\ +\infty & \text{otherwise,} \end{cases}$$

where, K_0 is given by the assumption (ii) of (A1) and

$$K := \{z \in H_0^1(\Omega); 0 \le z \le 1 \text{ a.e. in } \Omega\}.$$

Let δ_0 be a fixed positive number. For each $t \in [0,T]$ we define a closed convex set $\mathcal{V}(-\delta_0, t)$ by

$$\mathcal{V}(-\delta_0,t) := \left\{v \in W^{1,2}(-\delta_0,t;L^2(\Omega)); V_{[-\delta_0,t]}(v) < \infty\right\}$$

with

$$V_{[-\delta_0,t]}(v) := \sup_{-\delta_0 \le s \le t} \varphi_0(v(s)) + |v(0)|^2_{L^2(\Omega)} + |v'|^2_{L^2(-\delta_0,t;L^2(\Omega))}$$

where $v'(t) = \frac{d}{dt}(v(t))$.

In the paper [12], we use the family $\{\varphi^s(v,\cdot)\}_{0\le s\le t}$ of time-dependent convex functions $\varphi^s(v,\cdot)$ for each $v \in \mathcal{V}(-\delta_0,t;L^2(\Omega))$, which satisfies the following there conditions:

(Φ1) $\varphi^s(v;z)$ is proper, l.s.c., non-negative and convex in $z \in L^2(\Omega)$, and it is determined by $s \in [0,t]$ and v on $[-\delta_0, s]$; namely, for v_1, $v_2 \in \mathcal{V}(-\delta_0,t)$, we have $\varphi^s(v_1;\cdot) = \varphi^s(v_2;\cdot)$ on $L^2(\Omega)$;

(Φ2) $\varphi^s(v;z) \ge \varphi_0(z)$, $\forall v \in \mathcal{V}(-\delta_0,t)$, $0 \le \forall s \le \forall t \le T$;

(Φ3) If $0 \le s_k \le t \le T$, $v_k \in \mathcal{V}(-\delta_0,t)$, $\sup_{k\in\mathbb{N}} V_{[-\delta_0,t]}(v_k) < \infty$, $s_k \to s$ and $v_k \to v$ in $C([-\delta_0,t];L^2(\Omega))$, then $\varphi^{s_k}(v_k;\cdot) \to \varphi^s(v;\cdot)$ on $L^2(\Omega)$ in the sense of Mosco.

For each $t \in [0,T]$, we define $\mathcal{V}^t_+$ by

$$\mathcal{V}^t_+ := \{v \in \mathcal{V}(-\delta_0,t); 0 \le v \le 1\},$$

and for each $v \in \mathcal{V}^t_+$, we define $\varphi^s(v;\cdot)$ by

$$\varphi^s(v;z) = \begin{cases} \dfrac{1}{2}\displaystyle\int_\Omega k_n(s,x,[\Lambda(t)v](s,x))|\nabla z|^2 dx & \text{if } z \in L^2(\Omega),\ z \in K(s;v), \\ +\infty & \text{otherwise,} \end{cases}$$

where $\Lambda(t)$ is defined by Def.2.1. and

$$K(s;v) := \{z \in H_0^1(\Omega); 0 \le z \le 1 - [\Lambda(t)v](s) \text{ a.e. in } \Omega\}.$$

Lemma 3.1. For each $s \in [0,t]$ and $v \in \mathcal{V}_+^t$, $\varphi^s(v;z)$ satisfies the above conditions ($\Phi 1$), ($\Phi 2$) and ($\Phi 3$).

(Proof) It is clear that the conditions ($\Phi 1$) and ($\Phi 2$) are satisfied. Then, we show only that the condition ($\Phi 3$) is satisfied. We put $w_k = \Lambda_1(t)v_k$, $w = \Lambda_1(t)v$, $z_k = \Lambda(t)v_k$ and $z = \Lambda(t)v$. It is easily that the following convergences holds:

$$w_k \to w \quad \begin{cases} \text{in} & C([0,t];L^2(\Omega)) \cap L^2(0,t;H^1(\Omega)), \\ \text{weakly in} & W^{1,2}(0,t;L^2(\Omega)) \cap L^2(0,t;H^2(\Omega)), \\ \text{in} & L^\infty(0,t;H^1(\Omega)). \end{cases}$$

Then, we see from the above convergence that there exist constants $K_3, K_4 > 0$ such that the following inequality holds for all $s \in [0,t]$:

$$\begin{aligned} |z_k(s) - z(s)|^2_{L^2(\Omega)} &\le K_3 \int_\Omega \left| \int_0^s (w_k(x,\tau) - w(x,\tau))d\tau \right|^2 dx \\ &\le K_4 |w_k - w|^2_{C([0,t];L^2(\Omega))}. \end{aligned}$$

Hence, we get the following convergences:

$$z_k \to z \ \text{ in } C([0,t];L^2(\Omega)),$$

and

$$z_k(s_k) \to z(s) \ \text{ in } L^2(\Omega).$$

At first, we show $\liminf_{k\to\infty} \varphi^{s_k}(v_k;z) \ge \varphi^s(v;z)$ for any $\theta \in L^2(\Omega)$. If $\liminf_{k\to\infty} \varphi^{s_k}(v_k;\theta) = \infty$, then we already proved. Hence, we only consider the case $C = \liminf_{k\to\infty} \varphi^{s_k}(v_k;\theta) < \infty$. We assume $C < \varphi^s(v;\theta)$. Fixed $C' \in (C, \varphi^s(v;\theta))$, we can take a subsequence such that

$$\varphi^{s_k}(v_k;\theta) \le \frac{C+C'}{2}, \quad \forall k \in \mathbb{N}.$$

This implies $\theta \in K(s_k;v_k)$. Then,

$$\theta \in H_0^1(\Omega) \text{ with } 0 \le \theta \le 1 - z_k(s_k) \text{ a.e. in } \Omega.$$

We take a limit as $k \to \infty$, it is clear that

$$\theta \in H_0^1(\Omega) \text{ with } 0 \le \theta \le 1 - z(s) \text{ a.e. in } \Omega.$$

Therefore, we have

$$z \in K(s;v) \text{ and } \lim_{k\to\infty} \varphi^{s_k}(v_k;\theta) = \varphi^s(v;\theta).$$

Hence, $C < \varphi^s(v;\theta) \leq \frac{C+C'}{2}$. This is a contradiction.

Secondly, let $\theta \in K(s;v)$ and put $\theta_k := \min\{\theta, 1 - z_k(s_k)\}$. It is clear that $z_k \in K(s_k;v_k)$ and $\lim_{k\to\infty}\theta_k = \theta$ a.e. in Ω. Moreover, since $\Omega_k := \{x \in \Omega; \theta(x) > 1 - z_k(x,s_k)\}$, there exists a positive constant K_5 such that

$$\begin{aligned}
|\theta_k - \theta|^2_{H^1_0(\Omega)} &= \int_{\Omega_k} |\nabla z_k(x,s_k)|^2 dx \\
&\leq 2\int_{\Omega_k} |\nabla f_0(x)|^2 dx + 2K_3 \int_{\Omega_k} \left(\int_0^{s_k} |\nabla w_k(x,\tau)| d\tau\right)^2 dx \\
&\leq 2|\nabla f_0|^2_{C(\overline{\Omega_k})}|\Omega_k| + 2K_3 T|\Omega_k|^{\frac{1}{2}} \int_0^t |\nabla w_k(\tau)|^2_{L^4(\Omega_k)} d\tau \\
&\leq K_5|\Omega_k|^{\frac{1}{2}},
\end{aligned}$$

which implies that $\theta_k \to \theta$ in $H^1_0(\Omega)$, that is $\varphi^{s_k}(v_k;\theta_k) \to \varphi^s(v;\theta)$ as $k \to \infty$.■

Lemma 3.2. There are non-negative functions $\alpha \in L^2(0,T)$ and $\beta \in L^1(0,T)$ such that the following condition is fulfilled:

For any $t \in [0,T]$, $v \in \mathcal{V}^t_+$, $s_1, s_2 \in [0,t]$ and any $z \in D(\varphi^{s_1}(v;\cdot))$, there exists $\tilde{z} \in D(\varphi^{s_2}(v;\cdot))$ such that

$$|\tilde{z} - z|_{L^2(\Omega)} \leq \int_{s_1}^{s_2} \alpha(\tau)d\tau(1 + \varphi^{s_1}(v;z)^{\frac{1}{2}})$$

and

$$\varphi^{s_2}(v;\tilde{z}) - \varphi^{s_1}(v;z) \leq \int_{s_1}^{s_2} \beta(\tau)d\tau(1 + \varphi^{s_1}(v;z)).$$

(Proof) We put $\tilde{z}(x) := z(x) - [\Lambda v](s_1,x) + [\Lambda v](s_2,x)$. There is a positive number K_6 such that

$$\begin{aligned}
|\tilde{z} - z|_{L^2(\Omega)} &= |[\Lambda(t)v](s_1) - [\Lambda(t)v](s_2)|_{L^2(\Omega)} \\
&\leq |s_2 - s_1|^{\frac{1}{2}} \left(\int_{s_1}^{s_2} \left|\frac{d}{d\tau}([\Lambda(t)v](\tau))\right|^2_{L^2(\Omega)} d\tau\right)^{\frac{1}{2}}
\end{aligned}$$

$$\leq |s_2 - s_1|^{\frac{1}{2}} \left(\int_{s_1}^{s_2} \delta^2 \left| [\Lambda_1(t)v](\tau) \right|^2_{L^2(\Omega)} d\tau \right)^{\frac{1}{2}}$$

$$\leq |s_2 - s_1|^{\frac{1}{2}} \left(\int_{s_1}^{s_2} \delta^2 \left(|m_0|^2_{L^2(\Omega)} + K_6 T |\Omega| \right) d\tau \right)^{\frac{1}{2}}$$

$$\leq |s_2 - s_1| \delta \left(|m_0|_{L^2(\Omega)} + K_6^{\frac{1}{2}} T^{\frac{1}{2}} |\Omega|^{\frac{1}{2}} \right)$$

and

$$\varphi^{s_2}(v; \tilde{z}) - \varphi^{s_1}(v; z)$$

$$\leq \frac{1}{2} \int_\Omega k_n(s_2, x, [\Lambda(t)v](s_2, x)) |\nabla \tilde{z}|^2 dx - \frac{1}{2} \int_\Omega k_n(s_1, x, [\Lambda(t)v](s_1, x)) |\nabla z|^2 dx$$

$$\leq \frac{1}{2} \int_\Omega k_n(s_2, x, [\Lambda(t)v](s_2, x)) (|\nabla \tilde{z}|^2 - |\nabla z|^2) dx.$$

$$+ \frac{1}{2} \int_\Omega \{ k_n(s_2, x, [\Lambda(t)v](s_2, x)) - k_n(s_1, x, [\Lambda(t)v](s_1, x)) \} |\nabla z|^2 dx.$$

We have the following inequalities by the above first term,

$$\frac{1}{2} \int_\Omega k_n(s_2, x, [\Lambda(t)v](s_2, x)) (|\nabla \tilde{z}|^2 - |\nabla z|^2) dx$$

$$= \frac{1}{2} \int_\Omega k_n(s_2, x, [\Lambda(t)v](s_2, x)) (|\nabla (z - [\Lambda v](s_1, x) + [\Lambda v](s_2, x))|^2 - |\nabla z|^2) dx$$

$$\leq \frac{C_1}{2} \int_\Omega k_n(s_2, x, [\Lambda(t)v](s_2, x)) (|\nabla ([\Lambda v](s_1, x) - [\Lambda v](s_2, x))|^2) dx$$

$$\leq \frac{C_1 K_1}{2} \int_\Omega |\nabla ([\Lambda v](s_1, x) - [\Lambda v](s_2, x))|^2 dx$$

$$\leq \frac{C_1 K_1}{2} \int_\Omega \int_{s_1}^{s_2} \left| \frac{d}{dr} (\nabla ([\Lambda v](s_1, x))) \right|^2 dr dx$$

$$\leq \frac{C_1 K_1}{2} \int_{s_1}^{s_2} \left| \frac{d}{dr} (\nabla ([\Lambda v](s_1, \cdot))) \right|^2_{L^2(\Omega)} dr$$

$$\leq \frac{C_1 K_1}{2} C_2 (|f_0|^2_{W^{1,\infty}(\Omega)} |m_0|^2_{L^2(\Omega)} + |m_0|^4_{H^1(\Omega)} + |m_0|^2_{H^1(\Omega)}) \int_{s_1}^{s_2} |\nabla v|^2_{L^2(\Omega)} ds$$

$$\leq C_3 \int_{s_1}^{s_2} |\nabla v|^2_{L^2(\Omega)} ds,$$

and the second term,

$$
\begin{aligned}
&\frac{1}{2}\int_\Omega \{k_n(s_2,x,[\Lambda(t)v](s_2,x)) - k_n(s_1,x,[\Lambda(t)v](s_1,x))\}|\nabla z|^2dx \\
&\le \frac{1}{2}\int_\Omega |k_n(s_2,x,[\Lambda(t)v](s_2,x)) - k_n(s_2,x,[\Lambda(t)v](s_1,x))||\nabla z|^2dx \\
&\qquad +\frac{1}{2}\int_\Omega |k_n(s_2,x,[\Lambda(t)v](s_1,x)) - k_n(s_1,x,[\Lambda(t)v](s_1,x))||\nabla z|^2dx \\
&\le \frac{1}{2}\int_\Omega K_2|[\Lambda(t)v](s_2,x) - [\Lambda(t)v](s_1,x)||\nabla z|^2dx \\
&\qquad +\frac{1}{2}\int_\Omega\int_{s_1}^{s_2}\left|\frac{d}{dr}\left(k_n(r,x,[\Lambda(t)v](s_1,x))\right)\right||\nabla z|^2dx \\
&\le \frac{K_2+1}{2}\int_{s_1}^{s_2}\int_\Omega\left\{\left|\frac{d}{dr}[\Lambda(t)v](r,x)\right| + \left|\frac{d}{dr}\left(k_n(r,x,[\Lambda(t)v](s_1,x))\right)\right|\right\}|\nabla z|^2dxdr \\
&\le \frac{K_2+1}{2}\int_{s_1}^{s_2}\left\{\left|\frac{d}{dr}[\Lambda(t)v](r,\cdot)\right|_{L^\infty(\Omega)} + \left|\frac{d}{dr}\left(k_n(r,\cdot,[\Lambda(t)v](s_1,\cdot))\right)\right|_{L^\infty(\Omega)}\right\}|\nabla z|^2_{L^2(\Omega)}dr \\
&\le \frac{K_2+1}{2}\int_{s_1}^{s_2}\left\{C_4\,|\nabla v|_{L^2(\Omega)} + \left|\frac{d}{dr}\left(k_n(r,\cdot,[\Lambda(t)v](s_1,\cdot))\right)\right|_{L^\infty(\Omega)}\right\}|\nabla z|^2_{L^2(\Omega)}dr \\
&\le \int_{s_1}^{s_2} C_5\left\{|\nabla v|_{L^2(\Omega)} + \left|\frac{d}{dr}\left(k_n(r,\cdot,[\Lambda(t)v](s_1,\cdot))\right)\right|_{L^\infty(\Omega)}\right\}|\nabla z|^2_{L^2(\Omega)}dr,
\end{aligned}
$$

where, C_i $(i = 1,2,3,4,5)$ are some constants.

Then, we put the functions $\alpha(\tau) := \delta\left(|m_0|_{L^2(\Omega)} + K_6^{\frac{1}{2}}T^{\frac{1}{2}}|\Omega|^{\frac{1}{2}}\right)$ and

$$
\beta(\tau) := (C_5+1)\,|\nabla v(\tau)|_{L^2(\Omega)} + \left|\frac{d}{d\tau}\left(k_n(\tau,\cdot,[\Lambda(t)v](s_1,\cdot))\right)\right|_{L^\infty(\Omega)},
$$

the above inequalities are satisfied.■

4 The auxiliary problem

We consider the following initial value problem with subdifferential operator. For each $t \in [0,T]$, $v \in \mathcal{V}(-\delta_0,t)$ and $w \in L^\infty(0,T;H_0^1(\Omega))$,

$$
\text{(AP1)}\begin{cases} n'(s) + \partial\varphi^s(v;n(s)) \ni G(s,w(s),[\Lambda(t)w](s)) \text{ in } L^2(\Omega), \text{ a.e. } s \in (0,t), \\ n(s) = n_0(s) \text{ in } L^2(\Omega),\ \forall s \in [-\delta_0,0], \end{cases}
$$

where $\varphi^s(v;\cdot)$ is defined convex function in above section, $\partial\varphi^s(v;\cdot)$ is subdifferential operator of $\varphi^s(v;\cdot)$ with respect to the second variable and G is the functional defined by

$$G(s,w(s),[\Lambda(t)w](s)) := -\lambda\nabla\cdot(w\nabla[\lambda(t)w])+\mu w(1-w-[\Lambda(t)w]) \text{ in } L^2(\Omega).$$

Proposition 4.1. (cf.[14]) The problem (AP1) has a unique solution n. And there exists a positive number K_7 such that

$$|n'|^2_{L^2(Q_t)}+\sup_{0\le s\le t}\varphi^s(v;n(s)) \le K_7\left(1+|n_0|^2_{H^1_0(\Omega)}+|G(\cdot,w,[\Lambda(t)w])|^2_{L^2(Q_t)}\right).$$

We get a uniform estimate of perturbation G for the following lemma.

Lemma 4.1. There exists a positive number K_8 and strictly increasing functions $K_9(\cdot)$ on $[0,T]$ with $K_8(0)=0$ such that

$$\begin{aligned}|G(\cdot,w,[\Lambda(t)w])|^2_{L^2(Q_t)} &\le K_8\left(|\lambda|_{L^\infty(Q_t)}|f_0|_{H^2(\Omega)}+|\mu|_{L^\infty(Q_t)}\right)\\ &+K_9(t)|\lambda|_{L^\infty(Q_t)}(|f_0|_{W^{1,\infty}(\Omega)}+1)(|f_0|_{W^{1,\infty}(\Omega)}+|m_0|_{H^2(\Omega)}+|w|_{L^\infty(0,T;H^1_0(\Omega))})^2.\end{aligned}$$

In this paper, we omit the proof of this Lemma, because that is already proved by [3]. Using the above lemma, we can get the solution of the next auxiliary problem.

Proposition 4.1. For each $t\in[0,T]$ and $v\in\mathcal{V}(-\delta_0,t)$, there are positive numbers M_1 and $T_0\in(0,T]$ such that the following problem (AP2),

$$\text{(AP2)}\begin{cases} n'(t)+\partial\varphi^s(v;n(t))\ni G(t,n(t),[\Lambda(T_0)n](t)) \text{ in } L^2(\Omega), \text{ a.e. } s\in(0,T_0),\\ n(t)=n_0(t) \text{ in } L^2(\Omega),\ \forall t\in[-\delta_0,0],\end{cases}$$

has the unique solution n_v satisfying

$$|n'_v|^2_{L^2(Q_{T_0})}+\sup_{0\le t\le T_0}\varphi^t(v;n_v(t)) \le M_1.$$

(Proof) We fix a positive number M_1 such that

$$M_1 > K_7\left(1+|n_0|_{H^1_0(\Omega)}+K_8(|\lambda|_{L^\infty(Q_T)}|f_0|_{H^2(\Omega)}+|\mu|_{L^\infty(Q_T)})\right),$$

and define a non-empty, closed and convex set by

$$W_{M_1} := \left\{ w \in \mathcal{V}(-\delta_0, T);\ |w'|^2_{L^2(Q_{T_0})} + \sup_{0 \le t \le T_0} \varphi_0(w(t)) \le M_1 \right\}.$$

For each $t \in [0,T]$, $v \in \mathcal{V}(-\delta_0, t)$ and $w \in W_{M_1}$, by the proposition 4.1. and Lemma 4.1., there is a positive number $T_0 \in (0,T]$ such that

$$K_9(T_0) \le \frac{M_1 - K_7\left(1 + |n_0|_{H_0^1(\Omega)} + K_8(|\lambda|_{L^\infty(Q_T)}|f_0|_{H^2(\Omega)} + |\mu|_{L^\infty(Q_T)})\right)}{K_7|\lambda|_{L^\infty(Q_t)}(|f_0|_{W^{1,\infty}(\Omega)} + 1)(|f_0|_{W^{1,\infty}(\Omega)} + |m_0|_{H^2(\Omega)} + |w|_{L^\infty(0,T;H_0^1(\Omega))})^2},$$

hence, the solution of (AP2) is $n_{vw} \in W_{M_1}$.

Next, we define the operator $\mathcal{S}(v)$ on W_{M_1} by

$$[\mathcal{S}(v)w](s) = \begin{cases} n_0(s) & \text{if } s \in [-\delta_0, 0] \\ n_{vw}(s) & \text{if } s \in (0, T_0] \\ n_{vw}(T_0) & \text{if } s \in (T_0, T] \end{cases} \quad \text{for } \forall w \in W_{M_1}.$$

Then, $\mathcal{S}(v) : W_{M_1} \to W_{M_1}$ holds. We show that $\mathcal{S}(v)$ is continuous in $C([0,T]; L^2(\Omega))$. Let be $w_k, w \in W_{M_1}$ and $w_k \to w$ in $C([0,T]; L^2(\Omega))$ as $k \to \infty$. Then, we see that the following convergences hold:

$$\Lambda_1(T)w_k \to \Lambda_1(T)w \quad \begin{cases} \text{in } C([0,T]; H^1(\Omega)) \cap L^2(0,T; H^2(\Omega)), \\ \text{*-weakly in } L^\infty(0,T; H^2(\Omega)), \end{cases}$$

$$(\Lambda_1(T)w_k)' \to (\Lambda_1(T)w)' \quad \text{weakly in } L^2(0,T; H^1(\Omega)).$$

Then, we have that $G(\cdot, w_k, \Lambda(T_0)w_k) \to G(\cdot, w, \Lambda(T_0)w)$ weakly in $L^2(Q_{T_0})$. And We derive $\mathcal{S}(v)w_k \to \mathcal{S}(v)w$ in $C([0,T]; L^2(\Omega))$.

Hence, we use the Schauder's fixed point theorem, we see that $\mathcal{S}(v)$ has at least one fixed point $\tilde{n}$, i.e. $\mathcal{S}(v)\tilde{n} = \tilde{n}$ in W_{M_1}. Then, $\tilde{n}$ is a solution of (AP2) on $[0, T_0]$.

Finally, we show the uniqueness of solutions of (AP2). Let n_1, n_2 be solutions of (AP2) on $[0, T_0]$. We consider the following system with $m_i = \Lambda_1(T_0)n_i$, $(i = 1, 2)$:

$$(m_1 - m_2)' - k_m\Delta(m_1 - m_2) + C_1(m_1 - m_2) = C_2(n_1 - n_2) \qquad (1)$$
$$\nabla(m_1 - m_2) \cdot \nabla\mathbf{n} = 0$$
$$(m_1 - m_2)(0) = 0$$

We multiply (4.1) by $(m_1 - m_2)$ and ∇(4.1) by $\nabla(m_1 - m_2)$, and the following inequality is satisfied:

$$\sup_{0\le s\le t} |m_1(s) - m_2(s)|^2_{H^1(\Omega)} + \int_0^t |m_1(s) - m_2(s)|^2_{H^2(\Omega)} ds$$
$$\le K_{10} \int_0^t |n_1(s) - n_2(s)|^2_{H^1_0(\Omega)} ds,$$

for $\forall r \in [0, T_0]$, where K_{10} is a some positive constant. And we consider the energy inequality for the tumor equation, the following inequality holds:

$$\frac{1}{2}\frac{d}{dt}|n_1 - n_2|_{L^2(\Omega)} + 2\varphi_0(n_1 - n_2)$$
$$\le (G(n_1, \Lambda(T_0)n_1) - G(n_2, \Lambda(T_0)n_2), n_1 - n_2)_{L^2(\Omega)}.$$

Next, we show the estimate of perturbation. Since the following inequalities are satisfied;

$$(G(n_1, \Lambda(T_0)n_1) - G(n_2, \Lambda(T_0)n_2), n_1 - n_2)_{L^2(\Omega)}$$
$$= -\int_\Omega \lambda\nabla\cdot(n_1 - n_2)\nabla(\Lambda(T_0)n_1 - \Lambda(T_0)n_2)(n_1 - n_2)dx$$
$$+ \int_\Omega \mu(n_1 - n_2)^2(1 - (n_1 - n_2) - (\Lambda(T_0)n_1 - \Lambda(T_0)n_2))dx$$
$$\le \frac{|\lambda|_{L^\infty(\Omega)}}{2K_0}\int_\Omega |\nabla(\Lambda(T_0)n_1 - \Lambda(T_0)n_2)|^2 dx + \varphi_0(n_1 - n_2) + \int_\Omega |\mu| dx,$$

and

$$\int_\Omega |\nabla(\Lambda(T_0)n_1 - \Lambda(T_0)n_2)|^2 dx \le 2t\delta^2 \int_0^t |\nabla(m_1 - m_2)|_{L^2(\Omega)} 2ds,$$

there are a positive constants K_{11} which depend on some constants K_0, k_m, C_1, δ, C_2, T, $|\Omega|$, $|\lambda|_{L^\infty(Q_{T_0})}$ and $|\mu|_{L^\infty(Q_{T_0})}$, such that

$$\frac{d}{dt}|n_1 - n_2|_{L^2(\Omega)} + \varphi_0(n_1 - n_2) \le K_{11}\int_0^t |n_1 - n_2|^2_{L^2(\Omega)} ds.$$

We put the functional $\Phi(t)$ by

$$\Phi(t) = |n_1 - n_2|^2_{L^2(\Omega)} + K_{11}\int_0^t |n_1 - n_2|^2_{L^2(\Omega)} ds.$$

By the Gronwall's inequality, $\Phi(t) \le e^{K_{11}T}\Phi(0) = 0$ holds. Namely,

$$|n_1 - n_2|^2_{L^2(\Omega)} + K_{11}\int_0^t |n_1 - n_2|^2_{L^2(\Omega)} ds \le 0.$$

Hence $n_1(t) = n_2(t)$ in $L^2(\Omega)$ for $t \in [0, T_0]$.■

5 Proof of Theorem 2.1.

Let M_1 and T_0 be the same one as the above section. We define a non-empty, closed and convex set $\mathcal{W}_{M_1}(T_0)$ too, by

$$\mathcal{W}_{M_1}(T_0) := \left\{ v \in \mathcal{V}(-\delta_0, T_0);\ |v'|^2_{L^2(Q_{T_0})} + \sup_{0 \le t \le T_0} \varphi_0(v(t)) \le M_1 \right\},$$

and the solution operator $\mathfrak{S}$ from $\mathcal{W}_{M_1}(T_0)$ by $\mathfrak{S}v = n_v$ for all $v \in \mathcal{W}_{M_1}(T_0)$ (n_v is the solution of (AP2) by the proposition 4.1.).

It is clear that $\mathfrak{S}v \in \mathcal{W}_{M_1}(T_0)$. Next, we show that the operator $\mathfrak{S}$ is continuous in $C([0,T_0]; L^2(\Omega))$. Take $\{v_k\} \subset \mathcal{W}_{M_1}(T_0)$ and $v \in \mathcal{W}_{M_1}(T_0)$ so that

$$v_k \to v \quad \begin{cases} \text{in } C([0,T_0]; L^2(\Omega)), \\ \text{weakly in } W^{1,2}(0,T_0; L^2(\Omega)), \\ \text{*-weakly in } L^\infty(0,T_0; H^1_0(\Omega)). \end{cases}$$

For each $k \in \mathbb{N}$, we define $n_k := \mathfrak{S}v_k$. By the definition of closed set $\mathcal{W}_{M_1}(T_0)$, there exists n such that

$$n_k \to n \quad \begin{cases} \text{in } C([0,T_0]; L^2(\Omega)), \\ \text{weakly in } W^{1,2}(0,T_0; L^2(\Omega)), \\ \text{*-weakly in } L^\infty(0,T_0; H^1_0(\Omega)). \end{cases}$$

For each $k \in \mathbb{N}$, we define $m_k := \Lambda_1(T_0)n_k$, and $f_k := \Lambda(T_0)n_k$, we observe that

$$m_k \to m \quad \begin{cases} \text{in } C([0,T_0]; H^1(\Omega)), \\ \text{weakly in } W^{1,2}(0,T_0; H^1(\Omega)), \\ \text{*-weakly in } L^\infty(0,T_0; H^2(\Omega)), \end{cases}$$

and

$$f_k \to f \quad \begin{cases} \text{in } C([0,T_0]; H^1(\Omega)), \\ \text{*-weakly in } L^\infty(0,T_0; H^2(\Omega)), \end{cases}$$

$$f'_k \to f' \quad \text{weakly in } W^{1,2}(0,T_0; H^1(\Omega)),$$

where $m := \Lambda_1(T_0)n$ and $f := \Lambda(T_0)n$. Furthermore, the perturbation G has the following continuous;

$$G(n_k, f_k) \to G(n,f) \quad \text{weakly in } L^2(Q_{T_0}),$$

by the estimate of G in the above section. For any $\eta \in L^2(0,T_0;H_0^1(\Omega))$ with $\eta \in K(t,n)$, we put $\eta_k := \min\{\eta, 1-\Lambda(T_0)n_k\}$, then $\eta_k \in K(t,n_k)$. Hence, the following inequality is satisfied;

$$\begin{aligned}&\int_0^{T_0}(n_k', n_k - z_k)_{L^2(\Omega)}dt + \int_0^{T_0}(k_n\nabla n_k, \nabla(n_k-\eta_k))_{L^2(\Omega)}dt \\ &\leq \int_0^{T_0}(G(n_k,\Lambda(T_0)n_k), n_k-\eta_k)dt.\end{aligned}$$

Since $\Lambda(T_0)n_k \to \Lambda(T_0)n$ in $C([0,T_0];H^1(\Omega))$ as $k\to\infty$, we take the limit in the above inequality. We see that the following inequality holds;

$$\begin{aligned}&\int_0^{T_0}(n', n - z)_{L^2(\Omega)}dt + \int_0^{T_0}(k_n\nabla n, \nabla(n-\eta))_{L^2(\Omega)}dt \\ &\leq \int_0^{T_0}(G(n,\Lambda(T_0)n), n-\eta)dt.\end{aligned}$$

Hence, n is the solution of (P) on $[0,T_0]$. Namely, $n = \mathfrak{S}v$. Therefore, the operator $\mathfrak{S} : \mathcal{W}_{M_1}(T_0) \to \mathcal{W}_{M_1}(T_0)$ is continuous in $C([0,T_0];L^2(\Omega))$.

Using the Schauder's fixed point theorem, $\mathfrak{S}$ has at least one fixed point n in $\mathcal{W}_{M_1}(T_0)$ i.e. $n = \mathfrak{S}n$. We can check from Definition 2.2. that $\{n,f,m\}$ is a solution of (P) on $[0,T_0]$, easily. ■

Reference

[1] M.A.J.Chaplain and A.R.A.Anderson, Mathematical modelling of tissue invasion, in Cancer Modelling and Simulation, Mathematical Biology and Medicine Series, Chapman&Hall/CRC, Boca Raton, 2003, 269-297.

[2] Z.Szymańska, J.Urbański and A.Marciniak-Czochra, Mathematical Modelling of the influence of heat shock proteins on cancer invasion of tissue, J.Math.Biol.58 (2009),819-844, Springer-Verlag.

[3] R.Kano, A.Ito, K.Yamamoto and H.Nakayama, Quasi-variational inequality approach to tumor invasion models with constraionts, GAKUTO International Series Mathematical Sciences and Applications, Vol.32 (2010) 365-388.

[4] R.Kano and A.Ito, The Existence of Time Global Solutions for Tumor Invasion Models with Constraints, to appear.

[5] A.Bensoussan and J.L.Lions, Nouvelle formulation de problémes de contrôle impulsionnel et applications, C.R.Acad.Sci.Paris Sér. A, 276(1973), 1189-1192.

[6] A. Bensoussan, M. Goursat and J.L. Lions, Contrôle impulsionnel et inéquations quasivariationnelles stationnaires, C. R. Acad. Sci. Paris Ser. A, vol.276(1973), 1279-1284.

[7] M. Kunze and J. Rodrigues, An elliptic quasi-variational inequality with gradient constraints and some of its applications, Math. Methods Appl. Sci., 23(2000) Issue 10, 897.908.

[8] U.Stefanelli, Nonlocal quasivariational evolution problems, J.Differential Equations, 229(2006), 204-228.

[9] J.L. Joly and U. Mosco, Sur les inéquations quasi-variationnelles, C. R. Acad. Sci. Paris Ser. A, 279(1974), 499-502.

[10] J.L. Joly and U. Mosco, A propos de l'existence et de la régularité des solutions de certaines inéquations quasi-variationnelles, J. Functional Analysis, 34(1979), 107-137.

[11] R. Kano, N. Kenmochi and Y. Murase, Existence theorems for elliptic quasi-variational inequalities in Banach spaces, Recent Advance in Nonlinear Analysis: Proceedings of the International Conference on Nonlinear Analysis, World Sci. Publ., Hackensack, NJ, (2008),pp.149-169.

[12] R.Kano, N.Kenmochi and Y.Murase, Nonlinear evolution equations generated by subdifferentials with nonlocal constraints, Banach Center Publications, 86 (2009),175-194.

[13] R.Kano, The existence of solutions for tumor invasion models with time and place dependent diffusion, preprint.

[14] N.Kenmochi, Solvability of nonlinear evolution equations with time-dependent constraints and applications, Bull. Fac. Education, Chiba Univ., 30(1981),1-87.

[15] T.Fukao, N.Kenmochi, Stefan problems with convection governed by Navier-Stokes equations Adv. Math. Sci. Appl.15 No.1 (2005) 29–48.