Global Weak Solutions to a Mathematical Model Using Aptamers in Chemotherapy and Imaging

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Abstract

We investigate the model suggested by [1] dealing with the effect of aptamers on the efficiency of anticancer drugs. The system is described by nonlinear parabolic equations. The boundary condition on the inhibitor concentration is a nonlinear Michaelis-Menton form while the others are zero flux conditions. Due to the nonlinearity of the Michaelis-Menton boundary condition, the operator associated to the problem is nonlinear so we will use theory of perturbation of maximal monotone operators by pseudomonotones ones associated with Schauder fixed point theorem to get our main result.

1 The model equations and main result

Many anti-cancer drugs need to penetrate the cell membrane to perform their functions. K. Boushaba, H.A. Levine and M. Nilsen Hamilton [1] propose in their recent work that the intracellular concentration and the effectiveness of a drug might be increased by the presence, inside the cell, of a means of capturing the drug and moving it through the cytoplasm. As a drug binding agent, they use an aptamer: aptamers are small single stranded nucleic acids that have been selected for tight and spedific binding to a target molecule, which in this case is the drug. The authors studied the efficiency of the aptamers by comparing the system without aptamers and with aptamers.

1.1 The chemical kinetics (Protein-Inhibitor)

We are given an enzyme, an inhibitor, and a product, denoted by E, I, P. We use the notation $E(x,t) = [E](t)$ because species are distributed in space as well as time. The mecanism

$$E + I \rightleftharpoons^{k_1}_{k_{-1}} P$$

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is not assumed to be in equilibrium. Suppose
(1) The reaction takes place in a bounded region Ω of the three space (the cytoplasm of a cell)
(2) The enzyme decays with rate $\mu_e > 0$. The enzyme-inhibitor complex $P = \{E : I\}$ decays with rate $\mu_{ei} \geq 0$. The inhibitor may decay with rate $\nu \geq 0$.
(3) The inhibitor species, I, diffuses much faster than E, P.
(4) The cell functions as a steady source for the enzyme and the aptamer (if any), i.e. there is a nonnegative function $S_e(x)$ supported in a region $\Omega_E \subset \Omega$ for all nonnegative times that defines the cellular rate of production of the enzyme.
These assupmtions and the law of mass action lead to the following where Δ denotes the Laplacian

$$\begin{cases} \partial_t E(t,x) = D_e \Delta E + k_{-1}P - k_1 EI - \mu_e E + S_e(x), \ \ \mathbb{R}^+ \times \Omega, \\ \partial_t P = D_e \Delta P - k_{-1}P + k_1 EI - \mu_{ei} P, \ \ \mathbb{R}^+ \times \Omega, \\ \partial_t I = D \Delta I + k_{-1}P - k_1 EI - \nu I, \ \ \mathbb{R}^+ \times \Omega \\ I(0,x) = I_0(x) \geq 0, \ P(0,x) = P_0(x) \geq 0, \ E(0,x) = E_0(x) \geq 0, \\ D_e \partial_n E = 0, \ D_e \partial_n P = 0, \quad -D\partial_n I(x,t) = \frac{K_c(I(x,t)-i_b)}{(K_m + I(x,t))} + T_e(I - J) \quad on \ \ \partial\Omega. \end{cases} \tag{1}$$

where i_b is the backgroud concentration of the drug in the cell due solely to membrane transport, T_e the membrane permeability of the inhibitor, J is the concentration of the drog on the apical side of the celle membrane and is asumed to be constant, where K_c, K_m may be thought of Michealis-Menten constants for transport of inhibitor through the cell membrane.
The meaning of the Michaelis-Menton boundary condition is the following: If the concentration of I is larger than the threshold value i_b, the contribution to the flux out of the cell by the active transport will be positive that is, I will leave the cell. If the concentration is smaller than the threshold value, this contribution to the flux out will be negative. Likewise if $I > J$, the passive diffusion will contribute positively to the flux out of the cell while if $I < J$, the passive diffusion will contribute positively to the flux into the cell. [1].

1.2 The chemical kinetics (Enzyme-inhibitor-Aptamer)

We consider the effect of an aptamer on the efficiency of the enzyme reaction $E + I \rightleftharpoons P = IE$. The aptamer has a single binding site for the inhibitor only and interacts with it via $A + I \rightleftharpoons^{l_1}_{l_{-1}} Q = AI$. The aptamer source $S_a(x)$ is supported on $\Omega_A \subset \Omega$. Mass action consideration lead to

$$\begin{cases} \partial_t I = D \Delta I + k_{-1}P - k_1 EI + l_{-1}Q - l_1 AI - \nu I, \ \ \mathbb{R}^+ \times \Omega, \\ \partial_t A = D_a \Delta A + l_{-1}Q - (l_1 I + \nu_a)A + S_a(x), \ \ \mathbb{R}^+ \times \Omega, \\ \partial_t Q = D_a \Delta Q + l_1 AI - (l_{-1} + \nu_{ai})Q, \ \ \mathbb{R}^+ \times \Omega, \\ \partial_t E(t,x) = D_e \Delta E + k_{-1}P - (k_1 I + \nu_e)E + S_e(x), \ \ \mathbb{R}^+ \times \Omega, \\ \partial_t P = D_e \Delta P + k_1 EI - (k_{-1} + \mu_{ei})P, \ \ \mathbb{R}^+ \times \Omega, \\ I(0,x) = I_0(x) \geq 0, \quad A(0,x) = A_0(x) \geq 0, \quad Q(0,x) = Q_0(x) \geq 0, \\ P(0,x) = P_0(x) \geq 0, \ E(0,x) = E_0(x) \geq 0, \\ D_a \partial_n A = D_a \partial_n Q = 0, \quad D_e \partial_n E = 0, \ D_e \partial_n P = 0, \quad \text{on} \ \ \partial\Omega, \\ -D\partial_n I(x,t) = \frac{K_c(I(x,t)-i_b)}{K_m + I(x,t)} + T_e(I - J) \quad \text{on} \ \ \partial\Omega. \end{cases} \tag{2}$$

We assume that the molecular wheights are ordered via $M_I \ll M_A \ll M_E$. The smallest molecule I, will be the most diffusible. Therefore $D = D_i > D_a = D_{AI} = D_a \geq D_e \geq 0$.

Definition 1. *Let (I, P, Q) satifiying*

$$I, P, Q \in L^2(\mathbb{R}^+; H^1(\Omega)), \partial_t I, \partial_t P, \partial_t Q \in L^2(\mathbb{R}^+; (H^1(\Omega))'),$$

and (A, E) such that

$$A, E \in L^2(\mathbb{R}^+; H^1(\Omega)), \quad \partial_t A, \partial_t E \in L^2(\mathbb{R}^+; L^2(\Omega)).$$

We say that (A, E, I, P, Q) is a global weak solution to (2) if
1-The second and fourth equations of (2) are satisfied a.e. and the boundary conditions $\partial_n A = \partial_n E = 0$ are satisfied in $H^{-\frac{1}{2}}(\Omega)$.
2- $(A, E, I, P, Q)(0) = (A_0, E_0, I_0, P_0, Q_0)$ in $L^2(\Omega)$,
3-For all $\varphi, \psi, \eta \in V$

$$\begin{aligned}
&\frac{d}{dt}\int_\Omega I\varphi dx = -\int_\Omega \nabla I \cdot \nabla\varphi dx - K_c \int_{\partial\Omega} \frac{I - i_b}{K_m + I}\varphi d\sigma - T_e \int_{\partial\Omega}(I - J)\varphi d\sigma \\
&+ \int_\Omega (k_{-1}P - k_1 EI + l_{-1}Q - l_1 AI - \nu I)\varphi dx = 0, \\
&\frac{d}{dt}\int_\Omega Q\psi dx = -D_a \int_\Omega \nabla Q \cdot \nabla\psi dx + \int_\Omega (l_1 AI - (l_{-1} + \nu_{ai})Q)\psi dx = 0, \\
&\frac{d}{dt}\int_\Omega P\eta dx = -D_e \int_\Omega \nabla P \cdot \nabla\eta dx + \int_\Omega (k_1 EI - (k_{-1} + \nu_{ei}))\eta dx = 0.
\end{aligned} \tag{3}$$

Theorem 1. *Assume*

$$\begin{aligned}
&S_a,\ S_e \geq 0,\ S_a,\ S_e \in L^\infty(\Omega), \\
&l_1 \leq l_{-1} + \nu_{ai},\ \ k_1 \leq k_{-1} + \mu_{ei},\ \ l_{-1} + k_{-1} \leq \nu,\ \ \ l_{-1} + \|S_a\|_\infty \leq \nu_a,\ \ k_{-1} + \|S_e\|_\infty \leq \nu_e, \\
&0 \leq I_0, Q_0, P_0, E_0, A_0 \leq 1,\ \ (I_0, P_0, Q_0, A_0, E_0) \in (H^1(\Omega))^5, \\
&(\Delta I_0, \Delta P_0, \Delta Q_0, \Delta A_0, \Delta E_0) \in (L^2(\Omega))^2.
\end{aligned} \tag{4}$$

Then, there exists a global weak solution (A, E, I, P, Q) to (2) such that $0 \leq A, E, I, P, Q \leq 1$.

2 Preliminary results

2.1 Step I: Parabolic problem for given aptamer and enzyme

Denote by

$$\begin{aligned}
&V = H^1(\Omega);\ \ H = L^2(\Omega);\ \ V' = (H^1(\Omega))', \\
&\mathcal{V} = L^2(0, T; H^1(\Omega));\ \ \mathcal{H} = L^2(0, T; L^2(\Omega)), \\
&\mathcal{V}' = L^2(0, T; (H^1(\Omega))'),\ \ \mathcal{C} = \{v \in \mathcal{V},\ \partial_t v \in \mathcal{V}',\ v(0) = 0\}.
\end{aligned} \tag{5}$$

where V' is the dual of V, the norm in H will be denoted by $\|\|$.
Let us recall the principal definitions

Definition 2. *[3], [6], [5]*
Let V be a reflexive Banach space; consider an operator $\mathcal{A} : V \to V'$.
1-$\mathcal{A}$ is type M if $u_n \rightharpoonup u$, $\mathcal{A}u_n \rightharpoonup f$ and $\limsup \mathcal{A}u_n(u_n) \leq f(u)$ imply that $\mathcal{A}u = f$.
2-The function $\mathcal{A}$ is coercive if $\frac{\mathcal{A}u(u)}{\|u\|} \to \infty$ as $\|u\| \to \infty$.
3- $\mathcal{A}$ is hemicontinuous if for each $u, v \in V$ the real-valued function $t \to \mathcal{A}(u + tv)(v)$ is continuous.
4- $\mathcal{A}$ is bounded if S bounded in V implies the image $\mathcal{A}(S)$ is bounded in V'.
5-$\mathcal{A}$ is monotone if $\langle \mathcal{A}(u) - \mathcal{A}(v); u - v\rangle \geq 0$ for all $u, v \in V$.
6-$\mathcal{A}$ is strictly monotone if $\langle \mathcal{A}(u) - \mathcal{A}(v); u - v\rangle > 0$ for all $u, v \in V$, $u \neq v$.
7-$\mathcal{A}$ is strongly continuous if and only if

$$u_n \rightharpoonup u \ \ as \ \ n \to +\infty \tag{6}$$

implies

$$\mathcal{A}u_n \to \mathcal{A}u \ \ as \ \ n \to +\infty \tag{7}$$

8- $\mathcal{A}$ is demicontinuous if

$$u_n \to u \ \ as \ \ n \to +\infty \tag{8}$$

implies

$$\mathcal{A}u_n \rightharpoonup \mathcal{A}u \ \ as \ \ n \to +\infty \tag{9}$$

Let $\tilde{A},\ \tilde{E} \in L^\infty_{loc}(\mathbb{R}^+;\ L^2(\Omega))$, $0 \le \tilde{A},\ \tilde{E} \le 1$ be given and consider the nonlinear parabolic system

$$\begin{cases} \partial_t I = D\Delta I + k_{-1}P - k_1\tilde{E}I + l_{-1}Q - l_1\tilde{A}I - \nu I, \ \ \mathbb{R}^+ \times \Omega, \\ \partial_t Q = D_a \Delta Q + l_1\tilde{A}I - (l_{-1} + \nu_{ai})Q, \ \ \mathbb{R}^+ \times \Omega, \\ \partial_t P = D_e \Delta P + k_1\tilde{E}I - (k_{-1} + \mu_{ei})P, \ \ \mathbb{R}^+ \times \Omega \\ I(0,x) = I_0(x) \ge 0, \ \ Q(0,x) = Q_0(x) \ge 0, P(0,x) = P_0(x) \ge 0, \\ D_a\partial_n Q = 0, \ \ D_e\partial_n P = 0, \ \ -D\partial_n I(x,t) = \frac{K_c(I(x,t)-i_b)}{K_m+I(x,t)} + T_e(I-J) \ \ \ on \ \ \partial\Omega. \end{cases} \tag{10}$$

Theorem 2. *Assume*

$$\begin{aligned} &l_1 \le l_{-1} + \nu_{ai}, \ \ k_1 \le k_{-1} + \mu_{ei}; \ \ l_{-1} + k_{-1} \le \nu, \\ &0 \le I_0, Q_0, P_0 \le 1, \ \ (I_0, P_0, Q_0) \in V, \ \ (\Delta I_0, \Delta P_0, \Delta Q_0) \in H. \end{aligned} \tag{11}$$

Then, there exists a unique global weak solution $(I,P,Q) \in \mathcal{V}^3$ such that $\partial_t(I,P,Q) \in (\mathcal{V}')^3$. Moreover, $0 \le I, Q, P \le 1$ and the following energy estimate holds

$$\begin{aligned} &\tfrac{d}{2dt}\int_\Omega (|I|^2 + |P|^2 + |Q|^2)dx + D\int_\Omega |\nabla I|^2 dx + D_e \int_\Omega |\nabla P|^2 dx + D_a \int_\Omega |\nabla Q|^2 dx + \nu\|I\|^2 \\ &+ \int_\Omega k_1\tilde{E}|I|^2 + l_1\tilde{A}|I|^2 dx + (l_{-a} + \nu_{ai})\|Q\|^2 + (k_{-1} + \mu_{ei})\|P\|^2 \\ &+ K_c \int_{\partial\Omega} \tfrac{I^2}{K_m + I} + T_e I^2 d\sigma = \int_\Omega k_{-1}PI + l_{-1}QI + l_1\tilde{A}IQ + k_1\tilde{E}IPdx \\ &+ i_b K_c \int_{\partial\Omega} \tfrac{I}{K_m+I} + T_e IJ d\sigma. \end{aligned} \tag{12}$$

Proof. Without loss of the generality, the proof will be done in the case when $P_0 = Q_0 = I_0 = 0$ in order to apply approximation method of evolution operators by stationnary ones. The proof in the case when the initial conditions does not vanish is obtained in the same way by setting $\tilde{I} = I - I_0$, $\tilde{P} = P - P_0$, $\tilde{Q} = Q - Q_0$ and repeating the same arguments.
In order to get solutions (which are concentrations) satisfying $0 \le I, P, Q \le 1$, we will study, for given $0 \le \tilde{E}, \tilde{A} \le 1$ the following problem where $f^+ = max(f, 0)$

$$\begin{cases} \partial_t I = D\Delta I + k_{-1}P^+ - k_1\tilde{E}I + l_{-1}Q^+ - l_1\tilde{A}I - \nu I, \ \ \mathbb{R}^+ \times \Omega, \\ \partial_t Q = D_a\Delta Q + l_1\tilde{A}\min(I^+, 1) - (l_{-1} + \nu_{ai})Q, \ \ \mathbb{R}^+ \times \Omega, \\ \partial_t P = D_e\Delta P + k_1\tilde{E}\min(I^+, 1) - (k_{-1} + \mu_{ei})P, \ \ \mathbb{R}^+ \times \Omega, \\ I(0,x) = 0, \ \ Q(0,x) = 0, P(0,x) = 0, \\ D_a\partial_n Q = 0, \ \ D_e\partial_n P = 0, \ \ -D\partial_n I(x,t) = \frac{K_c(I^+(x,t)-i_b)}{K_m+I^+(x,t)} + T_e(I-J) \ \ \ on \ \ \partial\Omega. \end{cases} \tag{13}$$

Let $\mathcal{A}$ be the operator defined on H^3 by

$$
\begin{aligned}
&\mathcal{A}U = (-D\Delta u_1 + u_1, -D_a\Delta u_2 + u_2, -D_e\Delta u_3 + u_3), \ \ \text{for } \ U = (u_1, u_2, u_3)\\
&\mathcal{D}(\mathcal{A}) = \{U \in V^3, \, \mathcal{A}U \in H^3, \partial_n u_2 = \partial_n u_3 = 0, -D\partial_n u_1 = \tfrac{K_c(u_1^+ - i_b)}{K_m + u_1^+} + T_e(u_1 - J)\}.
\end{aligned}
\tag{14}
$$

The linear operator $\mathcal{A}$ is not monotone because $u_1^+ - i_b$ and $u_1 - J$ may change signe on the boundary. Let $\mathcal{B}$ the operator associated with $\mathcal{A}$, that is $\mathcal{B} : \mathcal{V} \to \mathcal{V}'$ defined by

$$
\begin{aligned}
&\mathcal{B}U(W) = \textstyle\int_{(0,T)\times\Omega} UW + \nabla U \cdot \nabla W dxdt + K_c \int_{(0,T)\times\partial\Omega} \tfrac{u_1^+ - i_b}{K_m + u_1^+} w_1 d\sigma dt\\
&+T_e \textstyle\int_{(0,T)\times\partial\Omega} (u_1 - J) w_1 d\sigma dt,
\end{aligned}
\tag{15}
$$

where $U = (u_1, u_2, u_3) \in \mathcal{V}$, $W = (w_1, w_2, w_3) \in \mathcal{V}$ and define $K : \mathcal{C}^3 \to \mathcal{H}^3$ by

$$
K(u_1, u_2, u_3) = \begin{pmatrix} -k_{-1}u_3^+ + k_1\tilde{E}u_1^+ - l_{-1}u_2^+ + l_1\tilde{A}u_1 + \nu u_1 \\ -l_1\tilde{A}\min(u_1^+, 1) + (l_{-1} + \nu_{ai})u_2 \\ -k_1\tilde{E}\min(u_1^+, 1) + (k_{-1} + \nu_{ei})u_3 \end{pmatrix}
\tag{16}
$$

Lemma 1. *The operator $\mathcal{B}$ is monotone.*

Proof. By definition of $\mathcal{B}$, we have

$$
\begin{aligned}
&\langle \mathcal{B}U - \mathcal{B}W; U - W\rangle =\\
&\textstyle\int_{\Omega_T} D|\nabla(u_1 - w_1)|^2 + D_a|\nabla(u_2 - w_2)|^2 + D_e|\nabla(u_3 - w_3)|^2 dxdt\\
&+ \textstyle\int_{\Omega_T} |U - W|^2 dxdt + K_c \int_{\partial\Omega_T} \left(\tfrac{u_1^+ - i_b}{K_m + u_1^+} - \tfrac{w_1^+ - i_b}{K_m + w_1^+}\right)(u_1 - w_1) d\sigma dt\\
&+T_e \textstyle\int_{\partial\Omega_T} (u_1 - w_1)^2 d\sigma dt.
\end{aligned}
\tag{17}
$$

Then

$$
\begin{aligned}
&\langle \mathcal{B}U - \mathcal{B}W; U - W\rangle =\\
&\textstyle\int_{\Omega_T} D|\nabla(u_1 - w_1)|^2 + D_a|\nabla(u_2 - w_2)|^2 + D_e|\nabla(u_3 - w_3)|^2 dxdt\\
&+ \textstyle\int_{\Omega_T} |U - W|^2 dxdt + K_c(i_b + K_m) \displaystyle\int_{\partial\Omega_T} \frac{(u_1^+ - w_1^+)}{(K_m + u_1^+)(K_m + w_1^+)}(u_1 - w_1) d\sigma dt\\
&+T_e \int_{\partial\Omega_T} (u_1 - w_1)^2 d\sigma dt.
\end{aligned}
\tag{18}
$$

Hence, writing $u_1 - w_1 = (u_1^+ - w_1^+) - (u_1^- - w_1^-)$ we get

$$
\begin{aligned}
&\langle \mathcal{B}U - \mathcal{B}W; U - W\rangle =\\
&\textstyle\int_{\Omega_T} D|\nabla(u_1 - w_1)|^2 + D_a|\nabla(u_2 - w_2)|^2 + D_e|\nabla(u_3 - w_3)|^2 dxdt\\
&+ \textstyle\int_{\Omega_T} |U - W|^2 dxdt + K_c(i_b + K_m) \displaystyle\int_{\partial\Omega_T} \frac{(u_1^+ - w_1^+)^2}{(K_m + u_1^+)(K_m + w_1^+)} d\sigma dt\\
&+K_c(i_b + K_m) \int_{\partial\Omega_T} \frac{u_1^+ w_1^- + u_1^- w_1^+}{(K_m + u_1^+)(K_m + w_1^+)} d\sigma dt\\
&+T_e \int_{\partial\Omega_T} (u_1 - w_1)^2 d\sigma dt \geq 0.
\end{aligned}
\tag{19}
$$

$\square$

Lemma 2. *The operator $K : \mathcal{C}^3 \to \mathcal{H}^3$ is strongly continuous.*

Proof. Set $K_1 : \mathcal{C}^3 \to \mathcal{H}^3$ defined by

$$K_1(u_1,u_2,u_3) = \begin{pmatrix} -k_{-1}u_3 + k_1\tilde{E}u_1 - l_{-1}u_2 + l_1\tilde{A}u_1 + \nu u_1 \\ -l_1\tilde{A}u_1 + (l_{-1}+\nu_{ai})u_2 \\ -k_1\tilde{E}u_1 + (k_{-1}+\nu_{ei})u_3 \end{pmatrix} \tag{20}$$

K_1 is compact and linear then K_1 is strongly continuous (Cf. [6] Proposition 26-2 p. 555). Since the mappings $(u_1,u_2,u_3) \to u_i^+$ and $(u_1,u_2,u_3) \to \min(u_i,1)$ are Lipschitz continous from $\mathcal{H}$ to $\mathcal{H}$ then K being a composition of a strongly continuous mapping with Lipschitz mapping so K is strongly continuous. □

Lemma 3. *The operator $\mathcal{B}+K$ is coercive.*

Proof. Since

$$\frac{\mathcal{B}U(U)}{\|U\|_{\mathcal{V}}} = \|U\|_{\mathcal{V}} + K_c\frac{\int_{(0,T)\times\partial\Omega}\frac{u_1^+-i_b}{u_1^++K_m}u_1 d\sigma dt}{\|U\|_{\mathcal{V}}} + T_e\frac{\int_{(0,T)\times\partial\Omega}(u_1-J)u_1 d\sigma dt}{\|U\|_{\mathcal{V}}}. \tag{21}$$

Then

$$\frac{\mathcal{B}U(U)}{\|U\|_{\mathcal{V}}} \geq \|U\|_{\mathcal{V}} - K_c i_b\frac{\int_{(0,T)\times\partial\Omega}\frac{u_1^+}{u_1^++K_m}d\sigma dt}{\|U\|_{\mathcal{V}}} - T_eJ\frac{\int_{(0,T)\times\partial\Omega}u_1 d\sigma dt}{\|U\|_{\mathcal{V}}}. \tag{22}$$

On the other hand

$$\int_{(0,T)\times\Omega} KU.U dxdt \geq C\|U\|_{\mathcal{V}}^2 - \int_{(0,T)\times\Omega} l_{-1}|u_2| + k_{-1}|u_3| dxdt. \tag{23}$$

for some positive constant C depending on the constants occuring in the system ($C>0$ thanks to the hypothesis $l_{-1}+k_{-1}\leq\nu$). Hence

$$\begin{aligned}\frac{[(\mathcal{B}+K)]U(U)}{\|U\|_{\mathcal{V}}} &\geq (1+C)\|U\|_{\mathcal{V}} - K_c i_b\frac{\int_{(0,T)\times\partial\Omega}\frac{u_1^+}{u_1^++K_m}d\sigma dt}{\|U\|_{\mathcal{V}}} - T_eJ\frac{\int_{(0,T)\times\partial\Omega}u_1 d\sigma dt}{\|U\|_{\mathcal{V}}} \\ &- \frac{\int_{(0,T)\times\Omega} l_{-1}|u_2|+k_{-1}|u_3|dxdt}{\|U\|_{\mathcal{V}}}.\end{aligned} \tag{24}$$

The second term of the RHS of the last inequality goes to 0 as $\|U\|_{\mathcal{V}}$ goes to ∞, while the third and the fourth term of RHS are bounded. It follows that $\frac{[(\mathcal{B}+K)]U(U)}{\|U\|_{\mathcal{V}}}$ goes to ∞ as $\|U\|_{\mathcal{V}}$ goes to ∞ and $\mathcal{B}+K$ is coercive. □

Lemma 4. *$\mathcal{B}$ is type M, bounded and hemicontinuous.*

Proof. Assume that

$$U_n \rightharpoonup U \text{ in } \mathcal{V}, \;\; \mathcal{B}U_n \rightharpoonup f \text{ in } \mathcal{V}', \;\; \limsup \mathcal{B}U_n(U_n) \leq f(U). \tag{25}$$

First $U_n \rightharpoonup U$ and $\limsup \mathcal{B}U_n(U_n) \leq f(U)$ imply that U_n and ∇U_n are bounded in $\mathcal{H}$. Consequently $u_n \to u$ in $L^2(0,T;\partial\Omega)$ strong. It follows from Lebesgue's convergence theorem that $\frac{u_n^+-i_b}{K_m+u_n^+} \to \frac{u^+-i_b}{K_m+u^+}$ and $u_n - J \to u-J$ in $L^2((0,T)\times\partial\Omega)$ strong. Then, for all $V\in\mathcal{V}$

$$\int_{\partial\Omega_T}\frac{(u_n^+-i_b)}{K_m+u_n^+}v d\sigma dt \to \int_{\partial\Omega_T}\frac{(u^+-i_b)}{K_m+u^+}v d\sigma dt, \; \int_{\partial\Omega_T}(u_n-J)v d\sigma dt \to \int_{\partial\Omega_T}(u-J)v d\sigma dt. \tag{26}$$

Moreover $\mathcal{A}u_n \rightharpoonup f$ in $\mathcal{V}'$ writes

$$\int_{\Omega_T} U_nV + \nabla U_n\cdot\nabla V dxdt + K_c\int_{\partial\Omega_T}\frac{u_n^+-i_b}{K_m+u_n^+}v d\sigma + T_e\int_{\partial\Omega_T}(u_n-J)v \to f(V) \tag{27}$$

for all $V \in \mathcal{V}$. Then passing to the limit we get $\mathcal{B}U = f$ in $\mathcal{V}'$ so $\mathcal{B}$ is type M.
We check easily that $\mathcal{B}$ is bounded and hemicontinuous. Consequently $\mathcal{B}$ is pseudomonotone (Cf. [6] proposition 27-6 p. 586). Next, we will apply the following result to prove existence of solutions to (10). $\square$

Theorem 3. *[6] Corollary 32.25 p.867*
Suppose
(H1) C is a nonempty closed convex set in the real B-Space X.
(H2) The mapping $A : C \to 2^{X'}$ is maximal monotone.
(H3) The mapping $B : C \to X'$ is pseudomonotone, bounded, and demicontinuous.
Suppose moreover that one of the following two conditions is satisfied
(i) C is bounded.
(ii) C is unbounded, and B is A-coercive, i.e. there exists $u_0 \in C \cap \mathcal{D}(A)$ such that

$$\frac{\langle Bu, u - u_0\rangle}{\|u\|} \to +\infty \ \text{ as } \ \|u\| \to +\infty \ \text{ in } \ C. \tag{28}$$

Then, $R(A + B) = X'$. That is, for each $b \in X'$, the original problem $b \in Au + Bu$, $u \in C$, has a solution.

Corollary 1. *For each $f \in \mathcal{V}'$, the following abstract Cauchy problem*

$$\begin{cases} U'(t) + \mathcal{B}U(t) + KU(t) = f(t), \ \ 0 < t < T, \\ u(0) = 0. \end{cases} \tag{29}$$

has a unique solution $U \in \mathcal{C}$.

Proof. Set

$$\Lambda : D(\Lambda) \to \mathcal{H} \to \mathcal{H}, \ \ \Lambda u = u', \ \ D(\Lambda) = \{u \in L^2(0, T; V)), u' \in L^2(0, T; V')), u(0) = 0\}. \tag{30}$$

We will apply the previous Theorem in the case when $\mathcal{C} = D(\Lambda)$, $A = \Lambda$, $B = \mathcal{B} + K$ and $u_0 = 0$. By virtue of [6] Proposition 32.10 p. 855, A is maximal monotone.
As $\mathcal{B}$ is bounded, hemicontinuous and monotone then $\mathcal{B}$ is pseudomonotone (Cf. [3] p. 179 or [6] Proposition 27.6 p. 586). Since K is strongly continuous then $\mathcal{B} + K$ is pseudomonotone thanks to [6] Proposition 27.6 p. 586. Moreover, by virtue of the previous lemma $\mathcal{B} + K$ is coercive. Finally, we check easily that $\mathcal{B} + K$ is demicontinuous, hence by virtue of the previous theorem where we take $u_0 = 0$, there exists at least one solution $U \in \mathcal{C}$ solution to (29).
For the uniqueness, let $U_i \in \mathcal{C}, i = 1, 2$ be two solutions to (29) and set $U = U_1 - U_2$. We have

$$\frac{1}{2}\|U(T)\|^2_H + \langle \mathcal{B}U_1 - \mathcal{B}U_2; U_1 - U_2\rangle + \langle K(U_1 - U_2); U_1 - U_2\rangle = 0 \tag{31}$$

Since $\mathcal{B}$ is monotone

$$\frac{1}{2}\|U(T)\|^2_{\mathcal{H}} \leq -\langle K(U_1 - U_2); U_1 - U_2\rangle \tag{32}$$

As $K : H \to H$ is Lipschitz then

$$\|U(T)\|^2_{\mathcal{H}} \leq C \int_0^T \|U\|^2_H(s)ds \tag{33}$$

Then by Gronwall's Lemma we get $\|U\|_H(T) = 0$ for arbitrary $T > 0$ then the solution is unique. $\square$

Next, we will prove that $U \geq 0$. Indeed, multiplying the first Eq of (13) by I^-

$$-\frac{d}{2dt}\int_\Omega |I^-|^2(t)dx = D\|\nabla I^-\|^2 + k_1\int_\Omega \tilde{E}|I^-|^2dx + l_{-1}\int_\Omega Q^+I^-dx + l_1\int_\Omega \tilde{A}|I^-|^2dx$$
$$+\nu\int_\Omega |I^-|^2dx + i_bK_c\int_{\partial\Omega}\frac{I^-}{K_m+I^+}d\sigma + T_e\int_{\partial\Omega}|I^-|^2 + JI^-d\sigma + k_{-1}\int_\Omega P^+I^- \geq 0, \tag{34}$$

hence, assuming that $I_0 \geq 0$ we get

$$\int_\Omega |I^-|^2(t)dx \leq \int_\Omega |I_0^-|^2dx = 0, \tag{35}$$

then $I^- = 0$ a.e. i.e. $I \geq 0$ a.e.. Moreover

$$-\frac{d}{2dt}\int_\Omega |Q^-|^2(t)dx = D_a\|\nabla Q^-\|^2 + l_1\int_\Omega \tilde{A}\min(I^+,1)Q^-dx + (l_{-1}+\nu_{ai})\int_\Omega |Q^-|^2dx \geq 0 \tag{36}$$

$$-\frac{d}{2dt}\int_\Omega |P^-|^2(t)dx = D_e\|\nabla P^-\|^2 + k_1\int_\Omega \tilde{E}\min(I^+,1)P^-dx + (k_{-1}+\mu_{ai})\int_\Omega |Q^-|^2dx \geq 0 \tag{37}$$

then we proceed similarly to prove $Q \geq 0, \quad P \geq 0$ a.e. as soon as $Q_0 \geq 0, P_0 \geq 0$. Next assuming hypotheses of theorem, we get $I, P, Q \leq 1$. Indeed

$$\frac{d}{2dt}\|(1-P)^-\|^2(t) = -D_e\|\nabla(1-P)^-\|^2 + k_1\int_\Omega \tilde{E}\min(I^+,1)(1-P)^-dx$$
$$-(k_{-1}+\mu_{ei})\|(1-P)^-\|^2 - (k_{-1}+\mu_{ei})\int_\Omega(1-P)^-dx. \tag{38}$$

then

$$\frac{d}{2dt}\|(1-P)^-\|^2(t) \leq k_1\int_\Omega \tilde{E}\min(I^+,1)(1-P)^-dx - (k_{-1}+\mu_{ei})\int_\Omega(1-P)^-dx$$
$$\leq [k_1 - (k_{-1}+\mu_{ei})]\int_\Omega(1-P)^-dx. \tag{39}$$

Under hypothesis $k_1 \leq k_{-1} + \mu_{ei}$ we get $\frac{d}{2dt}\|(1-P)^-\|^2(t) \leq 0$ hence $P \leq 1$ as soon as $P_0 \leq 1$. Similarly

$$\frac{d}{2dt}\|(1-Q)^-\|^2(t) = -D_a\|\nabla(1-Q)^-\|^2 + l_1\int_\Omega \tilde{E}\min(I^+,1)(1-Q)^-dx$$
$$-(l_{-1}+\nu_{ai})\|(1-Q)^-\|^2 - (l_{-1}+\nu_{ai})\int_\Omega(1-Q)^-dx, \tag{40}$$

then

$$\frac{d}{2dt}\|(1-Q)^-\|^2(t) \leq l_1\int_\Omega \tilde{E}\min(I^+,1)(1-Q)^-dx - (l_{-1}+\nu_{ai})\int_\Omega(1-Q)^-dx$$
$$\leq [l_1 - (l_{-1}+\nu_{ai})]\int_\Omega(1-Q)^-dx, \tag{41}$$

as $l_1 \leq l_{-1} + \nu_{ai}$ by hypotheses, $\frac{d}{2dt}\|(1-Q)^-\|^2(t) \leq 0$ hence $Q \leq 1$ as soon as $Q_0 \leq 1$. Finally

$$\frac{d}{2dt}\|(1-I)^-\|^2(t) = -D\|\nabla(1-I)^-\|^2 + k_{-1}\int_\Omega P^+(1-I)^-dx - k_1\int_\Omega \tilde{E}|(1-I)^-|^2dx$$
$$-k_1\int_\Omega \tilde{E}(1-I)^-dxl_{-1}\int_\Omega Q^+(1-I)^-dx - l_1\int_\Omega \tilde{A}|(1-I)^-|^2dx - l_1\int_\Omega \tilde{A}(1-I)^-dx$$
$$-\nu\|(1-I)^-\|^2 - \nu\int_\Omega(1-I)^-dx, \tag{42}$$

hence

$$\frac{d}{2dt}\|(1-I)^-\|^2(t) \leq k_{-1}\int_\Omega P^+(1-I)^-dx + l_{-1}\int_\Omega Q^+(1-I)^-dx - \nu\int_\Omega(1-I)^-dx$$
$$\leq (k_{-1}+l_{-1}-\nu)\int_\Omega(1-I)^-dx, \tag{43}$$

then assuming that $k_{-1} + l_{-1} - \nu \leq 0$ we get $I \leq 1$ as soon as $I_0 \leq 1$. $\square$

2.2 Step II: Parabolic problem for given $\tilde{I}, \tilde{Q}, \tilde{P}$

For given $S_a, S_e \in L^\infty(\Omega)$, $\tilde{I}$, $\tilde{Q}$, $\tilde{P} \in \mathcal{C}$, $0 \le \tilde{I}$, $\tilde{P}$, $\tilde{Q} \le 1$, consider the linear parabolic problem

$$\begin{cases} \partial_t A = D_a \Delta A + l_{-1}\tilde{Q} - (l_1 \tilde{I} + \nu_a)A + S_a(x), \ \ \mathbb{R}^+ \times \Omega, \\ \partial_t E(t,x) = D_e \Delta E + k_{-1}\tilde{P} - (k_1 \tilde{I} + \nu_e)E + S_e(x), \ \ \mathbb{R}^+ \times \Omega, \\ A(0,x) = A_0(x) \ge 0, \ \ E(0,x) = E_0(x) \ge 0, \\ D_a \partial_n A = 0, \ D_e \partial_n E = 0 \ \ on \ \ \partial\Omega. \end{cases} \tag{44}$$

Theorem 4. *Assume that*

$$\begin{aligned} &S_a, \ S_e \ge 0, \ S_a, \ S_e \in L^\infty(\Omega) \\ &l_{-1} + \|S_a\|_\infty \le \nu_a, \ \ k_{-1} + \|S_e\|_\infty \le \nu_e. \end{aligned} \tag{45}$$

There exists a unique mild solution $(A, E) \in \mathcal{C}^0(0,\infty; L^2(\Omega) \times \mathcal{C}^0(0,\infty; L^2(\Omega)$ to (44). Moreover, assuming that $(A_0, E_0) \in H^1(\Omega) \times H^1(\Omega)$, $(\Delta A_0, \Delta E_0) \in L^2(\Omega) \times L^2(\Omega)$, we get $A, E \in L^2(0,T; H^1(\Omega))$, $\Delta A, \Delta E \in L^2(0,T; L^2(\Omega))$, $\partial_t A, \partial_t E \in L^2(0,T; L^2(\Omega))$. In addition, if $0 \le A_0, E_0 \le 1$ then $0 \le A, E \le 1$.
Furthermore, there exists $C > 0$ such that the following energy estimate holds

$$\begin{aligned} &\tfrac{d}{2dt}(\|A\|^2 + \|E\|^2)(t) + D_a\|\nabla A\|^2(t) + D_e\|\nabla E\|^2(t) + \nu_a\|A\|^2(t) + \nu_e\|E\|^2(t) \\ &+ l_1 \textstyle\int_\Omega \tilde{I}|A|^2 dx + k_1 \int_\Omega \tilde{I}|E|^2 dx = l_{-1}\int_\Omega \tilde{Q} A dx + k_{-1}\int_\Omega \tilde{P} E dx + \int_\Omega S_a(x) A dx \\ &+ \textstyle\int_\Omega S_e(x) E dx \end{aligned} \tag{46}$$

Proof. Let $0 \le \tilde{Q}, \tilde{I}, \tilde{P} \le 1$ be given. We notice that A and E are independent then we can solve separately

$$\partial_t A = D_a \Delta A + l_{-1}\tilde{Q} - (l_1 \tilde{I} + \nu_a)A + S_a(x), \ \ A(0,x) = A_0(x), \ \ , \partial_n A = 0 \ \ on \ \ \partial\Omega. \tag{47}$$

$$\partial_t E(t,x) = D_e \Delta E + k_{-1}\tilde{P} - (k_1 \tilde{I} + \nu_e)E + S_e(x), \ E(0,x) = E_0(x), \ \ \partial_n E = 0 \ \ on \ \ \partial\Omega. \tag{48}$$

Consider the operator $\mathcal{B}$ defined on $L^2(\Omega)$ and $F : L^2(\Omega) \to L^2(\Omega)$ by

$$\begin{aligned} &\mathcal{B}(u) = D_a \Delta u; \ \mathcal{D}(\mathcal{B}) = \{u \in H^1(\Omega), \ \mathcal{B}(u) \in L^2(\Omega), \ \partial_n u = 0 \ \} \\ &F(u) = l_{-1}\tilde{Q} - (l_1 \tilde{I} + \nu_a)u + S_a(x) \end{aligned} \tag{49}$$

$\mathcal{B}$ is self-adjoint and negative and F is Lipschitz in $L^2(\Omega)$ uniformly in time then there exists a unique mild solution $u \in \mathcal{C}^0(0,\infty; L^2(\Omega))$ to (47). Assuming that $A_0 \in \mathcal{D}(\mathcal{B})$, we get $A \in L^2(0,T; H^1(\Omega))$, $\Delta A \in L^2(0,T; L^2(\Omega))$ and then $\partial_t A \in L^2(0,T; L^2(\Omega))$ Cf. [2]. We proceed similarly for E.
Next, we will prove $A, E \ge 0$. Indeed, multiplying (47) by A^- and integrating by parts, we get

$$-\frac{d}{2dt}\|A^-\|^2 = D_a\|\nabla A^-\|^2 + l_{-1}\int_\Omega \tilde{Q} A^- dx + \int_\Omega l_1(\tilde{I} + \nu_a)|A^-|^2 dx + \int_\Omega S_a(x) A^- dx \tag{50}$$

The right hand side of the last equatily is nonnegative hence $\|A^-\|^2(t) \le \|A_0^-\|^2 = 0$ so $A \ge 0$ a.e. We procced similarly for $E \ge 0$.
Next, we will prove that $A, E \le 1$. We have

$$-\partial_t(1 - A) = -D_a \Delta(1 - A) + l_{-1}\tilde{Q} - (l_1 \tilde{I} + \nu_a)A + S_a(x), \tag{51}$$

then

$$\begin{aligned} &\partial_t\|(1-A)^-\|^2 = -D_a\|\nabla(1-A)^-\|^2 + l_{-1}\textstyle\int_\Omega \tilde{Q}(1-A)^- dx - \int_\Omega (l_1\tilde{I} + \nu_a)A(1-A)^- dx \\ &+ \textstyle\int_\Omega S_a(x)(1-A)^- dx, \end{aligned} \tag{52}$$

in other words

$$\partial_t\|(1-A)^-\|^2 = -D_a\|\nabla(1-A)^-\|^2 + l_{-1}\int_\Omega \tilde{Q}(1-A)^-dx + \int_\Omega (l_1\tilde{I}+\nu_a)(1-A)(1-A)^-dx$$
$$- \int_\Omega (l_1\tilde{I}+\nu_a)(1-A)^-dx + \int_\Omega S_a(x)(1-A)^-dx \tag{53}$$

then

$$\partial_t\|(1-A)^-\|^2 = -D_a\|\nabla(1-A)^-\|^2 + l_{-1}\int_\Omega \tilde{Q}(1-A)^-dx - \int_\Omega (l_1\tilde{I}+\nu_a)|(1-A)^-|^2dx$$
$$- \int_\Omega (l_1\tilde{I}+\nu_a)(1-A)^-dx + \int_\Omega S_a(x)(1-A)^-dx, \tag{54}$$

consequently, by the assumption on $\|S_a\|_\infty$

$$\partial_t\|(1-A)^-\|^2 \le l_{-1}\int_\Omega (1-A)^-dx - \nu_a\int_\Omega (1-A)^-dx + \|S_a(x)\|_\infty \int_\Omega (1-A)^-dx \le 0, \tag{55}$$

hence $A \le 1$ as soon as $A_0 \le 1$. On the other hand

$$\partial_t\|(1-E)^-\|^2 = k_{-1}\int_\Omega \tilde{P}(1-E)^-dx - \int_\Omega (k_1\tilde{I}+\nu_e)E(1-E)^-dx + \int_\Omega S_e(x)(1-E)^-dx \tag{56}$$

then

$$\begin{aligned}\partial_t\|(1-E)^-\|^2 &= k_{-1}\int_\Omega \tilde{P}(1-E)^-dx + \int_\Omega (k_1\tilde{I}+\nu_e)(1-E)(1-E)^-dx\\ &- \int_\Omega (k_1\tilde{I}+\nu_e)(1-E)^-dx + \int_\Omega S_e(x)(1-E)^-dx,\end{aligned} \tag{57}$$

hence

$$\partial_t\|(1-E)^-\|^2 = k_{-1}\int_\Omega \tilde{P}(1-E)^-dx - \int_\Omega (k_1\tilde{I}+\nu_e)|(1-E)^-|^2dx - \int_\Omega (k_1\tilde{I}+\nu_e)(1-E)^-dx$$
$$+ \int_\Omega S_e(x)(1-E)^-dx \tag{58}$$

By virtue of hypothesis on $\|S_e(x)\|_\infty$

$$\partial_t\|(1-E)^-\|^2 \le k_{-1}\int_\Omega (1-E)^-dx - \nu_e\int_\Omega (1-E)^-dx + \|S_e(x)\|_\infty \int_\Omega (1-E)^-dx \le 0 \tag{59}$$

then $E \le 1$ whenever $E_0 \le 1$. □

3 Fixed point procedure and proof of the main theorem

We will apply Schauder's fixed point theorem to solve the nonlinear parabolic problem

$$\begin{cases} \partial_t I = D\Delta I + k_{-1}P - k_1EI + l_{-1}Q - l_1AI - \nu I, \;\; \mathbb{R}^+\times\Omega,\\ \partial_t A = D_a\Delta A + l_{-1}Q - (l_1I+\nu_a)A + S_a(x), \;\; \mathbb{R}^+\times\Omega,\\ \partial_t Q = D_a\Delta Q + l_1AI - (l_{-1}+\nu_{ai})Q, \;\; \mathbb{R}^+\times\Omega,\\ \partial_t E(t,x) = D_e\Delta E + k_{-1}P - (k_1I+\nu_e)E + S_e(x), \;\; \mathbb{R}^+\times\Omega,\\ \partial_t P = D_e\Delta P + k_1EI - (k_{-1}+\mu_{ei})P, \;\; \mathbb{R}^+\times\Omega\\ I(0,x) = I_0(x)\ge 0, \;\; A(0,x) = A_0(x)\ge 0, \;\; Q(0,x) = Q_0(x)\ge 0,\\ P(0,x) = P_0(x)\ge 0, \; E(0,x) = E_0(X)\ge 0,\\ D_a\partial_n A = D_a\partial_n Q = 0, \;\; D_e\partial_n E = 0, \; D_e\partial_n P = 0,\\ -D\partial_n I(x,t) = \frac{K_c(I(x,t)-i_b)}{K_m+I(x,t)} + T_e(I-J) \;\; \text{on} \;\; \partial\Omega. \end{cases} \tag{60}$$

Set

$$W = \left\{ \begin{array}{l} (u,v) \in L^2(0,T;H^1(\Omega)) \times L^2(0,T;H^1(\Omega)) \\ \\ \partial_t(u,v) \in L^2(0,T;L^2(\Omega)) \times L^2(0,T;L^2(\Omega)), \quad 0 \le u,v \le 1 \end{array} \right\} \tag{61}$$

We check that W is a convex, compact subset of $L^2(0,T;L^2(\Omega))$. Next, define the operator $\mathcal{L}$ on W by

$$\mathcal{L}(A,E) = (A^\star, E^\star), \tag{62}$$

where $(A^\star, E^\star)$ is the solution to (44) given by Theorem 4 associated to (I,P,Q) which is the solution to (10) given by Theorem 2 for $\tilde{E} = E$ and $\tilde{A} = A$. It follows from Theorem 2 and 4 that $\mathcal{L}(W) \subset W$.

Our aim is to prove that $\mathcal{L}$ is Lipschitz on $L^2(0,T;L^2(\Omega)) \times L^2(0,T;L^2(\Omega))$.

Let $(A_i, E_i) \in W$, $i = 1,2$ and (I_i, P_i, Q_i) the solution to (10) associated to $\tilde{A} = A_i$ et $\tilde{E} = E_i$. Set

$$\begin{aligned} &(A_i^\star, E_i^\star) = \mathcal{L}(A_i, E_i), \quad A^\star = A_1^\star - A_2^\star, \quad E^\star = E_1^\star - E_2^\star, \\ &Q = Q_1 - Q_2, \quad P = P_1 - P_2, \quad I = I_1 - I_2, \quad A = A_1 - A_2, \quad E = E_1 - E_2. \end{aligned} \tag{63}$$

By definition of operateur $\mathcal{L}$, we have

$$\left\{ \begin{array}{l} \partial_t A_i^\star = D_a \Delta A_i^\star + l_{-1} Q_i - (l_1 I_i + \nu_a) A_i^\star + S_a(x), \\ \\ \partial_t E_i^\star(t,x) = D_e \Delta E_i^\star + k_{-1} P_i - (k_1 I_i + \nu_e) E_i^\star + S_e(x), \\ \\ A_i^\star(0,x) = A_0(x) \ge 0, \quad E_i^\star(0,x) = E_0(x) \ge 0, \\ \\ D_a \partial_n A_i^\star = 0, \quad D_e \partial_n E_i^\star = 0 \; on \;\; \partial\Omega. \end{array} \right. \tag{64}$$

Consequently

$$\left\{ \begin{array}{l} \partial_t A^\star = D_a \Delta A^\star + l_{-1} Q - l_1 (I_1 A_1^\star - I_2 A_2^\star) - \nu_a A^\star, \\ \\ \partial_t E^\star = D_e \Delta E^\star + k_{-1} P - k_1 (I_1 E_1^\star - I_2 E_2^\star) - \nu_e E^\star, \\ \\ A^\star(0) = 0, \quad E^\star(0) = 0, \quad \partial_n A^\star = 0; \;\; \partial_n E^\star = 0. \;\; \partial\Omega. \end{array} \right. \tag{65}$$

Then

$$\left\{ \begin{array}{l} \partial_t A^\star = D_a \Delta A^\star + l_{-1} Q - l_1 (I_1 A^\star + I A_2^\star) - \nu_a A^\star, \\ \\ \partial_t E^\star = D_e \Delta E^\star + k_{-1} P - k_1 (I_1 E^\star - I E_2^\star) - \nu_e E^\star, \\ \\ A^\star(0) = 0, \quad E^\star(0) = 0, \quad \partial_n A^\star = \partial_n E^\star = 0; \quad \partial\Omega. \end{array} \right. \tag{66}$$

Hence

$$\frac{d}{2dt}\|A^\star\|^2 + D_a\|\nabla A^\star\|^2 + \nu_a\|A^\star\|^2 + l_1\int_\Omega I_1|A^\star|^2 dx = l_{-1}\int_\Omega QA^\star dx - l_1\int_\Omega IA^\star A_2^\star dx, \tag{67}$$

$$\begin{aligned} &\tfrac{d}{2dt}\|E^\star\|^2 + D_e\|\nabla E^\star\|^2 + k_1\int_\Omega I_1|E^\star|^2 + \nu_e|E^\star|^2 dx = k_{-1}\int_\Omega PE^\star dx \\ &-k_1\int_\Omega IE_2^\star E^\star dx. \end{aligned} \tag{68}$$

Consequently

$$\begin{aligned} &\tfrac{d}{2dt}(\|A^\star\|^2 + \|E^\star\|^2) + D_a\|\nabla A^\star\|^2 + D_e\|\nabla E^\star\|^2 + \nu_a\|A^\star\|^2 + \nu_e\|E^\star\|^2 + l_1\int_\Omega I_1|A^\star|^2 dx \\ &+k_1\int_\Omega I_1|E^\star|^2 dx = l_{-1}\int_\Omega QA^\star dx + k_{-1}\int_\Omega PE^\star dx - l_1\int_\Omega IA^\star A_2^\star dx - k_1\int_\Omega IE_2^\star E^\star dx. \end{aligned} \tag{69}$$

Finally, using Gronwall's lemma, for arbitrary $T > 0$, there exists $C_T > 0$ depending on $T, l_1, l_{-1}, k_1, k_{-1}$ such that

$$(\|A^\star\|^2 + \|E^\star\|^2)(t) \leq C_T \int_0^T (\|I\|^2 + \|Q\|^2 + \|P\|^2)(s)ds, \quad t \in [0,T]. \tag{70}$$

On the other hand, for given A_i, E_i

$$\begin{cases} \partial_t(I_1 - I_2) = D\Delta(I_1 - I_2) + k_{-1}(P_1 - P_2) - k_1(E_1 I_1 - E_2 I_2) + l_{-1}(Q_1 - Q_2) \\ +l_1(A_1 I_1 - A_2 I_2) - \nu(I_1 - I_2), \\ \partial_t(Q_1 - Q_2) = D_a\Delta(Q_1 - Q_2) + l_1(A_1 I_1 - A_2 I_2) - (l_{-1} + \nu_{ai})(Q_1 - Q_2), \\ \partial_t(P_1 - P_2) = D_e\Delta(P_1 - P_2) + k_1(E_1 I_1 - E_2 I_2) - (k_{-1} + \mu_{ei})(P_1 - P_2), \\ (P_1 - P_2)(0,x) = 0,\ (Q_1 - Q_2)(0,x) = 0,\ (I_1 - I_2)(0,x) = 0, \\ \partial_n(Q_1 - Q_2) = 0, \ \ \partial_n(P_1 - P_2) = 0, \\ -D\partial_n(I_1 - I_2) = \frac{K_c(K_m + i_b)(I_1 - I_2)}{(K_m + I_1)(K_m + I_2)} + T_e(I_1 - I_2). \end{cases} \tag{71}$$

Setting $Q = Q_1 - Q_2,\ P = P_1 - P_2,\ I = I_1 - I_2,\ A = A_1 - A_2,\ E = E_1 - E_2$ we get

$$\begin{cases} \partial_t I = D\Delta I + k_{-1}P - k_1(EI_1 + E_2 I) + l_{-1}Q + l_1(AI_1 + A_2 I) - \nu I, \\ \partial_t Q = D_a\Delta Q + l_1(AI_1 + A_2 I) - (l_{-1} + \nu_{ai})Q, \\ \partial_t P = D_e\Delta P + k_1(EI_1 + E_2 I) - (k_{-1} + \mu_{ei})P, \\ P(0,x) = 0,\ Q(0,x) = 0,\ I(0,x) = 0, \\ \partial_n Q = 0, \ \ \partial_n P = 0, \ \ -D\partial_n I = \frac{K_c(K_m + i_b)I}{(K_m + I_1)(K_m + I_2)} + T_e I. \end{cases} \tag{72}$$

Hence

$$\begin{aligned} &\tfrac{d}{2dt}(\|I\|^2 + \|Q\|^2 + \|P\|^2) + D\|\nabla I\|^2 + D_a\|\nabla Q\|^2 + D_e\|\nabla P\|^2 + \nu\|I\|^2 + T_e\|I\|^2_{\partial\Omega} \\ &+(l_{-1} + \nu_{ai})\|Q\|^2 + (k_{-1} + \mu_{ei})\|P\|^2 + \int_{\partial\Omega} \frac{K_c(K_m + i_b)|I|^2}{(K_m + I_1)(K_m + I_2)} d\sigma + k_1 \int_\Omega E_2|I|^2 dx \\ &+l_1 \textstyle\int_\Omega A_2|I|^2 dx = k_{-1}\displaystyle\int_\Omega PI dx + l_{-1}\int_\Omega QI dx + l_1 \int_\Omega AII_1 dx + l_1 \int_\Omega AQI_1 dx \\ &+l_1 \int_\Omega A_2 IQ dx + k_1 \int_\Omega EPI_1 dx + k_1 \int_\Omega E_2 IP dx - k_1 \int_\Omega EII_1 dx. \end{aligned} \tag{73}$$

Then, it follows from Gronwall's lemma that for $T > 0$, there exsits $C'_T > 0$ depending on T and the constants occuring in the system such that

$$(\|I\|^2 + \|Q\|^2 + \|P\|^2)(t) \leq C'_T \int_0^T (\|A\|^2 + \|E\|^2)ds, \quad t \in [0,T]. \tag{74}$$

Finally, we conclude from (70) and (74) that

$$\|\mathcal{L}(A_1, E_1) - \mathcal{L}(A_2, E_2)\|_{L^2(0,T;L^2(\Omega))} \leq C_T\|(A_1, E_1) - (A_2, E_2)\|_{L^2(0,T;L^2(\Omega))} \tag{75}$$

for some positive constant $C_T > 0$ depending only on $T > 0$ and the constants occuring in the system. It derives from Schauder fixed point theorem that operatoe $\mathcal{L}$ has a fixed point and the proof of Theorem 1 follows.

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