Analysis of a PDE model of the swelling of mitochondria accounting for spatial movement

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Dedicated, in admiration, to academician Roald Sagdeev on the occasion of his 85th birthday

Abstract

We analyze existence and asymptotic behavior of a system of semilinear diffusion-reaction equations that arises in the modeling of the mitochondria swelling process. The model itself expands previous work in which the mitochondria were assumed to be stationary, whereas now their movement is modeled by linear diffusion. While in the previous model certain formal structural conditions were required for the rate functions describing the swelling process, we show that these are not required in the extended model. Numerical simulations are included to visualise the solutions of the new model and to compare them with the solutions of the previous model.

Keywords: diffusion-reaction system, mitochondria swelling

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1 Introduction

Mitochondria are double-membrane enclosed organelles in eukaryotic cells. They play an important role in the death of mammalian cells by activating apoptosis. This involves the permeabilization of the inner mitochondrial membrane, resulting in the swelling of the mitochondrial matrix. Mitochondrial permeability transition is caused by the opening of pores in the inner membrane, e.g ., under pathological conditions such as high Ca^{2+} concentrations. The increased permeability leads to an influx of solutes and water into the mitochondrial matrix. This causes swelling of the mitochondrion. Eventually the outer membrane ruptures. This is a critical event, because apoptosis is irreversibly triggered by the release of several proapoptotic factors from the intermembrane space [9]. Intact mitochondria store calcium in their matrix. This calcium is released if swelling is induced [9]. Consequently the remaining mitochondria experience higher calcium concentrations, which accelerates the process.

In this paper, we further develop the model for mitochondria swelling that we introduced in [4, 5, 7] and take into account spatial effects. More precisely, two spatial effects directly influence the process of mitochondria swelling: on the one hand, the extent of mitochondrial damage due to calcium is highly dependent on the position of the particular mitochondrion and the local calcium ion concentration there. On the other hand, at a high fractions of swollen mitochondria the effect of positive feedback becomes relevant as the residual mitochondria are confronted with a higher calcium ion load [9].

In accordance with theoretical [8] and experimental [16] findings, we consider three subpopulations of mitochondria with different corresponding volumes: $N_1(x,t)$ describes the density of intact, unswollen mitochondria, $N_2(x,t)$ is the density of mitochondria that are in the swelling process but not completely swollen, and $N_3(x,t)$ is the density of completely swollen mitochondria. The swelling process is controlled by, and affects, the local Ca^{2+} concentration, which is denoted by $u(x,t)$, and subject to Fickian diffusion.

The transition of intact mitochondria over swelling to completely swollen ones proceeds in dependence on the local calcium ion concentration. In [4, 5, 7] we assumed that mitochondria do not move in any direction and hence spatial effects are only introduced by the calcium evolution. In this case, the evolution of the mitochondrial subpopulations is modeled by a system of ODEs (see (1.2)-(1.4) below), that depends on the space variable x via the calcium ion concentration.

In [4, 5, 7], we analyzed the swelling of mitochondria on a bounded domain $\Omega \subset \mathbb{R}^n$ with $n = 2, 3$. This domain could either be a test tube or the whole cell. The initial calcium concentration $u(x,0)$ describes the added amount of Ca^{2+} to induce the swelling process. This leads to the following coupled PDE-ODE system determined by the non-negative model functions f and g:

$$\partial_t u = d_1 \Delta_x u + d_2 g(u) N_2 \tag{1.1}$$

$$\partial_t N_1 = -f(u) N_1 \tag{1.2}$$

$$\partial_t N_2 = f(u) N_1 - g(u) N_2 \tag{1.3}$$

$$\partial_t N_3 = g(u) N_2 \tag{1.4}$$

with diffusion constant $d_1 > 0$ and feedback parameter $d_2 > 0$. Equations (1.1)-(1.4) were complemented by inhomogeneous Robin boundary conditions (containing as a particular cases the Neumann and Dirichlet boundary conditions), as well as the initial conditions

$$u(x,0) = u_0(x), \quad N_1(x,0) = N_{1,0}(x), \quad N_2(x,0) = N_{2,0}(x), \quad N_3(x,0) = N_{3,0}(x).$$

Note that by virtue of (1.2)-(1.4) the total mitochondrial population

$$\bar{N}(x,t) := N_1(x,t) + N_2(x,t) + N_3(x,t)$$

does not change in time, that is, $\partial_t \bar{N}(x,t) = 0$, and is given by the sum of the initial data:

$$\bar{N}(x,t) = \bar{N}(x) := N_{1,0}(x) + N_{2,0}(x) + N_{3,0}(x) \ \forall t \geq 0 \ \forall x \in \Omega.$$

For the convenience of the reader we recall below the role of model functions f and g (see also [4, 5, 6, 7]).

Model function f. The process of mitochondrial permeability transition is dependent on the calcium ion concentration. If the local concentration of Ca^{2+} is sufficiently high, the pores open and mitochondrial swelling is initiated. This incident is mathematically described by the transition of mitochondria from N_1 to N_2. The corresponding transition function $f(u)$ is zero up to a certain threshold C^-, denoting the calcium ion concentration which is needed to start the whole process. Whenever this threshold is reached, the local transition at this point from N_1 to N_3 over N_2 is inevitably triggered. According to [12], this process is calcium ion dependent with higher concentrations leading to faster pore opening. Hence the function $f(u)$ is increasing in u.

The transfer from unswollen to swelling mitochondria is related to pore opening, hence we also postulate that there is some saturation rate f^* displaying the maximal transition rate. This is biologically explained by a bounded rate of pore opening with increasing calcium ion concentrations.

Remark 1. *The initiation threshold C^- of f is crucial for the whole swelling procedure. Dependent on the amount and location of added calcium ions, it can happen that in the beginning the local concentration was enough to induce swelling in this region, but after some time due to diffusion the concentration drops below C^-. If this depletion occurs before all mitochondria are engaged in swelling, we only have partial swelling and eventually there can still be intact mitochondria left.*

Model function g. The mitochondrial population N_2 changes due to initiation of swelling ($N_1 \to N_2$, a source) and due to mitochondria swelling completely ($N_2 \to N_3$, a sink). The transition from N_2 to N_3 is modeled by the transition function $g(u)$. In contrast to the function f, there is no initiation threshold and the transition takes place in wherever calcium ions are present, $u > 0$. This property is based on a biophysical mechanism. The permeabilization of the inner membrane due to pore opening leads to water influx and hence unstoppable swelling of the mitochondrial matrix. Due to a limited pore size, this effect also has its restriction and, thus, we have saturation at level g^*.

The third population N_3 of completely swollen mitochondria grows continuously due to the unstoppable transition from N_2 to N_3. All mitochondria that started to swell will be completely swollen in the end.

Calcium evolution. The model consists of spatial developments in terms of diffusing calcium ions. In addition to the diffusion term, the equation for the calcium concentration contains a production term dependent on N_2, which is justified by the following: in an earlier study [8], it was shown that it is essential to include a positive feedback mechanism. This accelerating effect is induced by stored calcium inside the mitochondria, which is additionally released once the mitochondrion is completely swollen. Due to a fixed amount of stored Ca^{2+}, we assume that the additionally released calcium amount is proportional to the newly completely swollen mitochondria only, i.e., those mitochondria leaving N_2 and entering N_3. Here, the feedback parameter d_2 is the rate at which stored calcium is released.

The outline of the paper is as follows. In Section 2 we state the governing equations which take into account the assumption that mitochondria move within a cell under certain circumstances. Under this assumption we prove in Section 2 well-posedness for the corresponding initial boundary value problem. Section 3 deals with asymptotic behaviour of solutions. Section 4 contains some numerical simulations which illustrate the analytical results.

2 A PDE-PDE model and its well-posedness

We especially emphasise that in the previous studies [4, 5, 7] we made the assumption that mitochondria do not diffuse within cell walls, leading to a PDE-ODE coupling (system (1.1)-(1.4)). However, there are indications that mitochondria do move under certain circumstances depending, e.g., on the cell cycle [10]. This means that mitochondrial subpopulations $N_i(t,x)$, in contrast to what we had in the previous papers, obey now partial instead of ordinary differential equations. We have the following PDE-PDE system:

$$\boldsymbol{\partial_t}\begin{pmatrix} u \\ N_1 \\ N_2 \\ N_3 \end{pmatrix} + \begin{pmatrix} d_1\Delta u \\ d_3\Delta N_1 \\ d_4\Delta N_2 \\ d_5\Delta N_3 \end{pmatrix} + \begin{pmatrix} -d_2 g(u)N_2 \\ f(u)N_1 \\ -f(u)N_1 + g(u)N_2 \\ -g(u)N_2 \end{pmatrix} = \mathbf{0}. \tag{2.1}$$

We denote $H := (L^2(\Omega))^4$ and

$$\mathbf{v} = \begin{pmatrix} u \\ N_1 \\ N_2 \\ N_3 \end{pmatrix},\ \mathbf{Av} := -\begin{pmatrix} d_1\Delta u \\ d_3\Delta N_1 \\ d_4\Delta N_2 \\ d_5\Delta N_3 \end{pmatrix},\ \mathbf{Bv} := \begin{pmatrix} -d_2 g(u)N_2 \\ f(u)N_1 \\ -f(u)N_1 + g(u)N_2 \\ -g(u)N_2 \end{pmatrix}.$$

We impose the initial condition:

$$\mathbf{v}|_{t=0} = \mathbf{v}_0(x) = \begin{pmatrix} u_0(x) \\ N_{1,0}(x) \\ N_{2,0}(x) \\ N_{3,0}(x) \end{pmatrix} \tag{2.2}$$

as well as Neumann boundary condition for $\mathbf{N} = (N_1, N_2, N_3)^T$:

$$\frac{\partial \mathbf{N}}{\partial n}\bigg|_{\partial\Omega} = \begin{pmatrix} \frac{\partial N_1}{\partial n} \\ \frac{\partial N_2}{\partial n} \\ \frac{\partial N_3}{\partial n} \end{pmatrix}\bigg|_{\partial\Omega} = \mathbf{0} \tag{2.3}$$

and three types boundary conditions for u:

(N) Neumann BC: $\frac{\partial u}{\partial n} = 0$.

(R) Robin BC: $-\frac{\partial u}{\partial n} = a(x)\,(u(x) - \alpha)$, where α is nonnegative constant and $a \in C^1(\partial\Omega),\ a(x) \geq 0,\ a(\cdot) \not\equiv 0$.

(D) Dirichlet BC: $u(x) = 0$.

In the Robin BC case, in order to reduce the problem to the semi-linear setting, we set $\overline{u} = u - \alpha$, then $\overline{u}$ satisfies the linear boundary condition

$$-\partial_\nu \overline{u} = a(x)\,\overline{u} \quad \text{on } \partial\Omega \tag{2.4}$$

and equation (2.1) with $u, f(\cdot), g(\cdot)$ are replaced by $\overline{u}$, $\overline{f}(v) = f(v+\alpha)$ and $\overline{g}(v) = g(v+\alpha)$ respectively. In what follows, we designate $\overline{u}$, $\overline{f}(\cdot)$ and $\overline{g}(\cdot)$ again by $u, f(\cdot)$ and $g(\cdot)$, if no confusion arises. Here we note that $\overline{f}$ and $\overline{g}$ also satisfy Condition 1 which will be introduced later.

We introduce the following functionals on $L^2(\Omega)$:

$$\varphi_a(u) := \begin{cases} \dfrac{1}{2}\displaystyle\int_\Omega |\nabla u|^2\,dx + \dfrac{1}{2}\int_{\partial\Omega} a(x)\,|u|^2\,dS & \text{if } \ u \in H^1(\Omega), \\ +\infty & \text{if } \ u \in L^2(\Omega)\setminus H^1(\Omega), \end{cases}$$

$$\varphi_D(u) := \begin{cases} \dfrac{1}{2}\displaystyle\int_\Omega |\nabla u|^2\,dx & \text{if } \ u \in H^1_0(\Omega), \\ +\infty & \text{if } \ u \in L^2(\Omega)\setminus H^1_0(\Omega). \end{cases}$$

Then $\varphi_a(\cdot)$ and $\varphi_D(\cdot)$ become lower semi-continuous functions from $L^2(\Omega)$ into $[0,+\infty]$ and their subdifferentials are given by

$$\partial\varphi_a(u) = \partial\varphi_D(u) = -\Delta u,$$

$$D(\partial\varphi_0) = \{\, u \in H^2(\Omega)\,;\ -\tfrac{\partial u}{\partial n} = 0 \ \text{ on } \partial\Omega \,\} : \text{Neumann BC},$$

$$D(\partial\varphi_a) = \{\, u \in H^2(\Omega)\,;\ -\tfrac{\partial u}{\partial n} = a(x)\,u(x) \ \text{ on } \partial\Omega \,\} : \text{Robin BC},$$

$$D(\partial\varphi_D) = \{\, u \in H^2(\Omega)\,;\, u \in H^1_0(\Omega) \,\} : \text{Dirichlet BC}.$$

According to the boundary conditions posed on u, we set

$$D(\mathbf{A}) = \left\{ \mathbf{v} \in (H^2(\Omega))^4\,;\ \frac{\partial \mathbf{N}}{\partial n}\bigg|_{\partial\Omega} = \mathbf{0},\ \frac{\partial u}{\partial n} = 0 \ \text{ or } \ -\frac{\partial u}{\partial n} = a\,u \ \text{ or } \ u = 0 \text{ on } \partial\Omega \right\},$$

for Neumann, Robin or Dirichlet boundary condition respectively.

System (2.1)-(2.2) with boundary conditions (N), (R) and (D) can then be rewritten as

$$\begin{cases} \partial_t \mathbf{v} + \mathbf{A}\mathbf{v} + \mathbf{B}\mathbf{v} = \mathbf{0}, & (2.5) \\ \mathbf{v}(0,x) = \mathbf{v}_0(x). & (2.6) \end{cases}$$

Moreover set

$$\begin{aligned}\varphi(\mathbf{v}) &= d_1\,\varphi_1(u) + \frac{d_2}{2}\int_\Omega |\nabla N_1|^2 dx + \frac{d_3}{2}\int_\Omega |\nabla N_2|^2 dx + \frac{d_4}{2}\int_\Omega |\nabla N_3|^2 dx,\\ \varphi_1(u) &= \varphi_0(u),\ \ \varphi_a(u)\ \text{ or }\ \varphi_D(u).\end{aligned}$$

Then $\varphi(\cdot)$ becomes a lower semi-continuous convex function on H and it holds that (see [2, 3])

$$\mathbf{A}(\mathbf{v}) = \partial\varphi(\mathbf{v}) \quad \forall \mathbf{v} \in D(\mathbf{A}) = D(\partial\varphi), \tag{2.7}$$

$$D(\mathbf{A}^{1/2}) = D(\varphi) = \{\,\mathbf{v}\,;\,\varphi(\mathbf{v}) < +\infty\,\}, \quad \|\mathbf{A}^{1/2}\mathbf{v}\|^2 = 2\,\varphi(\mathbf{v}). \tag{2.8}$$

We here give precise conditions on model functions f, g as explained in the Introduction.

Condition 1. *The model functions $f : \mathbb{R} \to \mathbb{R}$ and $g : \mathbb{R} \to \mathbb{R}$ have the following properties:*

(i) Non-negativity:

$$f(s) \geq 0 \qquad \forall s \in \mathbb{R},$$
$$g(s) \geq 0 \qquad \forall s \in \mathbb{R}.$$

(ii) Boundedness:

$$f(s) \leq f^* < \infty \qquad \forall s \in \mathbb{R},$$
$$g(s) \leq g^* < \infty \qquad \forall s \in \mathbb{R} \qquad \textit{with } f^*, g^* > 0.$$

(iii) Lipschitz continuity:

$$|f(s_1) - f(s_2)| \leq L_f |s_1 - s_2| \qquad \forall s_1, s_2 \in \mathbb{R},$$

$$|g(s_1) - g(s_2)| \le L_g |s_1 - s_2| \qquad \forall s_1, s_2 \in \mathbb{R}$$

with L_f, $L_g \ge 0$.

Theorem 2. *Let f and g satisfy Condition 1. Then for any $\mathbf{v}_0 = (u_0, N_{1,0}, N_{2,0}, N_{3,0}) \in H$ there exists a unique solution of (2.5)-(2.6) such that*

$$\begin{cases} \mathbf{v} \in C([0,\infty), H), \ \sqrt{t}\,\partial_t \mathbf{v}, \sqrt{t}\,\mathbf{A}\mathbf{v} \in L^2(0,T,H), \\ \varphi(\mathbf{v}) \in L^1(0,T), \ t\,\varphi(\mathbf{v}) \in L^\infty(0,T) \text{ for any } T > 0. \end{cases}$$

Proof. Note that, due to *Condition 1* we obtain

$$|\mathbf{B}\mathbf{v}|_H^2 \le d_2^2 (g^*)^2 |N_2|_{L^2}^2 + 2(f^*)^2 |N_1|_{L^2}^2 + 2(g^*)^2 |N_3|_{L^2}^2 \le C |\mathbf{v}|_H^2,$$

which assures conditions (A5) and (A6) in Theorems III and IV from [11], respectively, and as a result local and global existence of solutions to (2.5)-(2.6)). Thus, applying to (2.5)-(2.6) the results from [11], we obtain existence of solutions to (2.5)-(2.6). Next we prove uniqueness. Let $\mathbf{v}_i = (u_i, N_{1,i}, N_{2,i}, N_{3,i})$ for $i = 1, 2$ be two solutions of the system. Then

$$\partial_t(\mathbf{v}_1 - \mathbf{v}_2) + \tilde{\mathbf{A}}(\mathbf{v}_1 - \mathbf{v}_2) + \tilde{\mathbf{B}}\mathbf{v}_1 - \tilde{\mathbf{B}}\mathbf{v}_2 = \mathbf{0}, \quad \tilde{\mathbf{A}}\mathbf{v} = \mathbf{A}\mathbf{v} + \mathbf{v}, \quad \tilde{\mathbf{B}}\mathbf{v} = \mathbf{B}\mathbf{v} - \mathbf{v}. \tag{2.9}$$

Multiplying both sides of (2.9) by $\delta\mathbf{v} = \mathbf{v}_1 - \mathbf{v}_2$ and integrating over Ω, we obtain

$$\frac{1}{2}\frac{d}{dt}\|\delta\mathbf{v}(t)\|_H^2 + \|\tilde{\mathbf{A}}^{1/2}\delta\mathbf{v}\|_H^2 \le \|\tilde{\mathbf{B}}\mathbf{v}_1 - \tilde{\mathbf{B}}\mathbf{v}_2\|_H \|\delta\mathbf{v}\|_H, \tag{2.10}$$

and

$$\begin{aligned} \|\tilde{\mathbf{B}}\mathbf{v}_1 - \tilde{\mathbf{B}}\mathbf{v}_2\|_H \le (d_2+2) \Big(& \|g(u_1)N_{2,1} - g(u_2)N_{2,2}\|_{L^2} \\ + & \|f(u_1)N_{1,1} - f(u_2)N_{1,2}\|_{L^2}\Big) + \|\delta\mathbf{v}\|_H. \end{aligned}$$

Note that

$$\begin{aligned}\|g(u_1)N_{2,1}-g(u_2)N_{2,2}\|_{L^2} &\le \|g(u_1)\,\delta N_2\|_{L^2}+\|(g(u_1)-g(u_2))N_{2,2}\|_{L^2}\\ &\le g^*\|\delta N_2\|_{L^2}+L_g\|\delta u\|_{H^1}\|N_{2,2}\|_{H^1}. \qquad (2.11)\end{aligned}$$

Analogously, we obtain

$$\|f(u_1)N_{1,1}-f(u_2)N_{1,2}\|_{L^2}\le f^*\|\delta N_1\|_{L^2}+L_f\|\delta u\|_{H^1}\|N_{1,2}\|_{H^1}. \qquad (2.12)$$

Hence, since $\|\tilde{\mathbf{A}}^{1/2}\delta\mathbf{v}\|_H$ is equivalent to the H^1-norm of $\mathbf{v}$, from (2.10), (2.11) and (2.12) it follows that there exists a constant C such that

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|\delta\mathbf{v}\|_H^2 &+ \|\tilde{\mathbf{A}}^{1/2}\delta\mathbf{v}\|_H^2\\ &\le (d_2+2)\Big(g^*\|\delta N_2\|_{L^2}+L_g\|\delta u\|_{H^1}\|N_{2,2}\|_{H^1}\\ &\quad +f^*\|\delta N_1\|_{L^2}+L_f\|\delta u\|_{H^1}\|N_{1,2}\|_{H^1}\Big)\|\delta\mathbf{v}\|_H+\|\delta\mathbf{v}\|_H^2\\ &\le (d_2+2)(g^*+f^*+1)\|\delta\mathbf{v}\|_H^2\\ &\quad +(d_2+2)\left(L_g\|N_{2,2}\|_{H^1}+L_fN_{1,2}\|_{H^1}\right)\|\delta\mathbf{v}\|_{H^1}\|\delta\mathbf{v}\|_H\\ &\le (d_2+2)\left((g^*+f^*+1)+C\left(L_g\|N_{2,2}\|_{H^1}+L_f\|N_{1,2}\|_{H^1}\right)^2\right)\|\delta\mathbf{v}\|_H^2\\ &\quad +\frac{1}{2}\|\tilde{\mathbf{A}}^{1/2}\delta\mathbf{v}\|_H^2.\end{aligned}$$

Hence

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|\delta\mathbf{v}\|_H^2 &+ \frac{1}{2}\|\tilde{\mathbf{A}}^{1/2}\delta\mathbf{v}\|_H^2\\ &\le (d_2+2)\Big((g^*+f^*+1)+C\left(L_g\|N_{2,2}\|_{H^1}+L_f\|N_{1,2}\|_{H^1}\right)^2\Big)\|\delta\mathbf{v}\|_H^2\\ &=: C_2(t)\,\|\delta\mathbf{v}\|_H^2. \qquad (2.13)\end{aligned}$$

Integrating (2.13) over $[0,T]$, noting the fact that $\varphi(\mathbf{v}_2)\in L^1(0,T)$ implies

$C_2 \in L^1(0,T)$ and using the Gronwall inequality, we obtain

$$\|\delta \mathbf{v}(t)\|_H^2 \le e^{\int_0^t 2C_2(\sigma)\, d\sigma} \|\delta \mathbf{v}(0)\|_H^2. \tag{2.14}$$

Since $\mathbf{v}_1$ and $\mathbf{v}_2$ are the solutions of (2.5)-(2.6) with the same initial conditions, estimate (2.14) leads to uniqueness of solutions to (2.5)-(2.6). Thus the well-posedness is proved. □

Our next step is to prove non-negativity of our spatial evolution mitochondria model, which is an important necessary biological property.

Proposition 3. *Let $u_0(x) \ge 0,\ N_{i,0}(x) \ge 0,\ i = 1,2,3$. Then any solution of (2.5)-(2.6) satisfies*

$$u(x,t) \ge 0,\ N_i(x,t) \ge 0 \quad \textit{for any } t \ge 0,\ \textit{a.e. } x \in \Omega,\ i = 1,2,3.$$

Proof. Consider first

$$\partial_t N_1 - d_1 \Delta N_1 = -f(u) N_1$$

and multiply it by $N_1^-(x,t) := \max(-N_1, 0)$ and integrate over domain Ω. Then we obtain

$$-\frac{1}{2}\frac{d}{dt}\|N_1^-(t)\|_{L^2}^2 - d_3 \|\nabla N_1^-(t)\|_{L^2}^2 = \int_\Omega f(u)|N_1^-(x,t)|^2 dx.$$

Hence

$$\frac{d}{dt}\|N_1^-(t)\|_{L^2}^2 + d_3 \|\nabla N_1^-(t)\|_{L^2}^2 = -\int_\Omega f(u)|N_1^-(x,t)|^2 dx \le 0.$$

Integrating the last inequality over $[0,t]$, $t > 0$, we have

$$\|N_1^-(t)\|_{L^2}^2 \le \|N_1^-(0)\|_{L^2}^2 = 0 \implies N_1^-(x,t) \equiv 0 \text{ a.e. } x \in \Omega.$$

To prove the same property for N_2 we act in the same way, namely we multiply

$$\partial_t N_2 + d_4 \Delta N_2 = f(u) N_1(t,x) - g(u) N_2(t,x).$$

by $N_2^-(t,x)$ and integrate over Ω to obtain

$$-\frac{1}{2}\frac{d}{dt}\|N_2^-(t)\|_{L^2}^2 - d_4\|\nabla N_2^-(t)\|_{L^2}^2 = \underbrace{\int_\Omega f(u) N_1 N_2^- dx}_{\geq 0} + \int_\Omega g(u)|N_2^-(x,t)|^2 dx,$$

so that

$$\frac{1}{2}\frac{d}{dt}\|N_2^-(t)\|_{L^2}^2 + d_4\|\nabla N_2^-(t)\|_{L^2}^2 \leq -\int_\Omega g(u)|N_2^-(x,t)|^2 dx \leq 0. \tag{2.15}$$

Integrating (2.15) over $[0,t]$ and using the Gronwall inequality, we have $N_2^-(x,t) = 0$, $\forall t > 0$ and a.e. $x \in \Omega$. Hence, $N_2(x,t) \geq 0$ for any $t > 0$ and a.e. $x \in \Omega$. For $N_3(x,t)$ we act in the same way. For completeness we will present a proof for $N_3(x,t) \geq 0$ as well as $u(x,t) \geq 0$. Indeed, let $N_3(x,t)$ be a solution of

$$\partial_t N_3 - d_5 \Delta N_3 = g(u) N_2(x,t). \tag{2.16}$$

Multiplying (2.16) by $N_3^-(t,x)$ and integrating over Ω, we get

$$-\frac{1}{2}\frac{d}{dt}\|N_3^-(t)\|_{L^2}^2 - d_5\|\nabla N_3^-(t)\|_{L^2}^2 = \int_\Omega g(u) N_2 N_3^- dx. \tag{2.17}$$

Since $N_2(x,t) \geq 0$, then from (2.17) it follows that

$$\frac{d}{dt}\|N_3^-(t)\|_{L^2}^2 + 2d_5\|\nabla N_3^-(t)\|_{L^2}^2 = -2\int_\Omega g(u) N_2 N_3^- dx \leq 0. \tag{2.18}$$

Integrating (2.18) over $[0,t]$ for any $t > 0$, we obtain

$$\|N_3^-(t)\|_{L^2}^2 \leq \|N_3^-(0)\|_{L^2}^2.$$

Hence $N_3^-(x,t) \equiv 0$ and as a result, $N_3(x,t) \geq 0$ for any $t > 0$ and a.e. $x \in \Omega$.

Analogously multiplying

$$\partial_t u - d_1 \Delta u = d_2 g(u) N_2$$

by $u^-(x,t)$ and integrating over Ω and taking into account that $N_2(x,t) \geq 0$ for a.e. $x \in \Omega$ and $t > 0$, we obtain

$$-\frac{1}{2}\frac{d}{dt}\|u^-(t)\|_{L^2}^2 - d_1\|\nabla u^-(t)\|_{L^2}^2 = d_2 \underbrace{\int_\Omega g(u)N_2(x,t)u^- \, dx}_{\geq 0}. \tag{2.19}$$

Consequently integrating (2.19) over $[0,t]$, we have

$$\|u^-(t)\|_{L^2} \leq \|u^-(0)\|_{L^2}$$

which leads to $u(x,t) \geq 0$ for all $t > 0$ and a.e. $x \in \Omega$. □

3 Asymptotic behaviour of solutions

Having established well-posedness of (2.5)-(2.6), our next task is to study the asymptotic behaviour of solutions as time goes to infinity. First we study the asymptotics of subpopulations $N_i(x,t)$. Recall that they satisfy

$$\begin{cases} \partial_t N_1 = d_3 \Delta N_1 - f(u) N_1, \\ \partial_t N_2 = d_4 \Delta N_2 + f(u) N_1 - g(u) N_2, \\ \partial_t N_3 = d_5 \Delta N_2 + g(u) N_2 \end{cases} \tag{3.1}$$

with $\frac{\partial N_i}{\partial n}|_{\partial\Omega} = 0$ and $N_i(x,0) = N_{i,0}(x)$. Integrating (3.1) over Ω, we obtain

$$\begin{cases} \dfrac{d}{dt}\displaystyle\int_\Omega N_1(x,t)\,dx = -\int_\Omega f(u)N_1(x,t)\,dx, \\ \dfrac{d}{dt}\displaystyle\int_\Omega N_2(x,t)\,dx = \int_\Omega f(u)N_1(x,t)\,dx - \int_\Omega g(u)N_2(x,t)\,dx, \\ \dfrac{d}{dt}\displaystyle\int_\Omega N_3(x,t)\,dx = \int_\Omega g(u)N_2(x,t)\,dx. \end{cases} \tag{3.2}$$

Let $\alpha_i(t) := \int_\Omega N_i(x,t)\,dx$. Obviously $\alpha_i(t) \geq 0$ for all $t > 0$. We define $\alpha(t) := \alpha_1(t) + \alpha_2(t) + \alpha_3(t)$. Then by (3.2), we get

$$\frac{d}{dt}\alpha(t) = 0.$$

Thus, $\alpha(t) \equiv \alpha(0) = \int_\Omega [N_{1,0}(x) + N_{2,0}(x) + N_{3,0}(x)]\, dx$, $\forall t \geq 0$.

From the first equation of (3.2) we obtain $\alpha_1(t)$ is non-increasing in t and $\alpha_1(t)$ is bounded below by 0. This yields the convergence

$$\alpha_1(t) \overset{t\to\infty}{\longrightarrow} \alpha_1^\infty \geq 0.$$

From the last equation of (3.2) we obtain $\alpha_3(t)$ is non-decreasing in t and bounded above by $\alpha(0)$. Hence

$$\alpha_3(t) \overset{t\to\infty}{\longrightarrow} \alpha_3^\infty \geq 0.$$

Since $\alpha_2(t) = \alpha(0) - \alpha_1(t) - \alpha_3(t)$, we obtain $\alpha_2(t)$ convergence to $\alpha_2^\infty = \alpha(0) - \alpha_1^\infty - \alpha_3^\infty$. Integrating (3.2) over $[0,\infty)$ with respect to t, we obtain

$$\begin{cases} \displaystyle\int_0^\infty \left(\int_\Omega f(u) N_1(x,t)\, dx \right) dt \leq C_0, \\ \displaystyle\int_0^\infty \left(\int_\Omega g(u) N_2(x,t)\, dx \right) dt \leq C_0, \end{cases} \tag{3.3}$$

where C_0 is some positive constant.

Multiplying the first equation of (3.1) by $N_1(x,t)$ and integrating over Ω, we get

$$\frac{1}{2}\frac{d}{dt}\|N_1(t)\|^2_{L^2(\Omega)} + d_3\|\nabla_x N_1(t)\|^2_{L^2(\Omega)} = -\int_\Omega f(u)|N_1(x,t)|^2\, dx \leq 0.$$

Integrating this inequality over t, we conclude that

$$\sup_{t>0}\|N_1(t)\|_{L^2(\Omega)} \leq \|N_{1,0}\|_{L^2(\Omega)},$$

as well as

$$\int_0^\infty \int_\Omega f(u(x,t)) N_1^2(x,t)\, dxdt \leq C_* \quad \text{and} \quad \int_0^\infty \int_\Omega |\nabla N_1(x,t)|^2\, dxdt \leq C_*,$$

where C_* is some positive constant. Consequently, due to Condition 1 we obtain

$$\int_0^\infty \int_\Omega |f(u(x,t))N_1(x,t)|^2\, dxdt \le f^*\, C_*. \tag{3.4}$$

Based on estimates (3.4), we shall study the asymptotic behaviour of subpopulations $N_i(x,t),\ i = 1, 2, 3$ first. We start with $N_1(x,t)$. To this end, we decompose

$$\begin{aligned} N_1(x,t) &= n_1(t) + N_1^\perp(x,t), \text{ where } N_1(x,t) \in H^\perp; \\ H^\perp &:= \left\{ w \in L^2(\Omega) \mid \int_\Omega w(x)dx = 0 \right\}. \end{aligned}$$

Then for any $t > 0$

$$\int_\Omega N_1(x,t)\, x = \int_\Omega n_1(t)\, dx = n_1(t)\, |\Omega|,$$

where $|\Omega|$ is denotes by the volume of bounded domain $\Omega \subset \mathbb{R}^n$.

Hence, $n_1(t) = \frac{1}{|\Omega|}\alpha_1(t)$. Therefore as $t \to \infty$, we have

$$n_1(t) \overset{t\to\infty}{\longrightarrow} n_1^\infty := \frac{1}{|\Omega|}\alpha_1^\infty. \tag{3.5}$$

Next we study asymptotics as $t \to \infty$ of $N_1^\perp(x,t)$. To this end, we multiply first equation of (3.1) by $-\Delta N_1$ and integrate over Ω. Then we get

$$\begin{aligned} \frac{1}{2}\frac{d}{dt}\|\nabla N_1(t)\|_{L^2}^2 + d_3\|\Delta N_1(t)\|_{L^2}^2 &\le \|f(u)N_1\|_{L^2} \cdot \|\Delta N_1\|_{L^2} \\ &\le \frac{d_3}{2}\|\Delta N_1(t)\|_{L^2}^2 + \frac{1}{2d_3}\|f(u)N_1\|_{L^2}^2. \end{aligned} \tag{3.6}$$

Therefore we have

$$\frac{1}{2}\frac{d}{dt}\|\nabla N_1(t)\|_{L^2}^2 + \frac{d_3}{2}\|\Delta N_1(t)\|_{L^2}^2 \le \frac{1}{2d_3}\|f(u)N_1\|_{L^2}^2.$$

By Wirtinger's inequality, we have

$$\|\nabla N_1(t)\|_{L^2} = \|\nabla N_1^{\perp}(t)\|_{L^2} \leq C_W \|\Delta N_1^{\perp}(t)\|_{L^2} = C_W \|\Delta N_1(t)\|_{L^2}. \tag{3.7}$$

Then from (3.6) and (3.7), we get

$$\frac{d}{dt}\|\nabla N_1(t)\|_{L^2}^2 + \frac{d_3}{C_W}\|\nabla N_1(t)\|_{L^2}^2 \leq \frac{1}{d_3}\|f(u)N_1(t)\|_{L^2}^2.$$

Since (3.4) implies $\|f(u)N_1(t)\|_{L^2}^2 \in L^1(0,\infty)$, we conclude with Proposition 4 in [6] that

$$\|\nabla N_1^{\perp}(t)\|_{L^2} = \|\nabla N_1(t)\|_{L^2} \to 0 \text{ as } t \to \infty. \tag{3.8}$$

Thus, by (3.5) and (3.8) we get

$$N_1(x,t) \to n_1^{\infty} \quad \text{as} \quad t \to \infty$$

strongly in $H^1(\Omega)$.

Next we study the asymptotics of $N_2(x,t)$. To this end, we decompose

$$N_2(x,t) = \; n_2(t) + N_2^{\perp}(x,t),$$

where $N_2^{\perp}(x,t) \in H^{\perp}$. In the same manner as we did for $N_1(x,t)$, we obtain

$$n_2(t) = \frac{1}{|\Omega|}\alpha_2(t), \quad \alpha_2(t) := \int_{\Omega} N_2(x,t)\,dx$$

as well as

$$n_2(t) \to n_2^{\infty} := \frac{1}{|\Omega|}\alpha_2^{\infty} \quad \text{as} \quad t \to \infty. \tag{3.9}$$

To study the asymptotics of $N_2(x,t)$ as $t \to \infty$, it remains to study $N_2^{\perp}(x,t)$ as $t \to \infty$. For this purpose, we multiply the second equation of (3.1) by $N_2^{\perp}(x,t)$ and integrate over Ω. This yields

$$\frac{1}{2}\frac{d}{dt}\|N_2^{\perp}(t)\|_{L^2}^2 + d_4\|\nabla N_2^{\perp}(t)\|_{L^2}^2$$

$$\leq \quad \varepsilon\|N_2^{\perp}(t)\|_{L^2}^2 + \frac{1}{4\varepsilon}\|f(u)N_1\|_{L^2}^2 - \int_\Omega g(u)N_2(x,t)(N_2(x,t) - n_2(t))\,dx. \tag{3.10}$$

From (3.10) it follows that

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|N_2^{\perp}(t)\|_{L^2}^2 &+ \frac{d_4}{2}\|\nabla N_2^{\perp}(t)\|_{L^2}^2 + \left(\frac{d_4}{2C_W^2} - \varepsilon\right)\|N_2^{\perp}(t)\|_{L^2}^2 + \int_\Omega g(u)N_2^2(x,t)\,dx \\ &\leq \int_\Omega g(u)n_2(t)N_2(x,t)\,dx + \frac{1}{4\varepsilon}\|f(u)N_1\|_{L^2}^2. \end{aligned} \tag{3.11}$$

By virtue of (3.9), we get

$$\sup_{t>0}\|n_2(t)\|_{L^\infty} \leq C_0.$$

Then by (3.3), we obtain

$$\int_0^\infty \int_\Omega g(u)n_2(t)N_2(t,x)dxdt \leq \int_0^\infty \|n_2(t)\|_{L^\infty} \cdot \|g(u)N_2(t)\|_{L^1}\ dt \leq \tilde{C}_0,$$

where $\tilde{C}_0$ is a general constant independent of t. By virtue of Proposition 4 in [6] based on the last inequality and (3.4), we obtain

$$\|N_2^{\perp}(t)\|_{L^2} \to 0 \quad \text{as} \quad t \to \infty. \tag{3.12}$$

Furthermore, integrating (3.11) over $[0, \infty)$, we have

$$\int_0^\infty \int_\Omega g(u)N_2^2(x,t)\,dxdt \leq \tilde{C}_0, \quad \text{hence} \quad \int_0^\infty \|g(u)N_2(t)\|_{L^2}^2\ dt \leq \tilde{C}_0. \tag{3.13}$$

Our next step is to obtain convergence of $N_2(x,t)$ as $t \to +\infty$ strongly in $H^1(\Omega)$. To this end, we multiply the second equation of (3.1) by $-\Delta N_2$. Then we get

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|\nabla N_2(t)\|_{L^2}^2 \quad &+ \quad d_4\|\Delta N_2(t)\|_{L^2}^2 \\ &\leq \quad \frac{d_4}{2}\|\Delta N_2(t)\|_{L^2}^2 + \frac{1}{2d_4}\left(\|f(u)N_1(t)\|_{L^2}^2 + \|g(u)N_2(t)\|_{L^2}^2\right). \end{aligned}$$

Hence by Wirtinger's inequality (see [6]) and taking into account $\nabla_x N_2(x,t) = \nabla_x N_2^{\perp}(x,t)$ we have

$$\begin{aligned}\frac{d}{dt}\|\nabla N_2(t)\|_{L^2}^2 &+ \frac{d_4}{2C_W^2}\|\nabla N_2(t)\|_{L^2}^2 + \frac{d_4}{2}\|\Delta N_2(t)\|_{L^2}^2 \\ &\leq \frac{2}{d_4}\left(\|f(u)N_1(t)\|_{L^2}^2 + \|g(u)N_2(t)\|_{L^2}^2\right).\end{aligned}$$

Therefore in view of (3.4) and (3.13), we deduce from Proposition 4 in [6] that

$$\|\nabla N_2(t)\|_{L^2}^2 = \|\nabla N_2^{\perp}(t)\|_{L^2}^2 \to 0 \text{ as } t \to \infty \tag{3.14}$$

as well as

$$\int_0^{\infty} \|\Delta N_2(t)\|_{L^2}^2 dt \leq \tilde{C}_0.$$

Thus, (3.9), (3.12) and (3.14) imply that

$$N_2(x,t) \to n_2^{\infty} \quad \text{as} \quad t \to \infty \quad \text{strongly in } H^1(\Omega).$$

In the same manner, we can study asymptotic behavior of $N_3(x,t)$ as $t \to +\infty$. Indeed, let

$$N_3(x,t) = \ n_3(t) + N_3^{\perp}(x,t)$$

where $N_3^{\perp}(x,t) \in H^{\perp}$. Then one can easily see that

$$n_3(t) \to n_3^{\infty} := \frac{1}{|\Omega|}\alpha_3^{\infty} \quad \text{as} \quad t \to +\infty.$$

Multiplying the last equation of (3.1) by $-\Delta N_3$, we get

$$\frac{d}{dt}\|N_3(t)\|_{L^2}^2 + \frac{d_5}{2C_W^2}\|\nabla N_3(t)\|_{L^2}^2 + \frac{d_5}{2}\|\Delta N_3(t)\|_{L^2}^2 \leq \frac{1}{d_5}\|g(u)N_2(t)\|_{L^2}^2.$$

Using exactly the same arguments as we did for $N_1(x,t)$ and $N_2(x,t)$, we obtain

$$N_3(x,t) \to n_3^{\infty} \quad \text{strongly in } H^1(\Omega) \quad \text{as } t \to \infty$$

and

$$\int_0^\infty \|\Delta N_3(t)\|_{L^2}^2 dt \leq \tilde{C}_0.$$

It remains to obtain asymptotic behaviour of calcium evolution $u(x,t)$.

Neumann BC case: We begin with the Neumann BC case, i.e., u satisfies

$$\begin{cases} \partial_t u = d_1 \Delta u + d_2 g(u) N_2(x,t), \ x \in \Omega, \ t > 0, \\ \left.\dfrac{\partial u}{\partial n}\right|_{\partial\Omega} = 0, \ u|_{t=0} = u_0(x). \end{cases} \tag{3.15}$$

Integrating (3.15) over Ω, we get

$$\frac{\partial}{\partial t}\int_\Omega u(x,t)\,dx = d_2 \int_\Omega g(u) N_2(x,t)\,dx.$$

Hence, by (3.2), we obtain

$$\begin{aligned} \int_\Omega u(x,t)\,dx &= \int_\Omega u_0(x)\,dx + d_2 \int_0^t \left(\int_\Omega g(u) N_2(x,t)\,dx \right) dt \\ &= \int_\Omega u_0(x)\,dx + d_2(\alpha_3(t) - \alpha_3(0)). \end{aligned}$$

Let

$$u(x,t) = a(t) + \varphi^\perp(x,t),$$

where $\varphi^\perp \in H^\perp$. Then since $\alpha_3(t) \to \alpha_3^\infty$ as $t \to \infty$, we easily find that

$$a(t) := \int_\Omega u(x,t)\,dx \to \tilde{a}_\infty := \int_\Omega u_0(x)\,dx + d_2(\alpha_3^\infty - \alpha_3(0)) \quad \text{as} \quad t \to \infty. \tag{3.16}$$

Multiplying (3.15) by $-\Delta u$, we have

$$\frac{1}{2}\frac{d}{dt}\|\nabla u(t)\|_{L^2}^2 + d_1\|\Delta u(t)\|_{L^2}^2 \leq \frac{d_1}{2}\|\Delta u(t)\|_{L^2}^2 + \frac{d_2^2}{2d_1}\|g(u)N_2(t)\|_{L^2}^2.$$

Hence by Wirtinger's inequality we get

$$\frac{d}{dt}\|\nabla u(t)\|_{L^2}^2 + \frac{d_1}{4}\|\Delta u(t)\|_{L^2}^2 + \frac{d_1}{4C_W^2}\|\nabla u(t)\|_{L^2}^2 \leq \frac{d_2^2}{d_1}\|g(u)N_2(t)\|_{L^2}^2.$$

Taking into account that $\|g(u)N_2(t)\|_{L^2}^2 \in L^1(0,\infty)$ and using Proposition 4 in [6], we obtain

$$\|\nabla u(t)\|_{L^2} = \|\nabla \varphi^{\perp}(t)\|_{L^2} \to 0 \quad \text{as} \quad t \to \infty. \tag{3.17}$$

Thus, in view of (3.16) and (3.17), we conclude that

$$u(x,t) \to \tilde{a}^{\infty} \quad \text{strongly in } H^1(\Omega) \quad \text{as} \quad t \to \infty.$$

Uniform convergence. Furthermore, since we already obtained a priori bound for $\|\nabla N_2(t)\|_{L^2}$ (see (3.14)), following the arguments in the proof of Theorem 7 in [7], we can derive the boundedness of

$$\sup_{t\geq\delta} \|\Delta\varphi^{\perp}(t)\|_{L^2} = \sup_{t\geq\delta} \|\Delta u(t)\|_{L^2} \leq C_\delta,$$

where C_δ is a constant depending on $\delta > 0$. Thus, by the Sobolev embedding theorem and the standard interpolation inequality, see [15], we find that there exist $\alpha, \theta \in (0,1)$ and C_θ such that

$$\begin{aligned} \|u(t) - \tilde{a}^{\infty}\|_{C^\alpha(\Omega)} &\leq C_\theta \|\Delta(u(t) - \tilde{a}^{\infty})\|_{L^2}^{1-\theta} \|\nabla(u(t) - \tilde{a}^{\infty})\|_{L^2}^{\theta} \\ &\leq C_\theta \|\Delta\varphi^{\perp}(t)\|_{L^2}^{1-\theta} \|\nabla\varphi^{\perp}(t)\|_{L^2}^{\theta}. \end{aligned}$$

Hence from the boundedness of $\Delta\varphi^{\perp}(t)$, it follows that

$$\|u(t) - \tilde{a}^{\infty}\|_{C^\alpha(\Omega)} \leq \tilde{C}_\delta^{1-\theta} C_\theta \|\nabla\varphi^{\perp}\|_{L^2(\Omega)}^{\theta} \quad \forall t \geq \delta,$$

whence follows

$$\|u(t) - \tilde{a}^{\infty}\|_{C^\alpha(\Omega)} \to 0 \quad \text{as} \quad t \to \infty. \tag{3.18}$$

Robin BC case: Multiplying (3.15) with Robin BC by $-\Delta u = \partial\varphi_a(u)$, we have

$$\frac{d}{dt}\varphi_a(u(t)) + d_1\|\Delta u(t)\|_{L^2}^2 \leq \frac{d_1}{2}\|\Delta u(t)\|_{L^2}^2 + \frac{d_2^2}{2d_1}\|g(u)\,N_2\|_{L^2}^2. \tag{3.19}$$

Hence, from Proposition 4 of [7], we derive

$$u(x,t) \to 0 \quad \text{strongly in} \quad H^1(\Omega) \quad \text{as} \quad t \to \infty.$$

Thus, as before we conclude that

$$\|u(t)\|_{C^\alpha(\Omega)} \to 0 \quad \text{as} \quad t \to \infty. \tag{3.23}$$

Remark 4. *Due to the presence of the Laplacian in the equations of subpopulations $N_i(t,x)$, we could obtain (3.18) without any structural assumptions on f, g such as required in [6] (PDE-ODE coupling).*

Remark 5. *As it was shown in Proposition 3 of [6] and Proposition 2 of [5], for Neumann BC and Robin BC with $\alpha > 0$, one can show that there exists $t_0 > 0$ and $\rho > 0$ such that*

$$u(x,t) \geq \rho \text{ for all } t \geq t_0, \text{ a.e. } x \in \Omega.$$

Assume that $\min_{s \geq \rho} g(s) = g_\rho > 0$. Then multiplying the second equation of (3.1) by $N_2(t,x)$, we get

$$\frac{1}{2}\frac{d}{dt}\|N_2(t)\|_{L^2}^2 + d_4\|\nabla N_2(t)\|_{L^2}^2 + \int_\Omega g(u)(N_2(x,t))^2 dx \leq \int_\Omega f(u) N_1 N_2 dx. \tag{3.24}$$

It follows from (3.24) that

$$\frac{1}{2}\frac{d}{dt}\|N_2(t)\|_{L^2}^2 + g_\rho\|N_2(t)\|_{L^2}^2 \leq \frac{g_\rho}{2}\|N_2(t)\|_{L^2}^2 + \frac{1}{2g_\rho}\|f(u)N_1\|_{L^2}^2.$$

Since $\|f(u)N_1(t)\|_{L^2} \in L^1(0,\infty)$, then by Proposition 4 in [6], we obtain

$$\|N_2(t)\|_{L^2(\Omega)} \to 0 \text{ as } t \to \infty$$

and consequently $n_2^\infty = 0$.

Remark 6. *As for the case for Dirichlet BC and Robin BC with $\alpha = 0$, under suitable condition on g, one can show that $n_2^\infty \neq 0$ (see Theorem 4.4 of [4] and Theorem 5.2 of [5]).*

Remark 7. *Analogously to the PDE-ODE case (cf. [4, 5, 6], one can classify the asymptotic behavior of solution into two categories, i.e., partial swelling and complete swelling in terms of relation between $\alpha, C^-, \tilde{a}^\infty$:*

(N) *Neumann BC case:*

- *(i) If $0 \leq \tilde{a}^\infty < C^-$, then partial swelling occurs, i.e., there exists $T_p \in (0, \infty)$ such that $\alpha_1(t) \equiv \alpha_1(T_p) > 0$ for all $t \geq T_p$.*
- *(ii) If $C^- < \tilde{a}^\infty$, then complete swelling occurs, i.e., $\alpha_1^\infty = 0$.*

(R) *Robin BC case:*

- *(i) If $0 \leq \alpha < C^-$, then partial swelling occurs.*
- *(ii) If $C^- < \alpha$, then complete swelling occurs.*

(D) *Dirichlet BC case: The partial swelling always occurs.*

4 Numerical illustrations

We illustrate the previous results on longtime behaviour with numerical simulations in 1D (for easier visualisation), over the interval $x \in (0, 1)$. For this, we have to specify appropriate functions $f(u)$ and $g(u)$. Following [4, 5, 6, 7] we choose

$$f(u) = \begin{cases} 0, & 0 \leq u \leq C^-, \\ \frac{f^*}{2}\left(1 - \cos \frac{(u - C^-)\pi}{C^+ - C^-}\right), & C^- \leq u \leq C^+, \\ f^*, & u > C^+, \end{cases}$$

and

$$g(u) = \begin{cases} \frac{g^*}{2}\left(1 - \cos\frac{u\pi}{C^+}\right), & 0 \le u \le C^+, \\ g^*, & u > C^+. \end{cases}$$

The model parameters used are summarized in *Table 1*. They have been taken from our previous studies [4, 5, 6, 7] and chosen primarily to support, demonstrate, and emphasize the mathematical results, not for quantitative prediction. We assume here that the diffusion coefficients are the same for all three classes of mitochondria, and that motility of mitochondria is smaller than diffusion of calcium ions.

The initial data for the calcium ion concentration are chosen such that at $x = 0$ the concentration is higher than C^+ and at $x = 1$ it is lower than C^-, connected by a cosine wave.

$$u(x,0) = \hat{C} \cdot (1 + cos(x\pi)), \quad x \in (0,1),\ \hat{C} = 250$$

and

$$N_1(x,0) = 1, \quad N_2(x,0) = 0, \quad N_3(x,0) = 0, \quad x \in \Omega,$$

i.e. we assume that initially swelling has not yet been initiated.

All our simulations show non-negativity of u, N_1, N_2, N_3 and that the solution converges to a spatially homogeneous steady state as $t \to \infty$. More specifically we find $N_1 \to 0$ $N_2 \to 0$, $N_3 \to 1$. With our assumption that the the mitochondrial fractions have the same diffusion coefficients, we obtain from the model equations that $N := N_1 + N_2 + N_3$ satisfies the heat equation

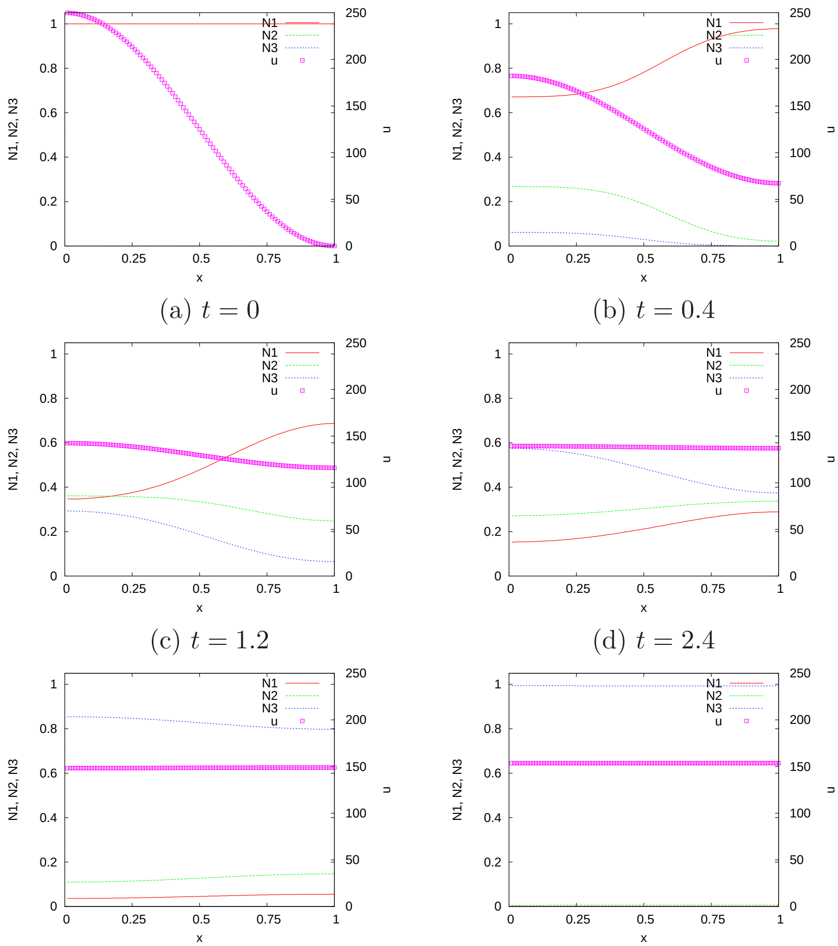
$$\partial_t N = d_m \Delta N.$$

Table 1: Default parameter values, cf also [4, 6, 7, 5]

parameter	symbol	value	remark
lower (initiation) swelling threshold	C^{-}	20	
upper (maximum) swelling threshold	C^{+}	200	
maximum transition rate for $N_1 \to N_2$	f^*	1	
maximim transition rate for $N_2 \to N_3$	g^*	1	
feedback parameter	d	30	
diffusion coefficient of calcium ions	d_1	0.2	
diffusion coefficient of mitochondria	$d_m = d_{2,3,4}$	(varied)	

Which, under our initial and boundary conditions, has the solution $N(x,t) \equiv 1$. Our numerical simulations satisfy this with at least 6 digits (data not shown).

In Figure 1 we visualise the results of a typical simulation, where we choose for the diffusion coefficients of the mitochondria $d_m = d_{2,3,4} = 0.02 < d_1$. The evolution of the calcium ion concentration is initially dominated by diffusion, leading to an obliteration of the spatial gradients that were introduced by the initial conditions. At about $t = 2.4$ it appears stratified, from where on the evolution is dominated by slight growth until steady state is reached. The calcium ion concentration gradients in the initial data lead immediately to gradients in the mitochondria distribution. The mitochondria fraction N_1 starts immediately declining, whereas N_2 and N_3 immediately increase. The rates that determine the swelling process depend on the calcium ion concentration which introduces gradients in the mitochondrial fractions. In the initial phase, where u is highest, N_1 is lowest and N_2 and N_3 are highest. The calcium ion concentration stratifies quickly, which induces also stratification of the mitochondrial populations, however, at a slower pace. Noteworthy is that between $t = 1.2$ and

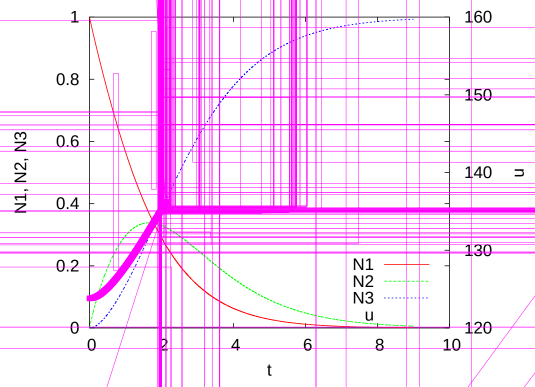


(a) $t = 0$ (b) $t = 0.4$

(c) $t = 1.2$ (d) $t = 2.4$

(e) $t = 4.4$ (f) $t = 9.0$

Figure 1: Snapshot of model simulation at different time instances. Shown are the spatial profiles of the calcium ion concentration u (symbols), and of the mitochondrial fractions N_1, N_2, N_3 (solid lines).



N1, N2, N3
u
t
N1
N2
N3
u

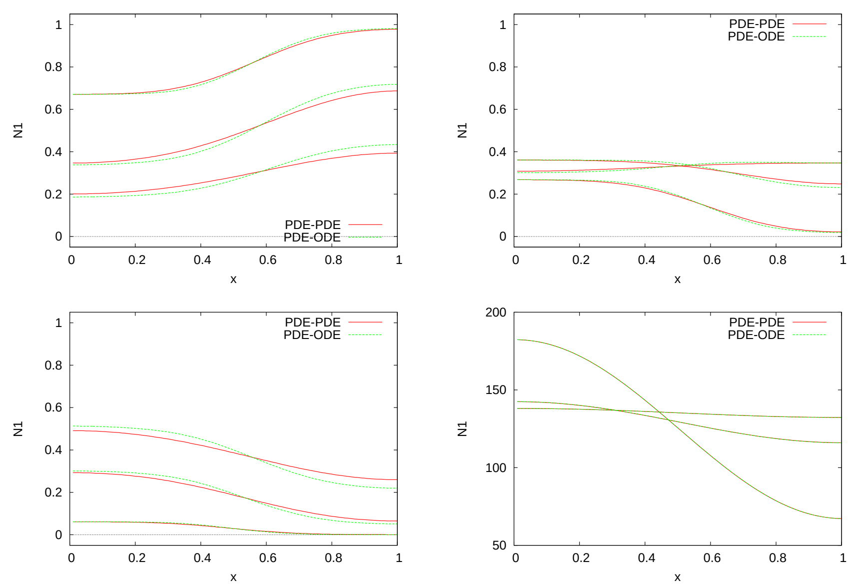


Figure 3: Comparison of the solutions of the PDE-PDE model with diffusion of mitochondria with the results of the PDE-ODE model without mitochondrial movement. Plotted are the spatial profiles at times $t = 0.4, 1.2, 2.0$.

gate the effect that this has we repeat the above simulation with $d_m = d_{3,4,5} = 0$, i.e. the case of the PDE-ODE coupled system of [4, 6, 7, 5]. In Figure 3 we show for selected time instances the solutions of the model with mitochondria diffusion *vis-a-vis* the corresponding solutions of the model without. The differences between both solutions are only minor. In the mitochondrial fractions, the differences in N_1 and N_3 are largest. In these cases the mitochondria gradients are slightly higher in the case of the PDE-ODE model than in the case of the PDE-PDE model, as a consequence of Fickian diffusion obliterating gradients. In the case of the calcium ion concentrations the differences are close to plotting accuracy. This suggests that (for the parameters tested here), the spatial gradients in the mitochondrial populations do not affect the spatial calcium ion distribution. In Figure 3, the solutions of the PDE-ODE model are (slightly) larger in some places and (slightly) smaller in other places than the solutions of the PDE-PDE model. This suggests that the differences neutralize each other when the spatial averages of the dependent variables are taken. We verified this by comparing the average data as functions of time and found negligible differences between both models (data not shown).

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