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MATHEMATICAL ANALYSIS OF AN *IN VIVO* MODEL OF MITOCHONDRIAL SWELLING

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Abstract. We analyze the effect of Robin boundary conditions in a mathematical model for a mitochondria swelling in a living organism. This is a coupled PDE/ODE model for the dependent variables calcium ion contration and three fractions of mitochondria that are distinguished by their state of swelling activity. The model assumes that the boundary is a permeable 'membrane', through which calcium ions can both enter or leave the cell. Under biologically relevant assumptions on the data, we prove the well-posedness of solutions of the model and study the asymptotic behavior of its solutions. We augment the analysis of the model with computer simulations that illustrate the theoretically obtained results.

1. Introduction.

The main function of mitochondria is to produce ATP as source for chemical energy for many eukaryotic cells. However, these double-membrane enclosed organelles also play an important role in cell death by their ability to trigger apoptosis. One of the key factors in this process is the permeabilization of the inner mitochondrial membrane, resulting in the swelling of the mitochondrial matrix.

Mitochondrial permeability transition is effectuated by the opening of a pore in the inner membrane, which happens under pathological conditions like high Ca^{2+} concentrations. The increased permeability leads to an osmotically driven influx of solutes and water into the mitochondrial matrix, which in turn causes swelling. This process culminates in the rupture of the outer membrane. Outer membrane rupture is a critical event, because apoptosis is irreversibly triggered by the release of several proapoptotic factors from the intermembrane space [8].

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Intact mitochondria store calcium in their matrix. If swelling is induced, this stored calcium is additionally released [8] and the remaining mitochondria are confronted with an even higher calcium load, leading to an acceleration of the process.

Swelling can be induced by Ca^{2+} and it can be measured on the basis of light scattering. While intact mitochondria show high light scattering values, the more mitochondria are swollen the less light is deflected. The volume increase is indirectly displayed by a decreasing optical density. This relation is shown to be linear [7], [10].

Although the process of mitochondrial swelling induced by calcium has been studied for more than 30 years, mathematical modeling has only started recently. At this point, there are two conceptually different approaches: microscale models focusing on a detailed description of all biochemical processes in single mitochondria, and macroscale models which aim to describe the swelling of a whole population of mitochondria [7].

Existing mitochondrial swelling models focus only on time evolution but do not account for spatial effects, working with spatially averaged values instead, cf. [7] and the references therein. However, experimental evidence suggests that spatial heterogeneity might not be negligible. The same amount of Ca^{2+} added in different concentrations can lead to different shapes of the corresponding swelling curves, which only can be traced back to the different calcium distributions. Obviously, this implies the influence of spatial effects.

The dependence on local processes becomes particularly important when we think of the mitochondrial swelling taking place *in vivo*. There are two mechanisms that lead to intracellular Ca^{2+} increase [11]: internal release from the endoplasmic reticulum and the external calcium influx from the extracellular milieu. Both calcium sources are highly localized.

The outline of the paper is as follows: In section 2 we state the governing equations and define the properties of the coefficient functions. In section 3 the well-posedness of the problem is shown. Section 4 contains auxiliary results that are needed in section 5, where we give some conditions under which the model predicts partial or complete swelling of mitochondria and estimates for the convergence rates to steady state. Section 6 contains some numerical simulations to illustrate the analytical results. Finally, section 7 contains some concluding remarks.

2. **The mitochondria model.** In this paper, we further develop the model that we introduced in [6] and that takes into account the above mentioned 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 large amount of swollen mitochondria the effect of positive feedback becomes relevant as the residual mitochondria are confronted with a higher calcium ion load. This results in a coupled ODE-PDE system, see (1)-(4) below. The extension *vis-a-vis* [6] is that we now permit Robin boundary conditions instead of the homogenaous Neumann conditions that were previously used, as suggested in [6] as future work. This generalises the model, making it applicable to a wider range of biological and physical scenarios, such as *in vivo* vs. *in vitro* systems, at the expense of requiring a substantial extension of the mathematical theory.

In accordance with theoretical [7] and experimental [14] 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. Furthermore we assume that mitochondria do not move in any direction and hence the spatial effects are only introduced by the calcium evolution. The evolution of the mitochondrial subpopulations is modeled by a system of ODEs, that depends on the space variable x in terms of a parameter.

We analyze 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 ODE-PDE system determined by the non-negative model functions f and g:

$$\begin{aligned} \partial_t u &= d_1 \Delta u + d_2 g(u) N_2 && (1)\\ \partial_t N_1 &= -f(u) N_1 && (2)\\ \partial_t N_2 &= f(u) N_1 - g(u) N_2 && (3)\\ \partial_t N_3 &= g(u) N_2 && (4) \end{aligned}$$

with diffusion constant $d_1 > 0$ and feedback parameter $d_2 > 0$.

As we are interested in the *in vivo* case, we assume the boundary to be the permeable "limit membrane". Here calcium ions can enter or leave the cell over this membrane. The concentration gradient between the cell and the extracellular regime needs always be maintained, hence we assume inhomogeneous Robin boundary conditions

$$-\partial_\nu u(x,t) = a(x)\,(u(x,t) - \beta\, C_{ext}) \quad \text{for } x \in \partial\Omega\,. \tag{5}$$

Here $C_{ext} \geq 0$ denotes the constant extracellular calcium ion concentration and $\beta > 0$ represents the concentration gradient.

For instance, with the constants reported in [11], we have $C_{in} = 100$ nM $= 10^{-7}$ M and $C_{ext} = 1$ mM $= 10^{-3}$ M, and hence the concentration gradient is of order 10^{-4} and we take $\beta = 10^{-4}$.

Remark 1. 1) In general the extracellular calcium concentration is not constant, however due to its largeness compared to the cell size, single calcium ion peaks are dissolved very fast.

2) By the choice of the function $a(x)$ we can distinguish between different parts of the membrane. The previously mentioned case $\partial\Omega = \Gamma_1 \cup \Gamma_2$ hence could be realized by setting $a(x) = 0$ for $x \in \Gamma_2$ representing the closed parts of the membrane. This leads to zero flux on Γ_2 and concentration-dependent flux on Γ_1, just as we described the situation for the original membrane.

3) By the choice of $a(\cdot)$ we can switch between Dirichlet and Neumann type boundary conditions. If $a(\cdot)$ is very small, the flux over the boundary is also very small and in the limit case $a(\cdot) \to 0$ we have homogeneous Neumann boundary conditions. On the other hand, for high values of $a(\cdot)$ the solution soon approaches $u = \beta\, C_{ext}$ on the boundary, i.e., we can expect a behavior similar to non-homogeneous Dirichlet boundary conditions.

The initial conditions are specified as

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

Note that by virtue of (2)-(4), the total mitochondrial population

$$\overline{N}(x,t) := N_1(x,t) + N_2(x,t) + N_3(x,t) \tag{6}$$

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

$$\overline{N}(x,t) = \overline{N}(x) := N_{1,0}(x) + N_{2,0}(x) + N_{3,0}(x) \quad \forall t \geq 0 \ \ \forall x \in \Omega. \tag{7}$$

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 on the inner membrane are forced to 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 [10], this process is calcium-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 and the number and the size of pores have upper bounds, 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 concentrations.

Remark 2. 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 some region, but after some time due to diffusion the concentration may drop below C^-. If this depletion occurs before all mitochondria engaged in swelling, we only have partial swelling and eventually there will 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 rate function $g(u)$. In contrast to the function f, there is no initiation threshold and the transition takes place wherever calcium ions are present, i.e. where $u > 0$. 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 as follows: in an earlier study [7], it was shown that it is essential to include a positive feedback mechanism when modelling the swelling process. This accelerating effect is induced by stored calcium ions inside the mitochondria, which are 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.

We now give precise mathematical assumptions on f and g.

Condition 2.1. 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:

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

(iii) Lipschitz continuity:

$$|f(s_1) - f(s_2)| \leq L_f |s_1 - s_2| \qquad \forall s_1, s_2 \in \mathbb{R},$$
$$|g(s_1) - g(s_2)| \leq L_g |s_1 - s_2| \qquad \forall s_1, s_2 \in \mathbb{R} \qquad \text{with } L_f,\, L_g \geq 0.$$

In order to derive the uniform convergence of solutions, we need to introduce additional structure conditions on f and g. To do this, we distinguish between two cases, the cases $\alpha = 0$ and $\alpha > 0$. For the case $\alpha = 0$, we assume conditions similar to those for Dirichlet BC case and for $\alpha > 0$, similar to those for Neumann BC case.

Condition 2.2. (The case $\alpha = 0$) Let f and g fulfill Condition 2.1. In addition we assume that there exist constants $C^- > 0$, $m_1 > 0$, $m_2 > 0$, $\delta_0 > 0$ and $\varrho_0 > 0$ such that the following assertions hold:

(i) Starting threshold:

$$f(s) = 0 \qquad \forall s \leq C^-,$$
$$g(s) = 0 \qquad \forall s \leq 0.$$

(ii) Smoothness of f and g near starting threshold $[C^-, C^- + \delta_0]$ and $[0, \rho_0]$:

$$|f'(s)| \leq m_f\, s \qquad \forall s \in [C^-, C^- + \delta_0],$$
$$|g'(s)| \leq m_g\, s \qquad \forall s \in [0, \rho_0].$$

(iii) Lower bounds:

$$f(s) \geq f(C^- + \delta_0) > 0 \qquad \forall s \geq C^- + \delta_0,$$
$$g(s) \geq g(\varrho_0) > 0 \qquad \forall s \geq \varrho_0 > 0.$$

(iv) Dominance of g over f: There exists a constant $B > 0$ such that

$$f(s) \leq B\, g(s) \qquad \forall s \in [0, \infty).$$

Remark 3. It is easy to verify that Condition (2.2) is satisfied by monotone increasing functions $f,\ g \in C^2(\mathbb{R}^1)$ with $f(0) = g(0) = f'(C^-) = g'(0) = 0$.

Condition 2.3. (The case $\alpha > 0$) Let f and g fulfill Condition 2.1. We furthermore assume that there exist constants $C^- > 0$, $\delta_0 > 0$ and K_f such that the following assertions hold:

(i) Starting threshold:

$$f(s) = 0 \qquad \forall s \le C^-,$$
$$g(s) = 0 \qquad \forall s \le 0.$$

(ii) Smoothness of f near starting threshold $[C^-, C^- + \delta_0]$:

$$f(s) > 0 \qquad \forall s \in (C^-, C^- + \delta_0],$$
$$\frac{|f'(s)|^2}{f(s)} \le K_f \qquad \forall s \in (C^-, C^- + \delta_0].$$

(iii) Lower bound:

$$f(s) \ge f(C^- + \delta_0) > 0 \qquad \forall s \ge C^- + \delta_0,$$

Remark 4. The above condition is similar to but weaker than Condition 2 assumed for Neumann BC case in [6],i.e.,

$(\mathrm{C})_N$ $\exists\, ; m_1, m_2$ such that $m_1(s-C^-) \le f'(s) \le m_2(s-C^-) \quad \forall s \in [C^-, C^-+\delta_0]$.

In fact, since this gives $m_1(s - C^-)^2/2 \le f(s) \le m_2(s - C^-)^2/2$, we easily have

$$\frac{|f'(s)|^2}{f(s)} \le \frac{m_2^2\,(s - C^-)^2}{\frac{1}{2} m_1\,(s - C^-)^2} \le \frac{2\,m_2^2}{m_1}.$$

The boundedness of $|\nabla N_2(t)|_{L^2}$ can be derived also for Neumann BCs with $(\mathrm{C})_N$ replaced by 2 of Condition 2.3 from much the simpler proof to be given later without distinguishing between two cases $u^\infty \le C^-$ and $u^\infty > C^-$.

3. Well-posedness and asymptotic behavior of solutions.

For the analysis of (1)-(4), we write the Robin boundary condition in the form

$$-\,\partial_\nu u = a(x)(u - \alpha) \text{ on } \partial\Omega. \tag{8}$$

The constant $\alpha \ge 0$ represents here the balance of concentration that is to be maintained. The boundary function $a(x)$ may be used to distinguish between different parts of the cell membrane.

As is mentioned in (2) of Remark 1, we here allow that $a(x)$ can vanish somewhere on $\partial\Omega$:

$$a(\cdot) \in C^1(\partial\Omega)\,, \quad 0 \le a(x) \quad \text{for a.e. } x \in \partial\Omega \quad \text{and } a(\cdot) \not\equiv 0. \tag{9}$$

Remark 5. The assumption $a(\cdot) \in C^1(\partial\Omega)$ in (9) can be replaced by $a(\cdot) \in L^\infty(\partial\Omega)$ in the following arguments except in Proposition 2 and Theorem 5.2, where C^1-regularity of $a(\cdot)$ is needed to assure the classical regularity of some functions, e.g, $\underline{\mathrm{v}}(\cdot)$ and $\varphi_1(\cdot)$ which appear in the proofs of Proposition 2 and Theorem 5.2.

In the following we denote by (u, N_1, N_2, N_3) the corresponding solution of the Robin problem (1) - (4) with (8). Here many of the mathematical tools used in [4, 6] do not apply anymore and different arguments are required:

We state now our first main result:

Theorem 3.1. *Let $\Omega \subset \mathbb{R}^n$ be bounded. Assume Condition (2.1) and (9), then it holds:*

1. *For all initial data $u_0 \in L^2(\Omega)$ and $N_{i,0} \in L^\infty(\Omega)$ $(i = 1, 2, 3)$, the system (1)-(4) with boundary condition (8) possesses a unique global solution (u, N_1, N_2, N_3) the components of which satisfy $u \in C([0, T]; L^2(\Omega))$; $\sqrt{t}\partial_t u, \sqrt{t}\Delta u \in L^2([0, T]; L^2(\Omega))$; $N_i \in L^\infty([0, T]; L^\infty(\Omega))$ $(\, i = 1, 2, 3)$ for all $T > 0$.*

2. *Assume further that* u_0, $N_{1,0}$, $N_{2,0}$ *and* $N_{3,0} \geq 0$. *Then the solution* (u, N_1, N_2, N_3) *preserves non-negativity. Furthermore,* N_1, N_2, N_3 *are uniformly bounded in* $\Omega \times [0, \infty)$.
3. *We have the strong convergence results :*

$$N_1(x,t) \xrightarrow{t\to\infty} N_1^\infty(x) \geq 0 \qquad \text{in } L^p(\Omega), \quad 1 \leq p < \infty, \tag{10}$$

$$N_2(x,t) \xrightarrow{t\to\infty} N_2^\infty(x) \geq 0 \qquad \text{in } L^p(\Omega), \quad 1 \leq p < \infty, \tag{11}$$

$$N_3(x,t) \xrightarrow{t\to\infty} N_3^\infty(x) \leq \|\overline{N}\|_{L^\infty} \qquad \text{in } L^p(\Omega), \quad 1 \leq p < \infty, \tag{12}$$

$$u(x,t) \xrightarrow{t\to\infty} u^\infty(x) \equiv \alpha \qquad \text{in } L^2(\Omega)\,. \tag{13}$$

4. *Let* $\alpha > 0$ *and assume the following additional condition on* g:

   Condition 3.2. There exists $\rho_0 > 0$ such that $g(s)$ is strictly monotone increasing on $[0, \rho_0]$ and $g(\rho_0) \leq g(s)$ for all $\rho_0 \leq s$.

   Then we have $N_2^\infty(x) \equiv 0$.

Proof. **1. The existence of a unique global solution.**

We put $\overline{u} = u - \alpha$, then $\overline{u}$ satisfies the boundary condition

$$-\partial_\nu \overline{u} = a(x)\,\overline{u} \quad \text{ on } \partial\Omega \tag{14}$$

and equations (1)-(4) with $u, f(\cdot), g(\cdot)$ 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 2.1. Set

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

Then it is easy to show that $\varphi : L^2(\Omega) \to [0, \infty]$ becomes a lower semi-continuous convex functional and its subdifferential $\partial\varphi$ (a notion of generalized Fréchet deivative, see H. Brézis [2, 3]) coincides with the self-adjoint operator A defined by

$$A\,u = -\Delta\,u \quad \text{ with domain } \quad D(A) = \{\, u \in H^2(\Omega)\,;\, -\partial_\nu u = a(x)\,u \text{ on } \partial\Omega\,\}. \tag{15}$$

In order to assure the local and global existence of a solution (u, N_1, N_2, N_3) to the original system, we can repeat the same arguments as for the Neumann boundary case, see [6].

We first note that by (7) the essential unknown functions can be taken as (u, N_1, N_2). Let $X_T := C([0,T]; L^2(\Omega))$ and define the mapping

$$\mathcal{B} : u \in X_T \mapsto N^u := (\,N_1^u, N_2^u\,) \mapsto \hat{u} = \mathcal{B}(u).$$

Here for a given $u \in X_T$, $N^u = (N_1^u, N_2^u)$ denotes the solution of the ODE problem:

$$\partial_t N^u = (-f(u)N_1^u,\ \ f(u)N_1^u - g(u)N_2^u) =: F^u(N^u),\ N^u(x,0) = (N_{1,0}(x), N_{2,0}(x)) \tag{16}$$

and $\hat{u}$ denotes the solution of the PDE problem :

$$\partial_t \hat{u} = d_1 \Delta \hat{u} + d_2 g(\hat{u}) N_2^u, \quad \partial_\nu \hat{u} + a(x)\,\hat{u}\big|_{\partial\Omega} = 0, \quad \hat{u}(x,0) = u_0(x), \tag{17}$$

which is reduced to the abstract problem in $H = L^2(\Omega)$:

$$\frac{d}{dt}\hat{u}(t) + d_1\,\partial\varphi(\hat{u}(t)) + B(\hat{u}(t)) = 0, \quad \hat{u}(0) = u_0, \quad \text{with } B(u)(\cdot,t) = -d_2\,g(u(\cdot,t)).$$

Since, by Condition 2.1 F^u is Lipschitz continuous from $Y = L^\infty(\Omega) \times L^\infty(\Omega)$ into itself, the Picard-Lindelöf theorem assures the existence of the unique global solution $N^u \in C([0,\infty);Y)$ of (16) for each $u \in X_T$. Furthermore, since the mapping $u \mapsto B(u) = g(u)N_2^u$ is Lipschitz continuous from $L^2(\Omega)$ into itself by Condition 2.1, the standard argument shows that (17) has the unique solution $\hat{u} \in C([0,\infty);L^2(\Omega))$ satisfying $\sqrt{t}\,\partial_t\hat{u}, \sqrt{t}\,\Delta\hat{u} \in L^2_{loc}((0,\infty);L^2(\Omega))$ (see, e.g., [2, 3, 9]).

Then, in view of the fact :

$$(\partial\varphi(u),u) = \int_\Omega |\nabla u|^2 dx + \int_{\partial\Omega} a\,|u|^2 dS \geq 0 \qquad \forall u \in D(A),$$

we can repeat exactly the same arguments as for the Neumann BC case in [6] and show that $\mathcal{B}$ becomes a contraction mapping in X_T for a sufficiently small $T_0 \in (0,1]$ and $T_0 > 0$ does not depend on the choice of the initial data. Hence this local solution can be continued up to $[0,T]$ for any T. □

In order to discuss the positivity and the asymptotic behavior of the solution, we need to first prepare some auxiliary results.

Proposition 1 (Comparison Theorem). *Let $d > 0$, $\alpha \in \mathbb{R}^1$, $a(x) \geq 0$ and $h(\cdot) : \mathbb{R}^1 \to \mathbb{R}^1$ be Lipschitz continuous. Let $u_i \in \{u \in C([0,T];L^2(\Omega); \sqrt{t}\;\partial_t u, \sqrt{t}\;\Delta u \in L^2(0,T;L^2(\Omega))\}$ $(i = 1,2)$ satisfy*

$$\begin{cases} \partial_t u_1 - d\,\Delta u_1 \geq h(u_1), & (x,t) \in \Omega \times (0,T), \\ \partial_t u_2 - d\,\Delta u_2 \leq h(u_2), & (x,t) \in \Omega \times (0,T), \\ -\partial_\nu u_1 \leq a(x)\,(u_1 - \alpha), & (x,t) \in \partial\Omega \times (0,T), \\ -\partial_\nu u_2 \geq a(x)\,(u_2 - \alpha), & (x,t) \in \partial\Omega \times (0,T), \\ u_1(x,0) \geq u_2(x,0), & x \in \Omega. \end{cases}$$

Then we have $u_1(x,t) \geq u_2(x,t)$ for a.e. $x \in \Omega$ and all $t > 0$.

Proof. Let $w(t) = u_1(t) - u_2(t)$, then $w(t)$ satisfies

$$\partial_t w(t) - d\,\Delta w(t) \geq h(u_1(t)) - h(u_2(t)) \;\text{ in } \Omega,$$

$$-\partial_\nu w(t) \leq a(x)\,w(t) \;\text{ on } \partial\Omega, \;\; w(0) \geq 0 \;\text{ in } \Omega.$$

Then multiplying this by $w^-(t) = \max(0, -w(t))$, we get

$$\frac{1}{2}\frac{d}{dt}\|w^-(t)\|^2_{L^2} + d\,\|\nabla w^-(t)\|^2_{L^2} + d\int_{\partial\Omega} \partial_\nu w\,w^-\,dS \leq L_h\,\|w^-(t)\|^2_{L^2},$$

where L_h is the Lipschitz constant of $h(\cdot)$. Noting that $\partial_\nu w\,w^- \geq -aww^- = a|w^-|^2$ on $\partial\Omega$, we obtain

$$\frac{1}{2}\frac{d}{dt}\|w^-(t)\|^2_{L^2} + d\,\|\nabla w^-(t)\|^2_{L^2} + d\int_{\partial\Omega} a\,|w^-|^2\,dS \leq L_h\,\|w^-(t)\|^2_{L^2}.$$

Then Gronwall's inequality implies that $|w^-(t)|^2 \leq |w^-(0)|^2\,e^{L_h t} = 0$, whence follows $w^-(t) = 0$, i.e., $u_2(t) \leq u_1(t)$ for all $t > 0$. □

Corollary 1 (Positivity). *Let $d > 0$, $\alpha \geq 0$ and $a(x) \geq 0$ and let u satisfy*

$$\partial_t\,u(t) - d\,\Delta\,u(t) \geq 0, \quad -\partial_\nu u(t) \leq a(x)\,(u(t) - \alpha), \quad u(0) \geq 0.$$

Then it holds that $u(x,t) \geq 0$ for a.e. $x \in \Omega$ and all $t > 0$.

Proof. Since $\underline{u}(\cdot,t) \equiv 0$ satisfies

$$\partial_t \underline{u}(t) - d\,\Delta\,\underline{u}(t) = 0, \quad \underline{u}(\cdot,0) = 0, \quad -\partial_\nu \underline{u}(t) = 0 \geq -\alpha\, a(x) = a(x)\,(\underline{u}(t) - \alpha),$$

Proposition 1 with $h(\cdot) \equiv 0$ assures that $u(x,t) \geq \underline{u}(x,t) \equiv 0$ for a.e. $x \in \Omega$ and all $t > 0$. □

Proposition 2 (Strict positivity). *Let $d > 0$, $\alpha > 0$ and (9) be satisfied. Suppose that u satisfies*

$$\begin{cases} \partial_t u - d\,\Delta u \geq 0 \quad (x,t) \in \Omega \times (0,T), \\ -\,\partial_\nu u \leq a(x)\,(u - \alpha) \quad (x,t) \in \partial\Omega \times (0,T), \\ u(x,0) = u_0(x) \geq 0. \end{cases}$$

Then for any $t_* > 0$, there exists $\rho = \rho(t_*) > 0$ such that

$$u(x,t) \geq \rho \quad \textit{for a.e. } x \in \Omega \quad \textit{and all} \quad t \geq t_*.$$

Proof. Let $\underline{v}(\cdot,t)$ be the unique solution of

$$\partial_t\, \underline{v}(t) = d\,\Delta\,\underline{v}(t) \quad \text{in } \Omega, \quad -\,\partial_\nu \underline{v}(t) = a(x)\,(\,\underline{v}(t) - \alpha\,) \quad \text{on } \partial\Omega, \quad \underline{v}(0) = u_0 \quad \text{in } \Omega.$$

Then by Proposition 1 with $h(\cdot) \equiv 0$ and Corollary 1, we get $u(x,t) \geq \underline{v}(x,t) \geq 0$ for a.e. $x \in \Omega$ and all $t > 0$. Furthermore, by the strong parabolic maximum principle, we know $\underline{v}(x,t) > 0$ for all $(x,t) \in \Omega \times (0,T)$. For any $t_* > 0$, suppose that $\underline{v}(x_0,t_*) = 0$ for some $x_0 \in \partial\Omega$, then by virtue of Hopf's maximum principle, we get $\partial_\nu \underline{v}(x_0,t_*) < 0$, which implies

$$0 < -\,\partial_\nu\, \underline{v}(x_0,t_*) = a(x_0)\,(\,\underline{v}(x_0,t_*) - \alpha\,) = -\,a(x_0)\,\alpha \leq 0,$$

which leads to a contradiction. Hence there exists a positive constant $\rho_0 = \rho_0(t_*)$ such that

$$u(x,t_*) \;\geq\; \underline{v}(x,t_*) \;\geq\; \min_{x\in\bar{\Omega}} \underline{v}(x,t_*) = \rho_0 \quad \text{for a.e. } x \in \Omega.$$

Then putting $\rho = \rho(t_*) = \min\left(\rho_0(t_*), \alpha\right) > 0$, we get

$$(\partial_t \;-d\,\Delta)\,\rho = 0, \quad -\,\partial_\nu\,\rho = 0 \geq a(x)\,(\rho - \alpha), \quad u(x,t_*) \geq \rho.$$

Then it follows from Proposition 1 with $h(\cdot) \equiv 0$ that $u(x,t) \geq \rho$ for a.e. $x \in \Omega$ and all $t \geq t_*$. □

Now we are in the position to continue our proof of Theorem 3.1.

it Proof of Theorem 3.1(continued).

2. Non-negativity of solutions. Multiplying the corresponding equations for $N_i(x,t)$ by $N_i^-(x,t) = \max\left(-N_1(x,t), 0\right)$ and using assumptions $f(u) \geq 0$, $g(u) \geq 0$, we can deduce that $d\|N_i(t)\|_{L^2}/dt \leq 0$, whence follows $\|N_i^-(t)\|_{L^2} \leq \|N_i^-(0)\|_{L^2} = 0$, i.e., $N_i(x,t) \geq 0$. So u satisfies $\partial_t u(t) - d_1\,\Delta\,u(t) = d_2\,g(u(t))\,N_2(t) \geq 0$, then Corollary 1 assures that $u(x,t) \geq 0$. Furthermore the non-negativity of $N_i(t)$ and the conservation law (7) imply the uniform boundedness of N_i such that $0 \leq N_i(x,t) \leq \|\bar{N}\|_{L^\infty}$ $(i = 1,2,3)$ for a.e. $x \in \Omega$ and all $t > 0$.

3. Convergence. **(1)** From (2) and the non-negativity result it holds in the point-wise sense

$$\partial_t N_1(x,t) = -f\big(u(x,t)\big)N_1(x,t) \leq 0 \quad \forall t \geq 0 \quad \text{a.e.} x \in \Omega\,.$$

Hence the sequence is non-increasing and bounded below by 0, whence follows the convergence

$$N_1(x,t) \xrightarrow{t\to\infty} N_1^\infty(x) \geq 0 \quad \text{a.e.} x \in \Omega\,. \tag{18}$$

Furthermore, by (7) we get

$$|N_1^\infty(x)| \le \|\overline{N}\|_{L^\infty}, \quad N_1(x,t) = |N_1(x,t)| \le \|\overline{N}\|_{L^\infty} \quad \text{a.e.} x \in \Omega, \ t \in (0,\infty).$$

Then by virtue of the Lebesgue dominated convergence theorem, we conclude that $N_1(\cdot,t)$ converges to $N_1^\infty(\cdot)$ strongly in $L^1(\Omega)$ as $t \to \infty$. Thus to deduce (10), it suffices to use the relation

$$\|N_1(t) - N_1^\infty\|_{L^p}^p \le (\|N_1(t)\|_{L^\infty} + \|N_1^\infty\|_{L^\infty})^{p-1} \|N_1(t) - N_1^\infty\|_{L^1}.$$

(2) As for $N_3(x,t)$, since (4) implies that $N_3(x,t)$ is monotone increasing, we can repeat the same argument as above to get (12).

(3) Combining (7) with (10) and (12), we can easily deduce (11).

(4) Here we are going to show that if $\alpha > 0$ and Condition 3.2 is satisfied, then $N_2^\infty(x) \equiv 0$. To this end, we first note that the integration of (4) on $(0,t)$ gives

$$0 \le \int_0^t g(u(x,s))\, N_2(x,s)\, dt = N_3(x,t) - N_3(x,0) \le \|\overline{N}\|_{L^\infty} \quad \forall t > 0. \tag{19}$$

Here take any $t_* > 0$ and we put $\underline{\rho} = \underline{\rho}(t_*) := \min(\rho(t_*), \rho_0)$, then Proposition 2 and Condition 3.2 assure

$$0 < g(\underline{\rho}) \le g(u(t)) \quad \text{for a.e. } x \in \Omega \ \text{ and } \ t \ge t_*. \tag{20}$$

Then by (19) and (20), we get

$$g(\underline{\rho}) \int_{t_*}^\infty \|N_2(t)\|_{L^1} dt \le \int_\Omega \int_0^t g(u(x,s)) N_2(x,s)\, ds\, dx \le |\Omega|\, \|\overline{N}\|_{L^\infty}.$$

Hence there exists a sequence $\{t_k\}_{k\in\mathbb{N}}$ with $t_k \to \infty$ such that

$$\lim_{k\to\infty} \|N_2(t_k)\|_{L^1(\Omega)} = 0\,.$$

Then (11) implies

$$\lim_{k\to\infty} \int_\Omega N_2(x,t_k)\, dx = \int_\Omega N_2^\infty(x)\, dx = 0,$$

whence follows $N_2^\infty(x) \equiv 0$ for a.e. $x \in \Omega$.

(5) In the following we are going to show that u converges to α strongly in $L^2(\Omega)$. Here we can neither apply Wirtinger's nor Poincaré's inequality, but the following lemma finds a remedy:

Lemma 3.3 (Poincaré-Friedrichs' inequality). *Let (9) be satisfied, then there exists a positive constant C_F such that*

$$\|w\|_{L^2}^2 \le C_F \left(\|\nabla w\|_{L^2}^2 + \int_{\partial\Omega} a(x) |w|^2\, dS \right) \quad \forall w \in H^1(\Omega). \tag{21}$$

See e.g. [1], [12].

We again put $\overline{u} = u - \alpha$ and $\overline{g}(v) = g(v+\alpha)$ and recall that $\overline{u}$ satisfies the homogeneous boundary condition (14) and equation (1) with g replaced by $\overline{g}$. Multiplying (1) by $\overline{u}$ and using (9), we get

$$\frac{1}{2}\frac{d}{dt}\|\overline{u}\|_{L^2}^2 + d_1 \int_\Omega |\nabla \overline{u}|^2\, dx + d_1 \int_{\partial\Omega} a(x)\, |\overline{u}|^2\, dS \le d_2\, \|\overline{g}(\overline{u}) N_2\|_{L^2} \|\overline{u}\|_{L^2}\,. \tag{22}$$

Then by (21), we obtain

$$\frac{1}{2}\frac{d}{dt}\, \|\overline{u}\|_{L^2}^2 + \frac{d_1}{C_F} \|\overline{u}\|_{L^2}^2 \le d_2\, \|\overline{g}(\overline{u})\, N_2\|_{L^2}\, \|\overline{u}\|_{L^2}$$

and Young's inequality yields

$$\frac{1}{2}\frac{d}{dt}\|\overline{u}\|_{L^2}^2+\frac{d_1}{2\,C_F}\|\overline{u}\|_{L^2}^2\leq\frac{d_2^2\,C_F}{2\,d_1}\|\overline{g}(\overline{u})\,N_2\|_{L^2}^2\,. \tag{23}$$

Here we note that (19) and the boundedness of $\|N_2(t)\|_{L^\infty}$ and $g(\cdot)$ imply

$$\int_0^\infty\|\overline{g}(\overline{u}(t))\,N_2(t)\|_{L^2}^2dt\leq\int_0^\infty\!\!\int_\Omega g(u(x,s))\,N_2(x,s)\,dx\,ds\,g^*\,\|\overline{N}\|_{L^\infty}\leq g^*\,|\Omega|\,\|\overline{N}\|_{L^\infty}^2. \tag{24}$$

Then applying (ii) of Proposition 4 in [6](note that this result is stated for $y\in C^1([t_0,\infty))$, but it obviously holds also for $y(t)=\|\overline{u(t)}\|_{L^2}^2\in W^{1,1}(t_0,\infty)$ with $\gamma_0=\frac{d_1}{2C_F}$, $a(t)=\frac{d_2^2\,C_F}{2\,d_1}\|\overline{g}(\overline{u})\,N_2\|_{L^2}^2$ and $t_0=0$, we can deduce that $\|\overline{u}(t)\|_{L^2}\to 0$ as $t\to\infty$, which is equivalent to (13). □

As for the *a priori* estimates for $\overline{u}(t)$, we can obtain more minute information. If fact, integrating (22) over $(0,\infty)$ and using Poincaré-Friedrichs' inequality and (24), we have

$$\int_0^\infty\|\overline{u}(t)\|_{H^1}^2\,dt\leq C_0, \tag{25}$$

where C_0 is a general constant depending on $\|u_0\|_{L^2}$. Furthermore, multiplying (1) by $-\Delta\overline{u}$, we get

$$\frac{1}{2}\frac{d}{dt}\left(\|\nabla\overline{u}(t)\|_{L^2}^2+\int_{\partial\Omega}a(x)\,|\overline{u}(t)|^2\,dS\right)+d_1\,\|\Delta\overline{u}(t)\|_{L^2}^2\leq d_2\,\|\overline{g}(\overline{u})N_2\|_{L^2}\,\|\Delta\overline{u}(t)\|_{L^2}. \tag{26}$$

Here by (21) we have

$$\|\Delta v\|_{L^2}\,\|v\|_{L^2}\geq(-\Delta v,v)_{L^2}=2\,\varphi(v)(t)\geq\sqrt{2\,\varphi(v)(t)}\,\frac{1}{\sqrt{C_F}}\,\|v\|_{L^2}\qquad\forall u\in H^1(\Omega). \tag{27}$$

Hence combining (26) and (27), we obtain

$$\frac{d}{dt}\,\varphi(\overline{u})(t)+\frac{d_1}{4}\,\|\Delta\overline{u}(t)\|_{L^2}^2+\frac{d_1}{C_F}\,\varphi(\overline{u})(t)\leq\frac{d_2^2}{d_1}\,\|\overline{g}(\overline{u}(t))\,N_2(t)\|_{L^2}^2. \tag{28}$$

Since $\|\overline{g}(\overline{u}(t))\,N_2(t)\|_{L^2}^2\in L^1(0,\infty)$ by (24) and $\overline{u}(\delta)\in H^1(\Omega)$ for some arbitrarily small $\delta>0$ by (25), (ii) of Proposition 4 in [6] with $y(t)=\varphi(\overline{u})(t)$, $\gamma_0=\frac{d_1}{2\,C_F}$, $a(t)=\frac{d_2^2}{d_1}\|\overline{g}(\overline{u})\,N_2\|_{L^2}^2$ and $t_0=\delta$, we can deduce that $\varphi(\overline{u})(t)\to 0$ as $t\to\infty$, which gives:

$$\sup_{t>\delta}\,\|\overline{u}(t)\|_{H^1}\leq C_0(\delta),\quad\|\nabla\overline{u}(t)\|_{L^2}^2+\int_{\partial\Omega}a(x)\,|\overline{u}(t)|^2\,dS\to 0\quad\text{as }t\to\infty, \tag{29}$$

where $C_0(\delta)$ is a general constant depending only on $\|u_0\|_{L^2}$ and δ. Moreover, integrating (28) over $(0,\delta)$, we obtain

$$\int_\delta^\infty\|\Delta\,\overline{u}(t)\|_{L^2}^2\,dt=\int_\delta^\infty\|\Delta\,u(t)\|_{L^2}^2\,dt\leq C_0(\delta). \tag{30}$$

4. **Uniform convergence of u.** In order to analyze more minute asymptotic behavior of solutions, we need the uniform convergence of u. For this purpose, we first prepare the following lemma.

Lemma 4.1. *Let Ω be a bounded domain in $\mathbb{R}^n$ with $n \leq 3$ and assume Condition* (2.1) *and* (9). *Furthermore suppose that the following estimate holds :*

$$\sup_{t\geq 0} \|N_2(t)\|_{H^1} \leq C_{N_2} < \infty. \tag{31}$$

Then we have

$$\max_{x\in\overline{\Omega}} |u(x,t) - \alpha| \to 0 \quad \text{as } t \to \infty. \tag{32}$$

Proof. We first note that $H^2(\Omega)$ is continuously embedded in the Hölder space $C^\alpha(\Omega)$ with order $\alpha \in (0,1)$, since $n \leq 3$. Furthermore by virtue of the interpolation inequality, we get

$$\|u(t) - \alpha\|_{C^\alpha(\Omega)} \leq C_\theta \,\|u(t) - \alpha\|^{\theta}_{H^1}\, \|u(t) - \alpha\|^{1-\theta}_{H^2} \quad \theta \in (0,1). \tag{33}$$

Hence, by virtue of (13) and (29), we find that in order to derive (32), it suffices to show that $\|\Delta u(t)\|_{L^2}$ is bounded on $[1,\infty)$. So we are going to show below that $\|\Delta u(t)\|_{L^2}$ is uniformly bounded. In what follows, we again denote $\overline{u}$, $\overline{g}$, $\overline{f}$ simply by u, g, f if no confusion arises. Here we recall the following facts on $A^{\frac{1}{2}}$, the fractional power of order $\frac{1}{2}$ of the operator A defined by (15):

$$D(A^{\frac{1}{2}}) = H^1(\Omega), \quad \|A^{\frac{1}{2}}\, u\|^2_{L^2} = (A\,u, u) = \|\nabla u\|^2_{L^2} + \int_{\partial\Omega} a\,|u|^2 dS. \tag{34}$$

Applying $A^{\frac{1}{2}}$ to (1), we consider the following auxiliary equation :

$$\partial_t\, A^{\frac{1}{2}} u + d_1 A^{\frac{3}{2}} u = d_2\, A^{\frac{1}{2}}\, (g(u)N_2)\ .$$

By (25), (31) and (34), it is easy to see that $A^{\frac{1}{2}}\,(g(u)N_2) \in L^2_{loc}([0,\infty); L^2(\Omega))$. Standard regularity results assure that $\partial_t A^{\frac{1}{2}} u$ and $A^{\frac{3}{2}} u$ belong to $L^2_{loc}((0,\infty); L^2(\Omega))$. Then multiplying by $A^{\frac{3}{2}} u$, we have for almost every $t \in (0,\infty)$

$$\frac{1}{2}\frac{d}{dt}\|Au(t)\|^2_{L^2} + d_1 \|A^{\frac{3}{2}} u(t)\|^2_{L^2} = d_2 \big(A^{\frac{1}{2}}\,(g(u(t))N_2(t))\,, A^{\frac{3}{2}} u(t)\big)_{L^2}.$$

Hence by (34), we obtain

$$\begin{aligned}
&\frac{1}{2}\frac{d}{dt}\|\Delta u(t)\|^2_{L^2} + \frac{d_1}{2}\|A^{\frac{3}{2}} u(t)\|^2_{L^2} \leq \frac{{d_2}^2}{2d_1}\|A^{\frac{1}{2}}\,(g(u(t))N_2(t))\,\|^2_{L^2} \\
&\leq \frac{{d_2}^2}{d_1}\Big(\|g'(u(t))\nabla u(t) N_2(t)\|^2_{L^2} + \|g(u(t))\nabla N_2(t)\|^2_{L^2} + \|a\|_{L^\infty}(g^*)^2\|N_2(t)\|^2_{L^2(\partial\Omega)}\Big) \\
&\leq \frac{{d_2}^2}{d_1}\Big(L_g^2\,\|\overline{N}\|^2_{L^\infty}\,\|\nabla u(t)\|^2_{L^2} + (g^*)^2\,\|\nabla N_2(t)\|^2_{L^2} + C_\gamma\,\|a\|_{L^\infty}\,(g^*)^2\,\|N_2(t)\|^2_{H^1}\Big),
\end{aligned} \tag{35}$$

where C_γ is the embedding constant for $\|w\|^2_{L^2(\partial\Omega)} \leq C_\gamma\,\|w\|^2_{H^1(\Omega)}$.

Here we note that (21) and (34) yield $\|u\|^2_{L^2} \leq C_F\,\|A^{\frac{1}{2}} u\|^2_{L^2}$. Hence we get

$$\begin{aligned}
\|A^{\frac{1}{2}} u\|^2_{L^2} &= (A^{\frac{1}{2}} u, A^{\frac{1}{2}} u)_{L^2} = (Au, u)_{L^2} \leq \|Au\|_{L^2}\,\|u\|_{L^2} \\
&\leq \|Au\|_{L^2}\,\sqrt{C_F}\,\|A^{\frac{1}{2}} u\|_{L^2} \\
\|A^{\frac{1}{2}} u\|^2_{L^2} &\leq C_F\,\|Au\|^2_{L^2} \\
\|Au\|^2_{L^2} &= (Au, Au)_{L^2} = (A^{\frac{1}{2}} u, A^{\frac{3}{2}} u)_{L^2} \leq \|A^{\frac{1}{2}} u\|_{L^2}\,\|A^{\frac{3}{2}} u\|_{L^2} \\
&\leq \sqrt{C_F}\,\|Au\|_{L^2}\|A^{\frac{3}{2}} u\|_{L^2} \\
\|Au\|^2_{L^2} &\leq C_F\,\|A^{\frac{3}{2}} u\|^2_{L^2}.
\end{aligned}$$

Hence by virtue of (35) and (36), we obtain

$$\frac{1}{2}\frac{d}{dt}\|\Delta u(t)\|_{L^2}^2 + \frac{d_1}{2\,C_F}\|\Delta u(t)\|_{L^2}^2 \leq a_A(t),$$

where

$$a_A(t) = \frac{{d_2}^2}{d_1}\Big(L_g^2\,\|\overline{N}\|_{L^\infty}^2\,\|\nabla u(t)\|_{L^2}^2 + (g^*)^2\,\|\nabla N_2(t)\|_{L^2}^2 + C_\gamma\,\|a\|_{L^\infty}\,(g^*)^2\,\|N_2(t)\|_{H^1}^2\Big).$$

Here we recall that (29) and (31) assure that $\sup_{t\in[\delta,\infty)} a_A(t) \leq C_A(\delta)$ and that (30) implies that there exists $\delta_1 \in (\delta, 2\delta)$ such that $\|\Delta u(\delta_1)\|_{L^2} < \infty$. Thus applying (i) of Proposition 4 of [6] with $y(t) = \|\Delta u(t)\|_{L^2}^2$, $\gamma_0 = \frac{d_1}{2\,C_F}$, $a(t) \equiv C_A(\delta)$, $t_0 = \delta_1$ and $t_1 = \infty$, we can deduce

$$\sup_{t\in[\delta_1,\infty)} \|\Delta u(t)\|_{L^2}^2 \leq \|\Delta u(\delta_1)\|_{L^2}^2 + \frac{2\,C_F\,C_A(\delta)}{d_1},$$

whence follows the uniform boundedness of $\|\Delta u(t)\|_{L^2}$ on $[1,\infty)$. □

Boundedness of $\|\nabla N_2(t)\|_{L^2}$: Here we are going to show the boundedness of $\|\nabla N_2(t)\|_{L^2}$, for which we here assume the following :

Condition 4.2. $N_{1,0},\ N_{2,0} \in H^1(\Omega)$.

(Case $\alpha > 0$). As for the case where $\alpha > 0$, our result is stated as follows.

Lemma 4.3. *Let $\alpha > 0$ and let all assumptions in Lemma 4.1 except (31) be satisfied. Further assume that Conditions 2.3, 3.2 and 4.2 are satisfied. Then there exists a constant C_N such that*

$$\sup_{t>0}\ (\,\|\nabla N_1(t)\|_{L^2} + \|\nabla N_2(t)\|_{L^2}\,) \leq C_N. \tag{36}$$

Proof. Solving (2) point-wisely, we first get $N_1(x,t) = N_{1,0}(x)\,e^{-\int_0^t f(u(x,s))\,ds}$, which implies $N_1(t) \in H^1(\Omega)$ for all $t > 0$. Then applying the gradient to (2), we have

$$\partial_t \nabla N_1 = -f'(u)\,\nabla u\,N_1 - f(u)\,\nabla N_1. \tag{37}$$

Multiply (37) by $\nabla N_1(t)$, then we get

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|\nabla N_1(t)\|_{L^2}^2 \leq & \int_\Omega |f'(u(x,t))||\nabla u(x,t)||N_1(x,t)||\nabla N_1(x,t)|\,dx \\ & - \int_\Omega f(u(x,t))|\nabla N_1(x,t)|^2\,dx\,.\end{aligned} \tag{38}$$

In view of Condition 2.3, we decompose Ω into 3 parts :

$$\begin{aligned}\Omega_1(t) &:= \{\, x\in\Omega\,;\ u(x,t) \leq C^-\,\},\\ \Omega_2(t) &:= \{\, x\in\Omega\,;\ C^- < u(x,t) \leq C^- + \delta_0]\,\},\\ \Omega_3(t) &:= \{\, x\in\Omega\,;\ C^- + \delta_0 < u(x,t)\,\}.\end{aligned} \tag{39}$$

By virtue of Condition 2.3, we get

$$\begin{aligned}&\int_\Omega |f'(u)||\nabla u||N_1||\nabla N_1|dx \leq \\ &\leq \frac{1}{2}\int_{\Omega_2(t)\cup\Omega_3(t)} \frac{|f'(u)|^2}{f(u)}\,|N_1|^2\,|\nabla u|^2 dx + \frac{1}{2}\int_\Omega f(u)\,|\nabla N_1|^2 dx\end{aligned}$$

$$\leq \frac{1}{2}\left(K_f\,\|\overline{N}\|^2_{L^\infty} + \frac{L_f^2\,\|\overline{N}\|^2_{L^\infty}}{f(C^- + \delta_0)}\right)\|\nabla u\|^2_{L^2} + \frac{1}{2}\int_\Omega f(u)\,|\nabla N_1|^2\,dx.$$

Hence

$$\frac{1}{2}\frac{d}{dt}\|\nabla N_1(t)\|^2_{L^2} \leq \frac{1}{2}\left(K_f\,\|\overline{N}\|^2_{L^\infty} + \frac{L_f^2\,\|\overline{N}\|^2_{L^\infty}}{f(C^- + \delta_0)}\right)\|\nabla u(t)\|^2_{L^2} \quad \text{for all } t > 0.$$

Then integrating this over $(0,t)$ and using (25), we deduce that there exists a constant C_{N_1} such that

$$\sup_{t>0}\|\nabla N_1(t)\|_{L^2} \leq C_{N_1}. \tag{40}$$

By much the same argument as for (37), we get

$$\partial_t \nabla N_2 = f'(u)\,\nabla u\,N_1 + f(u)\,\nabla N_1 - g'(u)\,\nabla u\,N_2 - g(u)\,\nabla N_2. \tag{41}$$

Multiplication of (41) by ∇N_2 leads to

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}&\|\nabla N_2(t)\|^2_{L^2} = \\ &= \int_\Omega f'(u(t))\nabla u(t) N_1(t)\nabla N_2(t)\,dx + \int_\Omega f(u(t))\nabla N_1(t)\nabla N_2(t)\,dx \\ &- \int_\Omega g'(u(t))\nabla u(t) N_2(t)\nabla N_2(t)\,dx - \int_\Omega g(u(t))|\nabla N_2(t)|^2\,dx\,.\end{aligned} \tag{42}$$

Then Condition 2.1 yields

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|\nabla N_2(t)\|^2_{L^2} &\leq (L_f + L_g)\|\overline{N}\|_{L^\infty}\int_\Omega |\nabla u(t)||\nabla N_2(t)|\,dx \\ &+ f^*\int_\Omega |\nabla N_1(t)||\nabla N_2(t)|\,dx - \int_\Omega g(u(t))|\nabla N_2(t)|^2\,dx\,.\end{aligned}$$

Hence by Young's inequality and (40), for any $\eta > 0$, there exists a constant $C_{N_2}(\eta)$ such that

$$\begin{aligned}\frac{d}{dt}\|\nabla N_2(t)\|^2_{L^2} \leq& \,\eta\,\|\nabla N_2(t)\|^2_{L^2} + C_{N_2}(\eta)\,\left(1 + \|\nabla u(t)\|^2_{L^2}\right) \\ &- 2\int_\Omega g(u(t))|\nabla N_2(t)|^2\,dx.\end{aligned} \tag{43}$$

Then (43) with $\eta = 1$ and Gronwall's inequality give

$$\|\nabla N_2(t)\|^2_{L^2} \leq \Big(\|\nabla N_{2,0}\|^2_{L^2} + C_{N_2}(1)\,\big(t_* + \int_0^{t_*}\|\nabla u(t)\|^2_{L^2}\,dt\big)\Big)e^{t_*} \quad \forall t \in [0, t_*], \tag{44}$$

where $t_* > 0$ is the number given in Proposition 2. As in the verification for $N_2^\infty(x) \equiv 0$, Proposition 2 and Condition 4.2 assure that

$$g(u(x,t)) \geq g(\underline{\rho}) > 0 \quad \forall t \geq t_* \tag{45}$$

with $\underline{\rho} = \underline{\rho}(t_*) = \min(\rho(t_*), \rho_0)$ as defined earlier. Substituting this into the last term of (43) with $\eta = g(\underline{\rho})$, we get

$$\frac{d}{dt}\|\nabla N_2(t)\|^2_{L^2} + g(\underline{\rho})\|\nabla N_2(t)\|^2_{L^2} \leq C_{N_2}(g(\underline{\rho}))\,\left(1 + \|\nabla u(t)\|^2_{L^2}\right) \quad \forall t \geq t_*.$$

Then in view of (29), we can apply (i) of Proposition 4 in [6] with

$$y(t) = \|\nabla N_2(t)\|^2_{L^2}, \quad t_0 = t_*, \quad t_1 = \infty, \quad \gamma_0 = g(\underline{\rho}),$$

and

$$C = C_{N_2}(g(\underline{\rho}))\left(1 + \sup_{t\geq t_*} \|\nabla u(t)\|_{L^2}^2\right).$$

Thus together with (44), we achieved (36). □

(Case $\alpha = 0$). For the case where $\alpha = 0$, we can not use the fact that $u(x,t)$ is bounded below by the positive constant $\underline{\rho}$, so we here need to introduce more complicated arguments than before. Our result for the case where $\alpha = 0$ is stated as follows.

Lemma 4.4. *Let $\alpha = 0$ and let all assumptions in Lemma 4.1 except (31) be satisfied. Further assume that Conditions 2.2 and 4.2 are satisfied. Then there exists a constant C_N such that*

$$\sup_{t>0} \left(\|\nabla N_1(t)\|_{L^2} + \|\nabla N_2(t)\|_{L^2} \right) \leq C_N. \tag{46}$$

Proof. We define again $\Omega_i(t)$ $(i = 1,2,3)$ by (39), then in view of (38), by using $|f'(u)| \leq m_f\,|u|$ for $x \in \Omega_2(t)$, we have

$$\begin{aligned}
&\int_\Omega f'(u)\,\nabla u\,N_1\,\nabla N_1\,dx = \int_{\Omega_2(t)} f'(u)\,\nabla u\,N_1\,\nabla N_1\,dx + \int_{\Omega_3(t)} f'(u)\,\nabla u\,N_1\,\nabla N_1\,dx \\
&\leq m_f\,\|N_1\|_{L^\infty}\int_{\Omega_2(t)} |u|\,|\nabla u|\,|\nabla N_1|\,dx + \|N_1\|_{L^\infty}\int_{\Omega_3(t)} \frac{|f'(u)|}{\sqrt{f(u)}}\,|\nabla u|\,\sqrt{f(u)}\,|\nabla N_1|\,dx \\
&\leq m_f\,\|N_1\|_{L^\infty}\int_\Omega |u||\nabla u||\nabla N_1|\,dx + \frac{L_f^2\,\|N_1\|_{L^\infty}^2}{f(C^- + \delta_0)}\int_\Omega |\nabla u|^2\,dx + \frac{1}{4}\int_\Omega f(u)\,|\nabla N_1|^2\,dx.
\end{aligned}$$

In view of (42), we put

$$\begin{aligned}
J_1(t) &:= \int_\Omega |f'(u)|\,|\nabla u|\,|N_1|\,|\nabla N_2|\,dx, \quad J_2(t) := \int_\Omega f(u)\,|\nabla N_1|\,|\nabla N_2|\,dx, \\
J_3(t) &:= \int_\Omega |g'(u)|\,|\nabla u|\,|\nabla N_2|\,|N_2|\,dx, \quad J_4(t) := \int_\Omega g(u)\,|\nabla N_2|^2\,dx.
\end{aligned}$$

It is obvious that for arbitrary $K > 0$ (which will be fixed later)

$$J_2(t) \leq \frac{K}{4}\int_\Omega f(u)\,|\nabla N_1|^2\,dx + \frac{1}{K}\int_\Omega f(u)\,|\nabla N_2|^2\,dx.$$

To estimate J_1 and J_3 we make the same trick as above:

$$\begin{aligned}
|J_1(t)| \leq &\int_{\Omega_2(t)} |f'(u)|\,|\nabla u|\,|\nabla N_2|\,|N_2|\,dx + \int_{\Omega_3(t)} |f'(u)|\,|\nabla u|\,|\nabla N_2|\,|N_2|\,dx \\
\leq &m_f\,\|N_2\|_{L^\infty}\int_\Omega |u|\,|\nabla N_2|\,|\nabla u|\,dx \\
&+ \|N_2\|_{L^\infty}\int_{\Omega_3(t)} \frac{f'(u)}{\sqrt{f(u)}}\,|\nabla u|\,\sqrt{f(u)}\,|\nabla N_2|\,dx \\
\leq &m_f\,\|N_2\|_{L^\infty}\int_\Omega |u|\,|\nabla N_2|\,|\nabla u|\,dx + \frac{A^2 L_f^2\|N_1\|_{L^\infty}^2}{f(C^- + \delta_0)}\int_\Omega |\nabla u|^2\,dx \\
&+ \frac{1}{4K}\int_\Omega f(u)\,|\nabla N_2|^2\,dx.
\end{aligned}$$

$$|J_3(t)| \leq \int_\Omega |g'(u)|\,|\nabla u|\,|\nabla N_2|\,|N_2|\,dx$$

$$\begin{aligned}
\leq&\|N_2\|_{L^\infty}\int_{\{u\leq\rho_0\}}|g'(u)|\,|\nabla u|\,|\nabla N_2|\,dx+\|N_2\|_{L^\infty}\int_{\{u>\rho_0\}}|g'(u)|\,|\nabla u|\,|\nabla N_2|\,dx\\
\leq& m_g\,\|N_2\|_{L^\infty}\int_{\{u\leq\rho_0\}}|u|\,|\nabla u|\,|\nabla N_2|\,dx\\
&+\|N_2\|_{L^\infty}\int_{\{u>\rho_0\}}\frac{g'(u)}{\sqrt{g(u)}}\,|\nabla u|\,\sqrt{g(u)}\,|\nabla N_2|\,dx\\
\leq& m_g\,\|N_2\|_{L^\infty}\int_\Omega|u|\,|\nabla u|\,|\nabla N_2|\,dx+\frac{L_g^2\,\|N_2\|_{L^\infty}^2}{g(\rho_0)}\int_\Omega|\nabla u|^2dx\\
&+\frac{1}{4}\int_\Omega g(u)\,|\nabla N_2|^2\,dx.
\end{aligned}$$

Hence there exists a constant C_1 such that

$$\begin{aligned}
\partial_t\|\nabla N_1(t)\|_{L^2}^2\leq& C_1\int_\Omega|u|\,|\nabla u|\,|\nabla N_1|\,dx+C_1\int_\Omega|\nabla u|^2\,dx-\frac{3}{4}\int_\Omega f(u)\,|\nabla N_1|^2\,dx,\\
\partial_t\|\nabla N_2(t)\|_{L^2}^2\leq& C_1\int_\Omega|u|\,|\nabla u|\,|\nabla N_2|\,dx+C_1\int_\Omega|\nabla u|^2\,dx+\frac{K}{4}\int_\Omega f(u)\,|\nabla N_1|^2\,dx\\
&+\frac{5}{4K}\int_\Omega f(u)\,|\nabla N_2|^2\,dx-\frac{3}{4}\int_\Omega g(u)\,|\nabla N_2|^2\,dx.
\end{aligned}$$

Let $y(t):=K\,\|\nabla N_1(t)\|_{L^2}^2+\|\nabla N_2(t)\|_{L^2}^2$, then we have

$$\begin{aligned}
\partial_t\,y(t)\leq& C_1\int_\Omega|u|\,|\nabla u|\,(K\,|\nabla N_1|+|\nabla N_2|)\,dx+C_1\,(K+1)\int_\Omega|\nabla u|^2\,dx\\
&-\frac{3K}{4}\int_\Omega f(u)\,|\nabla N_1|^2\,dx+\frac{K}{4}\int_\Omega f(u)\,|\nabla N_1|^2\,dx\\
&+\frac{5}{4K}\int_\Omega f(u)\,|\nabla N_2|^2\,dx-\frac{3}{4}\int_\Omega g(u)\,|\nabla N_2|^2\,dx.
\end{aligned}$$

Choosing $K=2B$ (B is given in Condition 2.2), we obtain

$$\begin{aligned}
\partial_t\,y(t)\leq& C_1\int_\Omega|u|\,|\nabla u|\,(K\,|\nabla N_1|+|\nabla N_2|)\,dx+C_1\,(K+1)\int_\Omega|\nabla u|^2\,dx\\
\leq&\,2\,C_2\,\|u\|_{L^4}\|\nabla u\|_{L^4}(K\,\|\nabla N_1\|_{L^2}^2+\|\nabla N_2\|_{L^2}^2)^{\frac{1}{2}}+C_1\,(K+1)\,\|\nabla u\|_{L^2}^2\\
\leq&\,2\,C_2\,\|u\|_{H^1}\|u\|_{H^2}\,(K\,\|\nabla N_1\|_{L^2}^2+\|\nabla N_2\|_{L^2}^2)^{\frac{1}{2}}+C_1\,(K+1)\,\|\nabla u\|_{L^2}^2\\
\leq&\,C_2\,\|u\|_{H^1}^2(K\,\|\nabla N_1\|_{L^2}^2+\|\nabla N_2\|_{L^2}^2)+C_2\,\|u\|_{H^2}^2+C_1\,(K+1)\,\|\nabla u\|_{L^2}^2\\
\leq&\,C_2\,\|u\|_{H^1}^2\,y(t)+C_2\,\|u\|_{H^2}^2+C_1\,(K+1)\,\|\nabla u\|_{L^2}^2,
\end{aligned}$$

where C_2 is a constant depending on C_1 and some embedding constants. Integrating the last inequality over (δ,t), we obtain

$$y(t)\leq y(\delta)+\int_\delta^t C_2\,\|u\|_{H^1}^2\,y(s)\,ds+\int_\delta^t\left(C_2\,\|u\|_{H^2}^2+C_1(K+1)\,\|\nabla u\|_{L^2}^2\right)\,ds.$$

Hence, the Gronwall inequality leads to

$$y(t)\leq\left[y(\delta)+C_2\int_\delta^\infty\|u\|_{H^2}^2\,ds+C_1\,(K+1)\int_0^\infty\|\nabla u\|_{L^2}^2\,ds\right]\,\exp\left(\int_0^\infty C_2\|u\|_{H^1}^2\,ds\right).\tag{47}$$

Here in view of (38) and (42), we get

$$\frac{d}{dt}\|\nabla N_1(t)\|_{L^2} \le L_f\,\|\overline{N}\|_{L^\infty}\,\|\nabla u\|_{L^2},$$
$$\frac{d}{dt}\|\nabla N_2(t)\|_{L^2} \le (L_f+L_g)\,\|\overline{N}\|_{L^\infty}\,\|\nabla u\|_{L^2} + f^*\,\|\nabla N_1(t)\|_{L^2}.$$

Integrating these inequalities over $(0,\delta)$ with respect to t and using the fact that $N_{1,0}, N_{2,0} \in H^1(\Omega)$ and (25), we can deduce the a priori bound for $y(\delta)$. Thus (46) is derived from (47) together with (25) and (30). □

5. **Partial swelling and complete swelling.** The mitochondrial swelling process depends on the local calcium ion concentration. If the initial concentration u_0 stays below the initiation threshold C^- at all points $x \in \Omega$, and if $N_2(x,0) \equiv 0$, then no swelling will happen and we have $N_i(x,t) \equiv N_{i,0}(x)$ $\forall x \in \Omega$, $i = 1,2,3$. Another possible scenario that can be observed in experiments is **"partial swelling"**.

This occurs when the initial calcium concentration lies above C^- in a small region, but decreases due to diffusion and falls below the initiation threshold eventually, say at $T_p > 0$. This leads to the fact that $N_1(x,t) = N_1(x,T_p)$ $\forall t \ge T_p$ and after T_p, $N_2(x,t) \downarrow N_2^\infty(x)$, $N_3(x,t) \uparrow N_3^\infty(x)$ as $t \uparrow \infty$. Thirdly, if the initial calcium distribution together with the influence of the positive feedback is sufficiently high, then it occurs **"complete swelling"**, which means $N_1(x,t) \to 0$, $N_2(x,t) \to 0$, $N_3(x,t) \to \overline{N}(x)$ for all $x \in \Omega$ as $t \to \infty$.

5.1. **Partial swelling.** We first consider the case where $\alpha \in (0, C^-)$.

Case 1. $0 < \alpha < C^-$.

For this case, it occurs the partial swelling. More precisely we have:

Theorem 5.1. *Let all assumptions in Lemma 4.3 be satisfied and let $\alpha \in (0, C^-)$. Then there exists a finite time $T_p > 0$ such that*

$$N_1(x,t) = N_1(x,T_p) \quad \forall t \ge T_p, \tag{48}$$

and the following exponential convergences hold.

$$
\begin{aligned}
N_2(x,t) &\xrightarrow{t\to\infty} 0 && \text{in } \mathcal{O}(e^{-g(\underline{\rho})t}) \quad \text{for a.e. } x \in \Omega,\\
N_3(x,t) &\xrightarrow{t\to\infty} \overline{N}(x) - N_1(x,T_p) && \text{in } \mathcal{O}(e^{-g(\underline{\rho})t}) \quad \text{for a.e. } x \in \Omega,\\
\|u(t)-\alpha\|_{L^2}^2 &\xrightarrow{t\to\infty} 0 && \text{in } \mathcal{O}(e^{-\gamma_1 t}),\\
\|\nabla u(t)\|_{L^2}^2 &\xrightarrow{t\to\infty} 0 && \text{in } \mathcal{O}(e^{-\gamma_1 t}),
\end{aligned}
$$

where $\underline{\rho} = \underline{\rho}(T_p) = \min(\rho(T_p), \rho_0)$ with $\rho(\cdot)$ earlier given in Proposition 2 and γ_1 is any number satisfying $0 < \gamma_1 < \min\left(\frac{d_1}{C_F}, 2\,g(\underline{\rho})\right)$. Here the terminology $v(t) \xrightarrow{t\to\infty} v^\infty$ in $\mathcal{O}(e^{-kt})$ means that there exists some constant $C > 0$ such that

$$|v(t) - v^\infty| \le C\,e^{-kt} \quad \textit{for all } t \ge T_p.$$

Proof. By virtue of Lemmas 4.1 and 4.3, we find that u converges to $\alpha < C^-$ uniformly. Then there exists a finite time T_p such that $u(x,t) \le C^-$ for all $t \ge T_p$, which together with (i) of Condition 2.3 implies $f(u(x,t)) \equiv 0$ for all $t \ge T_p$. Then by (2), we get $N_1(x,t) = N_1(x,T_p)\ \forall t \geq T_p$. Hence by (3) and (20) (or (45)), we get

$$\partial_t N_2(x,t) = -g(u(x,t))\, N_2(x,t) \leq -g(\underline{\rho})\, N_2(x,t) \quad t \geq T_p,$$

$$N_2(x,t) \leq N_2(x,T_p)\, \exp(-g(\underline{\rho})\,(t-T_p)) \quad \forall t \in [T_p,\infty), \tag{49}$$

where $\underline{\rho} = \underline{\rho}(T_p) = \min\,(\rho(T_p),\rho_0) > 0$ and $\rho(\cdot)$ is given in (20) and Proposition 2. In order to see the exponential convergence of $N_3(x,t)$, it suffices to recall the conservation law (7) for $\overline{N}(x,t)$.

As for the convergence of $\overline{u}(t) = u(t) - \alpha$, by putting $\tilde{\gamma}_0 = \frac{d_1}{C_F}$, we obtain by (23) and (49) forall $t \geq T_p$ that

$$\frac{d}{dt}\,\|\overline{u}(t)\|_{L^2}^2 + \tilde{\gamma}_0\,\|\overline{u}\|_{L^2}^2 \leq \frac{d_2^2}{\tilde{\gamma}_0}\|\overline{g}(\overline{u})\,N_2\|_{L^2}^2 \leq \frac{d_2^2}{\tilde{\gamma}_0}\,(g^*)^2\,\|\overline{N}\|_{L^\infty}^2\,|\Omega|^2\,e^{2g(\underline{\rho})T_p}\,e^{-2g(\underline{\rho})t}. \tag{50}$$

Here let γ_1 be any number satisfying

$$0 < \gamma_1 < \min\Big(\frac{d_1}{C_F}, 2\,g(\underline{\rho})\Big).$$

Then by (50), we get

$$\partial_t\,\big(e^{\gamma_1 t}\,\|\overline{u}(t)\|_{L^2}^2\,\big) \leq C_\gamma\, e^{-(2g(\underline{\rho})-\gamma_1)t} \quad \forall t \geq T_p,$$

where

$$C_\gamma = \frac{d_2^2}{\tilde{\gamma}_0}\,(g^*)^2\,\|\overline{N}\|_{L^\infty}^2\,|\Omega|^2\,e^{2g(\underline{\rho})T_p}.$$

Hence integrating this over (T_p,t), we obtain the exponential decay of $\|\overline{u}(t)\|_{L^2}^2$:

$$\|\overline{u}(t)\|_{L^2}^2 \leq \Big(e^{\gamma_1 T_p}\,\sup_{s>0}\|\overline{u}(s)\|_{L^2}^2 + \frac{C_\gamma}{2\,g(\underline{\rho})-\gamma_1}\,e^{-(2g(\underline{\rho})-\gamma_1)T_p}\Big)\,e^{-\gamma_1 t},$$

which implies

$$\|\overline{u}(t)\|_{L^2}^2 \xrightarrow{t\to\infty} 0 \text{ in } \mathcal{O}(e^{-\gamma_1 t}) \quad \text{for any } \gamma_1 \in (0, \min\,(\,d_1/C_F, 2\,g(\underline{\rho}))\,).$$

As for $\varphi(\overline{u}(t))$, from (28) we now get

$$\frac{d}{dt}\,\varphi(\overline{u})(t) + \frac{d_1}{C_F}\,\varphi(\overline{u})(t) \leq \frac{d_2^2}{d_1}\,(g^*)^2\|N_2(t)\|_{L^2}^2\,.$$

Thus repeating the same argument as for $\|\overline{u}(t)\|_{L^2}^2$, we can obtain the convergence

$$\|\overline{u}(t)\|_{H^1}^2 = \|\nabla u(t)\|_{L^2}^2 + \|u(t)-\alpha\|_{L^2}^2 \xrightarrow{t\to\infty} 0 \quad \text{in } \mathcal{O}(e^{-\gamma_1 t})\,.$$

□

Case 2. $\boldsymbol{\alpha = 0}$. We next consider the case where $\alpha = 0$. For this case, it also occurs partial swelling.

However the asymptotic behavior of $N_2(x,t)$ is quite different from that of the previous case.

Theorem 5.2. *Let all assumptions in Lemma 4.4 be satisfied. Then there exists a finite time $T_p > 0$ such that (48) holds. Furthermore, if $g(s)$ is monotone increasing in $[0,\rho_0]$ (ρ_0 is the parameter given in Condition 2.2) and if there exist $T_1 \in [0,\infty)$ and $\rho_1 > 0$ such that $N_2(x,T_1) \geq \rho_1$ for a.e. $x \in \Omega$. Then there exists $\rho_2 > 0$ such that*

$$N_2^\infty(x) \geq \rho_2 \quad a.e.\ x \in \Omega.$$

Proof. The first part can be derived from Lemmas 4.1 and 4.4 as before. To establish the positive lower bound for $N_2^\infty(x)$, we are going to construct a sub-solution for $N_2(x,t)$. To this end, we first construct a super-solution for $u(x,t)$ by making use of the first eigenfunction of the following eigenvalue problem:

$$(\mathrm{E})_\lambda \quad \begin{cases} -\Delta\,\varphi = \lambda\,\varphi & \text{in } \Omega \\ -\partial_\nu \varphi = a(x)\,\varphi & \text{on } \partial\Omega. \end{cases}$$

Let

$$R(\varphi) := \frac{\int_\Omega |\nabla\varphi|^2\,dx + \int_\Omega a(x)|\varphi(x)|^2\,dx}{\int_\Omega |\varphi(x)|^2\,dx}.$$

Using the standard compactness argument, one can easily prove that there exists a global minimizer φ_1 of $R(\cdot)$ in $H^1(\Omega)$. Since $R(|\varphi|) = R(\varphi)$, without loss of generality we can take φ_1 such that $\varphi_1 \ge 0$, i.e., φ_1 satisfies $R(\varphi_1) = \inf_{v\in H^1(\Omega)} R(v) = \lambda_1 > 0$ and λ_1 is the first eigenvalue and φ_1 the first eigenfunction for $(\mathrm{E})_\lambda$. Here we normalize the first eigenfunction such that $\max_{x\in\overline{\Omega}} \varphi_1(x) = 1$. From the strong maximum principle, it follows that $\varphi_1(x) > 0$ in Ω. Moreover it holds that $\varphi_1(x) > 0$ in $\overline{\Omega}$. Indeed, assume on the contrary that there exists $x_0 \in \partial\Omega$ such that $\varphi_1(x_0) = 0$, then Hopf's strong maximum principle assures $\partial_\nu\varphi_1(x_0) < 0$, which contradicts the boundary condition $\partial_\nu\varphi_1(x_0) = -a(x)\,\varphi_1(x_0) = 0$. Hence, $\varphi_1(x) > 0$ on $\overline{\Omega}$ and there exists C^* such that $\min_{x\in\overline{\Omega}} \varphi_1(x) \ge \frac{C^*}{\rho_0} > 0$, where ρ_0 is the same as in Condition 2.2. Since $\|u(t)\|_{L^\infty} \to 0$ as $t \to \infty$, there exists $T_0 > 0$ such that

$$d_2\, m_g\, \|N_2\|_{L^\infty}\, \|u(t)\|_{L^\infty} \le d_1\,\lambda_1, \quad \|u(t)\|_{L^\infty} \le \min\left(C^*,\, \rho_0,\, C^-\right) \quad \text{for all } t \ge T_0.$$

Then due to the inequality $|g'(s))| \le m_g\,|s|$ for all $|u| \le \rho_0$ in Condition 2.2, we have

$$|d_2\, g(u(t))\, N_2(t)| \le d_2\,\frac{1}{2}\,m_g\,|u(t)|^2\,\|N_2(t)\|_{L^\infty} \le \frac{1}{2}\,d_1\,\lambda_1\,|u(t)| \quad \text{for all } t \ge T_0. \tag{51}$$

Let $\overline{u}(x,t) := \lambda(t)\,\varphi_1(x)$ and $\lambda(t)$ be the solution of

$$\begin{cases} \lambda'(t) + \dfrac{1}{2}\,d_1\,\lambda_1\,\lambda(t) = 0 & \text{for } t \ge T_0, \\ \lambda(T_0) = \rho_0, \end{cases}$$

more explicitly

$$\lambda(t) = \rho_0\,\exp\left(-\frac{1}{2}\,d_1\,\lambda_1\,(t - T_0)\right) \quad \text{for } t \ge T_0.$$

Then

$$|\overline{u}(x,t)| = |\lambda(t)\,\varphi_1(x)| \le \rho_0 \quad \text{for } t \ge T_0$$

and $\overline{u}(x,t)$ satisfies

$$\begin{cases} \partial_t\,\overline{u}(x,t) = d_1\,\Delta\,\overline{u}(x,t) + \dfrac{1}{2}\,d_1\,\lambda_1\,\overline{u}(x,t) & (x,t) \in \Omega \times (T_0,\infty), \\ \overline{u}(x,T_0) = \rho_0\,\varphi_1(x) \quad x \in \Omega, \; -\partial_\nu\overline{u} = a(x)\,\overline{u}(x) & (x,t) \in \partial\Omega \times (T_0,\infty). \end{cases}$$

Here by (51), we note

$$\partial_t\,u - d_1\,\Delta\,u = d_2\,g(u)\,N_2(x,t) \le \frac{1}{2}\,d_1\,\lambda_1\,u(x,t) \quad \text{for a.e. } x \in \Omega \text{ and all } t \ge T_0,$$

$$u(x,T_0) \le C^* = \frac{C^*}{\rho_0}\cdot\rho_0 \le \varphi_1(x)\cdot\lambda(T_0) = \overline{u}(x,T_0).$$

Thus by the comparison theorem Proposition 1 with $h(u) = \frac{1}{2}\, d_1\, \lambda_1\, u$ and with 0 replaced by T_0, we have

$$u(x,t) \le \overline{u}(x,t) \le \lambda(t) \le \rho_0\, e^{-\frac{1}{2}d_1\lambda_1(t-T_0)} \ \ \forall t \ge T_0 \ \text{ for a.e. } x \in \Omega \text{ and all } t \ge T_0.$$

Since $g(s)$ is monotone increasing on $[0, \rho_0]$, by the 2nd property of Condition 2.2, we obtain

$$g(u(x,t)) \le g(\rho_0\, e^{-\frac{1}{2}d_1\lambda_1(t-T_0)}) \le \frac{m_g}{2}\, \rho_0^2\, e^{-d_1\lambda_1(t-T_0)} \ \text{ for a.e. } x \in \Omega \text{ and} \forall\ t \ge T_0.$$

Moreover, taking into account that $\|u(x,t)\|_{L^\infty} \le C^-$ for $t \ge T_0$, we have $f(u(x,t)) = 0$ and consequently

$$\partial_t\, N_2(x,t) = -g(u(x,t))\, N_2(x,t).$$

Thus $\partial_t\, N_2(x,t) \ge -\frac{1}{2}\, m_g\, \rho_0^2\, e^{-d_1\lambda_1(t-T_0)}\, N_2(x,t)$ for all $t \ge T_0$, whence follows

$$\int_{T_0}^{t} \frac{dN_2}{N_2} \ge -\int_{T_0}^{t} \frac{1}{2}\, m_g\, \rho_0^2\, e^{-d_1\lambda_1(t-T_0)}\, dt.$$

Hence

$$\log \frac{N_2(x,t)}{N_2(x,T_0)} \ge \left[\frac{1}{2}\, \frac{1}{d_1\lambda_1}\, m_g\, \rho_0^2\, e^{-d_1\lambda_1(s-T_0)} \right]_{s=T_0}^{s=t} = \frac{m_g\rho_0^2}{2d_1\lambda_1} \left[e^{-d_1\lambda_1(t-T_0)} - 1 \right].$$

Since $\partial_t N_2(x,t) < 0$ for $t \ge T_0$ we have

$$\frac{N_2(x,t)}{N_2(x,T_0)} < 1 \ \text{ and } \ \log \frac{N_2(x,t)}{N_2(x,T_0)} < 0.$$

Consequently,

$$\frac{N_2(x,T_0)}{N_2(x,t)} \le e^{\frac{m_g\rho_0^2}{2d_1\lambda_1}[1-e^{-d_1\lambda_1(t-T_0)}]}$$

and letting $t \to \infty$, we get

$$N_2^\infty(x) \ge N_2(x,T_0)\, e^{\frac{m_g\rho_0^2}{2d_1\lambda_1}}.$$

Then to complete the proof, it suffices to show that $\inf_{x\in\Omega} N_2(x,T_0) > 0$. For the case where $T_0 \le T_1$, it is clear that we can repeat the same argument above with T_0 replaced by T_1. Hence the conclusion is obvious. As for the case where $T_1 < T_0$, we note that N_2 satisfies

$$\partial_t N_2(x,t) \ge -\, g^*\, N_2(x,t) \quad \text{for all } t > 0,$$

which implies

$$\partial_t \left[N_2(x,t)\, e^{g^*(t-T_1)} \right] \ge 0 \quad \Rightarrow \quad N_2(x,t)\, e^{g^*(t-T_1)} \ge N_2(x,T_1).$$

Thus we obtain

$$N_2(x,T_0) \ge e^{-g^*(T_0-T_1)}\, N_2(x,T_1) \ge e^{-g^*(T_0-T_1)}\, \rho_1 > 0 \quad \text{for a.e. } x \in \Omega.$$

□

Remark 6. The following two assumptions are sufficient conditions for $N_2(T_1, x) \ge \rho_1 > 0$ for a.e. $x \in \Omega$ with $T_1 \in [0, \infty)$.

(1) $\inf_{x\in\Omega} N_2(x,0) > 0$.

(2) $\inf_{x\in\Omega} u(x,0) > C^-$, $\inf_{x\in\Omega} N_1(x,0) > 0$ and $f(s)$ is strictly monotone increasing on $[C^-, C^- + \delta_0]$.

In fact, it is clear that we can take $T_1 = 0$ for the case (1). As for the case (2), by assumption, there exist $t_1 > 0$ and $\bar{\rho}_1 > 0$ such that

$$f(u(x,t))\, N_1(x,t) \geq \bar{\rho}_1 > 0 \quad \text{for all } t \in [0, t_1].$$

Here we note that N_2 satisfies

$$\partial_t N_2(x,t) \geq f(u(x,t))\, N_1(x,t) - g^*\, N_2(x,t).$$

Hence we get

$$N_2(x,t) \geq e^{-g^* t} \int_0^t e^{g^* s} f(u(s,x))\, N_1(s,x)\, ds \geq \bar{\rho}_1\, t \quad \text{for all } t \in (0, t_1].$$

Thus we can take $T_1 = t_1$ and $\rho_1 = \bar{\rho}_1\, t_1$.

5.2. **Complete swelling.** We here consider the case where $C^- < \alpha$.

Theorem 5.3. *Let $C^- < \alpha$, then there exists some $T_c > 0$ such that the following exponential convergences hold.*

$$\begin{aligned}
N_1(x,t) &\xrightarrow{t\to\infty} 0 && \text{in } \mathcal{O}(e^{-\eta_1 t}) \quad \text{for a.e. } x \in \Omega,\\
N_2(x,t) &\xrightarrow{t\to\infty} 0 && \text{in } \mathcal{O}(e^{-\eta_2 t}) \quad \text{for a.e. } x \in \Omega,\\
N_3(x,t) &\xrightarrow{t\to\infty} \overline{N}(x) && \text{in } \mathcal{O}(e^{-\eta_2 t}) \quad \text{for a.e. } x \in \Omega,\\
\|u(t) - \alpha\|_{L^2}^2 &\xrightarrow{t\to\infty} 0 && \text{in } \mathcal{O}(e^{-\gamma_2 t}),\\
\|\nabla u(t)\|_{L^2}^2 &\xrightarrow{t\to\infty} 0 && \text{in } \mathcal{O}(e^{-\gamma_2 t}),
\end{aligned}$$

where η_1 is a positive number depending on $f(\cdot)$ and $C^- + \delta_0$, η_2 is any number satisfying $0 < \eta_2 < \min\,(\,\eta_1, g(\underline{\rho})\,)$ with $\underline{\rho} = \underline{\rho}(T_c) > 0$ and γ_2 is any number satisfying $0 < \gamma_2 < \min\,(\,\frac{d_1}{C_F}, 2\,\eta_2\,)$. Here the terminology $v(t) \xrightarrow{t\to\infty} v^\infty$ in $\mathcal{O}(e^{-kt})$ means that there exists some constant $C > 0$ such that

$$|v(t) - v^\infty| \leq C\, e^{-kt} \quad \textit{for all } t \geq T_c.$$

Proof. The uniform convergence of $u(x,t)$ to α implies that for any $\beta \in (0, \alpha - C^-)$, there exists a finite time $T_c = T_c(\beta) > 0$ such that

$$u(x,t) \geq C^- + \beta > C^- \quad \forall x \in \Omega \quad \forall t \geq T_c.$$

In order to derive the strict positivity of $f(u(x,t))$, we have to distinguish between two cases in accordance with Condition 2.3:

(i) Case where $\beta \geq \delta_0$ (δ_0 is the parameter appearing in Condition 2.3)
Since $u(x,t) \geq C^- + \beta \geq C^- + \delta_0$, it follows from (iii) of Condition 2.3 that

$$f(u(x,t)) \geq f(C^- + \delta_0) > 0 \quad \forall x \in \Omega \quad \forall t \geq T_c.$$

(ii) Case where $0 < \beta \leq \delta_0$
For this case, since $u(x,t) \in [C^- + \beta, C^- + \delta_0]$, from (ii) of Condition 2.3, we get

$$f(u(x,t)) \geq \eta_0 := \min\{\, f(s)\,;\, s \in [C^- + \beta, C^- + \delta_0]\,\} > 0 \quad \forall x \in \Omega \quad \forall t \geq T_c.$$

In summary we conclude

$$f(u(x,t)) \geq \eta_1 := \min\,(\, f(C^- + \delta_0), \eta_0\,) > 0 \quad \forall x \in \Omega \quad \forall t \geq T_c. \tag{52}$$

Substituting (52) into (2), we obtain the exponential decay estimate for $N_1(x,t)$:

$$N_1(x,t) \leq N_1(x,T_c)\, e^{-\eta_1 (t - T_c)} \leq \|\overline{N}\|_{L^\infty}\, e^{\eta_1 T_c}\, e^{-\eta_1 t} \quad \forall x \in \Omega \quad \forall t \geq T_c.$$

Furthermore substituting this into (3) and recalling (20), we get

$$\partial_t N_2(x,t) \le C_0\, e^{-\eta_1 t} - g(\underline{\rho})\, N_2(x,t), \quad \underline{\rho} = \rho(T_c), \quad C_0 = f^* \|\overline{N}\|_{L^\infty}\, e^{\eta_1 T_c}. \quad (53)$$

Let η_2 be any number satisfying $0 < \eta_2 < \min(\eta_1, g(\underline{\rho}))$. Then by (53), we easily get

$$\partial_t \left(e^{\eta_2 t} N_2(x,t)\right) \le C_0\, e^{-(\eta_1 - \eta_2)t} \quad \forall x \in \Omega \quad \forall t \ge T_c. \quad (54)$$

Hence integrating (54) over (T_c, t), we obtain the exponential decay of $N_2(x,t)$:

$$N_2(x,t) \le \left(e^{\eta_2 T_c} \|\overline{N}\|_{L^\infty} + \frac{C_0}{\eta_1 - \eta_2}\, e^{-(\eta_1 - \eta_2)T_c} \right) e^{-\eta_2 t} \quad \forall x \in \Omega \quad \forall t \ge T_c\,.$$

In analogy to the previous case, the conservation law together with the exponential decay obtained above implies

$$N_3^\infty(x) = \overline{N}(x) \quad \text{and} \quad N_3(x,t) \xrightarrow{t\to\infty} \overline{N}(x) \quad \text{in} \quad \mathcal{O}(e^{-\eta_2 t}) \quad \forall x \in \Omega \quad \forall t \ge T_c.$$

The exponential convergence of $\|u(t) - \alpha\|_{L^2}^2$ and $\|\nabla u(t)\|_{L^2}^2$ can be derived from the same reasoning as for the partial swelling case in Theorem 5.1 with $g(\underline{\rho})$ replaced by η_2. □

Remark 7. If $C^- < \alpha$ and $u_0(x) \ge \alpha$, then assertions of Theorem 5.3 hold true without assuming any structure conditions on f and g except Condition 2.1. In fact, let $\underline{u}^\alpha(x,t) \equiv \alpha$, then $\underline{u}^\alpha$ satisfies

$$\partial_t \underline{u}^\alpha(x,t) - d_1\, \Delta\, \underline{u}^\alpha = 0 \le d_2\, g(\underline{u}^\alpha)\, N_2 \quad \text{in } \Omega, \quad -\partial_\nu \underline{u}^\alpha = a(x)\,(\underline{u}^\alpha - \alpha) \quad \text{on } \partial\Omega.$$

Then from Proposition 1, we derive that $u(x,t) \ge \underline{u}^\alpha(x,t) \equiv \alpha$ for $a.e.x \in \Omega$ and all $t > 0$. Hence we can repeat the same arguments in the proof of Theorem 5.3.

6. Numerical illustrations.

We illustrate the previous results on longtime behavior with numerical simulations. For this, we have to specify appropriate functions $f(u)$ and $g(u)$. Following [4, 5] we choose

$$f(u) = \begin{cases} 0, & 0 \le u \le C^-, \\ \frac{f^*}{2}\left(1 - \cos\frac{(u - C^-)\pi}{C^+ - C^-}\right), & C^- \le u \le C^+, \\ f^*, & u > C^+, \end{cases} \quad (55)$$

and

$$g(u) = \begin{cases} \frac{g^*}{2}\left(1 - \cos\frac{u\pi}{C^+}\right), & 0 \le u \le C^+, \\ g^*, & u > C^+. \end{cases} \quad (56)$$

The model parameters used are summarized in Table 1. They have been chosen primarily to support, demonstrate, and emphasize the mathematical results. As in [4], as domain $\Omega \subset \mathbb{R}^2$ we choose a disc with diameter 1. In our simulations we use the radially symmetric initial data

$$u(0,x) = 2C^+ \left[\left(1 - \sqrt{x_1^2 + x_2^2}\right) \left(1 + \sqrt{x_1^2 + x_2^2}\right) \right]^4, \quad r := \sqrt{x_1^2 + x_2^2} \quad x \in \Omega$$

and

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

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

According to Theorems 5.1,5.2,5.3, important for the qualitative behavior of solutions is the external Ca^{2+} concentration value α, relative to the swelling induction threshold C^-. This is the parameter that we vary in our simulations. We choose $\alpha \in \{0, 10, 17, 25, 100, 250\}$. The first of these values reflects the situation in Theorem 5.2, the next two values represent the case $0 < \alpha < C^-$ of Theorem 5.1, and

TABLE 1. Default parameter values, cf also [5]

parameter	symbol	value	remark
lower (initiation) swelling threshold	C^-	20	(varied)
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	
diffusion coefficient	d_1	0.2	(varied)
feedback parameter	d_2	30	

the three largest values correspond to $C^- < \alpha$ as in Theorem 5.3. Note that for the largest value we have $\alpha > C^+$, whereas $C^- < \alpha < C^+$ holds for the other two values.

In Figure 1 we show for selected time instances u, N_1, N_2, N_3 for the simulation with external calcium ion concentration $\alpha = 10 < C^-$. The numerical results confirm the analysis in Theorem 5.1: The calcium ion concentration eventually attains $u = \alpha$ everywhere. The unswollen mitochondrial population N_1 remains unchanged after some initial period. In particular we note that in a layer close to the boundary almost no swelling is induced, whereas in the inner core swelling is induced everywhere. The mitochondrial population N_2 in the intermediate swelling state eventually goes to 0 everywhere.

Finally, the completely swollen mitochondria attain values close to 1 in the inner core and and close to 0 in an outer layer at the boundary, mirroring the distribution of N_1.

For the case $\alpha = 0$ we show in Figure 2 the spatial distribution of unswollen mitochondria N_1 for selected time instances. As predicted in Theorem 5.2, this distribution does not change after some finite time. Note that the second part of the assertion of Theorem 5.2, an assertion on the mitochondria in the swelling stage, N_2, does not apply to the case of our initial conditions, which are chosen such that at the boundary of the domain $u = 0$. Since also the boundary condition enforces very small values for u at the boundary for $t > 0$, the swelling threshold C^- is never exceeded there, wherefore the hypothesis of the theorem that $N_2(T_1, x) > \rho_1$ almost everywhere for some positive ρ_1 is not satisfied (see Remark 6).

To illustrate this claim, we ran a second set of simulations, with different initial conditions for u, chosen such that initially $u > 0$ everywhere in the domain. More specifically we used initial data defined using

$$u_0(x) = u_{base} + 2C^- \frac{\tilde{u}(x)}{\|\tilde{u}\|_\infty} \tag{57}$$

where the heterogeneity $\tilde{u}$ is defined as

$$\tilde{u}(x) = 2e^{-2\sqrt{x_1^2+x_2^2}} + \sin\left((x+y)\pi\right) + 1 \tag{58}$$

and the base concentration $u_{base} \in \{0, 15, 50, 100, 150, 220\}$ was varied.

In Figure 3 we plot the minimum values of N_2 in Ω as a function of t for these different choices. We observe that in all cases N_2 is bounded from below by a constant that depends on the initial data. For the base concentrations $u_{base} > C^-$, the minimum value of N_2 plateaus first at some high level (the higher the higher u_{base} and then at some T^* (the smaller the higher u_{base}) begins to drop to a lower value (the lower the higher u_{base}) that it eventually attains. Also in Figure 3 we plot

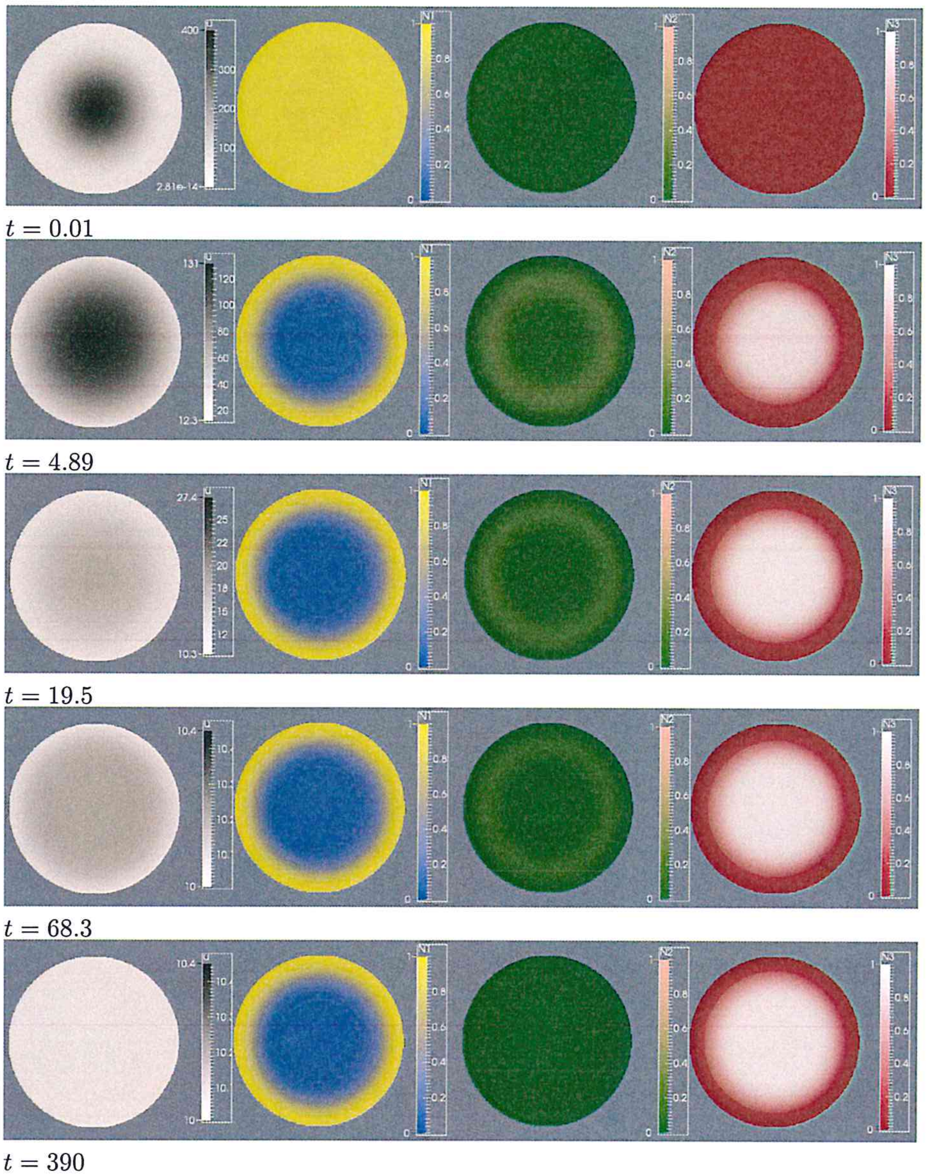

FIGURE 1. Model simulation with $\alpha = 10 < C^-$: Shown are u, N_1, N_2, N_3 for selected times.

for $u_{base} = 100$ the spatial distribution of mitochondrial populations N_1, N_2, N_3 at steady state, showing that $N_1 > 0$ a layer close to the boundary, illustrating partial swelling. Not that the spatially heterogeneities of the initial data of u have been largely obliterated and nearly, but not exactly, radially symmetric mitochondrial populations are found. The lack of complete radial symmetry is due to the fact that close to the boundary u drops below the swelling induction threshold C^- quickly, preventing further initiation of swelling there. Due to diffusion, the calcium ion concentration eventually attains 0 everywhere (data not shown).

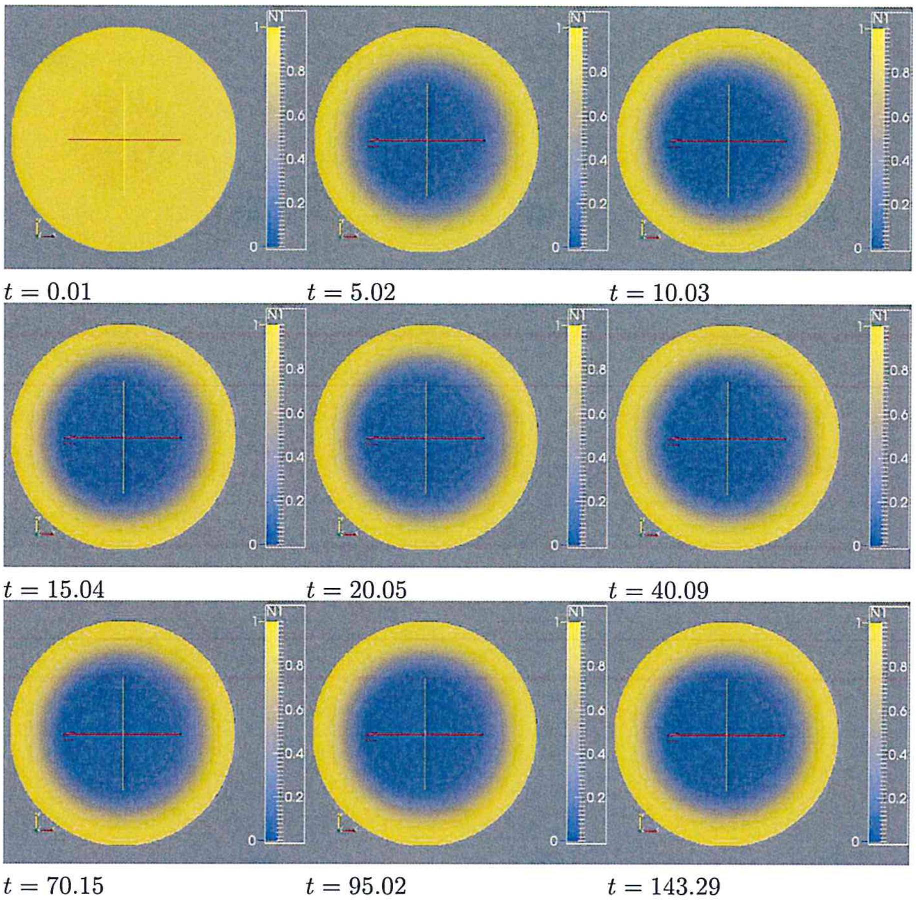

FIGURE 2. Model simulation with $\alpha = 10 < C^-$: Shown is N_1 for selected times.

To verify the longterm exponential convergence of the solutions we plot in Figure 4 for each of our choices of α the mitochondrial population densities N_1 and N_2 as a function of time for three different points of the domain that lay on a line through its center: point A is close to the boundary, B half way between the boundary and the center, and C is close to the center.

In all cases, for large enough t these curves negative sloped lines in the logscale, indicating exponential decrease.

In case $\alpha = 250$ very rapidly the calcium ion concentration is above C^+ in the entire domain leading to maximum swelling rates everywhere, whence the corresponding curves in all points overlay each other. In the cases $\alpha = 25$ and $\alpha = 100$ complete swelling occurs, i.e. both N_1 and N_2 go to 0 in all three points, where the curves of corresponding populations have the same or similar slope. In the cases $\alpha = 10$ and $\alpha = 17$, where partial swelling is observed, N_1 attains horizontal tangents for large t whereas the curves for N_2 decline. Note that convergence of N_2 is much slower for the lower external calcium ion concentration $\alpha = 10$ than for $\alpha = 17$. In the case $\alpha = 0$ eventually both N_1 and N_2 have horizontal tangents.

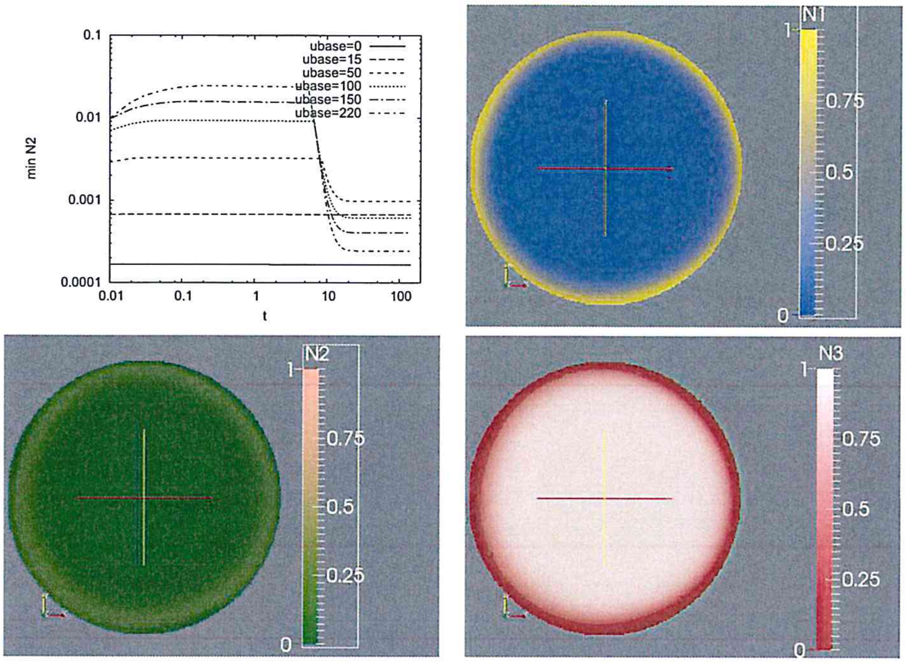

FIGURE 3. Simulation to illustrate partial swelling in Theorem 5.2, using initial data (refT2init:eq): shown is the minimum value of N_2 as a function of time for different base calcium ion concentrations u_{base} (top left), along with the steady state distributions for N_1 (top right), N_2 (bottom left), and N_3 (bottom right) in the case $u_{base} = 100$.

In the two simulations with lowest external calcium ion concentrations, $\alpha = 0$ and $\alpha = 10$ no swelling is induced at the point A close to the boundary, and N_1 remains at unity there, whereas $N_2 = N_3 = 0$.

The simulation for case $\alpha > C^-$, i.e Theorem 5.3, in Figure 4 shows that for the larger calcium ion concentrations, $\alpha = 100$ and $\alpha = 250$ both N_1 and N_2 converge to 0 and thus complete swelling occurs. For the remaining case $\alpha = 25 > C^-$, i.e. the case with lowest external calcium ion concentration, N_1 and N_2 also eventually decrease, but the simulation was stopped before the both populations approached 0. Comparing the cases for $\alpha \in \{25, 100, 250\}$ shows, as suggested by the analysis that the rate at which the populations N_1 and N_2 decline depend on the boundary data.

7. **Conclusion.** Biologically the convergence of $u(x,t)$ to α is exactly the result we expected. Additional Ca^{2+} is removed from the cell and the calcium gradient is again stabilized. Furthermore we have a complete classification of the swelling, i.e., $\alpha > C^-$ leading to complete swelling and $\alpha < C^-$ inducing partial swelling.

Here it is interesting to take a look at the relation with the classification of partial and complete swelling, obtained for the *in vitro* model in [6], where it is shown that

- u converges to a constant function u_∞ and $N_2 \to 0$ as $t \to \infty$,
- If $u_\infty < C^-$, then partial swelling occurs,

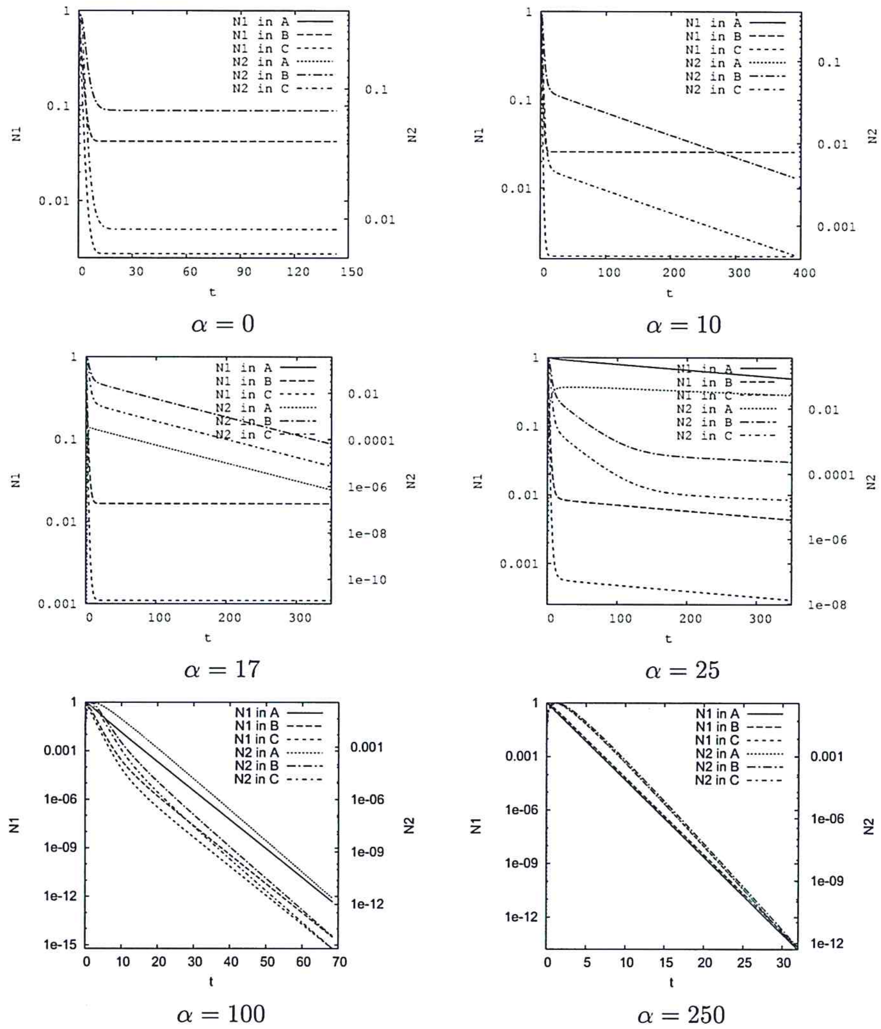

FIGURE 4. Mitochondria populations N_1 and N_2 as a function of time in three points of the domain on a line through the center point: A (close to the boundary), B (half way between boundary and center), C (in the center), for six different values of the external calcium ion concentration α.

- If $C^- < u_\infty$, then complete swelling occurs.

The threshold for C^- to determine partial swelling or complete swelling is given by u_∞ for the *in vitro* model and α for our *in vivo* model. The limit constant function u_∞ depends heavily on the choices of parameter values and initial data. To the contrary, α depends only on the constant extracellular calcium ion concentration C_{ext} and the concentration gradient β. In this sense, our *in vivo* model is regarded as more robust than *in vitro* model.

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