On an ODE-PDE coupling model of the mitochondrial swelling process

S. Eisenhofer[1] *, M.A. Efendiev[1], M. Ôtani[2] †, S. Schulz[3] and H. Zischka[3]

[1] Institute of Computational Biology, Helmholtz Center Munich, Ingolstädter, Landstrasse 1, 85764 Neuherberg, Germany
[2] Department of Applied Physics, School of Science and Engineering, Waseda University, 3-4-1, Okubo, Shinjuku-ku, Tokyo, Japan 169-8555
[3] Institute of Molecular Toxicology and Pharmscology, Helmholtz Center Munich, Ingolstädter, Landstrasse 1, 85764 Neuherberg, Germany

Abstract

Mitochondrial swelling has huge impact to multicellular organisms since it triggers apoptosis, the programmed cell death. In this paper we present a new mathematical model of this phenomenon. As a novelty it includes spatial effects, which are of great importance for the *in vivo* process. Our model considers three mitochondrial subpopulations varying in the degree of swelling. The evolution of these groups is dependent on the present calcium concentration and is described by a system of ODEs, whereas the calcium propagation is modeled by a reaction-diffusion equation taking into account spatial effects. We analyze the derived model with respect to existence and long-time behavior of solutions and obtain a complete mathematical classification of the swelling process.

1 Introduction

Biological background Mitochondria are often termed the cell's powerhouse due to their main function as energy supplier for almost all eukaryotic cells [1]. However, these double-membrane enclosed organelles also play a decisive 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 [13], 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 [14]. The increased permeability leads to an osmotically driven influx of solutes and water into the mitochondrial matrix, which in turn causes swelling [8], [14]. This process culminates in the rupture of the outer membrane [20]. Outer membrane rupture denotes

*Email: sabine.eisenhofer@gmail.com

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a critical event, since now apoptosis is irreversibly triggered by the release of several proapoptotic factors from the intermembrane space [15].

Intact mitochondria store calcium in their matrix. If swelling is induced, this stored calcium is additionally released [15] and the remaining mitochondria are confronted with an even higher calcium load, leading to an acceleration of the process.

Experimental procedure The swelling of mitochondria is 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. Hence the volume increase is indirectly displayed by a decreasing optical density. This relation is shown to be linear [5], [11], [21]. The experiments were performed at the Helmholtz Zentrum München, Institute of Molecular Toxicology and Pharmacology using rat liver mitochondria and Ca^{2+} as swelling inducer.

Existing models Although the process of mitochondrial swelling induced by calcium is known for more than 30 years, mathematical modeling has only started recently. At this there are two conceptually different approaches: The microscale models focussing on a detailed description of all biochemical processes in single mitochondria [22], [25], and the macroscale models which directly aim to represent the swelling of a whole population [5], [11], [17].

In our previous publication [11], we presented a mathematical model that is for the first time capable to describe the whole time progress of mitochondrial swelling. The model is based on the observation that mitochondria vary within subpopulation concerning their sensitivity for swelling induction as it was described in [26]. It consists of one ODE for the fraction of swollen mitochondria and a delay equation to determine the corresponding population volume. This model is in great accordance with the experimentally obtained data and shows consistent parameter values with increasing Ca^{2+} concentrations. In [10], it has been shown (see Fig2.1, page 15) the dependence of swelling curves at different calcium concentrations and how the swelling curves can be modeled with the simple mathematical model. The most important parameters of the model among others is the feedback parameter and the parameter depicting the average swelling time of mitochondria. The analysis of the simple model also yielded that the experimental swelling curves can only be described in an accurate way by including the positive feedback, otherwise one could not receive the correct shape of the swelling curves.

Furthermore, different swelling inducers and mitochondria from different organs can be classified by comparing the corresponding optimal parameter values.

Spatial effects Experiments revealed the necessity to take into account spatial effects. In fact, models taking into account of spatial effects are discussed in [2] and [3].

The same amount of Ca^{2+} is added in different concentrations, i.e. mitochondria are exposed to identical calcium quantities with varying levels of concentration profiles. This leads to different shapes of the corresponding swelling curves, which only trace back to the different calcium distributions. Obviously this implies the influence of spatial effects.

In particular the dependence on local processes gets important when thinking of mitochondrial swelling taking place *in vivo*. There are two mechanisms that lead to intracellular Ca^{2+} increase (see e.g. [23], [24]): Internal release from the endoplasmic reticulum or external calcium influx from the extracellular milieu. Both calcium sources are highly localized. Furthermore mitochondria within cells are not distributed randomly but reside in three main regions [18], which enforces the influence of spatial effects.

2 The mitochondria model

In this work we introduce a new mathematical model that takes into account the above mentioned spatial effects. This results in a coupled ODE-PDE system.

2.1 Description

In accordance with our theoretical [11] and experimental [26] findings, we assume that three subpopulations of mitochondria with different corresponding volumes exist. Here $N_1(x,t)$ describes the density of intact, unswollen mitochondria, $N_2(x,t)$ contains mitochondria that are in the swelling process but not completely swollen and $N_3(x,t)$ denotes the density of completely swollen mitochondria. The Ca^{2+} concentration is denoted by $u(x,t)$.

The transition of intact mitochondria over swelling to completely swollen ones proceeds in dependence on the local calcium concentration. At this we can 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 the 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:

$$\partial_t u = d_1 \Delta u + d_2 g(u) N_2 \quad (1)$$

$$\partial_t N_1 = -f(u) N_1 \quad (2)$$

$$\partial_t N_2 = f(u) N_1 - g(u) N_2 \quad (3)$$

$$\partial_t N_3 = g(u) N_2 \quad (4)$$

with diffusion constant $d_1 > 0$ and feedback parameter $d_2 > 0$. The boundary conditions are given by

$$\partial_\nu u = 0 \quad \text{on } \partial\Omega \quad (5)$$

and we have initial values

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

Model function f The process of mitochondrial permeability transition is dependent on the calcium 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^- displaying the concentration which is needed to start the whole process. Whenever this Ca^{2+} threshold is reached, the local transition at this point from N_1 to N_3 over N_2 is inevitably triggered. It is written e.g. in [21] that 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, hence we also postulate that there is some saturation rate f^* displaying the maximal transition rate. This is biologically explained by a bounded speed of pore opening with increasing calcium concentrations.

Remark
The initiation threshold of f is crucial for the whole swelling procedure. Dependent on the amount and location of added calcium, 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 threshold C^- is not reached anymore. Thus we only have partial swelling and after the whole process there are still intact mitochondria left. Nevertheless, there are no mitochondria in the intermediate state N_2.

Model function g The change of the population N_2 consists of mitochondria entering the swelling process (coming from N_1) and mitochondria getting completely swollen (leaving to N_3). The transition from N_2 to N_3 is modeled by the transition function $g(u)$. In contrast to the function f, here we have no initiation threshold and this transition can not be avoided. This property is based on the biological mechanism. The permeabilization of the inner membrane due to pore opening leads to water influx and hence unstoppable swelling of the mitochondrial matrix. This process itself is independent of the present calcium concentration. Due to a limited pore size, this effect also has its restriction and thus we have saturation at level g^*. However, biologically it is not clear if there are other influences of calcium to this second transition, e.g. by the opening of additional pores. To include such possibilities, we allow for general increasing g with saturation at level g^*.

In [26], they proved that there are different mitochondrial subpopulations and gave the shapes of the functions f and g as described in the section "Numerical Simulations" discussed with biologists.

The third population N_3 of completely swollen mitochondria grow 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. 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 our earlier ODE approach [11] we showed that it is essential to include a positive feedback mechanism. It is not possible to display the correct swelling behavior without the positive feedback, even with the much more simple model. In the biological community there is no doubt about the existence of the positive feedback. This accelerating effect is induced by stored calcium inside the mitochondria, which is additionally released once the mitochondrion gets 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, i.e., those mitochondria leaving N_2 and entering N_3. Here the feedback parameter d_2 describes the amount of stored calcium.

In this paper we are interested in the well-posedness and long-time behavior of solutions. The unique existence of the global solution is obtained by the contraction mapping principle. Furthermore we present a classification of limiting profiles. Depending on an a-priori given threshold, we show two possible scenarios, i.e., partial and complete swelling.

2.2 Well-posedness

The coupled ODE-PDE model (1) - (5) describing the mitochondrial swelling process will now be analyzed mathematically. At first we want to show the global existence and uniqueness of the solution (u, N_1, N_2, N_3) on the phase space $L^2(\Omega)$. For that purpose we introduce some assumptions to the model functions f and g.

Condition 1
For the model functions $f : \mathbb{R} \to \mathbb{R}$ and $g : \mathbb{R} \to \mathbb{R}$ it holds:

(i) Non-negativity and Boundedness:

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

(ii) Lipschitz continuity:

$$\begin{aligned} &|f(s_1) - f(s_2)| \le L_f\, |s_1 - s_2|, \quad \forall s_1, s_2 \in \mathbb{R}, \\ &|g(s_1) - g(s_2)| \le L_g\, |s_1 - s_2| \quad \forall s_1, s_2 \in \mathbb{R} \quad \text{with } 0 \le L_f, L_g. \end{aligned}$$

One remarkable characteristic of the model is the following conservation law:

$$\overline{N}(x,t) = \overline{N}(x) = N_{1,0}(x) + N_{2,0}(x) + N_{3,0}(x) \qquad \forall t \ge 0 \quad \forall x \in \Omega\,, \tag{6}$$

i.e. the total population $\overline{N} := N_1(x,t) + N_2(x,t) + N_3(x,t)$ does not change and is given by the sum of the initial data. In fact, adding three equations (2) + (3) + (4), we obtain $\partial_t \overline{N} = 0$. The following theorem yields the desired result of well-posedness.

Theorem 1
Let Ω be a bounded domain in $\mathbb{R}^n$ and let Condition 1 be satisfied. Then for all initial data $u_0 \in L^2(\Omega)$, $N_{i,0} \in L^\infty(\Omega)$ $(i = 1, 2, 3)$, the system (1) - (5) possesses a unique global solution (u, N_1, N_2, N_3) satisfying

$$\begin{aligned} &u \in C([0,T]; L^2(\Omega)),\ N_i \in L^\infty(0,T; L^\infty(\Omega)), \quad (i = 1,2,3)\,, \\ &\sqrt{t}\, \partial_t u,\ \sqrt{t}\, \Delta u \in L^2(0,T; L^2(\Omega)), \quad \textit{for all } T > 0. \end{aligned}$$

Proof
We first note that by (6) 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 :

$$\partial_t N^u = (-f(u) N_1^u, \quad f(u) N_1^u - g(u) N_2^u) =: F^u(N^u),\ N^u(x,0) = (N_{1,0}(x), N_{2,0}(x)) \tag{7}$$

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

$$\partial_t \hat{u} = d_1 \Delta \hat{u} + d_2 g(\hat{u}) N_2^u, \quad \partial_\nu \hat{u}\big|_{\partial\Omega} = 0, \quad \hat{u}(x,0) = u_0(x). \tag{8}$$

Obviously, by Condition 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 (7) for each $u \in X_T$. Furthermore, since the mapping $u \mapsto g(u)N_2^u$ is Lipschitz continuous from $L^2(\Omega$ into itself by Condition 1, the standard argument shows that (8) 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. [4], [9] or in a more abstract way in [6], [19]).
In order to show that $\mathcal{B}$ becomes a contraction mapping in X_T for a sufficiently small $T \in (0,1]$, we are going to establish a priori estimates for the difference of two solutions. We put

$$\delta u = u_1 - u_2, \quad \delta N_j = N_j^{u_1} - N_j^{u_2} \ (j = 1,2), \quad \delta\hat{u} = \hat{u}_1 - \hat{u}_2,$$

where $N^{u_i} = (N_1^{u_i}, N_2^{u_i})$ is the solution of (7) with $u = u_i,\ N^{u_i}(x,0) = (N_{1,0}(x), N_{2,0}(x))$ and $\hat{u}_i$ is the solution of (8) with $N_2^u = N_2^{u_i},\ \hat{u}_i(x,0) = u_0(x)$. Then δN_j and $\delta\hat{u}$ satisfy

$$\partial_t \delta N_1 = -f(u_1)\delta N_1 + \big(f(u_2) - f(u_1)\big) N_1^{u_2}, \tag{9}$$

$$\partial_t \delta N_2 = f(u_1)\delta N_1 + \big(f(u_1) - f(u_2)\big) N_1^{u_2} - g(u_1)\delta N_2 + \big(g(u_2) - g(u_1)\big) N_2^{u_2}, \tag{10}$$

$$\partial_t \delta\hat{u} = d_1 \Delta \delta\hat{u} + d_2 g(\hat{u}_1)\delta N_2 + d_2\big(g(\hat{u}_1) - g(\hat{u}_2)\big) N_2^{u_2}, \tag{11}$$

$$\delta N_1(0) = 0, \quad \delta N_2(0) = 0, \quad \delta\hat{u}(0) = 0. \tag{12}$$

Then by virtue of the boundedness of f and g, we obtain

$$\|N_1^{u_i}(t)\|_{L^\infty(\Omega)} \le \|N_{1,0}\|_{L^\infty(\Omega)}\, e^{f^* t} := C_1(t) \quad \forall t > 0, \tag{13}$$

$$\|N_2^{u_i}(t)\|_{L^\infty(\Omega)} \le \big(\|N_{1,0}\|_{L^\infty(\Omega)}\, e^{f^* t} + \|N_{2,0}\|_{L^\infty(\Omega)}\big)\; e^{g^* t} := C_2(t) \quad \forall t > 0. \tag{14}$$

Step 1 Multiplying (9) by δN_1 and using the Lipschitz continuity and positivity of f, we get

$$\frac{d}{dt}\|\delta N_1(t)\|_{L^2(\Omega)} \le L_f\, \|N_1^{u_2}\|_{L^\infty(\Omega)}\, \|\delta u(t)\|_{L^2(\Omega)}\, \|\delta N_1(t)\|_{L^2(\Omega)}.$$

Hence by (12) and (13), we get

$$\|\delta N_1(t)\|_{L^2(\Omega)} \le L_f C_1(T) \int_0^t \|\delta u(s)\|_{L^2(\Omega)}\, ds \quad \forall t \in [0,T]\,. \tag{15}$$

Step 2 Multiplying (10) by δN_2 and using the Lipschitz continuity of f, g, the positivity of g, boundedness of f, (13) and (14), we now have

$$\begin{aligned}\frac{d}{dt}\|\delta N_2\|_{L^2(\Omega)} &\le f^*\, \|\delta N_1\|_{L^2(\Omega)} + L_f\, \|\delta u\|_{L^2(\Omega)}\, \|N_1^{u_2}\|_{L^\infty(\Omega)} + L_g\, \|\delta u\|_{L^2(\Omega)}\, \|N_2^{u_2}\|_{L^\infty(\Omega)} \\ &\le f^*\, \|\delta N_1\|_{L^2(\Omega)} + \underbrace{\big(L_f\, C_1(T) + L_g\, C_2(T)\big)}_{=:C_{1,2}(T)} \|\delta u(t)\|_{L^2(\Omega)}.\end{aligned}$$

Then by (12) and (15), we get

$$\|\delta N_2(t)\|_{L^2(\Omega)} \le \underbrace{\big(f^*\, L_f\, C_1(T)\, T + C_{1,2}(T)\big)}_{=:C_3(T)} \int_0^t \|\delta u(s)\|_{L^2(\Omega)}\, ds \quad \forall t \in [0,T] \tag{16}$$

Step 3 Multiplying (11) by δu and using the Lipschitz continuity and boundedness of g, we have

$$\frac{d}{dt}\|\delta\hat{u}(t)\|_{L^2(\Omega)} \leq d_2\, g^*\, \|\delta N_2(t)\|_{L^2(\Omega)} + d_2\, L_g\, \|\delta\hat{u}(t)\|_{L^2(\Omega)}\, \|N_2^{u_2}(t)\|_{L^2(\Omega)}.$$

Hence by (16) and (12), we obtain for any $t \in (0, S]$ and $S \in (0, T]$

$$\|\delta\hat{u}(t)\|_{L^2(\Omega)} \leq d_2\, g^* C_3(T)\, S^2 \max_{0\leq t\leq S} \|\delta u(t)\|_{L^2(\Omega)} + d_2\, L_g\, C_2(T)\int_0^t \|\delta\hat{u}(s)\|_{L^2(\Omega)}\, ds$$

Consequently we find

$$\begin{aligned}\|\mathcal{B}(u_1) - \mathcal{B}(u_2)\|_{X_S} = \|\delta\hat{u}\|_{X_S} &\leq d_2\, g^* C_3(T) S^2\, e^{d_2 L_g C_2(T) S}\, \|\delta u\|_{X_S} \\ &= d_2\, g^* C_3(T) S^2\, e^{d_2 L_g C_2(T) S}\, \|u_1 - u_2\|_{X_S}.\end{aligned}$$

Thus there exists a sufficiently small T_0 depending on T and other parameters but not on the initial data such that $\mathcal{B}$ possesses a unique fixed point $u \in X_{T_0}$. In other words, (u, N_1^u, N_2^u) gives a solution of the system (1) - (5). The uniqueness of (N_1^u, N_2^u) follows from (15) and (16) directly. Since $T_0 > 0$ does not depend on the choice of initial data, it is easy to see that this local solution can be continued up to $[0, T]$ for any T.

□

The model variables have a biological meaning and hence it is important to show that they are non-negative. This is done in the following.

Proposition 2
Let all assumptions of Theorem 1 hold and in addition assume that

$$u_0 \geq 0, \quad N_{1,0} \geq 0, \quad N_{2,0} \geq 0, \quad N_{3,0} \geq 0\,.$$

Then the solution (u, N_1, N_2, N_3) *preserves non-negativity. Furthermore* N_1*,* N_2 *and* N_3 *are uniformly bounded in* $\Omega \times [0, \infty)$*.*

Proof
1.) Non-negativity
Multiply the equations by the negative part of solutions $(u^-, N_1^-, N_2^-, N_3^-)$, $v^- = \max(-u, 0)$. Then by using the Lipschitz continuity of f, g and Gronwall's inequality, we can deduce that $(u^-(t), N_1^-(t), N_2^-(t), N_3^-(t))$ are all 0 for all $t > 0$.

2.) Uniform boundedness of (N_1, N_2, N_3)
From the conservation law (6) and the proved non-negativity of the ODE parts N_1, N_2 and N_3 it follows immediately

$$0 \leq N_i(x,t) \leq \|\overline{N}\|_{L^\infty(\Omega)} \quad \forall t \geq 0\,,\ \text{a.e. } x \in \Omega\,,\ i = 1, 2, 3\,. \tag{17}$$

□

2.3 Asymptotic behavior of solutions

Now the longtime behavior of the solution (u, N_1, N_2, N_3) is studied. This behavior is highly dependent on the special structure of the model functions f and g.

Proposition 3
Let all assumptions of Theorem 1 and Proposition 2 hold and in addition assume $u_0 \not\equiv 0$. Then the unique solution u is strictly positive for $t > 0$ and becomes bounded below by a strictly positive constant:

$$\exists\, t_* > 0 \text{ and } \exists\, \varrho > 0 : \quad u(x,t) \geq \varrho > 0 \quad \forall t \geq t_* \quad \forall x \in \Omega.$$

Proof

The solution u fulfills the PDE problem

$$\partial_t u = d_1 \Delta u + d_2 g(u) N_2, \quad \partial_\nu u\big|_{\partial\Omega} = 0, \quad u(x,0) = u_0(x). \tag{18}$$

For the proof we introduce a subsolution $\underline{u}$ of (18) by

$$\partial_t \underline{u} = d_1 \Delta \underline{u}, \quad \partial_\nu \underline{u}\big|_{\partial\Omega} = 0, \quad \underline{u}(x,0) = u_0(x). \tag{19}$$

Since $d_2 g(u) N_2 \geq 0$, it follows from the comparison principle that

$$\underline{u}(x,t) \leq u(x,t) \quad \forall (x,t) \in \Omega_T := \Omega \times (0,T]\,.$$

Comparing $\underline{u}$ with the subsolution $\underline{\underline{u}} \equiv 0$ of (19) and applying the strong parabolic maximum principle, we obtain the strict bound $u(x,t) > 0$.
Furthermore, we note that Hop's maximum principle together with the fact $u(x,t) > 0$ and the homogeneous Neumann boundary condition assures the strict positivity of $u(x,t) > 0$ on the boundary. Thus we find that

$$\exists\, t_* > 0,\ \exists\, \varrho > 0 \ \text{ such that } \ \min_{x \in \bar\Omega} u(x, t_*) \geq \varrho > 0\,.$$

Then $\underline{u}_\varrho \equiv \varrho$ satisfies

$$\partial_t \underline{u}_\varrho - d_1 \Delta \underline{u}_\varrho = \partial_t \underline{u} - d_1 \Delta \underline{u} \quad \partial_\nu \underline{u}_\varrho\big|_{\partial\Omega} = \partial_\nu \underline{u}\big|_{\partial\Omega} = 0,\ \forall t \geq t_*, \quad \underline{u}_\varrho(x,t_*) \leq \underline{u}(x,t_*).$$

Again applying the comparison principle, we obtain

$$u(x,t) \geq \underline{u}(x,t) \geq \underline{u}_\varrho \equiv \varrho \qquad \forall t \geq t_* \quad \forall x \in \Omega\,.$$

□

This result is now used to obtain information about the type of convergence as time goes to infinity. For that we need additional assumptions on the functions f and g.

Condition 2
Let the model functions $f : \mathbb{R} \to \mathbb{R}$ and $g : \mathbb{R} \to \mathbb{R}$ fulfill Condition 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:

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

(ii) Smoothness in $[C^-, C^- + \delta_0]$:

$$m_1(s - C^-) \leq f'(s) \leq m_2(s - C^-) \quad \forall s \in [C^-, C^- + \delta_0].$$

(iii) Lower bounds:

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

(iv) Monotonicity in $[0, \varrho_0]$:

$$g'(s) > 0 \quad \forall s \in [0, \varrho_0].$$

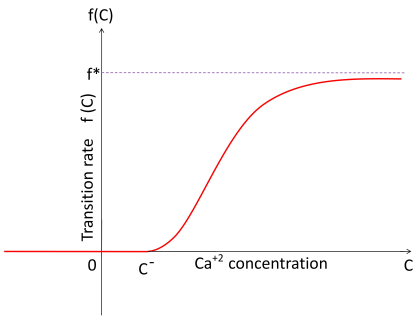

Figure 1 – A typical example of f

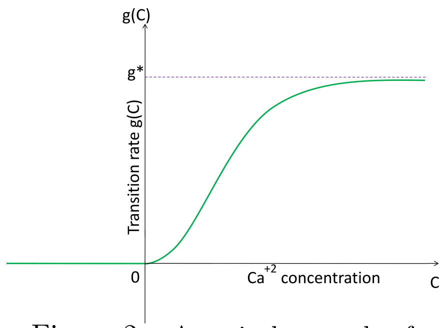

Figure 2 – A typical example of g

In order to show several convergence results we need the following proposition, which can be easily derived from the standard Gronwall's Lemma.

Proposition 4
Let $y(t)$ and $a(t)$ be non-negative functions with $y \in C^1([t_0, t_1))$ and $a \in C([t_0, t_1))$ for $0 \leq t_0 < t_1 \leq \infty$. Suppose that y satisfies for some $\gamma_0 > 0$

$$\frac{d}{dt} y(t) + \gamma_0 \, y(t) \leq a(t) \quad t_0 \leq t < t_1. \tag{20}$$

Then the following estimates hold true.

(i) If $a(t) \equiv C$ in $[t_0, t_1)$, then $y(t) \leq y(t_0) + \dfrac{C}{\gamma_0} \quad \forall t \in [t_0, t_1)$.

(ii) If $t_1 = +\infty$ and $\int_{t_0}^{\infty} a(t)\, dt < \infty$, then $y(t) \leq y(s)\, e^{-\gamma_0 (t-s)} + \int_s^{\infty} a(t)\, dt$ for all $s \in [t_0, +\infty)$. In particular $y(t) \to 0$ as $t \to +\infty$.

Multiplying the differential inequality by $e^{\gamma_0 t}$, we easily get

$$y(t) \leq y(t_0)\, e^{-\gamma_0 (t - t_0)} + \int_{t_0}^{t} a(s)\, e^{-\gamma_0 (t-s)}\, ds\,.$$

Hence with the aid of simple calculations, we can deduce statements above.

The next theorem gives information about the strong convergence of the solution.

Theorem 5
Let Condition 2 and assumptions in Proposition 2 be satisfied. Then we have the following strong convergence results:

$$N_1(x,t) \xrightarrow{t\to\infty} N_1^\infty(x) \geq 0 \qquad \textit{in } L^p(\Omega), \quad 1 \leq p < \infty \tag{21}$$

$$N_2(x,t) \xrightarrow{t\to\infty} N_2^\infty(x) \equiv 0 \qquad \textit{in } L^p(\Omega), \quad 1 \leq p < \infty \tag{22}$$

$$N_3(x,t) \xrightarrow{t\to\infty} N_3^\infty(x) \leq \|\overline{N}\|_{L^\infty(\Omega)} \quad \textit{in } L^p(\Omega), \quad 1 \leq p < \infty \tag{23}$$

$$u(x,t) \xrightarrow{t\to\infty} u^\infty(x) \equiv C \qquad \textit{in } L^2(\Omega)\,. \tag{24}$$

Proof

(1) From the model equation (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

$$N_1(x,t) \xrightarrow{t\to\infty} N_1^\infty(x) \geq 0 \quad \text{a.e.} x \in \Omega\,. \tag{25}$$

Furthermore, by (17) we find

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

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 (21), it suffices to use the relation

$$\|N_1(t) - N_1^\infty\|_{L^p(\Omega)}^p \leq \big(\|N_1(t)\|_{L^\infty(\Omega)} + \|N_1^\infty\|_{L^\infty(\Omega)}\big)^{p-1}\,\|N_1(t) - N_1^\infty\|_{L^1(\Omega)}.$$

(2) As for $N_3(x,t)$, the model equation (4) gives

$$\partial_t N_3(x,t) = g\big(u(x,t)\big)N_2(x,t) \geq 0 \quad \forall t \geq 0 \quad \text{a.e.} x \in \Omega\,.$$

Since $N_3(x,t)$ is bounded above by $\|\overline{N}\|_{L^\infty(\Omega)}$, the monotonicity yields the almost everywhere convergence

$$N_3(x,t) \xrightarrow{t\to\infty} N_3^\infty(x) \leq \|\overline{N}\|_{L^\infty(\Omega)} \qquad \text{for a.e. } x \in \Omega\,. \tag{26}$$

Moreover $|N_3(x,t)|$ is also dominated by $\|\overline{N}\|_{L^\infty(\Omega)}$, then by the same arguments for N_1 above we can deduce (23).

(3) Combining (6) with (25) and (26), we easily obtain the almost everywhere convergence for N_2

$$N_2(x,t) \to N_2^\infty(x) := \overline{N}(x) - N_1^\infty(x) - N_3^\infty(x) \qquad \text{for a.e. } x \in \Omega\,.$$

and the convergence in $L^p(\Omega)$ follows immediately as before.

$$N_2(\cdot,t) \to N_2^\infty(x) \geq 0 \quad \text{strongly in } L^p(\Omega)\ (1 \leq p < \infty) \text{ as } t \to \infty. \tag{27}$$

(4) Here we are going to show that $N_2^\infty(x) \equiv 0$. To this end, we first note that the integration of (4) on $(0,t)$ gives

$$0 \le \int_0^t g(u(x,s))\, N_2(x,s)\, dt = N_3(x,t) - N_3(x,0) \le \|\overline{N}\|_{L^\infty(\Omega)} \quad \forall t > 0. \tag{28}$$

Then by (28), Proposition 3 and (iii), (iv) of Condition 2, it holds

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

where $\underline{\varrho} := \min(\varrho, \varrho_0) > 0$. Hence we obtain

$$\int_{t_*}^\infty \|N_2(t)\|_{L^1(\Omega)}\, dt = \|N_2\|_{L^1(t_*,\infty;L^1(\Omega))} \le \frac{|\Omega|}{g(\underline{\varrho})} \|\overline{N}\|_{L^\infty(\Omega)}\,. \tag{29}$$

Therefore 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 (27) 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 order to show the convergence properties of u, we use the following orthogonal decomposition

$$u(x,t) = a_1(t)\, \varphi_1(x) + \varphi^\perp(x,t), \tag{30}$$

where $\varphi_1(x) \equiv C_\varphi = |\Omega|^{-1/2}$ is the eigenfunction for the first eigenvalue $\lambda_1 = 0$ of $-\Delta$ with the homogeneous Neumann boundary condition and $\varphi^\perp(x,t)$ is orthogonal to $\varphi_1(x)$, i.e.,

$$\varphi^\perp(x,t) \in H^\perp := \{\, w \in H^2(\Omega)\,;\, \int_\Omega w(x)\, dx = 0,\ \partial_\nu w\big|_{\partial\Omega} = 0\,\}. \tag{31}$$

Multiplying (1) by $\varphi_1(x)$ and using the integration by parts, we get

$$\frac{d}{dt} a_1(t) = d_2\, C_\varphi \int_\Omega g(u(x,t)) N_2(x,t)\, dx \ge 0\,, \quad a_1(t) = C_\varphi \int_\Omega u(x,t)\, dx. \tag{32}$$

Hence the function $a_1(t)$ is non-decreasing in t. Furthermore, substituting the relation $g(u(x,t))N_2(x,t) = \partial_t N_3(x,t)$ into (32), we obtain

$$\begin{aligned} a_1(t) &= a_1(0) + d_2 C_\varphi \left(\int_\Omega N_3(x,t)\, dx - \int_\Omega N_3(x,0)\, dx \right) \\ &\le C_\varphi\, |\Omega|^{1/2} \|u_0\|_{L^2(\Omega)} + d_2\, C_\varphi\, |\Omega| \|\overline{N}\|_{L^\infty(\Omega)} =: C_{a_1} < \infty. \end{aligned} \tag{33}$$

Thus we find

$$a_1(t) \to a_1^\infty \quad \text{as } t \to \infty. \tag{34}$$

In order to show that u converges to a constant function, it is thus sufficient to show that $\varphi^\perp(t,x) \to 0$ as $t \to \infty$ for a.e. $x \in \Omega$.
Here by Wirtinger's inequality (see [7]), we get

$$\|v\|_{L^2(\Omega)} \le C_W \|\nabla v\|_{L^2(\Omega)} \quad \text{for all } v \in \{\, v \in H^1(\Omega)\,;\, \int_\Omega v(x)\,dx = 0\,\}.$$

Furthermore, for any $v \in H^\perp$, using the fact that v satisfies the homogeneous Neumann boundary condition and Wirtinger's inequality again, we get

$$\|\nabla v\|^2_{L^2(\Omega)} = (v, -\Delta v)_{L^2(\Omega)} \le \|v\|_{L^2(\Omega)} \|\Delta v\|_{L^2(\Omega)} \le C_W \|\nabla v\|_{L^2(\Omega)} \|\Delta v\|_{L^2(\Omega)} \quad \forall v \in H^\perp.$$

Thus we obtain

$$\|v\|_{L^2(\Omega)} \le C_W \|\nabla v\|_{L^2(\Omega)} \le C_W^2 \|\Delta v\|_{L^2(\Omega)} \quad \forall v \in H^\perp. \tag{35}$$

Substitution of the decomposition (30) into the PDE (1) leads to

$$\frac{d}{dt} a_1(t)\varphi_1 + \partial_t \varphi^\perp(x,t) = d_1 \Delta \varphi^\perp(x,t) + d_2\, g(u(x,t))\, N_2(x,t) \tag{36}$$

Multiplying (36) by $\varphi^\perp$, we get

$$\frac{1}{2}\frac{d}{dt}\|\varphi^\perp(t)\|^2_{L^2(\Omega)} + d_1 \|\nabla \varphi^\perp(t)\|^2_{L^2(\Omega)} = d_2 \int_\Omega g(u(x,t)) N_2(x,t) \varphi^\perp(x,t)\,dx\,. \tag{37}$$

Then by (35) and Hölder's inequality, we obtain

$$\frac{d}{dt}\|\varphi^\perp(t)\|^2_{L^2(\Omega)} + \frac{d_1}{(C_W)^2}\|\varphi^\perp(t)\|^2_{L^2(\Omega)} \le \frac{{d_2}^2 {C_W}^2}{d_1} \|g(u(t))N_2(t)\|^2_{L^2(\Omega)}\,. \tag{38}$$

Here we note (29) implies

$$\int_0^\infty \int_\Omega |g(u(x,t))N_2(x,t)|^2\,dx\,dt \le |\Omega|\, \frac{{g^*}^2}{g(\underline{\varrho})} \|\overline{N}\|^2_{L^\infty(\Omega)} < \infty\,. \tag{39}$$

Then applying (ii) of Proposition 4 with

$$y(t) := \|\varphi^\perp(t)\|^2_{L^2(\Omega)}, \quad a(t) = \frac{{d_2}^2 {C_W}^2}{d_1} \|g(u(t))N_2(t)\|^2_{L^2(\Omega)} \text{ and } \gamma_0 = \frac{d_1}{(C_W)^2},$$

we deduce

$$\varphi^\perp(x,t) \to 0 \quad \text{as } t \to \infty \quad \text{strongly in } L^2(\Omega), \tag{40}$$

which implies (24) with $u^\infty(x) = a_1^\infty\, C_\varphi$. □

We can obtain further estimates:

Proposition 6
Under the assumptions of Theorem 5 the following additional facts hold:

$$\nabla\varphi^{\perp}(x,t) = \nabla u(x,t) \xrightarrow{t\to\infty} 0 \ \textit{in}\ L^2(\Omega), \tag{41}$$

$$\sup_{t>0} \|u(t)\|_{L^2(\Omega)} < \infty, \quad \sup_{t>0} \|\varphi^{\perp}(t)\|_{L^2(\Omega)} < \infty, \quad \int_0^\infty \|\nabla\varphi^{\perp}(t)\|^2_{L^2(\Omega)}\, dt < \infty, \tag{42}$$

$$\sup_{t\geq\delta} \|\nabla\varphi^{\perp}(t)\|_{L^2(\Omega)} < \infty, \quad \int_\delta^\infty \|\Delta\varphi^{\perp}(t)\|^2_{L^2(\Omega)}\, dt < \infty \quad \textit{for all } \delta > 0. \tag{43}$$

Proof
Since $u \in C([0,\infty); L^2(\Omega))$, the facts that $u(x,t) = a_1(t)\, C_\varphi + \varphi^{\perp}(x,t) \to a_1^\infty\, C_\varphi$ and $\varphi^{\perp}(x,t) \to 0$ in $L^2(\Omega)$ as $t \to \infty$ imply the uniform boundedness of $u(t)$ and $\varphi^{\perp}(t)$ in $L^2(\Omega)$. Hence integrating (37) on $(0,\infty)$ with respect to t, we deduce (42).
The convergence (41) can be obtained by the arguments similar to the previous case $\varphi^{\perp}(x,t) \to 0$. In fact, multiplying (36) by $-\Delta\varphi^{\perp}$ and using (35), we obtain

$$\frac{d}{dt}\|\nabla\varphi^{\perp}(t)\|^2_{L^2(\Omega)} + \frac{d_1}{(C_W)^2}\|\nabla\varphi^{\perp}(t)\|^2_{L^2(\Omega)} \leq \frac{{d_2}^2 (C_W)^2}{d_1}\, \|g(u(t))N_2(t)\|^2_{L^2(\Omega)}\, . \tag{44}$$

Then in order to derive (41), it suffices to apply Proposition 4 in $[t_0,\infty)$ with $t_0 > 0$ and $u(t_0) \in H^1(\Omega)$ (see (39)). The existence of such a positive time t_0 is assured by the last relation of (42). For any $\delta > 0$, choose $0 < t_0 < \delta$ so that $u(t_0) \in H^1(\Omega)$. Since

$$\frac{(d_2\, C_W)^2}{d_1}\, \|g(u(t))N_2(t)\|^2_{L^2(\Omega)} \leq \frac{(d_2\, C_W)^2}{d_1}\, g^*\, \|\overline{N}\|^2_{L^2(\Omega)}, \tag{45}$$

we can apply (i) of Proposition 4 with $t_0 = t_0,\ t_1 = \infty,\ \gamma_0 = \frac{d_1}{(C_W)^2}$ and $C = \frac{(d_2\, C_W)^2}{d_1} g^* \|\overline{N}\|^2_{L^2(\Omega)}$ to conclude that $\sup_{t\geq\delta} \|\nabla u(t)\|_{L^2(\Omega)} = \sup_{t\geq\delta} \|\nabla\varphi^{\perp}(t)\|_{L^2(\Omega)} < \infty$. The multiplication of (36) by $-\Delta\varphi^{\perp}$ also gives

$$\frac{d}{dt}\|\nabla\varphi^{\perp}(t)\|^2_{L^2(\Omega)} + d_1\, \|\Delta\varphi^{\perp}(t)\|^2_{L^2(\Omega)} \leq \frac{{d_2}^2}{d_1}\, \|g(u(t))N_2(t)\|^2_{L^2(\Omega)}. \tag{46}$$

Here we used the Cauchy-Schwarz inequality for the right hand side. Hence integrating (46) over $[\delta,\infty)$, we deduce (43). □

2.4 Classification of partial and complete swelling

The mitochondrial swelling process and its extent is dependent on the local calcium dose. If the initial concentration u_0 stays below the initiation threshold C^- at any point $x \in \Omega$ and $N_{2,0} = 0$, then no swelling will happen and we have $N_i(x,t) \equiv N_{i,0}(x)\ \forall x \in \Omega$, $i = 1, 2, 3$ for all $t > 0$.

Another possible scenario is the so-called "partial swelling". This effect of partial swelling occurs in the experiments and can also be seen in the simulations when the initial calcium concentration lies above C^- at a small region but due to diffusion it does not stay above this threshold for the whole time. This leads to the case where there exists a finite time T_1 such that $N_1(x,t) = N_1(x,T_1)\ \forall t \geq T_1$.

But if the initial calcium distribution together with the influence of the positive feedback is sufficiently high, then "complete swelling" occurs which means $N_1(x,t) \to 0$ and $N_3(x,t) \to \overline{N}(x)$ for all $x \in \Omega$ as $t \to \infty$.

As it was shown before, for both cases it holds that $N_2(x,t) \to 0$ as $t \to \infty$.

Condition 3

Let the assumption of Conditions 1 and 2 hold. In addition we assume more regularity of the initial data:

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

A crucial point to distinguish between partial and complete swelling is to check if $f(u)$ stays positive for all times. For that it is necessary to have uniform convergence of $u(x,t)$ to $u^\infty \equiv a_1^\infty C_\varphi$. Up to now we only have the strong convergence in $L^2(\Omega)$. So our aim now is to show the uniform convergence, which turns out to be an extensive task.

Theorem 7

Let $N \leq 3$ and Condition 3 be satisfied, then the following additional statements hold:

$$\sup_{t>0}\ (\|\nabla N_1(t)\|_{L^2(\Omega)} + \|\nabla N_2(t)\|_{L^2(\Omega)}) < \infty, \tag{47}$$

$$\sup_{t\geq\delta} \|\Delta\varphi^\perp(t)\|_{L^2(\Omega)} < \infty \quad \textit{for all } \delta > 0\,, \tag{48}$$

$$\|u(t) - u^\infty\|_{L^\infty(\Omega)} \longrightarrow 0 \quad \textit{as } t \to \infty\,. \tag{49}$$

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 with the aid of (35), we get

$$\begin{aligned}
\|u(t) - u^\infty\|_{C^\alpha(\Omega)} &\leq C_\theta \|\nabla(u(t) - u^\infty)\|^\theta_{L^2(\Omega)} \|\Delta(u(t) - u^\infty)\|^{1-\theta}_{L^2(\Omega)} \\
&= C_\theta \|\nabla\varphi^\perp(t)\|^\theta_{L^2(\Omega)} \|\Delta\varphi^\perp(t)\|^{1-\theta}_{L^2(\Omega)} \\
&\leq C_\theta \sup_{t\geq 1} \|\Delta\varphi^\perp(t)\|^{1-\theta}_{L^2(\Omega)} \|\nabla\varphi^\perp(t)\|^\theta_{L^2(\Omega)} \quad \forall t \in [1,\infty).
\end{aligned}$$

Hence it is easy to see that (49) follows from (48), since we already know $\|\nabla\varphi^\perp(t)\|_{L^2(\Omega)} \xrightarrow{t\to\infty} 0$ by (41). In order to show (48), we introduce an auxiliary equation. Applying $A^{\frac{1}{2}}$ to the PDE (1), we get

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

Since it will be shown later that $A^{\frac{1}{2}}\,(g(u)N_2) \in L^2_{loc}([0,\infty); L^2(\Omega))$, the standard regularity result assures that $\partial_t\, A^{\frac{1}{2}} u$ and $A^{\frac{3}{2}} u$ also belong to $L^2_{loc}([0,\infty); L^2(\Omega))$. Then multiplying by $A^{\frac{3}{2}} u$, we obtain

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

Hence we obtain

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|\Delta u(t)\|^2_{L^2(\Omega)} + \frac{d_1}{2}\|A^{\frac{3}{2}}u(t)\|^2_{L^2(\Omega)} &\leq \frac{{d_2}^2}{2d_1}\|\nabla\left(g(u(t))N_2(t)\right)\|^2_{L^2(\Omega)}\\ &\leq \frac{{d_2}^2}{d_1}\|g'(u(t))\nabla u(t)N_2(t)\|^2_{L^2(\Omega)} + \frac{{d_2}^2}{d_1}\|g(u(t))\nabla N_2(t)\|^2_{L^2(\Omega)}.\end{aligned}$$

Here it is clear that $Au = A\varphi^\perp = -\Delta\varphi^\perp$ and $\int_\Omega -\Delta\varphi^\perp\,dx = 0$, so we can apply Wirtinger's inequality for $-\Delta\varphi^\perp$. Thus we obtain

$$\begin{aligned}&\frac{d}{dt}\|\Delta\varphi^\perp(t)\|^2_{L^2(\Omega)} + \frac{d_1}{{C_W}^2}\|\Delta\varphi^\perp(t)\|^2_{L^2(\Omega)}\\ &\quad\leq \frac{2{d_2}^2}{d_1}L_g^2\|\overline{N}\|^2_{L^\infty(\Omega)}\|\nabla\varphi^\perp(t)\|^2_{L^2(\Omega)} + \frac{2{d_2}^2}{d_1}g^{*2}\|\nabla N_2(t)\|^2_{L^2(\Omega)}.\end{aligned} \tag{50}$$

Here we assume the following estimate, which will be shown later.

$$\sup_{t\geq 0}\|\nabla N_2(t)\|_{L^2(\Omega)} \leq C_{N_2} < \infty, \tag{51}$$

which assures that the second term of the right-hand side of (50) is bounded by some constant C_4 for all $t \in (0,\infty)$.

Furthermore, since by Theorem 1 the solution u fulfills $\sqrt{t}\,\Delta u \in L^2(0,T;L^2(\Omega))$, for each $\delta > 0$, there exist a constant C_5 and $\underline{\delta} \in (0,\delta)$ such that

$$\|\Delta\varphi^\perp(\underline{\delta})\|^2_{L^2(\Omega)} \leq \frac{1}{\underline{\delta}}\,C_5.$$

Moreover (43) assures that the first term of the right-hand side of (50) is bounded by some constant C_6 for all $t \in (\underline{\delta},\infty)$.
Thus in order to deduce (48), it suffices to apply Proposition 4 to (50) with

$$t_0 = \underline{\delta},\quad t_1 = \infty,\quad \gamma_0 = \frac{d_1}{{C_W}^2},\quad C = C_4 + C_6.$$

Then in order to show the uniform convergence of $u(t)$ to u^∞, it suffices to verify (51). For this purpose, we begin with the estimate for $\nabla N_1(t)$.

Application of the gradient to the model equation (2) leads to

$$\partial_t\nabla N_1 = -f'(u)\nabla u\,N_1 - f(u)\nabla N_1. \tag{52}$$

Here we note that since f is Lipschitz and $u \in H^1(\Omega)$, $f'(u)\nabla$ exist a.e. $x \in \Omega$ and belongs to $H^1(\Omega)$ (see e.g. [12] and [16]). Then multiplying (52) by $\nabla N_1(t)$, we get

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|\nabla N_1(t)\|^2_{L^2(\Omega)} \leq &\int_\Omega |f'(u(x,t))||\nabla u(x,t)||N_1(x,t)||\nabla N_1(x,t)|\,dx\\ &- \int_\Omega f(u(x,t))|\nabla N_1(x,t)|^2\,dx.\end{aligned} \tag{53}$$

Here we recall

$$u(x,t) = a_1(t)\, C_\varphi + \varphi^\perp(x,t) \quad a_1(t)\, C_\varphi \uparrow u^\infty = a_1^\infty\, C_\varphi \quad \text{as } t \uparrow \infty. \tag{54}$$

In view of Condition 2, we decompose Ω into 3 parts :

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

Then (i) of Condition 2 implies that $f'(u(x,t)) = 0$ in $\Omega_1(t)$. According to the behavior of $f'(u(x,t))$ in $\Omega_2(t)$, we have to distinguish between the two cases

$$\text{(I) } u^\infty \le C^- \quad \text{and} \quad \text{(II) } u^\infty > C^- \,.$$

Case (I) We first take a look at the case $u^\infty \le C^-$.
On $\Omega_2(t)$, in view of (ii) of Condition 2 and (54), we have

$$\begin{aligned}
0 \le m_1 \left(u(x,t) - C^-\right) \le f'\left(u(x,t)\right) &\le m_2 \left(u(x,t) - C^-\right)\\
&\le m_2 \left(u^\infty + \varphi^\perp(x,t) - C^-\right) \le m_2 \varphi^\perp(x,t)\\
\Rightarrow |f'(u(x,t))| \le m_2 |\varphi^\perp(x,t)| &\ \text{ on } \Omega_2(t)\,.
\end{aligned}$$

Substituting this estimate into (53), we get

$$\begin{aligned}
\frac{1}{2}\frac{d}{dt}\|\nabla N_1(t)\|^2_{L^2(\Omega)} \le m_2 \|\overline{N}\|_{L^\infty(\Omega)} &\int_{\Omega_2(t)} |\varphi^\perp(x,t)||\nabla u(x,t)||\nabla N_1(x,t)|\, dx\\
+ \|\overline{N}\|_{L^\infty(\Omega)} &\int_{\Omega_3(t)} |f'(u(x,t))||\nabla u(x,t)||\nabla N_1(x,t)|\, dx \qquad (55)\\
- &\int_\Omega f(u(x,t))|\nabla N_1(x,t)|^2\, dx\,.
\end{aligned}$$

The first integral can be further estimated as follows :

$$\begin{aligned}
\int_{\Omega_2(t)} |\varphi^\perp(x,t)||\nabla u(x,t)||\nabla N_1(x,t)|\, dx &\le \|\varphi^\perp(t)\nabla u(t)\|_{L^2(\Omega)}\|\nabla N_1(t)\|_{L^2(\Omega)}\\
&\le \|\varphi^\perp(t)\|_{L^4(\Omega)}\|\nabla u(t)\|_{L^4(\Omega)}\|\nabla N_1(t)\|_{L^2(\Omega)}\\
&\le C_{H^1}^2 \|\varphi^\perp(t)\|_{H^1(\Omega)}\|\nabla u(t)\|_{H^1(\Omega)}\|\nabla N_1(t)\|_{L^2(\Omega)}\\
&\le C_7\, \|\nabla\varphi^\perp(t)\|_{L^2(\Omega)}\|\Delta\varphi^\perp(t)\|_{L^2(\Omega)}\|\nabla N_1(t)\|_{L^2(\Omega)}\,.
\end{aligned}$$

Here we used the Sobolev embedding theorem, the elliptic estimate in $L^2(\Omega)$ and Wirtinger's inequality (C_{H^1} is the embedding constant for $H^1(\Omega) \subset L^4(\Omega)$ and C_7 is a constant depending on $C_{H^1},\ C_W$).

For the second integral over $\Omega_3(t)$, recalling that $f(u(x,t)) \geq f(C^- + \delta_0) > 0$ in $\Omega_3(t)$ by (iii) of Condition 2, we artificially insert $\frac{\sqrt{f(u(x,t))}}{\sqrt{f(u(x,t))}}$ and get

$$\begin{aligned}
&\|\overline{N}\|_{L^\infty(\Omega)} \int_{\Omega_3(t)} \frac{|f'(u(x,t))|}{\sqrt{f(u(x,t))}} |\nabla u(x,t)| \sqrt{f(u(x,t))} \, |\nabla N_1(x,t)| \, dx \\
&\quad \leq \frac{\|\overline{N}\|^2_{L^\infty(\Omega)}}{2} \int_{\Omega_3(t)} \frac{|f'(u(x,t))|^2}{f(u(x,t))} |\nabla u(x,t)|^2 \, dx + \frac{1}{2} \int_{\Omega_3(t)} f(u(x,t)) |\nabla N_1(x,t)|^2 \, dx \\
&\quad \leq \frac{\|\overline{N}\|^2_{L^\infty(\Omega)}}{2} \frac{L_f^2}{f(C^- + \delta_0)} \|\nabla \varphi^\perp(t)\|^2_{L^2(\Omega)} + \frac{1}{2} \int_\Omega f(u(x,t)) |\nabla N_1(x,t)|^2 \, dx \, .
\end{aligned}$$

Substitution of these findings into (55) leads to

$$\begin{aligned}
\frac{1}{2}\frac{d}{dt} \|\nabla N_1(t)\|^2_{L^2(\Omega)} &\leq m_2 \|\overline{N}\|_{L^\infty(\Omega)} C_7 \, \|\nabla \varphi^\perp(t)\|_{L^2(\Omega)} \|\Delta \varphi^\perp(t)\|_{L^2(\Omega)} \|\nabla N_1(t)\|_{L^2(\Omega)} \\
&\quad + \frac{\|\overline{N}\|^2_{L^\infty(\Omega)}}{2} \frac{L_f^2}{f(C^- + \delta_0)} \|\nabla \varphi^\perp(t)\|^2_{L^2(\Omega)} - \frac{1}{2} \int_\Omega f(u(x,t)) |\nabla N_1(x,t)|^2 \, dx \, .
\end{aligned}$$

The last term can be omitted and by Young's inequality, there exists a constant C_8 such that

$$\frac{d}{dt} \|\nabla N_1(t)\|^2_{L^2(\Omega)} \leq C_8 \|\nabla \varphi^\perp(t)\|^2_{L^2(\Omega)} + C_8 \|\Delta \varphi^\perp(t)\|^2_{L^2(\Omega)} \|\nabla N_1(t)\|^2_{L^2(\Omega)} \, .$$

Integration of this over (δ, t) yields

$$\begin{aligned}
\|\nabla N_1(t)\|^2_{L^2(\Omega)} \leq \|\nabla N_1(\delta)\|^2_{L^2(\Omega)} &+ C_8 \int_0^\infty \|\nabla \varphi^\perp(t)\|^2_{L^2(\Omega)} \, dt \\
&+ C_8 \int_\delta^t \|\Delta \varphi^\perp(s)\|^2_{L^2(\Omega)} \|\nabla N_1(s)\|^2_{L^2(\Omega)} \, ds \, .
\end{aligned} \tag{56}$$

Here we note that (53) gives

$$\frac{d}{dt} \|\nabla N_1(t)\|_{L^2(\Omega)} \leq L_f \|\nabla \varphi^\perp(t)\|_{L^2(\Omega)} \, \|\overline{N}\|_{L^\infty(\Omega)},$$

whence follows

$$\|\nabla N_1(\delta)\|_{L^2(\Omega)} \leq \|\nabla N_{1,0}\|_{L^2(\Omega)} + L_f \, \|\overline{N}\|_{L^\infty(\Omega)} \left(\int_0^\delta \|\nabla \varphi^\perp(t)\|^2_{L^2(\Omega)} dt \right)^{1/2} \sqrt{\delta} < \infty. \tag{57}$$

Thus, in view of (42) and (43) we deduce from (57) and (56) that

$$\sup_{0 \leq t < \infty} \|\nabla N_1(t)\|_{L^2(\Omega)} < +\infty. \tag{58}$$

This result is now used to show that $\nabla N_2(t)$ also stays bounded in $L^2(\Omega)$. For that we apply the gradient to model equation (3) and get

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

Multiplication by ∇N_2 and integration over Ω leads to

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

Then (ii), (iii) of Condition 1 yields

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

Hence by Young's inequality and (58), for any $\eta>0$, there exists a constant $C_{9,\eta}$ such that

$$\begin{aligned}\frac{d}{dt}\|\nabla N_2(t)\|^2_{L^2(\Omega)} \le & \,\eta\,\|\nabla N_2(t)\|^2_{L^2(\Omega)} + C_{9,\eta}\left(1+\|\nabla\varphi^\perp(t)\|^2_{L^2(\Omega)}\right) \\ & - 2\int_\Omega g(u(x,t))|\nabla N_2(x,t)|^2\,dx.\end{aligned} \tag{59}$$

Then (59) with $\eta=1$ and Gronwall's inequality give

$$\|\nabla N_2(t)\|^2_{L^2(\Omega)} \le \Big(\|\nabla N_{2,0}\|^2_{L^2(\Omega)} + C_{9,1}\left(t_* + \int_0^{t_*}\|\nabla\varphi^\perp(t)\|^2_{L^2(\Omega)}\,dt\right)\Big)e^{t_*} \quad \forall t\in[0,t_*], \tag{60}$$

where $t_*>0$ is the number given in Proposition 3, from which we know that for all $x\in\Omega$ it holds $u(x,t)\ge\varrho>0$ $\forall t\ge t_*$ and consequently (iii) and (iv) of Condition 2 imply

$$g(u(x,t)) \ge g(\underline{\varrho}) > 0 \quad \forall t\ge t_*$$

with $\underline{\varrho}=\min(\varrho,\varrho_0)$ as defined earlier. Substituting this into the last term of (59) with $\eta=g(\underline{\varrho})$, we get

$$\frac{1}{2}\frac{d}{dt}\|\nabla N_2(t)\|^2_{L^2(\Omega)} + \frac{1}{2}g(\underline{\varrho})\|\nabla N_2(t)\|^2_{L^2(\Omega)} \le \frac{C_{9,\eta}}{2}\left(1+\|\nabla\varphi^\perp(t)\|^2_{L^2(\Omega)}\right) \quad \forall t\ge t_*.$$

Then in view of (42) and (43), we can apply (i) of Proposition 4 with

$$t_0=t_*,\quad t_2=\infty,\quad \gamma_0=\frac{1}{2}g(\underline{\varrho}),\quad C=\frac{C_{9,\eta}}{2}\left(1+\sup_{t\ge t_*}\|\nabla\varphi^\perp(t)\|^2_{L^2(\Omega)}\right).$$

Thus together with (60), we achieved (51).

Case II We now take a look at the case $u^\infty > C^-$.
Let $x\in\Omega_2(t)$, i.e., $C^-\le u(x,t)\le C^-+\delta_0$, then recalling (ii) of Condition 2 :

$$m_1\,(s-C^-) \le f'(s) \quad \forall s\in[C^-,C^-+\delta_0],$$

and integrating this over $(C^-, u(x,t))$ with respect to s, we get

$$f(u(x,t)) \geq \frac{1}{2} m_1 \left(u(x,t) - C^-\right)^2 . \tag{61}$$

Due to the condition $u^\infty > C^-$ and the monotonicity of $a_1(t)$ with (54) it follows: For all α with $0 < \alpha < (u^\infty - C^-)$, there exists $T_\alpha > 0$ such that

$$a_1(t) C_\varphi \geq C^- + \alpha \quad \text{for all } t \geq T_\alpha .$$

Substituting this into (61), we obtain with Young's inequality

$$\begin{aligned} f(u(x,t)) &\geq \frac{m_1}{2} \left(a_1(t) C_\varphi + \varphi^\perp(x,t) - C^-\right)^2 \geq \frac{m_1}{2} \left(\alpha + \varphi^\perp(x,t)\right)^2 \\ &\geq \frac{m_1}{2} \left(\alpha^2 - 2\alpha|\varphi^\perp(x,t)| + |\varphi^\perp(x,t)|^2\right) \\ &\geq \frac{m_1}{2} \left(\frac{1}{2}\alpha^2 - |\varphi^\perp(x,t)|^2\right) \qquad \text{for all } t \geq T_\alpha \text{ and } x \in \Omega_2(t). \end{aligned}$$

Moreover since this estimate is still valid for the case where $u(x,t) = C^- + \delta_0$, (iii) of Condition 2 implies

$$f(u(x,t)) \geq f(C^- + \delta_0) \geq \frac{m_1}{2} \left(\frac{1}{2}\alpha^2 - |\varphi^\perp(x,t)|^2\right) \quad \text{for all } t \geq T_\alpha \text{ and } x \in \Omega_3(t) .$$

Since $f(u(x,t)) = 0 = f'(u(x,t))$ in $\Omega_1(t)$ for $t \geq T_\alpha$, substituting these estimates for $f(u(x,t))$ into (53), we have

$$\begin{aligned} \frac{1}{2}\frac{d}{dt}\|\nabla N_1(t)\|^2_{L^2(\Omega)} &\leq L_f \|\overline{N}\|_{L^\infty(\Omega)} \int_{\Omega_2(t)\,\cup\,\Omega_3(t)} |\nabla(u(x,t))||\nabla N_1(x,t)|\, dx \\ &\quad - \frac{m_1}{4}\alpha^2 \int_{\Omega_2(t)\,\cup\,\Omega_3(t)} |\nabla N_1(x,t)|^2\, dx + \frac{m_1}{2} \int_{\Omega_2(t)\,\cup\,\Omega_3(t)} |\varphi^\perp(x,t)|^2 |\nabla N_1(x,t)|\, dx \quad \forall t \geq T_\alpha. \end{aligned}$$

Hence by Young's inequality, Wirtinger's inequality and the Sobolev space embedding $H^2(\Omega) \hookrightarrow L^\infty(\Omega)$, there exists a constant C_{10} such that

$$\begin{aligned} \frac{d}{dt}\|\nabla N_1(t)\|^2_{L^2(\Omega)} &\leq \frac{2L_f^2 \|\overline{N}\|^2_{L^\infty(\Omega)}}{m_1 \alpha^2} \|\nabla u(t)\|^2_{L^2(\Omega)} + m_1 \|\varphi^\perp(t)\|^2_{L^\infty(\Omega)} \|\nabla N_1(t)\|^2_{L^2(\Omega)} . \\ &\leq C_{10} \left(\|\nabla\varphi^\perp(t)\|^2_{L^2(\Omega)} + \|\Delta\varphi^\perp(t)\|^2_{L^2(\Omega)} \|\nabla N_1(t)\|^2_{L^2(\Omega)}\right) \quad \forall t \geq T_\alpha. \end{aligned}$$

Integrating this over (T_α, t) and applying Gronwall's inequality, in view of (42) and (43), we find that

$$\begin{aligned} \|\nabla N_1(t)\|^2_{L^2(\Omega)} &\leq \left(\|\nabla N_1(T_\alpha)\|^2_{L^2(\Omega)} + C_{10} \int_{T_\alpha}^t \|\nabla\varphi^\perp(s)\|^2_{L^2(\Omega)}\, ds\right) e^{C_{10} \int_{T_\alpha}^\infty \|\Delta\varphi^\perp(t)\|^2_{L^2(\Omega)}\, dt} \\ &< \infty \quad \text{for all } t \geq T_\alpha . \end{aligned}$$

Here by the same reasoning as for (57), we get $\sup_{t\in[0,T_\alpha]}\|\nabla N_1(t)\|_{L^2(\Omega)} < \infty$. Thus we obtain

$$\sup_{t\geq 0}\|\nabla N_1(t)\|_{L^2(\Omega)} < \infty\,.$$

The boundedness of $\nabla N_2(t)$ in $L^2(\Omega)$ can be shown in exactly the same way as for case 1) $u^\infty \leq C^-$, since for the estimation of $\|\nabla N_2(t)\|_{L^2(\Omega)}$ we did not use the relation between u^∞ and C^-. This yields

$$\sup_{t\geq 0}\|\nabla N_2(t)\|_{L^2(\Omega)} < \infty.$$

Thus (51) is verified and the proof is completed. □

Under the assumptions of Condition 3, the long-time behavior can be further characterized as follows:

Theorem 8
Let Condition 3 be satisfied, then the following asymptotic behavior of solution hold.

1.) Partial swelling

Let $u^\infty < C^-$, then there exists a finite time $T_p > 0$ such that

$$N_1(x,t) \equiv N_1(x,T_p) \quad \textit{for all } x\in\Omega,\ t\geq T_p$$

and we have the following exponential convergence rates for all $x\in\Omega$ and $t\geq T_p$:

$$\begin{aligned}
N_2(x,t) &\xrightarrow{t\to\infty} 0 && \textit{in } \mathcal{O}(e^{-g(\underline{\varrho})t})\,,\\
N_3(x,t) &\xrightarrow{t\to\infty} \overline{N}(x) - N_1(x,T_p) && \textit{in } \mathcal{O}(e^{-g(\underline{\varrho})t})\,,\\
a_1(t) &\xrightarrow{t\to\infty} a_1^\infty && \textit{in } \mathcal{O}(e^{-g(\underline{\varrho})t})\,,\\
\|\varphi^\perp(t)\|^2_{L^2(\Omega)} &\xrightarrow{t\to\infty} 0 && \textit{in } \mathcal{O}(e^{-\gamma_1 t})\,,\\
\|\nabla\varphi^\perp(t)\|^2_{L^2(\Omega)} &\xrightarrow{t\to\infty} 0 && \textit{in } \mathcal{O}(e^{-\gamma_1 t})\,.
\end{aligned}$$

These rates are dependent on the model function g and the earlier defined parameter $\underline{\varrho} = \min(\varrho,\varrho_0)$ in correspondence to Condition 2 and Proposition 3 and we have $\gamma_1 = \min\left(\frac{d_1}{2C_W^2}, g(\underline{\varrho})\right) > 0$.

2.) Complete swelling

Let $u^\infty > C^-$, then there exists some $T_c > 0$ such that for all $x\in\Omega$ and all $t\geq T_c$ the following exponential convergence rates hold.

$$\begin{aligned}
N_1(x,t) &\xrightarrow{t\to\infty} 0 && \textit{in } \mathcal{O}(e^{-f(C^-+\gamma)\,t})\,,\\
N_2(x,t) &\xrightarrow{t\to\infty} 0 && \textit{in } \mathcal{O}(e^{-\eta\,t})\,,\\
N_3(x,t) &\xrightarrow{t\to\infty} \overline{N}(x) && \textit{in } \mathcal{O}(e^{-\eta\,t})\,,\\
a_1(t) &\xrightarrow{t\to\infty} a_1^\infty && \textit{in } \mathcal{O}(e^{-\eta\,t})\,,\\
\|\varphi^\perp(t)\|^2_{L^2(\Omega)} &\xrightarrow{t\to\infty} 0 && \textit{in } \mathcal{O}(e^{-\gamma_2\,t})\,,\\
\|\nabla\varphi^\perp(t)\|^2_{L^2(\Omega)} &\xrightarrow{t\to\infty} 0 && \textit{in } \mathcal{O}(e^{-\gamma_2\,t})\,,
\end{aligned}$$

where γ and η are positive constants depending on $(u^\infty - C^-, \delta_0)$ and $(u^\infty - C^-, \rho_0, f(\cdot), g(\cdot))$ respectively and $\gamma_2 = \min\left(\frac{d_1}{2C_W^2}, \eta\right) > 0$.

Here the terminology $v(t) \xrightarrow{t\to\infty} v^\infty$ *in* $\mathcal{O}(e^{-k\,t})$ *means that there exists some constant* $C > 0$ *such that*

$$|v(t) - v^\infty| \leq C \quad e^{-k\,t}.$$

Proof

1.) Partial swelling We start with the partial swelling case. By the uniform convergence of $u(x,t)$ to $u^\infty < C^-$ assures the existence of a time $T_p > 0$ such that

$$u(x,t) \leq C^- \qquad \forall x \in \Omega \quad \forall t \geq T_p$$

and consequently

$$f(u(x,t)) = 0 \qquad \forall x \in \Omega \quad \forall t \geq T_p. \tag{62}$$

Hence by (2), we have

$$N_1(x,t) \equiv N_1(x,T_p) \qquad \forall t \geq T_p\,.$$

For equation (3), by (62) and the definition of $\underline{\varrho}$, it holds for all $t \geq T_p$

$$\partial_t N_2(x,t) = -g(u(x,t))\, N_2(x,t) \leq -g(\underline{\varrho})\, N_2(x,t)\,,$$

which gives

$$N_2(x,t) \leq N_2(x,T_p)\, e^{-g(\underline{\varrho})(t-T_p)} \leq \|\overline{N}\|_{L^\infty(\Omega)}\, e^{g(\underline{\varrho})\,T_p}\, e^{-g(\underline{\varrho})t} \quad \forall x \in \Omega \quad \forall t \geq T_p \tag{63}$$

i.e., we have exponential convergence of $N_2(x,t)$ to 0. From the conservation law we know

$$N_3(x,t) = \overline{N}(x) - N_1(x,T_p) - N_2(x,t) \quad \forall t \geq T_p\,,$$

whence follows

$$N_3^\infty(x) = \overline{N}(x) - N_1(x,T_p) \quad \text{and} \quad |N_3(x,t) - N_3^\infty(x)| = N_2(x,t) \quad \text{for } t \geq T_p,$$

which together with (63) yields

$$|N_3(x,t) - N_3^\infty(x)| \leq \|\overline{N}\|_{L^\infty(\Omega)}\, e^{g(\underline{\varrho})\,T_p}\, e^{-g(\underline{\varrho})t} \quad \forall x \in \Omega \quad \forall t \geq T_p\,. \tag{64}$$

Now, in view of (33) and (64), we can easily see that

$$a_1(t) \xrightarrow{t\to\infty} a_1^\infty \text{ in } \mathcal{O}(e^{-g(\underline{\varrho})t})\,.$$

As for the convergence of $\|\varphi^\perp(t)\|^2_{L^2(\Omega)}$, we apply (ii) of Proposition 4 with $y(t) = \|\varphi^\perp(t)\|^2_{L^2(\Omega)}$, $\gamma_0 = \frac{d_1}{C_W^2}$ and $t_0 = \frac{t}{2}$ to (38). Then we obtain by (63)

$$\begin{aligned}
\|\varphi^\perp(t)\|^2_{L^2(\Omega)} &\leq \|\varphi^\perp(t_0)\|^2_{L^2(\Omega)} e^{-\gamma_0\,(t-t_0)} + \frac{d_2^2 C_W^2}{d_1}\, g^* \int_{t_0}^t \|N_2(s)\|^2_{L^2(\Omega)}\, ds \\
&\leq \sup_{t>0} \|\varphi^\perp(t)\|^2_{L^2(\Omega)} e^{-\frac{\gamma_0}{2}\,t} + \frac{d_2^2 C_W^2}{d_1}\, g^*\, \|\overline{N}\|^2_{L^\infty(\Omega)}\, e^{2g(\underline{\varrho})\,T_p} \int_{t_0}^t e^{-2g(\underline{\varrho})\,s}\, ds \\
&\leq \sup_{t>0} \|\varphi^\perp(t)\|^2_{L^2(\Omega)} e^{-\frac{\gamma_0}{2}\,t} + \frac{d_2^2 C_W^2}{d_1 2g(\underline{\varrho})}\, g^*\, \|\overline{N}\|^2_{L^\infty(\Omega)}\, e^{2g(\underline{\varrho})\,T_p}\, e^{-g(\underline{\varrho})\,t}\,,
\end{aligned}$$

which implies

$$\|\varphi^{\perp}(t)\|^2_{L^2(\Omega)} \xrightarrow{t\to\infty} 0 \text{ in } \mathcal{O}(e^{-\gamma_1 t}) \quad \text{with } \gamma_1 = \min\left(\frac{d_1}{2C_W^2}, g(\underline{\varrho})\right).$$

As for $\|\nabla\varphi^{\perp}(t)\|^2_{L^2(\Omega)}$, from (44) we now get

$$\frac{d}{dt}\|\nabla\varphi^{\perp}(t)\|^2_{L^2(\Omega)} + \frac{d_1}{C_W^2}\|\nabla\varphi^{\perp}(t)\|^2_{L^2(\Omega)} \le \frac{d_2^2 C_W^2}{d_1}\, g^* \|N_2(t)\|^2_{L^2(\Omega)}\,.$$

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

$$\|\nabla\varphi^{\perp}(t)\|^2_{L^2(\Omega)} \xrightarrow{t\to\infty} 0 \quad \text{in } \mathcal{O}(e^{-\gamma_1 t})\,.$$

2.) Complete swelling In the complete swelling case where $u^\infty > C^-$, the uniform convergence of $u(x,t)$ to u^∞ implies that for any $\beta \in (0, u^\infty - C^-)$, there exists a time $T_c = T_c(\beta) > 0$ such that

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

In order to derive the strict positivity of $f(u(x,t))$, we have to distinguish between two cases in accordance with Condition 2:

- $u(x,t) \ge C^- + \delta_0$, where $\delta_0 > 0$ denotes the constant from Condition 2, i.e., $\beta \ge \delta_0$. In this case, it follows from (iii) of Condition 2 that

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

- $u(x,t) \in (C^-, C^- + \delta_0)$, which means we are in the case (ii) of Condition 2, where we have the relation $f'(u(x,t)) \ge m_1\beta > 0$, whence follows

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

In summary we conclude

$$f(u(x,t)) \ge f(C^- + \gamma) > 0 \quad \forall x \in \Omega \quad \forall t \ge T_c\,, \text{ where } \gamma := \min\,(\beta, \delta_0) \tag{65}$$

and in addition by (iii) and (iv) of Condition 2

$$g(u(x,t)) \ge g(\zeta) > 0 \qquad \forall x \in \Omega \quad \forall t \ge T_c\,, \text{ where } \zeta := \min\,(\varrho_0, C^- + \beta)\,. \tag{66}$$

Substituting relation (65) into the model equation (2), we obtain the exponential decay of $N_1(x,t)$ to 0:

$$N_1(x,t) \le N_1(x,T_c)\, e^{-f(C^-+\gamma)\,(t-T_c)} \le \|\overline{N}\|_{L^\infty(\Omega)}\, e^{f(C^-+\gamma)\,T_c}\, e^{-f(C^-+\gamma)\,t} \quad \forall x \in \Omega \quad \forall t \ge T_c\,.$$

Furthermore the second model equation (3)

$$\partial_t N_2(x,t) = f(u(x,t))\, N_1(x,t) - g(u(x,t))\, N_2(x,t)$$

can be estimated by means of the previous result, (ii) of Condition 1 and (66) as follows.

$$\partial_t N_2(x,t) \le C_0\, e^{-f(C^- +\gamma)t} - g(\zeta) N_2(x,t), \quad C_0 = f^*\, \|\overline{N}\|_{L^\infty(\Omega)}\, e^{f(C^- +\gamma)T_c}. \tag{67}$$

Here let η be any number satisfying

$$0 < \eta < \min\,\big(\, f(C^- + \gamma),\, g(\zeta)\,\big).$$

Then by (67), we easily get

$$\partial_t \left(e^{\eta t}\, N_2(x,t)\right) \le C_0\, e^{-\,(f(C^- +\gamma)\,-\,\eta)\,t} \quad \forall x \in \Omega \quad \forall t \ge T_c. \tag{68}$$

Hence integrating (68) over (T_c, t), we obtain the exponential decay of $N_2(x,t)$:

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

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

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

The exponential convergence for $a_1(t)$, $\|\varphi^\perp(t)\|^2_{L^2(\Omega)}$ and $\|\nabla\varphi^\perp(t)\|^2_{L^2(\Omega)}$ can be derived from the same reasoning as for the partial swelling case with $g(\underline{\varrho})$ replaced by η.

□

3 Numerical simulation

The presented model will now be analyzed numerically. Here we consider the *in vitro* case, i.e. the domain Ω describes a test tube containing purified mitochondria. We are interested in the effects of adding a certain calcium amount to intact mitochondria. The time development of the calcium concentration u and the mitochondrial subpopulations N_1 (intact), N_2 (swelling) and N_3 (completely swollen) is simulated using MATLAB.

Based on biological observations mentioned in the beginning we assume a sigmoidal shape of the model functions f and g determined in the following way:

$$f(s) = \begin{cases} 0 & \text{for } s < C^- \\ f^* & \text{for } s > C^+ \\ -\frac{f^*}{2}\cos\left(\frac{s - C^-}{C^+ - C^-}\,\pi\right) + \frac{f^*}{2} & \text{else,} \end{cases}$$

$$g(s) = \begin{cases} g^* & \text{for } s > C^+ \\ -\frac{g^*}{2}\cos\left(\frac{s}{C^+}\,\pi\right) + \frac{g^*}{2} & \text{else.} \end{cases}$$

The model parameters we used for the simulations are noted in Table 1.
The calcium concentrations C^- and C^+ are adapted from [10], the other parameters are chosen exemplary. The step size of space discretization is 1/40 and the number of grid points = 40^2.

Name	Description	Value
d_1	diffusion parameter	0.2
d_2	feedback parameter	30
f^*	maximal transition rate $N_1 \curvearrowright N_2$	1
g^*	maximal transition rate $N_2 \curvearrowright N_3$	0.1
C^-	threshold of initiating $N_1 \curvearrowright N_2$	20
C^+	saturation threshold	200
$h_x = \frac{1}{N}$	step size of space discretization	$\frac{1}{40}$
h_t	step size of time discretization	1

Table 1 – Model parameters

Numerical approximation

The PDE describing the calcium diffusion process is discretized with respect to space by means of the standard finite difference approach. Here the Laplacian is approximated by use of the five point star. Doing so, the PDE is transferred into an ODE and we end up with an ODE system on the discrete domain. Due to the low numerical complexity of the model, this can be easily achieved by using the explicit Euler method. The homogeneous Neumann boundary condition is realized by introducing phantom points in order to calculate the normal derivative at the boundary.

Initial values

As we pointed out earlier, in the beginning all mitochondria are intact and with that neither in the swelling process nor completely swollen, i.e.

$$N_{1,0}(x) \equiv 1, \quad N_{2,0}(x) \equiv 0, \quad N_{3,0}(x) \equiv 0\,.$$

For the calcium concentration it is not so clear how to determine the initial state. The initial value $u_0(x)$ defines the distribution of the added Ca^{2+} amount. At this the rate of diffusion progression as well as the dosage location is of great importance. Therefore one can imagine different possible initial states for a fixed total amount C_{tot} of added calcium. For the simulations we used $C_{tot} = 30 \cdot (N+1)^2$ dependent on the space discretization and the initial calcium distribution is assumed to be the normal distribution restricted to the sector $[-1, 3]$ projected onto the discrete domain. For the calcium concentration, it is not clear how to determine initial state. Therefore the initial calcium concentration is determined by a sector of the standard normal distribution (see [10], pages 89,90].) The simulations show that this calcium amount is high enough to induce *complete swelling*.

Results: Complete Swelling

The columns in Figure 3 show the evolution of the model variables u, N_1, N_2 and N_3. Here the first row displays the described initial data and then every row displays the different states at increasing time steps ($t = 0, 35, 150, 250, 300, 370, 400, 520, 750, 4100$) also in Figures 4 and 5.

Remark
One has to be aware of different time scales. The calcium diffusion occurs slower than the development of the mitochondrial populations and the constant state is reached later ($t = 4100$ for the calcium evolution, $t = 1900$ for the mitochondrial populations).

Based on the initial calcium distribution swelling does not start on the whole domain immediately, but only on the regions where the concentrations exceeds the swelling threshold C^{-}. One remarkable result is the clearly visible spreading calcium wave, which particularly becomes obvious in the evolution of N_2. If we compare the dynamics with those of simple diffusion without any feedback, the resulting calcium evolution induced by mitochondrial swelling is indeed completely different. In accordance with the analytical results, in the end all mitochondria are completely swollen and the calcium concentration is constant on the whole domain.

Results: Partial swelling

Now we consider a much lower total amount of calcium, $C_{tot} = 2.1 \cdot (N+1)^2$ added in two varying initial distributions. The simulations show that this small change in the degree of localization decides between complete and partial swelling. In Figures 4 and 5 we only show the evolution of u and N_1 in order to get a qualitative description of the difference between complete and partial swelling , by which it is shown how a slightly modified initial condition can lead to partial swelling (on the right side) or complete swelling (left).

Conclusion

The developed mathematical model is in total accordance with the biologically expected results. It provides a deep understanding of the underlying mechanism with focus on the spatial development. This is of great importance for the understanding of the processes taking place *in vivo*.

The mathematical analysis yields interesting results and in particular we were able to obtain a complete classification of the mitochondrial swelling process. The robustness and validity of the derived model were shown.

This model can also be adapted to the swelling process taking place in cells instead of test tubes by changing the boundary condition. A cell is not a closed system anymore and hence there is a calcium flux over the boundary leading to Robin boundary conditions.

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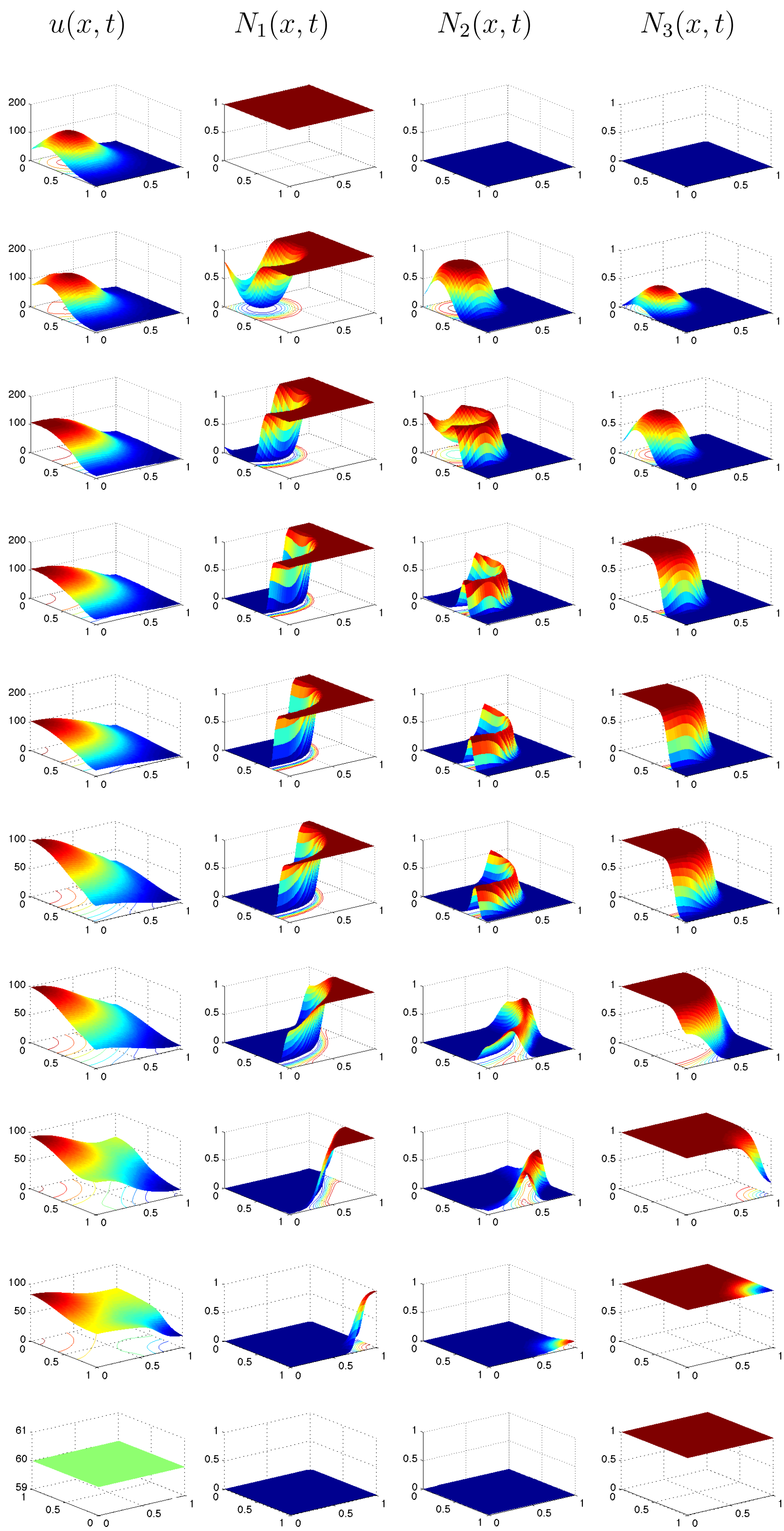
Figure 3 – Evolution of the model variables



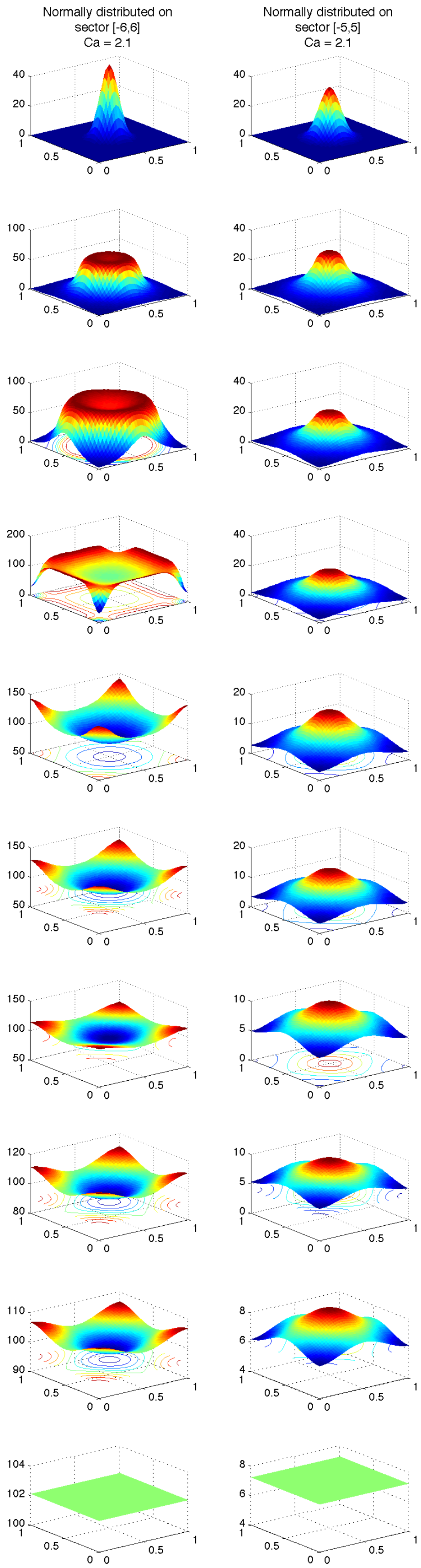


Figure 4 – $u(x,t)$: Comparison of complete and partial swelling

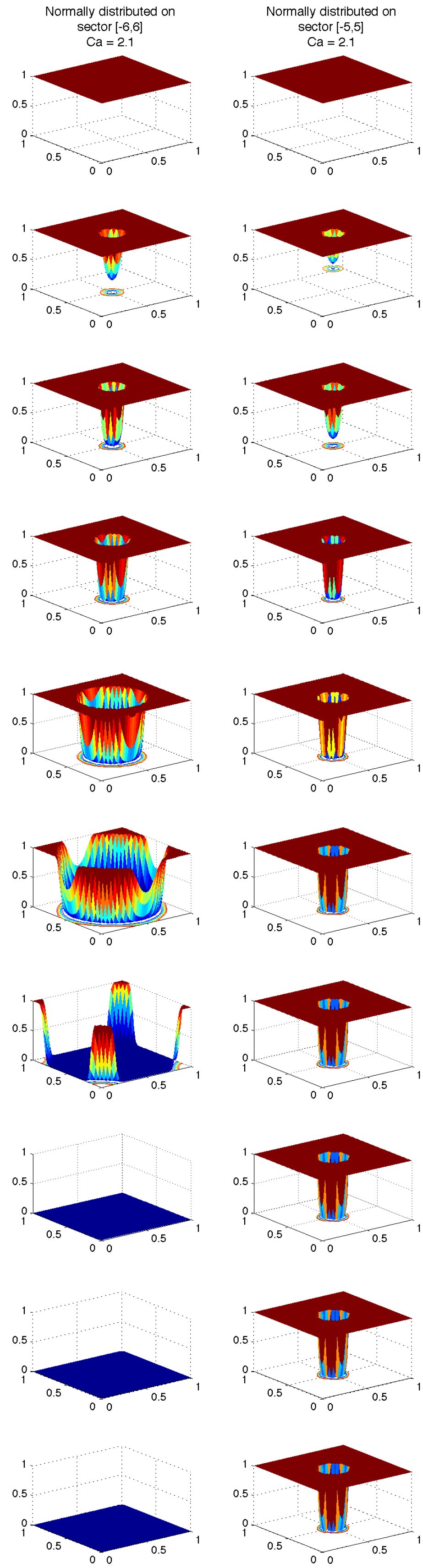


Figure 5 – $N_1(x,t)$: Comparison of complete and partial swelling

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