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LOCAL VS NONLOCAL MODELS FOR MITOCHONDRIA SWELLING

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Abstract. In this paper, we consider deterministic, continuous, nonlocal models for the mitochondrial permeability transition, i.e. mitochondrial swelling. Based on seminal papers [1], [2], [3], [5] and the book [4], in which ODE-PDE and PDE-PDE local models for the swelling of mitochondria have been considered, we suggest here new nonlocal models for this process. This new nonlocal deterministic continuous model for mitochondrial swelling scenario contains nonlocal diffusion, nonlocal chemotaxis, as well as nonlocal source term. We would like to especially emphasize that some of the new nonlocal models that we consider in this paper do not have local counterparts in the literature.

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1 Introduction

Mitochondria are often termed as the cell's powerhouse due to their main function as an energy supplier for almost all eukaryotic cells. The number of mitochondria in a cell varies widely related to the specific energy consumption from a few organelles in thrombocytes up to thousands in muscle cells or neurons. Despite the process of mitochondrial swelling induced by mitochondrial permeability transition is known for more than 50 years, many important issues concerning the mitochondrial permeability transition have still remained unanswered or controversial. For that reason, mathematical modelling is of great importance. Indeed, it provides the possibility to verify and predict properties of the underlying biological mechanism that possibly can not be obtained from experimental data alone.

In [6] a mathematical model, consisting of ordinary differential equations (ODEs), for the swelling process of mitochondrial populations was presented, suitable for cell types with hundreds of mitochondria. The model is based on a division of the mitochondrial population into three subgroups; the mitochondria that are yet intact, N_1; those that are currently undergoing swelling, N_2; and those that already have completed the swelling process, N_3. Initiations and completion of the swelling process are controlled by the intracellular concentration u of calcium ions Ca^{2+}, that is, they are described by the rate functions f(u) and g(u). The swelling process begins when Ca^{2+} reaches a certain threshold level. The higher it rises the more mitochondria engage in swelling, and the faster the swelling process is. During the swelling process, the calcium concentration (Ca^{2+}) increases locally, leading to feedback in the process.

In the experiments, the common mitochondrial permeability transition inducer calcium (Ca^{2+}) is used. As reported in [9], there are many indicators that calcium plays an important role in several forms of apoptosis, even when the mitochondrial permeability transition is initiated by other substances, for example, the huge amount of calcium in the endoplasmic reticulum, which is then released and targets the mitochondrial membrane permeability. Experimental results on mitochondrial swelling [10] suggested to consider spatial effects that directly influence the process of mitochondrial swelling by calcium as an inducer. Indeed, on the one hand, mitochondrial swelling due to calcium is highly dependent on the position of the particular mitochondrion. If the mitochondrion is located near to the calcium source, then it is exposed to a higher dose compared to mitochondria residing further away and consequently, it will be damaged to a higher degree. By diffusion, the locally high calcium dose is diminished and the remaining mitochondria are confronted with a lower concentration. On the other hand, at a high amount of swollen mitochondria, the effect of positive feedback gets relevant and here the residual mitochondria are confronted with a comparatively higher dose calcium challenge. Moreover, the experimental results of [10] demonstrated that not all mitochondria may be swollen to the same degree, which implies that they do not react homogeneously. Consequently, it is vitally important to include the calcium evolution into the bio-mathematical model and to introduce the spatial effects by means of calcium diffusion. Indeed in the seminal papers [1], [2], [3], [5] and in the book [4] mitochondria swelling scenarios that take the spatial effect of calcium concentrations into account have been considered. The governing equations in these papers which described the spatiotemporal model for the swelling of

the mitochondria can be written:

$$\begin{cases} \partial_t u = d_1 \Delta_x u + d_2 g(u(t,x)) N_2(t,x) & , \ x \in \Omega, \ t > 0. \\ \partial_t N_1 = -f(u(t,x)) N_1(t,x) & , \ x \in \Omega, \ t > 0, \\ \partial_t N_2 = f(u(t,x)) N_1(t,x) - g(u(t,x)) N_2(t,x) & , \ x \in \Omega, \ t > 0, \\ \partial_t N_3 = g(u(t,x)) N_2(t,x) & , \ x \in \Omega, \ t > 0, \end{cases} \tag{1}$$

where $\Omega \subset \mathbb{R}^d$ is a bounded domain, $N_i(t,x), i = 1,2,3$ are concentrations of mitochondrial subpopulations, $f(\cdot)$ and $g(\cdot)$ are given functions, d_1, d_2 are nonnegative numbers. The term $d_2 g(u(t,x)) N_2(t,x)$ is called positive feedback which was observed experimentally in [8] and [10] and Δ_x is the Laplacian. Equation (1) describes the situation when mitochondria subpopulations do not move in space. The equation is complemented by appropriate initial data and by appropriate boundary conditions that will reflect spatiotemporal models in vitro and in vivo. Here $u(t,x)$ describes a calcium concentration that triggers the swelling of mitochondria.

As it was shown in [10] mitochondrial subpopulations indeed can move in space as well which leads to PDE-PDE coupling.

$$\begin{cases} \partial_t u = d_1 \Delta_x u + d_2 g(u(t,x)) N_2(t,x) & , \ x \in \Omega, \ t > 0, \\ \partial_t N_1 = d_3 \Delta_x N_1 - f(u(t,x)) N_1(t,x) & , \ x \in \Omega, \ t > 0, \\ \partial_t N_2 = d_4 \Delta_x N_2 + f(u(t,x)) N_1(t,x) - g(u(t,x)) N_2(t,x) & , \ x \in \Omega, \ t > 0, \\ \partial_t N_3 = d_5 \Delta_x N_3 + g(u(t,x)) N_2(t,x) & , \ x \in \Omega, \ t > 0, \end{cases} \tag{2}$$

with appropriate boundary conditions that reflect in vitro and in vivo model and initial conditions. In what follows we call models for the swelling of mitochondria which are described by the equations (1) and (2) "local" models.

In this paper, we suggest some new nonlocal deterministic continuous models for the swelling of mitochondria. These nonlocal models will be reflected, in particular both by the diffusion of calcium concentration and the positive feedback term (so-called external forces or source term) which were observed in experiments in the study of mitochondrial swelling. Moreover, we will consider new local models for the swelling of mitochondria for nondegenerate diffusion vs nonlocal chemotaxis term (migration). We would like to especially emphasize that the nonlocal mitochondrial models which we are going to propose in this paper are completely new, leading to nonlocal ODE-PDE, nonlocal PDE-PDE coupling and will be very interesting for the mathematical community. Indeed, the well-posedness, non-negativity of solutions, and long-time dynamics of their solutions(partial swelling, complete swelling) become very challenging, because the presence of non-local terms in diffusion, chemotaxis as well as in the source term destroy usual structures which were very useful and greatly used for mathematical analysis in the local models. As it was pointed out by A.Muradova(shortly A.M), N.Muradov(shortly N.M) and H. Zischka(shortly H.Z), it is at present unknown whether all mitochondria within a cell are equally sensitive to undergo swelling. For example mitochondria located around the nucleus may be less sensitive to calcium (Ca^{2+}) than mitochondria residing near the cell membrane. According to our opinion, the mathematical models that we suggested in this

paper may help to understand the swelling of mitochondria for biologically and pharmacologically more relevant cases. Furthermore, since up to now we do not have enough data of the processes in a living cell, the proposed models and their analysis and numerical simulation will definitely bring these very challenging processes that are mitochondrial swelling processes to the next level of understanding.

It is worth noting, that when we are saying that so far modelling of swelling of mitochondria had a local nature, we mean that interaction between components of the governing equations (1) and (2) was pointwise. The swelling of mitochondria may trigger the swelling process in neighbourhood mitochondria. Then, the question arises, to which extent other mitochondria would be affected. As was suggested by A.Muradova and N.Muradov local assumptions (pointwise calculation) may not hold or cannot explain some natural questions arising in the modelling of swelling mitochondria, e.g. sensitivity of mitochondria subpopulations $N_i(t,x), i = 1,2,3$ to calcium concentration depending of their location. These and their other suggestions mentioned above initiate to consider nonlocal models for the swelling of mitochondria with appropriate boundary conditions and initial conditions. Note that nonlocality can be included in the model under consideration in a different way, namely via nonlocal diffusion, nonlocal convection as well as nonlocal reaction terms. (see below Type 1 - Type 4)

2 Nonlocal swelling of mitochondria: Type 1

The Type 1 nonlocal spatial model deals with local diffusion for the calcium concentration Ca^{2+} and the nonlocal positive feedback term, more precisely **Type 1**

$$\begin{cases} \dfrac{\partial u}{\partial t} = d_1\Delta_x u + d_2 N_2(t,x)\Big(\displaystyle\int_\Omega K(|x-y|)g(u(t,y))dy\Big) & , \ x\in\Omega,\ t>0, \\ \dfrac{\partial N_1}{\partial t} = -f(u(t,x))N_1(t,x) & , \ x\in\Omega,\ t>0, \\ \dfrac{\partial N_2}{\partial t} = f(u(t,x))N_1(t,x) - \Big(\displaystyle\int_\Omega K(|x-y|)g(u(t,y))dy\Big)N_2(t,x) & , \ x\in\Omega,\ t>0, \\ \dfrac{\partial N_3}{\partial t} = \Big(\displaystyle\int_\Omega K(|x-y|)g(u(t,y))dy\Big)N_2(t,x) & , \ x\in\Omega,\ t>0, \end{cases} \tag{3}$$

where the kernel $K : \mathbb{R}_+ \to \mathbb{R}_+$, $\mathbb{R}_+ = [0,\infty)$ of the integral term describes nonlocal interaction satisfying for mathematical study

$$\int_\Omega\int_\Omega K(|x-y|)dxdy < \infty \text{ and } \sup_{x\in\Omega}\int_\Omega K(|x-y|)dy < \infty.$$

In (3), Ω is a bounded domain in $\mathbb{R}^d$, which is a test tube in vitro model and living cell in vivo model.

Remark 1. Examples for the kernels satisfying mentioned assumptions above are Newton potential, i.e. $K(|x|) = \kappa_d|x|^{2-d}$ for $d > 2$ and $K(|x|) = -\kappa_2 \log|x|$ for $d = 2$, with appropriate constants κ_d.

Remark 2. Note that the rate of change $u(t,x)$ at time t and at position x depends on the influence of neighbouring $u(t,x)$ at all position y. Such a model is represented mathematically by $\int_\Omega K(|x-y|)g(u(t,y))dy$, where $K(|x-y|)$ is the kernel function which quantifies the effect of neighbouring $u(t,y)$ has on $u(t,x)$. The form equation here assumes that the influence depends only on the distance from x to y.

3 Nonlocal swelling of mitochondria: Type 2

The Type 2 nonlocal spatial model for mitochondrial swelling scenarios deals with nonlocal diffusion as well as nonlocal reaction term, that is **Type 2:**

$$\begin{cases} \dfrac{\partial u}{\partial t} = -d_1(-\Delta_x)^s u + d_2 N_2(t,x)\Big(\displaystyle\int_\Omega K(|x-y|)g(u(t,y))dy\Big) & , \ x\in\Omega,\ t>0, \\ \dfrac{\partial N_1}{\partial t} = -f(u(t,x))N_1(t,x) & , \ x\in\Omega,\ t>0, \\ \dfrac{\partial N_2}{\partial t} = f(u(t,x))N_1(t,x) - N_2(t,x)\Big(\displaystyle\int_\Omega K(|x-y|)g(u(t,y))dy\Big) & , \ x\in\Omega,\ t>0, \\ \dfrac{\partial N_3}{\partial t} = N_2(t,x)\Big(\displaystyle\int_\Omega K(|x-y|)g(u(t,y))dy\Big) & , \ x\in\Omega,\ t>0, \end{cases} \tag{4}$$

where Ω is a bounded domain in $\mathbb{R}^d$ and $(-\Delta_x)^s$, $s\in(0,1]$. The Type 2 model describes a particular case of anomalous diffusion actively treated in the context of different applications, such as in plasma physics and turbulence, surface diffusion, semiconductors and so on. Anomalous diffusion can be described as a random process of particle motion characterized by the probability density distribution of jump length. The moments of this density distribution are finite in the case of normal diffusion (the Laplacian), but this is not the case for superdiffusion. Note that an analogous model of Type 2 for the swelling of mitochondria can be used to study damage mechanics, the temperature distribution in thermodynamics. In molecular biology, the space variable x corresponds to the cell genotype, $(u(t,x), N_1(t,x), N_2(t,x), N_3(t,x))$ stands for the cell density distributions for various groups of cells as functions of their genotype and time. As in (2), here Ω is a bounded domain in $\mathbb{R}^d$, $d\geq 1$, which can be a test tube in vitro model and living cell in vivo model for the swelling of mitochondria.

4 Nonlocal swelling of mitochondria: Type 3

As was pointed out in [7] and in our several discussions with A.M, N.M and H.Z that mitochondria subpopulations $N_1(t,x)$ – unswollen, $N_2(t,x)$ – swollen, $N_3(t,x)$ –completely swollen mitochondrial subpopulations can move not only in time and also in space that leads to PDE-PDE non-local coupling:

$$\begin{cases} \dfrac{\partial u}{\partial t} = -d_1(-\Delta_x)^s u + d_2 N_2(t,x)\Big(\displaystyle\int_\Omega K(|x-y|)g(u(t,y))dy\Big),\ x\in\Omega,\ t>0, \\ \dfrac{\partial N_1}{\partial t} = -(-\Delta_x)^s N_1 - f(u(t,x))N_1(t,x),\ x\in\Omega,\ t>0, \\ \dfrac{\partial N_2}{\partial t} = -(-\Delta_x)^s N_2 + f(u(t,x))N_1(t,x) - N_2(t,x)\Big(\displaystyle\int_\Omega K(|x-y|)g(u(t,y))dy\Big), \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad x\in\Omega,\ t>0, \\ \dfrac{\partial N_3}{\partial t} = -(-\Delta_x)^s N_3 + N_2(t,x)\Big(\displaystyle\int_\Omega K(|x-y|)g(u(t,y))dy\Big),\ x\in\Omega,\ t>0, \end{cases} \tag{5}$$

where Ω is a bounded domain in $\mathbb{R}^d$, $d \geq 1$, $s \in (0,1]$. The components of governing equation (5), i.e. $(u(t,x), N_1(t,x), N_2(t,x), N_3(t,x))$ satisfies depending on in vitro or in vivo model appropriate boundary conditions with given initial concentrations.

5 Nonlocal swelling of mitochondria: Type 4

Recently it was also suggested by A.M, N.M and H.Z that it will be crucial for the mitochondrial swelling scenario to understand the crosstalk between neighbouring mitochondria as well as dynamics of this communication. Hypothetically, mitochondria may communicate with each other via the release of soluble signalling molecules, such as reactive oxygen species or calcium that can propagate through the cytoplasm. This is driven by the diffusion signals from source organelles to all surrounding organelles, and is limited by diffusion distances. For cell-to-cell communication, non-selective diffusible signals exert indiscriminate effects on multiple surrounding mitochondria rather than on a single receiver mitochondrion. Therefore, it will be useful for the mitochondria swelling scenario to take into account the nonlocal chemotaxis effect, the latter is the directed movement of cells in response to chemical gradients, which unlike diffusion directs the motion up a concentration gradient. However, the experimental evidence for the role of chemotaxis in mitochondria swelling seems meager. Consequently, mathematical modelling might be able to guide further laboratory efforts. We would like especially to emphasize that incorporating nonlocality in chemotaxis model is not new and already appeared in the classical chemotaxis model in the literature. Indeed, for a quasistationary model of the classical parabolic-parabolic chemotaxis model, we have elliptic equations for the chemoattractant (this is the case when the chemoattractant diffuses much faster than the cell population). For the Newton kernel (see Remark 1), using potential theory and adjusting boundary conditions one can obtain the nonlocal parabolic equation. In this way the obtained nonlocal parabolic equation for chemotaxis model (quasistationary case) is different from the nonlocal model for chemotaxis which we consider below. In our nonlocal chemotaxis model for the swelling of mitochondria, the nonlocal chemotaxis term measures the environment of mitochondria subpopulations along their outer membranes.

Hence, the governing equation taking the non-local chemotaxis model into account can be written as following:

$$\begin{cases} \dfrac{\partial u}{\partial t} = d_1\Delta_x u - \nabla(u^a P(x,D)N_2(t,x)) + d_2 N_2(t,x)\Big(\displaystyle\int_\Omega K(|x-y|)g(u(t,y))dy\Big), \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad x\in\Omega,\ t>0, \\ \dfrac{\partial N_1}{\partial t} = -f(u(t,x))N_1(t,x),\ x\in\Omega,\ t>0, \\ \dfrac{\partial N_2}{\partial t} = f(u(t,x))N_1(t,x) - N_2(t,x)\Big(\displaystyle\int_\Omega K(|x-y|)g(u(t,y))dy\Big),\ x\in\Omega,\ t>0, \\ \dfrac{\partial N_3}{\partial t} = N_2(t,x)\Big(\displaystyle\int_\Omega K(|x-y|)g(u(t,y))dy\Big),\ x\in\Omega,\ t>0, \end{cases} \tag{6}$$

where Ω is a bounded domain in $\mathbb{R}^d$, and $a>0$ is some constant. Equation (6) is supplemented by appropriate initial data for $(u(t,x),N_1(t,x),N_2(t,x),N_3(t,x))$ and boundary conditions in vitro and in vivo for calcium concentration $u(t,x)$. It will be interesting to carry out the mathematical analysis and numerical simulations of equations (3) - (6).

Remark 3. We would suspect that such nonlocality would prevent the application of compact stencil methods, and that the resulting algebraic systems (after discretisation) will be computationally more costly.

6 CONCLUSION

In this paper, we study nonlocal spatial models for the swelling of mitochondria. At present due to the seminal papers [1], [2], [3], [5] and the book [4] local models for the swelling of mitochondria lead to ODE-PDE and PDE-PDE systems between calcium concentration $u(t,x)$ and mitochondrial subpopulations $N_i(t,x), i=1,2,3$. On the other hand, it is well known that a spatial nonlocality - for the diffusion, chemotaxis, external loading - can be incorporated into a model in a non-unique way and may be very challenging both from a modelling viewpoint and for mathematical analyses as well, due to, in particular, the degeneracy of governing of the ODE-PDE system, as well as the introduced nonlocality that can destroy useful structures that possessed local counterparts, namely for the well-posedness, long-time dynamics, and numerical analysis.

Heuristically, the dynamics of an ODE-PDE coupled dissipative system should depend on the monotonicity properties of the ODE component. In the case where ODE is "monotone" that is, it cannot produce the internal instability (and all of the instability of the ODE-PDE system is driven by the coupling with the PDE component), one expects the asymptotic compactness and the existence of a smooth finite-dimensional global attractor with "good" properties. In contrast to that, in the "non-monotone" of ODE's component, the ODE-instability may produce the asymptotic discontinuities (there is numerical evidence for that in some ODE-PDE models related to forest kinetics model) and even may completely destroy the initially smooth spatial profile. Thus, in that case, the smoothing effect from PDE-component is not strong enough in order to suppress the development of discontinuities provided by the internal instabilities of ODE-component, and as a result,

spatial discontinuities and extremely complicated (greatly unexpected) spatial structures may appear in forest kinetic models. Based on the arguments mentioned above, we conjecture that depending on the dominance of nonlocal diffusion effects for calcium ions over their nonlocal production in the long term, all mitochondria will either be still intact or have completed swelling. On the other hand, if the calcium ion nonlocal production dominates over local(nonlocal)diffusion then in contrast to the local ODE-PDE model, we will not have partial swelling, that is, some mitochondria will also remain in the intermediate state where swelling has been initiated but not completed. Moreover, for the models of swelling of mitochondria that include a nonlocality in chemotaxis (where classical gradient sensing term is replaced by pseudo-differential operator order 1) vs local diffusion, we expect the existence of global bounded solutions for bounded domains in any dimension unlike classical local models, in higher dimensions. With this paper, we are sending to the mathematical society, especially the sections that deal with the methods of infinite-dimensional dynamical systems arising in biology and medicine to develop appropriate mathematical theories and justify the above heuristic approach in a mathematically rigorous way, as well as to apply the expected theory for a quite general class of ODE-PDE and PDE-PDE local vs nonlocal coupling arising in the modelling of life science problems. Finally, apart from mitochondrial movement covered here, constant mitochondrial fission and fusion has recently become a clear research focus. Thus, one challenging question is the mathematical description of the mitochondrial swelling process under this fission/fusion scenario. In the forthcoming paper we will deal with the mathematical modeling for this issue.

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