Homogenization of fast diffusion on surfaces with a two-step method and an application to T-cell signaling

Isabell Graf[a], Malte A. Peter[b,c]

[a]Department of Mathematics, Simon Fraser University, Burnaby BC, Canada
[b]Institute of Mathematics, University of Augsburg, Universitätsstraße 14, 86159 Augsburg, Germany
[c]Augsburg Centre for Innovative Technologies, University of Augsburg, 86135 Augsburg, Germany

Abstract

In the context of periodic homogenization based on two-scale convergence, a nonlinear system of six coupled partial differential equations is homogenized. The system describes the process of signaling in a T cell (thymus lymphocyte) including the dynamics of calcium and of the molecule Stim1. Two of the six equations are defined on the finely structured surface of the endoplasmic reticulum and to make global diffusion after homogenization possible, we extend the existing theoretical convergence results and introduce the two-step method. Therefore the membrane of the endoplasmic reticulum is given an extent in normal direction such that it has a volume with width $0 < \delta \ll 1$. For convergence of the functions defined on the membrane we can now use well-known two-scale convergence results and obtain fast diffusion after homogenization. To come back to the original shape of the surface, δ tends to zero in the reference cell, if some compactness results are satisfied, which leads to a non-standard cell problem, and we obtain global diffusion on the surface of the endoplasmic reticulum. The results justify a model for signaling in a T-cell recently proposed heuristically.

Keywords: Periodic homogenization, two-scale convergence, T cell signaling, fast surface diffusion, reaction–diffusion system.
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1. Introduction

Periodic homogenization is a method for upscaling rigorously mathematical models of multiscale processes. Often, the multiscale nature of the given problem proceeds from a microstructure of the material. Resolving the microstructure in detail is much too costly and mostly unnecessary, so upscaling the models by homogenization is a suitable way to be on a level with the larger scale still regarding the fine structure of the material. In periodic homogenization, we assume the microstructure of the material to be periodic with respect to a reference cell and consider the limit as the periodicity length approaches zero. Monographs on the subject include [5, 28, 26, 20, 9, 23].

An elegant technique for performing periodic homogenization is by using two-scale convergence developed in [2, 25]. When it comes to homogenizing processes, e.g. diffusion on hypersurfaces, the theory is only moderately developed. For results in the context of slow diffusion, we refer to [3, 24]. In order to handle fast diffusion on hypersurfaces, a different approach seems useful: A two-step convergence method, see section 2 below, is a tool to determine macroscopic diffusion on hypersurfaces. The main idea is to regard the surface as a thin layer of width $0 < \delta \ll 1$. Partial differential equations defined on this layer, which has a positive volume, can be homogenized by using well-known results from two-scale convergence. After homogenization, the thin layer, which is now a subset of the reference cell, is shrunk back to a surface by letting δ tend to

Email addresses: grafisab@gmail.com (Isabell Graf), malte.peter@math.uni-augsburg.de (Malte A. Peter)

zero, making sure the macroscopic equation and the cell problem satisfy some compactness results. A similar approach using Γ-convergence can be found in [7, 6], in a wider setting the articles [22, 8, 4] are of interest.

Another question of practical relevance in the context of homogenization, which seems to have received little attention in the literature, is the passage to the two-scale limit in Robin-boundary terms at the exterior boundary of the domain under consideration. In section 3, we introduce a way to homogenize systems with non-homogeneous Neumann or even nonlinear Robin boundary terms, where we regard the outer boundary of the domain as a separate periodic domain and use two-scale convergence in one dimension less.

Having proved these general results, we apply them to the problem of homogenization of a system of differential equations modeling T-cell signaling in section 4. One result of this analysis is a rigorous justification of a heuristically derived model for T-cell signaling not resolving the cell microstructure, which has been recently suggested in [12]. For this purpose, we examine a system of six coupled nonlinear partial differential equations, which describes the dynamics of calcium and Stim1 molecules in a single cell. During this procedure the Stim1 molecules, which only exist on the finely structured surface of the endoplasmic reticulum, diffuse to the plasma membrane of the cell and induce so-called CRAC channels to open to let calcium from the intercellular space into the cytosol. This leads to a high concentration of calcium in the cytosol, which is normally poor of calcium, and the cell is in an activated state. More details on the process are found in section 4. Since the geometry of the cell plays an important role, we use the two-step approach in the context of periodic homogenization to handle the fine structure of the surface of the endoplasmic reticulum, which divides the cell into cytosol and lumen of the endoplasmic reticulum.

In section 5, we prove the a-priori estimates and show strong convergence of the functions. Further, we show the existence of a solution in section 6. In section 7, we identify the two-scale limit and in section 8 we let δ tend to zero by using two-step convergence, which gives us the final macroscopic system of equations. Finally, we prove uniqueness of the limit system in section 9.

2. Two-step convergence

The two-step convergence is a mathematical tool to determine macroscopic diffusion on hypersurfaces in the context of periodic homogenization. The idea is to regard the hypersurface as a thin domain with thickness $\delta > 0$. Using homogenization on these blown up domains we are able to apply well known homogenization results valid on subsets of $\mathbf{R}^n$ with positive volume. After homogenization the limit equation is defined on the homogeneous domain Ω and the unit cell Y, which contains a characteristical part of the still blown up hypersurface. To get the initial shape of the domain back, we let δ tend to zero in the unit cell Y of the homogenized system. A similar idea using Γ-convergence is found in [7, 6].

2.1. A generic problem

Let $\Omega \subset \mathbf{R}^n$ be a domain and $\Gamma \subset Y = [0,1]^n$ be a smooth, compact and periodic hypersurface, such that $\Gamma_\varepsilon = \bigcup_{k\in\mathbf{Z}^n} \varepsilon(k+\Gamma)$ is smooth and connected for a small parameter $0 < \varepsilon \ll 1$. We define $Y^\delta = \{y + dn_y |\ y \in \Gamma, d \in (-\delta,\delta)\} \subset Y$ for a small $\delta > 0$, which means that the manifold gets a volume through an additional component pointing in the normal n_y-direction in every point $y \in \Gamma$.

Let $f \in C(\Omega, C_\#(Y))$ with $f_\varepsilon(x) := f(x, \frac{x}{\varepsilon})$ and $h \in C(\partial\Omega, C_\#(\partial_o Y))$ with $h_\varepsilon(x) := h(x, \frac{x}{\varepsilon})$, where $\partial_o Y$ is one side of the outer boundary of Y. The index # of the function space denotes periodicity of the contained functions. Furthermore, let $\Omega_\varepsilon = \bigcup_{k\in\mathbf{Z}^n} \varepsilon(k+Y^\delta) \cap \Omega$ and u_ε be the solution of the initial boundary value problem

$$\begin{aligned} \partial_t u_\varepsilon - D\Delta u_\varepsilon + u_\varepsilon &= f_\varepsilon && \text{in } \Omega_\varepsilon \\ -D\nabla u_\varepsilon \cdot n &= a(u_\varepsilon - h_\varepsilon) && \text{on } \partial\Omega_\varepsilon \cap \partial\Omega \end{aligned} \tag{1}$$

with constant diffusion coefficient $D > 0$ and constant $a > 0$. Let the initial value $u_\varepsilon(0)$ be smooth and bounded. With standard estimations, results on two-scale convergence from [2] and Theorem 5 for the Robin boundary term we find the weak limit equation for $\varepsilon \to 0$ with $u \in L^2([0,T], H^1(\Omega))$ and $u_1 \in L^2([0,T], L^2(\Omega, H^1_\#(Y^\delta)))$ satisfying

$$|Y^\delta| \int_\Omega \partial_t u^\delta \psi \mathrm{d}x + D \int_\Omega \int_{Y^\delta} [\nabla_x u^\delta + \nabla_y u_1^\delta][\nabla_x \psi + \nabla_y \psi_1] \mathrm{d}y \mathrm{d}x \\ + |Y^\delta| \int_\Omega u^\delta \psi \mathrm{d}x + \int_{\partial\Omega} \int_{\partial_o Y^\delta} a(u^\delta - h)\psi \mathrm{d}\sigma_y \mathrm{d}\sigma_x = \int_\Omega \int_{Y^\delta} f\psi \mathrm{d}y \mathrm{d}x \quad (2)$$

for all $\psi \in H^1(\Omega)$ and $\psi_1 \in L^2(\Omega, H^1_\#(Y^\delta))$, where u_1^δ is related to u^δ through the solution of a cell problem $\mu_k^\delta \in H^1_\#(Y^\delta)$ with $\int_{Y^\delta} \mu_k^\delta \mathrm{d}y = 0$ and the superscript stresses the dependence of the solution on the parameter δ. The cell problem is found by setting $\psi = 0$ and using $\nabla_y u_1^\delta = \sum_{k=1}^n \nabla_y \mu_k^\delta \partial_{x_k} u^\delta$ in equation (2), which leads to

$$D \int_\Omega \sum_{k=1}^n \partial_{x_k} u^\delta \int_{Y^\delta} \left[e_k + \nabla_y \mu_k^\delta\right] \nabla_y \psi_1 \mathrm{d}y \mathrm{d}x = 0. \quad (3)$$

The scalar product and norm on $L^2(\Omega)$ is given by $(v,w)_\Omega = \int_\Omega vw\mathrm{d}x$ and $\|v\|_\Omega^2 = (v,v)_\Omega$ for $v, w \in L^2(\Omega)$, respectively.

In the following Theorem 1 we consider the behavior of equations (2) and (3) for δ tending to zero.

Theorem 1. *Let there be given a generic problem as* (1)*, which two-scale converges to* (2)*. Then, for $\delta \to 0$, the solution u must satisfy the weak limit equation*

$$|\Gamma| \int_\Omega \partial_t u\psi \, dx + \int_\Omega P \nabla_x u \nabla_x \psi \, dx + |\Gamma| \int_\Omega u\psi \, dx + |\partial\Gamma| \int_{\partial\Omega} au\psi \, d\sigma_x \\ = \int_\Omega \int_\Gamma f\psi \, d\sigma_y \, dx + \int_{\partial\Omega} \int_{\partial_o\Gamma} ah\psi \, d\sigma_y \, d\sigma_x \quad (4)$$

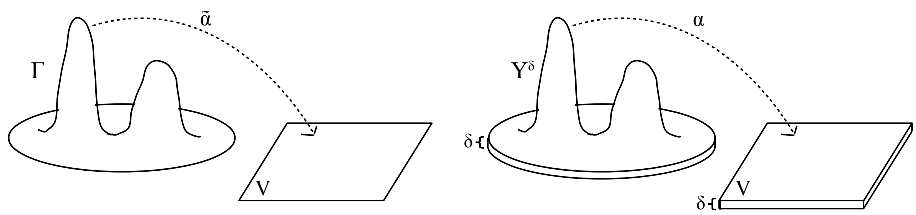
with $P_{ij} = D \int_\Gamma \left(P_\Gamma(e_j + \nabla_\Gamma \mu_j)\right)_i d\sigma_y$ for $i,j = 1,\ldots,n$ and μ_j satisfying

$$\begin{aligned} \nabla_\Gamma \cdot (P_\Gamma(e_j + \nabla_\Gamma \mu_j)) &= 0 \qquad \text{in } \Gamma, \\ P_\Gamma(e_j + \nabla_\Gamma \mu_j) \cdot n &= 0 \qquad \text{on } \partial\Gamma, \end{aligned} \quad (5)$$

with μ_j being Y-periodic. Here, P_Γ is the orthogonal projection to Γ.

Before we start the proof, we briefly illustrate the setting. Let $\{(\tilde{U}_\lambda, \tilde{\alpha}_\lambda)\}$ be an atlas of the manifold Γ such that $\bigcup_\lambda \tilde{U}_\lambda = \Gamma$ and $\tilde{\alpha}_\lambda : \tilde{U}_\lambda \to V_\lambda \subset \mathbf{R}^{n-1}$. With n_y being the normal vector of Γ in the point $y \in \Gamma$ we define another atlas $\{(U_\lambda, \alpha_\lambda)\}$ of the blown up domain Y^δ with $\bigcup_\lambda U_\lambda = Y^\delta$ by

$$\alpha_\lambda^{-1} : V_\lambda \times (-\delta, \delta) \to U_\lambda$$
$$\alpha_\lambda^{-1}(\xi_1, \ldots, \xi_{n-1}, \xi_n) = \underbrace{\tilde{\alpha}_\lambda^{-1}(\xi_1, \ldots, \xi_{n-1})}_{\in \tilde{U}_\lambda} + \xi_n n_y.$$



Note that the last component of the local coordinates affects just the normal direction of Γ, which yields for the Riemannian metric tensor g_{ij}, $i, j = 1, \dots, n$ that $g_{in} = g^{in} = g_{ni} = g^{ni} = 0$ for $i = 1, \dots, n-1$, where g^{ij}, $i, j = 1, \dots n$ are the components of the inverse of the matrix $(g_{ij})_{i,j=1,\dots,n}$. The nth basis vector is given by

$$\frac{\mathrm{d}}{\mathrm{d}\xi^n} = \frac{\mathrm{d}}{\mathrm{d}t}_{|t=0} \alpha_\lambda^{-1}(\xi + te_n) = \frac{\mathrm{d}}{\mathrm{d}t}_{|t=0} \left(\tilde{\alpha}_\lambda^{-1}(\xi_1, \dots, \xi_{n-1}) + (\xi_n + t)n_y\right) = n_y$$

and consequently, $g_{nn} = n_y^T n_y = 1$. We choose the Riemannian metric tensor g_{ij}, such that $g_{ij} = g^{ij} = 0$ also holds for any $i \neq j$ on the manifold Γ, which means that the basis vectors $\frac{\mathrm{d}}{\mathrm{d}\xi^i}$, $i = 1, \dots, n$ are orthogonal. Note that $g_{ii} = \left\langle \frac{\mathrm{d}}{\mathrm{d}\xi^i}, \frac{\mathrm{d}}{\mathrm{d}\xi^i} \right\rangle > 0$. The gradient of a function $\mu : Y^\delta \to \mathbf{R}$ in U_λ in new coordinates is given by

$$\nabla \mu = \sum_{i=1}^n g^{ii} \frac{\partial(\mu \circ \alpha_\lambda^{-1})}{\partial \xi_i} \frac{\mathrm{d}}{\mathrm{d}\xi^i}.$$

The divergence on Y^δ of a function $\mu : Y^\delta \to \mathbf{R}^n$ in new coordinates is given by

$$\nabla \circ \mu = \frac{1}{\sqrt{\det\, g}} \sum_{i=1}^n \frac{\mathrm{d}}{\mathrm{d}\xi^i} \left(\mu^i \sqrt{\det\, g}\right).$$

Here μ^i is the ith component of μ in the basis vectors $\frac{\mathrm{d}}{\mathrm{d}\xi^i}$.

Proof of Theorem 1

The proof is composed of three steps. First we show that the terms, where the limit formation takes place, are bounded. In the second step we let δ tend to zero and consider the consequences in the various terms. In the last step we deduce the cell problem and the macroscopic limit equation.

For the charts we use the abbreviating notation $\alpha(x) = \alpha_\lambda(x)$ for $x \in U_\lambda \subset Y^\delta$. In the proof we indicate the δ dependence of the functions u and u_1 by u^δ and u_1^δ.

Step 1. Boundedness of $\|\nabla \mu_k^\delta\|_{Y^\delta}$.

Testing the cell problem, equation (3), with $\psi_1 = \mu_k^\delta$ for every $k = 1, \dots, n$, leads to

$$\begin{aligned}\int_\Omega \int_{Y^\delta} \nabla_y \mu_k^\delta \nabla_y \mu_k^\delta \mathrm{d}y\mathrm{d}x = -\int_\Omega \int_{Y^\delta} e_k \nabla_y \mu_k^\delta \mathrm{d}y\mathrm{d}x &\leq \|e_k\|_{\Omega\times Y^\delta} \|\nabla_y \mu_k^\delta\|_{\Omega\times Y^\delta} \\ &= \sqrt{|\Omega| \cdot |Y^\delta|} \|\nabla_y \mu_k^\delta\|_{\Omega\times Y^\delta},\end{aligned}$$

where we used the Cauchy–Schwarz inequality. It follows that

$$\frac{1}{|\Omega| \cdot |Y^\delta|} \|\nabla_y \mu_k^\delta\|^2_{\Omega\times Y^\delta} \leq 1,$$

which means that the norm of $\nabla_y \mu_k^\delta$ remains bounded independently of the size of the domain Y^δ, since $|Y^\delta| \leq 1$.

Boundedness of $\|\nabla_x u^\delta + \nabla_y u_1^\delta\|_{\Omega\times Y^\delta}$.

To show boundedness also for the diffusion term in the macroscopic problem we consider equation (2), where we perform a substitution by using charts $\alpha : V \times (-\delta, \delta) \to Y^\delta$. Thereby, the terms $|Y^\delta|$ and $|\partial Y^\delta|$ are equal to $2\delta|\Gamma|$ and $2\delta|\partial_o\Gamma|$ in their first order approximation, respectively.

$$\begin{aligned}(2\delta|\Gamma| + \mathcal{O}(\delta^2)) \int_\Omega \partial_t u^\delta \psi \mathrm{d}x + D \int_{\Omega\times Y^\delta} [\nabla_x u^\delta + \nabla_y u_1^\delta][\nabla_x \psi + \nabla_y \psi_1] \mathrm{d}y\mathrm{d}x \\ + (2\delta|\Gamma| + \mathcal{O}(\delta^2)) \int_\Omega u^\delta \psi \mathrm{d}x + a(2\delta|\partial_o\Gamma| + \mathcal{O}(\delta^2)) \int_{\partial\Omega} u^\delta \psi \mathrm{d}\sigma_x \\ = \int_\Omega \int_{V\times(-\delta,\delta)} f\psi \sqrt{\det\, g} \mathrm{d}\xi \mathrm{d}d\mathrm{d}x + \int_{\partial\Omega} \int_{\partial_o V\times(-\delta,\delta)} h\psi \sqrt{\det\, g} \mathrm{d}\sigma_\xi \mathrm{d}d\mathrm{d}\sigma_x\end{aligned}$$

for all $(\psi,\psi_1)\in H^1(\Omega)\times L^2(\Omega,H^1_\#(Y^\delta))$. Now we test with the functions $\psi=u^\delta$ and $\psi_1=u_1^\delta$,

$$
\begin{aligned}
(2\delta|\Gamma|+\mathcal{O}(\delta^2))\int_\Omega \partial_t u^\delta u^\delta \mathrm{d}x + D\|\nabla_x u^\delta+\nabla_y u_1^\delta\|^2_{\Omega\times Y^\delta}&\\
+(2\delta|\Gamma|+\mathcal{O}(\delta^2))\|u^\delta\|^2_\Omega + a(2\delta|\partial_o\Gamma|+\mathcal{O}(\delta^2))\|u^\delta\|^2_{\partial\Omega}&\\
=\int_\Omega u^\delta\int_{V\times(-\delta,\delta)} f\sqrt{\det g}\mathrm{d}\xi\mathrm{d}d\mathrm{d}x+\int_{\partial\Omega}u^\delta\int_{\partial_o V\times(-\delta,\delta)} h\sqrt{\det g}\mathrm{d}\sigma_\xi\mathrm{d}d\mathrm{d}\sigma_x&
\end{aligned}
$$

Furthermore, we substitute $(\xi_1,\dots,\xi_{n-1},\frac{\xi_n}{\delta})=z=(z_1,\dots,z_{n-1},z_n)$, with $\mathrm{d}\xi=\mathrm{d}\xi_1\dots\mathrm{d}\xi_n=\mathrm{d}z_1\dots\mathrm{d}z_{n-1}\delta\mathrm{d}z_n$, and continue with

$$
\begin{aligned}
(2\delta|\Gamma|+\mathcal{O}(\delta^2))\int_\Omega \partial_t u^\delta u^\delta \mathrm{d}x + D\|\nabla_x u^\delta+\nabla_y u_1^\delta\|^2_{\Omega\times Y^\delta}&\\
+(2\delta|\Gamma|+\mathcal{O}(\delta^2))\|u^\delta\|^2_\Omega + a(2\delta|\partial_o\Gamma|+\mathcal{O}(\delta^2))\|u^\delta\|^2_{\partial\Omega}&\\
=\delta\int_\Omega u^\delta\int_{V\times(-1,1)} f\sqrt{\det g}\mathrm{d}z\mathrm{d}d\mathrm{d}x+\delta\int_{\partial\Omega}u^\delta\int_{\partial V_o\times(-1,1)} h\sqrt{\det g}\mathrm{d}\sigma_z\mathrm{d}d\mathrm{d}\sigma_x&
\end{aligned}
$$

and divide by δ to find

$$
\begin{aligned}
(2|\Gamma|+\mathcal{O}(\delta))\int_\Omega \partial_t u^\delta u^\delta \mathrm{d}x + \frac{1}{\delta}D\|\nabla_x u^\delta+\nabla_y u_1^\delta\|^2_{\Omega\times Y^\delta}&\\
+(2|\Gamma|+\mathcal{O}(\delta))\|u^\delta\|^2_\Omega + a(2|\partial_o\Gamma|+\mathcal{O}(\delta))\|u^\delta\|^2_{\partial\Omega}&\\
\le\frac{1}{2}\|u^\delta\|^2_\Omega+\frac{1}{2}\|\int_{V\times(-1,1)} f\sqrt{\det g}\mathrm{d}z\mathrm{d}d\|^2_\Omega&\\
+\frac{1}{2\lambda}\|u^\delta\|^2_{\partial\Omega}+\frac{\lambda}{2}\|\int_{\partial_o V\times(-1,1)} h\sqrt{\det g}\mathrm{d}\sigma_z\mathrm{d}d\|^2_{\partial\Omega}&
\end{aligned}
$$

for any $\lambda>0$. This yields, after integration with respect to time,

$$
\begin{aligned}
(2|\Gamma|+\mathcal{O}(\delta))\frac{1}{2}\|u^\delta\|^2_\Omega+\frac{1}{\delta}D\|\nabla_x u^\delta+\nabla_y u_1^\delta\|^2_{\Omega\times Y^\delta,t}+(2|\Gamma|+\mathcal{O}(\delta))\|u^\delta\|^2_{\Omega,t}&\\
+\left(a(2|\partial_o\Gamma|+\mathcal{O}(\delta))-\frac{1}{2\lambda}\right)\|u^\delta\|^2_{\partial\Omega,t}\le c_1+c_2\frac{\lambda}{2}+\frac{1}{2}\|u^\delta\|^2_{\Omega,t}+\frac{1}{2}\|u(0)\|^2_\Omega,&
\end{aligned}
$$

where we choose λ such that $\lambda>\frac{1}{4a|\partial\Gamma|}$, but finite. The constants c_1,c_2 and λ are independent of δ. We find with Gronwall's lemma that

$$
\begin{aligned}
(2|\Gamma|+\mathcal{O}(\delta))\frac{1}{2}\|u^\delta\|^2_\Omega+\frac{1}{\delta}D\|\nabla_x u^\delta+\nabla_y u_1^\delta\|^2_{\Omega\times Y^\delta,t}+(2|\Gamma|+\mathcal{O}(\delta))\|u^\delta\|^2_{\Omega,t}&\\
+\left(a(2|\partial_o\Gamma|+\mathcal{O}(\delta))-\frac{1}{2\lambda}\right)\|u^\delta\|^2_{\partial\Omega,t}<C&
\end{aligned}
$$

for a constant $C>0$ independent of δ.

Step 2. Limit of the linear terms.

Now, with u^δ bounded in $H^1(\Omega)$ we deduce the existence of a weakly converging subsequence. The equation (2) is now tested with functions $(\psi,\psi_1)\in C^\infty(\Omega)\times C^\infty(\Omega,C^\infty_\#(Y))$.

First we consider the limit for $\delta\to 0$ of the first term,

$$(2|\Gamma|+\mathcal{O}(\delta))\int_\Omega \partial_t u^\delta\psi\mathrm{d}x\to 2|\Gamma|\int_\Omega\partial_t u\psi\mathrm{d}x.$$

It also easily follow that

$$(2|\Gamma| + \mathcal{O}(\delta)) \int_\Omega u^\delta \psi \mathrm{d}x \overset{\delta\to 0}{\longrightarrow} 2|\Gamma| \int_\Omega u\psi \mathrm{d}x.$$

Limit of the diffusion term.
To perform the limit formation in the diffusion term we use the same substitutions, which we used in Step 1. We consider the diffusion term of equation (2) and use the gradient formula on manifolds.

$$\frac{1}{\delta} D \int_\Omega \int_{Y^\delta} [\nabla_x u^\delta + \nabla_y u_1^\delta][\nabla_x \psi + \nabla_y \psi_1] \mathrm{d}y \mathrm{d}x$$
$$= \frac{1}{\delta} D \int_\Omega \int_{V\times(-\delta,\delta)} \left[\nabla_x u^\delta + \sum_{k=1}^n \partial_{x_k} u^\delta \sum_{i=1}^n g^{ii} \frac{\partial(\mu_k^\delta \circ \alpha^{-1})}{\partial \xi_i} \frac{\mathrm{d}}{\mathrm{d}\xi^i} \right]$$
$$\left[\nabla_x \psi + \sum_{j=1}^n g^{jj} \frac{\partial(\psi_1 \circ \alpha^{-1})}{\partial \xi_j} \frac{\mathrm{d}}{\mathrm{d}\xi^j} \right] \sqrt{\det g} \mathrm{d}\xi \mathrm{d}x.$$

We substitute $(\xi_1, \ldots, \xi_{n-1}, \frac{\xi_n}{\delta}) = z = (z_1, \ldots, z_{n-1}, z_n)$, with
$\mathrm{d}\xi = \mathrm{d}\xi_1 \ldots \mathrm{d}\xi_n = \mathrm{d}z_1 \ldots \mathrm{d}z_{n-1} \delta \mathrm{d}z_n$. We define functions $\bar{\mu}^\delta$ and $\bar{\psi}_1$ as

$$(\bar{\mu}^\delta \circ \alpha^{-1})(z) := (\mu^\delta \circ \alpha^{-1})(z_1, z_2, \delta z_3), \; (\bar{\psi}_1 \circ \alpha^{-1})(z) := (\psi_1 \circ \alpha^{-1})(z_1, z_2, \delta z_3),$$

respectively, and continue with

$$\delta \frac{1}{\delta} D \int_\Omega \int_{V\times(-1,1)} \left[\nabla_x u^\delta + \sum_{k=1}^n \partial_{x_k} u^\delta \sum_{i=1}^n g^{ii} \frac{\partial(\bar{\mu}_k^\delta \circ \alpha^{-1})}{(1+\delta_{ni}(\delta-1)) \cdot \partial z_i} \frac{\mathrm{d}}{\mathrm{d}z^i} \right]$$
$$\left[\nabla_x \psi + \sum_{j=1}^n g^{jj} \frac{\partial(\bar{\psi}_1 \circ \alpha^{-1})}{(1+\delta_{nj}(\delta-1)) \cdot \partial z_j} \frac{\mathrm{d}}{\mathrm{d}z^j} \right] \sqrt{\det g} \mathrm{d}z \mathrm{d}x$$

with $\delta_{nj} = 0$, if $j = 1, \ldots, n-1$ and $\delta_{nj} = 1$, if $j = n$. From Step 1 we know that

$$\frac{1}{(2|\Gamma| + \mathcal{O}(\delta))} \int_{V\times(-1,1)} \left| \sum_{i=1}^n g^{ii} \frac{\partial(\bar{\mu}_k^\delta \circ \alpha^{-1})}{(1+\delta_{ni}(\delta-1)) \cdot \partial z_i} \frac{\mathrm{d}}{\mathrm{d}z^i} \right|^2 \mathrm{d}\xi \mathrm{d}d = \frac{1}{|Y^\delta|} \|\nabla_y \mu_k^\delta\|_{Y^\delta}^2 \le 1.$$

Taking a look at the nth summand we deduce

$$\left| \frac{1}{\delta} \frac{\partial(\bar{\mu}_k^\delta \circ \alpha^{-1})}{\partial z_n} \right| \le C \qquad \text{yields} \qquad \left| \frac{\partial(\bar{\mu}_k^\delta \circ \alpha^{-1})}{\partial z_n} \right| \le C\delta \overset{\delta\to 0}{\longrightarrow} 0.$$

This implies that $\frac{\partial(\bar{\mu}_k^\delta \circ \alpha^{-1})}{\partial z_n}$ converges strongly to zero and with $\mu_k^\delta \circ \alpha^{-1}$ bounded in $H^1_\#(V \times (-1,1))$ independently of δ there exists a weakly converging subsequence $\mu_k^\delta \circ \alpha^{-1} \overset{\delta\to 0}{\rightharpoonup} \mu_k \circ \alpha^{-1}$ in $H^1_\#(V \times (-1,1))$ such that $\bar{\mu}_k \circ \alpha^{-1}$ is independent of z_n. To deduce the limit of $\nabla_x u^\delta$ for δ tending to zero, we set $\psi = 0$ and arrive at

$$D \int_\Omega \int_{V\times(-1,1)} \left[\nabla_x u^\delta + \sum_{k=1}^n \partial_{x_k} u^\delta \sum_{i=1}^n g^{ii} \frac{\partial(\bar{\mu}_k^\delta \circ \alpha^{-1})}{(1+\delta_{ni}(\delta-1))\partial z_i} \frac{\mathrm{d}}{\mathrm{d}z^i} \right]$$
$$\left[\sum_{j=1}^n g^{jj} \frac{\partial(\bar{\psi}_1 \circ \alpha^{-1})}{(1+\delta_{nj}(\delta-1))\partial z_j} \frac{\mathrm{d}}{\mathrm{d}z^j} \right] \sqrt{\det g} \mathrm{d}z \mathrm{d}x.$$

Now $\nabla_x u^\delta$ is written as $\sum_i \langle \frac{\mathrm{d}}{\mathrm{d}z^i}, \nabla_x u^\delta \rangle \frac{\mathrm{d}}{\mathrm{d}z^i}$ and we use the definition of the scalar product on Γ, where here $\langle a, b\rangle = \sum_i g_{ii} a_i b_i$ for $a, b \in T_y Y^\delta$,

$$D \int_\Omega \int_{V\times(-1,1)} \sum_{i=1}^{n-1} g_{ii} \left[\left\langle \frac{\mathrm{d}}{\mathrm{d}z^i}, \nabla_x u^\delta \right\rangle + \sum_{k=1}^{n} \partial_{x_k} u^\delta g^{ii} \frac{\partial(\bar{\mu}_k^\delta \circ \alpha^{-1})}{\partial z_i} \right] \left[g^{ii} \frac{\partial(\bar{\psi}_1 \circ \alpha^{-1})}{\partial z_i} \right]$$
$$+ \left[\frac{1}{\delta} \left\langle \frac{\mathrm{d}}{\mathrm{d}z^n}, \nabla_x u^\delta \right\rangle + \frac{1}{\delta} \sum_{k=1}^{n} \partial_{x_k} u^\delta g^{nn} \frac{\partial(\tilde{\mu}_k^\delta \circ \alpha^{-1})}{\delta \partial z_n} \right] g^{nn} \frac{\partial(\tilde{\psi}_1 \circ \alpha^{-1})}{\partial z_n} \sqrt{\det g}\mathrm{d}z\mathrm{d}x$$

for any $\psi_1 \in C^\infty(\Omega, C_\#^\infty(Y))$. Because $\|\nabla_x u^\delta + \nabla_y u_1^\delta\|^2_{\Omega\times V\times(-1,1)}$ is bounded (see Step 1) and $\frac{\partial(\tilde{\mu}_k^\delta \circ \alpha^{-1})}{\partial z_n} \overset{\delta\to 0}{\longrightarrow} 0$ for $k = 1, \dots, n$, we deduce by considering the nth summand that

$$\underbrace{\left\langle \frac{\mathrm{d}}{\mathrm{d}z^n}, \nabla_x u^\delta \right\rangle}_{\to 0!} + \sum_{k=1}^{n} \underbrace{\partial_{x_k} u^\delta g^{nn}}_{\text{bounded}} \underbrace{\frac{\partial(\tilde{\mu}_k^\delta \circ \alpha^{-1})}{\delta \partial z_n}}_{\to 0} \le C\delta \to 0$$

and conclude that

$$\nabla_x u^\delta = \sum_{i=1}^{n} \left\langle \frac{\mathrm{d}}{\mathrm{d}z^i}, \nabla_x u^\delta \right\rangle \overset{\delta\to 0}{\longrightarrow} \sum_{i=1}^{n-1} \left\langle \frac{\mathrm{d}}{\mathrm{d}z^i}, \nabla_x u \right\rangle = P_\Gamma \nabla_x u,$$

where P_Γ is the projection onto the tangent space $T_y\Gamma$.

Since we know that $g^{nn} = g_{nn} = 1$, we use $\sqrt{\det g} = \sqrt{\det(g_{ij})_{i,j=1,\dots,n-1}}$. Because $\bar{\mu}_k$ and μ_k just differ in the last component, but also are independent of this component, we rewrite the integral using μ_k, $k = 1, \dots, n$ and $\int_{-1}^{1} \mathrm{d}z_n = 2$.

$$2D \int_\Omega \int_V \left[P_\Gamma \nabla_x u + \sum_{k=1}^{n} \partial_{x_k} u \sum_{i=1}^{n-1} g^{ii} \frac{\partial(\mu_k \circ \alpha^{-1})}{\partial z_i} \frac{\mathrm{d}}{\mathrm{d}z^i} \right] \sum_{j=1}^{n-1} g^{jj} \frac{\partial(\psi_1 \circ \alpha^{-1})}{\partial z_j} \frac{\mathrm{d}}{\mathrm{d}z^j} \sqrt{\det g}\mathrm{d}z_1 \dots \mathrm{d}z_{n-1}\mathrm{d}x$$
$$= 2D \int_\Omega \int_\Gamma \left[P_\Gamma \nabla_x u + \sum_{k=1}^{n} \partial_{x_k} u \nabla_\Gamma \mu_k \right] \nabla_\Gamma \psi_1 \mathrm{d}\sigma_y \mathrm{d}x,$$

for all $\psi_1 \in C^\infty(\Omega, C_\#^\infty(\Gamma))$, where ∇_Γ is the gradient respective to the tangent space. Hence, the limit diffusion term is given by

$$2D \int_\Omega \int_\Gamma \sum_{k=1}^{n} \partial_{x_k} u \left[P_\Gamma e_k + \nabla_\Gamma \mu_k \right] \left[\nabla_x \psi + \nabla_\Gamma \psi_1 \right] \mathrm{d}\sigma_y \mathrm{d}x.$$

Limit of the right-hand side.
For δ tending to zero, the right-hand side has the following behavior. With f continuous, it easily holds that

$$\int_\Omega \int_{V\times(-1,1)} f(x, z_1, \dots, z_{n-1}, \delta z_n) \psi(x, z_1, \dots, z_{n-1}, \delta z_n) \sqrt{\det g}\mathrm{d}z\mathrm{d}x$$
$$\overset{\delta\to 0}{\longrightarrow} 2 \int_\Omega \int_V f(x, z_1, \dots, z_{n-1}, 0) \psi(x, z_1, \dots, z_{n-1}, 0) \sqrt{\det g}\mathrm{d}z\mathrm{d}x$$
$$= 2 \int_\Omega \int_\Gamma f(x, y) \psi(x, y) \mathrm{d}\sigma_y \mathrm{d}x.$$

Analogously, we find because of h continuous

$$\int_{\partial\Omega} \int_{\partial_o V\times(-1,1)} h(x, z_1, \dots, z_{n-1}, \delta z_n) \psi(x, z_1, \dots, z_{n-1}, \delta z_n) \sqrt{\det g}\mathrm{d}\sigma_z \mathrm{d}\sigma_x$$
$$\overset{\delta\to 0}{\longrightarrow} 2 \int_{\partial\Omega} \int_{\partial_o\Gamma} h(x, y) \psi(x, y) \mathrm{d}\sigma_y \mathrm{d}\sigma_x.$$

Hence, for $\delta \to 0$ we arrive at the equation

$$2|\Gamma| \int_\Omega \partial_t u\psi \mathrm{d}x + 2D \int_\Omega \int_\Gamma \sum_{k=1}^n \partial_{x_k} u \left[P_\Gamma e_k + \nabla_\Gamma \mu_k\right] \left[\nabla_x \psi + \nabla_\Gamma \psi_1\right] \mathrm{d}\sigma_y \mathrm{d}x$$
$$+ 2|\Gamma| \int_\Omega u\psi \mathrm{d}x + 2a|\partial_o \Gamma| \int_{\partial\Omega} u\psi \mathrm{d}\sigma_x$$
$$= 2 \int_\Omega \int_\Gamma f(x,y)\psi(x,y) \mathrm{d}\sigma_y \mathrm{d}x + 2a \int_{\partial\Omega} \int_{\partial_o\Gamma} h\psi \mathrm{d}\sigma_y \mathrm{d}\sigma_x$$

and may divide by 2.
Step 3. The limit cell problem.
It is left to find the cell problem and therefore we set again $\psi = 0$ and obtain for $k = 1, \ldots, n$ that $\int_\Gamma (P_\Gamma e_k + \nabla_\Gamma \mu_k) \nabla_\Gamma \psi_1 \mathrm{d}\sigma_y = 0$. Then, the strong formulation of the cell problem is given by (5).
The limit diffusion tensor.
By setting ψ_1 to zero we can find the diffusion tensor P by considering the diffusion term

$$D \int_\Omega \int_\Gamma \sum_j \partial_{x_j} u P_\Gamma (e_j + \nabla_\Gamma \mu_j) \nabla_x \psi \mathrm{d}\sigma_y \mathrm{d}x = \int_\Omega P \nabla_x u \nabla_x \psi \mathrm{d}x$$

with the diffusion tensor $P = (P_{ij})_{ij}$ given by $P_{ij} = D \int_\Gamma \left(P_\Gamma(e_j + \nabla_\Gamma \mu_j)\right)_i \mathrm{d}\sigma_y$. This leads to the desired result (4).

□

Remark 2. If there are more linear or nonlinear terms, which are independent of y, i.e multiplied by a factor $|Y^\delta|$, theorem 1 also holds and the factor $|Y^\delta|$ becomes $2|\Gamma|$ for $\delta \to 0$.

3. Limit behavior on Neumann and Robin boundaries

In practical applications, an important question, which seems to have attracted little attention in the literature, is what happens with Neumann and Robin boundary conditions at the exterior boundary of a domain $\Omega \subset \mathbf{R}^n$ when performing homogenization. If we consider the outer boundary as a periodic domain – the shape of the unit cell is the shape of the outer boundaries of the unit cell Y – and if the functions defined on that boundary are elements of $L^2(\partial\Omega)$, then we could use two-scale convergence in dimension $n-1$. Therefore, the outer boundary $\partial_o\Omega_\varepsilon$ must be a union of squares, such that $\partial_o\Omega_\varepsilon$ is ε-periodic. For example, the shape of a circle or ellipsoid is not possible.

We define $\partial_o\Omega_\varepsilon$ as the outer boundary of Ω_ε and $\partial_o Y$ as one side of the outer boundary of the unit cell Y, cf. fig. 3. Then we have a periodic structure on $\partial_o\Omega_\varepsilon$ with unit cell $\partial_o Y$. We prove the following theorem describing the two-scale convergence on $\partial_o\Omega_\varepsilon$.

Theorem 3. *Let $\Omega_\varepsilon \subset \mathbf{R}^n$ be a domain as described above and let $g \in C(\partial\Omega, C_\#(\partial_o Y))$ with $g_\varepsilon(x) = g(x, \frac{x}{\varepsilon})$ be $\partial_o Y$-periodic in its second argument. Then*

$$\int_{\partial_o\Omega_\varepsilon} g_\varepsilon(x)\varphi\left(x, \frac{x}{\varepsilon}\right) d\sigma_x \overset{\text{2-scale}}{\longrightarrow} \int_{\partial\Omega} \int_{\partial_o Y} g(x,y)\varphi(x,y)\, d\sigma_y\, d\sigma_x$$

for all $\varphi \in C^\infty(\Omega, C_\#^\infty(Y))$.

Proof. In the given setting, the domain $\partial_o\Omega_\varepsilon$ is ε-periodic with period $\partial_o Y$. Because the test functions $\varphi \in C^\infty(\Omega, C_\#^\infty(Y))$ are smooth, they also work as test functions on $\partial_o\Omega_\varepsilon$. Then, with classical homogenization, see [2], the claim follows. □

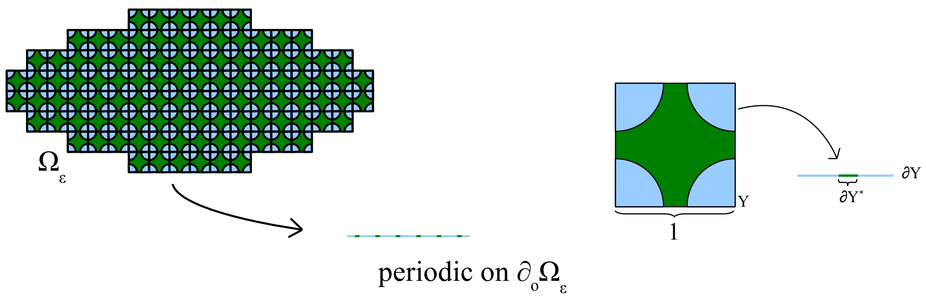


Figure 1: Domain with periodic microstructure (left) and reference cell (right), depicting the periodicity of the exterior boundary.

Remark 4. Theorem 3 can be used for homogenization of partial differential equations with Neumann boundary condition with right-hand side g_ε at the outer boundary.

The situation is more complicated for Robin boundary conditions, because we need to identify the function in the boundary term at the outer boundary with the solution of the partial differential equation in the domain Ω_ε. The following theorem secures two-scale convergence of the function u_ε on $\partial_o\Omega_\varepsilon$, if u_ε satisfies certain conditions.

Theorem 5. *a) Let $u_\varepsilon \in H^1(\Omega)$ be a sequence of functions such that $\|u_\varepsilon\|_\Omega + \|\nabla u_\varepsilon\|_\Omega < C$ for a constant $C > 0$ independent of ε. Let u_ε weakly converge to a limit function $u_0 \in H^1(\Omega)$ and let $\partial_o Y^* \subset \partial_o Y$. Then, up to a subsequence,*

$$\chi_\varepsilon \gamma(u_\varepsilon) \rightharpoonup |\partial_o Y^*| \gamma(u_0) \qquad \text{weakly in } L^2(\partial\Omega),$$

where χ_ε is the characteristic function on $\bigcup_{k\in\mathbf{Z}^n} \varepsilon(k + \partial_o Y^*) \cap \partial\Omega$ and $\gamma : H^1(\Omega) \to H^{\frac{1}{2}}(\partial\Omega)$ is the trace operator.

b) Let $u_\varepsilon \in L^2([0,T], H^1(\Omega)) \cap H^1([0,T], H^1(\Omega)')$, then there exists a subsequence of u_ε, also denoted by u_ε, such that

$$\gamma(u_\varepsilon) \to \gamma(u_0) \quad \text{strongly in } L^2([0,T], L^2(\partial\Omega))$$

and

$$\chi_\varepsilon f(\gamma(u_\varepsilon)) \rightharpoonup |\partial_o Y^*| f(u_0) \quad \text{weakly in } L^2([0,T], L^2(\partial\Omega))$$

for any bounded and continuous function $f : \mathbf{R} \to \mathbf{R}$.

Proof. a) We know that the function $u_\varepsilon \in H^1(\Omega)$ has a weak limit u_0 in $H^1(\Omega)$ such that up to a subsequence,

$$(u_\varepsilon - u_0, \varphi)_{H^1(\Omega)\times H^1(\Omega)'} \xrightarrow{\varepsilon\to 0} 0$$

for all $\varphi \in H^1(\Omega)'$ using classical weak convergence. With the trace operator $\gamma : H^1(\Omega) \to H^{\frac{1}{2}}(\partial\Omega)$, which is linear and bounded, we obtain

$$\langle \gamma(u_\varepsilon) - \gamma(u_0), \gamma(\varphi) \rangle_{H^{\frac{1}{2}}(\partial\Omega)\times H^{\frac{1}{2}}(\partial\Omega)'} \xrightarrow{\varepsilon\to 0} 0$$

for all $\varphi \in C^\infty(\Omega)$. Moreover, $H^{\frac{1}{2}}(\partial\Omega)$ is compactly embedded in $L^2(\partial\Omega)$ and hence, there exists a strongly converging subsequence $\gamma(u_\varepsilon) \to \gamma(u_0)$ in $L^2(\partial\Omega)$. Using the characteristic function χ_ε on

$\bigcup_{k\in\mathbf{Z}^n} \varepsilon(k+\partial_o Y^*) \cap \partial\Omega$ we ensure that the domain, where the convergence holds, does not change with ε. Now we conclude with standard results, e.g. lemma 6 in [19], that

$$\langle \chi_\varepsilon \gamma(u_\varepsilon), \varphi\rangle_{L^2(\partial\Omega)} \overset{\varepsilon\to 0}{\to} |\partial_o Y^*| \langle \gamma(u_0), \varphi\rangle_{L^2(\partial\Omega)}$$

for all $\varphi \in C^\infty(\Omega)$.

b) With the condition $u_\varepsilon \in L^2([0,T], H^1(\Omega)) \cap H^1([0,T], H^1(\Omega)')$ we find with the trace operator that $\gamma(u_\varepsilon) \in L^2([0,T], H^{\frac{1}{2}}(\partial\Omega)) \cap H^1([0,T], H^{\frac{3}{2}}(\partial\Omega)')$. The embedding theorems in Sobolev spaces and Lemma 5.10 in [13], based on the lemma of Lions–Aubin, yield a strongly converging subsequence of $\gamma(u_\varepsilon)$ in $L^2([0,T], L^2(\partial\Omega))$. Using the Nemytskii operator, see [29], we also find that $f(\gamma(u_\varepsilon))$ strongly converges to $f(\gamma(u_0))$ in $L^2([0,T], L^2(\partial\Omega))$. Because χ_ε is only a weak converging sequence, we deduce that

$$\langle \chi_\varepsilon f(\gamma(u_\varepsilon)), \varphi\rangle_{L^2(\partial\Omega)} \to |\partial_o Y^*| \langle f(\gamma(u_0)), \varphi\rangle_{L^2(\partial\Omega)}$$

for all $\varphi \in C^\infty(\Omega)$.

□

4. Signaling in Lymphocytes: Stim1 and Orai1

Our immune system is a very complex machinery which is orchestrated by different kinds of cells and organs. Still many functions and procedures are not completely or just partially understood. A leading part of the immune system are the T cells (or thymus lymphocytes). Their purpose is to pour out messengers if they detect alien substances in the body (helper T cell) or to kill the intruder directly (cytotoxic T cell). To accomplish their tasks, complex signaling cascades take place inside these cells. One important step is the store-operated calcium entry through CRAC (Calcium Release-Activated Calcium) channels. If this step is defective, immunodeficiency syndromes may develop in human patients.

To understand the function of the CRAC channels we briefly need to explain the situation in T cells. In a non-activated T cell the calcium concentration in the cytosol is $[Ca^{2+}]_i \approx 50 - 100nM$, the calcium concentration in the intercellular space is $[Ca^{2+}]_e \approx 1mM$, and in the lumen of the endoplasmic reticulum it is $[Ca^{2+}]_{\mathrm{ER}} \approx 500\mu M$, see [15]. This means that the concentration in the cytosol is at least 5000 times lower than in the neighboring domains. To sustain such a strong gradient there are several pumps working to pump permanently calcium out of the cell (PMCA, NCX) or into the lumen of the endoplasmic reticulum (SERCA). The pump PMCA pumps calcium with the aid of ATP, the pump NCX exchanges calcium with sodium.

On the surface of the endoplasmic reticulum (ER) the molecule Stim1 (Stromal interaction molecule 1) exists. Usually it binds to two calcium molecules Ca^{2+} which are in the lumen of the ER. Furthermore, on the plasma membrane of the cell there are molecules Orai1 (calcium release-activated calcium channel protein 1) to which Stim1 can also bind to.

To get the procedure of the activation of the T cell started, the lumen of the ER must be induced to release its calcium. This can happen through molecules named IP3 directly, or a molecule TG closes the SERCA pumps and calcium is not pumped back into the lumen of the ER. But in general IP3 is the trigger. After depletion of the ER there is no calcium left for the Stim1 molecules to bind to. But on the surface of the ER, that is near to the plasma membrane, unbound Stim1 bind to Orai1. There two Stim1 molecules can bind to one Orai1 molecule. Stim1 molecules diffuse on the surface of the ER and, in this way, reach the plasma membrane. Once four Stim1 are connected to two Orai1, they build a CRAC channel, which lets calcium diffuse from the intercellular space into the cytosol. This state holds on as long as IP3 is present in the T cell. When IP3 is depleted, calcium moves back into in the lumen of the ER and can bind to Stim1 again. A Stim1 molecule, that binds to Orai1 and Ca^{2+}, quickly breaks away from Orai1 and the CRAC channel closes. The calcium pumps restore the original state soon.

We take a closer look to the flux I_{CRAC} of calcium molecules at the plasma membrane due to the opening CRAC channels. It is important to know that the flux through the channels at the plasma membrane always depends on a potential gradient. In resting state the membrane potential is about $\sim -70mV$, the inside of

the cell is negatively charged. Ionic channels are mainly responsible for the potential fluxes, amongst others for example the CRAC channel with flux I_{CRAC}. But also the CAN channel with flux/current I_{CAN}, the K channel with flux/current I_{K} and the K(Ca) channel with flux/current $I_{\mathrm{K(Ca)}}$ are important. The plasma membrane acts as a capacitor with capacity C_{m}. The relation between the current I and the potential V at a capacitor is $\frac{\mathrm{d}V}{\mathrm{d}t} = -\frac{I}{C_{\mathrm{m}}}$. For more details and the equations describing the dependences of the channels see [12].
The channel dynamic at the plasma membrane builds a system of ordinary differential equations and, hence, performing periodic homogenization has no bearing on it. Therefore, we omit the dynamics of the channels to clear up and focus on the more relevant compartments of the model seen from the angle of homogenization. We note that the influx I_{CRAC} depends on the amount of Stim1 molecules bound to the plasma membrane in a nonlinear way, but is Lipschitz-continuous and bounded almost everywhere if the amount of the Stim1 molecules is bounded.

This information and more details on the biological background can be found in [15, 14, 16, 21, 30].

4.1. Micromodel

An effective model for the process described above is due to Patrick Fletcher and Yue-Xian Li [12]. It was derived phenomenologically without taking into account the cell microstructure. It is the aim here to derive a model by homogenization taking into account the microstructure of the cell explicitly.

Let $\Omega \subset \mathbf{R}^n$ be a domain with Lipschitz-boundary Γ^1. We assume Ω to be representable by a finite union of axis-parallel cuboids with corner coordinates in $\mathbb{Q}^n$. To build the domains depending on the small parameter $\varepsilon > 0$, the following characteristical parts Y^1, Y^2, Y^{ER}, $\Gamma^{\mathrm{ER}} \subset Y = [0,1]^n$ are defined,

Cell	Ω,
Plasma membrane	Γ^1,
Part of cytosol	Y^1,
Part of lumen of the ER	Y^2,
Part of blown up surface of the ER, width $\delta > 0$	Y^{ER},
Part of surface of the ER	Γ^{ER}.

Then we define $\Omega_\varepsilon^1 = \bigcup_{k\in\mathbf{Z}^n} \varepsilon(k+Y^1)\cap\Omega$, $\Omega_\varepsilon^2 = \bigcup_{k\in\mathbf{Z}^n} \varepsilon(k+Y^2)\cap\Omega$ and $\Omega_\varepsilon^{\mathrm{ER}} = \bigcup_{k\in\mathbf{Z}^n} \varepsilon(k+Y^{\mathrm{ER}})\cap\Omega$. Further, Γ^{ER} is a smooth, compact manifold, such that $\Gamma_\varepsilon^{\mathrm{ER}} = \bigcup_{k\in\mathbf{Z}^n} \varepsilon(k+\Gamma^{\mathrm{ER}})\cap\Omega$ is smooth, connected and periodic. The scalar products are given by $(u,v)_{\Omega_\varepsilon^1} = \int_{\Omega_\varepsilon^1} uv\mathrm{d}x$, respectively on Ω_ε^1 and $\Omega_\varepsilon^{\mathrm{ER}}$. On the Riemannian manifolds $\Gamma_\varepsilon^{\mathrm{ER}}$ and Γ^1 the scalar products are given by $\langle u,v\rangle_{\Gamma_\varepsilon^{\mathrm{ER}}} = \int_{\Gamma_\varepsilon^{\mathrm{ER}}} g_\varepsilon uv\mathrm{d}\sigma_x$, respectively on Γ^1, where g_ε is the Riemannian metric tensor. The concentrations of the molecules are labeled as the following:

Calcium in the cytosol	C_ε,
Calcium in the lumen of the ER	$C_{e,\varepsilon}$,
Two unbound Stim1 on the surface of the ER	S_ε,
Two Stim1 bound to 4 calcium on the surface of the ER	$S_{C,\varepsilon}$,
Two Stim1 bound to Orai1 on the plasma membrane	$S_{O,\varepsilon}$,
Two Stim1 bound to Orai1 and 4 calcium on the plasma membrane	$S_{CO,\varepsilon}$.

For convenience we introduce several abbreviations

$$f_{\mathrm{SERCA}}(C_\varepsilon) = v_{\mathrm{SERCA}}\frac{C_\varepsilon^2}{C_\varepsilon^2 + K_{\mathrm{SERCA}}^2}, \qquad f_{\mathrm{P}}(C_\varepsilon) = v_{\mathrm{P}}\frac{C_\varepsilon^2}{C_\varepsilon^2 + K_{\mathrm{P}}^2},$$
$$f_{\mathrm{NCX}}(C_\varepsilon) = v_{\mathrm{NCX}}\frac{C_\varepsilon^4}{C_\varepsilon^4 + K_{\mathrm{NCX}}^4}, \qquad f_e(C_{e,\varepsilon}) = v_e\frac{C_{e,\varepsilon}^4}{C_{e,\varepsilon}^4 + K_e^4}.$$

for $K_{\mathrm{SERCA}}, K_{\mathrm{P}}, K_{\mathrm{NCX}}, K_e, v_{\mathrm{SERCA}}, v_{\mathrm{P}}, v_{\mathrm{NCX}}, v_e > 0$. All theses functions are nonnegative, smooth and bounded by $v_{\mathrm{SERCA}}, v_{\mathrm{P}}, v_{\mathrm{NCX}}, v_e$ respectively. We define the following function spaces

$$\begin{aligned}
\mathcal{V}(\Omega_\varepsilon^1) &:= L^2([0,T], H^1(\Omega_\varepsilon^1)) \cap H^1([0,T], H^1(\Omega_\varepsilon^1)'),\\
\mathcal{V}(\Omega_\varepsilon^2) &:= L^2([0,T], H^1(\Omega_\varepsilon^2)) \cap H^1([0,T], H^1(\Omega_\varepsilon^2)'),\\
\mathcal{V}(\Omega_\varepsilon^{\mathrm{ER}}) &:= L^2([0,T], H^1(\Omega_\varepsilon^{\mathrm{ER}})) \cap H^1([0,T], H^1(\Omega_\varepsilon^{\mathrm{ER}})'),\\
\mathcal{V}(\Gamma^1 \cap \partial\Omega_\varepsilon^{\mathrm{ER}}) &:= L^2([0,T], L^2(\Gamma^1 \cap \partial\Omega_\varepsilon^{\mathrm{ER}})) \cap H^1([0,T], L^2((\Gamma^1 \cap \partial\Omega_\varepsilon^{\mathrm{ER}})).
\end{aligned}$$

For the test functions we define the function spaces

$$\begin{aligned}
V(\Omega_\varepsilon^1) &:= H^1(\Omega_\varepsilon^1), \qquad V(\Omega_\varepsilon^2) := H^1(\Omega_\varepsilon^2),\\
V(\Omega_\varepsilon^{\mathrm{ER}}) &:= H^1(\Omega_\varepsilon^{\mathrm{ER}}), \qquad V(\Gamma^1 \cap \partial\Omega_\varepsilon^{\mathrm{ER}}) := L^2(\Gamma^1 \cap \partial\Omega_\varepsilon^{\mathrm{ER}}).
\end{aligned}$$

The weak formulation is given by finding $(C_\varepsilon, C_{e,\varepsilon}, S_\varepsilon, S_{C,\varepsilon}, S_{O,\varepsilon}, S_{CO,\varepsilon}) \in \mathcal{V}(\Omega_\varepsilon^1) \times \mathcal{V}(\Omega_\varepsilon^2) \times \mathcal{V}(\Omega_\varepsilon^{\mathrm{ER}}) \times \mathcal{V}(\Omega_\varepsilon^{\mathrm{ER}}) \times \mathcal{V}(\Gamma^1 \cap \partial\Omega_\varepsilon^{\mathrm{ER}}) \times \mathcal{V}(\Gamma^1 \cap \partial\Omega_\varepsilon^{\mathrm{ER}})$ such that

$$\begin{aligned}
(\partial_t C_\varepsilon, \psi_\varepsilon^1)_{\Omega_\varepsilon^1} + D_C(\nabla C_\varepsilon, \nabla\psi_\varepsilon^1)_{\Omega_\varepsilon^1} + \varepsilon\langle (L_0 + L_{\mathrm{IP3}})(C_\varepsilon - C_{e,\varepsilon}) + f_{\mathrm{SERCA}}, \psi_\varepsilon^1\rangle_{\Gamma_\varepsilon^{\mathrm{ER}}}&\\
+\langle \alpha I_{\mathrm{CRAC}}(S_{O,\varepsilon}) + f_{\mathrm{P}} + f_{\mathrm{NCX}}, \psi_\varepsilon^1\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^1} &= 0\\
(\partial_t C_{e,\varepsilon}, \psi_\varepsilon^2)_{\Omega_\varepsilon^2} + D_{\mathrm{ER}}(\nabla C_{e,\varepsilon}, \nabla\psi_\varepsilon^2)_{\Omega_\varepsilon^2}&\\
+\varepsilon\langle (L_0 + L_{\mathrm{IP3}})(C_{e,\varepsilon} - C_\varepsilon) - f_{\mathrm{SERCA}}, \psi_\varepsilon^2\rangle_{\Gamma_\varepsilon^{\mathrm{ER}}} &= 0\\
(\partial_t S_\varepsilon, \psi_\varepsilon^3)_{\Omega_\varepsilon^{\mathrm{ER}}} + D_S(\nabla S_\varepsilon, \nabla\psi_\varepsilon^3)_{\Omega_\varepsilon^{\mathrm{ER}}} + (k_C^+ f_e(C_{e,\varepsilon})S_\varepsilon - k_C^- S_{C,\varepsilon}, \psi_\varepsilon^3)_{\Omega_\varepsilon^{\mathrm{ER}}}&\\
+\langle k_O^+ S_\varepsilon - k_O^- S_{O,\varepsilon}, \psi_\varepsilon^3\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}} &= 0\\
(\partial_t S_{C,\varepsilon}, \psi_\varepsilon^3)_{\Omega_\varepsilon^{\mathrm{ER}}} + D_{SC}(\nabla S_{C,\varepsilon}, \nabla\psi_\varepsilon^3)_{\Omega_\varepsilon^{\mathrm{ER}}} + (k_C^- S_{C,\varepsilon} - k_C^+ f_e(C_{e,\varepsilon})S_\varepsilon, \psi_\varepsilon^3)_{\Omega_\varepsilon^{\mathrm{ER}}}&\\
+\langle k_{CO}^+ S_{C,\varepsilon} - k_{CO}^- S_{CO,\varepsilon}, \psi_\varepsilon^3\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}} &= 0\\
\langle \partial_t S_{O,\varepsilon}, \psi_\varepsilon^4\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}} + \langle k_O^- S_{O,\varepsilon} - k_O^+ S_\varepsilon, \psi_\varepsilon^4\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}}&\\
+\langle -k_C^- S_{CO,\varepsilon} + k_C^+ f_e(C_{e,\varepsilon})S_{O,\varepsilon}, \psi_\varepsilon^4\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}} &= 0\\
\langle \partial_t S_{CO,\varepsilon}, \psi_\varepsilon^4\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}} + \langle k_{CO}^- S_{CO,\varepsilon} - k_{CO}^+ S_{C,\varepsilon}, \psi_\varepsilon^4\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}}&\\
+\langle -k_C^+ f_e(C_{e,\varepsilon})S_{O,\varepsilon} + k_C^- S_{CO,\varepsilon}, \psi_\varepsilon^4\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}} &= 0
\end{aligned} \tag{6}$$

for all $\psi_\varepsilon^1 \in V(\Omega_\varepsilon^1)$, $\psi_\varepsilon^2 \in V(\Omega_\varepsilon^2)$, $\psi_\varepsilon^3 \in V(\Omega_\varepsilon^{\mathrm{ER}})$ and $\psi_\varepsilon^4 \in V(\Gamma^1 \cap \partial\Omega_\varepsilon^{\mathrm{ER}})$.

4.2. Limit macromodel

Here we state the macroscopic limit equations of problem or (6). The following system results after homogenization and after the limit passage of width δ of the blown up domain Y^{ER} to zero. The convergence for $\varepsilon \to 0$ is proven in section 7, the convergence for $\delta \to 0$ in section 8. Let $(C, C_e, S, S_C, S_O, S_{CO}) \in \mathcal{V}(\Omega)^4 \times \mathcal{V}(\Gamma^1)^2$ be such that

$$
\begin{aligned}
|Y^1|(\partial_t C,\varphi)_\Omega+&(P^C\nabla C,\nabla\varphi)_\Omega\\
&+|\Gamma^{\mathrm{ER}}|((L_0+L_{\mathrm{IP3}})(C-C_e)+f_{\mathrm{SERCA}}(C),\varphi)_\Omega\\
&+|\partial_o Y^1|\langle\alpha I_{\mathrm{CRAC}}(S_O),\varphi\rangle_{\Gamma^1}+|\partial_o Y^1|\langle f_P(C)+f_{\mathrm{NCX}}(C),\varphi\rangle_{\Gamma^1}=0,\\[1ex]
|Y^2|(\partial_t C_e,\varphi)_\Omega+&(P^e\nabla C_e,\nabla\varphi)_\Omega\\
&+|\Gamma^{\mathrm{ER}}|((L_0+L_{\mathrm{IP3}})(C_e-C)-f_{\mathrm{SERCA}}(C),\varphi)_\Omega=0,\\[1ex]
|\Gamma^{\mathrm{ER}}|(\partial_t S,\varphi)_\Omega+&(P^S\nabla S,\nabla\varphi)_\Omega\\
&+|\Gamma^{\mathrm{ER}}|(k_C^+f_e(C_e)S-k_C^-S_C,\varphi)_\Omega+|\partial_o\Gamma^{\mathrm{ER}}|\langle k_O^+S-k_O^-S_O,\varphi\rangle_{\Gamma^1}=0,\\[1ex]
|\Gamma^{\mathrm{ER}}|(\partial_t S_C,\varphi)_\Omega+&(P^{SC}\nabla S_C,\nabla\varphi)_\Omega\\
&+|\Gamma^{\mathrm{ER}}|(k_C^-S_C-k_C^+f_e(C_e)S,\varphi)_\Omega+|\partial_o\Gamma^{\mathrm{ER}}|\langle k_{CO}^+S_C-k_{CO}^-S_{CO},\varphi\rangle_{\Gamma^1}=0,\\[1ex]
\langle\partial_t S_O,\varphi\rangle_{\Gamma^1}+&\langle k_O^-S_O-k_O^+S-k_C^-S_{CO}+k_C^+f_e(C_e)S_O,\varphi\rangle_{\Gamma^1}=0,\\[1ex]
\langle\partial_t S_{CO},\varphi\rangle_{\Gamma^1}+&\langle k_{CO}^-S_{CO}-k_{CO}^+S_C+k_C^-S_{CO}-k_C^+f_e(C_e)S_O,\varphi\rangle_{\Gamma^1}=0,
\end{aligned}
\tag{7}
$$

for all $\varphi\in C^\infty(\Omega)$.

The cell problems for C and C_e are given by

$$
\begin{aligned}
\nabla_y\cdot(e_j+\nabla_y\mu_j^{C,e})&=0 &&\text{in } Y^{1,2},\\
(e_j+\nabla_y\mu_j^{C,e})\cdot n_{1,2}&=0 &&\text{on } \Gamma^{\mathrm{ER}},
\end{aligned}
\tag{8}
$$

and $\mu_j^{C,e}$ must be Y-periodic for $j=1,\dots,n$. The diffusion tensors are $P_{ij}^C:=\int_{Y^1}D_C(\delta_{ij}+\partial_{y_i}\mu_j^C)\mathrm{d}y$ and $P_{ij}^e:=\int_{Y^2}D_{ER}(\delta_{ij}+\partial_{y_i}\mu_j^e)\mathrm{d}y$.

Furthermore, the cell problem for S and S_C is given by

$$
\begin{aligned}
\nabla_\Gamma\cdot(P_\Gamma e_j+\nabla_\Gamma\mu_j^S)&=0 &&\text{in } \Gamma^{\mathrm{ER}},\\
(P_\Gamma e_j+\nabla_\Gamma\mu_j^S)\cdot n&=0 &&\text{on } \partial\Gamma^{\mathrm{ER}}
\end{aligned}
\tag{9}
$$

with μ_j^S being Y-periodic for $j=1,\dots,n$. We note, that $P_\Gamma e_j$ is depending on y and $\nabla_y\cdot P_\Gamma e_j$ is not equal to 0 in general. The diffusion tensors are defined as $P_{ij}^S:=\int_{\Gamma^{\mathrm{ER}}}D_S(P_\Gamma e_j+\nabla_\Gamma\mu_j^S)_i\mathrm{d}\sigma_y$ and $P_{ij}^{SC}:=\int_{\Gamma^{\mathrm{ER}}}D_{SC}(P_\Gamma e_j+\nabla_\Gamma\mu_j^S)_i\mathrm{d}\sigma_y$.

In the mathematical model by Patrick Fletcher and Yue-Xian Li in [12], the cytosol, the membrane and the lumen of the ER are merged to a homogeneous cytoplasmic domain. Here, in micromodel (6), the process is decribed in more detail, because the domains, where the molecules occur, are considered explicitly. Furthermore, by periodic homogenization the model is rigorously upscaled to an effective model (cf. (7)).

By performing homogenization we find a similar model to the one in article [12], whereby the form of the differential equation is the same but some of the coefficients differ. This means that the form of the system of partial differential equations in [12] is mathematically confirmed by our considerations and the coefficients are improved.

The remainder of this paper is devoted to proving the convergence of solutions of (6) to solutions of (7) in the limit as $\varepsilon\to0$ and $\delta\to0$.

5. A priori estimates for the Calcium–Stim1 model

In this section we show that the functions C_ε, $C_{e,\varepsilon}$, S_ε and $S_{C,\varepsilon}$ are elements of H^1 and L^∞ and that the functions $S_{O,\varepsilon}$ and $S_{CO,\varepsilon}$ are elements of L^2 and L^∞. This is necessary to apply the standard theorems of homogenization, [2], and to show strong convergence of a subsequence, see Remark 13.

Before we start with the estimations, we prove that the inverse trace inequality does not depend on ε, where the inverse trace operator maps from the outer boundary $\partial\Omega_\varepsilon \cap \partial\Omega$ of an ε-depending domain $\Omega_\varepsilon \subset \Omega \subset \mathbf{R}^n$.

Lemma 6. *Let $\Omega \subset \mathbf{R}^n$ and Ω_ε be an ε-periodic subset of Ω, where Ω is representable by a finite union of axis-parallel cuboids, each of which is assumed to have corner coordinates in $\mathbb{Q}^n$. Then it holds for any function $f_\varepsilon \in H^1(\Omega_\varepsilon)$ that*

$$\|f_\varepsilon\|^2_{L^2(\partial\Omega_\varepsilon\cap\partial\Omega)} \leq c\|f_\varepsilon\|^2_{H^1(\Omega_\varepsilon)}$$

with $c > 0$ independent of ε.

Proof. The extension operator from the article [17] gives an extension $\tilde{f}_\varepsilon \in H^1(\Omega)$ with $f_\varepsilon = \tilde{f}_\varepsilon$ in Ω_ε such that $\|\tilde{f}_\varepsilon\|_{H^1(\Omega)} \leq \tilde{c}\|f_\varepsilon\|_{H^1(\Omega_\varepsilon)}$, where $\tilde{c}$ is independent of ε. The trace operator $\gamma_\varepsilon : H^1(\Omega_\varepsilon) \to L^2(\partial\Omega_\varepsilon \cap \partial\Omega)$ maps $f_\varepsilon \mapsto \gamma_\varepsilon(f_\varepsilon)$ and $\tilde{f}_\varepsilon \mapsto \gamma_\varepsilon(\tilde{f}_\varepsilon)$ with $\gamma_\varepsilon(f_\varepsilon) = \gamma_\varepsilon(\tilde{f}_\varepsilon)$ on $\partial\Omega_\varepsilon \cap \partial\Omega$, because $f_\varepsilon = \tilde{f}_\varepsilon$ in Ω_ε. This means for the trace operator $\gamma : H^1(\Omega) \to L^2(\partial\Omega)$ that $\gamma_\varepsilon(\tilde{f}_\varepsilon) = \tilde{f}_{\varepsilon|\partial\Omega_\varepsilon\cap\partial\Omega} = \gamma(\tilde{f}_\varepsilon)$ on $\partial\Omega_\varepsilon \cap \partial\Omega$.

We deduce the following estimation

$$\|\gamma_\varepsilon(f_\varepsilon)\|^2_{L^2(\partial\Omega_\varepsilon\cap\partial\Omega)} = \|\gamma_\varepsilon(\tilde{f}_\varepsilon)\|^2_{L^2(\partial\Omega_\varepsilon\cap\partial\Omega)} \leq \|\gamma(\tilde{f}_\varepsilon)\|^2_{L^2(\partial\Omega)} \leq c_0\|\tilde{f}_\varepsilon\|^2_{H^1(\Omega)} \leq \tilde{c}c_0\|f_\varepsilon\|^2_{H^1(\Omega_\varepsilon)},$$

where c_0 is bounded, because γ is linear and continuous, and c_0 is independent of ε, since Ω is independent of ε. □

Now we start with the estimations for the system (6). We note again that the term $I_{\mathrm{CRAC}}(S_{O,\varepsilon})$ is bounded almost everywhere in $[0,T] \times \Gamma^1 \cap \partial\Omega^1_\varepsilon$ independently of ε, if $S_{O,\varepsilon}$ is bounded almost everywhere in $[0,T] \times \Gamma^1 \cap \partial\Omega^{\mathrm{ER}}_\varepsilon$ independently of ε.

The following lemma is necessary to find a lower bound for the functions. By obtaining an upper bound, too, in Lemma 9 the functions $S_\varepsilon, S_{C,\varepsilon}, S_{O,\varepsilon}$ and $S_{CO,\varepsilon}$ are L^∞-functions.

Lemma 7. (Positivity of S_ε, $S_{C,\varepsilon}$, $S_{O,\varepsilon}$ and $S_{CO,\varepsilon}$)
For almost every $x \in \Omega^{ER}_\varepsilon$ and $t \in [0,T]$ it holds that $S_\varepsilon(x,t) \geq 0$ and $S_{C,\varepsilon}(x,t) \geq 0$. For almost every $x \in \Gamma^1 \cap \partial\Omega^{ER}_\varepsilon$ and $t \in [0,T]$ it holds that $S_{O,\varepsilon}(x,t) \geq 0$ and $S_{CO,\varepsilon}(x,t) \geq 0$.

Proof. We test the weak formulations of S_ε, $S_{C,\varepsilon}$, $S_{O,\varepsilon}$, and $S_{CO,\varepsilon}$ with $k^+_O S_{\varepsilon-}$, $k^+_{CO} S_{C,\varepsilon-}$, $k^-_O S_{O,\varepsilon-}$, and $k^-_{CO} S_{CO,\varepsilon-}$, respectively. We start with S_ε and $S_{O,\varepsilon}$, add the equations, and multiply both sides by -1,

$$\begin{aligned}
&k^+_O(\partial_t S_{\varepsilon-}, S_{\varepsilon-})_{\Omega^{\mathrm{ER}}_\varepsilon} + k^-_O\langle\partial_t S_{O,\varepsilon-}, S_{O,\varepsilon-}\rangle_{\Gamma^1\cap\partial\Omega^{\mathrm{ER}}_\varepsilon} + D_S k^+_O\|\nabla S_{\varepsilon-}\|^2_{\Omega^{\mathrm{ER}}_\varepsilon}\\
&\quad + k^+_C k^+_O\|\sqrt{f_e(C_{e,\varepsilon})}S_{\varepsilon-}\|^2_{\Omega^{\mathrm{ER}}_\varepsilon} + k^+_C k^-_O\|\sqrt{f_e(C_{e,\varepsilon})}S_{O,\varepsilon-}\|^2_{\Gamma^1\cap\partial\Omega^{\mathrm{ER}}_\varepsilon}\\
&\qquad + \|k^+_O S_{\varepsilon-} - k^-_O S_{O,\varepsilon-}\|^2_{\Gamma^1\cap\partial\Omega^{\mathrm{ER}}_\varepsilon}\\
&\leq -k^-_C k^+_O(S_{C,\varepsilon}, S_{\varepsilon-})_{\Omega^{\mathrm{ER}}_\varepsilon} - k^-_C k^-_O\langle S_{CO,\varepsilon}, S_{O,\varepsilon-}\rangle_{\Gamma^1\cap\partial\Omega^{\mathrm{ER}}_\varepsilon}\\
&\leq k^-_C k^+_O(S_{C,\varepsilon-}, S_{\varepsilon-})_{\Omega^{\mathrm{ER}}_\varepsilon} + k^-_C k^-_O\langle S_{CO,\varepsilon-}, S_{O,\varepsilon-}\rangle_{\Gamma^1\cap\partial\Omega^{\mathrm{ER}}_\varepsilon}\\
&\leq k^-_C k^+_O\left(\|S_{C,\varepsilon-}\|^2_{\Omega^{\mathrm{ER}}_\varepsilon} + \|S_{\varepsilon-}\|^2_{\Omega^{\mathrm{ER}}_\varepsilon}\right) + k^-_C k^-_O\left(\|S_{CO,\varepsilon-}\|^2_{\Gamma^1\cap\partial\Omega^{\mathrm{ER}}_\varepsilon} + \|S_{O,\varepsilon-}\|^2_{\Gamma^1\cap\partial\Omega^{\mathrm{ER}}_\varepsilon}\right).
\end{aligned}$$

Integration from 0 to t, dropping some positive terms, and merging the constants yields

$$\begin{aligned}
&\|S_{\varepsilon-}\|^2_{\Omega^{\mathrm{ER}}_\varepsilon} + \|S_{O,\varepsilon-}\|^2_{\Gamma^1\cap\partial\Omega^{\mathrm{ER}}_\varepsilon}\\
&\qquad\leq c_1\left(\|S_{C,\varepsilon-}\|^2_{\Omega^{\mathrm{ER}}_\varepsilon,t} + \|S_{\varepsilon-}\|^2_{\Omega^{\mathrm{ER}}_\varepsilon,t} + \|S_{CO,\varepsilon-}\|^2_{\Gamma^1\cap\partial\Omega^{\mathrm{ER}}_\varepsilon,t} + \|S_{O,\varepsilon-}\|^2_{\Gamma^1\cap\partial\Omega^{\mathrm{ER}}_\varepsilon,t}\right),
\end{aligned}$$

where we used that the initial conditions are nonnegative. We perform corresponding operations for the equations for $S_{C,\varepsilon}$ and $S_{CO,\varepsilon}$, and find

$$\begin{aligned}
&\|S_{C,\varepsilon-}\|^2_{\Omega^{\mathrm{ER}}_\varepsilon} + \|S_{CO,\varepsilon-}\|^2_{\Gamma^1\cap\partial\Omega^{\mathrm{ER}}_\varepsilon}\\
&\qquad\leq c_1\left(\|S_{C,\varepsilon-}\|^2_{\Omega^{\mathrm{ER}}_\varepsilon,t} + \|S_{\varepsilon-}\|^2_{\Omega^{\mathrm{ER}}_\varepsilon,t} + \|S_{CO,\varepsilon-}\|^2_{\Gamma^1\cap\partial\Omega^{\mathrm{ER}}_\varepsilon,t} + \|S_{O,\varepsilon-}\|^2_{\Gamma^1\cap\partial\Omega^{\mathrm{ER}}_\varepsilon,t}\right).
\end{aligned}$$

Then we add the two inequalities and find

$$\begin{aligned}\|S_{\varepsilon-}\|^2_{\Omega_\varepsilon^{\mathrm{ER}}} + \|S_{O,\varepsilon-}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}} + \|S_{C,\varepsilon-}\|^2_{\Omega_\varepsilon^{\mathrm{ER}}} + \|S_{CO,\varepsilon-}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}} \\ \le c_1\left(\|S_{C,\varepsilon-}\|^2_{\Omega_\varepsilon^{\mathrm{ER}},t} + \|S_{\varepsilon-}\|^2_{\Omega_\varepsilon^{\mathrm{ER}},t} + \|S_{CO,\varepsilon-}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}},t} + \|S_{O,\varepsilon-}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}},t}\right).\end{aligned}$$

Using the lemma of Gronwall yields

$$\|S_{\varepsilon-}\|^2_{\Omega_\varepsilon^{\mathrm{ER}}} + \|S_{O,\varepsilon-}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}} + \|S_{C,\varepsilon-}\|^2_{\Omega_\varepsilon^{\mathrm{ER}}} + \|S_{CO,\varepsilon-}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}} \le 0.$$

Hence, the functions S_ε, $S_{C,\varepsilon}$, $S_{O,\varepsilon}$ and $S_{CO,\varepsilon}$ are nonnegative. □

Lemma 8. (Boundedness of S_ε, $S_{C,\varepsilon}$, $S_{O,\varepsilon}$ and $S_{CO,\varepsilon}$ in H^1 or L^2)
There exists a constant $C > 0$, independent of ε, such that

$$\|S_\varepsilon\|^2_{\Omega_\varepsilon^{ER}} + \|S_{C,\varepsilon}\|^2_{\Omega_\varepsilon^{ER}} + \|\nabla S_\varepsilon\|^2_{\Omega_\varepsilon^{ER},t} + \|\nabla S_{C,\varepsilon}\|^2_{\Omega_\varepsilon^{ER},t} + \|S_{O,\varepsilon}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{ER}} + \|S_{CO,\varepsilon}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{ER}} \le C.$$

Proof. We test the weak formulations for S_ε and $S_{C,\varepsilon}$ with the functions S_ε and $S_{C,\varepsilon}$, respectively, add the equations and integrate from 0 to t. With the binomial theorem we get for any $\lambda > 0$

$$\begin{aligned}\frac{1}{2}\|S_\varepsilon\|^2_{\Omega_\varepsilon^{\mathrm{ER}}} + \frac{1}{2}\|S_{C,\varepsilon}\|^2_{\Omega_\varepsilon^{\mathrm{ER}}} + D_S\|\nabla S_\varepsilon\|^2_{\Omega_\varepsilon^{\mathrm{ER}},t} + D_{SC}\|\nabla S_{C,\varepsilon}\|^2_{\Omega_\varepsilon^{\mathrm{ER}},t} \\ + k_O^+\|S_\varepsilon\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}},t} + k_{CO}^+\|S_{C,\varepsilon}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}},t} \\ \le \frac{1}{2}\|S_\varepsilon(0)\|^2_{\Omega_\varepsilon^{\mathrm{ER}}} + \frac{1}{2}\|S_{C,\varepsilon}(0)\|^2_{\Omega_\varepsilon^{\mathrm{ER}}} + c_1\|S_\varepsilon\|^2_{\Omega_\varepsilon^{\mathrm{ER}},t} + c_2\|S_{C,\varepsilon}\|^2_{\Omega_\varepsilon^{\mathrm{ER}},t} + c_3\frac{1}{\lambda}\|S_\varepsilon\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}},t} \\ + c_4\lambda\|S_{O,\varepsilon}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}},t} + c_5\frac{1}{\lambda}\|S_{C,\varepsilon}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}},t} + c_6\lambda\|S_{CO,\varepsilon}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}},t}.\end{aligned}$$

Using the trace inequality with lemma 6, merging the constants and dropping some positive terms yield

$$\begin{aligned}\|S_\varepsilon\|^2_{\Omega_\varepsilon^{\mathrm{ER}}} + \|S_{C,\varepsilon}\|^2_{\Omega_\varepsilon^{\mathrm{ER}}} + \left(D_S - c_1c_0\frac{1}{\lambda}\right)\|\nabla S_\varepsilon\|^2_{\Omega_\varepsilon^{\mathrm{ER}},t} + \left(D_{SC} - c_2c_0\frac{1}{\lambda}\right)\|\nabla S_{C,\varepsilon}\|^2_{\Omega_\varepsilon^{\mathrm{ER}},t} \\ \le c_3 + c_4\|S_\varepsilon\|^2_{\Omega_\varepsilon^{\mathrm{ER}},t} + c_5\|S_{C,\varepsilon}\|^2_{\Omega_\varepsilon^{\mathrm{ER}},t} + c_6\lambda\|S_{O,\varepsilon}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}},t} + c_7\lambda\|S_{CO,\varepsilon}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}},t}.\end{aligned}$$

Now we do similar estimates for the equations for $S_{O,\varepsilon}$ and $S_{CO,\varepsilon}$ and find for any $\lambda > 0$

$$\begin{aligned}\frac{1}{2}\|S_{O,\varepsilon}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}} + \frac{1}{2}\|S_{CO,\varepsilon}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}} \\ \le \frac{1}{2}\|S_{O,\varepsilon}(0)\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}} + \frac{1}{2}\|S_{CO,\varepsilon}(0)\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}} + c_1\lambda\|S_{O,\varepsilon}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}},t} + c_2\lambda\|S_{CO,\varepsilon}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}},t} \\ + c_3c_0\frac{1}{\lambda}\|S_\varepsilon\|^2_{\Omega_\varepsilon^{\mathrm{ER}},t} + c_3c_0\frac{1}{\lambda}\|\nabla S_\varepsilon\|^2_{\Omega_\varepsilon^{\mathrm{ER}},t} + c_4\frac{1}{\lambda}c_0\|S_{C,\varepsilon}\|^2_{\Omega_\varepsilon^{\mathrm{ER}},t} + c_4\frac{1}{\lambda}c_0\|\nabla S_{C,\varepsilon}\|^2_{\Omega_\varepsilon^{\mathrm{ER}},t}.\end{aligned}$$

We sum up all inequalities to find

$$\begin{aligned}\|S_\varepsilon\|^2_{\Omega_\varepsilon^{\mathrm{ER}}} + \|S_{C,\varepsilon}\|^2_{\Omega_\varepsilon^{\mathrm{ER}}} + \left(D_S - c_0c_1\frac{1}{\lambda}\right)\|\nabla S_\varepsilon\|^2_{\Omega_\varepsilon^{\mathrm{ER}},t} \\ + \left(D_{SC} - c_2c_0\frac{1}{\lambda}\right)\|\nabla S_{C,\varepsilon}\|^2_{\Omega_\varepsilon^{\mathrm{ER}},t} + \|S_{O,\varepsilon}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}} + \|S_{CO,\varepsilon}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}} \\ \le c_3 + c_4\|S_\varepsilon\|^2_{\Omega_\varepsilon^{\mathrm{ER}},t} + c_5\|S_{C,\varepsilon}\|^2_{\Omega_\varepsilon^{\mathrm{ER}},t} + c_6\lambda\|S_{O,\varepsilon}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}},t} + c_7\lambda\|S_{CO,\varepsilon}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}},t}.\end{aligned}$$

For λ greater than $c_0c_2 + c_0c_1$, but finite, Gronwall's lemma yields

$$\|S_\varepsilon\|^2_{\Omega_\varepsilon^{\mathrm{ER}}} + \|S_{C,\varepsilon}\|^2_{\Omega_\varepsilon^{\mathrm{ER}}} + \|\nabla S_\varepsilon\|^2_{\Omega_\varepsilon^{\mathrm{ER}},t} + \|\nabla S_{C,\varepsilon}\|^2_{\Omega_\varepsilon^{\mathrm{ER}},t} + \|S_{O,\varepsilon}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}} + \|S_{CO,\varepsilon}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}} \le C.$$

□

Next, we want to show that the functions that represent the concentration of Stim1 molecules are bounded, i.e. they are L^∞ functions.

Lemma 9. (Boundedness of S_ε, $S_{C,\varepsilon}$, $S_{O,\varepsilon}$ and $S_{CO,\varepsilon}$ in L^∞)
There exists a constant $C>0$, independent of ε, such that

$$\|S_\varepsilon\|_{L^\infty(\Omega_\varepsilon^{ER})}+\|S_{C,\varepsilon}\|_{L^\infty(\Omega_\varepsilon^{ER})}+\|S_{O,\varepsilon}\|_{L^\infty(\Gamma^1\cap\partial\Omega_\varepsilon^{ER})}+\|S_{CO,\varepsilon}\|_{L^\infty(\Gamma^1\cap\partial\Omega_\varepsilon^{ER})}<C$$

for almost every $t\in[0,T]$.

Proof. Let $k>0$. We define the function

$$M(t)=\max\{\|S_\varepsilon(0)\|_{L^\infty},\|S_{C,\varepsilon}(0)\|_{L^\infty},\|S_{O,\varepsilon}(0)\|_{L^\infty},\|S_{CO,\varepsilon}(0)\|_{L^\infty}\}e^{kt}$$

with $t\in[0,T]$. Note that the initial values are L^∞ functions, so that M is well-defined and finite for all $t\in[0,T]$.

We test the equations for S_ε, $S_{C,\varepsilon}$, $S_{O,\varepsilon}$ and $S_{CO,\varepsilon}$ with $(k_O^+S_\varepsilon-M)_+$, $(k_{CO}^+S_{C,\varepsilon}-M)_+$, $(k_O^-S_{O,\varepsilon}-M)_+$ and $(k_{CO}^-S_{CO,\varepsilon}-M)_+$, respectively, add the results and consider the time and spatial derivative of M to obtain

$$\begin{aligned}
&\frac{1}{k_O^+}(\partial_t(k_O^+S_\varepsilon-M)_+,(k_O^+S_\varepsilon-M)_+)_{\Omega_\varepsilon^{\mathrm{ER}}}+\frac{1}{k_{CO}^+}(\partial_t(k_{CO}^+S_{C,\varepsilon}-M)_+,(k_{CO}^+S_{C,\varepsilon}-M)_+)_{\Omega_\varepsilon^{\mathrm{ER}}}\\
&\quad+\frac{1}{k_O^+}D_S\|\nabla(k_O^+S_\varepsilon-M)_+\|^2_{\Omega_\varepsilon^{\mathrm{ER}}}+\frac{1}{k_{CO}^+}D_{SC}\|\nabla(k_{CO}^+S_{C,\varepsilon}-M)_+\|^2_{\Omega_\varepsilon^{\mathrm{ER}}}\\
&\quad+\frac{1}{k_O^-}\langle\partial_t(k_O^-S_{O,\varepsilon}-M)_+,(k_O^-S_{O,\varepsilon}-M)_+\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}}\\
&\quad+\frac{1}{k_{CO}^-}\langle\partial_t(k_{CO}^-S_{CO,\varepsilon}-M)_+,(k_{CO}^-S_{CO,\varepsilon}-M)_+\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}}\\
&\quad+(k_C^+f_e(C_{e,\varepsilon})S_\varepsilon-k_C^-S_{C,\varepsilon},(k_O^+S_\varepsilon-M)_+-(k_{CO}^+S_{C,\varepsilon}-M)_+)_{\Omega_\varepsilon^{\mathrm{ER}}}\\
&\quad+\langle k_C^+f_e(C_{e,\varepsilon})S_{O,\varepsilon}-k_C^-S_{CO,\varepsilon},(k_O^-S_{O,\varepsilon}-M)_+-(k_{CO}^-S_{CO,\varepsilon}-M)_+\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}}\\
&\quad+\|(k_O^+S_\varepsilon-M)_+-(k_O^-S_{O,\varepsilon}-M)_+\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}}+\|(k_{CO}^+S_{C,\varepsilon}-M)_+-(k_{CO}^-S_{CO,\varepsilon}-M)_+\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}}\\
&\le-(\frac{1}{k_O^+}kM,(k_O^+S_\varepsilon-M)_+)_{\Omega_\varepsilon^{\mathrm{ER}}}-(\frac{1}{k_{CO}^+}kM,(k_{CO}^+S_{C,\varepsilon}-M)_+)_{\Omega_\varepsilon^{\mathrm{ER}}}\\
&\quad-\langle\frac{1}{k_O^-}kM,(k_O^-S_{O,\varepsilon}-M)_+\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}}-\langle\frac{1}{k_{CO}^-}kM,(k_{CO}^-S_{CO,\varepsilon}-M)_+\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}}.
\end{aligned}$$

We drop some positive terms, integrate from 0 to t and use the binomial theorem. With $f_e(C_{e,\varepsilon})$ bounded and $\|(\varphi-M)_+\|_{\Omega_\varepsilon^{\mathrm{ER}}}\le\|\varphi\|_{\Omega_\varepsilon^{\mathrm{ER}}}$ for $\varphi=S_\varepsilon,S_{C,\varepsilon}$ and $\|(\varphi-M)_+\|_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}}\le\|\varphi\|_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}}$ for $\varphi=S_{O,\varepsilon},S_{CO,\varepsilon}$ we find

$$\begin{aligned}
&\frac{1}{2k_O^+}\|(k_O^+S_\varepsilon-M)_+\|^2_{\Omega_\varepsilon^{\mathrm{ER}}}+\frac{1}{2k_{CO}^+}\|(k_{CO}^+S_{C,\varepsilon}-M)_+\|^2_{\Omega_\varepsilon^{\mathrm{ER}}}\\
&\quad+\frac{1}{2k_O^-}\|(k_O^-S_{O,\varepsilon}-M)_+\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}}+\frac{1}{2k_{CO}^-}\|(k_{CO}^-S_{CO,\varepsilon}-M)_+\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}}\\
&\quad\le c_1-(\frac{1}{k_O^+}kM,(k_O^+S_\varepsilon-M)_+)_{\Omega_\varepsilon^{\mathrm{ER}},t}-(\frac{1}{k_{CO}^+}kM,(k_{CO}^+S_{C,\varepsilon}-M)_+)_{\Omega_\varepsilon^{\mathrm{ER}},t}\\
&\quad\quad-\langle\frac{1}{k_O^-}kM,(k_O^-S_{O,\varepsilon}-M)_+\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}},t}-\langle\frac{1}{k_{CO}^-}kM,(k_{CO}^-S_{CO,\varepsilon}-M)_+\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}},t}.
\end{aligned}$$

Now we distinguish two cases.

- There exists a non-nullset $V \subset \Omega_\varepsilon^{\rm ER}$ such that $(k_O^+ S_\varepsilon - M)_+ > 0$ in V or $(k_{CO}^+ S_{C,\varepsilon} - M)_+ > 0$ in V; or there exists a non-nullset $V \subset \Gamma^1 \cap \partial\Omega_\varepsilon^{\rm ER}$ such that $(k_O^- S_{O,\varepsilon} - M)_+ > 0$ in V or $(k_{CO}^- S_{CO,\varepsilon} - M)_+ > 0$ in V. Then there exists a $\delta > 0$ such that

$$(\frac{1}{k_O^+}M, (k_O^+ S_\varepsilon - M)_+)_{\Omega_\varepsilon^{\rm ER},t} + (\frac{1}{k_{CO}^+}M, (k_{CO}^+ S_{C,\varepsilon} - M)_+)_{\Omega_\varepsilon^{\rm ER},t} > \delta$$

or

$$\langle \frac{1}{k_O^-}M, (k_O^- S_{O,\varepsilon} - M)_+\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^{\rm ER},t} + \langle \frac{1}{k_{CO}^-}M, (k_{CO}^- S_{CO,\varepsilon} - M)_+\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^{\rm ER},t} > \delta.$$

We choose k to be $k\delta > c_1$, which is possible since k and δ is growing with k, and we find

$$\frac{1}{2k_O^+}\|(k_O^+ S_\varepsilon - M)_+\|^2_{\Omega_\varepsilon^{\rm ER}} + \frac{1}{2k_{CO}^+}\|(k_{CO}^+ S_{C,\varepsilon} - M)_+\|^2_{\Omega_\varepsilon^{\rm ER}} \\ + \frac{1}{2k_O^-}\|(k_O^- S_{O,\varepsilon} - M)_+\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\rm ER}} + \frac{1}{2k_{CO}^-}\|(k_{CO}^- S_{CO,\varepsilon} - M)_+\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^{\rm ER}} \le 0.$$

That contradicts the existence of such a subset V and the proof is complete.

- Otherwise it holds that $(k_O^+ S_\varepsilon - M)_+ \le 0$, $(k_{CO}^+ S_{C,\varepsilon} - M)_+ \le 0$, $(k_O^- S_{O,\varepsilon} - M)_+ \le 0$ and $(k_{CO}^- S_{CO,\varepsilon} - M)_+ \le 0$ almost everywhere and we are finished.

□

Now we show that C_ε and $C_{e,\varepsilon}$ are H^1-functions.

Lemma 10. (Boundedness of C_ε and $C_{e,\varepsilon}$ in H^1)
It holds that

$$\|C_\varepsilon\|^2_{\Omega_\varepsilon^1} + \|C_{e,\varepsilon}\|^2_{\Omega_\varepsilon^2} + \|\nabla C_\varepsilon\|^2_{\Omega_\varepsilon^1,t} + \|\nabla C_{e,\varepsilon}\|^2_{\Omega_\varepsilon^2,t} + \varepsilon\|C_\varepsilon - C_{e,\varepsilon}\|^2_{\Gamma_\varepsilon^{ER},t} \le C$$

for a constant $C > 0$, independent of ε.

Proof. We test the weak formulation for C_ε with C_ε and get

$$(\partial_t C_\varepsilon, C_\varepsilon)_{\Omega_\varepsilon^1} + D_C\|\nabla C_\varepsilon\|^2_{\Omega_\varepsilon^1} + \varepsilon(L_0 + L_{\rm IP3})\langle C_\varepsilon - C_{e,\varepsilon}, C_\varepsilon\rangle_{\Gamma_\varepsilon^{\rm ER}} + \varepsilon\langle f_{\rm SERCA}, C_\varepsilon\rangle_{\Gamma_\varepsilon^{\rm ER}} \\ + \langle \alpha I_{\rm CRAC} + f_{\rm P} + f_{\rm NCX}, C_\varepsilon\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^1} = 0.$$

Also, we test the weak formulation for $C_{e,\varepsilon}$ with $C_{e,\varepsilon}$ and get

$$(\partial_t C_{e,\varepsilon}, C_{e,\varepsilon})_{\Omega_\varepsilon^2} + D_{\rm ER}\|\nabla C_{e,\varepsilon}\|^2_{\Omega_\varepsilon^2} + \varepsilon(L_0 + L_{\rm IP3})\langle C_{e,\varepsilon} - C_\varepsilon, C_{e,\varepsilon}\rangle_{\Gamma_\varepsilon^{\rm ER}} - \varepsilon\langle f_{\rm SERCA}, C_{e,\varepsilon}\rangle_{\Gamma_\varepsilon^{\rm ER}} = 0.$$

Adding the equations gives for any $\lambda > 0$

$$\begin{aligned}(\partial_t C_\varepsilon, C_\varepsilon)_{\Omega_\varepsilon^1} &+ D_C\|\nabla C_\varepsilon\|^2_{\Omega_\varepsilon^1} + (\partial_t C_{e,\varepsilon}, C_{e,\varepsilon})_{\Omega_\varepsilon^2} + D_{\rm ER}\|\nabla C_{e,\varepsilon}\|^2_{\Omega_\varepsilon^2} + \varepsilon(L_0 + L_{\rm IP3})\|C_\varepsilon - C_{e,\varepsilon}\|^2_{\Gamma_\varepsilon^{\rm ER}} \\ &= -\langle f_{\rm P} + f_{\rm NCX} + \alpha I_{\rm CRAC}, C_\varepsilon\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^1} + \varepsilon\langle f_{\rm SERCA}, C_{e,\varepsilon} - C_\varepsilon\rangle_{\Gamma_\varepsilon^{\rm ER}} \\ &\le \underbrace{\frac{\lambda}{2}\|f_{\rm P} + f_{\rm NCX} + \alpha I_{\rm CRAC}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^1} + \varepsilon\|f_{\rm SERCA}\|^2_{\Gamma_\varepsilon^2}}_{\le c_1} + \frac{c_0}{2\lambda}\left(\|C_\varepsilon\|^2_{\Omega_\varepsilon^1} + \|\nabla C_\varepsilon\|^2_{\Omega_\varepsilon^1}\right) \\ &\quad + c_0\left(\|C_{e,\varepsilon}\|^2_{\Omega_\varepsilon^2} + \varepsilon^2\|\nabla C_{e,\varepsilon}\|^2_{\Omega_\varepsilon^2}\right) + c_0\left(\|C_\varepsilon\|^2_{\Omega_\varepsilon^1} + \varepsilon^2\|\nabla C_\varepsilon\|^2_{\Omega_\varepsilon^1}\right).\end{aligned}$$

Note, that we used two different trace inequalities, the standard one for homogenization and lemma 6. We deduce

$$\begin{aligned}(\partial_t C_\varepsilon, C_\varepsilon)_{\Omega_\varepsilon^1} + \left(D_C - \frac{c_0}{2\lambda} - \varepsilon^2 c_0\right) \|\nabla C_\varepsilon\|^2_{\Omega_\varepsilon^1} \\ + (\partial_t C_{e,\varepsilon}, C_{e,\varepsilon})_{\Omega_\varepsilon^2} + \left(D_{\mathrm{ER}} - c_0\varepsilon^2\right) \|\nabla C_{e,\varepsilon}\|^2_{\Omega_\varepsilon^2} + \varepsilon(L_0 + L_{\mathrm{IP3}})\|C_\varepsilon - C_{e,\varepsilon}\|^2_{\Gamma_\varepsilon^{\mathrm{ER}}} \\ \leq \lambda c_1 + c_2\|C_\varepsilon\|^2_{\Omega_\varepsilon^1} + c_3\|C_{e,\varepsilon}\|^2_{\Omega_\varepsilon^2}\end{aligned}$$

for some constants c_1, c_2 and c_3. By integration from 0 to t we get

$$\begin{aligned}\frac{1}{2}\|C_\varepsilon\|^2_{\Omega_\varepsilon^1} + \left(D_C - \frac{c_0}{2\lambda} - \varepsilon^2 c_0\right) \|\nabla C_\varepsilon\|^2_{\Omega_\varepsilon^1,t} \\ + \frac{1}{2}\|C_{e,\varepsilon}\|^2_{\Omega_\varepsilon^2} + \left(D_{\mathrm{ER}} - c_0\varepsilon^2\right) \|\nabla C_{e,\varepsilon}\|^2_{\Omega_\varepsilon^2,t} + \varepsilon(L_0 + L_{\mathrm{IP3}})\|C_\varepsilon - C_{e,\varepsilon}\|^2_{\Gamma_\varepsilon^{\mathrm{ER}},t} \\ \leq \lambda c_1 + c_2\|C_\varepsilon\|^2_{\Omega_\varepsilon^1,t} + c_3\|C_{e,\varepsilon}\|^2_{\Omega_\varepsilon^2,t} + \frac{1}{2}\|C_\varepsilon(0)\|^2_{\Omega_\varepsilon^1} + \frac{1}{2}\|C_{e,\varepsilon}(0)\|^2_{\Omega_\varepsilon^2}.\end{aligned}$$

For λ big enough but finite, and small ε we conclude with the lemma of Gronwall that

$$\|C_\varepsilon\|^2_{\Omega_\varepsilon^1} + \|\nabla C_\varepsilon\|^2_{\Omega_\varepsilon^1,t} + \|C_{e,\varepsilon}\|^2_{\Omega_\varepsilon^2} + \|\nabla C_{e,\varepsilon}\|^2_{\Omega_\varepsilon^2,t} + \varepsilon\|C_\varepsilon - C_{e,\varepsilon}\|^2_{\Gamma_\varepsilon^{\mathrm{ER}},t} \leq C$$

for a merged constant C. □

Next, we show that C_ε and $C_{e,\varepsilon}$ are also bounded in L^∞.

Lemma 11. (Boundedness of C_ε and $C_{e,\varepsilon}$ in L^∞)
There exists a constant $C > 0$, independent of ε, such that

$$\|C_\varepsilon\|_{L^\infty(\Omega_\varepsilon^1)} + \|C_{e,\varepsilon}\|_{L^\infty(\Omega_\varepsilon^2)} < C$$

for almost every $t \in [0, T]$.

Proof. Let $k > 0$. We define the function $M(t) := \max\{\|C_\varepsilon(0)\|_{L^\infty}, \|C_{e,\varepsilon}(0)\|_{L^\infty}\}e^{kt}$, test the equations for C_ε and $C_{e,\varepsilon}$ with $(C_\varepsilon - M)_+$ and $(C_{e,\varepsilon} - M)_+$, respectively, add them up and consider the time and spatial derivatives. Integration from 0 to t yields

$$\begin{aligned}\frac{1}{2}\|(C_\varepsilon - M)_+\|^2_{\Omega_\varepsilon^1} + D_C\|\nabla(C_\varepsilon - M)_+\|^2_{\Omega_\varepsilon^1,t} + \frac{1}{2}\|(C_{e,\varepsilon} - M)_+\|^2_{\Omega_\varepsilon^2} + D_{\mathrm{ER}}\|\nabla(C_{e,\varepsilon} - M)_+\|^2_{\Omega_\varepsilon^2,t} \\ + \varepsilon(L_0 + L_{\mathrm{IP3}})\langle(C_\varepsilon - M) - (C_{e,\varepsilon} - M), (C_\varepsilon - M)_+ - (C_{e,\varepsilon} - M)_+\rangle_{\Gamma_\varepsilon^{\mathrm{ER}},t} \\ \leq \alpha\langle|I_{\mathrm{CRAC}}|, (C_\varepsilon - M)_+\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^1,t} - (kM, (C_\varepsilon - M)_+)_{\Omega_\varepsilon^1,t} - (kM, (C_{e,\varepsilon} - M)_+)_{\Omega_\varepsilon^2,t}.\end{aligned}$$

Hence, with $\langle(C_\varepsilon - M) - (C_{e,\varepsilon} - M), (C_\varepsilon - M)_+ - (C_{e,\varepsilon} - M)_+\rangle_{\Gamma_\varepsilon^{\mathrm{ER}},t} = \|(C_\varepsilon - M)_+ - (C_{e,\varepsilon} - M)_+\|^2_{\Gamma_\varepsilon^{\mathrm{ER}},t} + \langle(C_\varepsilon - M)_-, (C_{e,\varepsilon} - M)_+\rangle_{\Gamma_\varepsilon^{\mathrm{ER}},t} + \langle(C_{e,\varepsilon} - M)_-, (C_\varepsilon - M)_+\rangle_{\Gamma_\varepsilon^{\mathrm{ER}},t} \geq \|(C_\varepsilon - M)_+ - (C_{e,\varepsilon} - M)_+\|^2_{\Gamma_\varepsilon^{\mathrm{ER}},t}$ we continue with

$$\begin{aligned}&\frac{1}{2}\|(C_\varepsilon - M)_+\|^2_{\Omega_\varepsilon^1} + D_C\|\nabla(C_\varepsilon - M)_+\|^2_{\Omega_\varepsilon^1,t} + \frac{1}{2}\|(C_{e,\varepsilon} - M)_+\|^2_{\Omega_\varepsilon^2} \\ &\quad + D_{\mathrm{ER}}\|\nabla(C_{e,\varepsilon} - M)_+\|^2_{\Omega_\varepsilon^2,t} + \varepsilon(L_0 + L_{\mathrm{IP3}})\|(C_\varepsilon - M)_+ - (C_{e,\varepsilon} - M)_+\|^2_{\Gamma_\varepsilon^{\mathrm{ER}},t} \\ &\leq \underbrace{\alpha\|I_{\mathrm{CRAC}}\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^1,t} + c_0\left(\|(C_\varepsilon - M)_+\|^2_{\Omega_\varepsilon^1,t} + \|\nabla(C_\varepsilon - M)_+\|^2_{\Omega_\varepsilon^1,t}\right)}_{\leq c_1} \\ &\quad - (kM, (C_\varepsilon - M)_+)_{\Omega_\varepsilon^1,t} - (kM, (C_{e,\varepsilon} - M)_+)_{\Omega_\varepsilon^2,t} \\ &\leq c_1 - (kM, (C_\varepsilon - M)_+)_{\Omega_\varepsilon^1,t} - (kM, (C_{e,\varepsilon} - M)_+)_{\Omega_\varepsilon^2,t}.\end{aligned}$$

Now we distinguish two cases.

- There exists a non-nullset $V \subset \Omega_\varepsilon^1$ or $V \subset \Omega_\varepsilon^2$ with $(C_\varepsilon - M)_+ > 0$ or $(C_{e,\varepsilon} - M)_+ > 0$ in V, respectively. Then there exists a $\delta > 0$ such that $(M, (C_\varepsilon - M)_+)_{\Omega_\varepsilon^1,t} > \delta$ or $(M, (C_{e,\varepsilon} - M)_+)_{\Omega_\varepsilon^2,t} > \delta$, respectively, and we choose $k\delta = c_1$. Then it follows that

$$\begin{aligned}\frac{1}{2}\|(C_\varepsilon - M)_+\|^2_{\Omega_\varepsilon^1} + D_C\|\nabla(C_\varepsilon - M)_+\|^2_{\Omega_\varepsilon^1,t} + \frac{1}{2}\|(C_{e,\varepsilon} - M)_+\|^2_{\Omega_\varepsilon^2} \\ + D_{\mathrm{ER}}\|\nabla(C_{e,\varepsilon} - M)_+\|^2_{\Omega_\varepsilon^2,t} + \varepsilon(L_0 + L_{\mathrm{IP3}})\|(C_\varepsilon - M)_+ - (C_{e,\varepsilon} - M)_+\|^2_{\Gamma_\varepsilon^{\mathrm{ER}},t} \\ \leq c_1 - (kM, (C_\varepsilon - M)_+)_{\Omega_\varepsilon^1,t} - (kM, (C_{e,\varepsilon} - M)_+)_{\Omega_\varepsilon^2,t} \leq 0.\end{aligned}$$

  But this contradicts $(C_\varepsilon - M)_+ > 0$ or $(C_{e,\varepsilon} - M)_+ > 0$ in a non-nullset and we are finished.

- It holds that $(C_\varepsilon - M)_+ = 0$ and $(C_{e,\varepsilon} - M)_+ = 0$ almost everywhere.

From the above we conclude that C_ε and $C_{e,\varepsilon}$ are bounded from above. Because C_ε and $C_{e,\varepsilon}$ could be negative, we also show that they have a lower bound. Biologically it does not make sense for C_ε or $C_{e,\varepsilon}$ to be negative, but the system is created such that mathematically we can not exclude it. Therefore, we test the weak formulations with $(C_\varepsilon + M)_-$ and $(C_{e,\varepsilon} + M)_-$. With similar transformations as above we obtain that $\|(C_\varepsilon + M)_-\|^2_{\Omega_\varepsilon^1} + \|(C_{e,\varepsilon} + M)_-\|^2_{\Omega_\varepsilon^2} \leq 0$. □

Finally, we estimate the time derivatives.

Lemma 12. (Boundedness of $\partial_t C_\varepsilon$, $\partial_t C_{e,\varepsilon}$, $\partial_t S_\varepsilon$, $\partial_t S_{C,\varepsilon}$, $\partial_t S_{O,\varepsilon}$ and $\partial_t S_{CO,\varepsilon}$ in H^{-1})
There exists a constant $C > 0$, independent of ε, such that

$$\begin{aligned}\|\partial_t C_\varepsilon\|_{L^2([0,T],H^{-1}(\Omega_\varepsilon^1))} + \|\partial_t C_{e,\varepsilon}\|_{L^2([0,T],H^{-1}(\Omega_\varepsilon^2))} < C, \\ \|\partial_t S_\varepsilon\|_{L^2([0,T],H^{-1}(\Omega_\varepsilon^{ER}))} + \|\partial_t S_{C,\varepsilon}\|_{L^2([0,T],H^{-1}(\Omega_\varepsilon^{ER}))} < C, \\ \|\partial_t S_{O,\varepsilon}\|_{L^2([0,T],L^2(\Gamma^1\cap\partial\Omega_\varepsilon^{ER})')} + \|\partial_t S_{CO,\varepsilon}\|_{L^2([0,T],L^2(\Gamma^1\cap\partial\Omega_\varepsilon^{ER})')} < C.\end{aligned}$$

Proof. We start with $\partial_t C_\varepsilon$ and the definition of the H^{-1} norm. We drop the boundary terms, because test functions in H_0^1 are zero at the boundary.

$$\begin{aligned}\|\partial_t C_\varepsilon\|_{H^{-1}(\Omega_\varepsilon^1)} &= \sup_{\varphi\in H_0^1(\Omega_\varepsilon^1),\|\varphi\|=1} (\partial_t C_\varepsilon, \varphi)_{H_0^1(\Omega_\varepsilon^1)'\times H_0^1(\Omega_\varepsilon^1)} \\ &= \sup_{\varphi\in H_0^1(\Omega_\varepsilon^1),\|\varphi\|=1} \Big(-D_C(\nabla C_\varepsilon, \nabla\varphi)_{H_0^1(\Omega_\varepsilon^1)'\times H_0^1(\Omega_\varepsilon^1)} - \underbrace{\varepsilon\langle(L_0 + L_{\mathrm{IP3}})(C_\varepsilon - C_{e,\varepsilon}) + f_{\mathrm{SERCA}}(C_\varepsilon), \varphi\rangle_{\Gamma_\varepsilon^{\mathrm{ER}}}}_{=0} \\ &\qquad - \underbrace{\langle\alpha I_{\mathrm{CRAC}}(S_{O,\varepsilon}) + f_P(C_\varepsilon) + f_{\mathrm{NCX}}(C_\varepsilon), \varphi\rangle_{\Gamma^1\cap\partial\Omega_\varepsilon^1}}_{=0}\Big) \\ &\leq \sup_{\varphi\in H_0^1(\Omega_\varepsilon^1),\|\varphi\|=1} (D_C\|\nabla C_\varepsilon\|_{L^2(\Omega_\varepsilon^1)}\|\nabla\varphi\|_{L^2(\Omega_\varepsilon^1)}) \\ &\leq c_1\|\nabla C_\varepsilon\|_{L^2(\Omega_\varepsilon^1)}.\end{aligned}$$

Integration from 0 to T leads to $\|\partial_t C_\varepsilon\|_{L^2([0,T],H^{-1}(\Omega_\varepsilon^1))} \leq c_1\|\nabla C_\varepsilon\|_{L^2([0,T]\times\Omega_\varepsilon^1)} \leq C$, see Lemma 10. Analogously we estimate $\|\partial_t C_{e,\varepsilon}\|_{L^2([0,T],H^{-1}(\Omega_\varepsilon^2))}$ and the other estimations. □

Remark 13. With the estimations found in the lemmas of this section we know that $C_\varepsilon \in L^2([0,T], H^1(\Omega_\varepsilon^1)) \cap L^\infty([0,T]\times\Omega_\varepsilon^1) \cap H^1([0,T], H^{-1}(\Omega_\varepsilon^1))$. We apply the extension operator from [17] to deduce that there exists an extension $\tilde{C}_\varepsilon$ of function C_ε such that $\tilde{C}_\varepsilon \in L^2([0,T], H^1(\Omega)) \cap L^\infty([0,T]\times\Omega) \cap H^1([0,T], H^{-1}(\Omega))$. Now we denote $\tilde{C}_\varepsilon$ again as C_ε for convenience.

Analogously, we find that $C_{e,\varepsilon} \in L^2([0,T], H^1(\Omega)) \cap L^\infty([0,T]\times\Omega) \cap H^1([0,T], H^{-1}(\Omega))$, $S_\varepsilon \in L^2([0,T], H^1(\Omega)) \cap L^\infty([0,T]\times\Omega) \cap H^1([0,T], H^{-1}(\Omega))$ and $S_{C,\varepsilon} \in L^2([0,T], H^1(\Omega)) \cap L^\infty([0,T]\times\Omega) \cap H^1([0,T], H^{-1}(\Omega))$.

On the boundary Γ^1 we deduce that $S_{O,\varepsilon} \in L^2([0,T], H^{\frac{1}{2}}(\Gamma^1 \cap \partial\Omega_\varepsilon^{\mathrm{ER}}))$. Using also Lemma 9 and Lemma 12 we find with the extension operator that $S_{O,\varepsilon},\ S_{CO,\varepsilon} \in L^2([0,T], H^{\frac{1}{2}}(\Gamma^1)) \cap L^\infty([0,T] \times \Gamma^1) \cap H^1([0,T], L^2(\Gamma^1))$.

With Lemma 5.10 in [13] we deduce strong convergence for the functions C_ε, $C_{e,\varepsilon}$, S_ε and $S_{C,\varepsilon}$ in $L^2([0,T] \times \Omega)$ and strong convergence for the functions $S_{O,\varepsilon}$ and $S_{CO,\varepsilon}$ in $L^2([0,T] \times \Gamma^1)$. With Theorem 5 we deduce also strong convergence on the outer boundary Γ^1 for the functions C_ε, $C_{e,\varepsilon}$, S_ε and $S_{C,\varepsilon}$.

6. Existence of a solution

The purpose of this section is to show that there exists at least one solution of the weak formulation (6) for every $\varepsilon > 0$, where we will use Schauder's fixed point theorem, cf. e.g. [31]. At first we note, that for every $\varepsilon > 0$ existence of $S_{O,\varepsilon}$ and $S_{CO,\varepsilon}$ (defined in (6)) easily can be shown by using Carathéodory's existence theorem, see [10], because these functions are defined by ordinary differential equations. Furthermore, the following estimate easily follows by standard techniques

$$\|S_{O,\varepsilon}\|^2_{L^2([0,\tau],H^{\frac{1}{2}-\delta}(\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}))} + \|S_{CO,\varepsilon}\|^2_{L^2([0,\tau],H^{\frac{1}{2}-\delta}(\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}}))} \\ \leq c\left(r + \|S_\varepsilon\|^2_{L^2([0,\tau],H^{1-\delta}(\Omega_\varepsilon^{\mathrm{ER}}))} + \|S_{C,\varepsilon}\|^2_{L^2([0,\tau],H^{1-\delta}(\Omega_\varepsilon^{\mathrm{ER}}))} + \|C_{e,\varepsilon}\|^2_{L^2([0,\tau],H^{1-\delta}(\Omega_\varepsilon^{\mathrm{ER}}))}\right).$$

for a constant $c > 0$, if $\|S_{O,\varepsilon}(0)\|^2_{H^{\frac{1}{2}-\delta}(\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}})} < r$ and $\|S_{CO,\varepsilon}(0)\|^2_{H^{\frac{1}{2}-\delta}(\Gamma^1\cap\partial\Omega_\varepsilon^{\mathrm{ER}})} < r$ for a $r > 0$ and $S_\varepsilon, S_{C,\varepsilon}, C_{e,\varepsilon} \in L^2([0,\tau], H^{1-\delta}(\Omega_\varepsilon^{\mathrm{ER}}))$ for a $\delta \in [0, \frac{1}{2})$ and a $\tau \in (0,T]$.

Because the functions f_X for $X \in \{\mathrm{SERCA}, \mathrm{P}, \mathrm{NCX}, e\}$ fulfill the growth condition $|f_X(x)| \leq c|x|^{\frac{p}{q}}$ for a constant $c > 0$ and $p = q = 2$ and are bounded and continuous, we deduce with the theorem of Nemytskii (see [29]) that $F_X : L^2 \to L^2$ are continuous and bounded. We also find that there are constants L_{SERCA}, L_P, L_{NCX}, L_e and L_{CRAC} such that $(F_{\mathrm{SERCA}}(C_\varepsilon))(t) \leq L_{\mathrm{SERCA}} C_\varepsilon(t)$, $(F_{\mathrm{P}}(C_\varepsilon))(t) \leq L_{\mathrm{P}} C_\varepsilon(t)$, $(F_{\mathrm{NCX}}(C_\varepsilon))(t) \leq L_{\mathrm{NCX}} C_\varepsilon(t)$, $(F_e(C_{e,\varepsilon}))(t) \leq L_e C_{e,\varepsilon}(t)$ and $I_{\mathrm{CRAC}}(S_{O,\varepsilon}) \leq L_{\mathrm{CRAC}} S_{O,\varepsilon}$.

Now we apply Schauder's fixed point theorem to ensure a solution of the complete system of differential equations (6).

Theorem 14. (Existence)
The system of differential equations (6) *has at least one solution* $(C_\varepsilon, C_{e,\varepsilon}, S_\varepsilon, S_{C,\varepsilon})$ *in* $\mathcal{V}(\Omega_\varepsilon^1) \times \mathcal{V}(\Omega_\varepsilon^2) \times \mathcal{V}(\Omega_\varepsilon^{ER}) \times \mathcal{V}(\Omega_\varepsilon^{ER})$.

Proof. We show existence on a small time interval $[0,\tau]$. The existing solutions must be patched together bit by bit.

For a $\delta \in (0, \frac{1}{2})$ we define the spaces $V_1 := L^2([0,\tau], H^{1-\delta}(\Omega_\varepsilon^1))$, $V_2 := L^2([0,\tau], H^{1-\delta}(\Omega_\varepsilon^2))$ and $V^{\mathrm{ER}} := L^2([0,\tau], H^{1-\delta}(\Omega_\varepsilon^{\mathrm{ER}}))$.

Further, we define the function

$$T : V^1 \times V^2 \times \left(V^{\mathrm{ER}}\right)^2 \longrightarrow \{u \in L^2([0,\tau], H^1(\Omega_\varepsilon^1)) |\ \partial_t u \in L^2([0,\tau], H^1(\Omega_\varepsilon^1)')\} \\ \times \{u \in L^2([0,\tau], H^1(\Omega_\varepsilon^2)) |\ \partial_t u \in L^2([0,\tau], H^1(\Omega_\varepsilon^2)')\} \\ \times \{u \in L^2([0,\tau], H^1(\Omega_\varepsilon^{\mathrm{ER}})) |\ \partial_t u \in L^2([0,\tau], H^1(\Omega_\varepsilon^{\mathrm{ER}})')\}^2$$

with

$$T(\tilde{C}_\varepsilon, \tilde{C}_{e,\varepsilon}, \tilde{S}_\varepsilon, \tilde{S}_{C,\varepsilon}) := (C_\varepsilon, C_{e,\varepsilon}, S_\varepsilon, S_{C,\varepsilon}),$$

given by

$$\begin{aligned}
\partial_t C_\varepsilon - D_C \Delta C_\varepsilon &= 0\\
-D_C \nabla C_\varepsilon \cdot n &= \varepsilon(L_0 + L_{\rm IP3})(\tilde C_\varepsilon - \tilde C_{e,\varepsilon}) + \varepsilon F_{\rm SERCA}(\tilde C_\varepsilon)\\
-D_C \nabla C_\varepsilon \cdot n &= \alpha I_{\rm CRAC}(S_{O,\varepsilon}) + F_{\rm P}(\tilde C_\varepsilon) + F_{\rm NCX}(\tilde C_\varepsilon)\\
-D_C \nabla C_\varepsilon \cdot n &= 0
\end{aligned}$$

$$\begin{aligned}
\partial_t C_{e,\varepsilon} - D_{\rm ER} \Delta C_{e,\varepsilon} &= 0\\
-D_{\rm ER} \nabla C_{e,\varepsilon} \cdot n &= \varepsilon(L_0 + L_{\rm IP3})(\tilde C_{e,\varepsilon} - \tilde C_\varepsilon) - \varepsilon F_{\rm SERCA}(\tilde C_\varepsilon)\\
-D_{\rm ER} \nabla C_{e,\varepsilon} \cdot n &= 0
\end{aligned}$$

$$\begin{aligned}
\partial_t S_\varepsilon - D_S \Delta S_\varepsilon &= -k_C^+ f_e(\tilde C_{e,\varepsilon})\tilde S_\varepsilon + k_C^- \tilde S_{C,\varepsilon}\\
-D_S \nabla S_\varepsilon \cdot n &= k_O^+ \tilde S_\varepsilon - k_O^- S_{O,\varepsilon}(\tilde C_{e,\varepsilon}, \tilde S_\varepsilon, \tilde S_{C,\varepsilon})\\
-D_S \nabla S_\varepsilon \cdot n &= 0
\end{aligned}$$

$$\begin{aligned}
\partial_t S_{C,\varepsilon} - D_{SC} \Delta S_{C,\varepsilon} &= k_C^+ f_e(\tilde C_{e,\varepsilon})\tilde S_\varepsilon - k_C^- \tilde S_{C,\varepsilon}\\
-D_{SC} \nabla S_{C,\varepsilon} \cdot n &= k_{CO}^+ \tilde S_{C,\varepsilon} - k_{CO}^- S_{CO,\varepsilon}(\tilde C_{e,\varepsilon}, \tilde S_\varepsilon, \tilde S_{C,\varepsilon})\\
-D_{SC} \nabla S_{C,\varepsilon} \cdot n &= 0
\end{aligned}$$

The solution of this system is unique and the operator T is continuous, where $S_{O,\varepsilon}(\tilde C_{e,\varepsilon}, \tilde S_\varepsilon, \tilde S_{C,\varepsilon})$ and $S_{CO,\varepsilon}(\tilde C_{e,\varepsilon}, \tilde S_\varepsilon, \tilde S_{C,\varepsilon})$ depend on $\tilde C_{e,\varepsilon}$, $\tilde S_\varepsilon$ and $\tilde S_{C,\varepsilon}$.

The space $\{u \in L^2([0,\tau], H^1(\Omega_\varepsilon^1)) |\ \partial_t u \in L^2([0,\tau], H^1(\Omega_\varepsilon^1)')\}$ is compactly embedded in V_1, $\{u \in L^2([0,\tau], H^1(\Omega_\varepsilon^2)) |\ \partial_t u \in L^2([0,\tau], H^1(\Omega_\varepsilon^2)')\}$ is compactly embedded in V_2 and $\{u \in L^2([0,\tau], H^1(\Omega_\varepsilon^{\rm ER})) |\ \partial_t u \in L^2([0,\tau], H^1(\Omega_\varepsilon^{\rm ER})')\}$ is compactly embedded in $V^{\rm ER}$ (lemma of Lions–Aubin [29] and Rellich–Kondrachov theorem [11]), and we denote the embedding with I. We deduce that the fixed-point operator that maps $(\tilde C_\varepsilon, \tilde C_{e,\varepsilon}, \tilde S_\varepsilon, \tilde S_{C,\varepsilon}) \in V^1 \times V^2 \times (V^{\rm ER})^2$ to $(C_\varepsilon, C_{e,\varepsilon}, S_\varepsilon, S_{C,\varepsilon}) \in V^1 \times V^2 \times (V^{\rm ER})^2$ is continuous and compact.

It is left to show that for the initial value $y_0 = (C_\varepsilon(0), C_{e,\varepsilon}(0), S_\varepsilon(0), S_{C,\varepsilon}(0), S_{O,\varepsilon}(0), S_{CO,\varepsilon}(0))$ it holds that $\left(\tilde C_\varepsilon, \tilde C_{e,\varepsilon}, \tilde S_\varepsilon, \tilde S_{C,\varepsilon}\right) \in B_{y_0}(r)$ implies $(I \circ T)\left(\tilde C_\varepsilon, \tilde C_{e,\varepsilon}, \tilde S_\varepsilon, \tilde S_{C,\varepsilon}\right) \in B_{y_0}(r)$. This means that $\|\tilde C\|^2_{V^1} + \|\tilde C_{e,\varepsilon}\|^2_{V^2} + \|\tilde S_\varepsilon\|^2_{V^{\rm ER}} + \|\tilde S_{C,\varepsilon}\|^2_{V^{\rm ER}} \le r$ should imply $\|C_\varepsilon\|^2_{V^1} + \|C_{e,\varepsilon}\|^2_{V^2} + \|S_\varepsilon\|^2_{V^{\rm ER}} + \|S_{C,\varepsilon}\|^2_{V^{\rm ER}} \le r$ for some $r > 0$, where we may assume that the initial conditions are smaller than r.

We test the weak formulation of the equation for C_ε with C_ε and integrate from 0 to $t \le \tau$.

$$\begin{aligned}
&\frac{1}{2}\|C_\varepsilon\|^2_{\Omega_\varepsilon^1} + D_C\|\nabla C_\varepsilon\|^2_{\Omega_\varepsilon,t}\\
&\le c_1\varepsilon\|\tilde C_\varepsilon\|^2_{\Gamma_\varepsilon^{\rm ER},t} + \varepsilon^{2-n}c_1|\tilde C_\varepsilon|^2_{L^2([0,t],H^{\frac12-\delta}(\Gamma_\varepsilon^{\rm ER}))} + c_2\varepsilon\|\tilde C_{e,\varepsilon}\|^2_{\Gamma_\varepsilon^{\rm ER},t}\\
&\quad + \varepsilon^{2-n}c_2|\tilde C_{e,\varepsilon}|^2_{L^2([0,t],H^{\frac12-\delta}(\Gamma_\varepsilon^{\rm ER}))} + c_3\varepsilon\|C_\varepsilon\|^2_{\Gamma_\varepsilon^{\rm ER},t} + c_4\frac{1}{\lambda}\|C_\varepsilon\|^2_{L^2([0,t],H^{\frac12}(\Gamma^1\cap\partial\Omega_\varepsilon^1))}\\
&\quad + c_5\lambda\|\tilde S_\varepsilon\|^2_{L^2([0,t],H^{1-\delta}(\Omega_\varepsilon^{\rm ER}))} + c_5\lambda\|\tilde S_{C,\varepsilon}\|^2_{L^2([0,t],H^{1-\delta}(\Omega_\varepsilon^{\rm ER}))} + c_6\frac{1}{\lambda}\|C_\varepsilon\|^2_{\Gamma^1\cap\partial\Omega_\varepsilon^1,t}\\
&\quad + c_7\lambda\|\tilde C_\varepsilon\|^2_{L^2([0,t],H^{\frac12-\delta}(\Gamma^1\cap\partial\Omega_\varepsilon^1))} + c_8 r.
\end{aligned}$$

Using the trace inequality and Lemma 3.24 from [27] we obtain

$$\begin{aligned}\|C_\varepsilon\|^2_{\Omega^1_\varepsilon} &+ \left(D_C - c_3\varepsilon^2 - \frac{1}{\lambda}c_4 - \frac{1}{\lambda}c_5\right)\|\nabla C_\varepsilon\|^2_{\Omega^1_\varepsilon,t}\\ &\le c_1\frac{1}{\lambda}\|C_\varepsilon\|^2_{\Omega^1_\varepsilon,t} + c_2\lambda\varepsilon^{-n}\underbrace{\|\tilde{C}_\varepsilon\|^2_{L^2([0,t],H^{1-\delta}(\Omega^1_\varepsilon))}}_{\le r} + c_3\varepsilon^{-n}\underbrace{\|\tilde{C}_{e,\varepsilon}\|^2_{L^2([0,t],H^{1-\delta}(\Omega^2_\varepsilon))}}_{\le r}\\ &\qquad + c_4\lambda\underbrace{\|\tilde{S}_\varepsilon\|^2_{L^2([0,t],H^{1-\delta}(\Omega^{\mathrm{ER}}_\varepsilon))}}_{\le r} + c_4\lambda\underbrace{\|\tilde{S}_{C,\varepsilon}\|^2_{L^2([0,t],H^{1-\delta}(\Omega^{\mathrm{ER}}_\varepsilon))}}_{\le r} + c_5 r\end{aligned}$$

with c_2, c_3 large but finite for $\varepsilon > 0$. For ε small enough and λ large enough we find with Gronwall's lemma that $\|C_\varepsilon\|^2_{\Omega^1_\varepsilon} + \|\nabla C_\varepsilon\|^2_{\Omega^1_\varepsilon,t} \le c_1 r$. This inequality yields $\|C_\varepsilon\|^2_{L^2([0,\tau],H^1(\Omega^1_\varepsilon))} \le c_1 r$ and $\|C_\varepsilon\|^2_{L^2([0,\tau]\times\Omega^1_\varepsilon)} \le \tau c_2 r$. With a standard interpolation inequality (cf. [1]) we find

$$\|C_\varepsilon\|^2_{V^1} \le c_3\|C_\varepsilon\|^{2-2\delta}_{L^2([0,\tau],H^1(\Omega^1_\varepsilon))}\|C_\varepsilon\|^{2\delta}_{L^2([0,\tau]\times\Omega^1_\varepsilon)} \le c_3(c_1 r)^{1-\delta}(\tau c_2 r)^\delta = cr\tau^\delta.$$

With similar transformations we also get the corresponding inequality for the equations for $C_{e,\varepsilon}$, S_ε and $S_{C,\varepsilon}$. In the end, we choose τ such that $\tau < \frac{1}{\sqrt[\delta]{4c}}$ and get

$$\|C_\varepsilon\|^2_{V^1} + \|C_{e,\varepsilon}\|^2_{V^2} + \|S_\varepsilon\|^2_{V^{\mathrm{ER}}} + \|S_{C,\varepsilon}\|^2_{V^{\mathrm{ER}}} \le r,$$

and the proof is complete. □

7. Identification of the limit problem as $\varepsilon \to 0$

In this section we determine the limit equation of the system (6) for ε tending to zero. We define $\chi^1(y)$, $\chi^2(y)$ and $\chi^{\mathrm{ER}}(y)$ with $y = \frac{x}{\varepsilon}$, which is 1 in Ω^1_ε, Ω^2_ε and $\Omega^{\mathrm{ER}}_\varepsilon$, respectively, and 0 otherwise.

Nonlinear terms and terms on the Robin boundary

To handle the nonlinear terms we apply Lemmas 10, 11, 8, 9, 12 and see that the functions C_ε, $C_{e,\varepsilon}$, S_ε and $S_{C,\varepsilon}$ each have a strongly converging subsequence in $L^2([0,T],L^2(\Omega))$ to C_0, $C_{e,0}$, S_0 and $S_{C,0}$, respectively.

We find that $S_{O,\varepsilon}$ and $S_{CO,\varepsilon}$ converge strongly in $L^2([0,T],L^2(\Gamma^1))$ to $S_{O,0}$ and $S_{CO,0}$, respectively, up to a subsequence.

- For the function f_{SERCA} on $\Gamma^{\mathrm{ER}}_\varepsilon$ we easily get that

  $$\lim_{\varepsilon\to 0}\varepsilon\langle f_{\mathrm{SERCA}}(C_\varepsilon),\varphi_\varepsilon\rangle_{L^2(\Gamma^{\mathrm{ER}}_\varepsilon)} = (|\Gamma^{\mathrm{ER}}|f_{\mathrm{SERCA}}(C_0),\varphi_0)_{L^2(\Omega)}$$

  with C_ε strongly converging to C_0.

- In the domain $\Omega^{\mathrm{ER}}_\varepsilon$ we find the nonlinear function $f_e(C_{e,\varepsilon})$ in the equations for S_ε and $S_{C,\varepsilon}$. Since $C_{e,\varepsilon}$ and S_ε converge strongly in $\Omega^{\mathrm{ER}}_\varepsilon$, we derive that

  $$\lim_{\varepsilon\to 0}\int_\Omega \chi^{\mathrm{ER}}\left(\frac{x}{\varepsilon}\right)k^+_C f_e(C_{e,\varepsilon})S_\varepsilon\varphi_\varepsilon \mathrm{d}x = \int_\Omega\int_{Y^{\mathrm{ER}}} k^+_C f_e(C_{e,0})S_0\varphi_0\mathrm{d}y\mathrm{d}x$$

  where χ^{ER} is equal to 1 for $\frac{x}{\varepsilon}$ in $\Omega^{\mathrm{ER}}_\varepsilon$ and 0 otherwise and $C_{e,\varepsilon}$ converges strongly to $C_{e,0}$.

- To find the limit of the term containing the influx $I_{\mathrm{CRAC}}(S_{O,\varepsilon})$ we use that $S_{O,\varepsilon}$ converges strongly to $S_{O,0}$ in $L^2([0,T],L^2(\Gamma^1))$, hence

  $$\lim_{\varepsilon\to 0}\int_{\Gamma^1}\chi^1\left(\frac{x}{\varepsilon}\right)I_{\mathrm{CRAC}}(S_{O,\varepsilon})\varphi_\varepsilon\mathrm{d}\sigma_x = \int_{\Gamma^1}\int_{\partial_0 Y^1} I_{\mathrm{CRAC}}(S_{O,0})\varphi_0\mathrm{d}\sigma_y\mathrm{d}\sigma_x$$

  for every $\varphi_0 \in C^\infty(\Omega)$.

- For the boundary term in the equation for C_ε we use theorem 5 b) to deduce that C_ε converges strongly in $L^2([0,T]\times\Gamma^1)$ and that

$$\lim_{\varepsilon\to 0}\int_{\Gamma^1}\chi^1\left(\frac{x}{\varepsilon}\right)(f_P(C_\varepsilon)+f_{\mathrm{NCX}}(C_\varepsilon))\varphi_\varepsilon \mathrm{d}\sigma_x = |\partial_o Y^1|\int_{\Gamma^1}(f_P(C_0)+f_{\mathrm{NCX}}(C_0))\varphi_0\mathrm{d}\sigma_x$$

for every $\varphi_0\in C^\infty(\Omega)$.

- We use again theorem 5 for the Robin boundary term in the equations for S_ε,

$$\lim_{\varepsilon\to 0}\int_{\Gamma^1}\chi^{\mathrm{ER}}\left(\frac{x}{\varepsilon}\right)k_O^+ S_\varepsilon\varphi_\varepsilon\mathrm{d}\sigma_x = |\partial_o Y^{\mathrm{ER}}|\int_{\Gamma^1}k_O^+ S_0\varphi_0\mathrm{d}\sigma_x$$

for all $\varphi_0\in C^\infty(\Omega)$.

- Analogously we find

$$\lim_{\varepsilon\to 0}\int_{\Gamma^1}\chi^{\mathrm{ER}}\left(\frac{x}{\varepsilon}\right)k_{CO}^+ S_{C,\varepsilon}\varphi_\varepsilon\mathrm{d}\sigma_x = |\partial_o Y^{\mathrm{ER}}|\int_{\Gamma^1}k_{CO}^+ S_{C,0}\varphi_0\mathrm{d}\sigma_x$$

for all $\varphi_0\in C^\infty(\Omega)$.

- With theorem 5 we deduce that $C_{e,\varepsilon}$ converges strongly in $L^2([0,T]\times\Gamma^1)$ and we find

$$\lim_{\varepsilon\to 0}\int_{\Gamma^1}\chi^{\mathrm{ER}}\left(\frac{x}{\varepsilon}\right)k_C^+ f_e(C_{e,\varepsilon})S_{O,\varepsilon}\varphi_\varepsilon\mathrm{d}x = \int_{\Gamma^1}\int_{\partial_o Y^{\mathrm{ER}}}k_C^+ f_e(C_{e,0})S_{O,0}\varphi_0\mathrm{d}\sigma_y\mathrm{d}\sigma_x$$

for all $\varphi_0\in C^\infty(\Omega)$.

For the following homogenization process we use the just derived limits of the nonlinear terms and on the boundaries. As test functions $\varphi_\varepsilon\in C^\infty(\Omega, C^\infty_\#(Y))$ we choose functions of the form

$$\varphi_\varepsilon\left(x,\frac{x}{\varepsilon}\right)=\varphi_0(x)+\varepsilon\varphi_1\left(x,\frac{x}{\varepsilon}\right)$$

with $(\varphi_0,\varphi_1)\in C^\infty(\Omega)\times C^\infty(\Omega, C^\infty_\#(Y))$.

Limit equation for C_ε and $C_{e,\varepsilon}$
We have the equation

$$\int_\Omega\chi^1\left(\frac{x}{\varepsilon}\right)\partial_t C_\varepsilon\varphi_\varepsilon\mathrm{d}x + D_C\int_\Omega\chi^1\left(\frac{x}{\varepsilon}\right)\nabla C_\varepsilon\nabla\varphi_\varepsilon\mathrm{d}x+\varepsilon\int_{\Gamma_\varepsilon^{\mathrm{ER}}}((L_0+L_{\mathrm{IP3}})(C_\varepsilon-C_{e,\varepsilon})+f_{\mathrm{SERCA}}(C_\varepsilon))\varphi_\varepsilon\mathrm{d}\sigma_x$$
$$+\int_{\Gamma^1}\chi^1\left(\frac{x}{\varepsilon}\right)I_{\mathrm{CRAC}}(S_{O,\varepsilon})\varphi_\varepsilon\mathrm{d}\sigma_x+\int_{\Gamma^1}\chi^1\left(\frac{x}{\varepsilon}\right)(f_P(C_\varepsilon)+f_{\mathrm{NCX}}(C_\varepsilon))\varphi_\varepsilon\mathrm{d}\sigma_x=0$$

for all admissible test functions $\varphi_\varepsilon\in C^\infty(\Omega, C^\infty_\#(Y))$. For $\varepsilon\to 0$ we get

$$\int_\Omega\int_{Y^1}\partial_t C_0\varphi_0\mathrm{d}y\mathrm{d}x + D_C\int_\Omega\int_{Y^1}[\nabla_x C_0+\nabla_y C_1][\nabla_x\varphi_0+\nabla_y\varphi_1]\mathrm{d}y\mathrm{d}x$$
$$+\int_\Omega\int_{\Gamma^{\mathrm{ER}}}((L_0+L_{\mathrm{IP3}})(C_0-C_{e,0})+f_{\mathrm{SERCA}}(C_0))\varphi_0\mathrm{d}y\mathrm{d}x+\int_{\Gamma^1}\int_{\partial_o Y^1}I_{\mathrm{CRAC}}(S_{O,0})\varphi_0\mathrm{d}\sigma_y\mathrm{d}\sigma_x$$
$$+|\partial_o Y^1|\int_{\Gamma^1}(f_P(C_0)+f_{\mathrm{NCX}}(C_0))\varphi_0\mathrm{d}\sigma_x=0$$

for all $(\varphi_0,\varphi_1)\in C^\infty(\Omega)\times C^\infty(\Omega, C^\infty_\#(Y))$, where $C_0\in L^2([0,T],H^1(\Omega))$ and $C_1\in L^2([0,T],L^2(\Omega,H^1_\#(Y^1)))$.

Analogously we find for $\varepsilon \to 0$

$$\int_\Omega \int_{Y^2} \partial_t C_{e,0} \varphi_0 \mathrm{d}y \mathrm{d}x + D_{\mathrm{ER}} \int_\Omega \int_{Y^2} [\nabla_x C_{e,0} + \nabla_y C_{e,1}][\nabla_x \varphi_0 + \nabla_y \varphi_1] \mathrm{d}y \mathrm{d}x \\ + \int_\Omega \int_{\Gamma^{\mathrm{ER}}} ((L_0 + L_{\mathrm{IP3}})(C_{e,0} - C_0) - f_{\mathrm{SERCA}}(C_0))\varphi_0 \mathrm{d}y \mathrm{d}x = 0$$

for all $(\varphi_0, \varphi_1) \in C^\infty(\Omega) \times C^\infty(\Omega, C^\infty_\#(Y))$, where $C_{e,0} \in L^2([0,T], H^1(\Omega))$ and $C_{e,1} \in L^2([0,T], L^2(\Omega, H^1_\#(Y^2)))$.

Limit equation for S_ε and $S_{C,\varepsilon}$
We have

$$\int_\Omega \chi^{\mathrm{ER}}\left(\frac{x}{\varepsilon}\right) \partial_t S_\varepsilon \varphi_\varepsilon \mathrm{d}x + D_S \int_\Omega \chi^{\mathrm{ER}}\left(\frac{x}{\varepsilon}\right) \nabla S_\varepsilon \nabla \varphi_\varepsilon \mathrm{d}x \\ + \int_\Omega \chi^{\mathrm{ER}}\left(\frac{x}{\varepsilon}\right) (k_C^+ f_e(C_{e,\varepsilon}) S_\varepsilon - k_C^- S_{C,\varepsilon})\varphi_\varepsilon \mathrm{d}x + \int_{\Gamma^1} \chi^{\mathrm{ER}}\left(\frac{x}{\varepsilon}\right) (k_O^+ S_\varepsilon - k_O^- S_{O,\varepsilon})\varphi_\varepsilon \mathrm{d}\sigma_x = 0$$

for all $\varphi_\varepsilon \in C^\infty(\Omega, C^\infty_\#(Y))$. For $\varepsilon \to 0$ we get

$$\int_\Omega \int_{Y^{\mathrm{ER}}} \partial_t S_0 \varphi_0 \mathrm{d}y \mathrm{d}x + D_S \int_\Omega \int_{Y^{\mathrm{ER}}} [\nabla_x S_0 + \nabla_y S_1][\nabla_x \varphi_0 + \nabla_y \varphi_1] \mathrm{d}y \mathrm{d}x \\ \int_\Omega \int_{Y^{\mathrm{ER}}} (k_C^+ f_e(C_{e,0}) S_0 - k_C^- S_{C,0})\varphi_0 \mathrm{d}y \mathrm{d}x + \int_{\Gamma^1} \int_{\partial_o Y^{\mathrm{ER}}} k_O^+ S_0 \varphi_0 \mathrm{d}\sigma_y \mathrm{d}\sigma_x \\ - \int_{\Gamma^1} \int_{\partial_o Y^{\mathrm{ER}}} k_O^- S_{O,0} \varphi_0 \mathrm{d}\sigma_y \mathrm{d}\sigma_x = 0$$

for all $(\varphi_0, \varphi_1) \in C^\infty(\Omega) \times C^\infty(\Omega, C^\infty_\#(Y))$, where $S_0 \in L^2([0,T], H^1(\Omega))$ and $S_1 \in L^2([0,T], L^2(\Omega, H^1_\#(Y^{\mathrm{ER}})))$.
Analogously we obtain

$$\int_\Omega \int_{Y^{\mathrm{ER}}} \partial_t S_{C,0} \varphi_0 \mathrm{d}y \mathrm{d}x + D_{SC} \int_\Omega \int_{Y^{\mathrm{ER}}} [\nabla_x S_{C,0} + \nabla_y S_{C,1}][\nabla_x \varphi_0 + \nabla_y \varphi_1] \mathrm{d}y \mathrm{d}x \\ \int_\Omega \int_{Y^{\mathrm{ER}}} (k_C^- S_{C,0} - k_C^+ f_e(C_{e,0}) S_0)\varphi_0 \mathrm{d}y \mathrm{d}x + \int_{\Gamma^1} \int_{\partial_o Y^{\mathrm{ER}}} k_{CO}^+ S_{C,0} \varphi_0 \mathrm{d}\sigma_y \mathrm{d}\sigma_x \\ - \int_{\Gamma^1} \int_{\partial_o Y^{\mathrm{ER}}} k_{CO}^- S_{CO,0} \varphi_0 \mathrm{d}\sigma_y \mathrm{d}\sigma_x = 0$$

for all $(\varphi_0, \varphi_1) \in C^\infty(\Omega) \times C^\infty(\Omega, C^\infty_\#(Y))$, where $S_{C,0} \in L^2([0,T], H^1(\Omega))$ and
$S_{C,1} \in L^2([0,T], L^2(\Omega, H^1_\#(Y^{\mathrm{ER}})))$.

Now we consider the functions $S_{O,\varepsilon}$ and $S_{CO,\varepsilon}$ which are only defined on the boundary $\Gamma^1 \cap \partial\Omega_\varepsilon^{\mathrm{ER}}$ and homogenization takes place in one dimension less.

Limit equation for $S_{O,\varepsilon}$ and $S_{CO,\varepsilon}$
The equation for $S_{O,\varepsilon}$ is given by

$$\int_{\Gamma^1} \chi^{\mathrm{ER}}\left(\frac{x}{\varepsilon}\right) \partial_t S_{O,\varepsilon} \varphi_\varepsilon \mathrm{d}\sigma_x + \int_{\Gamma^1} \chi^{\mathrm{ER}}\left(\frac{x}{\varepsilon}\right) (k_O^- S_{O,\varepsilon} - k_O^+ S_\varepsilon - k_C^- S_{CO,\varepsilon} + k_C^+ f_e(C_{e,\varepsilon}) S_{O,\varepsilon})\varphi_\varepsilon \mathrm{d}\sigma_x = 0$$

for all $\varphi_\varepsilon \in C^\infty(\Gamma^1, C^\infty_\#(\partial Y))$. For $\varepsilon \to 0$ we get

$$\int_{\Gamma^1} \int_{\partial_o Y^{\mathrm{ER}}} \partial_t S_{O,0} \varphi_0 \mathrm{d}\sigma_y \mathrm{d}\sigma_x \\ + \int_{\Gamma^1} \int_{\partial_o Y^{\mathrm{ER}}} (k_O^- S_{O,0} - k_O^+ S_0 - k_C^- S_{CO,0} + k_C^+ f_e(C_{e,0}) S_{O,0})\varphi_0 \mathrm{d}\sigma_y \mathrm{d}\sigma_x = 0$$

for all $\varphi_0 \in C^\infty(\Gamma^1, C^\infty_\#(\partial_o Y))$, where $S_{O,0} \in L^2([0,T], L^2(\Gamma^1, L^2(\partial_o Y^{\mathrm{ER}})))$.

Analogously we obtain

$$\int_{\Gamma^1}\int_{\partial_o Y^{\mathrm{ER}}} \partial_t S_{CO,0}\varphi_0 \mathrm{d}\sigma_y \mathrm{d}\sigma_x \\ + \int_{\Gamma^1}\int_{\partial_o Y^{\mathrm{ER}}} (k^-_{CO} S_{CO,0} - k^+_{CO} S_{C,0} + k^-_C S_{CO,0} - k^+_C f_e(C_{e,0}) S_{O,0})\varphi_0 \mathrm{d}\sigma_y \mathrm{d}\sigma_x = 0$$

for $\varepsilon \to 0$ for all $\varphi_0 \in C^\infty(\Gamma^1, C^\infty_\#(\partial_o Y))$, where $S_{CO,0} \in L^2([0,T], L^2(\Gamma^1, L^2(\partial_o Y^{\mathrm{ER}})))$.

Weak formulation of the homogeneous model

Now we consider the y-dependence of the functions and summarize some terms. Because the functions $C_{e,0}$, S_0 and $S_{C,0}$ and the initial conditions $S_{O,0}(0)$ and $S_{CO,0}(0)$ are y-independent and $S_{O,0}, S_{CO,0}$ are given by ordinary differential equations, also $S_{O,0}$ and $S_{CO,0}$ are y-independent and we simplify the just found equations to the following weak system of equations.

Let $(C_0, C_{e,0}, S_0, S_{C,0}, S_{O,0}, S_{CO,0}) \in \mathcal{V}(\Omega)^4 \times \mathcal{V}(\Gamma^1)^2$ and $(C_1, C_{e,1}, S_1, S_{C,1}) \in \mathcal{V}(\Omega, Y)$ such that

$$|Y^1|(\partial_t C_0, \varphi_0)_\Omega + D_C(\nabla_x C_0 + \nabla_y C_1, \nabla_x \varphi_0 + \nabla_y \varphi_1)_{\Omega\times Y^1} \\ + |\Gamma^{\mathrm{ER}}|((L_0 + L_{\mathrm{IP3}})(C_0 - C_{e,0}) + f_{\mathrm{SERCA}}(C_0), \varphi_0)_\Omega \\ + \langle \alpha I_{\mathrm{CRAC}}(S_{O,0}), \varphi_0\rangle_{\Gamma^1\times\partial_o Y^1} + |\partial_o Y^1| \langle f_P(C_0) + f_{\mathrm{NCX}}(C_0), \varphi_0\rangle_{\Gamma^1} = 0,$$

$$|Y^2|(\partial_t C_{e,0}, \varphi_0)_\Omega + D_{\mathrm{ER}}(\nabla_x C_{e,0} + \nabla_y C_{e,1}, \nabla_x \varphi_0 + \nabla_y \varphi_1)_{\Omega\times Y^2} \\ + |\Gamma^{\mathrm{ER}}|((L_0 + L_{\mathrm{IP3}})(C_{e,0} - C_0) - f_{\mathrm{SERCA}}(C_0), \varphi_0)_\Omega = 0,$$

$$|Y^{\mathrm{ER}}|(\partial_t S_0, \varphi_0)_\Omega + D_S(\nabla_x S_0 + \nabla_y S_1, \nabla_x \varphi_0 + \nabla_y \varphi_1)_{\Omega\times Y^{\mathrm{ER}}} \\ + |Y^{\mathrm{ER}}|(k^+_C f_e(C_{e,0}) S_0 - k^-_C S_{C,0}, \varphi_0)_\Omega \\ + |\partial_o Y^{\mathrm{ER}}| \langle k^+_O S_0 - k^-_O S_{O,0}, \varphi_0\rangle_{\Gamma^1} = 0,$$

$$|Y^{\mathrm{ER}}|(\partial_t S_{C,0}, \varphi_0)_\Omega + D_S(\nabla_x S_{C,0} + \nabla_y S_{C,1}, \nabla_x \varphi_0 + \nabla_y \varphi_1)_{\Omega\times Y^{\mathrm{ER}}} \\ + |Y^{\mathrm{ER}}|(k^-_C S_{C,0} - k^+_C f_e(C_{e,0}) S_0, \varphi_0)_\Omega \\ + |\partial_o Y^{\mathrm{ER}}| \langle k^+_{CO} S_{C,0} - k^-_{CO} S_{CO,0}, \varphi_0\rangle_{\Gamma^1} = 0,$$

$$\langle \partial_t S_{O,0}, \varphi_0\rangle_{\Gamma^1} + \langle k^-_O S_{O,0} - k^+_O S_0 - k^-_C S_{CO,0} + k^+_C f_e(C_{e,0}) S_{O,0}, \varphi_0\rangle_{\Gamma^1} = 0,$$

$$\langle \partial_t S_{CO,0}, \varphi_0\rangle_{\Gamma^1} + \langle k^-_{CO} S_{CO,0} - k^+_{CO} S_{C,0} + k^-_C S_{CO,0} - k^+_C f_e(C_{e,0}) S_{O,0}, \varphi_0\rangle_{\Gamma^1} = 0,$$

for all $\varphi_0 \in C^\infty(\Omega)$ and $\varphi_1 \in C^\infty(\Omega, C^\infty_\#(Y))$.

The next step is to shrink the blown up membrane Y^{ER} back to Γ^{ER}. From now on, we rename the functions $(C_0, C_{e,0}, S_0, S_{C,0}, S_{O,0}, S_{CO,0})$ by $(C, C_e, S, S_C, S_O, S_{CO})$ to avoid confusion.

8. Identification of the Calcium–Stim1 limit model

It is our aim to let Y^{ER} tend to Γ^{ER} as described in section 2. We use the two-step convergence and Theorem 1 for the functions S and S_C. The condition that Γ^{ER} is a smooth manifold and that $Y^{\mathrm{ER}} = \{p + dn_p |\ p \in \Gamma^{\mathrm{ER}}, d \in (-\delta, \delta)\}$ needs to be satisfied, where n_p is the outer normal in $p \in \Gamma^{\mathrm{ER}}$. This also implies $\partial_o Y^{\mathrm{ER}} = \{p + dn_p |\ p \in \partial_o \Gamma^{\mathrm{ER}}, d \in (-\delta, \delta)\}$.

First we consider the behavior of the functions S and S_C. The functions S_O and S_{CO} are hardly influenced by the δ-limit formation since we divided the corresponding equations by $|\partial_o Y^{\mathrm{ER}}|$. Then, we consider the impact of the limit formation for δ tending to zero for the functions C and C_e.

δ-limit for the equations for S and S_C
We are able to easily use the two-step convergence and Theorem 1, because the equations for S and S_C have the same form as used in Theorem 1. For equations of this form, boundedness independently of δ and limit passage are proven and performed in the proof of Theorem 1 and we deduce that

$$|\Gamma^{\mathrm{ER}}| \int_\Omega \partial_t S \varphi_0 \mathrm{d}x + \int_\Omega \sum_{i,j} \partial_{x_j} S \underbrace{D_S \int_{\Gamma^{\mathrm{ER}}} (P_\Gamma(e_j + \nabla_\Gamma \mu_j^S))_i \mathrm{d}\sigma_y}_{=P_{ij}^S} \partial_{x_i}\varphi_0 \mathrm{d}x$$
$$+ |\Gamma^{\mathrm{ER}}| \int_\Omega (k_C^+ f_e(C_e) S - k_C^- S_C)\varphi_0 \mathrm{d}x + |\partial_o \Gamma^{\mathrm{ER}}| \int_{\Gamma^1} (k_O^+ S - k_O^- S_O)\varphi_0 \mathrm{d}\sigma_x = 0$$

with

$$\begin{aligned} \nabla_\Gamma \cdot \big(P_\Gamma(e_j + \nabla_\Gamma \mu_j^S)\big) &= 0 \qquad \text{in } \Gamma^{\mathrm{ER}} \\ P_\Gamma(e_j + \nabla_\Gamma \mu_j^S) \cdot n &= 0 \qquad \text{on } \partial\Gamma^{\mathrm{ER}}, \end{aligned}$$

and μ_j^S being Y-periodic, where $S_1 = \sum_{i=1}^n \nabla_{x_i} S \mu_i^S$. Analogously we find the δ-limit for the equation for S_C.

δ-limit for the other functions
The cell problem of the equation for C is found by standard approach, see [18]. We find that $C_1 = \sum_{j=1}^n \partial_{x_j} C(x,t)\mu_j^C(y)$ with μ_j^C satisfying

$$\begin{aligned} \nabla_y \cdot D_C(e_j + \nabla_y \mu_j^C) &= 0 \qquad \text{in } Y^1, \\ D_C(e_j + \nabla_y \mu_j^C) \cdot n &= 0 \qquad \text{on } \Gamma^{\mathrm{ER}}, \end{aligned}$$

and μ_j^C must be Y-periodic for $j = 1, \ldots, n$. Further, we define the diffusion tensor $P_{ij}^C := \int_{Y^1} D_C(\delta_{ij} + \partial_{y_i}\mu_j^C)\mathrm{d}y$.

Analogously, we find for the cell problem of the equation for C_e the functions μ_j^e such that $C_{e,1} = \sum_{j=1}^n \partial_{x_j} C_e(x,t)\mu_j^e(y)$ with μ_j^e satisfying the cell problem

$$\begin{aligned} \nabla_y \cdot D_{\mathrm{ER}}(e_j + \nabla_y \mu_j^e) &= 0 \qquad \text{in } Y^2, \\ D_{\mathrm{ER}}(e_j + \nabla_y \mu_j^e) \cdot n &= 0 \qquad \text{on } \Gamma^{\mathrm{ER}}, \end{aligned}$$

and μ_j^e must be Y-periodic for $j = 1, \ldots, n$. Further, we define the diffusion tensor $P_{ij}^{\mathrm{ER}} := \int_{Y^2} D_{\mathrm{ER}}(\delta_{ij} + \partial_{y_i}\mu_j^e)\mathrm{d}y$.

Then, we obtain (7) as the final macroscopic problem after homogenization and $\delta \to 0$.

9. Uniqueness of the limit model

We conclude by showing that there exists just one solution of the limit model (7).

Theorem 15. (Uniqueness)
There exists at most one solution for the limit model (7).

Proof. First we note that the tensors P^C, P^e and P^S are unique, see [18] for details. To show uniqueness of the model (7), we assume there are two solutions
$(C_1, C_{e,1}, S_1, S_{C,1}, S_{O,1}, S_{CO,1})$ and $(C_2, C_{e,2}, S_2, S_{C,2}, S_{O,2}, S_{CO,2})$ of the system of equations (7) with the

same initial values. Starting with the equation for C_1 and C_2, we test the weak formulations with $\varphi = C_1 - C_2$ and subtract the two results.

$$\begin{aligned} |Y^1|(\partial_t(C_1 - C_2), C_1 - C_2)_\Omega + (P^C(\nabla C_1 - \nabla C_2), \nabla C_1 - \nabla C_2)_\Omega \\ + |\Gamma^{\mathrm{ER}}|(L_0 + L_{\mathrm{IP3}})(C_1 - C_2 - (C_{e,1} - C_{e,2}), C_1 - C_2)_\Omega \\ + \underbrace{|\Gamma^{\mathrm{ER}}|(f_{\mathrm{SERCA}}(C_1) - f_{\mathrm{SERCA}}(C_2), C_1 - C_2)_\Omega}_{\geq 0,\ \text{since } f_{\mathrm{SERCA}} \text{ monotone, increasing}} \\ + \alpha(I_{\mathrm{CRAC}}(S_{O,1}) - I_{\mathrm{CRAC}}(S_{O,2}), C_1 - C_2)_{\Gamma^1 \times \partial_o Y^1} \\ + \underbrace{|\partial_o Y^1|(f_P(C_1) + f_{\mathrm{NCX}}(C_1) - f_P(C_2) - f_{\mathrm{NCX}}(C_2), C_1 - C_2)_\Omega}_{\geq 0,\ \text{since } f_p,\ f_{\mathrm{NCX}} \text{ monotone, increasing}} = 0. \end{aligned}$$

Integrating from 0 to t gives

$$\begin{aligned} \frac{1}{2}|Y^1| \|C_1 - C_2\|_\Omega^2 + \|\sqrt{P^C}\nabla(C_1 - C_2)\|_{\Omega,t}^2 \\ \leq |\Gamma^{\mathrm{ER}}|(L_0 + L_{\mathrm{IP3}}) \left|(C_{e,1} - C_{e,2}, C_1 - C_2)_\Omega\right| + |\partial_o Y^1| \alpha L_{\mathrm{CRAC}} \left|(S_{O,1} - S_{O,2}, C_1 - C_2)_{\Gamma^1,t}\right|, \end{aligned}$$

where we used that I_{CRAC} is Lipschitz-continuous. The initial conditions for C_1 and C_2 cancel each other. Next, we use the binomial theorem with a factor λ and the trace inequality. We merge the constants leading to

$$\begin{aligned} \frac{1}{2}|Y^1| \|C_1 - C_2\|_\Omega^2 + (P^C - c_5\lambda)\|\nabla(C_1 - C_2)\|_{\Omega,t}^2 \\ \leq c_1 \|C_{e,1} - C_{e,2}\|_{\Omega,t}^2 + c_2\|C_1 - C_2\|_{\Omega,t}^2 + c_3\|S_{O,1} - S_{O,2}\|_{\Gamma^1,t}^2. \end{aligned}$$

We perform a similar estimation for C_e, S, S_C, S_O and S_{CO}. With Gronwall's lemma we deduce that

$$\begin{aligned} \|C_1 - C_2\|_\Omega^2 + \|C_{e,1} - C_{e,2}\|_\Omega^2 + \|S_1 - S_2\|_\Omega^2 + \|S_{C,1} - S_{C,2}\|_\Omega^2 \\ + \|S_{O,1} - S_{O,2}\|_{\Gamma^1}^2 + \|S_{CO,1} - S_{CO,2}\|_{\Gamma^1}^2 \leq 0 \end{aligned}$$

and uniqueness of the solution of system (7) holds.

□

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