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

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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, $\delta$ 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 $\delta$ tend to

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zero, making sure the macroscopic equation and the cell problem satisfy some compactness results. A similar approach using $\Gamma$-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 $\delta$ 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 $\mathbb{R}^n$ with positive volume. After homogenization the limit equation is defined on the homogeneous domain $\Omega$ 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 $\delta$ tend to zero in the unit cell $Y$ of the homogenized system. A similar idea using $\Gamma$-convergence is found in [7, 6].

2.1. A generic problem

Let $\Omega \subset \mathbb{R}^n$ be a domain and $\Gamma \subset Y = [0, 1]^n$ be a smooth, compact and periodic hypersurface, such that $\Gamma_\varepsilon = \bigcup_{k \in \mathbb{Z}^n} \varepsilon (k + \Gamma)$ is smooth and connected for a small parameter $0 < \varepsilon \ll 1$. We define $Y_\varepsilon = \{ y + d n_y | y \in \Gamma, d \in (-\delta, \delta) \} \subset Y$ 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 $h \in C(\partial \Omega, C_\#(\partial_\varepsilon Y))$ with $h_\varepsilon(x) := h(x, \frac{x}{\varepsilon})$, where $\partial_\varepsilon Y$ is one side of the outer boundary of $Y$. The index $\#$ of the function space denotes periodicity of the contained functions. Furthermore, let $\Omega_\varepsilon = \bigcup_{k \in \mathbb{Z}^n} \varepsilon (k + Y_\delta) \cap \Omega$ and $u_\varepsilon$ be the solution of the initial boundary value problem

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

(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

\[
|Y^\delta| \left| \int_\Omega \partial_t u^\delta \psi dx + D \int_\Omega \int_{Y^\delta} [\nabla_x u^\delta + \nabla_y u_1^\delta] [\nabla_x \psi + \nabla_y \psi_1] dy dx \right.
\]

\[
+ |Y^\delta| \left| \int_\Omega u^\delta \psi dx + \int_{\partial\Omega} \int_{\partial_\delta Y^\delta} a(u^\delta - h)\psi d\sigma_y d\sigma_x = \int_\Omega \int_{Y^\delta} f\psi dy dx \right. \tag{2}
\]

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

\[
D \int_\Omega \sum_{k=1}^n \partial_{x_k} u^\delta \int_{Y^\delta} [\varepsilon_k + \nabla_y u_k^\delta] \nabla_y \psi_1 dy dx = 0. \tag{3}
\]

The scalar product and norm on \( L^2(\Omega) \) is given by \( (v, w)_\Omega = \int_\Omega v w dx \) 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 \( \delta \) 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

\[
|\Gamma| \int_\Omega \partial_t u \psi dx + \int_\Omega P \nabla_x u \nabla_x \psi dx + |\Gamma| \int_\Omega u \psi dx + \int_{\partial \Gamma} a u \psi d\sigma_x
\]

\[
= \int_\Omega \int_\Gamma f \psi d\sigma_y d\sigma_x + \int_{\partial \Omega} \int_{\partial_\Gamma} a h \psi d\sigma_y d\sigma_x \tag{4}
\]

with \( P_{ij} = D \int_\Gamma (P_T(e_j + \nabla \Gamma \mu_j)) d\sigma_y \) for \( i, j = 1, \ldots, n \) and \( \mu_j \) satisfying

\[
\nabla \Gamma \cdot (P_T(e_j + \nabla \Gamma \mu_j)) = 0 \quad \text{in} \quad \Gamma,
\]

\[
P_T(e_j + \nabla \Gamma \mu_j) \cdot n = 0 \quad \text{on} \quad \partial \Gamma, \tag{5}
\]

with \( \mu_j \) being \( Y \)-periodic. Here, \( P_T \) is the orthogonal projection to \( \Gamma \).

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

\[
\alpha_\lambda^{-1} : V_\lambda \times (-\delta, \delta) \to U_\lambda
\]

\[
\alpha_\lambda^{-1}(\xi_1, \ldots, \xi_{n-1}, \xi_n) = \tilde{\alpha}_\lambda^{-1}(\xi_1, \ldots, \xi_{n-1}) + \xi_n n_y.
\]

\[ \varepsilon \]

\[ \delta \]

\[ \alpha \]

\[ \gamma \]

\[ \delta \]

\[ \delta \]

\[ \gamma \]
Note that the last component of the local coordinates affects just the normal direction of \(\Gamma\), which yields for the Riemannian metric tensor \(g_{ij}\), \(i, j = 1, \ldots, n\) that \(g_{ii} = g_{11} = 0\) for \(i = 1, \ldots, n - 1\),
where \(g^{ij}\), \(i, j = 1, \ldots, n\) are the components of the inverse of the matrix \((g_{ij})_{i,j=1,\ldots,n}\). The \(n\)th basis vector is given by

\[
\frac{d}{d\xi^n} = \frac{d}{dt}igg|_{t=0} \alpha^{-1}_n(\xi + t\varepsilon_n) = \frac{d}{dt}igg|_{t=0} \left(\alpha^{-1}_n(\xi_1, \ldots, \xi_{n-1}) + (\xi_n + t)n_y\right) = n_y
\]

and consequently, \(g_{nn} = n_n^Tn_y = 1\). 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 \(\Gamma\), which means that the basis vectors \(\frac{d}{d\xi^i}, i = 1, \ldots, n\) are orthogonal.

Note that \(g_{ii} = \left\langle \frac{d}{d\xi^i}, \frac{d}{d\xi^i} \right\rangle > 0\). The gradient of a function \(\mu : Y^\delta \to \mathbb{R}\) in \(U_\lambda\) in new coordinates is given by

\[
\nabla \mu = \sum_{i=1}^n g^{ij} \frac{\partial (\mu \circ \alpha^{-1}_i)}{\partial \xi^j} \frac{d}{d\xi^i}.
\]

The divergence on \(Y^\delta\) of a function \(\mu : Y^\delta \to \mathbb{R}^n\) in new coordinates is given by

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

Here \(\mu^i\) is the \(i\)th component of \(\mu\) in the basis vectors \(\frac{d}{d\xi^i}\).

**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 \(\delta\) 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 \(\delta\) dependence of the functions \(\psi\) and \(u_1\) by \(u^\delta\) and \(u^\delta_1\).

**Step 1. Boundedness of \(\|\nabla \mu\|\|Y^\delta\|\).**

Testing the cell problem, equation (3), with \(\psi_1 = \mu^\delta_k\) for every \(k = 1, \ldots, n\), leads to

\[
\int_{\Omega} \int_{Y^\delta} \nabla_y \mu^\delta_k \nabla_y \mu^\delta_k \, dy \, dx = -\int_{\Omega} \int_{Y^\delta} e_k \nabla_y \mu^\delta_k \, dy \, dx \leq \|e_k\|_{\Omega \times Y^\delta} \|\nabla_y \mu^\delta_k\|_{\Omega \times Y^\delta} = \sqrt{|\Omega| \cdot |Y^\delta|} \|\nabla_y \mu^\delta_k\|_{\Omega \times Y^\delta},
\]

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

\[
\frac{1}{|\Omega| \cdot |Y^\delta|} \|\nabla_y \mu^\delta_k\|_{\Omega \times Y^\delta}^2 \leq 1,
\]

which means that the norm of \(\nabla_y \mu^\delta_k\) remains bounded independently of the size of the domain \(Y^\delta\), since \(|Y^\delta| \leq 1\).

**Boundedness of \(\|\nabla_x u^\delta + \nabla_y u^\delta_1\|_{\Omega \times Y^\delta}\).**

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 \(2\delta|\partial \chi|\) in their first order approximation, respectively.

\[
(2\delta|\Gamma| + O(\delta^2)) \int_{\Omega} \partial_t u^\delta \psi \, dx + D \int_{\Omega \times Y^\delta} \left[ \nabla_x u^\delta + \nabla_y u^\delta_1 \right] [\nabla_x \psi + \nabla_y \psi_1] \, dy \, dx \\
\quad + (2\delta|\Gamma| + O(\delta^2)) \int_{\Omega} u^\delta \psi \, dx + a(2\delta|\partial \chi| + O(\delta^2)) \int_{\partial \Omega} u^\delta \psi \, d\sigma_x \\
\quad = \int_{\Omega} \int_{V \times (-\delta, \delta)} f \psi \sqrt{\det g} \, dx \, dy \, d\xi + \int_{\partial \Omega} \int_{\partial \chi \times (-\delta, \delta)} h \psi \sqrt{\det g} \, d\sigma_x \, d\xi \, d\sigma_x
\]
for all \((\psi, \psi_1) \in H^1(\Omega) \times L^2(\Omega, H^1_\#(Y^s))\). Now we test with the functions \(\psi = u^\delta\) and \(\psi_1 = u_1^\delta\),

\[
(2|\Gamma| + O(\delta^2)) \int_\Omega \partial_t u^\delta u^\delta \, dx + D\|\nabla_x u^\delta + \nabla_y u^\delta\|_{\Omega \times Y^s}^2 \\
+ (2|\Gamma| + O(\delta^2))\|u^\delta\|_{\Omega}^2 + a(2|\partial_t \Gamma| + O(\delta^2))\|u^\delta\|_{\Omega}^2 \\
= \int_\Omega u^\delta \int_{V \times (-\delta, \delta)} f \sqrt{\det g} d\xi \, dd\xi + \int_{\partial_0 V \times (-\delta, \delta)} h \sqrt{\det g} \sigma_{\xi} \, dd\sigma \, dx
\]
Furthermore, we substitute \((\xi_1, \ldots, \xi_{n-1}, \xi_n) = z = (z_1, \ldots, z_n-1, z_n)\), with 
\(d\xi = d\xi_1 \ldots d\xi_n = dz_1 \ldots dz_{n-1} \delta dz_n\), and continue with 

\[
(2|\Gamma| + O(\delta^2)) \int_\Omega \partial_t u^\delta u^\delta \, dx + D\|\nabla_x u^\delta + \nabla_y u^\delta\|_{\Omega \times Y^s}^2 \\
+ (2|\Gamma| + O(\delta^2))\|u^\delta\|_{\Omega}^2 + a(2|\partial_t \Gamma| + O(\delta^2))\|u^\delta\|_{\Omega}^2 \\
= \delta \int_\Omega u^\delta \int_{V \times (-1, 1)} f \sqrt{\det g} dz \, ddz + \delta \int_{\partial_0 V \times (-1, 1)} u^\delta \int_{\partial_0 V \times (-1, 1)} h \sqrt{\det g} dz \sigma dz \, dx \, ddz
\]
and divide by \(\delta\) to find

\[
(2|\Gamma| + O(\delta)) \int_\Omega \partial_t u^\delta u^\delta \, dx + \frac{1}{\delta} D\|\nabla_x u^\delta + \nabla_y u^\delta\|_{\Omega \times Y^s}^2 \\
+ (2|\Gamma| + O(\delta))\|u^\delta\|_{\Omega}^2 + a(2|\partial_t \Gamma| + O(\delta))\|u^\delta\|_{\Omega}^2 \\
\leq \frac{1}{2}|u^\delta|_{\Omega}^2 + \frac{1}{2} \int_{V \times (-1, 1)} f \sqrt{\det g} dz \, ddz \\
+ \frac{1}{2\lambda}|u^\delta|_{\Omega}^2 + \frac{\lambda}{2} \int_{\partial_0 V \times (-1, 1)} h \sqrt{\det g} dz \sigma dz \, dx \, ddz
\]
for any \(\lambda > 0\). This yields, after integration with respect to time,

\[
(2|\Gamma| + O(\delta)) \frac{1}{2}|u^\delta|_{\Omega}^2 + \frac{1}{\delta} D\|\nabla_x u^\delta + \nabla_y u^\delta\|_{\Omega \times Y^s, t}^2 + (2|\Gamma| + O(\delta))\|u^\delta\|_{\Omega, t}^2 \\
+ \left( a(2|\partial_t \Gamma| + O(\delta)) - \frac{1}{2\lambda} \right)\|u^\delta\|_{\Omega, t}^2 \leq c_1 + c_2 \frac{\lambda}{2} + \frac{1}{2}|u(0)|_{\Omega}^2 + \frac{1}{2}|u(0)|_{\Omega}^2,
\]
where we choose \(\lambda\) such that \(\lambda > \frac{C}{\|\partial_t \Gamma\|_{\Omega}}\), but finite. The constants \(c_1, c_2\) and \(\lambda\) are independent of \(\delta\). We find with Gronwall’s lemma that

\[
(2|\Gamma| + O(\delta)) \frac{1}{2}|u^\delta|_{\Omega}^2 + \frac{1}{\delta} D\|\nabla_x u^\delta + \nabla_y u^\delta\|_{\Omega \times Y^s, t}^2 + (2|\Gamma| + O(\delta))\|u^\delta\|_{\Omega, t}^2 \\
+ \left( a(2|\partial_t \Gamma| + O(\delta)) - \frac{1}{2\lambda} \right)\|u^\delta\|_{\Omega, t}^2 \leq C
\]
for a constant \(C > 0\) independent of \(\delta\).

**Step 2. Limit of the linear terms.**

Now, with \(u^\delta\) 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,

\[
(2|\Gamma| + O(\delta)) \int_\Omega \partial_t u^\delta \psi \, dx \to 2|\Gamma| \int_\Omega \partial_t u \psi \, dx.
\]
It also easily follow that
\[
(2|\Gamma| + O(\delta)) \int_{\Omega} u^s \psi dx \xrightarrow{\delta \to 0} 2|\Gamma| \int_{\Omega} u \psi dx.
\]

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.

\[
\frac{1}{\delta} D \int_{\Omega} \int_{Y^s} [\nabla_x u^\delta + \nabla_y u^\delta] [\nabla_x \psi + \nabla_y \psi_1] d\gamma d\delta
\]

\[
= \frac{1}{\delta} D \int_{\Omega} \int_{V \times (-\delta, \delta)} \left[ \nabla_x u^\delta + \sum_{k=1}^n \partial_{\xi_k} u^\delta \sum_{i=1}^n g^{ij} \frac{\partial (\mu_k^\delta \circ \alpha^{-1})}{\partial \xi_i} \frac{d}{d\xi^j} \right]
\]

\[
\left[ \nabla_x \psi + \sum_{j=1}^n g^{ij} \frac{\partial (\psi_1 \circ \alpha^{-1})}{\partial \xi_k} \frac{d}{d\xi^j} \right] \sqrt{\det g d\xi} dx.
\]

We substitute \((\xi_1, \ldots, \xi_{n-1}, \xi_n) = z = (z_1, \ldots, z_{n-1}, z_n)\), with
d\xi = d\xi_1 \ldots d\xi_n = dz_1 \ldots dz_{n-1} \delta dz_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

\[
\frac{1}{\delta} D \int_{\Omega} \int_{V \times (-1, 1)} \left[ \nabla_x u^\delta + \sum_{k=1}^n \partial_{\xi_k} u^\delta \sum_{i=1}^n g^{ij} \frac{\partial (\bar{\mu}_k^\delta \circ \alpha^{-1})}{\partial \xi_i} \frac{d}{d\xi^j} \right]
\]

\[
\left[ \nabla_x \psi + \sum_{j=1}^n g^{ij} \frac{\partial (\bar{\psi}_1 \circ \alpha^{-1})}{\partial \xi_k} \frac{d}{d\xi^j} \right] \sqrt{\det g d\xi} dx
\]

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

\[
\frac{1}{|Y^s|} \left| \int_{V \times (-1, 1)} \left[ \sum_{i=1}^n g^{ij} \frac{\partial (\bar{\mu}_k^\delta \circ \alpha^{-1})}{\partial \xi_i} \frac{d}{d\xi^j} \right] \right|^2 \sum_{j=1}^n \left| \sum_{i=1}^n g^{ij} \frac{\partial (\bar{\psi}_1 \circ \alpha^{-1})}{\partial \xi_k} \frac{d}{d\xi^j} \right|^2 \right| dx \leq 1.
\]

Taking a look at the \(n\)th summand we deduce

\[
\left| \frac{1}{\delta} \frac{\partial (\bar{\mu}_k^\delta \circ \alpha^{-1})}{\partial z_n} \right| \leq C\hspace{1cm}\text{yields}\hspace{1cm}\left| \frac{\partial (\bar{\mu}_k^\delta \circ \alpha^{-1})}{\partial z_n} \right| \leq C\delta \xrightarrow{\delta \to 0} 0.
\]

This implies that \(2(\mu_k^\delta \circ \alpha^{-1})\) converges strongly to zero and with \(\mu_k^\delta \circ \alpha^{-1}\) bounded in \(H^1_\#(V \times (-1, 1))\) independently of \(\delta\) there exists a weakly converging subsequence \(\mu_k^\delta \circ \alpha^{-1} \xrightarrow{\delta \to 0} \mu_k \circ \alpha^{-1}\) 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 \(\delta\) tending to zero, we set \(\psi = 0\) and arrive at

\[
D \int_{\Omega} \int_{V \times (-1, 1)} \left[ \nabla_x u^\delta + \sum_{k=1}^n \partial_{\xi_k} u^\delta \sum_{i=1}^n g^{ij} \frac{\partial (\bar{\mu}_k^\delta \circ \alpha^{-1})}{\partial \xi_i} \frac{d}{d\xi^j} \right]
\]

\[
\left[ \sum_{j=1}^n g^{ij} \frac{\partial (\bar{\psi}_1 \circ \alpha^{-1})}{\partial \xi_k} \frac{d}{d\xi^j} \right] \sqrt{\det g d\xi} dx.
\]
Now $\nabla_x u^\delta$ is written as $\sum_i (\frac{d}{dz_i} \nabla_x u^\delta) \frac{d}{dz_i}$ and we use the definition of the scalar product on $\Gamma$, where here $\langle a, b \rangle = \sum_i g_{ii} a_i b_i$ for $a, b \in T_y \Omega^\delta$.

$$D \int_\Omega \int_{\Gamma_{(\cdot,-1)}} \sum_{i=1}^{n-1} g_{ii} \left[ \left( \frac{d}{dz_i} \nabla_x u^\delta \right) + \sum_{k=1}^{n} \partial_{x_k} u^\delta g_{ij} \frac{\partial (\mu_k^{\alpha^{-1}})}{\partial z_i} \right] + \left[ \frac{1}{\delta} \sum_{i=1}^{n} \sum_{k=1}^{n} g_{ij} \frac{\partial (\mu_k^{\alpha^{-1}})}{\partial z_i} \right] g_{nn} \frac{\partial (\psi_0^{\alpha^{-1}})}{\partial z_n} \sqrt{\det g} dz dx$$

for any $\psi_1 \in C^\infty(\Omega, C_0^\infty(\Gamma))$. Because $\|\nabla_x u^\delta + \nabla_y u^\delta\|_{\Omega \times \Gamma_{(\cdot,-1)}}$ is bounded (see Step 1) and $\frac{\partial (\mu_k^{\alpha^{-1}})}{\partial z_n} \xrightarrow{\delta \to 0} 0$ for $k = 1, \ldots, n$, we deduce by considering the $n$th summand that

$$\left( \frac{d}{dz_n} \nabla_x u^\delta \right) + \sum_{k=1}^{n} \partial_{x_k} u^\delta g_{nn} \frac{\partial (\mu_k^{\alpha^{-1}})}{\partial z_n} \xrightarrow{\delta \to 0} 0$$

and conclude that

$$\nabla_x u^\delta = \sum_{i=1}^{n} \left( \frac{d}{dz_i} \nabla_x u^\delta \right) \xrightarrow{\delta \to 0} \sum_{i=1}^{n-1} \sum_{k=1}^{n} \partial_{x_k} u^\delta \nabla_x u^\delta = P_T \nabla_x u,$$

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

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

$$2D \int_\Omega \int_V \left[ P_T \nabla_x u + \sum_{k=1}^{n} \partial_{x_k} u g_{ij} \frac{\partial (\mu_k^{\alpha^{-1}})}{\partial z_i} \frac{d}{dz_j} \right] \sum_{j=1}^{n-1} g_{ij} \frac{\partial (\psi_0^{\alpha^{-1}})}{\partial z_j} \sqrt{\det g} dz_1 \ldots dz_{n-1} dx$$

$$= 2D \int_\Omega \int_\Gamma \left[ P_T \nabla_x u + \sum_{k=1}^{n} \partial_{x_k} u \nabla_{\Gamma} \mu_k \right] \nabla_{\Gamma} \psi_1 d\sigma_y dx,$$

for all $\psi_1 \in C^\infty(\Omega, C_0^\infty(\Gamma))$, where $\nabla_{\Gamma}$ is the gradient respective to the tangent space. Hence, the limit diffusion term is given by

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

**Limit of the right-hand side.**

For $\delta$ tending to zero, the right-hand side has the following behavior. With $f$ continuous, it easily holds that

$$\int_\Omega \int_{V_{(\cdot,-1)}} f(x, z_1, \ldots, z_{n-1}, \delta z_n) \psi(x, z_1, \ldots, z_{n-1}, \delta z_n) \sqrt{\det g} dz dx$$

$$\xrightarrow{\delta \to 0} 2 \int_\Omega \int_V f(x, z_1, \ldots, z_{n-1}, 0) \psi(x, z_1, \ldots, z_{n-1}, 0) \sqrt{\det g} dz dx$$

$$= 2 \int_\Omega \int_V f(x, y) \psi(x, y) d\sigma_y dx.$$

Analogously, we find because of $h$ continuous

$$\int_{\partial \Omega} \int_{\partial_{h} V_{(\cdot,-1)}} h(x, z_1, \ldots, z_{n-1}, \delta z_n) \psi(x, z_1, \ldots, z_{n-1}, \delta z_n) \sqrt{\det g} d\sigma_z d\sigma_x$$

$$\xrightarrow{\delta \to 0} 2 \int_{\partial \Omega} \int_{\partial_{h} V} h(x, y) \psi(x, y) d\sigma_y d\sigma_x.$$
Hence, for $\delta \to 0$ we arrive at the equation

$$2|\Gamma| \int_{\Omega} \partial_t u \psi dx + 2D \int_{\Omega} \sum_{k=1}^{n} \partial_{x_k} u [P_\Gamma e_k + \nabla \mu_k] [\nabla_x \psi + \nabla \psi_1] d\sigma_y dx$$

$$+ 2|\Gamma| \int_{\Omega} u \psi dx + 2a|\partial_o \Gamma| \int_{\partial_o \Gamma} u \psi d\sigma = 2 \int_{\Gamma} \int_{\Gamma} f(x, y) \psi(x, y) d\sigma_y dx + 2a \int_{\partial_o \Gamma} h \psi d\sigma_y d\sigma x$$

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 $\int_{\partial_o \Gamma} (P_\Gamma e_k + \nabla \mu_k) \nabla \psi_1 d\sigma_y = 0$. Then, the strong formulation of the cell problem is given by (5).

**The limit diffusion tensor.**

By setting $\psi_1$ to zero we can find the diffusion tensor $P$ by considering the diffusion term

$$D \int_{\Omega} \sum_j \partial_y u P_\Gamma (e_j + \nabla \mu_j) \nabla \psi d\sigma_y dx = \int_{\Omega} P \nabla \psi \psi d\sigma$$

with the diffusion tensor $P = (P_{ij})_{ij}$ given by $P_{ij} = D \int_{\Gamma} (P_\Gamma (e_j + \nabla \mu_j))_i d\sigma_y$. 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 $\Omega \subset \mathbb{R}^n$ 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 $\partial_o \Omega_e$ must be a union of squares, such that $\partial_o \Omega_e$ is $\varepsilon$-periodic. For example, the shape of a circle or ellipsoid is not possible.

We define $\partial_o \Omega_e$ as the outer boundary of $\Omega_e$ 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 $\partial_o \Omega_e$ with unit cell $\partial_o Y$. We prove the following theorem describing the two-scale convergence on $\partial_o \Omega_e$.

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

$$\int_{\partial_o \Omega_e} g_e(x) \varphi \left(x, \frac{x}{\varepsilon}\right) d\sigma_x \rightharpoonup \int_{\partial \Omega} \int_{\partial_o Y} g(x, y) \varphi(x, y) d\sigma_y d\sigma_x$$

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

**Proof.** In the given setting, the domain $\partial_o \Omega_e$ is $\varepsilon$-periodic with period $\partial_o Y$. Because the test functions $\varphi \in C^{\infty}(\Omega, C_\#(Y))$ are smooth, they also work as test functions on $\partial_o \Omega_e$. Then, with classical homogenization, see [2], the claim follows. □
Remark 4. Theorem 3 can be used for homogenization of partial differential equations with Neumann boundary condition with right-hand side $g_\varepsilon$ 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 $\Omega_\varepsilon$. The following theorem secures two-scale convergence of the function $u_\varepsilon$ on $\partial_o \Omega_\varepsilon$, if $u_\varepsilon$ satisfies certain conditions.

Theorem 5. a) Let $u_\varepsilon \in H^1(\Omega)$ be a sequence of functions such that $\|u_\varepsilon\|_\Omega + \|
abla u_\varepsilon\|_\Omega < C$ for a constant $C > 0$ independent of $\varepsilon$. Let $u_\varepsilon$ 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,

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

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

b) Let $u_\varepsilon \in L^2([0,T], H^1(\Omega)) \cap H^1([0,T], H^1(\Omega)^r)$, then there exists a subsequence of $u_\varepsilon$, also denoted by $u_\varepsilon$, such that

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

and

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

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

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,

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

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

$$(\gamma(u_\varepsilon) - \gamma(u_0), \varphi)_{H^{1/2}(\partial \Omega) \times H^{1/2}(\partial \Omega)^r} \xrightarrow{\varepsilon \to 0} 0$$

for all $\varphi \in C^\infty(\Omega)$. Moreover, $H^{1/2}(\partial \Omega)$ is compactly embedded in $L^2(\partial \Omega)$ and hence, there exists a strongly converging subsequence $\gamma(u_\varepsilon) \rightarrow \gamma(u_0)$ in $L^2(\partial \Omega)$. Using the characteristic function $\chi_\varepsilon$ on
In a non-activated T cell the calcium concentration in the cytosol is defective, immunodeficiency syndromes may develop in human patients. If this step is accomplished their tasks, complex signaling cascades take place inside these cells. One important step is the detection of alien substances in the body (helper T cell) or to kill the intruder directly (cytotoxic T cell). To accomplish these tasks, complex signaling cascades take place inside these cells. One important step is the detection of 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.

The 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 organs. To understand the function of the CRAC channels we briefly need to explain the situation in T cells.

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 $[Ca^{2+}]_c \approx 50 - 100nM$, the calcium concentration in the intercellular space is $[Ca^{2+}]_{i} \approx 1mM$, and in the lumen of the endoplasmic reticulum it is $[Ca^{2+}]_{ER} \approx 500\mu M$, 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.

The CA2+ concentrations of Stim1 and Orai1 are also regulated by the store-operated calcium channels (CRAC). The CRAC channels are activated by the release of IP3 from the ER, which triggers the opening of CRAC channels. The CRAC channels allow calcium to flow into the cytosol from the extracellular space, which in turn activates signaling cascades.

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 of 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 \( I_{\text{CRAC}} \). But also the CAN channel with flux/current \( I_{\text{CAN}} \), the K channel with flux/current \( I_K \) and the K(Ca) channel with flux/current \( I_{K(Ca)} \) 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 \( \frac{dV}{dt} = -\frac{I}{C_m} \). 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.

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

<table>
<thead>
<tr>
<th>Cell</th>
<th>( \Omega )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma membrane</td>
<td>( \Gamma^1 )</td>
</tr>
<tr>
<td>Part of cytosol</td>
<td>( Y^1 )</td>
</tr>
<tr>
<td>Part of lumen of the ER</td>
<td>( Y^2 )</td>
</tr>
<tr>
<td>Part of blown up surface of the ER, width ( \delta &gt; 0 )</td>
<td>( Y^{\text{ER}} )</td>
</tr>
<tr>
<td>Part of surface of the ER</td>
<td>( \Gamma^{\text{ER}} )</td>
</tr>
</tbody>
</table>

Then we define \( \Omega^1_\varepsilon = \bigcup_{k \in \mathbb{Z}^n} \varepsilon(k + Y^1) \cap \Omega \), \( \Omega^2_\varepsilon = \bigcup_{k \in \mathbb{Z}^n} \varepsilon(k + Y^2) \cap \Omega \) and \( \Omega^{\text{ER}}_\varepsilon = \bigcup_{k \in \mathbb{Z}^n} \varepsilon(k + Y^{\text{ER}}) \cap \Omega \). Further, \( \Gamma^{\text{ER}}_\varepsilon \) is a smooth, compact manifold, such that \( \Gamma^{\text{ER}}_\varepsilon = \bigcup_{k \in \mathbb{Z}^n} \varepsilon(k + \Gamma^{\text{ER}}) \cap \Omega \) is smooth, connected and periodic. The scalar products are given by \( (u, v)_{\Omega^1_\varepsilon} = \int_{\Omega^1_\varepsilon} u \sigma \cdot v \), respectively on \( \Omega^2_\varepsilon \) and \( \Omega^{\text{ER}}_\varepsilon \). On the Riemannian manifolds \( \Gamma^{\text{ER}}_\varepsilon \) and \( \Gamma^1 \) the scalar products are given by \( (u, v)_{\Gamma^{\text{ER}}_\varepsilon} = \int_{\Gamma^{\text{ER}}_\varepsilon} g_\varepsilon u \sigma \cdot v \), respectively on \( \Gamma^1 \), where \( g_\varepsilon \) is the Riemannian metric tensor. The concentrations of the molecules are labeled as the following:

- Calcium in the cytosol: \( C_\varepsilon \), \( C_{C,\varepsilon} \)
- Calcium in the lumen of the ER: \( C_\varepsilon \), \( C_{C,\varepsilon} \)
- Two unbound Stim1 on the surface of the ER: \( S_\varepsilon \), \( S_{C,\varepsilon} \)
- Two Stim1 bound to Orai1 on the surface of the ER: \( S_\varepsilon \), \( S_{C,\varepsilon} \)
- Two Stim1 bound to Orai1 and 4 calcium on the plasma membrane: \( S_{CO,\varepsilon} \)

For convenience we introduce several abbreviations

\[
\begin{align*}
 f_{\text{SERCA}}(C_\varepsilon) &= \frac{u_{\text{SERCA}} C_\varepsilon^2}{C_\varepsilon^2 + K_{\text{SERCA}}^2}, & f_P(C_\varepsilon) &= \frac{u_P C_\varepsilon^2}{C_\varepsilon^2 + K_P^2}, \\
 f_{\text{NCX}}(C_\varepsilon) &= \frac{u_{\text{NCX}} C_\varepsilon^4}{C_\varepsilon^4 + K_{\text{NCX}}^4}, & f_{\varepsilon}(C_{C,\varepsilon}) &= \frac{u_{C,\varepsilon} C_{C,\varepsilon}^4}{C_{C,\varepsilon}^4 + K_{\varepsilon}^4}.
\end{align*}
\]
for $K_{\text{SERCA}}, K_P, K_{\text{NCX}}, K_{\varepsilon}, v_{\text{SERCA}}, v_P, v_{\text{NCX}}, v_{\varepsilon} > 0$. All theses functions are nonnegative, smooth and bounded by $v_{\text{SERCA}}, v_P, v_{\text{NCX}}, v_{\varepsilon}$ respectively. We define the following function spaces

\[ V(\Omega_1^\varepsilon) := L^2([0, T], H^1(\Omega_1^\varepsilon)) \cap H^1([0, T], H^1(\Omega_1^\varepsilon)') \]

\[ V(\Omega_2^\varepsilon) := L^2([0, T], H^1(\Omega_2^\varepsilon)) \cap H^1([0, T], H^1(\Omega_2^\varepsilon)') \]

\[ V(\Omega_{\varepsilon}^{\text{ER}}) := L^2([0, T], H^1(\Omega_{\varepsilon}^{\text{ER}})) \cap H^1([0, T], H^1(\Omega_{\varepsilon}^{\text{ER}})') \]

\[ V(I^1 \cap \partial \Omega_{\varepsilon}^{\text{ER}}) := L^2([0, T], L^2(I^1 \cap \partial \Omega_{\varepsilon}^{\text{ER}})) \cap H^1([0, T], L^2((I^1 \cap \partial \Omega_{\varepsilon}^{\text{ER}}))). \]

For the test functions we define the function spaces

\[ V(\Omega_1^\varepsilon) := H^1(\Omega_1^\varepsilon), \quad V(\Omega_2^\varepsilon) := H^1(\Omega_2^\varepsilon), \]

\[ V(\Omega_{\varepsilon}^{\text{ER}}) := H^1(\Omega_{\varepsilon}^{\text{ER}}), \quad V(I^1 \cap \partial \Omega_{\varepsilon}^{\text{ER}}) := L^2(I^1 \cap \partial \Omega_{\varepsilon}^{\text{ER}}). \]

The weak formulation is given by finding $(C_{\varepsilon}, C_{\varepsilon}, S_{\varepsilon}, S_{C_{\varepsilon}, \Omega, \varepsilon}, S_{CO, \varepsilon}) \in V(\Omega_1^\varepsilon) \times V(\Omega_2^\varepsilon) \times V(\Omega_{\varepsilon}^{\text{ER}})$ such that

\[
(\partial_t C_{\varepsilon}, \psi_1^\varepsilon)_{\Omega_1^\varepsilon} + D_C(\nabla C_{\varepsilon}, \nabla \psi_1^\varepsilon)_{\Omega_1^\varepsilon} + \varepsilon((L_0 + L_{\text{IP3}})(C_{\varepsilon} - C_{\varepsilon}) + f_{\text{SERCA}, \varepsilon}(\psi_1^\varepsilon))_{\Gamma_{\varepsilon}^{\text{ER}}} + \langle \alpha \text{CRAC}(S_{\varepsilon}, f_P + f_{\text{NCX}, \varepsilon}(\psi_1^\varepsilon))_{\Gamma_{\varepsilon}^{\text{ER}}} = 0 \\
(\partial_t S_{\varepsilon}, \psi_2^\varepsilon)_{\Omega_2^\varepsilon} + D_S(\nabla C_{\varepsilon}, \nabla \psi_2^\varepsilon)_{\Omega_2^\varepsilon} + \varepsilon((L_0 + L_{\text{IP3}})(C_{\varepsilon} - C_{\varepsilon}) - f_{\text{SERCA}, \varepsilon}(\psi_2^\varepsilon))_{\Gamma_{\varepsilon}^{\text{ER}}} = 0 \\
(\partial_t S_{\varepsilon, \varepsilon}, \omega_{\varepsilon})_{\Omega_{\text{ER}}} + D_S(\nabla C_{\varepsilon}, \nabla \omega_{\varepsilon})_{\Omega_{\text{ER}}} + (k_C^+ f(C_{\varepsilon})S_{\varepsilon} - k_C^+ S_{\varepsilon, \varepsilon}(\psi_3^\varepsilon))_{\Omega_{\text{ER}}} + \langle k_C^+ S_{\varepsilon} - k_C^+ S_{\varepsilon, \varepsilon}(\psi_3^\varepsilon)_{\Gamma_{\varepsilon}^{\text{ER}}} = 0 \\
(\partial_t S_{CO, \varepsilon}, \psi_4^\varepsilon)_{\Omega_{\varepsilon}^{\text{ER}}} + (k_C^+ S_{CO, \varepsilon} - k_C^+ S_{CO, \varepsilon}(\psi_4^\varepsilon))_{\Omega_{\varepsilon}^{\text{ER}}} = 0 \\
(\partial_t S_{CO, \varepsilon}, \psi_4^\varepsilon)_{\Gamma_{\varepsilon}^{\text{ER}}} + (k_C^+ S_{CO, \varepsilon} - k_C^+ S_{CO, \varepsilon}(\psi_4^\varepsilon))_{\Gamma_{\varepsilon}^{\text{ER}}} = 0 \\
(\partial_t S_{CO, \varepsilon, \varepsilon}, \omega_{\varepsilon})_{\Gamma_{\varepsilon}^{\text{ER}}} + (k_C^+ S_{CO, \varepsilon} + k_C^+ f(C_{\varepsilon})S_{\varepsilon} + \langle k_C^+ S_{CO, \varepsilon} = 0 \\
(\partial_t S_{CO, \varepsilon, \varepsilon}, \omega_{\varepsilon})_{\Gamma_{\varepsilon}^{\text{ER}}} + (k_C^+ f(C_{\varepsilon})S_{\varepsilon} + k_C^+ S_{CO, \varepsilon}(\psi_4^\varepsilon))_{\Gamma_{\varepsilon}^{\text{ER}}} = 0 \\
\text{for all } \psi_1^\varepsilon \in V(\Omega_1^\varepsilon), \psi_2^\varepsilon \in V(\Omega_2^\varepsilon), \psi_3^\varepsilon \in V(\Omega_{\varepsilon}^{\text{ER}}) \text{ and } \psi_4^\varepsilon \in V(I^1 \cap \partial \Omega_{\varepsilon}^{\text{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 $\delta$ of the blown up domain $Y_{\varepsilon}^{\text{ER}}$ to zero. The convergence for $\varepsilon \to 0$ is proven in section 7, the convergence for $\delta \to 0$ in section 8. Let $(C, C_{\varepsilon}, S, S_{C_{\varepsilon}}, S_{CO, \varepsilon}) \in V(\Omega)^2 \times V(I^1)^2$ be such that
5. A priori estimates for the Calcium–Stim1 model

In this section we show that the functions \( C_\varepsilon, C_{e,\varepsilon}, S_\varepsilon \) and \( S_{C,\varepsilon} \) are elements of \( H^1 \) and \( L^\infty \) and that the functions \( S_{O,\varepsilon} \) and \( S_{CO,\varepsilon} \) are elements of \( L^2 \) and \( L^\infty \). 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 \( \varepsilon \), where the inverse trace operator maps from the outer boundary \( \partial \Omega_{\varepsilon} \cap \partial \Omega \) of an \( \varepsilon \)-depending domain \( \Omega_{\varepsilon} \subseteq \Omega \subseteq \mathbb{R}^n \).

**Lemma 6.** Let \( \Omega \subseteq \mathbb{R}^n \) and \( \Omega_{\varepsilon} \) be an \( \varepsilon \)-periodic subset of \( \Omega \), where \( \Omega \) 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

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

with \( c > 0 \) independent of \( \varepsilon \).

**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 \( \Omega_{\varepsilon} \) such that \( \| \tilde{f}_{\varepsilon} \|_{H^1(\Omega)} \leq \varepsilon \| f_{\varepsilon} \|_{H^1(\Omega_{\varepsilon})} \), where \( \varepsilon \) is independent of \( \varepsilon \). The trace operator \( \gamma_{\varepsilon} : H^1(\Omega_{\varepsilon}) \rightarrow L^2(\partial \Omega_{\varepsilon} \cap \partial \Omega) \) 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 \( \Omega_{\varepsilon} \). This means for the trace operator \( \gamma : H^1(\Omega) \rightarrow L^2(\partial \Omega) \) that \( \gamma_{\varepsilon}(f_{\varepsilon}) = f_{\varepsilon}|_{\partial \Omega_{\varepsilon} \cap \partial \Omega} = \gamma(f_{\varepsilon}) \) on \( \partial \Omega_{\varepsilon} \cap \partial \Omega \).

We deduce the following estimation

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

where \( c_0 \) is bounded, because \( \gamma \) is linear and continuous, and \( c_0 \) is independent of \( \varepsilon \), since \( \Omega \) is independent of \( \varepsilon \).

Now we start with the estimations for the system (6). We note again that the term \( I_{\text{CRAC}}(S_{O,\varepsilon}) \) is bounded almost everywhere in \([0, T] \times \Gamma^1 \cap \partial \Omega_{\varepsilon}^2 \) independently of \( \varepsilon \), if \( S_{O,\varepsilon} \) is bounded almost everywhere in \([0, T] \times \Gamma^1 \cap \partial \Omega_{\varepsilon}^2 \) independently of \( \varepsilon \).

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

**Lemma 7.** (Positivity of \( S_{l,\varepsilon}, S_{C,\varepsilon}, S_{O,\varepsilon} \) and \( S_{CO,\varepsilon} \)) For almost every \( x \in \Omega_{\varepsilon}^{ER} \) and \( t \in [0, T] \) it holds that \( S_{l,\varepsilon}(x, t) \geq 0 \) and \( S_{C,\varepsilon}(x, t) \geq 0 \). For almost every \( x \in \Gamma^1 \cap \partial \Omega_{\varepsilon}^2 \) 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 \( S_{l,\varepsilon}, S_{C,\varepsilon}, S_{O,\varepsilon} \), and \( S_{CO,\varepsilon} \) with \( k_{\text{CO}}^+ S_{C,\varepsilon}, k_{\text{CO}}^- S_{C,\varepsilon}, k_{\text{CO}}^- S_{O,\varepsilon} \), and \( k_{\text{CO}}^- S_{CO,\varepsilon} \), respectively. We start with \( S_{l,\varepsilon} \) and \( S_{O,\varepsilon} \), add the equations, and multiply both sides by \(-1\),

\[
\begin{align*}
&k_{\text{CO}}^+(\partial S_{l,\varepsilon} - S_{l,\varepsilon})_{\Omega_{\varepsilon}^2} + k_{\text{CO}}^- (\partial S_{O,\varepsilon} - S_{O,\varepsilon})_{\Gamma^1 \cap \partial \Omega_{\varepsilon}^2} + D_{\varepsilon} k_{\text{CO}}^-||\nabla S_{l,\varepsilon}||_{H^1(\Omega_{\varepsilon}^2)}^2 \\
&+ k_{\text{CO}}^+(S_{C,\varepsilon} - S_{C,\varepsilon})_{\Omega_{\varepsilon}^2} + k_{\text{CO}}^- (S_{CO,\varepsilon} - S_{CO,\varepsilon})_{\Gamma^1 \cap \partial \Omega_{\varepsilon}^2} + D_{\varepsilon} k_{\text{CO}}^-||\nabla S_{C,\varepsilon}||_{H^1(\Omega_{\varepsilon}^2)}^2 \\
&\leq -k_{\text{CO}}^+(S_{C,\varepsilon} - S_{C,\varepsilon})_{\Omega_{\varepsilon}^2} - k_{\text{CO}}^- (S_{CO,\varepsilon} - S_{CO,\varepsilon})_{\Gamma^1 \cap \partial \Omega_{\varepsilon}^2} \\
&\leq k_{\text{CO}}^+(||S_{C,\varepsilon}||_{H^1(\Omega_{\varepsilon}^2)}^2 + ||S_{O,\varepsilon}||_{H^1(\Omega_{\varepsilon}^2)}^2) + k_{\text{CO}}^- k_{\text{CO}}^- (||S_{CO,\varepsilon}||_{H^1(\Omega_{\varepsilon}^2)}^2 + ||S_{l,\varepsilon}||_{H^1(\Omega_{\varepsilon}^2)}^2).
\end{align*}
\]

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

\[
\begin{align*}
||S_{l,\varepsilon}||_{H^1(\Omega_{\varepsilon}^2)}^2 + ||S_{O,\varepsilon}||_{H^1(\Omega_{\varepsilon}^2)}^2 &\leq c_1 \left(||S_{C,\varepsilon}||_{H^1(\Omega_{\varepsilon}^2)}^2 + ||S_{O,\varepsilon}||_{H^1(\Omega_{\varepsilon}^2)}^2 + ||S_{CO,\varepsilon}||_{H^1(\Omega_{\varepsilon}^2)}^2 + ||S_{l,\varepsilon}||_{H^1(\Omega_{\varepsilon}^2)}^2 \right),
\end{align*}
\]

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

\[
\begin{align*}
||S_{C,\varepsilon}||_{H^1(\Omega_{\varepsilon}^2)}^2 + ||S_{CO,\varepsilon}||_{H^1(\Omega_{\varepsilon}^2)}^2 &\leq c_1 \left(||S_{C,\varepsilon}||_{H^1(\Omega_{\varepsilon}^2)}^2 + ||S_{O,\varepsilon}||_{H^1(\varepsilon)}^2 + ||S_{CO,\varepsilon}||_{H^1(\Omega_{\varepsilon}^2)}^2 + ||S_{l,\varepsilon}||_{H^1(\Omega_{\varepsilon}^2)}^2 \right).
\end{align*}
\]
Then we add the two inequalities and find
\[
\|S_t\|_{H^2} + \|S_{O,t}\|_{H^2}^2 + \|S_{C,t}\|_{H^2}^2 + \|S_{O,C,t}\|_{H^2}^2 \leq c_1 \left( \|S_{C,t}\|_{H^2}^2 + \|S_t\|_{H^2}^2 + \|S_{O,C,t}\|_{H^2}^2 \right).
\]

Using the lemma of Gronwall yields
\[
\|S_t\|_{H^2}^2 + \|S_{O,t}\|_{H^2}^2 + \|S_{C,t}\|_{H^2}^2 + \|S_{O,C,t}\|_{H^2}^2 \leq 0.
\]

Hence, the functions \(S_t, S_{C,t}, S_{O,t}\) and \(S_{O,C,t}\) are nonnegative.

**Lemma 8. (Boundedness of \(S_t, S_{C,t}, S_{O,t}\) and \(S_{O,C,t}\) in \(H^1\) or \(L^2\))**

There exists a constant \(C > 0\), independent of \(\varepsilon\), such that
\[
\|S_t\|_{H^2}^2 + \|S_{C,t}\|_{H^2}^2 + \|S_{O,t}\|_{H^2}^2 + \|S_{O,C,t}\|_{H^2}^2 \leq C.
\]

**Proof.** We test the weak formulations for \(S_t\) and \(S_{C,t}\) with the functions \(S_t\) and \(S_{C,t}\), respectively, add the equations and integrate from 0 to \(t\). With the binomial theorem we get for any \(\lambda > 0\)
\[
\frac{1}{2} \|S_t\|_{H^2}^2 + \frac{1}{2} \|S_{C,t}\|_{H^2}^2 + D_S \|\nabla S_t\|_{H^2}^2 + D_{S_C} \|\nabla S_{C,t}\|_{H^2}^2 + k^+_O \|S_{O,t}\|_{H^2}^2 + k^+_O \|S_{O,C,t}\|_{H^2}^2 \leq \frac{1}{2} \|S_t(0)\|_{H^2}^2 + \frac{1}{2} \|S_{C,t}(0)\|_{H^2}^2 + c_1 \|S_{C,t}\|_{H^2}^2 + c_2 \|S_{O,t}\|_{H^2}^2 + \frac{1}{\lambda} \|S_t\|_{H^2}^2 + \frac{1}{\lambda} \|S_{C,t}\|_{H^2}^2 + c_4 \|\nabla S_t\|_{H^2}^2 + c_5 \|\nabla S_{C,t}\|_{H^2}^2.
\]

Using the trace inequality with lemma 6, merging the constants and dropping some positive terms yield
\[
\|S_t\|_{H^2}^2 + \|S_{C,t}\|_{H^2}^2 + \left( D_S - c_1 c_0 \frac{1}{\lambda} \right) \|\nabla S_t\|_{H^2}^2 + \left( D_{S_C} - c_2 c_0 \frac{1}{\lambda} \right) \|\nabla S_{C,t}\|_{H^2}^2 \leq c_3 + c_4 \|S_{C,t}\|_{H^2}^2 + c_5 \|S_{C,t}\|_{H^2}^2 + c_6 \|S_{O,t}\|_{H^2}^2 + c_7 \|S_{O,C,t}\|_{H^2}^2 + c_8 \|\nabla S_{C,t}\|_{H^2}^2.
\]

Now we do similar estimates for the equations for \(S_{O,t}\) and \(S_{O,C,t}\) and find for any \(\lambda > 0\)
\[
\frac{1}{2} \|S_{O,t}\|_{H^2}^2 + \frac{1}{2} \|S_{O,C,t}\|_{H^2}^2 \leq \frac{1}{2} \|S_{O,t}(0)\|_{H^2}^2 + \frac{1}{2} \|S_{O,C,t}(0)\|_{H^2}^2 + c_1 \|S_{O,t}\|_{H^2}^2 + c_2 \|S_{O,C,t}\|_{H^2}^2 + \frac{1}{\lambda} \|S_{O,t}\|_{H^2}^2 + \frac{1}{\lambda} \|S_{O,C,t}\|_{H^2}^2 + c_4 \|\nabla S_{O,t}\|_{H^2}^2 + c_5 \|\nabla S_{O,C,t}\|_{H^2}^2.
\]

We sum up all inequalities to find
\[
\|S_t\|_{H^2}^2 + \|S_{C,t}\|_{H^2}^2 + \|S_{O,t}\|_{H^2}^2 + \|S_{O,C,t}\|_{H^2}^2 \leq c_3 + c_4 \|S_{C,t}\|_{H^2}^2 + c_5 \|S_{C,t}\|_{H^2}^2 + c_6 \|S_{O,t}\|_{H^2}^2 + c_7 \|S_{O,C,t}\|_{H^2}^2 + c_8 \|\nabla S_{C,t}\|_{H^2}^2 + c_9 \|\nabla S_{O,C,t}\|_{H^2}^2.
\]

For \(\lambda\) greater than \(c_0 c_2 + c_1 c_1\), but finite, Gronwall’s lemma yields
\[
\|S_t\|_{H^2}^2 + \|S_{C,t}\|_{H^2}^2 + \|S_{O,t}\|_{H^2}^2 + \|S_{O,C,t}\|_{H^2}^2 \leq C.
\]
Next, we want to show that the functions that represent the concentration of Stim1 molecules are bounded, i.e. they are $L^\infty$ functions.

**Lemma 9. (Boundedness of $S_\varepsilon$, $S_{C,\varepsilon}$, $S_{O,\varepsilon}$ and $S_{CO,\varepsilon}$ in $L^\infty$)**

There exists a constant $C > 0$, independent of $\varepsilon$, such that

$$
\|S_\varepsilon\|_{L^\infty(\Omega^\varepsilon_T)} + \|S_{C,\varepsilon}\|_{L^\infty(\Omega^\varepsilon_T)} + \|S_{O,\varepsilon}\|_{L^\infty(\Gamma^{r_1,\partial_0\Omega^\varepsilon_T})} + \|S_{CO,\varepsilon}\|_{L^\infty(\Gamma^{r_1,\partial_0\Omega^\varepsilon_T})} < C
$$

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

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

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

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

We test the equations for $S_\varepsilon$, $S_{C,\varepsilon}$, $S_{O,\varepsilon}$ and $S_{CO,\varepsilon}$ with $(k_0^+ S_\varepsilon - M)_+$, $(k_{CO}^+ S_{C,\varepsilon} - M)_+$, $(k_0^- S_{O,\varepsilon} - M)_+$ and $(k_{CO}^- S_{CO,\varepsilon} - M)_+$, respectively, add the results and consider the time and spatial derivative of $M$ to obtain

$$
\begin{align*}
\frac{1}{k_0} (\partial_t (k_0^+ S_\varepsilon - M)_+ + (k_0^+ S_\varepsilon - M)_+) \Omega^\varepsilon_T + \frac{1}{k_{CO}} (\partial_t (k_{CO}^+ S_{C,\varepsilon} - M)_+ + (k_{CO}^+ S_{C,\varepsilon} - M)_+) \Omega^\varepsilon_T + \frac{1}{k_0} D_S \| \nabla (k_0^+ S_\varepsilon - M)_+ \|_{\Omega^\varepsilon_T}^2 + \frac{1}{k_{CO}} D_{SC} \| \nabla (k_{CO}^+ S_{C,\varepsilon} - M)_+ \|_{\Omega^\varepsilon_T}^2 + \frac{1}{k_0} (\partial_t (k_0^- S_{O,\varepsilon} - M)_+ + (k_0^- S_{O,\varepsilon} - M)_+) \Gamma^{r_1,\partial_0\Omega^\varepsilon_T} + \frac{1}{k_{CO}} (\partial_t (k_{CO}^- S_{CO,\varepsilon} - M)_+ + (k_{CO}^- S_{CO,\varepsilon} - M)_+) \Gamma^{r_1,\partial_0\Omega^\varepsilon_T} + (k_C^+ f_e (C_{\varepsilon,\varepsilon}) S_\varepsilon - k_{CO} S_{C,\varepsilon}, (k_0^+ S_\varepsilon - M)_+ - (k_{CO}^+ S_{C,\varepsilon} - M)_+) \Omega^\varepsilon_T + (k_C^+ f_e (C_{\varepsilon,\varepsilon}) S_{O,\varepsilon} - k_{CO} S_{CO,\varepsilon}, (k_0^- S_{O,\varepsilon} - M)_+ - (k_{CO}^- S_{CO,\varepsilon} - M)_+) \Omega^\varepsilon_T + \|(k_0^+ S_\varepsilon - M)_+ - (k_0^- S_{O,\varepsilon} - M)_+ \|_{\Omega^\varepsilon_T}\|_{\Gamma^{r_1,\partial_0\Omega^\varepsilon_T}}^2 + \|(k_{CO}^+ S_{C,\varepsilon} - M)_+ - (k_{CO}^- S_{CO,\varepsilon} - M)_+ \|_{\Omega^\varepsilon_T}\|_{\Gamma^{r_1,\partial_0\Omega^\varepsilon_T}}^2
\end{align*}
$$

$$
\leq -\left(\frac{1}{k_0} kM, (k_0^+ S_\varepsilon - M)_+ \right)_{\Omega^\varepsilon_T} - \left(\frac{1}{k_{CO}} kM, (k_{CO}^+ S_{C,\varepsilon} - M)_+ \right)_{\Omega^\varepsilon_T} + \left(\frac{1}{k_0} kM, (k_0^- S_{O,\varepsilon} - M)_+ \right)_{\Gamma^{r_1,\partial_0\Omega^\varepsilon_T}} - \left(\frac{1}{k_{CO}} kM, (k_{CO}^- S_{CO,\varepsilon} - M)_+ \right)_{\Gamma^{r_1,\partial_0\Omega^\varepsilon_T}}.
$$

We drop some positive terms, integrate from 0 to $t$, and use the binomial theorem. With $f_e (C_{\varepsilon,\varepsilon})$ bounded and $\|\varphi - M\|_{\Omega^\varepsilon_T} \leq \|\varphi\|_{\Omega^\varepsilon_T}$ for $\varphi = S_\varepsilon, S_{C,\varepsilon}$ and $\|\varphi - M\|_{\Gamma^{r_1,\partial_0\Omega^\varepsilon_T}} \leq \|\varphi\|_{\Gamma^{r_1,\partial_0\Omega^\varepsilon_T}}$ for $\varphi = S_{O,\varepsilon}, S_{CO,\varepsilon}$, we find

$$
\begin{align*}
\frac{1}{2k_0} \| (k_0^+ S_\varepsilon - M)_+ \|_{\Omega^\varepsilon_T}^2 + \frac{1}{2k_{CO}} \| (k_{CO}^+ S_{C,\varepsilon} - M)_+ \|_{\Omega^\varepsilon_T}^2 + \frac{1}{2k_0} \| (k_0^- S_{O,\varepsilon} - M)_+ \|_{\Gamma^{r_1,\partial_0\Omega^\varepsilon_T}}^2 + \frac{1}{2k_{CO}} \| (k_{CO}^- S_{CO,\varepsilon} - M)_+ \|_{\Gamma^{r_1,\partial_0\Omega^\varepsilon_T}}^2
\end{align*}
$$

$$
\leq c_1 - \left(\frac{1}{k_0} kM, (k_0^+ S_\varepsilon - M)_+ \right)_{\Omega^\varepsilon_T} - \left(\frac{1}{k_{CO}} kM, (k_{CO}^+ S_{C,\varepsilon} - M)_+ \right)_{\Omega^\varepsilon_T} + \left(\frac{1}{k_0} kM, (k_0^- S_{O,\varepsilon} - M)_+ \right)_{\Gamma^{r_1,\partial_0\Omega^\varepsilon_T}} - \left(\frac{1}{k_{CO}} kM, (k_{CO}^- S_{CO,\varepsilon} - M)_+ \right)_{\Gamma^{r_1,\partial_0\Omega^\varepsilon_T}}.
$$

Now we distinguish two cases.
• There exists a non-nullset \( V \subset \Omega^\text{ER}_\varepsilon \) such that \((k_0^+ S_\varepsilon - M)_+ > 0 \) in \( V \) or \((k_{CO}^+ S_{C,\varepsilon} - M)_+ > 0 \) in \( V \); or there exists a non-nullset \( V \subset \Gamma^1 \cap \Omega^\text{ER}_\varepsilon \) such that \((k_0^- S_{O,\varepsilon} - M)_+ > 0 \) in \( V \) or \((k_{CO}^- S_{CO,\varepsilon} - M)_+ > 0 \) in \( V \). Then there exists a \( \delta > 0 \) such that

\[
\frac{1}{k_0^+} M, (k_0^+ S_\varepsilon - M)_+ \Omega^\text{ER}_\varepsilon + \frac{1}{k_{CO}^+} M, (k_{CO}^+ S_{C,\varepsilon} - M)_+ \Omega^\text{ER}_\varepsilon, t > \delta
\]

or

\[
\frac{1}{k_0^-} M, (k_0^- S_{O,\varepsilon} - M)_+ \Omega^\text{ER}_\varepsilon + \frac{1}{k_{CO}^-} M, (k_{CO}^- S_{CO,\varepsilon} - M)_+ \Omega^\text{ER}_\varepsilon, t > \delta.
\]

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

\[
\frac{1}{2k_0^+} \| (k_0^+ S_\varepsilon - M)_+ \|_{\Omega^\text{ER}_\varepsilon}^2 + \frac{1}{2k_{CO}^+} \| (k_{CO}^+ S_{C,\varepsilon} - M)_+ \|_{\Omega^\text{ER}_\varepsilon}^2
\]

\[
+ \frac{1}{2k_0^-} \| (k_0^- S_{O,\varepsilon} - M)_+ \|_{\Omega^\text{ER}_\varepsilon}^2 + \frac{1}{2k_{CO}^-} \| (k_{CO}^- S_{CO,\varepsilon} - M)_+ \|_{\Omega^\text{ER}_\varepsilon}^2 \leq 0.
\]

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

• Otherwise it holds that \((k_0^+ S_\varepsilon - M)_+ \leq 0 \), \((k_{CO}^+ S_{C,\varepsilon} - M)_+ \leq 0 \), \((k_0^- S_{O,\varepsilon} - M)_+ \leq 0 \) and \((k_{CO}^- S_{CO,\varepsilon} - M)_+ \leq 0 \) almost everywhere and we are finished.

\[\square\]

Now we show that \( C_\varepsilon \) and \( C_{C,\varepsilon} \) are \( H^1 \)-functions.

**Lemma 10. (Boundedness of \( C_\varepsilon \) and \( C_{C,\varepsilon} \) in \( H^1 \))**

It holds that

\[
\| C_\varepsilon \|_{H^1}^2 + \| C_{C,\varepsilon} \|_{H^1}^2 + \| \nabla C_\varepsilon \|_{H^1}^2 + \| \nabla C_{C,\varepsilon} \|_{H^1}^2 + \varepsilon \| C_\varepsilon - C_{C,\varepsilon} \|_{H^1}^2 \leq C
\]

for a constant \( C > 0 \), independent of \( \varepsilon \).

**Proof.** We test the weak formulation for \( C_\varepsilon \) with \( C_\varepsilon \) and get

\[
(\partial_t C_\varepsilon, C_\varepsilon)_{\Omega^\text{ER}_\varepsilon} + D_{\Omega^\text{ER}_\varepsilon} \| \nabla C_\varepsilon \|_{\Omega^\text{ER}_\varepsilon}^2 + \varepsilon (L_0 + L_{IP3})(C_\varepsilon - C_{C,\varepsilon} + C_\varepsilon)_{\Gamma^\text{ER}_\varepsilon} + \varepsilon (f_{\text{SERCA}}, C_\varepsilon)_{\Gamma^\text{ER}_\varepsilon} + (\alpha I_{\text{CRAC}} + f_P + f_{\text{NCX}}, C_\varepsilon)_{\Gamma^\text{ER}_\varepsilon} = 0.
\]

Also, we test the weak formulation for \( C_{C,\varepsilon} \) with \( C_{C,\varepsilon} \) and get

\[
(\partial_t C_{C,\varepsilon}, C_{C,\varepsilon})_{\Omega^\text{ER}_\varepsilon} + D_{\Omega^\text{ER}_\varepsilon} \| \nabla C_{C,\varepsilon} \|_{\Omega^\text{ER}_\varepsilon}^2 + \varepsilon (L_0 + L_{IP3})(C_\varepsilon - C_{C,\varepsilon} + C_\varepsilon)_{\Gamma^\text{ER}_\varepsilon} + \varepsilon (f_{\text{SERCA}}, C_{C,\varepsilon})_{\Gamma^\text{ER}_\varepsilon} = 0.
\]

Adding the equations gives for any \( \lambda > 0 \)

\[
(\partial_t C_{C,\varepsilon}, C_{C,\varepsilon})_{\Omega^\text{ER}_\varepsilon} + D_{\Omega^\text{ER}_\varepsilon} \| \nabla C_{C,\varepsilon} \|_{\Omega^\text{ER}_\varepsilon}^2 + (\partial_t C_{C,\varepsilon}, C_{C,\varepsilon})_{\Omega^\text{ER}_\varepsilon} + D_{\Omega^\text{ER}_\varepsilon} \| \nabla C_{C,\varepsilon} \|_{\Omega^\text{ER}_\varepsilon}^2 + \varepsilon (L_0 + L_{IP3})(C_\varepsilon - C_{C,\varepsilon} + C_\varepsilon)_{\Gamma^\text{ER}_\varepsilon}^2 + \varepsilon (f_{\text{SERCA}}, C_{C,\varepsilon} - C_\varepsilon)_{\Gamma^\text{ER}_\varepsilon}^2
\]

\[
\leq \frac{\lambda}{2} \varepsilon (f_P + f_{\text{NCX}} + \alpha I_{\text{CRAC}}, C_{C,\varepsilon})_{\Gamma^\text{ER}_\varepsilon}^2 + \varepsilon (f_{\text{SERCA}}, C_{C,\varepsilon} - C_\varepsilon)_{\Gamma^\text{ER}_\varepsilon}^2 + \varepsilon (\| C_{C,\varepsilon} \|_{\Omega^\text{ER}_\varepsilon}^2 + \varepsilon \| \nabla C_{C,\varepsilon} \|_{\Omega^\text{ER}_\varepsilon}^2) + \varepsilon (\| C_\varepsilon \|_{\Omega^\text{ER}_\varepsilon}^2 + \varepsilon \| \nabla C_\varepsilon \|_{\Omega^\text{ER}_\varepsilon}^2)
\]

\[\leq c_1 \left( \frac{\| C_{C,\varepsilon} \|_{\Omega^\text{ER}_\varepsilon}^2 + \varepsilon \| \nabla C_{C,\varepsilon} \|_{\Omega^\text{ER}_\varepsilon}^2}{\varepsilon^2} \right) + c_0 \left( \| C_\varepsilon \|_{\Omega^\text{ER}_\varepsilon}^2 + \varepsilon \| \nabla C_\varepsilon \|_{\Omega^\text{ER}_\varepsilon}^2 \right).
\]

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Note that we used two different trace inequalities, the standard one for homogenization and lemma 6. We deduce
\[
(\partial \epsilon C, C_\epsilon)_{\Omega_1^2} + \left( D_C - \frac{c_0}{2\lambda} - \epsilon^2 c_0 \right) \| \nabla C_\epsilon \|^2_{\Omega_1^2} \\
+ \left( (\partial \epsilon C_{\epsilon,t}, C_{\epsilon,t})_{\Omega_2^2} + (D_{\text{ER}} - c_0 \epsilon^2) \| \nabla C_{\epsilon,t} \|^2_{\Omega_2^2} + \epsilon (L_0 + L_{\text{IP3}}) \| C_\epsilon - C_{\epsilon,t} \|^2_{\Omega_2^2} \right) \\
\leq \lambda c_1 + c_2 \| C_\epsilon \|^2_{\Omega_1^2} + c_3 \| C_{\epsilon,t} \|^2_{\Omega_2^2}
\]
for some constants $c_1$, $c_2$ and $c_3$. By integration from 0 to $t$ we get
\[
\frac{1}{2} \| C_\epsilon \|^2_{\Omega_1^2} + \left( D_C - \frac{c_0}{2\lambda} - \epsilon^2 c_0 \right) \| \nabla C_\epsilon \|^2_{\Omega_1^2,t} \\
+ \frac{1}{2} \| C_{\epsilon,t} \|^2_{\Omega_2^2} + (D_{\text{ER}} - c_0 \epsilon^2) \| \nabla C_{\epsilon,t} \|^2_{\Omega_2^2,t} + \epsilon (L_0 + L_{\text{IP3}}) \| C_\epsilon - C_{\epsilon,t} \|^2_{\Omega_2^2,t} \\
\leq \lambda c_1 + c_2 \| C_\epsilon \|^2_{\Omega_1^2,t} + c_3 \| C_{\epsilon,t} \|^2_{\Omega_2^2,t} + \frac{1}{2} \| C_\epsilon(0) \|^2_{\Omega_1^2} + \frac{1}{2} \| C_{\epsilon,t}(0) \|^2_{\Omega_2^2}.
\]
For $\lambda$ big enough but finite, and small $\epsilon$ we conclude with the lemma of Gronwall that
\[
\| C_\epsilon \|^2_{\Omega_1^2} + \| \nabla C_\epsilon \|^2_{\Omega_1^2,t} + \| C_{\epsilon,t} \|^2_{\Omega_2^2} + \| \nabla C_{\epsilon,t} \|^2_{\Omega_2^2,t} + \epsilon \| C_\epsilon - C_{\epsilon,t} \|^2_{\Omega_2^2,t} \leq C
\]
for a merged constant $C$.

Next, we show that $C_\epsilon$ and $C_{\epsilon,t}$ are also bounded in $L^\infty$.

**Lemma 11. (Boundedness of $C_\epsilon$ and $C_{\epsilon,t}$ in $L^\infty$)**

There exists a constant $C > 0$, independent of $\epsilon$, such that
\[
\| C_\epsilon \|_{L^\infty(\Omega_1^2)} + \| C_{\epsilon,t} \|_{L^\infty(\Omega_2^2)} < C
\]
for almost every $t \in [0, T]$.

**Proof.** Let $k > 0$. We define the function $M(t) := \max\{\| C_\epsilon(0) \|_{L^\infty}, \| C_{\epsilon,t}(0) \|_{L^\infty} \} e^{kt}$, test the equations for $C_\epsilon$ and $C_{\epsilon,t}$ with $(C_\epsilon - M)_+$ and $(C_{\epsilon,t} - M)_+$, respectively, add them up and consider the time and spatial derivatives. Integration from 0 to $t$ yields
\[
\frac{1}{2} \| (C_\epsilon - M)_+ \|^2_{\Omega_1^2} + D_C \| \nabla (C_\epsilon - M)_+ \|^2_{\Omega_1^2,t} + \frac{1}{2} \| (C_{\epsilon,t} - M)_+ \|^2_{\Omega_2^2} + D_{\text{ER}} \| \nabla (C_{\epsilon,t} - M)_+ \|^2_{\Omega_2^2,t} \\
+ \epsilon (L_0 + L_{\text{IP3}}) ((C_\epsilon - M)_+ - (C_{\epsilon,t} - M)_+) \| \nabla (C_\epsilon - M)_+ \|^2_{\Omega_2^2,t} \\
\leq \alpha \| I_{\text{CRAC}} \|_t (C_\epsilon - M)_+ \| \Gamma \cap \partial \Omega_1^2 \|_t - (k M, (C_\epsilon - M)_+)_{\Omega_1^2,t} - (k M, (C_{\epsilon,t} - M)_+)_{\Omega_2^2,t}.
\]
Hence, with $\langle (C_\epsilon - M)_+, (C_\epsilon - M)_+ - (C_{\epsilon,t} - M)_+ \rangle_{\Omega_1^2,t} + \langle (C_{\epsilon,t} - M)_+, (C_{\epsilon,t} - M)_+ \rangle_{\Omega_2^2,t} \geq \langle (C_\epsilon - M)_+ - (C_{\epsilon,t} - M)_+, (C_{\epsilon,t} - M)_+ \rangle_{\Omega_2^2,t}$, we continue with
\[
\frac{1}{2} \| (C_\epsilon - M)_+ \|^2_{\Omega_1^2} + D_C \| \nabla (C_\epsilon - M)_+ \|^2_{\Omega_1^2,t} + \frac{1}{2} \| (C_{\epsilon,t} - M)_+ \|^2_{\Omega_2^2} \\
+ D_{\text{ER}} \| \nabla (C_{\epsilon,t} - M)_+ \|^2_{\Omega_2^2,t} + \epsilon (L_0 + L_{\text{IP3}}) \| (C_\epsilon - M)_+ - (C_{\epsilon,t} - M)_+ \|^2_{\Omega_2^2,t} \\
\leq \alpha \| I_{\text{CRAC}} \|_t \| \Gamma \cap \partial \Omega_1^2 \|_t - (k M, (C_\epsilon - M)_+)_{\Omega_1^2,t} - (k M, (C_{\epsilon,t} - M)_+)_{\Omega_2^2,t}.
\]
Now we distinguish two cases.
• There exists a non-nullset $V \subset \Omega^1$ or $V \subset \Omega^2$ with $(C_e - M)_+ > 0$ or $(C_{e,e} - M)_+ > 0$ in $V$, respectively. Then there exists a $\delta > 0$ such that $(M, (C_e - M)_+)_t > \delta$ or $(M, (C_{e,e} - M)_+)_t > \delta$, respectively, and we choose $k\delta = c_1$. Then it follows that

$$\frac{1}{2}\|(C_e - M)_+\|^2_{\Omega^1_T} + DC_e\|\nabla(C_e - M)_+\|^2_{\Omega^1_T} + \frac{1}{2}\|(C_{e,e} - M)_+\|^2_{\Omega^2_T}$$

$$+ D_{ER}\|\nabla(C_{e,e} - M)_+\|^2_{\Omega^2_T} + \varepsilon(L_0 + L_{IP})\|(C_e - M)_+ - (C_{e,e} - M)_+\|^2_{T^*} \leq c_1 - (kM, (C_e - M)_+)_t - (kM, (C_{e,e} - M)_+)_t \leq 0.$$

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

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

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

Finally, we estimate the time derivatives.

**Lemma 12. (Boundedness of $\partial_t C_e$, $\partial_t C_{e,e}$, $\partial_t S_e$, $\partial_t S_{e,e}$, $\partial_t S_{O,e}$ and $\partial_t S_{CO,e}$ in $H^{-1}$)**

There exists a constant $C > 0$, independent of $\varepsilon$, such that

$$\|\partial_t C_e\|_{L^2([0,T],H^{-1}(\Omega^1))} + \|\partial_t C_{e,e}\|_{L^2([0,T],H^{-1}(\Omega^2))} < C,$n

$$\|\partial_t S_e\|_{L^2([0,T],H^{-1}(\Omega^2))} + \|\partial_t S_{e,e}\|_{L^2([0,T],H^{-1}(\Omega^2))} < C,$n

$$\|\partial_t S_{O,e}\|_{L^2([0,T],L^2(\Gamma \cap \partial \Omega^2))} + \|\partial_t S_{CO,e}\|_{L^2([0,T],L^2(\Gamma \cap \partial \Omega^2))} < C.$n

**Proof.** We start with $\partial_t C_e$ and the definition of the $H^{-1}$ norm. We drop the boundary terms, because test functions in $H^1_0$ are zero at the boundary.

$$\|\partial_t C_e\|_{H^{-1}(\Omega^1)} = \sup_{\varphi \in H^1_0(\Omega^1), \|\varphi\| = 1} (\partial_t C_e, \varphi)_{H^1_0(\Omega^1)'}$$

$$\leq \sup_{\varphi \in H^1_0(\Omega^1), \|\varphi\| = 1} (DC_e\nabla(C_e, \nabla\varphi)_{H^1_0(\Omega^1)'} - \varepsilon((L_0 + L_{IP}) (C_e - C_{e,e}) + f_{SERCA}(C_e, \varphi)_{\Omega^{en}}$$

$$- \langle \alpha I_{CRAC}(S_{O,e}) + f_P(C_e) + f_{NCX}(C_e, \varphi)_{\Gamma \cap \partial \Omega^1}$$

$$\leq \|\nabla C_e\|_{L^2(\Omega^1)}\|\nabla\varphi\|_{L^2(\Omega^1)}).$$

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

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

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

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

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

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

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

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

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 $\mathcal{V}(\Omega^1_e) \times \mathcal{V}(\Omega^1_e) \times \mathcal{V}(\Omega^\text{ER}_e) \times \mathcal{V}(\Omega^\text{ER}_e)$.

**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 $V_1 := L^2([0,\tau], H^{1-\delta}(\Omega^1_e))$, $V_2 := L^2([0,\tau], H^{1-\delta}(\Omega^1_e))$ and $V_{\text{ER}} := L^2([0,\tau], H^{1-\delta}(\Omega^\text{ER}_e))$.

Further, we define the function

$$
T : V^1 \times V^2 \times (V_{\text{ER}})^2 \longrightarrow \{ u \in L^2([0,\tau], H^{1}(\Omega^1_e)) \} \times \{ \partial_t u \in L^2([0,\tau], H^{1}(\Omega^1_e)) \} \\
\times \{ \partial_t u \in L^2([0,\tau], H^{1}(\Omega^1_e)) \} \times \{ \partial_t u \in L^2([0,\tau], H^{1}(\Omega_{\text{ER}}^e)) \}
$$

with

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

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given by

\[\begin{align*}
\partial_t C - D_C \Delta C &= 0 \\
-D_C \nabla C \cdot n &= \epsilon (L_0 + L_{H^3})(\tilde{C} - \tilde{C}_{e,c}) + \epsilon F_{SERCA}(\tilde{C}) \\
-D_C \nabla C \cdot n &= \alpha F_{CRAC}(S_{O,c}) + F_{F}(\tilde{C}) + F_{NCX}(\tilde{C}) \\
-D_C \nabla C \cdot n &= 0
\end{align*}\]

\[\begin{align*}
\partial_t C_{e,c} - D_{E_R} \Delta C_{e,c} &= 0 \\
-D_{E_R} \nabla C_{e,c} \cdot n &= \epsilon (L_0 + L_{H^3})(\tilde{C}_{e,c} - \tilde{C}) - \epsilon F_{SERCA}(\tilde{C}) \\
-D_{E_R} \nabla C_{e,c} \cdot n &= 0
\end{align*}\]

\[\begin{align*}
\partial_t S_{e,c} - D_S \Delta S_{e,c} &= -k_C^+ f_e(\tilde{C}_{e,c})\tilde{S}_e + k_C^- \tilde{S}_{C,e} \\
-D_S \nabla S_{e,c} \cdot n &= k_D^+ \tilde{S}_e - k_D S_{O,c}(\tilde{C}_{e,c}, \tilde{S}_e, \tilde{S}_{C,e}) \\
-D_S \nabla S_{e,c} \cdot n &= 0
\end{align*}\]

\[\begin{align*}
\partial_t S_{C,e} - D_{SC} \Delta S_{C,e} &= k_C^+ f_e(\tilde{C}_{e,c})\tilde{S}_e - k_C^- \tilde{S}_{C,e} \\
-D_{SC} \nabla S_{C,e} \cdot n &= k_{CO}^+ \tilde{S}_{C,e} - k_{CO} S_{CO,e}(\tilde{C}_{e,c}, \tilde{S}_e, \tilde{S}_{C,e}) \\
-D_{SC} \nabla S_{C,e} \cdot n &= 0
\end{align*}\]

The solution of this system is unique and the operator \(T\) is continuous, where \(S_{D,c}(\tilde{C}_{e,c}, \tilde{S}_e, \tilde{S}_{C,e})\) and \(S_{CO,e}(\tilde{C}_{e,c}, \tilde{S}_e, \tilde{S}_{C,e})\) depend on \(\tilde{C}_{e,c}, \tilde{S}_e\) and \(\tilde{S}_{C,e}\).

The space \(\{u \in L^2([0, \tau], H^1(\Omega^2_1))\} \cap \partial_t u \in L^2([0, \tau], H^1(\Omega^2_1))\) is compactly embedded in \(V_1\), \(\{u \in L^2([0, \tau], \epsilon H^1(\Omega^2_1))\} \cap \partial_t u \in L^2([0, \tau], H^1(\Omega^2_1))\) is compactly embedded in \(V_2\) and \(\{u \in L^2([0, \tau], H^1(\Omega^2_{ER}))\} \cap \partial_t u \in L^2([0, \tau], H^1(\Omega^2_{ER}))\) is compactly embedded in \(V_{ER}\) (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 \((\tilde{C}_{e,c}, \tilde{S}_e, \tilde{S}_{C,e}) \in V^1 \times V^2 \times (V_{ER})^2\) to \((\tilde{C}_{e,c}, \tilde{S}_e, \tilde{S}_{C,e})\) is \(V^1 \times V^2 \times (V_{ER})^2\) and compact.

It is left to show that for the initial value \(y_0 = (C_0(0), C_{e,c}(0), S_0(0), S_{O,c}(0), S_{CO,c}(0))\) it holds that \((\tilde{C}_{e,c}, \tilde{C}_{e,c}, \tilde{S}_e, \tilde{S}_{C,e}) \in B_{r_0}(0)\) implies

\( (I \circ T)(\tilde{C}_{e,c}, \tilde{C}_{e,c}, \tilde{S}_e, \tilde{S}_{C,e}) \in B_{r_0}(r)\). This means that \(\|\tilde{C} \|_{V_1}^2 + \|\tilde{C}_{e,c}\|_{V_2}^2 + \|\tilde{S}_e\|_{V_{ER}}^2 + \|\tilde{S}_{C,e}\|_{V_{ER}}^2 \leq r\) should imply \(\|\tilde{C}\|_{V_1}^2 + \|\tilde{C}_{e,c}\|_{V_2}^2 + \|\tilde{S}_e\|_{V_{ER}}^2 + \|\tilde{S}_{C,e}\|_{V_{ER}}^2 \leq r\) 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 \(C_e\) with \(C_e\) and integrate from 0 to \(t\) for \(0 < t \leq \tau\).

\[\begin{align*}
\frac{1}{2} \|C_e\|_{\Omega^2}^2 + D_C \|\nabla C_e\|_{\Omega^2}^2 \\
&\leq c_1 \epsilon \|C_{e,c}\|_{L^2([0, \tau], H^1(\Omega^2_{ER}))}^2 + c_2 \epsilon \|\tilde{C}_{e,c}\|_{L^2([0, \tau], H^1(\Omega^2_{ER}))}^2 \\
&\quad + c_3 \epsilon \|\tilde{S}_e\|_{L^2([0, \tau], H^1(\Omega^2_{ER}))}^2 + c_4 \epsilon \|\tilde{S}_{C,e}\|_{L^2([0, \tau], H^1(\Omega^2_{ER}))}^2 \\
&\quad + c_5 \lambda \|\tilde{S}_e\|_{L^2([0, \tau], H^1(\Omega^2_{ER}))}^2 + c_6 \lambda \|\tilde{S}_{C,e}\|_{L^2([0, \tau], H^1(\Omega^2_{ER}))}^2 + c_7 \lambda \|\tilde{C}\|_{L^2([0, \tau], H^1(\Omega^2_{ER}))}^2 + c\eta \tau,
\end{align*}\]
Using the trace inequality and Lemma 3.24 from [27] we obtain
\[
\|C_\varepsilon\|^2_{\Omega} + \left( D_C - c_3 \varepsilon^2 \frac{1}{\lambda} c_4 - \frac{1}{\lambda} c_5 \right) \|\nabla C_\varepsilon\|^2_{\Omega_{\varepsilon}^1, t} \leq c_1 \frac{1}{\lambda} \|C_\varepsilon\|^2_{\Omega_{\varepsilon}^1, t} + c_2 \lambda \varepsilon^{-n} \left( \|C_\varepsilon\|^2_{L^2([0,t], H^1(\Omega_\varepsilon))} \right) + c_3 \varepsilon^{-n} \left( \|C_\varepsilon\|^2_{L^2([0,t], H^{1-\delta}(\Omega_\varepsilon))} \right) + c_4 \lambda \|\nabla y\|^2_{L^2(\Omega_\varepsilon^1, H^{1-\delta}(\Omega_\varepsilon))} + c_5 r
\]
with \(c_2, c_3\) large but finite for \(\varepsilon > 0\). For \(\varepsilon\) small enough and \(\lambda\) large enough we find with Gronwall’s lemma that \(\|C_\varepsilon\|_{\Omega}^2 + \|\nabla C_\varepsilon\|^2_{\Omega_{\varepsilon}^1, t} \leq c_1 r\). This inequality yields \(\|C_\varepsilon\|^2_{L^2([0,t], H^1(\Omega_\varepsilon))} \leq c_1 r\) and \(\|C_\varepsilon\|^2_{L^2([0,t], \Omega_\varepsilon)} \leq \tau c_2 r\).

With a standard interpolation inequality (cf. [1]) we find
\[
\|C_\varepsilon\|^2_{\Omega_\varepsilon^1} \leq c_2 \|C_\varepsilon\|^2_{L^2([0,t], H^1(\Omega_\varepsilon))} \|C_\varepsilon\|^2_{L^2([0,t], \Omega_\varepsilon^1)} \leq c_3 (c_1 r)^{1-\delta} (\tau c_2 r)^{\delta} = cr^{-\delta}.
\]
With similar transformations we also get the corresponding inequality for the equations for \(C_{e, \varepsilon}, S_{e}\) and \(S_{C, \varepsilon}\). In the end, we choose \(\tau\) such that \(\tau < \frac{1}{4c_4}\) and get
\[
\|C_\varepsilon\|^2_{\Omega_\varepsilon^1} + \|C_{e, \varepsilon}\|^2_{\Omega_\varepsilon^2} + \|S_{e}\|^2_{\Omega_\varepsilon^1} + \|S_{C, \varepsilon}\|^2_{\Omega_\varepsilon^1} \leq r,
\]
and the proof is complete. \(\square\)

7. Identification of the limit problem as \(\varepsilon \rightarrow 0\)

In this section we determine the limit equation of the system (6) for \(\varepsilon\) tending to zero. We define \(\chi^1(y), \chi^2(y)\) and \(\chi^{ER}(y)\) with \(y = \frac{x}{\varepsilon}\), which is \(1\) in \(\Omega_{\varepsilon}^1, \Omega_{\varepsilon}^2\) and \(\Omega_{\varepsilon}^{ER}\), 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 \(C_\varepsilon, C_{e, \varepsilon}, S_{e}\) 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 \(S_0,\varepsilon\) and \(S_{CO, \varepsilon}\) converge strongly in \(L^2([0,T], L^2(\Gamma_1))\) to \(S_{0,0}\) and \(S_{CO,0}\), respectively, up to a subsequence.

- For the function \(f_{SERCA}\) on \(\Gamma_{\varepsilon}^{ER}\) we easily get that
\[
\lim_{\varepsilon \to 0} \varepsilon (f_{SERCA}(C_\varepsilon), \varphi_{\varepsilon})_{L^2(\Gamma_{\varepsilon}^{ER})} = (f_{\varepsilon}^{ER}, f_{\varepsilon}^{ER})_{L^2(\Gamma_1)}
\]
with \(C_\varepsilon\) strongly converging to \(C_0\).

- In the domain \(\Omega_\varepsilon^{ER}\) we find the nonlinear function \(f_\varepsilon(C_{e, \varepsilon})\) in the equations for \(S_{e}\) and \(S_{C, \varepsilon}\). Since \(C_{e, \varepsilon}\) and \(S_{e}\) converge strongly in \(\Omega_\varepsilon^{ER}\), we derive that
\[
\lim_{\varepsilon \to 0} \int_{\Omega} \chi_\varepsilon^{ER} \left( \frac{x}{\varepsilon} \right) k_0 f_\varepsilon(C_{e, \varepsilon}) S_{e} \varphi_{\varepsilon} \, dx = \int_{\Omega} \int_{\Omega_{\varepsilon}^{ER}} k_0 f_\varepsilon(C_{e, 0}) S_{0} \varphi_{0} \, dy \, dx
\]
where \(\chi_\varepsilon^{ER}\) is equal to 1 for \(\frac{x}{\varepsilon} \in \Omega_\varepsilon^{ER}\) and 0 otherwise and \(C_{e, \varepsilon}\) converges strongly to \(C_{e, 0}\).

- To find the limit of the term containing the influx \(I_{CRAC}(S_{0, \varepsilon})\) we use that \(S_{0, \varepsilon}\) converges strongly to \(S_{0, 0}\) in \(L^2([0,T], L^2(\Gamma_1))\), hence
\[
\lim_{\varepsilon \to 0} \int_{\Gamma_1} \chi_\varepsilon \left( \frac{x}{\varepsilon} \right) I_{CRAC}(S_{0, \varepsilon}) \varphi_{\varepsilon} \, d\sigma_x = \int_{\Gamma_1} \int_{\Omega_{\varepsilon}^{ER}} I_{CRAC}(S_{0, 0}) \varphi_{0} \, d\sigma_{y} \, d\sigma_{z}
\]
for every \(\varphi_{0} \in C_{\infty}(\Omega)\).
For the boundary term in the equation for $C_\varepsilon$ we use theorem 5 b) to deduce that $C_\varepsilon$ converges strongly in $L^2([0,T] \times \Gamma^1)$ and that

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

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

We use again theorem 5 for the Robin boundary term in the equations for $S_\varepsilon$,

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

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

Analogously we find

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

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

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

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 $C_\varepsilon$ and $C_{e,\varepsilon}$**

We have the equation

$$
\int_{\Omega} \chi^1 \left( \frac{x}{\varepsilon} \right) \partial_t C_\varepsilon \varphi_\varepsilon \, dx + D_C \int_{\Omega} \chi^1 \left( \frac{x}{\varepsilon} \right) \nabla C_\varepsilon \nabla \varphi_\varepsilon \, dx + \varepsilon \int_{\Gamma_{\partial}^1} ((L_0 + L_{IP3})(C_0 - C_{e,\varepsilon}) + f_{SERCA}(C_0)) \varphi_\varepsilon \, d\sigma_x
$$

$$
+ \int_{\Gamma^1} \chi^1 \left( \frac{x}{\varepsilon} \right) I_{CRAC}(S_{O,\varepsilon}) \varphi_\varepsilon \, d\sigma_x + \int_{\Gamma^1} \chi^1 \left( \frac{x}{\varepsilon} \right) (f_P(C_\varepsilon) + f_{NCX}(C_\varepsilon)) \varphi_\varepsilon \, d\sigma_x = 0
$$

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

$$
\int_{\Omega} \int_{Y^1} \partial_t C_0 \varphi_0 \, dy \, dx + D_C \int_{\Omega} \int_{Y^1} (\nabla_y C_0 + \nabla_y C_1 \nabla_y \varphi_0 + \nabla_y \varphi_1) \, dy \, dx
$$

$$
+ \int_{\Omega} \int_{\Gamma_{\partial}^1} ((L_0 + L_{IP3})(C_0 - C_{e,0}) + f_{SERCA}(C_0)) \varphi_0 \, dy \, dx + \int_{\Gamma^1} \int_{\partial_\nu Y^1} I_{CRAC}(S_{O,0}) \varphi_0 \, d\sigma_y \, d\sigma_x
$$

$$
+ |\partial_\nu Y^1| \int_{\Gamma^1} (f_P(C_0) + f_{NCX}(C_0)) \varphi_0 \, d\sigma_x = 0
$$

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 $C_1 \in L^2([0,T], L^2(\Omega, H^1(\Gamma^1)))$.  

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Analogously we find for $\varepsilon \to 0$

$$\int_{\Omega} \int_{\Gamma \setminus \Gamma_{ER}} \partial_{t} C_{\varepsilon,0} \phi_{0} d\gamma d\sigma + D_{ER} \int_{\Omega} \int_{\Gamma \setminus \Gamma_{ER}} [\nabla_{x} C_{\varepsilon,0} + \nabla_{y} C_{\varepsilon,1}][\nabla_{x} \phi_{0} + \nabla_{y} \phi_{1}] d\gamma d\sigma$$

$$+ \int_{\Omega} \int_{\Gamma_{ER}} ((L_{0} + L_{IP_{3}})(C_{\varepsilon,0} - C_{0}) - f_{SERCA}(C_{0})) \varphi_{0} d\gamma d\sigma = 0$$

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

**Limit equation for $S_{\varepsilon}$ and $S_{C,\varepsilon}$**

We have

$$\int_{\Omega} \chi_{ER}^{\Omega} \left(\frac{x}{\varepsilon}\right) \partial_{t} S_{\varphi} \varphi d\sigma + D_{S} \int_{\Omega} \chi_{ER}^{\Omega} \left(\frac{x}{\varepsilon}\right) \nabla_{x} S_{\varphi} \nabla_{x} \varphi d\sigma$$

$$+ \int_{\Omega} \chi_{ER}^{\Omega} \left(\frac{x}{\varepsilon}\right) (k_{C}^{-} f_{C}(C_{\varepsilon}) S_{\varphi} - k_{C}^{-} S_{C,\varepsilon} \varphi_{0}) d\sigma d\sigma = 0$$

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

$$\int_{\Omega} \int_{\Omega_{ER}} \partial_{t} S_{\varphi} \varphi d\sigma + D_{S} \int_{\Omega} \int_{\Omega_{ER}} [\nabla_{x} S_{\varphi} + \nabla_{y} S_{1}] [\nabla_{x} \varphi_{0} + \nabla_{y} \varphi_{1}] d\sigma d\sigma$$

$$+ \int_{\Omega} \int_{\Omega_{ER}} (k_{C}^{-} f_{C}(C_{\varepsilon}) S_{\varphi} - k_{C}^{-} S_{C,\varepsilon} \varphi_{0}) d\sigma d\sigma + \int_{\Gamma_{1}} \int_{\partial_{y} Y_{ER}} k_{C}^{-} S_{\varphi} \varphi_{0} d\sigma y d\sigma x$$

$$- \int_{\Gamma_{1}} \int_{\partial_{y} Y_{ER}} k_{C}^{-} S_{C,\varepsilon} \varphi_{0} d\sigma y d\sigma x = 0$$

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

Analogously we obtain

$$\int_{\Omega} \int_{\Omega_{ER}} \partial_{t} S_{\varphi} \varphi d\sigma + D_{S} \int_{\Omega} \int_{\Omega_{ER}} [\nabla_{x} S_{\varphi} + \nabla_{y} S_{1}] [\nabla_{x} \varphi_{0} + \nabla_{y} \varphi_{1}] d\sigma d\sigma$$

$$+ \int_{\Omega} \int_{\Omega_{ER}} (k_{C}^{-} f_{C}(C_{\varepsilon}) S_{\varphi} - k_{C}^{-} S_{C,\varepsilon} \varphi_{0}) d\sigma d\sigma + \int_{\Gamma_{1}} \int_{\partial_{y} Y_{ER}} k_{C}^{-} S_{\varphi} \varphi_{0} d\sigma y d\sigma x$$

$$- \int_{\Gamma_{1}} \int_{\partial_{y} Y_{ER}} k_{C}^{-} S_{C,\varepsilon} \varphi_{0} d\sigma y d\sigma x = 0$$

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

Now we consider the functions $S_{\varphi,0} \varphi$ and $S_{C,\varphi,0}$ which are only defined on the boundary $\Gamma_{1} \setminus \partial Y_{ER}$ and homogenization takes place in one dimension less.

**Limit equation for $S_{\varphi,0} \varphi$ and $S_{C,\varphi,0}$**

The equation for $S_{\varphi,0} \varphi$ is given by

$$\int_{\Gamma_{1}} \chi_{ER}^{\Gamma_{1}} \left(\frac{x}{\varepsilon}\right) \partial_{t} S_{\varphi,0} \varphi d\sigma + \int_{\Gamma_{1}} \chi_{ER}^{\Gamma_{1}} \left(\frac{x}{\varepsilon}\right) (k_{C}^{-} S_{\varphi,0} - k_{C}^{+} S_{\varphi,0} - k_{C}^{-} S_{C,\varphi,0} + k_{C}^{+} f_{C}(C_{\varepsilon}) S_{\varphi,0}) \varphi d\sigma x = 0$$

for all $\varphi_{-} \in C^{\infty}(\Gamma_{1}, C^{\infty}_{\#}(\partial Y))$. For $\varepsilon \to 0$ we get

$$\int_{\Gamma_{1}} \int_{\partial_{y} Y_{ER}} \partial_{t} S_{\varphi,0} \varphi d\sigma y d\sigma x$$

$$+ \int_{\Gamma_{1}} \int_{\partial_{y} Y_{ER}} (k_{C}^{-} S_{\varphi,0} - k_{C}^{+} S_{\varphi,0} - k_{C}^{-} S_{C,\varphi,0} + k_{C}^{+} f_{C}(C_{\varepsilon}) S_{\varphi,0}) \varphi d\sigma y d\sigma x = 0$$

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for all $\varphi_0 \in C^\infty(\Gamma^1, C^\infty_\#(\partial_0 Y))$, where $S_{O,0} \in L^2([0,T], L^2(\Gamma^1, L^2(\partial_0 Y^{ER})))$.

Analogously we obtain

$$\int_{\Gamma^1} \int_{\partial_0 Y^{ER}} \partial_t S_{CO,0} \varphi_0 d\sigma_0 d\sigma_x + \int_{\Gamma^1} \int_{\partial_0 Y^{ER}} (k^-_{CO} S_{CO,0} - k^-_{CO} S_{C,0} + k^-_{C} f_c(C_{e,0}) S_{O,0}) \varphi_0 d\sigma_0 d\sigma_x = 0$$

for $\varepsilon \to 0$ for all $\varphi_0 \in C^\infty(\Gamma^1, C^\infty_\#(\partial_0 Y))$, where $S_{CO,0} \in L^2([0,T], L^2(\Gamma^1, L^2(\partial_0 Y^{ER})))$.

**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|^2(\partial_t C_{e,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} + |Y^{ER}|((L_0 + L_{IP3})(C_{e,0} - C_{e,1}) + f_{SERCA}(C_0), \varphi_0)_{\Omega} + \langle \partial_{1} C_{e,0}, \varphi_1 \rangle_{\Gamma^1 \times \partial_2 Y^1} + |\partial_0 Y|^1(f_{P}(C_0) + f_{NCX}(C_0), \varphi_0)_{\Gamma^1} = 0,$n

$$|Y|^2(\partial_t S_{CO,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^2} + |Y^{ER}|((k^+_C, f_c(C_{e,0}) S_0 - k^-_{CO} S_{CO,0}, \varphi_0)_{\Omega} + |\partial_0 Y^{ER}|(k^+_C S_0 - k^-_{CO} S_{CO,0}, \varphi_0)_{\Gamma^1} = 0,$n

$$|Y^{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^{ER}} + |Y^{ER}|((k^-_C, S_{C,0} - k^-_{C} f_c(C_{e,0}) S_{O,0}, \varphi_0)_{\Omega} + |\partial_0 Y^{ER}|(k^-_C S_{C,0} - k^-_{CO} S_{CO,0}, \varphi_0)_{\Gamma^1} = 0,$n

$$\langle \partial_t S_{O,0}, \varphi_1 \rangle_{\Gamma^1} + (k^-_{CO} S_{O,0} - k^-_{CO} S_{CO,0} + k^-_{C} f_c(C_{e,0}) S_{O,0}, \varphi_0)_{\Gamma^1} = 0,$n

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 $\Gamma^{ER}$. From now on, we rename the functions $(C_0, C_{e,0}, S_0, S_{C,0}, S_{O,0}, S_{CO,0})$ by $(C, C_{e}, S, C_{CO}, S_{O}, S_{CO})$ to avoid confusion.

**8. Identification of the Calcium–Stim1 limit model**

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

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

$\delta$-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 $\delta$ and limit passage are proven and performed in the proof of Theorem 1 and we deduce that

$$
[I_{\text{ER}}] \int \Omega \partial_t S \varphi_0 dx + \int \Omega \sum_{i,j} \partial_y S \mathcal{D} \int_{\Gamma_{\text{EN}}} (P(\varepsilon_j + \nabla \mu_j^S)) d\sigma_y \partial_x \varphi_0 dx + \int_{\Gamma_1} (k_C S - k_O S_O) \varphi_0 d\sigma_x = 0
$$

with

$$
\nabla \cdot (P(\varepsilon_j + \nabla \mu_j^S)) = 0 \quad \text{in } \Gamma_{\text{ER}},
$$

$$
P(\varepsilon_j + \nabla \mu_j^S) \cdot n = 0 \quad \text{on } \partial \Gamma_{\text{ER}},
$$

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

$\delta$-limit for the other functions

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

$$
\nabla_y \cdot D_C(\varepsilon_j + \nabla \mu_j^C) = 0 \quad \text{in } Y^1,
$$

$$
D_C(\varepsilon_j + \nabla \mu_j^C) \cdot n = 0 \quad \text{on } \Gamma_{\text{ER}},
$$

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

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

$$
\nabla_y \cdot D_{ER}(\varepsilon_j + \nabla \mu_j^c) = 0 \quad \text{in } Y^2,
$$

$$
D_{ER}(\varepsilon_j + \nabla \mu_j^c) \cdot n = 0 \quad \text{on } \Gamma_{\text{ER}},
$$

and $\mu_j^c$ must be $Y$-periodic for $j = 1, \ldots, n$. Further, we define the diffusion tensor $P_{ij}^{ER} := \int_{Y^2} D_{ER}(\delta_{ij} + \partial_y \mu_j^c) dy$.

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

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.

\[
|Y^1| (\partial_t(C_1 - C_2), C_1 - C_2)_\Omega + (D^C(\nabla C_1 - \nabla C_2), \nabla C_1 - \nabla C_2)_\Omega \\
+ |\Gamma^{ER}| (L_0 + L_{IP3})(C_1 - C_2 - (C_{e,1} - C_{e,2}), C_1 - C_2)_\Omega \\
+ |\Gamma^{ER}| (f_{SERCA}(C_1) - f_{SERCA}(C_2), C_1 - C_2)_\Omega \geq 0, \text{ since } f_{SERCA} \text{ monotone, increasing} \\
+ \alpha(I_{CRAC}(S_{O,1}) - I_{CRAC}(S_{O,2}), C_1 - C_2)_{\Gamma \times \partial_\Omega} \\
+ |\partial_t Y^1| (f_p(C_1) + f_{NCX}(C_1) - f_p(C_2) - f_{NCX}(C_2), C_1 - C_2)_\Omega = 0.
\]

Integrating from 0 to $t$ gives

\[
\frac{1}{2} |Y^1|^2 ||C_1 - C_2||^2_{\Omega,t} + \|D^C \nabla (C_1 - C_2)\|^2_{\Omega,t} \\
\leq |\Gamma^{ER}| (L_0 + L_{IP3}) ||C_{e,1} - C_{e,2}, C_1 - C_2||_{\Omega,t} + ||\partial_t Y^1| \alpha L_{CRAC} ||(S_{O,1} - S_{O,2}, C_1 - C_2)_{\Gamma \times \partial_\Omega}||,
\]

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 $\lambda$ and the trace inequality. We merge the constants leading to

\[
\frac{1}{2} |Y^1|^2 ||C_1 - C_2||^2_{\Omega,t} + (D^C - \epsilon_3 \lambda) \|\nabla (C_1 - C_2)\|^2_{\Omega,t} \\
\leq c_1 ||C_{e,1} - C_{e,2}||^2_{\Omega,t} + c_2 ||C_1 - C_2||^2_{\Omega,t} + c_3 \|S_{O,1} - S_{O,2}\|^2_{\Gamma \times \partial_\Omega}.
\]

We perform a similar estimation for $C_e$, $S$, $SC$, $SO$ and $SCO$. With Gronwall’s lemma we deduce that

\[
||C_1 - C_2||^2_{\Omega,t} + ||C_{e,1} - C_{e,2}||^2_{\Omega,t} + ||S_1 - S_2||^2_{\Omega,t} + ||SC_{1} - SC_{2}||^2_{\Omega} \\
+ \|S_{O,1} - S_{O,2}\|^2_{\Gamma \times \partial_\Omega} + \|SCO_{1} - SCO_{2}\|^2_{\Gamma \times \partial_\Omega} \leq 0
\]

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

\[\square\]

References


