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HOMOGENIZATION OF A CARCINOGENESIS MODEL WITH DIFFERENT SCALINGS WITH THE HOMOGENIZATION PARAMETER

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Abstract. In the context of periodic homogenization based on two-scale convergence, we homogenize a linear system of four coupled reaction-diffusion equations, two of which are defined on a manifold. The system describes the most important subprocesses modeling the carcinogenesis of a human cell caused by Benzo-[a]-pyrene molecules. These molecules are activated to carcinogens in a series of chemical reactions at the surface of the endoplasmic reticulum, which constitutes a fine structure inside the cell. The diffusion on the endoplasmic reticulum, modeled as a Riemannian manifold, is described by the Laplace-Beltrami operator. For the binding process to the surface of the endoplasmic reticulum, different scalings with powers of the homogenization parameter are considered. This leads to three qualitatively different models in the homogenization limit.

Keywords: periodic homogenization; two-scale convergence; carcinogenesis; reaction-diffusion system; surface diffusion

MSC 2010: 35B27, 35K51, 35K58, 92C37

1. Introdution

The method of periodic homogenization is a mathematical tool for upscaling rigorously models of multiscale processes. Often, the microstructure of the material leads to the multiscale nature of the given problem. Because it is too costly to resolve the microstructure in detail using numerical simulations, homogenized models are used to describe the process on a much larger observation scale and these are mostly entirely sufficient for practical purposes. The idea of periodic homogenization relies on the assumption of periodicity of the material with respect to a reference cell. The homogenized model is found by considering the limit as the periodicity length approaches zero. Monographs on the subject are [3], [24], [2], [14], [6], [15].

The endoplasmic reticulum of a biological cell is a bilayered membrane, which pervades the whole cytoplasm of the cell. Considering the problem on lengthscales of the order of the cell diameter, one can assume that, roughly speaking, the endoplasmic reticulum is everywhere and nowhere in the cell. To handle this fine structure, we use periodic homogenization based on two-scale convergence [1], [17], [16].

We apply two-scale convergence to homogenize a linear model for carcinogenesis of a human cell, where carcinogenic molecules invade a cell, perform chemical reactions to more aggressive molecules and enter the nucleus to bind to the DNA. The transformations to the aggressive molecules take place at the surface of the endoplasmic reticulum. The binding process to the surface of the endoplasmic reticulum is scaled with different powers of the homogenization parameter, $\varepsilon > 0$. This leads to three qualitatively different models in the homogenization limit. As a byproduct of the homogenization process of the carcinogenesis model, we indirectly find the homogenization limit of an ε-depending operator involving the heat kernel defined on a manifold.

This paper is organized as follows. In Section 2 the system of reaction-diffusion equations is introduced and its relation to carcinogenesis in a human cell is explained. Further, we show the a-priori estimates in Section 3, where boundedness in L^2 independent of ε is proven. In Section 4 the model is abbreviated by finding analytical solutions of the equations defined on the surface of the endoplasmic reticulum. This facilitates the verification of the existence of a solution for every $\varepsilon > 0$ in Section 5. The limit for ε tending to zero is characterized in Section 6. Finally we show uniqueness of the limit model in Section 7.

2. Statement of the problem on the microscale

One of the longest known and best understood causes for carcinogenesis is the molecule *Benzo-[a]-pyrene*, abbreviated by BP. It is found, for example, in coal tar, automobile exhaust fumes, cigarette smoke and charbroiled food. One of the main reasons for lung cancer (caused by inhaling cigarette smoke), testicular cancer and skin cancer is the contact with the molecule Benzo-[a]-pyrene (see [13], [11]).

The activation of BP to carcinogens mostly takes place on the surface of the endoplasmic reticulum induced by the enzyme system called MFO *(microsomal mixed-function oxidases)*. Normally the MFOs serve a detoxification role, but unfortunately not in this case (see [10], [23], [27], [18]). We abbreviate *endoplasmic reticulum* by ER.

The process of toxification is simplified by the following scenario: BP molecules pass the plasma membrane from the intercellular space to the cytosol inside of a human cell, where they diffuse freely, but they cannot enter the nucleus. They can bind to the surface of the endoplasmic reticulum. There, a series of chemical reactions takes place caused by the enzyme system MFO, which ultimately results in BP being chemically activated to a diol epoxide (DE), which can bind to DNA. From the mathematical point of view, we summarize the reactions to just one metabolism from BP to DE. Newly created DE molecules unbind from the surface of the endoplasmic reticulum and diffuse again in the cytosol of the cell. There they may enter the nucleus. Hence, BP cannot pass the nuclear membrane and DE cannot pass the plasma membrane, which describes a worst case scenario. Here, when DE molecules enter the nucleus, we stop our consideration. A nonlinear carcinogenesis model based on similar modelling assumptions is presented in [12]. It is also worth poiting out [4], in which the metabolism in the cell has been modelled similarly.

In order to formulate a mathematical model of this process, we require some notation. Let $\Omega \subset \mathbb{R}^n$ be a human cell with the domain occupied by the nucleus removed, which has Lipschitz boundary $\partial\Omega$. The process shall happen in the time interval $[0, T]$ for fixed $0 < T < \infty$. We suppose that the endoplasmic reticulum has a periodic structure. For this purpose we define a model district $Y = [0, 1]^n$. Let $Y^{**} \subset Y$ be such that the smooth manifold $\Gamma = \partial Y^{**}$ does not touch the boundary of Y. This is the lumen of the ER. The volume occupied by cytosol is given by $Y^* = (0, 1)^n \setminus \overline{Y^{**}}$. We pave the cell with the model districts of size $\varepsilon > 0$, $\varepsilon \ll 1$.

We denote the cell membrane by Γ_{C} and the boundary of nucleus by Γ_{N} so that $\partial\Omega = \Gamma_{\mathrm{C}} \cup \Gamma_{\mathrm{N}}$. Furthermore, Ω_ε and Γ_ε are defined as $\Omega_\varepsilon := \bigcup\limits_{k\in\mathbb{Z}^n} \varepsilon(Y^* + k) \cap \Omega$ and $\Gamma_\varepsilon := \bigcup\limits_{k\in\mathbb{Z}^n} \varepsilon(\Gamma + k) \cap \Omega$ and we assume that the geometry is such that $\Gamma_\varepsilon \cap \partial\Omega = \emptyset$.

Further, the concentration of BP molecules in cytosol is denoted by $u_\varepsilon\colon \Omega_\varepsilon \times [0, T] \to \mathbb{R}$ and the concentration of DE molecules in cytosol is $v_\varepsilon\colon \Omega_\varepsilon \times [0, T] \to \mathbb{R}$. The concentration of BP molecules bound to the surface of the endoplasmic reticulum is denoted by $s_\varepsilon\colon \Gamma_\varepsilon \times [0, T] \to \mathbb{R}$ and the concentration of DE molecules bound to the surface of the endoplasmic reticulum is denoted by $w_\varepsilon\colon \Gamma_\varepsilon \times [0, T] \to \mathbb{R}$. We set the initial values to be $u_\varepsilon(x, t) = u_I(x)$, $v_\varepsilon(x, t) = v_I(x)$ for $t = 0$, $x \in \Omega$ and $s_\varepsilon(x, t) = s_I(x)$, $w_\varepsilon(x, t) = w_I(x)$ for $t = 0$, $x \in \Gamma_\varepsilon$ and assume that the initial values are smooth, bounded and nonnegative. Further, at the membrane of the ER, Γ_ε, we multiply the binding-unbinding term by ε^l, for $l \geqslant 0$. The higher the exponent l, the slower is the exchange between bound and unbound molecules. An exchange in "normal" speed would be $l = 1$, because the binding process happens on a surface, see [20], [16], [5], but also other values would make sense for special binding-unbinding processes. For $l < 1$, the binding process is faster; for $l > 1$ it is slower. We denote the exponent of ε in the term that corresponds to the binding term for DE molecules by $m \geqslant 0$. More examples for homogenization of systems of equations describing chemical reactions and the influence of scaling can be found in [21], [22], [19].

For the weak formulation we need the function spaces $\mathcal{V}(\Omega_\varepsilon) = L^2([0,T], H^1(\Omega_\varepsilon)) \cap H^1([0,T], H^1(\Omega_\varepsilon)')$, $\mathcal{V}_{\rm N}(\Omega_\varepsilon) = \{u \in \mathcal{V}(\Omega_\varepsilon);\ u = 0 \text{ on } \Gamma_{\rm N}\}$, $\mathcal{V}_{\rm C0}(\Omega_\varepsilon) = \{u \in \mathcal{V}(\Omega_\varepsilon);\ u = 0 \text{ on } \Gamma_{\rm C}\}$, $\mathcal{V}_{\rm C}(\Omega_\varepsilon) = \{u \in \mathcal{V}(\Omega_\varepsilon);\ u = u_{\rm Boundary} \text{ on } \Gamma_{\rm C}\}$ and $\mathcal{V}(\Gamma_\varepsilon) = L^2([0,T], H^1(\Gamma_\varepsilon)) \cap H^1([0,T], H^1(\Gamma_\varepsilon)')$, where $u_{\rm Boundary} \in H^{1/2}(\Gamma_{\rm C})$. For the homogenization limits, we need the function spaces $\mathcal{V}(\Omega, Y) = L^2([0,T] \times \Omega, H^1_\#(Y))$ and $\mathcal{V}(\Omega, \Gamma) = L^2([0,T] \times \Omega, H^1(\Gamma))$. For the test functions we define the function spaces $V_{\rm C0}(\Omega_\varepsilon) = \{u \in H^1(\Omega_\varepsilon);\ u = 0 \text{ on } \Gamma_{\rm C}\}$, $V_{\rm N}(\Omega_\varepsilon) = \{u \in H^1(\Omega_\varepsilon);\ u = 0 \text{ on } \Gamma_{\rm N}\}$, $V(\Gamma_\varepsilon) = H^1(\Gamma_\varepsilon)$, $V(\Omega, Y) = L^2(\Omega, H^1_\#(Y))$ and $V(\Omega, \Gamma) = L^2(\Omega, H^1(\Gamma))$. For $u, v \in L^2(\Gamma_\varepsilon)$ we use the scalar product $\langle u, v\rangle_{\Gamma_\varepsilon} := \int_{\Gamma_\varepsilon} g_\varepsilon uv \,{\rm d}\sigma_x$, where g_ε is the metric tensor on Γ_ε, see [8].

Having fixed notation, we state the model equations in their weak form: Find $(u_\varepsilon, v_\varepsilon, s_\varepsilon, w_\varepsilon) \in \mathcal{V}_{\rm C}(\Omega_\varepsilon) \times \mathcal{V}_{\rm N}(\Omega_\varepsilon) \times \mathcal{V}(\Gamma_\varepsilon) \times \mathcal{V}(\Gamma_\varepsilon)$ with $(u_\varepsilon(x,0), v_\varepsilon(x,0), s_\varepsilon(x,0), w_\varepsilon(x,0)) = (u_I(x), v_I(x), s_I(x), w_I(x))$ such that for all $(\varphi_1, \varphi_2, \psi_3, \psi_4) \in V_{\rm C0}(\Omega_\varepsilon) \times V_{\rm N}(\Omega_\varepsilon) \times V(\Gamma_\varepsilon) \times V(\Gamma_\varepsilon)$ we have

$$
\begin{aligned}
(1)\qquad & (\partial_t u_\varepsilon, \varphi_1)_{\Omega_\varepsilon} + D_u(\nabla u_\varepsilon, \nabla\varphi_1)_{\Omega_\varepsilon} + \varepsilon^l l_s\langle u_\varepsilon - s_\varepsilon, \varphi_1\rangle_{\Gamma_\varepsilon} = 0,\\
& (\partial_t v_\varepsilon, \varphi_2)_{\Omega_\varepsilon} + D_v(\nabla v_\varepsilon, \nabla\varphi_2)_{\Omega_\varepsilon} + \varepsilon^m l_w\langle v_\varepsilon - w_\varepsilon, \varphi_2\rangle_{\Gamma_\varepsilon} = 0,\\
& \varepsilon\langle\partial_t s_\varepsilon, \psi_3\rangle_{\Gamma_\varepsilon} + \varepsilon D_s\langle\varepsilon\nabla_\Gamma s_\varepsilon, \varepsilon\nabla_\Gamma\psi_3\rangle_{\Gamma_\varepsilon} + \varepsilon f\langle s_\varepsilon, \psi_3\rangle_{\Gamma_\varepsilon}\\
&\qquad\qquad\qquad - \varepsilon^l l_s\langle u_\varepsilon - s_\varepsilon, \psi_3\rangle_{\Gamma_\varepsilon} = 0,\\
& \varepsilon\langle\partial_t w_\varepsilon, \psi_4\rangle_{\Gamma_\varepsilon} + \varepsilon D_w\langle\varepsilon\nabla_\Gamma w_\varepsilon, \varepsilon\nabla_\Gamma\psi_4\rangle_{\Gamma_\varepsilon} - \varepsilon f\langle s_\varepsilon, \psi_4\rangle_{\Gamma_\varepsilon}\\
&\qquad\qquad\qquad - \varepsilon^m l_w\langle v_\varepsilon - w_\varepsilon, \psi_4\rangle_{\Gamma_\varepsilon} = 0.
\end{aligned}
$$

The coefficients $D_u, D_v, D_s, D_w > 0$ describe the diffusion tensors, $l_s, l_w > 0$ are the binding and unbinding rates to the endoplasmic reticulum, and $f > 0$ is the transformation rate from s_ε to w_ε.

3. A priori estimates for the solutions of the micromodel

First we show that the concentrations of molecules stay nonnegative for nonnegative initial values. We then proceed by proving energy estimates.

Theorem 1 (Positivity). *The functions u_ε and v_ε are nonnegative for almost every $x \in \Omega_\varepsilon$ and $t \in [0,T]$. The functions s_ε and w_ε are nonnegative for almost every $x \in \Gamma_\varepsilon$ and $t \in [0,T]$.*

Proof. We define $u_{\varepsilon-} = -u_\varepsilon$ if $u_\varepsilon \leqslant 0$ pointwise and $u_{\varepsilon-} = 0$ otherwise. Analogously we define $u_{\varepsilon+}$, $v_{\varepsilon-}$, $s_{\varepsilon-}$ and $w_{\varepsilon-}$. We test the weak formulation for u_ε

and s_ε with $-u_{\varepsilon-}$ and $-s_{\varepsilon-}$, respectively,

$$\begin{aligned}&(\partial_t u_{\varepsilon-}, u_{\varepsilon-})_{\Omega_\varepsilon} + (D_u \nabla u_{\varepsilon-}, \nabla u_{\varepsilon-})_{\Omega_\varepsilon} + \varepsilon^l l_s \langle u_{\varepsilon-} + s_\varepsilon, u_{\varepsilon-}\rangle_{\Gamma_\varepsilon} = 0,\\ &\varepsilon\langle \partial_t s_{\varepsilon-}, s_{\varepsilon-}\rangle_{\Gamma_\varepsilon} + \varepsilon D_s \langle \varepsilon \nabla_\Gamma s_{\varepsilon-}, \varepsilon \nabla_\Gamma s_{\varepsilon-}\rangle_{\Gamma_\varepsilon} + \varepsilon f \langle s_{\varepsilon-}, s_{\varepsilon-}\rangle_{\Gamma_\varepsilon}\\ &\qquad + \varepsilon^l l_s \langle u_\varepsilon + s_{\varepsilon-}, s_{\varepsilon-}\rangle_{\Gamma_\varepsilon} = 0.\end{aligned}$$

We integrate from 0 to t and add the equations. With the assumption that $u_\varepsilon(0) \geqslant 0$ and $s_\varepsilon(0) \geqslant 0$ we get

$$\begin{aligned}&\tfrac{1}{2}\|u_{\varepsilon-}\|^2_{\Omega_\varepsilon} + D_u \|\nabla u_{\varepsilon-}\|^2_{\Omega_\varepsilon,t} + \tfrac{1}{2}\varepsilon \|s_{\varepsilon-}\|^2_{\Gamma_\varepsilon} + D_s \varepsilon^3 \|\nabla_\Gamma s_{\varepsilon-}\|^2_{\Gamma_\varepsilon,t}\\ &\quad + \varepsilon f \|s_{\varepsilon-}\|^2_{\Gamma_\varepsilon,t} + \varepsilon^l l_s \|u_{\varepsilon-} - s_{\varepsilon-}\|^2_{\Gamma_\varepsilon,t} + \varepsilon^l l_s \langle s_{\varepsilon+}, u_{\varepsilon-}\rangle_{\Gamma_\varepsilon,t} + \varepsilon^l l_s \langle u_{\varepsilon+}, s_{\varepsilon-}\rangle_{\Gamma_\varepsilon,t} = 0.\end{aligned}$$

This yields

$$\begin{aligned}&\tfrac{1}{2}\|u_{\varepsilon-}\|^2_{\Omega_\varepsilon} + D_u \|\nabla u_{\varepsilon-}\|^2_{\Omega_\varepsilon,t} + \tfrac{1}{2}\varepsilon \|s_{\varepsilon-}\|^2_{\Gamma_\varepsilon} + D_s \varepsilon^3 \|\nabla_\Gamma s_{\varepsilon-}\|^2_{\Gamma_\varepsilon,t}\\ &\qquad + \varepsilon f \|s_{\varepsilon-}\|^2_{\Gamma_\varepsilon,t} + \varepsilon^l l_s \|u_{\varepsilon-} - s_{\varepsilon-}\|^2_{\Gamma_\varepsilon,t} \leqslant 0.\end{aligned}$$

We deduce that $u_{\varepsilon-}(x,t) = 0$ for almost every $x \in \Omega_\varepsilon$ and $t \in [0,T]$ and $s_{\varepsilon-}(x,t) = 0$ for almost every $x \in \Gamma_\varepsilon$ and $t \in [0,T]$. This means that $u_\varepsilon(x,t) \geqslant 0$ for almost every $x \in \Omega_\varepsilon$ and $t \in [0,T]$ and $s_\varepsilon(x,t) \geqslant 0$ for almost every $x \in \Gamma_\varepsilon$ and $t \in [0,T]$. Analogously we find that $v_\varepsilon(x,t) \geqslant 0$ for almost every $x \in \Omega_\varepsilon$ and $t \in [0,T]$ and $w_\varepsilon(x,t) \geqslant 0$ for almost every $x \in \Gamma_\varepsilon$ and $t \in [0,T]$. □

Next, we show an a priori estimate in order to verify the conditions to use two-scale convergence results on Ω_ε for u_ε and v_ε. Further we want to use two-scale convergence on manifolds for s_ε and w_ε and we are going to show that the required conditions are fulfilled.

Lemma 2 (Boundedness in L^2)**.** *There is a constant $C > 0$ independent of ε such that*

$$\begin{aligned}&\|u_\varepsilon\|^2_{\Omega_\varepsilon} + D_u \|\nabla u_\varepsilon\|^2_{\Omega_\varepsilon,t} + \|v_\varepsilon\|^2_{\Omega_\varepsilon} + D_v \|\nabla v_\varepsilon\|^2_{\Omega_\varepsilon,t} + \varepsilon \|s_\varepsilon\|^2_{\Gamma_\varepsilon} + D_s \varepsilon^3 \|\nabla_\Gamma s_\varepsilon\|^2_{\Gamma_\varepsilon,t}\\ &\qquad + \varepsilon \|w_\varepsilon\|^2_{\Gamma_\varepsilon} + D_w \varepsilon^3 \|\nabla_\Gamma w_\varepsilon\|^2_{\Gamma_\varepsilon,t} + \varepsilon^l l_s \|u_\varepsilon - s_\varepsilon\|^2_{\Gamma_\varepsilon,t} + \varepsilon^m l_w \|v_\varepsilon - w_\varepsilon\|^2_{\Gamma_\varepsilon,t} \leqslant C\end{aligned}$$

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

Proof. To prove the claim we start with the weak formulation of our problem. We test the equations with the functions $(u_\varepsilon, v_\varepsilon, s_\varepsilon, w_\varepsilon)$ and add them up,

$$\begin{aligned}&(\partial_t u_\varepsilon, u_\varepsilon)_{\Omega_\varepsilon} + (\partial_t v_\varepsilon, v_\varepsilon)_{\Omega_\varepsilon} + D_u(\nabla u_\varepsilon, \nabla u_\varepsilon)_{\Omega_\varepsilon} + D_v(\nabla v_\varepsilon, \nabla v_\varepsilon)_{\Omega_\varepsilon}\\ &+ \varepsilon\langle \partial_t s_\varepsilon, s_\varepsilon\rangle_{\Gamma_\varepsilon} + \varepsilon\langle \partial_t w_\varepsilon, w_\varepsilon\rangle_{\Gamma_\varepsilon} + D_s \varepsilon^3 \langle \nabla_\Gamma s_\varepsilon, \nabla_\Gamma s_\varepsilon\rangle_{\Gamma_\varepsilon} + D_w \varepsilon^3 \langle \nabla_\Gamma w_\varepsilon, \nabla_\Gamma w_\varepsilon\rangle_{\Gamma_\varepsilon}\\ &+ \varepsilon f \langle s_\varepsilon, s_\varepsilon\rangle_{\Gamma_\varepsilon} - \varepsilon f \langle s_\varepsilon, w_\varepsilon\rangle_{\Gamma_\varepsilon} + \varepsilon^l l_s \langle u_\varepsilon - s_\varepsilon, u_\varepsilon - s_\varepsilon\rangle_{\Gamma_\varepsilon}\\ &\qquad\qquad + \varepsilon^m l_w \langle v_\varepsilon - w_\varepsilon, v_\varepsilon - w_\varepsilon\rangle_{\Gamma_\varepsilon} = 0.\end{aligned}$$

With $\frac{1}{2}(\mathrm{d}/\mathrm{d}t)\|u_\varepsilon(t)\|^2_{\Omega_\varepsilon} = (\partial_t u_\varepsilon, u_\varepsilon)_{\Omega_\varepsilon}$, integration from 0 to t and the binomial theorem it holds that

$$\begin{aligned}
&\tfrac{1}{2}\|u_\varepsilon\|^2_{\Omega_\varepsilon} + \tfrac{1}{2}\|v_\varepsilon\|^2_{\Omega_\varepsilon} + D_u\|\nabla u_\varepsilon\|^2_{\Omega_\varepsilon,t} + D_v\|\nabla v_\varepsilon\|^2_{\Omega_\varepsilon,t}\\
&\quad + \varepsilon\tfrac{1}{2}\|s_\varepsilon\|^2_{\Gamma_\varepsilon} + \varepsilon\tfrac{1}{2}\|w_\varepsilon\|^2_{\Gamma_\varepsilon} + D_s\varepsilon^3\|\nabla_\Gamma s_\varepsilon\|^2_{\Gamma_\varepsilon,t} + D_w\varepsilon^3\|\nabla_\Gamma w_\varepsilon\|^2_{\Gamma_\varepsilon,t}\\
&\quad + \varepsilon f\|s_\varepsilon\|^2_{\Gamma_\varepsilon,t} + \varepsilon^l l_s\|u_\varepsilon - s_\varepsilon\|^2_{\Gamma_\varepsilon,t} + \varepsilon^m l_w\|v_\varepsilon - w_\varepsilon\|^2_{\Gamma_\varepsilon,t}\\
&\leqslant \varepsilon f\|s_\varepsilon\|^2_{\Gamma_\varepsilon,t} + \varepsilon f\|w_\varepsilon\|^2_{\Gamma_\varepsilon,t} + \tfrac{1}{2}\|u_\varepsilon(0)\|^2_{\Omega_\varepsilon} + \tfrac{1}{2}\|v_\varepsilon(0)\|^2_{\Omega_\varepsilon} + \tfrac{1}{2}\varepsilon\|s_\varepsilon(0)\|^2_{\Gamma_\varepsilon} + \tfrac{1}{2}\varepsilon\|w_\varepsilon(0)\|^2_{\Gamma_\varepsilon}.
\end{aligned}$$

With initial conditions lying in L^2 we now deduce from Gronwall's lemma that

$$\begin{aligned}
\tfrac{1}{2}\|u_\varepsilon\|^2_{\Omega_\varepsilon} &+ \tfrac{1}{2}\|v_\varepsilon\|^2_{\Omega_\varepsilon} + D_u\|\nabla u_\varepsilon\|^2_{\Omega_\varepsilon,t} + D_v\|\nabla v_\varepsilon\|^2_{\Omega_\varepsilon,t}\\
&+ \varepsilon\tfrac{1}{2}\|s_\varepsilon\|^2_{\Gamma_\varepsilon} + \varepsilon\tfrac{1}{2}\|w_\varepsilon\|^2_{\Gamma_\varepsilon} + D_s\varepsilon^3\|\nabla_\Gamma s_\varepsilon\|^2_{\Gamma_\varepsilon,t} + D_w\varepsilon^3\|\nabla_\Gamma w_\varepsilon\|^2_{\Gamma_\varepsilon,t}\\
&+ \varepsilon^l l_s\|u_\varepsilon - s_\varepsilon\|^2_{\Gamma_\varepsilon,t} + \varepsilon^m l_w\|v_\varepsilon - w_\varepsilon\|^2_{\Gamma_\varepsilon,t} \leqslant C
\end{aligned}$$

and the proof is complete. □

Further, we need one more corollary.

Corollary 3. *There is a constant $C > 0$ independent of ε such that $\varepsilon\|u_\varepsilon\|^2_{\Gamma_\varepsilon,t} < C$ and $\varepsilon\|v_\varepsilon\|^2_{\Gamma_\varepsilon,t} < C$.*

Proof. We assume $\varepsilon < 1$. With the trace inequality and Lemma 2 we find $\varepsilon\|u_\varepsilon\|^2_{\Gamma_\varepsilon,t} \leqslant c_0(\|u_\varepsilon\|^2_{\Omega_\varepsilon,t} + \varepsilon^2\|\nabla u_\varepsilon\|^2_{\Omega_\varepsilon,t}) < C$. Analogous inequalities hold for v_ε. □

In the next section we are going to build an abbreviation of the model that is helpful to show existence of a solution.

4. Abbreviation of the model

The partial differential equation for the functions s_ε and w_ε is a standard non-homogeneous heat equation with an additional linear term on a domain without boundary conditions. For such equations, analytical solutions exist and are unique, see [9]. The right-hand side of the PDE for s_ε and w_ε depends on u_ε and v_ε, respectively; so, the analytical solution also will depend on u_ε or v_ε. We will need to deduce the solution on the Riemannian manifold Γ_ε.

To solve $\partial_t s_\varepsilon - D_s\varepsilon^2\Delta_\Gamma s_\varepsilon + (f + \varepsilon^{l-1}l_s)s_\varepsilon = \varepsilon^{l-1}l_s u_\varepsilon$ on Γ_ε from (1), we implicitly define an auxiliary function λ by $s_\varepsilon(x,t) = \lambda(x,t)\mathrm{e}^{-(f+\varepsilon^{l-1}l_s)t}$ as, e.g., in the proof of Theorem 26.1 in [28]. The solution of the resulting equation for λ is well-known, see [7], [9], and by retransforming, we find the solution s_ε given by

$$
\begin{aligned}
(2)\qquad F(u_\varepsilon) := s_\varepsilon(x,t) &= \mathrm{e}^{(D_s\varepsilon^2\Delta_\Gamma - f - \varepsilon^{l-1}l_s)t} s_I(x)\\
&\quad + \mathrm{e}^{-(f+\varepsilon^{l-1}l_s)t}\varepsilon^{l-1}l_s\int_0^t \mathrm{e}^{D_s\varepsilon^2\Delta_\Gamma(t-s)}u_\varepsilon(s,x)\mathrm{e}^{(f+\varepsilon^{l-1}l_s)s}\,\mathrm{d}s.
\end{aligned}
$$

Analogously, the solution w_ε can be written as

$$
\begin{aligned}
(3)\quad G(u_\varepsilon,v_\varepsilon) := w_\varepsilon(x,t) &= \mathrm{e}^{(D_w\varepsilon^2\Delta_\Gamma - \varepsilon^{m-1}l_w)t} w_I(x)\\
&\quad + \mathrm{e}^{-\varepsilon^{m-1}l_w t}\int_0^t \mathrm{e}^{D_w\varepsilon^2(t-s)\Delta_\Gamma}(\varepsilon^{m-1}l_w v_\varepsilon(s,x) + fF(u_\varepsilon)(s,x))\mathrm{e}^{\varepsilon^{m-1}l_w s}\,\mathrm{d}s.
\end{aligned}
$$

R e m a r k 4. The operators F and G are linear because $\mathrm{e}^{\Delta_\Gamma t}$ and integrals are linear operators.

To show existence of a solution in the next section, we need positivity and boundedness of the operators F and G.

Lemma 5. *The operators* $F\colon L^2([0,T]\times\Gamma_\varepsilon) \to L^2([0,T],H^1(\Gamma_\varepsilon))$ *and* $G\colon L^2([0,T]\times\Gamma_\varepsilon)^2 \to L^2([0,T],H^1(\Gamma_\varepsilon))$ *defined in* (2) *and* (3) *are positive and bounded.*

P r o o f. Davis proves in [7] that for the Laplace operator Δ, the function $\mathrm{e}^{\Delta t}$ has a strictly positive C^∞ kernel. This means there exists a smooth function $k_\varepsilon(t,x) > 0$ for each $t > 0$ (we denote $k_{\varepsilon,t} = k_\varepsilon(t,\cdot)$) such that $\mathrm{e}^{D_s\varepsilon^2\Delta t}f(x) = (f \star k_{\varepsilon,t})(x) = \int_{\Gamma_\varepsilon} k_\varepsilon(t,x-y)f(y)\,\mathrm{d}\sigma_y$ for every $f \in L^2(\Gamma_\varepsilon)$. Hence, for every function $f > 0$ it yields $\mathrm{e}^{\Delta t}f > 0$. The integral operator $f \mapsto \int f$ also is a positive operator. Hence, we have $F(u_\varepsilon) \geqslant 0$, if $u_\varepsilon \geqslant 0$, and $G(u_\varepsilon,v_\varepsilon) \geqslant 0$, if $u_\varepsilon, v_\varepsilon \geqslant 0$.

Since the integral operator and $\mathrm{e}^{\Delta t}$ are linear and bounded [7], the inequalities

$$
\|F(u_\varepsilon)\|^2_{\Gamma_\varepsilon,t} \leqslant c_1\|u_\varepsilon\|_{\Gamma_\varepsilon,t} \quad\text{and}\quad \|G(u_\varepsilon,v_\varepsilon)\|_{\Gamma_\varepsilon,t} \leqslant c_2\|v_\varepsilon\|_{\Gamma_\varepsilon,t} + c_3\|u_\varepsilon\|_{\Gamma_\varepsilon,t}
$$

hold true with $0 < c_1, c_2, c_3 < \infty$. $\square$

The weak formulation of the abbreviated form is given by $(u_\varepsilon, v_\varepsilon) \in \mathcal{V}_{\mathrm{C}}(\Omega_\varepsilon) \times \mathcal{V}_{\mathrm{N}}(\Omega_\varepsilon)$ such that

$$
\begin{aligned}
(4)\qquad (\partial_t u_\varepsilon, \varphi_1)_{\Omega_\varepsilon} &+ (\partial_t v_\varepsilon, \varphi_2)_{\Omega_\varepsilon} + D_u(\nabla u_\varepsilon, \nabla\varphi_1)_{\Omega_\varepsilon} + D_v(\nabla v_\varepsilon, \nabla\varphi_2)_{\Omega_\varepsilon}\\
&+ \varepsilon^l l_s\langle u_\varepsilon - F(u_\varepsilon), \varphi_1\rangle_{\Gamma_\varepsilon} + \varepsilon^m l_w\langle v_\varepsilon - G(u_\varepsilon,v_\varepsilon), \varphi_2\rangle_{\Gamma_\varepsilon} = 0
\end{aligned}
$$

for all $\varphi = (\varphi_1,\varphi_2) \in V_{\mathrm{C}0}(\Omega_\varepsilon) \times V_{\mathrm{N}}(\Omega_\varepsilon)$.

With the system of equations (4) we have an abbreviated version of the model (1). We are going to use this representation for showing existence of a solution.

5. Existence of a solution

To show existence of a solution of the system of equations (4) we use Proposition 3.2 in [26]. The proposition is summarized in Theorem 7. We briefly introduce the setting used in [26].

Let V and $\mathcal{V} = L^2([0,T],V)$ be separable Hilbert spaces with duals V' and $\mathcal{V}' = L^2([0,T],V')$, respectively. Let W be a Hilbert space with continuous injection $V \hookrightarrow W$ and V dense in W. We are given for every $t \in [0,T]$ an operator $\mathcal{A}(t) \in \mathcal{L}(V,V')$ such that $(\mathcal{A}(\cdot)u)v \in L^\infty([0,T])$ for each pair $u,v \in V$. Furthermore, let $\mathcal{B}(t) \in \mathcal{L}(W,W')$ be another family of operators with $(\mathcal{B}(\cdot)u)v \in L^\infty([0,T])$ for each pair $u,v \in W$. Finally, suppose that $u_0 \in W$ and $f \in L^2([0,T],V')$ are given.

The problem is given by: Find a $u \in \mathcal{V}$ such that

$$\frac{\mathrm{d}}{\mathrm{d}t}(\mathcal{B}(t)u(t)) + \mathcal{A}(t)u(t) = f(t) \quad \text{in } \mathcal{V}', \qquad (\mathcal{B})(0) = \mathcal{B}(0)u_0. \tag{5}$$

Definition 6. The family $\{\mathcal{B}(t);\ t \in [0,T]\}$ of operators given as above is called *regular* if for each pair $u,v \in V$ the function $(\mathcal{B}(\cdot)u)v$ is absolutely continuous on $[0,T]$ and there is a function $K \in L^1([0,T])$ such that

$$\left|\frac{\mathrm{d}}{\mathrm{d}t}(\mathcal{B}(t)u)v\right| \leqslant K(t)\|u\|\|v\|, \quad u,v \in V, \text{ a.e. } t \in [0,T].$$

Theorem 7. *Let the separable Hilbert spaces V,W and linear operators $\mathcal{A}(t)$, $\mathcal{B}(t)$, $0 \leqslant t \leqslant T$, the data $u_0 \in W$ and $f \in L^2([0,T],V')$ be given as above, and assume further that $\mathcal{B}(t)$ is a regular family of self-adjoint operators. Furthermore, let $\mathcal{B}(0)$ be monotone and let there be numbers $\kappa, \lambda > 0$ such that*

$$2(\mathcal{A}(t)v)v + \lambda(\mathcal{B}(t)v)v + (\mathcal{B}'(t)v)v \geqslant \kappa\|v\|^2, \quad v \in V,\ 0 \leqslant t \leqslant T. \tag{6}$$

Then the Problem (5) has at least one solution which satisfies

$$\|u\|_{\mathcal{V}} \leqslant C(\lambda,\kappa)(\|f\|^2_{\mathcal{V}'} + (\mathcal{B}(0)u_0)u_0)^{1/2}.$$

Transformation of the problem. Before we can use Theorem 7, the problem to solve (4) is going to be transformed to a suitable form. Therefore, the function u_B is defined by extending the boundary function $u_{\text{Boundary}} \in H^{1/2}(\Gamma_{\mathrm{C}})$ to the domain Ω_ε using the inverse trace operator $\gamma\colon\ H^{1/2}(\Gamma_{\mathrm{C}}) \to H^1(\Omega_\varepsilon)$ such that $\gamma(u_B) = u_{\text{Boundary}}$ on Γ_{C}. Further, we define $\tilde{u}_\varepsilon \in \mathcal{V}_{\mathrm{C}0}$ by $\tilde{u}_\varepsilon = u_\varepsilon - u_B$. Then the function $\tilde{u}_\varepsilon$ satisfies

$$\begin{aligned}(\partial_t\tilde{u}_\varepsilon + \partial_t u_B, \varphi_1)_{\Omega_\varepsilon} + (\partial_t v_\varepsilon, \varphi_2)_{\Omega_\varepsilon} + D_u(\nabla\tilde{u}_\varepsilon + \nabla u_B, \nabla\varphi_1)_{\Omega_\varepsilon} + D_v(\nabla v_\varepsilon, \varphi_2)_{\Omega_\varepsilon}\\ + \varepsilon^l l_s\langle\tilde{u}_\varepsilon + u_B - F(\tilde{u}_\varepsilon) - F(u_B), \varphi_1\rangle_{\Gamma_\varepsilon}\\ + \varepsilon^m l_w\langle v_\varepsilon - G(\tilde{u}_\varepsilon, v_\varepsilon) - G(u_B,0), \varphi_2\rangle_{\Gamma_\varepsilon} = 0.\end{aligned}$$

Hence, the problem (4) is equivalent to finding $(\tilde{u}_\varepsilon, v_\varepsilon) \in \mathcal{V}_{\mathrm{C}0} \times \mathcal{V}_{\mathrm{N}}$ with

$$
\begin{aligned}
(7) \qquad (\partial_t \tilde{u}_\varepsilon, \varphi_1)_{\Omega_\varepsilon} &+ (\partial_t v_\varepsilon, \varphi_2)_{\Omega_\varepsilon} + D_u(\nabla \tilde{u}_\varepsilon, \nabla\varphi_1)_{\Omega_\varepsilon} + D_v(\nabla v_\varepsilon, \varphi_2)_{\Omega_\varepsilon} \\
&+ \varepsilon^l l_s \langle \tilde{u}_\varepsilon - F(\tilde{u}_\varepsilon), \varphi_1\rangle_{\Gamma_\varepsilon} + \varepsilon^m l_w \langle v_\varepsilon - G(\tilde{u}_\varepsilon, v_\varepsilon), \varphi_2\rangle_{\Gamma_\varepsilon} \\
= &- (\partial_t u_B, \varphi_1)_{\Omega_\varepsilon} - D_u(\nabla u_B, \nabla\varphi_1)_{\Omega_\varepsilon} - \varepsilon^l l_s \langle u_B - F(u_B), \varphi_1\rangle_{\Gamma_\varepsilon} \\
&+ \varepsilon^m l_w \langle G(u_B, 0), \varphi_2\rangle_{\Gamma_\varepsilon}
\end{aligned}
$$

for all $(\varphi_1, \varphi_2) \in \mathcal{V}_{\mathrm{C}0} \times \mathcal{V}_{\mathrm{N}}$ with initial conditions $(\tilde{u}_\varepsilon(0), v_\varepsilon(0)) = (u_I - u_B, v_I)$ and then setting $u_\varepsilon = \tilde{u}_\varepsilon + u_B$.

Identification of the setting. For every $\varepsilon > 0$ we now identify the spaces, operators and functions in our setting with the ones used in Theorem 7.

We set $V = \{u \in H^1(\Omega_\varepsilon);\ u = 0 \text{ on } \Gamma_{\mathrm{C}}\} \times \{u \in H^1(\Omega_\varepsilon);\ u = 0 \text{ on } \Gamma_{\mathrm{N}}\}$ and $W = L^2(\Omega_\varepsilon) \times L^2(\Omega_\varepsilon)$. Then the conditions for the spaces are satisfied and the space $\mathcal{V}$ in (5) is equal to the space $\mathcal{V}_{\mathrm{C}0} \times \mathcal{V}_{\mathrm{N}}$. Further, we define $\mathcal{A}_\varepsilon(t) \in \mathcal{L}(V, V')$ by

$$
\begin{aligned}
(8) \qquad (\mathcal{A}_\varepsilon(t)w)\varphi = {} & (D_u \nabla w_1, \nabla\varphi_1)_{\Omega_\varepsilon} + (D_v \nabla w_2, \nabla\varphi_2)_{\Omega_\varepsilon} \\
&+ \varepsilon^l \langle l_s(w_1 - F(t)(w_1)), \varphi_1\rangle_{\Gamma_\varepsilon} + \varepsilon^m \langle l_w(w_2 - G(t)(w_1, w_2)), \varphi_2\rangle_{\Gamma_\varepsilon}
\end{aligned}
$$

for $w = (w_1, w_2) \in V$ and $\varphi = (\varphi_1, \varphi_2) \in V$. We are going to prove later that $(\mathcal{A}_\varepsilon(\cdot)u)v \in L^\infty([0,T])$. The operator $\mathcal{B}_\varepsilon(t)$ is independent of t and given by

$$
(9) \qquad (\mathcal{B}_\varepsilon(t)w)\varphi = (w_1, \varphi_1)_{\Omega_\varepsilon} + (w_2, \varphi_2)_{\Omega_\varepsilon}
$$

for $w, \varphi \in W$. Obviously, it holds that $(\mathcal{B}_\varepsilon(\cdot)u)v \in L^\infty([0,T])$. With u_I and v_I elements of $L^2(\Omega_\varepsilon)$, it follows that $u_0 = (u_I - u_B, v_I) \in W$. Finally, we identify the right-hand side $f \in L^2([0,T], V')$ by

$$
\begin{aligned}
f(t)\varphi = {} & -(\partial_t u_B, \varphi_1)_{\Omega_\varepsilon} - D_u(\nabla u_B, \nabla\varphi_1)_{\Omega_\varepsilon} - \varepsilon^l l_s \langle u_B - F(t)(u_B), \varphi_1\rangle_{\Gamma_\varepsilon} \\
&+ \varepsilon^m l_w \langle G(t)(u_B, 0), \varphi_2\rangle_{\Gamma_\varepsilon}
\end{aligned}
$$

for $\varphi \in V$. Then, problem (5) and problem (7) are equivalent. Now three preparing lemmas are stated before the existence of a solution is proven.

Lemma 8. *For $w, \varphi \in V$ and $F(t)$ defined in* (2), *$G(t)$ defined in* (3) *it holds that*

$$|\langle F(w_1), \varphi_1\rangle_{\Gamma_\varepsilon}| \leqslant c(T)\|w_1\|_{L^2(\Gamma_\varepsilon)}\|\varphi_1\|_{L^2(\Gamma_\varepsilon)}$$
$$|\langle G(w_1, w_2), \varphi_2\rangle_{\Gamma_\varepsilon}| \leqslant c(T)(\|w_1\|_{L^2(\Gamma_\varepsilon)} + \|w_2\|_{L^2(\Gamma_\varepsilon)})\|\varphi_2\|_{L^2(\Gamma_\varepsilon)}$$

for all $0 \leqslant t \leqslant T$.

Proof. We know from [7] that there exists a smooth function $k_\varepsilon(t, x) > 0$ for $t > 0$ with $k_{t,\varepsilon}(\cdot) = k_\varepsilon(t, \cdot) \in L^2(\Gamma_\varepsilon)$ such that $\mathrm{e}^{D_s\varepsilon^2\Delta t}f(x) = (f \star k_{t,\varepsilon})(x) = \int_{\Gamma_\varepsilon} k_\varepsilon(t, x-y)f(y)\,\mathrm{d}\sigma_y$ for every $f \in L^2(\Gamma_\varepsilon)$. This yields for $F(t)(w_1)$ with $w, \varphi \in V$ and $t > 0$ that

$$\begin{aligned}
|\langle F(w_1), \varphi_1\rangle_{\Gamma_\varepsilon}| = \bigg|\bigg\langle\bigg(&\mathrm{e}^{-(f+\varepsilon^{l-1}l_s)t}(w_1 \star k_{t,\varepsilon}) \\
&+ \mathrm{e}^{-(f+\varepsilon^{l-1}l_s)t}\varepsilon^{l-1}l_s\int_0^t (w_1 \star k_{t-s,\varepsilon})\mathrm{e}^{(f+\varepsilon^{l-1}l_s)s}\,\mathrm{d}s\bigg)\varphi_1\bigg\rangle_{\Gamma_\varepsilon}\bigg| \\
\leqslant{}& \|w_1 \star k_{t,\varepsilon}\|_{L^2(\Gamma_\varepsilon)}\|\varphi_1\|_{L^2(\Gamma_\varepsilon)} \\
&+ \|w_1 \star k_{t-\cdot,\varepsilon}\|_{L^2([0,T]\times\Gamma_\varepsilon)}\|\mathrm{e}^{(f+\varepsilon^{l-1}l_s)\cdot}\varepsilon^{l-1}l_s\varphi_1\|_{L^2([0,T]\times\Gamma_\varepsilon)} \\
\leqslant{}& \|k_{t,\varepsilon}\|_{L^1(\Gamma_\varepsilon)}\|w_1\|_{L^2(\Gamma_\varepsilon)}\|\varphi_1\|_{L^2(\Gamma_\varepsilon)} \\
&+ c(T)\|k_{t,\varepsilon}\|_{L^1([0,t]\times\Gamma_\varepsilon)}\|w_1\|_{L^2(\Gamma_\varepsilon)}\|\varphi_1\|_{L^2(\Gamma_\varepsilon)},
\end{aligned}$$

where we first used the Hölder inequality and then the Young inequality. With $\|k_{t,\varepsilon}\|_{L^1(\Gamma_\varepsilon)}$ and $\|k_{t,\varepsilon}\|_{L^1([0,t]\times\Gamma_\varepsilon)}$ bounded for $0 < t \leqslant T$, it holds that

$$|\langle F(w_1), \varphi_1\rangle_{\Gamma_\varepsilon}| \leqslant c(T)\|w_1\|_{L^2(\Gamma_\varepsilon)}\|\varphi_1\|_{L^2(\Gamma_\varepsilon)}.$$

For $t = 0$ we have $\mathrm{e}^{D_s\varepsilon^2\Delta t}f(x) = f(x)$ and it follows that

$$|\langle F(w_1), \varphi_1\rangle_{\Gamma_\varepsilon}| = |\langle w_1, \varphi_1\rangle_{\Gamma_\varepsilon}| \leqslant \|w_1\|_{L^2(\Gamma_\varepsilon)}\|\varphi_1\|_{L^2(\Gamma_\varepsilon)}.$$

Analogously we find that

$$|\langle G(w_1, w_2), \varphi_2\rangle_{\Gamma_\varepsilon}| \leqslant c(T)(\|w_1\|_{L^2(\Gamma_\varepsilon)} + \|w_2\|_{L^2(\Gamma_\varepsilon)})\|\varphi_2\|_{L^2(\Gamma_\varepsilon)}.$$

□

Lemma 9. *The family of operators $\mathcal{B}_\varepsilon(t)$ (defined in* (9)*) forms a regular family of self-adjoint operators W. Furthermore, $\mathcal{A}_\varepsilon(t)$ and $\mathcal{B}_\varepsilon(t)$ are linear and $\mathcal{B}_\varepsilon(0)$ and $\mathcal{B}_\varepsilon(t)$ are monotone and $(\mathcal{A}_\varepsilon(\cdot)u)\varphi \in L^\infty([0,T])$ for $u,\varphi \in V$.*

Proof. With $\mathcal{B}_\varepsilon(t)$ being the identity Id on W, $\mathcal{B}_\varepsilon(t)$ is monotone and self-adjoint for every $0 \leqslant t \leqslant T$. It also follows that $(\mathrm{d}/\mathrm{d}t)(\mathcal{B}_\varepsilon(t)u)\varphi = 0 \leqslant \|\varphi\|\|u\|$ for every $u,\varphi \in V$ and hence, $\mathcal{B}_\varepsilon(t)$ is regular. Because the Laplace operator Δ, the operators $F(t)$, $G(t)$ and the integral operator are linear, it follows that $\mathcal{A}_\varepsilon(t)$ and $\mathcal{B}_\varepsilon(t)$ are linear. To show $(\mathcal{A}_\varepsilon(\cdot)w)\varphi \in L^\infty([0,T])$ for $w,\varphi \in V$, we consider

$$\begin{aligned}|(\mathcal{A}_\varepsilon(t)w)\varphi| &= |(D_u\nabla w_1,\nabla\varphi_1)_{\Omega_\varepsilon} + (D_v\nabla w_2,\nabla\varphi_2)_{\Omega_\varepsilon}\\&\quad + \varepsilon^l\langle l_s(w_1 - F(t)(w_1)),\varphi_1\rangle_{\Gamma_\varepsilon} + \varepsilon^m\langle l_w(w_2 - G(t)(w_1,w_2)),\varphi_2\rangle_{\Gamma_\varepsilon}|\\&\leqslant D_u\|\nabla w_1\|_{\Omega_\varepsilon}\|\nabla\varphi_1\|_{\Omega_\varepsilon} + D_v\|\nabla w_2\|_{\Omega_\varepsilon}\|\nabla\varphi_2\|_{\Omega_\varepsilon} + \varepsilon^l l_s\|w_1\|_{\Gamma_\varepsilon}\|\varphi_1\|_{\Gamma_\varepsilon}\\&\quad + \varepsilon^l l_s c(T)\|w_1\|_{\Gamma_\varepsilon}\|\varphi_1\|_{\Gamma_\varepsilon} + \varepsilon^m l_w\|w_2\|_{\Gamma_\varepsilon}\|\varphi_2\|_{\Gamma_\varepsilon}\\&\quad + \varepsilon^m l_w c(T)(\|w_1\|_{\Gamma_\varepsilon} + \|w_2\|_{\Gamma_\varepsilon})\|\varphi_2\|_{\Gamma_\varepsilon},\end{aligned}$$

where we use Lemma 8. We continue by using Young's and trace inequality

$$\begin{aligned}|(\mathcal{A}_\varepsilon(t)w)\varphi| &\leqslant \|w_1\|^2_{\Omega_\varepsilon}(c_0\varepsilon^{l-1}l_s + c_0c(T)\varepsilon^{l-1}l_s + c_0\varepsilon^{m-1}l_w)\\&\quad + \|\nabla w_1\|^2_{\Omega_\varepsilon}(D_u + c_0\varepsilon^{l+1}l_s + c_0c(T)\varepsilon^{l+1}l_s + c_0c(T)\varepsilon^{m+1}l_w)\\&\quad + \|w_2\|^2_{\Omega_\varepsilon}(c_0\varepsilon^{m-1}l_w + c_0c(T)\varepsilon^{m-1}l_w) + \|\nabla w_2\|^2_{\Omega_\varepsilon}(D_v + c_0\varepsilon^{m+1}l_w + c_0c(T)\varepsilon^{m+1}l_w)\\&\quad + \|\varphi_1\|^2_{\Omega_\varepsilon}(c_0\varepsilon^{l-1}l_s + c_0c(T)\varepsilon^{l-1}l_s) + \|\nabla\varphi_1\|^2_{\Omega_\varepsilon}(D_u + c_0\varepsilon^{l+1}l_s + c_0c(T)\varepsilon^{l+1}l_s)\\&\quad + \|\varphi_2\|^2_{\Omega_\varepsilon}(c_0\varepsilon^{m-1}l_w + c_0c(T)\varepsilon^{m-1}l_w) + \|\nabla\varphi_2\|^2_{\Omega_\varepsilon}(D_v + c_0\varepsilon^{m+1}l_w + c_0c(T)\varepsilon^{m+1}l_w),\end{aligned}$$

which is bounded for every $\varepsilon > 0$ and T bounded, since w, $\varphi \in V$. □

Lemma 10. *The operators $\mathcal{A}_\varepsilon$ and $\mathcal{B}_\varepsilon$ defined in* (8) *and* (9)*, respectively, satisfy*

$$2(\mathcal{A}_\varepsilon(t)w)w + \lambda(\mathcal{B}_\varepsilon(t)w)w + (\mathcal{B}'_\varepsilon(t)w)w \geqslant \kappa\|w\|^2$$

for every $w \in V$ and $0 \leqslant t \leqslant T$ for constants $\lambda,\kappa > 0$.

Proof. With $\mathcal{B}_\varepsilon$ constant it follow that $\mathcal{B}'_\varepsilon(t) = 0$. We consider

$$\begin{aligned}2(\mathcal{A}_\varepsilon(t)w)w + \lambda(\mathcal{B}_\varepsilon(t)w)w &= 2(D_u\nabla w_1,\nabla w_1)_{\Omega_\varepsilon}\\&\quad + 2(D_v\nabla w_2,\nabla w_2)_{\Omega_\varepsilon} + 2\varepsilon^l\langle l_s(w_1 - F(t)(w_1)),w_1\rangle_{\Gamma_\varepsilon}\\&\quad + 2\varepsilon^m\langle l_w(w_2 - G(t)(w_1,w_2)),w_2\rangle_{\Gamma_\varepsilon} + \lambda(w_1,w_1)_{\Omega_\varepsilon} + \lambda(w_2,w_2)_{\Omega_\varepsilon}\\&= 2D_u\|\nabla w_1\|^2_{\Omega_\varepsilon} + 2D_v\|\nabla w_2\|^2_{\Omega_\varepsilon} + 2\varepsilon^l l_s\|w_1\|^2_{\Gamma_\varepsilon} - 2\varepsilon^l\langle l_sF(t)(w_1),w_1\rangle_{\Gamma_\varepsilon}\\&\quad + 2\varepsilon^m l_w\|w_2\|^2_{\Gamma_\varepsilon} - 2\varepsilon^m\langle l_wG(t)(w_1,w_2),w_2\rangle_{\Gamma_\varepsilon} + \lambda\|w_1\|^2_{\Omega_\varepsilon} + \lambda\|w_2\|^2_{\Omega_\varepsilon}.\end{aligned}$$

By Lemma 8 we deduce

$$\begin{aligned}
&2(\mathcal{A}_\varepsilon(t)w)w + \lambda(\mathcal{B}_\varepsilon(t)w)w \\
&\quad \geqslant 2D_u\|\nabla w_1\|^2_{\Omega_\varepsilon} + 2D_v\|\nabla w_2\|^2_{\Omega_\varepsilon} + 2\varepsilon^l l_s\|w_1\|^2_{\Gamma_\varepsilon} - 2c(T)\varepsilon^l l_s\|w_1\|^2_{\Gamma_\varepsilon} \\
&\quad + 2\varepsilon^m l_w\|w_2\|^2_{\Gamma_\varepsilon} - c(T)\varepsilon^m l_w\|w_1\|^2_{\Gamma_\varepsilon} - c(T)\varepsilon^m l_w\|w_2\|^2_{\Gamma_\varepsilon} \\
&\quad - 2c(T)\varepsilon^m l_w\|w_2\|_{\Gamma_\varepsilon} + \lambda\|w_1\|^2_{\Omega_\varepsilon} + \lambda\|w_2\|^2_{\Omega_\varepsilon}.
\end{aligned}$$

Dropping some positive terms and applying the trace inequality yields

$$\begin{aligned}
2(\mathcal{A}_\varepsilon(t)w)w + \lambda(\mathcal{B}_\varepsilon(t)w)w &\geqslant 2D_u\|\nabla w_1\|^2_{\Omega_\varepsilon} + 2D_v\|\nabla w_2\|^2_{\Omega_\varepsilon} \\
&- (2c_0c(T)\varepsilon^{l-1}l_s + c_0c(T)\varepsilon^{m-1}l_w)\|w_1\|^2_{\Omega_\varepsilon} \\
&- (2c_0c(T)\varepsilon^{l+1}l_s + c_0c(T)\varepsilon^{m+1}l_w)\|\nabla w_1\|^2_{\Omega_\varepsilon} \\
&- (c_0c(T)\varepsilon^{m-1}l_w + 2c_0c(T)\varepsilon^{m-1}l_w)\|w_2\|^2_{\Omega_\varepsilon} \\
&- (2c_0c(T)\varepsilon^{m+1}l_w + c_0c(T)\varepsilon^{m+1}l_w)\|\nabla w_2\|_{\Omega_\varepsilon} + \lambda\|w_1\|^2_{\Omega_\varepsilon} + \lambda\|w_2\|^2_{\Omega_\varepsilon} \\
&= \|w_1\|^2_{\Omega_\varepsilon}(\lambda - 2c_0c(T)\varepsilon^{l-1}l_s - c_0c(T)\varepsilon^{m-1}l_w) \\
&+ \|\nabla w_1\|^2_{\Omega_\varepsilon}(2D_u - 2c_0c(T)\varepsilon^{l+1}l_s - c_0c(T)\varepsilon^{m+1}l_w) \\
&+ \|w_2\|^2_{\Omega_\varepsilon}(\lambda - c_0c(T)\varepsilon^{m-1}l_w - 2c_0c(T)\varepsilon^{m-1}l_w) \\
&+ \|\nabla w_2\|^2_{\Omega_\varepsilon}(2D_v - 2c_0c(T)\varepsilon^{m+1}l_w - c_0c(T)\varepsilon^{m+1}l_w).
\end{aligned}$$

Because $l, m \geqslant 0$, the factors at the norm of gradients of w_1, w_2 are positive for ε small enough. If $l, m \leqslant 1$ one chooses λ big enough such that the factors at the norm of w_1, w_2 are positive even for small $\varepsilon > 0$. Then we merge the factors to a constant κ and conclude that

$$2(\mathcal{A}_\varepsilon(t)w)w + \lambda(\mathcal{B}_\varepsilon(t)w)w \geqslant \kappa\|w\|^2_V,$$

which completes the proof. □

Now we are ready to prove the existence of a solution.

Theorem 11. *The partial differential equation* (4) *has at least one solution* $(u_\varepsilon, v_\varepsilon)$ *in* $\mathcal{V}_C(\Omega_\varepsilon) \times \mathcal{V}_{\mathrm{N}}(\Omega_\varepsilon)$.

Proof. Using Theorem 7 we find a solution $(\tilde{u}_\varepsilon, v_\varepsilon)$ of the problem (7) in $\mathcal{V}_{\mathrm{C}0}(\Omega_\varepsilon) \times \mathcal{V}_{\mathrm{N}}(\Omega_\varepsilon)$ with initial condition $(\tilde{u}_\varepsilon(0), v_\varepsilon(0)) = (u_I - u_B, v_I)$, because the linear operators $\mathcal{A}_\varepsilon(t)$ and $\mathcal{B}_\varepsilon(t)$, defined in (8) and (9), satisfy the sufficient conditions (proven in Lemma 9 and Lemma 10). Furthermore, the right-hand side in (7) is in $L^2([0,T], V')$ and the initial conditions $(u_I - u_B, v_I)$ are an element of W. Setting $u_\varepsilon = \tilde{u}_\varepsilon + u_B$, we find a solution $(u_\varepsilon, v_\varepsilon) \in \mathcal{V}_C(\Omega_\varepsilon) \times \mathcal{V}_{\mathrm{N}}(\Omega_\varepsilon)$. □

Using (2) and (3), we find directly:

Corollary 12. *There exist solutions for s_ε and w_ε.*

6. Identification of the two-scale limit

In this section we derive the limit equations for the system of equations (1). At first, we consider the limit of the binding terms for different values for l and m. Then, we find the limit of the whole system.

Limit of the binding terms. To find the limit equations for u_ε, v_ε, s_ε and w_ε we need to distinguish different cases for l and m in the binding terms. The limit derivation for v_ε and w_ε is analogous to the limit derivation for u_ε and s_ε, respectively. Hence, we only consider u_ε and s_ε here.

In every case we use that $\varepsilon\|u_\varepsilon\|^2_{\Gamma_\varepsilon}$ and $\varepsilon\|s_\varepsilon\|^2_{\Gamma_\varepsilon}$ are bounded, see Corollary 3 and Lemma 2. Thus, by Theorem 1.2 of [16] we find u_0 and s_0 such that u_ε two-scale converges to u_0 and s_ε two-scale converges to s_0.

Further, we know that $\varepsilon^l\|u_\varepsilon - s_\varepsilon\|^2_{\Gamma_\varepsilon}$ is bounded, see Lemma 2, and we also use Theorem 1.2 of [16]. Therefore, we consider the following cases:

▷ For $l > 1$ and by Lemma 2 we obtain for ε tending to zero that

$$\varepsilon^l\|u_\varepsilon - s_\varepsilon\|^2_{\Gamma_\varepsilon} = \underbrace{\varepsilon^{l-1}}_{\to 0}\underbrace{\varepsilon\|u_\varepsilon - s_\varepsilon\|^2_{\Gamma_\varepsilon}}_{\text{bounded}} \xrightarrow{\varepsilon\to 0} 0. \tag{10}$$

▷ $l = 1$ is the standard case and we find using the definition of two-scale convergence that

$$\varepsilon\langle(u_\varepsilon - s_\varepsilon), \varphi_\varepsilon\rangle_{\Gamma_\varepsilon}\,\mathrm{d}\sigma_x \xrightarrow{\varepsilon\to 0} \langle(u_0(x,y,t) - s_0(x,y,t)), \varphi_0(x,y)\rangle_{\Omega\times\Gamma}. \tag{11}$$

▷ For $0 \leqslant l < 1$ and by Lemma 2 we get for $\varepsilon \to 0$ that

$$\underbrace{\varepsilon^l\|u_\varepsilon - s_\varepsilon\|^2_{\Gamma_\varepsilon}}_{\text{bounded}} = \underbrace{\varepsilon^{l-1}}_{\to\infty}\varepsilon\|u_\varepsilon - s_\varepsilon\|^2_{\Gamma_\varepsilon}. \tag{12}$$

Since the right-hand side remains bounded, it must hold that $\lim\limits_{\varepsilon\to\infty}\varepsilon\|u_\varepsilon - s_\varepsilon\|^2_{\Gamma_\varepsilon} = \|u_0 - s_0\|^2_{\Omega\times\Gamma} = 0$. Hence, $u_0 = s_0$ almost everywhere on $\Omega\times\Gamma$.

Now, knowing the limits of the binding terms, we continue with the limit derivation of the whole equations. The domain Ω_ε should not depend on ε, so we define the characteristic function $\chi\colon\ \Omega \to \mathbb{R}$ by $\chi(x/\varepsilon) = 1$ for $x \in \Omega_\varepsilon$ and 0 otherwise. We obtain the limit equations for u_ε, v_ε, s_ε and w_ε by using theorems from articles [1], [16]. In Lemma 2 we checked that the conditions are fulfilled. As test functions $\varphi_\varepsilon \in C^\infty(\Omega, C^\infty_\#(Y))$ we choose functions of the form $\varphi_\varepsilon(x, x/\varepsilon) = \varphi_0(x) + \varepsilon\varphi_1(x, x/\varepsilon)$ with $(\varphi_0, \varphi_1) \in C^\infty(\Omega) \times C^\infty(\Omega, C^\infty_\#(Y))$.

The case $l > 1$, $m > 1$. We start with the equation u_ε and test with the admissible test function φ_ε,

$$(\chi(x/\varepsilon)\partial_t u_\varepsilon(x,t), \varphi_\varepsilon(x, x/\varepsilon))_\Omega + (D_u\chi(x/\varepsilon)\nabla u_\varepsilon(x,t), \nabla\varphi_\varepsilon(x, x/\varepsilon))_\Omega \\ + \langle \varepsilon^l l_s(u_\varepsilon(x,t) - s_\varepsilon(x,t)), \varphi_\varepsilon(x, x/\varepsilon)\rangle_{\Gamma_\varepsilon} = 0.$$

For $\varepsilon \to 0$ we obtain the limit equation

$$(\partial_t u_0(x,t), \varphi_0(x))_{\Omega\times Y^*} \\ + (D_u[\nabla_x u_0(x,t) + \nabla_y u_1(x,y,t)],\ [\nabla_x\varphi_0(x) + \nabla_y\varphi_1(x,y)])_{\Omega\times Y^*} = 0 \tag{13}$$

for all admissible test functions $(\varphi_0, \varphi_1) \in V_{\mathrm{C}0}(\Omega) \times V(\Omega, Y)$, where $u_0 \in \mathcal{V}_{\mathrm{C}}(\Omega)$ is independent of y and $u_1 \in \mathcal{V}(\Omega, Y) = L^2([0,T] \times \Omega, H^1_\#(Y))$.

Analogously we obtain for $\varepsilon \to 0$

$$(\partial_t v_0(x,t), \varphi_0(x))_{\Omega\times Y^*} \\ + (D_v[\nabla_x v_0(x,t) + \nabla_y v_1(x,y,t)],\ [\nabla_x\varphi_0(x) + \nabla_y\varphi_1(x,y)])_{\Omega\times Y^*} = 0$$

for all admissible test functions $(\varphi_0, \varphi_1) \in V_N(\Omega) \times V(\Omega, Y)$, where $v_0 \in \mathcal{V}_{\mathrm{N}}(\Omega)$ is independent of y and $v_1 \in \mathcal{V}(\Omega, Y)$.

Now we determine the limit equations for s_ε and w_ε,

$$\varepsilon\langle\partial_t s_\varepsilon(x,t), \varphi_\varepsilon(x, x/\varepsilon)\rangle_{\Gamma_\varepsilon} + \varepsilon\langle D_s\varepsilon\nabla_\Gamma s_\varepsilon(x,t), \varepsilon\nabla_\Gamma\varphi_\varepsilon(x, x/\varepsilon)\rangle_{\Gamma_\varepsilon} \\ + \varepsilon\langle f s_\varepsilon(x,t), \varphi_\varepsilon(x, x/\varepsilon)\rangle_{\Gamma_\varepsilon} - \varepsilon^l\langle l_s(u_\varepsilon(x,t) - s_\varepsilon(x,t)), \varphi_\varepsilon(x, x/\varepsilon)\rangle_{\Gamma_\varepsilon} = 0.$$

We find the limit function $s_0 \in \mathcal{V}(\Omega, \Gamma)$ satisfying for $\varepsilon \to 0$

$$\langle\partial_t s_0(x,y,t), \varphi_0(x,y)\rangle_{\Omega\times\Gamma} + \langle D_s\nabla_\Gamma s_0(x,y,t), \nabla_\Gamma\varphi_0(x,y)\rangle_{\Omega\times\Gamma} \\ + \langle f s_0(x,y,t), \varphi_0(x,y)\rangle_{\Omega\times\Gamma} = 0$$

for all $\varphi_0 \in V(\Omega, \Gamma)$. We analogously find the limit function $w_0 \in \mathcal{V}(\Omega, \Gamma)$ satisfying

$$\langle\partial_t w_0(x,y,t), \varphi_0(x,y)\rangle_{\Omega\times\Gamma} + \langle D_w\nabla_\Gamma w_0(x,y,t), \nabla_\Gamma\varphi_0(x,y)\rangle_{\Omega\times\Gamma} \\ - \langle f s_0(x,y,t), \varphi_0(x,y)\rangle_{\Omega\times\Gamma} = 0$$

for all $\varphi_0 \in V(\Omega, \Gamma)$.

As described in [25], the cell problem for limit equations like (13) is given by

$$\begin{aligned} \nabla_y \cdot D_u(e_j + \nabla_y \mu_j) &= 0 \quad \text{in } Y^*, \\ D_u(e_j + \nabla_y \mu_j) \cdot n &= 0 \quad \text{on } \Gamma, \end{aligned} \tag{14}$$

where μ_j must be Y-periodic for all $j = 1, \dots, n$. Then, $u_1(x,y,t) = \sum_{j=1}^{n} \partial_{x_j} u_0(x,t)$ $\mu_j(y)$ and the elements of the diffusion tensor P^u are given by

$$P^u_{ij} = \int_{Y^*} D_u[\delta_{ij} + \partial_{y_i}\mu_j]\,\mathrm{d}y. \tag{15}$$

Analogously, we find that the cell problem for the equation for v is also given by (14) but with D_u replaced by D_v. Then $v_1(x,y,t) = \sum_{j=1}^{n} \partial_{x_j} v_0(x,t)\mu_j(y)$ and we define the diffusion tensor P^v by $P^v_{ij} = \int_{Y^*} D_v[\delta_{ij} + \partial_{y_i}\mu_j]\,\mathrm{d}y$.

We summarize our results with the weak macroscopic system of equations and use that u_0 and v_0 are independent of y. Let $(u_0, v_0, s_0, w_0) \in \mathcal{V}_{\mathrm{C}}(\Omega) \times \mathcal{V}_{\mathrm{N}}(\Omega) \times \mathcal{V}(\Omega,\Gamma)^2$ such that

$$\begin{aligned} &|Y^*|(\partial_t u_0, \varphi_1)_\Omega + (P^u \nabla u_0, \nabla\varphi_1)_\Omega = 0, \\ &|Y^*|(\partial_t v_0, \varphi_2)_\Omega + (P^v \nabla v_0, \nabla\varphi_2)_\Omega = 0, \\ &(\partial_t s_0, \psi)_{\Omega\times\Gamma} + (D_s \nabla_\Gamma s_0, \nabla_\Gamma \psi)_{\Omega\times\Gamma} + (f s_0, \psi)_{\Omega\times\Gamma} = 0, \\ &(\partial_t w_0, \psi)_{\Omega\times\Gamma} + (D_w \nabla_\Gamma w_0, \nabla_\Gamma \psi)_{\Omega\times\Gamma} - (f s_0, \psi)_{\Omega\times\Gamma} = 0 \end{aligned} \tag{16}$$

for all $(\varphi_1, \varphi_2, \psi) \in V_{\mathrm{C}0}(\Omega) \times V_{\mathrm{N}}(\Omega) \times V(\Omega,\Gamma)$.

We see that for $l > 1$ or $m > 1$ no BP molecules bind or unbind to the membrane of the ER, or no DE molecules bind or unbind to the membrane of the ER, respectively. Hence, no metabolism from BP to DE molecules takes place. Because we know from biological examinations that there are metabolisms in real life, we conclude that this model is not a good approximation to the reality for $l > 1$ or $m > 1$.

The case $l = 1$, $m = 1$. Here, we distinguish two cases. First, we consider the limit derivation of the system of equations (1). Secondly, we derive the limit equation for the abbreviated system of equations (4). Since it is unclear how to derive the limits $\lim_{\varepsilon\to 0} F(u_\varepsilon)$ and $\lim_{\varepsilon\to 0} G(u_\varepsilon, v_\varepsilon)$, as defined in (2) and (3), in the sense of two-scale convergence, we determine the limits for $F(u_\varepsilon)$ and $G(u_\varepsilon, v_\varepsilon)$ indirectly: With the systems (4) and (1) being equivalent, also the corresponding limit equations must be equivalent. In the limit we are going to identify these two limit equations with each other and are able to determine $\lim_{\varepsilon\to 0} F(u_\varepsilon)$ and $\lim_{\varepsilon\to 0} G(u_\varepsilon, v_\varepsilon)$.

For the limit derivations we may adopt the two-scale limit terms from the case $l, m > 1$ for the time-derivatives, the diffusion terms and the linear terms. The limit equations only differ in the binding terms, calculated in (11).

Identification of the two-scale limit of the model (1)**.** We start with the equation for u_ε and obtain for $\varepsilon \to 0$

$$\begin{aligned}
&(\partial_t u_0(x,t), \varphi_0(x))_{\Omega\times Y^*} \\
&\qquad + (D_u[\nabla_x u_0(x,t) + \nabla_y u_1(x,y,t)], [\nabla_x \varphi_0(x) + \nabla_y \varphi_1(x,y)])_{\Omega\times Y^*} \\
&\qquad + \langle l_s(u_0(x,t) - s_0(x,y,t)), \varphi_0(x)\rangle_{\Omega\times\Gamma} = 0
\end{aligned}$$

for all admissible test functions $(\varphi_0, \varphi_1) \in V_{\mathrm{C}0}(\Omega) \times V(\Omega, Y)$, where $u_0 \in L^2([0,T], H^1(\Omega))$ and $u_1 \in L^2([0,T]\times\Omega, H^1_\#(Y))$. For the equation with v_ε we find

$$\begin{aligned}
&(\partial_t v_0(x,t), \varphi_0(x))_{\Omega\times Y^*} \\
&\qquad + (D_v[\nabla_x v_0(x,t) + \nabla_y v_1(x,y,t)], [\nabla_x \varphi_0(x) + \nabla_y \varphi_1(x,y)])_{\Omega\times Y^*} \\
&\qquad + \langle l_w(v_0(x,t) - w_0(x,y,t)), \varphi_0(x)\rangle_{\Omega\times\Gamma} = 0
\end{aligned}$$

for all $(\varphi_0, \varphi_1) \in V_N(\Omega) \times V(\Omega, Y)$, where $v_0 \in L^2([0,T], H^1(\Omega))$ and $v_1 \in L^2([0,T]\times \Omega, H^1_\#(Y))$.

We find the limit function $s_0 \in L^2([0,T]\times\Omega, H^1_\#(Y))$ satisfying the limit equation

$$\begin{aligned}
&\langle \partial_t s_0(x,y,t), \varphi_0(x,y)\rangle_{\Omega\times\Gamma} + \langle D_s \nabla_\Gamma s_0(x,y,t), \nabla_\Gamma \varphi_0(x,y)\rangle_{\Omega\times\Gamma} \\
&\quad + \langle f s_0(x,y,t), \varphi_0(x,y)\rangle_{\Omega\times\Gamma} - \langle l_s(u_0(x,y,t) - s_0(x,y,t)), \varphi_0(x,y)\rangle_{\Omega\times\Gamma} = 0
\end{aligned}$$

for all admissible test functions $\varphi_0 \in V(\Omega, \Gamma)$. From the limit derivation above we see that u_0 is independent of y. Thus, we can simplify the terms $\int_\Gamma l_s u_0(x,t)\,\mathrm{d}\sigma_y$ to $|\Gamma| l_s u_0(x,t)$, where $|\Gamma|$ means the Lebesgue measure of Γ.

Analogously we obtain for the equation for $w_\varepsilon \in L^2([0,T]\times\Omega, H^1_\#(Y))$ and $\varepsilon \to 0$

$$\begin{aligned}
&\langle \partial_t w_0(x,y,t), \varphi_0(x,y)\rangle_{\Omega\times\Gamma} + \langle D_w \nabla_\Gamma w_0(x,y,t), \nabla_\Gamma \varphi_0(x,y)\rangle_{\Omega\times\Gamma} \\
&\quad - \langle f s_0(x,y,t), \varphi_0(x,y)\rangle_{\Omega\times\Gamma} - \langle l_w(v_0(x,y,t) - w_0(x,y,t)), \varphi_0(x,y)\rangle_{\Omega\times\Gamma} = 0
\end{aligned}$$

for all admissible test functions $\varphi_0 \in V(\Omega, \Gamma)$.

We find the same cell problem (14) as in the case $l, m > 1$, and the derivation of the diffusion tensors P^u and P^v is equivalent to (15).

We summarize our results with the macroscopic weak formulation. Let $(u_0, v_0, s_0, w_0) \in \mathcal{V}_{\mathrm{C}}(\Omega) \times \mathcal{V}_{\mathrm{N}}(\Omega) \times \mathcal{V}(\Omega,\Gamma)^2$ with $(u_0(x,0), v_0(x,0), s_0(x,0), w_0(x,0)) =$

(u_I, v_I, s_I, w_I) such that

$$
\begin{aligned}
(17)\quad & (|Y^*|\partial_t u_0, \varphi_1)_\Omega + (P^u \nabla u_0, \nabla\varphi_1)_\Omega + l_s|\Gamma|(u_0, \varphi_1)_\Omega - l_s(s_0, \varphi_1)_{\Omega\times\Gamma} = 0,\\
& (|Y^*|\partial_t v_0, \varphi_2)_\Omega + (P^v \nabla v_0, \nabla\varphi_2)_\Omega + l_w|\Gamma|(v_0, \varphi_2)_\Omega - l_w(w_0, \varphi_2)_{\Omega\times\Gamma} = 0,\\
& (\partial_t s_0, \psi)_{\Omega\times\Gamma} + (D_s \nabla_\Gamma s_0, \nabla_\Gamma \psi)_{\Omega\times\Gamma} + (f + l_s)(s_0, \psi)_{\Omega\times\Gamma} = l_s|\Gamma|(u_0, \psi)_\Omega,\\
& (\partial_t w_0, \psi)_{\Omega\times\Gamma} + (D_w \nabla_\Gamma w_0, \nabla_\Gamma \psi)_{\Omega\times\Gamma} - f(s_0, \psi)_{\Omega\times\Gamma} + l_w(w_0, \psi)_{\Omega\times\Gamma}\\
& \qquad = l_w|\Gamma|(v_0, \psi)_\Omega
\end{aligned}
$$

for all $(\varphi_1, \varphi_2, \psi) \in V_{\mathrm{C}0}(\Omega) \times V_{\mathrm{N}}(\Omega) \times V(\Omega, \Gamma)$.

Here again there is an analytical solution for s_0 and w_0 on the manifold Γ, because s_0 and w_0 are solutions of the well-known inhomogeneous heat equations. As in section 4, we obtain functions $F_0(u_0) = s_0$ and $G_0(u_0, v_0) = w_0$ with

$$
\begin{aligned}
(18)\quad & F_0(u_0) = \mathrm{e}^{(D_s\Delta_\Gamma - f - l_s)t} s_I(x)\\
& \qquad + \mathrm{e}^{-(f+l_s)t} \int_0^t \mathrm{e}^{D_s\Delta_\Gamma(t-s)} l_s u_0(s, x) \mathrm{e}^{(f+l_s)s} \,\mathrm{d}s = s_0,\\
(19)\quad & G_0(u_0, v_0) = \mathrm{e}^{(D_w\Delta_\Gamma - l_w)t} w_I(x)\\
& \qquad + \mathrm{e}^{-l_w t} \int_0^t \mathrm{e}^{D_w(t-s)\Delta_\Gamma} (l_w v_0(s, x) + f F_0(u_0)(s, x)) \mathrm{e}^{l_w s} \,\mathrm{d}s = w_0.
\end{aligned}
$$

The abbreviated limit equation of (17) is

$$
\begin{aligned}
(20)\quad & (|Y^*|\partial_t u_0, \varphi_1)_\Omega\\
& + (P^u \nabla u_0, \nabla\varphi_1)_\Omega + l_s|\Gamma|(u_0, \varphi_1)_\Omega - l_s(F_0(u_0), \varphi_1)_{\Omega\times\Gamma} = 0,\\
& (|Y^*|\partial_t v_0, \varphi_2)_\Omega\\
& + (P^v \nabla v_0, \nabla\varphi_2)_\Omega + l_w|\Gamma|(v_0, \varphi_2)_\Omega - l_w(G_0(u_0, v_0), \varphi_2)_{\Omega\times\Gamma} = 0
\end{aligned}
$$

for all $(\varphi_1, \varphi_2) \in V_{\mathrm{C}0}(\Omega) \times V_{\mathrm{N}}(\Omega)$.

Identification of the two-scale limit of the abbreviated model (4)**.** We may adopt the limit terms from the case $l, m > 1$ for the time-derivative, the diffusion term and the linear term. The equation

$$(\chi(x/\varepsilon)\partial_t u_\varepsilon, \varphi_\varepsilon)_\Omega + (\chi(x/\varepsilon)\nabla u_\varepsilon, \nabla\varphi_\varepsilon)_\Omega + \varepsilon\langle l_s(u_\varepsilon - F(u_\varepsilon)), \varphi_\varepsilon\rangle_{\Gamma_\varepsilon} = 0$$

yields for ε tending to zero

$$(|Y^*|\partial_t u_0, \varphi_0)_\Omega + (P^u \nabla u_0, \nabla\varphi_0)_\Omega + |\Gamma|(l_s u_0, \varphi_0)_\Omega - l_s \lim_{\varepsilon\to 0} \varepsilon\langle F(u_\varepsilon), \varphi_\varepsilon\rangle_{\Gamma_\varepsilon} = 0$$

for all admissible test functions $(\varphi_0, \varphi_1) \in V_{C0}(\Omega) \times V(\Omega, Y)$, where $u_0 \in L^2([0,T], H^1(\Omega))$ and $u_1 \in L^2([0,T] \times \Omega, H^1_{\#}(Y))$. As mentioned before, it is unclear initially how to find the limit $\lim_{\varepsilon\to 0} \varepsilon \int_{\Gamma_\varepsilon} F(u_\varepsilon)\varphi_\varepsilon \, \mathrm{d}\sigma_x$ directly. By comparing this limit model with model (20) we find that

$$\lim_{\varepsilon\to 0} \varepsilon\langle F(u_\varepsilon), \varphi_\varepsilon\rangle_{\Gamma_\varepsilon} = \langle F_0(u_0), \varphi_0\rangle_{\Omega\times\Gamma}$$

with F_0 as in (18). We analogously find $\lim_{\varepsilon\to 0} \varepsilon\langle G(u_\varepsilon, v_\varepsilon), \varphi_\varepsilon\rangle_{\Gamma_\varepsilon} = \langle G_0(u_0, v_0), \varphi_0\rangle_{\Omega\times\Gamma}$ with G_0 as in (19).

The case $l = m = 1$ seems the most relevant one from the biological point of view. The binding process of the molecules to the membrane of the ER has regular speed and hence we obtain four coupled limit equations for u_0, v_0, s_0, w_0. In this context we were also able to find a two-scale limit for the ε-dependent operators F and G, (2) and (3).

The case $l < 1$, $m < 1$. We are going to use the binding limit term (12) and recall that $u_0 = s_0$ on Γ in the limit for ε tending to zero. This means that in the limit, the solution u_0 will have to satisfy the limit equations for u_0 and for s_0. To be able to relate these limit equations for u_0 and for s_0, we add the equations for u_ε and s_ε before the limit derivation and test with φ_ε:

$$\begin{aligned}
&(\chi(x/\varepsilon)\partial_t u_\varepsilon(x,t), \varphi_\varepsilon(x, x/\varepsilon))_\Omega + \varepsilon\langle\partial_t s_\varepsilon(x,t), \varphi_\varepsilon(x, x/\varepsilon)\rangle_{\Gamma_\varepsilon}\\
&\quad + D_u(\chi(x/\varepsilon)\nabla u_\varepsilon(x,t), \nabla\varphi_\varepsilon(x, x/\varepsilon))_\Omega + \varepsilon\langle D_s\varepsilon\nabla_\Gamma s_\varepsilon(x,t), \varepsilon\nabla_\Gamma\varphi_\varepsilon(x, x/\varepsilon)\rangle_{\Gamma_\varepsilon}\\
&\quad + \varepsilon\langle f s_\varepsilon(x,t), \varphi_\varepsilon(x, x/\varepsilon)\rangle_{\Gamma_\varepsilon} = 0.
\end{aligned}$$

For ε tending to zero we find

$$\begin{aligned}
&(\partial_t u_0(x,t), \varphi_0(x))_{\Omega\times Y^*} + \langle\partial_t s_0(x,y,t), \varphi_0(x)\rangle_{\Omega\times\Gamma}\\
&\quad + (D_u[\nabla_x u_0(x,t) + \nabla_y u_1(x,y,t)], [\nabla_x\varphi_0(x) + \nabla_y\varphi_1(x,y)])_{\Omega\times Y^*}\\
&\quad + \langle D_s\nabla_\Gamma s_0(x,y,t), \nabla_\Gamma\varphi_0(x)\rangle_{\Omega\times\Gamma} + \langle f s_0(x,y,t), \varphi_0(x)\rangle_{\Omega\times\Gamma} = 0
\end{aligned}$$

for all $(\varphi_0, \varphi_1) \in V_{C0}(\Omega) \times V(\Omega, Y)$, where $u_1 \in L^2([0,T] \times \Omega, H^1_{\#}(Y))$ and $u_0 \in L^2([0,T], H^1(\Omega))$ and $s_0 \in L^2([0,T] \times \Omega, H^1_{\#}(Y))$.

Since $u_0 = s_0$ on Γ, we obtain

$$\begin{aligned}
&(|Y^*| + |\Gamma|)(\partial_t u_0(x,t), \varphi_0(x))_\Omega\\
&\quad + D_u([\nabla_x u_0(x,t) + \nabla_y u_1(x,y,t)], [\nabla_x\varphi_0(x) + \nabla_y\varphi_1(x,y)])_{\Omega\times Y^*}\\
&\quad + \langle D_s \underbrace{\nabla_\Gamma u_0(x,t),}_{=0} \nabla_\Gamma\varphi_0(x)\rangle_{\Omega\times\Gamma} + \langle f u_0(x,t), \varphi_0(x)\rangle_{\Omega\times\Gamma} = 0
\end{aligned}$$

where $\nabla_\Gamma u_0 = 0$ because u_0 is independent of y, and analogously for v_0 and w_0.

Again we refer to the cell problem (14) to see how the diffusion tensors P^u and P^v can be derived. Hence, we arrive at the macroscopic system of equations. The weak formulation of the macroscopic system of equations is given by $(u_0, v_0) \in V_{\mathrm{C}}(\Omega) \times V_{\mathrm{N}}(\Omega)$ such that

$$(21) \qquad \begin{aligned} &(|Y^*| + |\Gamma|)(\partial_t u_0, \varphi_1)_\Omega + (P^u \nabla u_0, \nabla \varphi_1)_\Omega + |\Gamma| f(u_0, \varphi_1)_\Omega = 0, \\ &(|Y^*| + |\Gamma|)(\partial_t v_0, \varphi_2)_\Omega + (P^v \nabla v_0, \nabla \varphi_2)_\Omega - |\Gamma| f(u_0, \varphi_2)_\Omega = 0 \end{aligned}$$

for all $(\varphi_1, \varphi_2) \in V_{\mathrm{C}0}(\Omega) \times V_{\mathrm{N}}(\Omega)$.

The third case with $l, m < 1$ is also interesting. We see that BP molecules directly transform into DE molecules. Hence, the metabolism takes place very quickly. In the next section we also will show uniqueness of the solution of system (21).

Combinations of these scalings, e.g. $l < 1$, $m > 1$, can be handled analogously.

7. Uniqueness of the limit model

In this section we are going to show that the solutions of systems (16) (case $l > 1$, $m > 1$), (17) (case $l = m = 1$) and the solution of system (21) (case $l < 1$, $m < 1$) are unique.

Theorem 13 (Uniqueness for $l > 1$, $m > 1$). *There exists at most one solution of the problem* (16).

P r o o f. To show uniqueness of the solution s_0 we assume the existence of two solutions s_1 and s_2. We test the difference of these two solutions with $\varphi = s_1 - s_2$, integrate from 0 to t, and find for the third equation of system (16) that

$$\tfrac{1}{2}\|s_1 - s_2\|^2_{\Omega\times\Gamma} + D_s\|\nabla_\Gamma(s_1 - s_2)\|^2_{\Omega\times\Gamma,t} + f\|s_1 - s_2\|^2_{\Omega\times\Gamma,t} = 0.$$

Hence, $s_1 = s_2$ almost everywhere on $\Omega \times \Gamma$. The tensors P^u and P^v are unique, see [25]. Then the differential equation for the functions u_0, v_0 and w_0 are standard heat equations with homogeneous or inhomogeneous right-hand sides, respectively, for which uniqueness can be obtained in a standard way, see [9]. $\square$

Theorem 14 (Uniqueness for $l = m = 1$). *There is at most one solution of the problem* (17).

P r o o f. First we note that the tensors P^u and P^v are unique, see [25] for details. We assume there are two solutions (u_1, v_1, s_1, w_1) and (u_2, v_2, s_2, w_2) and prove that these solutions must be equal.

We subtract the equations for u_2 from the equation for u_1 and test it with $\varphi = u_1 - u_2$. After integration from 0 to t, using the binomial theorem and considering that u_1 and u_2 have the same initial conditions we obtain

$$\begin{aligned}\tfrac{1}{2}\|u_1-u_2\|^2_\Omega + \|\sqrt{P^u}\nabla(u_1-u_2)\|^2_{\Omega,t} + l_s|\Gamma|\|u_1-u_2\|^2_{\Omega,t}\\ \leqslant l_s\tfrac{1}{2}\|s_1-s_2\|^2_{\Omega\times\Gamma,t} + l_s\tfrac{1}{2}\|u_1-u_2\|^2_{\Omega,t}.\end{aligned}$$

We find similar estimates for the other equations and add them up to deduce

$$\begin{aligned}&\|u_1-u_2\|^2_\Omega + \|v_1-v_2\|^2_\Omega + \|s_1-s_2\|^2_{\Omega\times\Gamma} + \|w_1-w_2\|^2_{\Omega\times\Gamma}\\ &\quad\leqslant c_1(\|u_1-u_2\|^2_{\Omega,t} + \|v_1-v_2\|^2_{\Omega,t} + \|s_1-s_2\|^2_{\Omega\times\Gamma,t} + \|w_1-w_2\|^2_{\Omega\times\Gamma,t})\end{aligned}$$

for a $c_1 > 0$ depending on l_s, l_w, f and $|\Gamma|$. By Gronwall's lemma it follows that

$$\|u_1-u_2\|^2_\Omega + \|v_1-v_2\|^2_\Omega + \|s_1-s_2\|^2_{\Omega\times\Gamma} + \|w_1-w_2\|^2_{\Omega\times\Gamma} = 0$$

for almost every $t \in [0,T]$ and hence $(u_1,v_1,s_1,w_1) = (u_2,v_2,s_2,w_2)$ almost everywhere. □

Theorem 15 (Uniqueness for $0 < l < 1$, $0 < m < 1$)**.** *There is at most one solution of the problem* (21).

P r o o f. We already know that the diffusion tensors P^u and P^v are unique from [25]. It remains to show that there is at most one solution u_0 and v_0 solving (21). We assume two solutions (u_1,v_1) and (u_2,v_2) and are going to show that they must be equal. Therefore we subtract the equation for (u_1,v_1) and for (u_2,v_2) and test it with $\varphi = u_1 - u_2$ and $\varphi = v_1 - v_2$, respectively, and integrate from 0 to t:

$$(|Y^*|+|\Gamma|)\tfrac{1}{2}\|u_1-u_2\|^2_\Omega + \|\sqrt{P^u}\nabla(u_1-u_2)\|^2_{\Omega,t} + |\Gamma|f\|u_1-u_2\|^2_{\Omega,t} = 0.$$

Hence, we find that $u_1 = u_2$ almost everywhere in Ω and for almost every $t \in [0,T]$. Similarly, we find that

$$(|Y^*|+|\Gamma|)\tfrac{1}{2}\|v_1-v_2\|^2_\Omega + \|\sqrt{P^v}\nabla(v_1-v_2)\|^2_{\Omega,t} = |\Gamma|f\|u_1-u_2\|^2_{\Omega,t} + |\Gamma|f\|v_1-v_2\|^2_{\Omega,t}.$$

By Gronwall's lemma we deduce

$$(|Y^*|+|\Gamma|)\tfrac{1}{2}\|v_1-v_2\|^2_\Omega + \|\sqrt{P^v}\nabla(v_1-v_2)\|^2_{\Omega,t} \leqslant 0$$

and obtain that $v_1 = v_2$ almost everywhere in Ω and for almost every $t \in [0,T]$. This completes the proof. □

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