SIAM J. MATH. ANAL.
Vol. 40, No. 1, pp. 215–237

DERIVATION OF A MACROSCOPIC RECEPTOR-BASED MODEL USING HOMOGENIZATION TECHNIQUES*

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Abstract. We study the problem of diffusive transport of biomolecules in the intercellular space, modeled as porous medium, and of their binding to the receptors located on the surface membranes of the cells. Cells are distributed periodically in a bounded domain. To describe this process we introduce a reaction-diffusion equation coupled with nonlinear ordinary differential equations on the boundary. We prove existence and uniqueness of the solution of this problem. We consider the limit, when the number of cells tends to infinity and at the same time their size tends to zero, while the volume fraction of the cells remains fixed. Using the homogenization technique of two-scale convergence, we show that the sequence of solutions of the original problem converges to the solution of the so-called macroscopic problem. To show the convergence of the nonlinear terms on the surfaces we use the unfolding method (periodic modulation). We discuss applicability of the result to mathematical description of membrane receptors of biological cells and compare the derived model with those previously considered.

Key words. homogenization, two-scale convergence, intercellular communication, receptor-ligand binding, reaction-diffusion equations, unfolding method (periodic modulation)

AMS subject classifications. 35B27, 74Q10, 74Q15, 35K57, 35K60

DOI. 10.1137/050645269

1. Introduction. Regulatory and signaling molecules (ligands) act by binding and activating receptor molecules. Receptors are usually located in the cell membrane, with some exceptions such as lipophilic ligands, which are located in the cytoplasm [24, 33, 34]. Some receptors interact with surface-bound ligands, such as adhesion proteins and extracellular matrix components. Other receptors bind soluble ligands, such as growth factors and cytokines. There are also many ligands which are present in both forms. As an example, antibodies, which are secreted by B cells as soluble molecules, become surface-bound ligands for the Fc receptors upon binding to antigens deposited on the surface [25].

Soluble molecules which are secreted to the intercellular space and transported via diffusion provide cell-to-cell communication, which results in the activation of processes in cells at a distance from the original signal. This happens, for example, in the case of the bystander effect. There is strong evidence that unirradiated bystander cells respond to signals emitted by irradiated cells [28]. In another case, the interplay between the spatial transport of virons and interferons results in the formation of patterns of infected and resistant cells [10]. Intercellular signaling can also lead to the formation of spatially nonhomogeneous structures, which is especially evident in developmental processes [33, 34]. The effects of the spatial transport of the soluble molecules are even visible in experiments in which only spatial averages are measured in order to understand the time dynamics of a signaling pathway. There is evidence

*Received by the editors November 15, 2005; accepted for publication (in revised form) August 31, 2007; published electronically April 16, 2008.
http://www.siam.org/journals/sima/40-1/64526.html

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that different mixing conditions strongly influence quantitative and also qualitative results of such experiments [17]. Therefore, there arises a need to explain how the intercellular transport of the molecules should be described on the macroscopic level.

Models proposed so far are mainly phenomenological and describe all the processes on the macroscale level represented by a two- or three-dimensional sheet of cells [29, 30, 31, 32, 42, 46]. However, the real geometry is much more complicated, and binding a soluble ligand to a cell surface receptor requires interaction of molecules diffusing in three-dimensional space with some molecules attached to a two-dimensional surface. Since the size of a cell is very small compared to the dimension of the whole tissue, systems that include cells have to be treated as multiscale systems.

The aim of the present work is to derive a macroscopic model of receptor-ligand binding, based on a microscopic description, using methods of asymptotic analysis. Such an approach is called homogenization and it hinges on demonstrating the convergence of solutions of a sequence of microscopic problems to the solution of the macroscopic problem in properly chosen function spaces. We use here the two-scale convergence, which was introduced in [2] and [36] for sequences of functions $\{u^\varepsilon\}$ bounded in L^2 or in H^1 on an ε-periodic domain. Then, in [37] and [3], the definition of two-scale convergence was extended to sequences of functions defined on ε-periodic hypersurfaces, with dependence on parameters. This extension was used to homogenize a diffusion-reaction process in a catalyst consisting of distributed bars [37]. A similar problem with convection was studied in [19] using the standard homogenization technique, the energy method. A model describing processes of diffusion, convection, and nonlinear reactions in a periodic array of cells was studied in [20]. In that paper, the convergence of the nonlinear terms was shown using their monotonicity. Homogenization of models of chemical reactive flows in domains with periodically distributed reactive solid grains was also recently studied by Conca et al. [9]. They considered a stationary reaction-diffusion model with nonlinear, fast growing but monotone kinetics on the the surface of reactive solid grains and a model of reaction-diffusion processes both inside and outside of grains. Homogenization of the reaction-diffusion-convection processes with linear reactions on the surface of microstructures was also considered by Hornung in [18].

The model presented in this paper includes the dynamics of molecule concentrations on the surface of microstructures described by nonlinear ordinary differential equations. Therefore, we apply the concept of two-scale convergence of functions from L^∞ on ε-periodic hypersurfaces. To show convergence of the nonlinear terms on the surface of microstructures we use the unfolding method (periodic modulation); see [5, 6, 7].

Our paper is organized as follows. First, we present a precise description of the considered ε-periodic geometry (section 2) and of the equations describing the microscopic nature of the receptor-ligand binding process (section 3). These equations are spatially scaled by ε. Then we show existence and uniqueness of solutions of the microscopic model (section 3.2) and a priori estimates (section 3.3). In section 4, after extension of the solutions from the porous domain to the whole domain, using a priori estimates, we show the convergence of solutions of the microscopic problem to the solutions of a macroscopic homogenized model. Effective macroscopic equations are derived in section 4.2 and formulated in Theorem 4.4. In section 5 we compare a derived macroscopic model of the receptor-ligand binding on cells surfaces with the phenomenological models previously discussed in the literature.

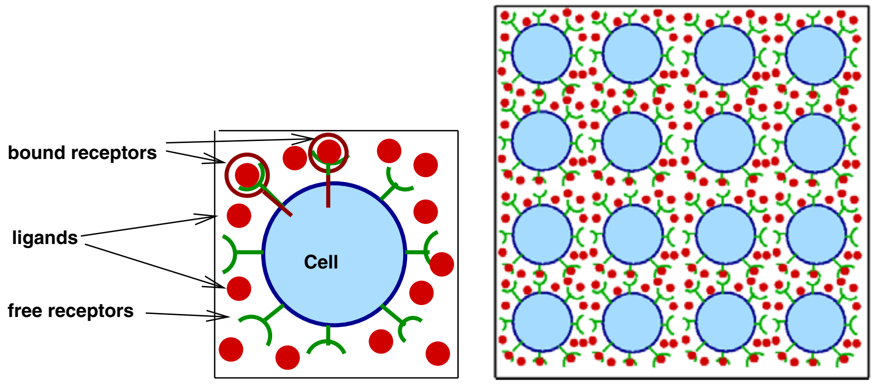

Fig. 1. *Geometry of the model. The array of the cells (on the right-hand side) consists of periodic repetition of the so-called standard cell, $Z = [0,1]^3$ (on the left-hand side), which corresponds to a single biological cell with the surrounding intercellular space.*

2. Problem formulation. We consider a model involving a system of cells, periodically distributed in a three-dimensional cube $\Omega = [a,b]^3$, $a, b \in \mathbb{R}$, $a < b$, with boundary Γ^N. For the mathematical formulation of the problem we consider the so-called standard cell, $Z = [0,1]^3$, periodically repeated over $\mathbb{R}^3$ with $Y_0 \subset Z$, an open subset with a smooth boundary Γ; $Y = Z \backslash \overline{Y}_0$; and ν, the outer normal of Y (see Figure 1).

Let $\varepsilon > 0$ be a given scale factor such that $\varepsilon = \frac{b-a}{n}$, $n \in \mathbb{N}$, denoting the ratio between the size of the cells and the size of the whole domain Ω. Then the geometric structure within the fixed domain Ω is obtained by intersecting the ε-multiple εZ with Ω. We define, for $k \in \mathbb{Z}^3$, a triple of integers; and e_i, unit vectors, $\Gamma^k = \Gamma + \sum_{i=1}^{3} k_i e_i$, $Y_0^k = Y_0 + \sum_{i=1}^{3} k_i e_i$, $Z^k = Z + \sum_{i=1}^{3} k_i e_i$, $\Gamma^* = \cup\{\Gamma^k, \ \ k \in \mathbb{Z}^3\}$, $Z^* = \cup\{Z^k, \ \ k \in \mathbb{Z}^3\}$. We further define $\Omega_0^\varepsilon = \cup\{\varepsilon Y_0^k | \varepsilon Z^k \subset \Omega, \ \ k \in \mathbb{Z}^3\}$, $\Omega^\varepsilon = \Omega \backslash \Omega_0^\varepsilon$, $\Gamma^\varepsilon = \cup\{\varepsilon \Gamma^k | \varepsilon Z^k \subset \Omega, \ \ k \in \mathbb{Z}^3\}$.

Remark 2.1. The geometry defined above fulfills the assumptions that

1. cells (holes in the domain) do not touch the boundary $\partial\Omega$;
2. cells do not touch each other;
3. cells have smooth boundary.

These assumptions allow for the definition of the functions on the cell boundaries using periodic repetition, and the definition of extension as proposed in [8]. Therefore, these assumptions are important for the methods applied in this paper. Homogenization of the Neumann problem in domains with more complicated geometry was considered in [1] and [4].

We assume that new ligands and new free receptors are produced on the cell surface through a combination of recycling (dissociation of bound receptors) and *de novo* production within the cell. Free receptors exist only on the surfaces, while ligands are transported by diffusion within the intercellular space, which is a porous medium. A ligand reversibly binds to a free receptor, which results in a bound receptor that can be internalized into the cell. Bound receptors also dissociate. Both ligands and free receptors undergo natural decay. We denote the concentration of ligands by $l^\varepsilon : (0,T) \times \Omega^\varepsilon \to \mathbb{R}$. Bound and free receptor densities are denoted by $r_b^\varepsilon : (0,T) \times \Gamma^\varepsilon \to \mathbb{R}$ and $r_f^\varepsilon : (0,T) \times \Gamma^\varepsilon \to \mathbb{R}$, respectively. For simplicity we assume that all binding processes are governed by the law of mass action without saturation effects.

3. Microscopic model.

3.1. Model assumptions. The microscopic model consists of the following equations:

Diffusion equation for ligands in the intercellular space,

$$\frac{\partial}{\partial t} l^\varepsilon(t,x) = \nabla \cdot (D^\varepsilon(t,x)\nabla l^\varepsilon(t,x)) - \mu_l^\varepsilon(t,x) l^\varepsilon(t,x) + p_l^\varepsilon(t,x,l^\varepsilon(x,t)) \quad \text{in } (0,T)\times\Omega^\varepsilon,$$

$$\nu^\varepsilon \cdot \nabla_x l^\varepsilon(t,x) = 0 \quad \text{on } (0,T)\times\Gamma^N,$$

$$l^\varepsilon(x,t) = l_0(x), \quad t=0,\ x\in\Omega^\varepsilon. \tag{1}$$

Binding equation on the surfaces,

$$-D^\varepsilon(t,x)\nabla l^\varepsilon(t,x)\cdot\nu^\varepsilon = \varepsilon(b^\varepsilon(t,x) l^\varepsilon(t,x) {r_f}^\varepsilon(t,x) - d^\varepsilon(t,x) r_b^\varepsilon(t,x)) \ \text{ on } (0,T)\times\Gamma^\varepsilon. \tag{2}$$

Reaction equations for receptors on the surfaces,

$$\frac{\partial}{\partial t}{r_f}^\varepsilon(x,t) = -\mu_f^\varepsilon(t,x){r_f}^\varepsilon(x,t) + p_r^\varepsilon(t,x,r_b^\varepsilon(x,t)) - b^\varepsilon(t,x){r_f}^\varepsilon(x,t) l^\varepsilon(x,t)$$

$$+ d^\varepsilon(t,x){r_b}^\varepsilon(x,t), \tag{3}$$

$$\frac{\partial}{\partial t}{r_b}^\varepsilon(x,t) = -\mu_b^\varepsilon(t,x){r_b}^\varepsilon(x,t) + b^\varepsilon(t,x){r_f}^\varepsilon(x,t) l^\varepsilon(x,t) - d^\varepsilon(t,x){r_b}^\varepsilon(x,t), \tag{4}$$

with initial conditions

$${r_f}^\varepsilon(x,t) = {r_f}_0(x), \quad t=0,\ x\in\Gamma^\varepsilon, \tag{5}$$

$${r_b}^\varepsilon(x,t) = r_{b0}(x), \quad t=0,\ x\in\Gamma^\varepsilon. \tag{6}$$

The following is a list of functional coefficients in these equations:

$\mu_l^\varepsilon : (0,T)\times\Omega\to\mathbb{R}$	rate of decay of ligands,
$p_l^\varepsilon : (0,T)\times\Omega\times\mathbb{R}\to\mathbb{R}$	production of ligands,
$D^\varepsilon : (0,T)\times\Omega\to\mathbb{R}^{3\times 3}$	diffusion coefficient for ligands,
$p_r^\varepsilon : (0,T)\times\Gamma^\varepsilon\times\mathbb{R}\to\mathbb{R}$	production of new free receptors,
$\mu_f^\varepsilon : (0,T)\times\Gamma^\varepsilon\to\mathbb{R}$	rate of decay of free receptors,
$\mu_b^\varepsilon : (0,T)\times\Gamma^\varepsilon\to\mathbb{R}$	rate of decay of bound receptors,
$d^\varepsilon : (0,T)\times\Gamma^\varepsilon\to\mathbb{R}$	rate of dissociation of bound receptors,
$b^\varepsilon : (0,T)\times\Gamma^\varepsilon\to\mathbb{R}$	rate of binding of ligands and free receptors,

where functions on Ω or Γ^ε are defined by Z-periodic function: $D^\varepsilon_{i,j}(t,x) = D_{i,j}(t,\frac{x}{\varepsilon})$, $p_l^\varepsilon(t,x,\xi) = p_l(t,\frac{x}{\varepsilon},\xi)$, $\mu_l^\varepsilon(t,x) = \mu_l(t,\frac{x}{\varepsilon})$, $\mu_f^\varepsilon(t,x) = \mu_f(t,\frac{x}{\varepsilon})$, $\mu_b^\varepsilon(t,x) = \mu_b(t,\frac{x}{\varepsilon})$, $b^\varepsilon(t,x) = b(t,\frac{x}{\varepsilon})$, $d^\varepsilon(t,x) = d(t,\frac{x}{\varepsilon})$, $p_r^\varepsilon(t,x,\xi) = p_r(t,\frac{x}{\varepsilon},\xi)$, defined on Z^* and Γ^*, respectively.

We assume that decay processes are linear and that binding is a product of the density of ligands and free receptors. The proposed functions are the simplest functions usually used to describe decay or binding processes (see the models described in [35]), modeled by the law of mass action. We assume that *de novo* production of free receptors, denoted by p_r, is regulated by bound receptors. We assume that p_r

is a bounded Lipschitz continuous function in r_b and is nonnegative for nonnegative values of r_b, for example a Michaelis–Menten function $p_r = \frac{m_1 r_b}{1+r_b}$. In addition, we assume that the production of ligands depends on their density. It could be regulated via some other receptors not considered in our model. Thus, we assume that p_l is a Lipschitz continuous function in l, nonnegative for nonnegative values of l.

Assumption 3.1.

1. $D \in L^\infty((0,T)\times Z)^{3\times 3}$, $\partial_t D \in L^\infty((0,T)\times Z)^{3\times 3}$, $(D(t,x)\xi,\xi) \geq d_0|\xi|^2$ for some $d_0 > 0$, for every $\xi \in \mathbb{R}^3$, a.a. $(t,x) \in (0,T)\times Z$.
2. $\mu_l \in L^\infty((0,T)\times Z)$ and $\mu_l \geq 0$ a.e. in $(0,T)\times Z$.
3. p_l is measurable in t and x, sublinear, i.e., $|p_l(t,x,\xi)| \leq c_1 + c_2|\xi|$ for a.a. $(t,x) \in (0,T)\times Z$, Lipschitz continuous in ξ, and $p_l(t,x,\xi) \geq 0$ for $\xi \geq 0$.
4. $b \in C([0,T]; C^{0,\alpha}(\Gamma))$, $b \geq 0$, in $[0,T]\times\Gamma$, $\partial_t b \in L^\infty((0,T)\times\Gamma)$.
5. $d \in C([0,T]; C^{0,\alpha}(\Gamma))$, $d \geq 0$, in $[0,T]\times\Gamma$, $\partial_t d \in L^\infty((0,T)\times\Gamma)$.
6. $\mu_f, \mu_b \in C([0,T]; C^{0,\alpha}(\Gamma))$, $\mu_f \geq 0$, $\mu_b \geq 0$, in $[0,T]\times\Gamma$.
7. $p_r(\xi) \in C([0,T]; C^{0,\alpha}(\Gamma))$ for all $\xi \in \mathbb{R}$, $p_r(t,x,\xi) \geq 0$ for $\xi \geq 0$, p_r is bounded, i.e., $|p_r(t,x,\xi)| \leq m_1$ for all $(t,x,\xi) \in (0,T)\times\Gamma\times\mathbb{R}$ and is Lipschitz continuous in ξ.

3.2. Existence of the solutions of the microscopic model. We start with a weak formulation of the microscopic model.

DEFINITION 3.2. *The triple $(l^\varepsilon, r_f^\varepsilon, r_b^\varepsilon)$ is a solution of problem* (1)–(6) *if $l^\varepsilon \in L^2((0,T); H^1(\Omega^\varepsilon))$, $\partial_t l^\varepsilon \in L^2((0,T)\times\Omega^\varepsilon)$, $l^\varepsilon \in L^\infty((0,T)\times\Omega^\varepsilon)$, r_f^ε, $r_b^\varepsilon \in L^\infty((0,T)\times\Gamma^\varepsilon)$, $\partial_t r_f^\varepsilon$, $\partial_t r_b^\varepsilon \in L^\infty((0,T)\times\Gamma^\varepsilon)$ such that*

1.
$$
\begin{aligned}
(\partial_t l^\varepsilon, \phi)_{(0,T)\times\Omega^\varepsilon} = &-(D^\varepsilon \nabla l^\varepsilon, \nabla\phi)_{(0,T)\times\Omega^\varepsilon} - (\mu_l^\varepsilon l^\varepsilon, \phi)_{(0,T)\times\Omega^\varepsilon} \\
&+ (d^\varepsilon r_b^\varepsilon - b^\varepsilon r_f^\varepsilon l^\varepsilon, \phi)_{(0,T)\times\Gamma^\varepsilon} + (p_l^\varepsilon(l^\varepsilon), \phi)_{(0,T)\times\Omega^\varepsilon}
\end{aligned}
\tag{7}
$$
for all $\phi \in L^2((0,T); H^1(\Omega^\varepsilon))$;
2. *l^ε satisfies the initial condition, i.e., $l^\varepsilon \to l_0$ in $L^2(\Omega^\varepsilon)$ as $t \to 0$;*
3.
$$
\begin{cases}
\dfrac{\partial}{\partial t} {r_f}^\varepsilon(x,t) = -\mu_f^\varepsilon {r_f}^\varepsilon(x,t) + p_r^\varepsilon(t,x,r_b^\varepsilon(x,t)) \\
\qquad\qquad\qquad - b^\varepsilon {r_f}^\varepsilon(x,t) l^\varepsilon(x,t) + d^\varepsilon {r_b}^\varepsilon(x,t), \\
\dfrac{\partial}{\partial t} {r_b}^\varepsilon(x,t) = -\mu_b^\varepsilon {r_b}^\varepsilon(x,t) + b^\varepsilon {r_f}^\varepsilon(x,t) l^\varepsilon(x,t) \\
\qquad\qquad\qquad - d^\varepsilon {r_b}^\varepsilon(x,t)
\end{cases}
\tag{8}
$$
a.e. $(0,T)\times\Gamma^\varepsilon$*;*
4. *${r_f}^\varepsilon, {r_b}^\varepsilon$ satisfy the initial conditions* (5)–(6).

Here $(u,v)_{(0,T)\times\Omega^\varepsilon} = \int_0^T \int_{\Omega^\varepsilon} u\, v\, dx\, dt$ and $(u,v)_{(0,T)\times\Gamma^\varepsilon} = \varepsilon \int_0^T \int_{\Gamma^\varepsilon} u\, v\, d\gamma_x\, dt$.

THEOREM 3.3. *Let Assumption* 3.1 *be satisfied and*

$$
l_0 \in C^{0,\alpha}(\overline{\Omega}),\ \ l_0 \in H^1(\Omega),\ \ l_0 \geq 0,
$$
$$
r_{f0}, r_{b0} \in C^{0,\alpha}(\overline{\Omega}),\ \ r_{f0} \geq 0,\ \ r_{b0} \geq 0.
$$

Then there exists a unique solution $(l^\varepsilon, r_f^\varepsilon, r_b^\varepsilon)$ of problem (1)–(6), *such that*

$$
\begin{aligned}
& l^\varepsilon \in H^1(0,T; L^2(\Omega^\varepsilon)),\ l^\varepsilon \in L^2(0,T; H^1(\Omega^\varepsilon)), \\
& l^\varepsilon \in C^{0,\beta/2}([0,T]; C^{0,\beta}(\overline{\Omega}^\varepsilon)), \\
& r_f^\varepsilon, r_b^\varepsilon \in C^1([0,T]; C^{0,\beta}(\Gamma^\varepsilon)), \quad \textit{where} \quad \beta \in (0,\alpha], \\
& \textit{and} \quad l^\varepsilon \geq 0, r_f^\varepsilon \geq 0, r_b^\varepsilon \geq 0.
\end{aligned}
$$

Proof. Existence. The existence of a solution of the system (1), (3), (4) will be proved by showing the existence of a fix point of the operator K defined on $C([0,T]\times\overline{\Omega}^\varepsilon)$ by $l^{n,\varepsilon}=K(l^{n-1,\varepsilon})$ with $l^{n,\varepsilon}$ given by

$$(9)\qquad \begin{cases} \partial_t\, l^{n,\varepsilon} = \nabla\cdot(D^\varepsilon\nabla l^{n,\varepsilon}) - \mu_l^\varepsilon l^{n,\varepsilon} + p_l^\varepsilon(l^{n-1,\varepsilon}), & t>0,\ x\in\Omega^\varepsilon,\\ \nabla l^{n,\varepsilon}\cdot\nu^\varepsilon = 0, & t>0,\ x\in\Gamma^N,\\ l^{n,\varepsilon} = l_0, & t=0,\ x\in\Omega^\varepsilon,\\ -D^\varepsilon\nabla l^{n,\varepsilon}\cdot\nu^\varepsilon = \varepsilon(b^\varepsilon l^{n,\varepsilon} {r_f}^{n,\varepsilon} - d^\varepsilon {r_b}^{n,\varepsilon}), & t>0,\ x\in\Gamma^\varepsilon,\end{cases}$$

$$(10)\qquad \begin{cases} \partial_t {r_f}^{n,\varepsilon} = -\mu_f^\varepsilon {r_f}^{n,\varepsilon} + p_r^\varepsilon({r_b}^{n,\varepsilon}) - b^\varepsilon {r_f}^{n,\varepsilon} l^{n-1,\varepsilon} + d^\varepsilon {r_b}^{n,\varepsilon}, & t>0,\ x\in\Gamma^\varepsilon,\\ \partial_t {r_b}^{n,\varepsilon} = -\mu_b^\varepsilon {r_b}^{n,\varepsilon} + b^\varepsilon {r_f}^{n,\varepsilon} l^{n-1,\varepsilon} - d^\varepsilon {r_b}^{n,\varepsilon}, & t>0,\ x\in\Gamma^\varepsilon,\\ {r_f}^{n,\varepsilon} \ = {r_f}_0, & t=0,\ x\in\Gamma^\varepsilon,\\ {r_b}^{n,\varepsilon} \ = r_{b0}, & t=0,\ x\in\Gamma^\varepsilon.\end{cases}$$

For a given $l^{n-1,\varepsilon}\in C([0,T]\times\overline{\Omega}^\varepsilon)$, $l^{n-1,\varepsilon}\geq 0$ on $[0,T]\times\overline{\Omega}^\varepsilon$, there exists a unique solution of system (10), $r_f^{n,\varepsilon}$, $r_b^{n,\varepsilon}\in C^1([0,T];C(\Gamma^\varepsilon))$, because the right-hand side of the system of ordinary differential equations (10) is Lipschitz continuous [45]. Since p_r is a nonnegative function for nonnegative values of r_b and $l^{n-1,\varepsilon}\geq 0$ on $[0,T]\times\Gamma^\varepsilon$ and $r_{f0}\geq 0$, $r_{b0}\geq 0$, we deduce that $r_f^{n,\varepsilon}\geq 0$, $r_b^{n,\varepsilon}\geq 0$ on $[0,T]\times\Gamma^\varepsilon$.

Using the Galerkin method and a priori estimates similar to the estimates in Lemma 3.4, we obtain the existence of a weak solution of (9), $l^{n,\varepsilon}\in L^2(0,T;H^1(\Omega^\varepsilon))$, $\partial_t l^{n,\varepsilon}\in L^2(0,T;L^2(\Omega^\varepsilon))$; see [23]. Since $l_0\in C^{0,\alpha}(\overline{\Omega})$, there exists $\max_{\overline{\Omega}^\varepsilon}|l_0|=M$. In addition, $r_f^{n,\varepsilon}\geq 0$ and $|r_b^{n,\varepsilon}|\leq C$. Thus, we may apply the result from [26] (Theorem 6.40) stating that for parabolic equations with uniformly elliptic operator, sublinear terms of lower order, bounded free terms, and bounded coefficients of Robin boundary conditions, the boundedness of the initial conditions implies the boundedness of the supremum of a solution. From this, we conclude that $\sup_{(0,T)\times\Omega^\varepsilon}|l^{n,\varepsilon}|\leq M_1$. Then, since $l_0\in C^{0,\alpha}(\overline{\Omega})$, $r_f^{n,\varepsilon}\geq 0$, and $r_b^{n,\varepsilon}\in C^1([0,T];C(\Gamma^\varepsilon))$, we conclude also that $l^{n,\varepsilon}\in C^{0,\beta/2}([0,T];C^{0,\beta}(\overline{\Omega}^\varepsilon))$ (see Theorem III.10.1 in [23], generalized for Robin boundary conditions, or [11] and [26]). Using the maximum principle and the continuity of $l^{n,\varepsilon}$, we obtain that $l^{n,\varepsilon}\geq 0$ in $[0,T]\times\overline{\Omega}^\varepsilon$ [12].

The space $C^{0,\beta/2}([0,T];C^{0,\beta}(\overline{\Omega}^\varepsilon))$ is compact embedded in $C([0,T]\times\overline{\Omega}^\varepsilon)$. Then, by virtue of the Schauder theorem, there exists a fixed point of K, a solution of the microscopic problem l^ε, r_f^ε, and r_b^ε. In addition, we obtain that $l^\varepsilon\geq 0$, $r_f^\varepsilon\geq 0$, and $r_b^\varepsilon\geq 0$. Since $r_{f0}, r_{b0}\in C^{0,\alpha}(\Omega)$ and $l^\varepsilon\in C^{0,\beta/2}([0,T];C^{0,\beta}(\overline{\Omega}^\varepsilon))$, we conclude also that $r_f^\varepsilon, r_b^\varepsilon\in C^1([0,T];C^{0,\beta}(\Gamma^\varepsilon))$.

Uniqueness. Suppose there are two solutions of the problem $(l^{1,\varepsilon}, r_f^{1,\varepsilon}, r_b^{1,\varepsilon})$ and $(l^{2,\varepsilon}, r_f^{2,\varepsilon}, r_b^{2,\varepsilon})$. We denote $l^\varepsilon=l^{1,\varepsilon}-l^{2,\varepsilon}$ and choose $\phi=l^\varepsilon$. We calculate

$$\frac{1}{2}\int_0^\tau\int_{\Omega^\varepsilon}\Big(\partial_t|l^\varepsilon|^2+(D^\varepsilon\nabla l^\varepsilon,\nabla l^\varepsilon)+\mu_l^\varepsilon|l^\varepsilon|^2\Big)\,dx\,dt=\int_0^\tau\int_{\Omega^\varepsilon}(p_l^\varepsilon(l^{1,\varepsilon})-p_l^\varepsilon(l^{2,\varepsilon}))l^\varepsilon\,dx\,dt$$

$$+\,\varepsilon\int_0^\tau\int_{\Gamma^\varepsilon}((d^\varepsilon r_b^{1,\varepsilon}-b^\varepsilon r_f^{1,\varepsilon}l^{1,\varepsilon})-(d^\varepsilon r_b^{2,\varepsilon}-b^\varepsilon r_f^{2,\varepsilon}l^{2,\varepsilon}))\,l^\varepsilon\,d\gamma\,dt$$

for any $\tau \in [0,T]$. For r_f^ε and r_b^ε we obtain

$$\frac{\partial}{\partial t}(r_f^{1,\varepsilon} - r_f^{2,\varepsilon}) = -\mu_f^\varepsilon(r_f^{1,\varepsilon} - r_f^{2,\varepsilon}) + (p_r^\varepsilon({r_b}^{1,\varepsilon}) - p_r^\varepsilon({r_b}^{2,\varepsilon})) - b^\varepsilon(r_f^{1,\varepsilon} l^{1,\varepsilon} - r_f^{2,\varepsilon} l^{2,\varepsilon}) + d^\varepsilon(r_b^{1,\varepsilon} - r_b^{2,\varepsilon}),$$

$$\frac{\partial}{\partial t}(r_b^{1,\varepsilon} - r_b^{2,\varepsilon}) = -\mu_b^\varepsilon(r_b^{1,\varepsilon} - r_b^{2,\varepsilon}) + b^\varepsilon(r_f^{1,\varepsilon} l^{1,\varepsilon} - r_f^{2,\varepsilon} l^{2,\varepsilon}) - d^\varepsilon(r_b^{1,\varepsilon} - r_b^{2,\varepsilon}).$$

Integrating by parts with respect to time and summing up side by side the last two equations, we obtain

$$|r_f^{1,\varepsilon} - r_f^{2,\varepsilon}| + |r_b^{1,\varepsilon} - r_b^{2,\varepsilon}| \le \int_0^\tau \Big(\mu_f^1 |r_f^{1,\varepsilon} - r_f^{2,\varepsilon}| + \mu_b^1 |r_b^{1,\varepsilon} - r_b^{2,\varepsilon}| + c_r |r_b^{1,\varepsilon} - r_b^{2,\varepsilon}|\Big) dt$$
$$+ \int_0^\tau \Big(2b_1 \max_{[0,T]\times\Gamma^\varepsilon} |l^{1,\varepsilon}||r_f^{1,\varepsilon} - r_f^{2,\varepsilon}| + 2b_1 \max_{[0,T]\times\Gamma^\varepsilon} |r_f^{2,\varepsilon}||l^{1,\varepsilon} - l^{2,\varepsilon}| + 2d_1 |r_b^{1,\varepsilon} - r_b^{2,\varepsilon}|\Big)\, dt,$$

where c_r is the Lipschitz constant of p_r, $\mu_f^1 = \sup_{[0,T]\times\Gamma^\varepsilon} |\mu_f^\varepsilon|$, $\mu_b^1 = \sup_{[0,T]\times\Gamma^\varepsilon} |\mu_b^\varepsilon|$, $b_1 = \sup_{[0,T]\times\Gamma^\varepsilon} |b^\varepsilon|$, $d_1 = \sup_{[0,T]\times\Gamma^\varepsilon} |d^\varepsilon|$. The Gronwall lemma implies

$$|r_f^{1,\varepsilon} - r_f^{2,\varepsilon}| + |r_b^{1,\varepsilon} - r_b^{2,\varepsilon}| \le C \int_0^\tau |l^{1,\varepsilon} - l^{2,\varepsilon}|\, dt. \tag{11}$$

Using the above estimate and nonnegativity of b^ε and $r_f^{2,\varepsilon}$, we obtain

$$\frac{1}{2}\int_0^\tau \int_{\Omega^\varepsilon} \partial_t |l^\varepsilon|^2\, dx\, dt + d_0 \int_0^\tau \int_{\Omega^\varepsilon} |\nabla l^\varepsilon|^2\, dx\, dt + \int_0^\tau \int_{\Omega^\varepsilon} \mu_l^\varepsilon |l^\varepsilon|^2\, dx\, dt$$
$$\le C d_1^2 \varepsilon \frac{1}{2\delta} \int_0^\tau \int_{\Gamma^\varepsilon} \int_0^t |l^\varepsilon|^2\, ds\, d\gamma\, dt + \varepsilon \frac{\delta}{2} \int_0^\tau \int_{\Gamma^\varepsilon} |l^\varepsilon|^2\, d\gamma\, dt + c_l \int_0^\tau \int_{\Omega^\varepsilon} |l^\varepsilon|^2\, dx\, dt$$
$$+ C b_1 \varepsilon \max_{[0,T]\times\Gamma^\varepsilon} |l^{1,\varepsilon}| \int_0^\tau \int_{\Gamma^\varepsilon} \int_0^t |l^\varepsilon|^2\, ds\, d\gamma\, dt + C b_1 \varepsilon \max_{[0,T]\times\Gamma^\varepsilon} |l^{1,\varepsilon}| \int_0^\tau \int_{\Gamma^\varepsilon} |l^\varepsilon|^2\, d\gamma\, dt,$$

where c_l is the Lipschitz constant of p_l. Furthermore, using the estimate

$$\varepsilon \int_0^\tau \int_{\Gamma^\varepsilon} |l^\varepsilon|^2\, d\gamma\, dt \le c \int_0^\tau \int_{\Omega^\varepsilon} |l^\varepsilon|^2\, dx\, dt + c\varepsilon^2 \int_0^\tau \int_{\Omega^\varepsilon} |\nabla l^\varepsilon|^2\, dx\, dt, \tag{12}$$

we obtain

$$\frac{1}{2}\int_{\Omega^\varepsilon} |l^\varepsilon|^2\, dx + (d_0 - \varepsilon^2\delta) \int_0^\tau \int_{\Omega^\varepsilon} |\nabla l^\varepsilon|^2\, dx\, dt + \int_0^\tau \int_{\Omega^\varepsilon} \mu_l^\varepsilon |l^\varepsilon|^2\, dx\, dt$$
$$\le C\frac{1}{\delta} \int_0^\tau \int_0^t \int_{\Omega^\varepsilon} (|l^\varepsilon|^2 + |\nabla l^\varepsilon|^2)\, dx\, ds\, dt + c_l \int_0^\tau \int_{\Omega^\varepsilon} |l^\varepsilon|^2\, dx\, dt.$$

From the Gronwall lemma and $\mu_l^\varepsilon \ge 0$, taking the supremum over $\tau \in [0,T]$, we conclude that

$$\int_{\Omega^\varepsilon} |l^\varepsilon|^2\, dx + C \int_0^T \int_{\Omega^\varepsilon} |\nabla l^\varepsilon|^2\, dx\, dt \le 0$$

and, therefore, $l^{1,\varepsilon} = l^{2,\varepsilon}$ in $(0,T)\times\Omega^\varepsilon$. Due to (11), also $r_f^{1,\varepsilon} = r_f^{2,\varepsilon}$ and $r_b^{1,\varepsilon} = r_b^{2,\varepsilon}$ on $[0,T]\times\Gamma^\varepsilon$. ∎

3.3. A priori estimates for the microscopic solutions.

LEMMA 3.4. *For any solution of problem* (1)–(6) *from Theorem* 3.3 *the following estimates hold:*

$$\|l^\varepsilon\|_{L^2(0,T;H^1(\Omega^\varepsilon))} \le C, \quad \|\partial_t l^\varepsilon\|_{L^2(0,T;L^2(\Omega^\varepsilon))} \le C,$$

$$\|r_f^\varepsilon\|_{L^\infty((0,T)\times\Gamma^\varepsilon)} \le C, \quad \|r_b^\varepsilon\|_{L^\infty((0,T)\times\Gamma^\varepsilon)} \le C,$$

$$\|\partial_t r_f^\varepsilon\|_{L^2((0,T)\times\Gamma^\varepsilon)} \le C, \quad \|\partial_t r_b^\varepsilon\|_{L^2((0,T)\times\Gamma^\varepsilon)} \le C,$$

where C is a constant independent on ε.

Proof. To show the estimates for r_f^ε and r_b^ε we add (3) and (4) side by side and obtain

$$\partial_t(r_f^\varepsilon + r_b^\varepsilon) \le m_1.$$

Since r_f^ε and r_b^ε are nonnegative (see Theorem 3.3), we conclude that

$$||r_f^\varepsilon||_{L^\infty((0,T)\times\Gamma^\varepsilon)} \le C \quad \text{and} \quad ||r_b^\varepsilon||_{L^\infty((0,T)\times\Gamma^\varepsilon)} \le C.$$

Now we show the estimates for l^ε. We choose $\phi = l^\varepsilon$ as a test function in (7) and calculate

$$\frac{1}{2}\int_0^\tau\int_{\Omega^\varepsilon} \partial_t |l^\varepsilon|^2\, dx\, dt + \int_0^\tau\int_{\Omega^\varepsilon} (D^\varepsilon \nabla l^\varepsilon, \nabla l^\varepsilon)\, dx\, dt + \int_0^\tau\int_{\Omega^\varepsilon} \mu_l^\varepsilon |l^\varepsilon|^2\, dx\, dt$$
$$= \varepsilon \int_0^\tau\int_{\Gamma^\varepsilon} (d^\varepsilon r_b^\varepsilon - b^\varepsilon r_f^\varepsilon l^\varepsilon)\, l^\varepsilon\, d\gamma\, dt + \int_0^\tau\int_{\Omega^\varepsilon} p_l^\varepsilon(l^\varepsilon) l^\varepsilon\, dx\, dt$$

for any $\tau \in [0,T]$. Applying the Young inequality we obtain

$$\frac{1}{2}\int_{\Omega^\varepsilon} |l^\varepsilon|^2\, dx + \int_0^\tau\int_{\Omega^\varepsilon} d_0 |\nabla l^\varepsilon|^2\, dx\, dt + \int_0^\tau\int_{\Omega^\varepsilon} \mu_l^\varepsilon |l^\varepsilon|^2\, dx\, dt$$
$$\le \frac{\varepsilon d_1}{2\delta}\int_0^\tau\int_{\Gamma^\varepsilon} |r_b^\varepsilon|^2\, d\gamma\, dt + \varepsilon\frac{\delta}{2}\int_0^\tau\int_{\Gamma^\varepsilon} |l^\varepsilon|^2\, d\gamma\, dt$$
$$- \varepsilon\int_0^\tau\int_{\Gamma^\varepsilon} b^\varepsilon r_f^\varepsilon |l^\varepsilon|^2\, d\gamma\, dt + c_1\int_0^\tau\int_{\Omega^\varepsilon} |l^\varepsilon|^2\, dx\, dt + \frac{1}{2}\int_{\Omega^\varepsilon} |l_0^\varepsilon|^2\, dx.$$

Now we use (12), $\mu_l^\varepsilon \ge 0$, $b^\varepsilon \ge 0$, and $r_f^\varepsilon \ge 0$ and obtain

$$\frac{1}{2}\int_{\Omega^\varepsilon} |l^\varepsilon|^2\, dx + \int_0^\tau\int_{\Omega^\varepsilon} \left(d_0 - \frac{\delta\varepsilon^2}{2}\right) |\nabla l^\varepsilon|^2\, dx\, dt$$
$$\le \frac{\varepsilon}{2\delta}\int_0^\tau\int_{\Gamma^\varepsilon} |r_b^\varepsilon|^2\, d\gamma\, dt + c_1\int_0^\tau\int_{\Omega^\varepsilon} |l^\varepsilon|^2\, dx\, dt + \frac{1}{2}\int_{\Omega^\varepsilon} |l_0^\varepsilon|^2\, dx.$$

Then, from the Gronwall lemma and the estimate for r_b^ε, it follows that

$$\int_\Omega |l^\varepsilon|^2\, dx + \int_0^T\int_{\Omega^\varepsilon} |\nabla l^\varepsilon|^2\, dx\, dt \le C.$$

Using the estimates for l^ε, r_f^ε, and r_b^ε, we conclude from (8) that

$$||\partial_t r_f^\varepsilon||_{L^2((0,T)\times\Gamma^\varepsilon)} \leq C,$$
$$||\partial_t r_b^\varepsilon||_{L^2((0,T)\times\Gamma^\varepsilon)} \leq C.$$

To obtain the estimates for $\partial_t l^\varepsilon$ we choose $\phi = \partial_t l^\varepsilon$ as a test function and calculate

$$\int_0^\tau \int_{\Omega^\varepsilon} |\partial_t l^\varepsilon|^2 \, dx \, dt + \frac{1}{2}\int_0^\tau \int_{\Omega^\varepsilon} \Big(\partial_t (D^\varepsilon \nabla l^\varepsilon, \nabla l^\varepsilon) - (\partial_t D^\varepsilon \nabla l^\varepsilon, \nabla l^\varepsilon)\Big) \, dx \, dt$$
$$= \int_0^\tau \int_{\Omega^\varepsilon} (p_l^\varepsilon(l^\varepsilon) - \mu_l^\varepsilon l^\varepsilon)\partial_t l^\varepsilon \, dx \, dt + \varepsilon \int_0^\tau \int_{\Gamma^\varepsilon} \Big(\partial_t(d^\varepsilon r_b^\varepsilon l^\varepsilon) - d^\varepsilon \partial_t r_b^\varepsilon l^\varepsilon - \partial_t d^\varepsilon r_b^\varepsilon l^\varepsilon\Big) d\gamma \, dt$$
$$+ \varepsilon \int_0^\tau \int_{\Gamma^\varepsilon} \Big(-\partial_t(b^\varepsilon r_f^\varepsilon |l^\varepsilon|^2) + b^\varepsilon \partial_t r_f^\varepsilon |l^\varepsilon|^2 + \partial_t b^\varepsilon r_f^\varepsilon |l^\varepsilon|^2\Big) d\gamma \, dt.$$

Using the Young inequality we obtain

$$\begin{aligned}
(1-\delta)&\int_0^\tau \int_{\Omega^\varepsilon} |\partial_t l^\varepsilon|^2 \, dx \, dt + \frac{d_0}{2}\int_{\Omega^\varepsilon} |\nabla l^\varepsilon|^2 \, dx \\
&\leq \frac{\varepsilon}{2\delta}\int_{\Gamma^\varepsilon} d_1^2 |r_b^\varepsilon|^2 d\gamma + D_2 \int_0^\tau \int_{\Omega^\varepsilon} |\nabla l^\varepsilon|^2 \, dx \, dt \\
&\quad + \varepsilon \frac{\delta}{2}\int_{\Gamma^\varepsilon} |l^\varepsilon|^2 \, d\gamma + \frac{\varepsilon}{2}\int_0^\tau \int_{\Gamma^\varepsilon} (d_1^2 |\partial_t r_b^\varepsilon|^2 + |\partial_t d|^2 |r_b^\varepsilon|^2) \, d\gamma \, dt \\
&\quad + \frac{\varepsilon}{2}\int_0^\tau \int_{\Gamma^\varepsilon} |l^\varepsilon|^2 \, d\gamma \, dt - \varepsilon \int_{\Gamma^\varepsilon} b^\varepsilon r_f^\varepsilon |l^\varepsilon|^2 \, d\gamma \\
&\quad + \frac{1}{2\delta}\int_0^\tau \int_{\Omega^\varepsilon} (|p_l^\varepsilon(l^\varepsilon)|^2 + \mu_l^\varepsilon |l^\varepsilon|^2) \, dx \, dt + \varepsilon \int_{\Gamma^\varepsilon} (d_1 r_{b0} l_0 + b_1 r_{f0} |l_0|^2) \, d\gamma \\
&\quad + D_1 \int_{\Omega^\varepsilon} |\nabla l_0|^2 \, dx + \varepsilon \int_0^\tau \int_{\Gamma^\varepsilon} (\partial_t b^\varepsilon r_f^\varepsilon + b^\varepsilon |\partial_t r_f^\varepsilon|) \, |l^\varepsilon|^2 \, d\gamma \, dt,
\end{aligned}$$

where $D_1 = \sup_{(0,T)\times\Omega} |D^\varepsilon|$, $D_2 = \sup_{(0,T)\times\Omega} |\partial_t D^\varepsilon|$. For the estimate of the last integral we use the embedding for a space of dimension $n = 3$, i.e., $L^\infty(0,T;H^1(\Omega^\varepsilon)) \subset L^4((0,T)\times\Gamma^\varepsilon)$,

$$\begin{aligned}
\varepsilon \int_0^\tau \int_{\Gamma^\varepsilon} b^\varepsilon |\partial_t r_f^\varepsilon| |l^\varepsilon|^2 \, d\gamma \, dt &\leq \frac{b_1^2 \varepsilon}{2\delta}\int_0^\tau \int_{\Gamma^\varepsilon} |\partial_t r_f^\varepsilon|^2 \, d\gamma \, dt + \frac{\delta\varepsilon}{2}\int_0^\tau \int_{\Gamma^\varepsilon} |l^\varepsilon|^4 \, d\gamma \, dt \\
&\leq \frac{b_1^2 \varepsilon}{2\delta}\int_0^\tau \int_{\Gamma^\varepsilon} |\partial_t r_f^\varepsilon|^2 \, d\gamma \, dt + \frac{\delta}{2}\sup_{[0,T]}\int_{\Omega^\varepsilon} |l^\varepsilon|^2 \, dx + \frac{\delta\varepsilon^2}{2}\sup_{[0,T]}\int_{\Omega^\varepsilon} |\nabla l^\varepsilon|^2 \, dx.
\end{aligned}$$

Using estimate (12) and the positivity of b^ε and r_f^ε we obtain

$$\int_0^T \int_{\Omega^\varepsilon} |\partial_t l^\varepsilon|^2 \, dx \, dt + \sup_{[0,T]}\int_{\Omega^\varepsilon} |\nabla l^\varepsilon|^2 \, dx \ \leq C. \qquad \square$$

To obtain a priori estimates for functions defined in the domain independent of ε, we extend functions l^ε defined on Ω^ε to functions $\bar{l}^\varepsilon$ defined on the whole Ω.

3.4. Extension of l^ε. Since l^ε is defined only on Ω^ε, we extend it onto Ω; see [8] or [19] for the proof.

LEMMA 3.5. 1. *For $l \in H^1(Y)$ there exists an extension $\tilde{l}$ to Z, such that*

$$\|\tilde{l}\|_{L^2(Z)} \leq c\|l\|_{L^2(Y)} \quad \text{and} \quad \|\nabla\tilde{l}\|_{L^2(Z)} \leq c\|\nabla l\|_{L^2(Y)}.$$

2. *For $l^\varepsilon \in H^1(\Omega^\varepsilon)$ there exists an extension $\tilde{l}^\varepsilon$ to Ω, such that*

$$\|\tilde{l}^\varepsilon\|_{H^1(\Omega)} \leq c\|l^\varepsilon\|_{H^1(\Omega^\varepsilon)}.$$

Remark 3.1. For $l^\varepsilon \in L^2(0,T;H^1(\Omega^\varepsilon))$ we define $\bar{l}^\varepsilon(\cdot,t) := \tilde{l}^\varepsilon(\cdot,t)$ for a.a. t. Since the extension operator is linear, then $\bar{l}^\varepsilon \in L^2(0,T;H^1(\Omega))$.

We identify l^ε with the extension $\bar{l}^\varepsilon$. For the extended functions, we obtain a priori estimate of the supremum norm of l^ε.

LEMMA 3.6. *For any solution of problem* (1)–(6), *the following estimate holds:*

$$||l^\varepsilon||_{L^\infty((0,T)\times\Omega)} \leq C, \tag{13}$$

where C is a constant independent on ε.

Estimate (13) follows from the nonnegativity of l^ε, r_f^ε, r_b^ε, the boundedness of r_b^ε and l_0, and the estimate in Lemma 3.5; see Theorem 6.40 in [26] (for the sketch of proof see Appendix 6.1).

4. Convergence of solutions of microscopic problem.

4.1. Convergence of l^ε, r_f^ε, and r_b^ε. To show the convergence results we apply the method of two-scale convergence, introduced in [2] and [36], and extended further in [3, 37]. The definition and theorems concerning the two-scale convergence, used in this section are outlined in Appendix 6.2.

To show the compactness of l^ε we use the following Hilbert space.

DEFINITION 4.1 (see [47]). *Let $W^{\beta,2}(\Omega)$ with $\beta \in \mathbb{R}$, $\beta > 0$ be a Hilbert space defined as the completion of $C^\infty(\Omega)$ with respect to the norm*

$$\|u\|_{W^{\beta,2}(\Omega)} = \|u\|_{W^{k,2}(\Omega)} + \Big\{\int_\Omega\int_\Omega \frac{|u(x)-u(y)|^2}{|x-y|^{n+2(\beta-k)}}dxdy\Big\}^{\frac{1}{2}},$$

where $k = [\beta]$.

LEMMA 4.2. 1. *For a function $v^\varepsilon \in H^1(\Omega^\varepsilon)$ the following estimate holds:*

$$\varepsilon\int_{\Gamma^\varepsilon} |v^\varepsilon|^2\, d\gamma_x \leq C\int_{\Omega^\varepsilon}|v^\varepsilon|^2 dx + C\varepsilon^2\int_{\Omega^\varepsilon}|\nabla v^\varepsilon|^2 dx,$$

where C is a constant independent on ε.

2. *For a function $v^\varepsilon \in W^{\beta,2}(\Omega^\varepsilon)$, where $\frac{1}{2} < \beta < 1$, the following estimate holds:*

$$\varepsilon\int_{\Gamma^\varepsilon} |v^\varepsilon|^2\, d\gamma_x \leq C\int_{\Omega^\varepsilon}|v^\varepsilon|^2 dx + C\varepsilon^{2\beta}\int_{\Omega^\varepsilon}\int_{\Omega^\varepsilon}\frac{|v^\varepsilon(x_1)-v^\varepsilon(x_2)|^2}{|x_1-x_2|^{n+2\beta}}dx_1dx_2,$$

where C is a constant independent on ε.

Proof. 1. For the proof see [19, Lemma 3].

2. For a function $v \in W^{\beta,2}(Y)$ the trace theorem implies

$$\int_\Gamma |v|^2\, d\gamma_y \leq C\int_Y |v|^2 dy + C\int_Y\int_Y \frac{|v(y_1)-v(y_2)|^2}{|y_1-y_2|^{n+2\beta}}dy_1dy_2.$$

Changing variables, $y = x/\varepsilon$, we obtain

$$\int_{\varepsilon\Gamma_i} |v^\varepsilon|^2 \frac{d\gamma_x}{\varepsilon^{n-1}} \le C \int_{\varepsilon Y_i} |v^\varepsilon|^2 \frac{dx}{\varepsilon^n} + C \int_{\varepsilon Y_i} \int_{\varepsilon Y_i} \frac{|v^\varepsilon(x_1) - v^\varepsilon(x_2)|^2}{|x_1 - x_2|^{n+2\beta}} \varepsilon^{n+2\beta} \frac{dx_1}{\varepsilon^n} \frac{dx_2}{\varepsilon^n}.$$

Multiplying the inequality side by side with ε^{-n} and summing up over i from 1 to N implies the estimate of the lemma. ∎

Using a priori estimates derived in section 3.3 and the concept of the two-scale convergence, we obtain the following compactness result.

LEMMA 4.3. *There exist functions l, r_f, and r_b such that*

1. $l^\varepsilon \rightharpoonup l$ *in* $L^2(0,T;H^1(\Omega))$, $\partial_t l^\varepsilon \rightharpoonup \partial_t l$ *in* $L^2((0,T)\times\Omega)$, $l^\varepsilon \overset{*}{\rightharpoonup} l$ *in* $L^\infty((0,T)\times\Omega)$,
2. $l^\varepsilon \to l$ *in* $L^2(0,T;W^{\beta,2}(\Omega))$ *for* $\frac{1}{2} < \beta < 1$ *and* $\lim_{\varepsilon\to 0} ||l^\varepsilon - l||_{L^2((0,T)\times\Gamma^\varepsilon)} = 0$,
3. $l^\varepsilon \to l$ *two-scale,* $\nabla l^\varepsilon \to \nabla_x l + \nabla_y l_1$ *two-scale,* $l_1 \in L^2((0,T)\times\Omega; H^1_{per}(Z)/\mathbb{R})$,
4. $r_f^\varepsilon \to r_f$, $r_b^\varepsilon \to r_b$ *two-scale and* $r_f, r_b \in L^\infty((0,T)\times\Omega\times\Gamma)$,
5. $\partial_t r_f^\varepsilon \to \partial_t r_f$, $\partial_t r_b^\varepsilon \to \partial_t r_b$ *two-scale, and* $\partial_t r_f, \partial_t r_b \in L^2((0,T)\times\Omega\times\Gamma)$.

Proof. From the a priori estimates in Lemma 3.4, we obtain weak convergence $l^\varepsilon \rightharpoonup l$ in $L^2(0,T;H^1(\Omega))$, $\partial_t l^\varepsilon \rightharpoonup \partial_t l$ in $L^2((0,T)\times\Omega)$, and $l^\varepsilon \overset{*}{\rightharpoonup} l$ in $L^\infty((0,T)\times\Omega)$.

To obtain strong convergence of l^ε in $L^2((0,T), W^{\beta,2}(\Omega))$, $\frac{1}{2} < \beta < 1$, we use the compact embedding of $W^{\beta,2}(\Omega)$ in $H^1(\Omega)$ and apply the Lions–Aubin lemma [27] with $B = W^{\beta,2}(\Omega)$. Applying Lemma 4.2 we obtain the inequality

$$\|l^\varepsilon\|^2_{\Gamma^\varepsilon} \le c\|l^\varepsilon\|^2_{W^{\beta,2}(\Omega^\varepsilon)}.$$

It follows that

$$\|l^\varepsilon - l\|_{L^2((0,T)\times\Gamma^\varepsilon)} \le c\|l^\varepsilon - l\|^2_{L^2(0,T;W^{\beta,2}(\Omega^\varepsilon))} \le c\|l^\varepsilon - l\|^2_{L^2(0,T;W^{\beta,2}(\Omega))} \to 0 \text{ for } \varepsilon \to 0.$$

Since l^ε is bounded in $L^2(0,T;H^1(\Omega))$, the compactness theorem (see Theorem 6.3 in Appendix 6.2) implies the two-scale convergence of l^ε to the same function l and the existence of a function $l_1 \in L^2((0,T)\times\Omega; H^1_{per}(Z)/\mathbb{R})$ such that, up to a subsequence, ∇l^ε two-scale converges to $\nabla_x l(x) + \nabla_y l_1(x,y)$.

Invoking Theorem 6.5 (see Appendix 6.2) we obtain the two-scale convergence of r_f^ε and r_b^ε to functions in $L^\infty((0,T)\times\Omega\times\Gamma)$. Due to $||\partial_t r_f^\varepsilon||_{L^2((0,T)\times\Gamma^\varepsilon)} \le C$ and [37, Theorem 2.2], we conclude that $\partial_t r_f^\varepsilon \to v$ two-scale and $v \in L^2((0,T)\times\Omega\times\Gamma)$. Then

$$\int_0^T \int_{\Gamma\times\Omega} v\,\phi\,dx\,d\gamma_y\,dt = \lim_{\varepsilon\to 0} \int_0^T \int_{\Gamma^\varepsilon} \partial_t r_f^\varepsilon\,\phi\,d\gamma_x\,dt$$

$$= -\lim_{\varepsilon\to 0} \int_0^T \int_{\Gamma^\varepsilon} r_f^\varepsilon\,\partial_t\phi\,d\gamma_x\,dt = -\int_0^T \int_{\Gamma\times\Omega} r_f\,\partial_t\phi\,dx\,d\gamma_y\,dt.$$

Consequently, we conclude that $v = \partial_t r_f$. Analogously we obtain the two-scale convergence of $\partial_t r_b^\varepsilon$ to $\partial_t r_b$. ∎

4.2. Macroscopic equations.

THEOREM 4.4. *As $\varepsilon \to 0$, the sequence of solutions of the microscopic problem* (1)–(6) *converges to the weak solution* (l, r_f, r_b), $l \in H^1(0,T;L^2(\Omega))$, $l \in L^2(0,T; H^1(\Omega))$, $l \in L^\infty((0,T)\times\Omega)$, r_f, $r_b \in H^1(0,T;L^2(\Omega\times\Gamma))$, r_f, $r_b \in L^\infty((0,T)\times\Omega\times\Gamma)$, *of the following macroscopic problem*:

(14)
$$\begin{cases} \partial_t l(t,x) = -\frac{1}{|Y|}\int_\Gamma (b(t,y)r_f(t,x,y)l(t,x) - d(t,y)r_b(t,x,y))d\gamma_y \\ \qquad + (\nabla(S(t)\nabla l(t,x))) + \tilde{p}_l(t,l(t,x)) - \tilde{\mu}_l(t)l(t,x), \quad t>0, x\in\Omega, \\ \nabla l(t,x)\cdot\nu = 0, \quad t>0, x\in\Gamma^N, \\ l(t,x) = l_0(x), \quad t=0, x\in\Omega, \end{cases}$$

(15)
$$\begin{cases} \partial_t r_f(t,x,y) = p_r(t,y,r_b(t,x,y)) - b(t,y)r_f(t,x,y)l(t,x) \\ \qquad + d(t,y)r_b(t,x,y) - \mu_f(t,y)r_f(t,x,y), \quad y\in\Gamma, x\in\Omega, \\ \partial_t r_b(t,x,y) = b(t,y)r_f(t,x,y)l(t,x) - d(t,y)r_b(t,x,y) \\ \qquad - \mu_b(t,y)r_b(t,x,y), \quad y\in\Gamma, x\in\Omega, \\ r_f(t,x,y) = r_{f0}(x,y), \quad t=0, y\in\Gamma, x\in\Omega, \\ r_b(t,x,y) = r_{b0}(x,y), \quad t=0, y\in\Gamma, x\in\Omega, \end{cases}$$

where $\tilde{\mu}_l(t) = \frac{1}{|Y|}\int_Y \mu_l(t,y)\,dy$, $\tilde{p}(t,l) = \frac{1}{|Y|}\int_Y p(t,y,l)\,dy$, *and the matrix* S *is defined as* $s_{ij} = \frac{1}{|Y|}\sum_{k=1}^3 \int_Y (D_{ij}(t,y) + D_{ik}(t,y)\partial_{y_k} w_j)\,dy$ *with* w_i *being the solutions of the cell problem*

$$-\nabla_y(D(t,y)\nabla_y w_i) = \sum_{k=1}^3 \partial_{y_k} D_{ki}(t,y) \quad in\ Y, \quad -D(t,y)\frac{\partial w_i}{\partial \nu} = \sum_{k=1}^3 D_{ki}(t,y)\nu_k \quad on\ \Gamma.$$

Proof. To derive a limit equation for l^ε we apply a standard two-scale convergence method and strong convergence of l^ε. Using in (7) a test function of the form $\phi(t,x) = \psi_0(t,x)+\varepsilon\psi_1(t,x,\frac{x}{\varepsilon})$, $\psi_0 \in C^\infty((0,T)\times\Omega)$, $\psi_1 \in C^\infty((0,T)\times\Omega; C^\infty_{per}(Z))$ and passing to the two-scale limit applying Lemma 4.3 yields

$$\begin{aligned} &|Y|\int_0^T\int_\Omega \partial_t l\psi_0(t,x)\,dx\,dt + |Y|\int_0^T\int_\Omega \tilde{\mu}_l(t)\,l(t,x)\,\psi_0(t,x)\,dx\,dt \\ &+ \int_0^T\int_\Omega\int_Y D(t,y)(\nabla_x l(t,x) + \nabla_y l_1(t,x,y))(\nabla_x\psi_0 + \nabla_y\psi_1)\,dy\,dx\,dt \\ &= -\int_0^T\int_\Omega\int_\Gamma [b(t,y)r_f(t,x,y)l(t,x) - d(t,y)r_b(t,x,y)]\psi_0(t,x)\,d\gamma_y\,dx\,dt \\ &+ |Y|\int_0^T\int_\Omega \tilde{p}_l(t,l)\,\psi_0\,dx\,dt. \end{aligned}$$

To show the convergence of the nonlinear term $b^\varepsilon r_f^\varepsilon l^\varepsilon$ of the boundary integral, we rewrite this integral as a sum of two integrals,

$$\begin{aligned} &\varepsilon\int_0^T\int_{\Gamma^\varepsilon} b^\varepsilon r_f^\varepsilon l^\varepsilon \left(\psi_0(t,x) + \varepsilon\psi_1\left(t,x,\frac{x}{\varepsilon}\right)\right) d\gamma_x\,dt \\ &\quad = \varepsilon\int_0^T\int_{\Gamma^\varepsilon} b^\varepsilon r_f^\varepsilon l \left(\psi_0(t,x) + \varepsilon\psi_1\left(t,x,\frac{x}{\varepsilon}\right)\right) d\gamma_x\,dt \\ &\qquad + \varepsilon\int_0^T\int_{\Gamma^\varepsilon} b^\varepsilon r_f^\varepsilon (l^\varepsilon - l) \left(\psi_0(t,x) + \varepsilon\psi_1\left(t,x,\frac{x}{\varepsilon}\right)\right) d\gamma_x\,dt. \end{aligned}$$

The first integral converges to $\int_0^T \int_\Omega \int_\Gamma b(t,y) r_f(t,x,y) l(t,x) \psi_0(t,x)\, d\gamma_y\, dx\, dt$ due to the two-scale convergence of r_f^ε. Since $||l^\varepsilon - l||_{L^2((0,T)\times\Gamma^\varepsilon)} \to 0$ as $\varepsilon \to 0$, we obtain for the second integral

$$\varepsilon \int_0^T \int_{\Gamma^\varepsilon} b^\varepsilon r_f^\varepsilon (l^\varepsilon - l) \left(\psi_0(t,x) + \varepsilon \psi_1\left(t, x, \frac{x}{\varepsilon}\right)\right) d\gamma_x\, dt$$

$$\leq \varepsilon \left(\int_0^T \int_{\Gamma^\varepsilon} |b^\varepsilon r_f^\varepsilon \psi_0|^2 d\gamma_x\, dt\right)^{1/2} \left(\int_0^T \int_{\Gamma^\varepsilon} |l^\varepsilon - l|^2 d\gamma_x\, dt\right)^{1/2}$$

$$+ \varepsilon^2 \left(\int_0^T \int_{\Gamma^\varepsilon} |b^\varepsilon r_f^\varepsilon \psi_1|^2 d\gamma_x\, dt\right)^{1/2} \left(\int_0^T \int_{\Gamma^\varepsilon} |l^\varepsilon - l|^2 d\gamma_x\, dt\right)^{1/2} \to 0 \quad \text{as} \quad \varepsilon \to 0.$$

To determine the unknown function $l_1 \in L^2((0,T)\times\Omega; H^1_{\text{per}}(Y)/\mathbb{R})$, we set $\psi_0 = 0$ and obtain the equation

$$\int_0^T \int_{\Omega\times Y} D(t,y)(\nabla_x l(t,x) + \nabla_y l_1(t,x,y)) \nabla_y \psi_1(t,x,y)\, dt\, dx\, dy = 0$$

for all ψ_1. From this it follows that l_1 depends linearly on $\nabla_x l$, and it can be written in the form

$$l_1 = \sum_{i=1}^n \frac{\partial l}{\partial x_i} \cdot w_i,$$

where the functions w_i are defined as solutions of the cell problem

$$-\nabla(D(t,y)\nabla w_i) = \sum_{k=1}^3 \partial_{y_k} D_{ki}(t,y) \text{ in } Y, \quad -D(t,y)\frac{\partial w_i}{\partial \nu} = \sum_{k=1}^3 D_{ki}(t,y)\, \nu_k \text{ on } \Gamma.$$

Next, setting $\psi_1 = 0$, we obtain

$$\int_0^T \int_\Omega \int_Y \sum_{i,j=1}^n D_{ij}(t,y)(\partial_{x_i} l(t,x) + \sum_{k=1}^n \partial_{y_i} w_k \partial_{x_k} l(t,x)) \partial_{x_j} \psi_0(t,x)\, dy\, dx\, dt$$

$$= |Y| \int_0^T \int_\Omega \sum_{i,j=1}^n s_{ij} \partial_{x_i} \psi_0(t,x) \partial_{x_j} l(t,x)\, dy\, dx\, dt$$

with $s_{ij} = \frac{1}{|Y|} \sum_{k=1}^3 \int_Y (D_{ij}(t,y) + D_{ik}(t,y) \partial_{y_k} w_j)\, dy$.

The difficulty arises in passing to the limit in nonlinear terms in the ordinary differential equations on the surface of microstructures. We have to show that p_r^ε $(t, x, r_b^\varepsilon(t,x)) \to p_r(t, y, r_b(t,x,y))$ in the two-scale sense. To cope with this difficulty we apply the unfolding method (periodic modulation), developed in [7, 5, 6]. Following [5] and [6], we define a dilation operator.

Definition 4.5. *For a given $\varepsilon > 0$, we define a dilation operator D^ε mapping measurable functions on $(0,T)\times\Gamma^\varepsilon$ to measurable functions on $(0,T)\times\Omega\times\Gamma$ by*

$$D^\varepsilon u(t,x,y) = u(t, c^\varepsilon(x) + \varepsilon y), \quad y \in \Gamma, \ \ (t,x) \in (0,T)\times\Omega,$$

where $c^\varepsilon(x)$ denotes the lattice translation point of the ε-cell domain containing x, $c^\varepsilon(x) = \varepsilon[\frac{x}{\varepsilon}]$. We extend $D^\varepsilon u$ from Γ to $\bigcup_k(\Gamma + k)$ periodically.

Remark 4.1. The dilation operator D^ε is well defined for all $(t, x, y) \in (0, T) \times \Omega \times \Gamma$ under the assumption on the geometry of domain Ω^ε (cf. Remark 2.1).

To proceed, we have to establish the link between the two-scale convergence and the weak convergence of the dilated sequences. Following [6], we formulate the lemma on the convergence of $D^\varepsilon u^\varepsilon : (0, T) \times \Omega \times \Gamma \to \mathbb{R}$. We define $L^2_{\text{per}}(\Gamma)$ as the space of functions $f \in L^2(\Gamma)$ defined on Γ and periodically extended to $\Gamma^* = \bigcup_k(\Gamma + k)$.

LEMMA 4.6. *If $D^\varepsilon u^\varepsilon \rightharpoonup u^*$ weakly in $L^2((0, T) \times \Omega; L^2_{per}(\Gamma))$ and $u^\varepsilon \to u$ two-scale, then $u^* = u$ a.e. in $(0, T) \times \Omega \times \Gamma$.*

Proof. Let u^* be a weak limit of $D^\varepsilon u^\varepsilon$. Then, for a test function $\psi(t, x)h(y)$, where $\psi \in C_0^\infty((0, T) \times \Omega)$ and $h \in C^\infty_{\text{per}}(\Gamma)$, we obtain

$$\int_0^T \int_{\Omega\times\Gamma} D^\varepsilon u^\varepsilon(t, x, y)\psi(t, x)h(y)d\gamma_y dxdt$$
$$\to \int_0^T \int_{\Omega\times\Gamma} u^*(t, x, y)\psi(t, x)h(y)d\gamma_y dxdt \quad \text{as } \varepsilon \to 0.$$

On the other hand, we have

$$\begin{aligned}
&\int_0^T \int_{\Omega\times\Gamma} D^\varepsilon u^\varepsilon(t, x, y)\psi(t, x)h(y)d\gamma_y dxdt \\
&\quad = \int_0^T \int_{\Omega\times\Gamma} u^\varepsilon(t, \varepsilon y + c^\varepsilon(x))\psi(t, x)h(y)d\gamma_y dxdt \\
&\quad = \sum_{k=1}^N \int_0^T \int_{\varepsilon(Z+k)} \int_\Gamma u^\varepsilon(t, \varepsilon y + c^\varepsilon(x))\psi(t, x)h(y)d\gamma_y dxdt.
\end{aligned}$$

Changing variables $z = \varepsilon(y + k)$, where $c^\varepsilon(x) = \varepsilon[\frac{x}{\varepsilon}] = \varepsilon k$, and using the periodicity of h, we obtain

$$\begin{aligned}
&\int_0^T \sum_{k=1}^N \varepsilon^{-2} \int_{\varepsilon(\Gamma+k)} u^\varepsilon(t, z)h\left(\frac{z}{\varepsilon}\right) \int_{\varepsilon(Z+k)} \psi(t, x)\, dx\, d\gamma_z\, dt \\
&\quad = \varepsilon \int_0^T \sum_{k=1}^N \int_{\varepsilon(\Gamma+k)} u^\varepsilon(t, z)h\left(\frac{z}{\varepsilon}\right)\psi(t, z)d\gamma_z dt + c\varepsilon^2 \\
&\quad \to \int_0^T \int_\Omega \int_\Gamma u(t, x, y)h(y)\psi(t, x)d\gamma_y dxdt,
\end{aligned}$$

since from the continuity of ψ we have the estimate

$$|\varepsilon^{-3} \int_{\varepsilon(Z+k)} \big(\psi(t, x) - \psi(t, z)\big)\, dx| \le c\varepsilon \ \text{ for } \ z \in \varepsilon(\Gamma + k).$$

Therefore, we conclude that $u^* = u$ a.e. in $(0, T) \times \Omega \times \Gamma$. ∎

In analogy to the above lemma and Lemma 2 in [5], we can prove the following properties of the dilation operator for oscillating surfaces.

LEMMA 4.7. *For $u \in L^2((0,T)\times\Gamma^\varepsilon)$*

$$||D^\varepsilon u||_{L^2(\Omega\times\Gamma)} = ||u||_{L^2(\Gamma^\varepsilon)}.$$

If $u \in L^2(\Omega\times\Gamma)$ is constant in y, then $D^\varepsilon u \to u$ as $\varepsilon \to 0$ strongly in $L^2(\Omega\times\Gamma)$.

Changing variables, $\Gamma^\varepsilon \ni x \to \varepsilon y + c^\varepsilon(x)$, $c^\varepsilon(x) = \varepsilon k$ for $x \in \Gamma^\varepsilon$, we obtain equations on the fixed domain $(0,T)\times\Omega\times\Gamma$,

$$\frac{\partial}{\partial t} D^\varepsilon {r_f}^\varepsilon(t,x,y) = -\mu_f(t,y) D^\varepsilon {r_f}^\varepsilon(t,x,y) + p_r(t,y,D^\varepsilon r_b^\varepsilon(t,x,y))$$

$$- b(t,y) D^\varepsilon {r_f}^\varepsilon(t,x,y) D^\varepsilon l^\varepsilon(t,x,y) + d(t,y) D^\varepsilon {r_b}^\varepsilon(t,x,y),$$

$$\frac{\partial}{\partial t} D^\varepsilon {r_b}^\varepsilon(t,x,y) = -\mu_b(t,y) D^\varepsilon {r_b}^\varepsilon(t,x,y)$$

$$+ b(t,y) D^\varepsilon {r_f}^\varepsilon(t,x,y) D^\varepsilon l^\varepsilon(t,x,y) - d(t,y) D^\varepsilon {r_b}^\varepsilon(t,x,y).$$

Applying the estimates for r_f^ε and r_b^ε, we obtain the estimates for $D^\varepsilon {r_f}^\varepsilon$ and $D^\varepsilon {r_b}^\varepsilon$ and the weak convergence of $D^\varepsilon {r_f}^\varepsilon$ to r_f and $D^\varepsilon {r_b}^\varepsilon$ to r_b in $L^2((0,T)\times\Omega; L^2_{\text{per}}(\Gamma))$ (see Lemma 4.6). Since $\sup_{[0,T]\times\overline{\Omega}} |l^\varepsilon| \le C$, we conclude that $\sup_{[0,T]\times\Omega\times\Gamma} |D^\varepsilon l^\varepsilon| \le C$.

Now we prove the strong convergence of $D^\varepsilon {r_f}^\varepsilon$ and $D^\varepsilon {r_b}^\varepsilon$ in $L^2((0,T)\times\Omega; L^2_{\text{per}}(\Gamma))$. For this we show that $D^\varepsilon {r_f}^\varepsilon$ and $D^\varepsilon {r_b}^\varepsilon$ are Cauchy sequences. We consider the equations for $D^{\varepsilon_n} {r_f}^{\varepsilon_n} - D^{\varepsilon_m} {r_f}^{\varepsilon_m}$ and $D^{\varepsilon_n} {r_b}^{\varepsilon_n} - D^{\varepsilon_m} {r_b}^{\varepsilon_m}$, with $n > m$, multiply them side by side with $D^{\varepsilon_n} {r_f}^{\varepsilon_n} - D^{\varepsilon_m} {r_f}^{\varepsilon_m}$ and $D^{\varepsilon_n} {r_b}^{\varepsilon_n} - D^{\varepsilon_m} {r_b}^{\varepsilon_m}$, respectively, and integrate over $\Omega\times\Gamma$.

$$\frac{\partial}{\partial t}\int_{\Omega\times\Gamma} |D^{\varepsilon_n} {r_f}^{\varepsilon_n} - D^{\varepsilon_m} {r_f}^{\varepsilon_m}|^2 dx d\gamma = -\int_{\Omega\times\Gamma} \mu_f(t,y) |D^{\varepsilon_n} {r_f}^{\varepsilon_n} - D^{\varepsilon_m} {r_f}^{\varepsilon_m}|^2 dx d\gamma$$

$$+ \int_{\Omega\times\Gamma} (p_r(t,y,D^{\varepsilon_n} {r_b}^{\varepsilon_n}) - p_r(t,y,D^{\varepsilon_m} r_b^{\varepsilon_m}))(D^{\varepsilon_n} {r_f}^{\varepsilon_n} - D^{\varepsilon_m} {r_f}^{\varepsilon_m}) dx d\gamma$$

$$- \int_{\Omega\times\Gamma} b(t,y)(D^{\varepsilon_n} {r_f}^{\varepsilon_n} D^{\varepsilon_n} l^{\varepsilon_n} - D^{\varepsilon_m} {r_f}^{\varepsilon_m} D^{\varepsilon_m} l^{\varepsilon_m})(D^{\varepsilon_n} {r_f}^{\varepsilon_n} - D^{\varepsilon_m} {r_f}^{\varepsilon_m}) dx d\gamma$$

$$- \int_{\Omega\times\Gamma} d(t,y)(D^{\varepsilon_n} {r_b}^{\varepsilon_n} - D^{\varepsilon_m} {r_b}^{\varepsilon_m})(D^{\varepsilon_n} {r_f}^{\varepsilon_n} - D^{\varepsilon_m} {r_f}^{\varepsilon_m}) dx d\gamma,$$

$$\frac{\partial}{\partial t}\int_{\Omega\times\Gamma} |D^{\varepsilon_n} {r_b}^{\varepsilon_n} - D^{\varepsilon_m} {r_b}^{\varepsilon_m}|^2 dx d\gamma = -\int_{\Omega\times\Gamma} \mu_b(t,y) |D^{\varepsilon_n} {r_b}^{\varepsilon_n} - D^{\varepsilon_m} {r_b}^{\varepsilon_m}|^2 dx d\gamma$$

$$+ \int_{\Omega\times\Gamma} b(t,y)(D^{\varepsilon_n} {r_f}^{\varepsilon_n} D^{\varepsilon_n} l^{\varepsilon_n} - D^{\varepsilon_m} {r_f}^{\varepsilon_m} D^{\varepsilon_m} l^{\varepsilon_m})(D^{\varepsilon_n} {r_b}^{\varepsilon_n} - D^{\varepsilon_m} {r_b}^{\varepsilon_m}) dx d\gamma$$

$$- \int_{\Omega\times\Gamma} d(t,y) |D^{\varepsilon_n} {r_b}^{\varepsilon_n} - D^{\varepsilon_m} {r_b}^{\varepsilon_m}|^2 \, dx d\gamma.$$

Using the Young inequality, we obtain

$$
\begin{aligned}
(16)\qquad \frac{\partial}{\partial t}\int_{\Omega\times\Gamma} &|D^{\varepsilon_n}{r_f}^{\varepsilon_n}-D^{\varepsilon_m}{r_f}^{\varepsilon_m}|^2 dxd\gamma \\
&\le C_1\int_{\Omega\times\Gamma}|D^{\varepsilon_n}{r_f}^{\varepsilon_n}-D^{\varepsilon_m}{r_f}^{\varepsilon_m}|^2 dxd\gamma \\
&\quad + C_2\int_{\Omega\times\Gamma}|D^{\varepsilon_n}{r_b}^{\varepsilon_n}-D^{\varepsilon_m}{r_b}^{\varepsilon_m}|^2 dxd\gamma \\
&\quad + b_1\sup_{(0,T)\times\Omega\times\Gamma}|D^{\varepsilon_n}l^{\varepsilon_n}|\int_{\Omega\times\Gamma}|D^{\varepsilon_n}{r_f}^{\varepsilon_n}-D^{\varepsilon_m}{r_f}^{\varepsilon_m}|^2 dxd\gamma \\
&\quad + C_3\int_{\Omega\times\Gamma}|D^{\varepsilon_n}l^{\varepsilon_n}-D^{\varepsilon_m}l^{\varepsilon_m}|^2 dxd\gamma,
\end{aligned}
$$

$$
\begin{aligned}
(17)\qquad \frac{\partial}{\partial t}\int_{\Omega\times\Gamma} &|D^{\varepsilon_n}{r_b}^{\varepsilon_n}-D^{\varepsilon_m}{r_b}^{\varepsilon_m}|^2 dxd\gamma \\
&\le C_4\int_{\Omega\times\Gamma}|D^{\varepsilon_n}{r_b}^{\varepsilon_n}-D^{\varepsilon_m}{r_b}^{\varepsilon_m}|^2 dxd\gamma \\
&\quad + b_1\sup_{(0,T)\times\Omega\times\Gamma}|D^{\varepsilon_n}l^{\varepsilon_n}|\int_{\Omega\times\Gamma}|D^{\varepsilon_n}{r_f}^{\varepsilon_n}-D^{\varepsilon_m}{r_f}^{\varepsilon_m}|^2 dxd\gamma \\
&\quad + C_5\int_{\Omega\times\Gamma}|D^{\varepsilon_n}l^{\varepsilon_n}-D^{\varepsilon_m}l^{\varepsilon_m}|^2 dxd\gamma.
\end{aligned}
$$

Due to Lemma 4.7 and strong convergence of l^ε on Γ^ε, we obtain

$$
\int_0^T\int_{\Omega\times\Gamma}|D^\varepsilon l^\varepsilon - D^\varepsilon l|^2 d\gamma dxdt = \varepsilon\int_0^T\int_{\Gamma^\varepsilon}|l^\varepsilon - l|^2 d\gamma_x dt \le C\varepsilon.
$$

Therefore, since $D^{\varepsilon_n} l \to l$ strongly in $L^2((0,T)\times\Omega\times\Gamma)$ (see Lemma 4.7),

$$
\begin{aligned}
\int_0^T\int_{\Omega\times\Gamma} &|D^{\varepsilon_n}l^{\varepsilon_n}-D^{\varepsilon_m}l^{\varepsilon_m}|^2 d\gamma dxdt \\
&\le \int_0^T\int_{\Omega\times\Gamma}\Big(|D^{\varepsilon_n}l^{\varepsilon_n}-D^{\varepsilon_n}l|^2+|D^{\varepsilon_n}l-l|^2\Big)d\gamma dxdt \\
&\quad + \int_0^T\int_{\Omega\times\Gamma}\Big(|D^{\varepsilon_m}l-l|^2+|D^{\varepsilon_m}l^{\varepsilon_m}-D^{\varepsilon_m}l|^2\Big)d\gamma dxdt \\
&\le \varepsilon_n\int_0^T\int_{\Gamma^{\varepsilon_n}}|l^{\varepsilon_n}-l|^2 d\gamma_x dt \\
&\quad \varepsilon_m\int_0^T\int_{\Gamma^{\varepsilon_m}}|l^{\varepsilon_m}-l|^2 d\gamma_x dt + \int_0^T\int_{\Omega\times\Gamma}\Big(|D^{\varepsilon_n}l-l|^2+|D^{\varepsilon_m}l-l|^2\Big)d\gamma dxdt \\
&\le C(\varepsilon_n+\varepsilon_m).
\end{aligned}
$$

We add (16) and (17) side by side and integrate with respect to time. Using additionally the boundedness of $D^\varepsilon l^\varepsilon$ on $(0,T)\times\Omega\times\Gamma$, we obtain

$$||D^{\varepsilon_n}{r_f}^{\varepsilon_n} - D^{\varepsilon_m}{r_f}^{\varepsilon_m}||^2 + ||D^{\varepsilon_n}{r_b}^{\varepsilon_n} - D^{\varepsilon_m}{r_b}^{\varepsilon_m}||^2$$

$$\leq C_1 \int_0^\tau \big(||D^{\varepsilon_n}{r_f}^{\varepsilon_n} - D^{\varepsilon_m}{r_f}^{\varepsilon_m}||^2 + ||D^{\varepsilon_n}{r_b}^{\varepsilon_n} - D^{\varepsilon_m}{r_b}^{\varepsilon_m}||^2\big)dt + C_2\frac{1}{n},$$

where $C_1 = C_1(\sup_{(0,T)\times\Omega}|l^\varepsilon|, \sup_{(0,T)\times\Gamma}|\mu_f|, \sup_{(0,T)\times\Gamma}|\mu_b|, \sup_{(0,T)\times\Gamma}|b|, \sup_{(0,T)\times\Gamma}|d|, \sup_{(0,T)\times\Gamma^\varepsilon}|r_f^\varepsilon|)$. Then the Gronwall lemma yields

$$||D^{\varepsilon_n}{r_f}^{\varepsilon_n} - D^{\varepsilon_m}{r_f}^{\varepsilon_m}||_{L^2(\Omega\times\Gamma)} \leq C\frac{1}{n},$$

$$||D^{\varepsilon_n}{r_b}^{\varepsilon_n} - D^{\varepsilon_m}{r_b}^{\varepsilon_m}||_{L^2(\Omega\times\Gamma)} \leq C\frac{1}{n}.$$

Using strong convergence of $D^\varepsilon {r_b}^\varepsilon$, continuity of p_r, and weak convergence of $p_r(t,y, D^\varepsilon r_b^\varepsilon)$, which results from the boundedness of p_r, we obtain that $p_r(t,y,D^\varepsilon r_b^\varepsilon)$ weakly converges to $p_r(t,y,r_b(t,x,y))$ in $L^2((0,T)\times\Omega; L^2_{\mathrm{per}}(\Gamma))$.

Now we can take the two-scale limit in the equations on the boundary,

$$\varepsilon\int_0^T\int_{\Gamma^\varepsilon} \partial_t r_f^\varepsilon \psi_1\left(t,x,\frac{x}{\varepsilon}\right)d\gamma_x\,dt = \varepsilon\int_0^T\int_{\Gamma^\varepsilon} p_r^\varepsilon(t,x,r_b^\varepsilon(t,x))\psi_1\left(t,x,\frac{x}{\varepsilon}\right)d\gamma_x\,dt$$

$$+\,\varepsilon\int_0^T\int_{\Gamma^\varepsilon}\Big(-b^\varepsilon r_f^\varepsilon(t,x)l^\varepsilon(t,x) + d^\varepsilon(t,x)r_b^\varepsilon(t,x) - \mu_f^\varepsilon r_f^\varepsilon(t,x)\Big)\psi_1\left(t,x,\frac{x}{\varepsilon}\right)\,d\gamma_x\,dt,$$

$$\varepsilon\int_0^T\int_{\Gamma^\varepsilon} \partial_t r_b^\varepsilon(t,x)\psi_1\left(t,x,\frac{x}{\varepsilon}\right)\,d\gamma_x\,dt = \varepsilon\int_0^T\int_{\Gamma^\varepsilon} b^\varepsilon r_f^\varepsilon(t,x)l^\varepsilon(t,x)\psi_1\,d\gamma_x\,dt$$

$$+\,\varepsilon\int_0^T\int_{\Gamma^\varepsilon}\Big(-d^\varepsilon r_b^\varepsilon(t,x) - \mu_b^\varepsilon r_b^\varepsilon(t,x)\Big)\psi_1\left(t,x,\frac{x}{\varepsilon}\right)\,d\gamma_x\,dt.$$

The linear terms converge two-scale to their limit functions. The proof of convergence for the nonlinear term $b^\varepsilon r_f^\varepsilon(t,x)l^\varepsilon(t,x)$ is the same as in the equation for l^ε. Due to boundedness of p_r^ε and Lemma 4.6, $p_r^\varepsilon(t,x,r_b^\varepsilon)$ converges two-scale to $p_r(t,y,r_b(t,x,y))$. Therefore, we obtain the macroscopic equations for r_f and r_b. ☐

The uniqueness of the solution of the macroscopic problem can be proved in the same way as for the microscopic problem.

Remark 4.2. Properties of the macroscopic model: Using the framework of bounded invariant rectangles (see [44]) we can show that solutions of system (14)–(15) remain positive for positive initial conditions and that they are also uniformly bounded. This results from the assumption of the nonnegativity of the model parameters and their boundedness independent of time. Methods outlined in [44, Chapter 14] can be used without major modifications.

5. Discussion. In this work, using homogenization techniques, we studied the macroscopic limit of the microscopic model describing receptor-ligand dynamics on cell membranes and in the intercellular space. We tried to answer the question of how processes which take place in different "spaces," such as cells membranes, intercellular space, and also intracellular space, can be described by macroscopic models operating in homogenized space. On one hand, this work provides a justification of previously proposed models, and on the other hand it is a starting point for further models.

Comparison of the macroscopic model (14)–(15) to the previously considered receptor-based model of the form

$$\begin{aligned}
&\frac{\partial}{\partial t} r_f = -\mu_f r_f + p_r(r_b) - b r_f l + d r_b,\\
&\frac{\partial}{\partial t} r_b = -\mu_b r_b + b r_f l - d r_b, \qquad (18)\\
&\frac{\partial}{\partial t} l = \frac{1}{\gamma}\frac{\partial^2}{\partial x^2} l - \mu_l l - b r_f l + p_l(l) + d r_b,
\end{aligned}$$

defined on the macroscopic domain Ω, shows in which cases the “older” models can be derived from the microscopic description. Model (14)–(15) is equivalent to model (18) in the case when neither the model parameters nor the initial conditions for r_f and r_b depend on the surface variable y. It means that the processes described are homogeneous within each cell and that there is no heterogeneity in the dissociation or binding processes on the cell surfaces. For nonadherent cells one can consider receptor production, binding, dissociation, or decay to be uniformly distributed on the cell surface, which results in model coefficients being constant with respect to the surface variable y. Under such assumptions we obtain a macroscopic model, in which the integral in the equation for the ligands disappears and the only difference with respect to model (18) is that the kinetics are multiplied by a coefficient $\int_\Gamma d\gamma_y/|Y|$. However, there is now considerable evidence of the existence of lipid raft microdomains, called membrane rafts, which organize the membrane into specialized functional units [14, 15, 38, 39, 41]. Rafts were described mainly for T-cells and T-cell receptor [15, 39, 40], but now it is clear that they play an important role for many different receptor classes [13, 41]. There are observations that the structure of lipid rafts could control cellular processes such as signaling cascades [40, 43] and receptor synthesis and trafficking [21] as well as cell adhesion and migration [16]. Some membrane proteins are located preferentially on the raft domains, whereas others are excluded from them [14]. Such a situation corresponds to the nonhomogeneous initial distribution of receptors on the cell surface and also *de novo* production terms depending on the surface variable. Our studies show that in such a case the “older” type of receptor-based model is not relevant.

Another example of cells with nonhomogeneous membrane properties are adherent cells. In the case of adherent cells there are two types of polarity, top-bottom and front-back, and it is not easy for the ligand to get in contact with the bottom of the cell. One can imagine that receptors may be concentrated on the frontal end of the cell (this determines cell motility in the case of chemotaxis), and, therefore, all the receptor-ligand processes are nonhomogeneous within the membrane [22].

6. Appendix.

6.1. Supremum estimate for l^ε. We present here a sketch of the proof of Lemma 3.6 used in section 4.

LEMMA. *For any solution of problem* (1)–(6), *the following estimate holds:*

$$||l^\varepsilon||_{L^\infty((0,T)\times\Omega)} \le C + 2k,$$

where C is a constant independent on ε and $k = \max\{1, \sup_\Omega |l_0|\}$.

Proof. To show the boundedness of l^ε we use the Moser iteration technique, described in the proof of [26, Theorem 6.15]. We choose as a test function $v = \psi(l^\varepsilon)(l^\varepsilon - k)_+$, where $\psi \geq 0$ is a bounded $C^1(\mathbb{R})$ function and which satisfies for $s > k$

$$0 \leq \frac{\psi^{'}(s)(s-k)}{\psi(s)} \leq k_1.$$

Due to the fact that $l_0 \leq k$, we obtain

$$\begin{aligned}
(19) \qquad & \int_\Omega \int_0^{l^\varepsilon} \psi(s)(s-k)_+ \, ds \chi^\varepsilon \, dx + \int_0^\tau \int_\Omega (D^\varepsilon \nabla l^\varepsilon, \psi(l^\varepsilon) \nabla l^\varepsilon) \chi^\varepsilon \, dx dt \\
& + \int_0^\tau \int_\Omega (D^\varepsilon \nabla l^\varepsilon, \psi^{'}(l^\varepsilon)(l^\varepsilon - k)_+ \nabla l^\varepsilon) \chi^\varepsilon \, dx dt \\
& + \int_0^\tau \int_\Omega \mu_l^\varepsilon l^\varepsilon \psi(l^\varepsilon)(l^\varepsilon - k)_+ \chi^\varepsilon dx dt \\
&= \int_0^\tau \int_\Omega p_l^\varepsilon(l^\varepsilon) \psi(l^\varepsilon)(l^\varepsilon - k)_+ \chi^\varepsilon \, dx dt \\
& + \varepsilon \int_0^\tau \int_{\Gamma^\varepsilon} (d^\varepsilon r_b^\varepsilon - b^\varepsilon r_f^\varepsilon l^\varepsilon) \psi(l^\varepsilon)(l^\varepsilon - k)_+ d\gamma_x dt,
\end{aligned}$$

where χ is a characteristic function of Y periodically extended to Z^*, and $\chi^\varepsilon(x) = \chi(\frac{x}{\varepsilon})$. From the properties of ψ, we obtain

$$\int_k^s \psi(t)(t-k) dt \geq \frac{1}{2+k_1} \psi(s)(s-k) \quad \text{ for } \; s \geq k.$$

The third and fourth terms on the left-hand side of (19) are nonnegative; the third term on the right-hand side is nonpositive. Using $l^\varepsilon \geq k \geq 1$ and Lemma 4.2, we obtain the estimate

$$\begin{aligned}
& \varepsilon \int_0^\tau \int_{\Gamma^\varepsilon} \psi(l^\varepsilon)(l^\varepsilon - k)_+ d\gamma_x dt \\
& \quad \leq C \int_0^\tau \int_{\Omega^\varepsilon} \Big(\psi(l^\varepsilon)(l^\varepsilon - k)_+ + \varepsilon^2 \nabla (\psi(l^\varepsilon)(l^\varepsilon - k)_+) \Big) dx dt \\
& \quad \leq C(1 + \frac{1}{\delta})(1+k_1) \int_0^\tau \int_\Omega \psi(l^\varepsilon) |l^\varepsilon|^2 \chi^\varepsilon dx dt + C \varepsilon^2 \delta \int_0^\tau \int_\Omega \psi(l^\varepsilon) |\nabla l^\varepsilon|^2 \chi^\varepsilon dx dt.
\end{aligned}$$

Then boundedness of coefficients and sublinearity of p_l yields

$$\begin{aligned}
& \int_\Omega \psi(l^\varepsilon)(l^\varepsilon - k)^2 \chi^\varepsilon dx + d_0 \int_0^\tau \int_\Omega \psi(l^\varepsilon) |\nabla l^\varepsilon|^2 \chi^\varepsilon dx dt \\
& \qquad \leq C(1+k_1)^2 \int_0^\tau \int_\Omega \psi(l^\varepsilon) |l^\varepsilon|^2 \chi^\varepsilon dx dt.
\end{aligned}$$

Choosing $\psi(s) = (\min\{s, Z\}(1 - k/s)_+)^q$, where q, Z are positive constants, applying the Gronwall and Young inequalities, and taking $Z \to \infty$ leads to

$$\int_0^T \int_\Omega |l^\varepsilon|^{q+2} \chi^\varepsilon \, dx dt \leq C(q) |\Omega| T k^{q+2}$$

for any positive q. Thus, for a fixed $q>1$ we can choose $\psi(s)=s^{2q-2}(1-\frac{k}{s})_+^{(n+2)(q-1)}$ and conclude that

$$\int_\Omega (l^\varepsilon)^{2q}\left(1-\frac{k}{l^\varepsilon}\right)_+^{(n+2)q-n}\chi^\varepsilon dx + c(d_0)\int_0^\tau\int_\Omega (l^\varepsilon)^{2q-2}\left(1-\frac{k}{l^\varepsilon}\right)_+^{(n+2)(q-1)}|\nabla l^\varepsilon|^2\chi^\varepsilon dxdt$$

$$\le Cq^2\int_0^\tau\int_\Omega (l^\varepsilon)^{2q}\left(1-\frac{k}{l^\varepsilon}\right)_+^{(n+2)(q-1)}\chi^\varepsilon dxdt.$$

Setting $h=(l^\varepsilon)^q((1-\frac{k}{l^\varepsilon})_+^{(n+2)q-n})^{1/2}$ gives $|\nabla h|^2\le c(n)q^2(l^\varepsilon)^{2q-2}(1-\frac{k}{l^\varepsilon})_+^{(n+2)(q-1)}$ $|\nabla l^\varepsilon|^2$. Using the property of extended function of l^ε, i.e., $||l^\varepsilon||_{H^1(\Omega)}\le C||l^\varepsilon||_{H^1(\Omega^\varepsilon)}$, with a constant C independent of ε, yields

$$\sup_{(0,T)}\int_\Omega h^2dx+\int_0^T\int_\Omega|\nabla h|^2dxdt\le Cq^4\int_0^T\int_\Omega (l^\varepsilon)^{2q}\left(1-\frac{k}{l^\varepsilon}\right)^{(n+2)(q-1)}dxdt.$$

Invoking the Sobolev embedding theorem on $(0,T)\times\Omega$, we obtain

$$\left(\int_0^T\int_\Omega h^{2\kappa}dxdt\right)^{1/\kappa}\le Cq^4\int_0^T\int_\Omega (l^\varepsilon)^{2q}\left(1-\frac{k}{l^\varepsilon}\right)_+^{(n+2)q-n-2}dxdt,$$

where $\kappa=(n+2)/n$. Iterating the last inequality for $q=1,\kappa,\kappa^2,\dots$, as in [26], implies that

$$\sup_{(0,T)\times\Omega}|l^\varepsilon|^2\left(1-\frac{k}{l^\varepsilon}\right)_+^{n+2}\le C\int_0^T\int_\Omega|l^\varepsilon|^2dxdt.$$

Considering separately the cases $\sup_{(0,T)\times\Omega} l^\varepsilon\le 2k$ and $\sup_{(0,T)\times\Omega} l^\varepsilon\ge 2k$ results in the estimate of the lemma. ∎

6.2. Two-scale convergence with parameters. We recall here the definition of two-scale convergence for functions dependent on parameters and several important results concerning this notion presented in [37]. The proofs are straightforward modifications of the proofs for the standard two-scale convergence method presented in [2].

DEFINITION 6.1. *Let (u_ε) be a sequence in $L^2(\Lambda\times\Omega)$, where ε is a sequence of strictly positive numbers, which tends to zero. (u_ε) is said to two-scale converge to a (unique) limit $u_0\in L^2(\Lambda\times\Omega\times Z)$ iff for any $\phi\in\mathcal{D}(\Lambda\times\Omega, C^\infty_{per}(Z))$ we have*

$$\lim_{\varepsilon\to0}\int_\Lambda\int_\Omega u_\varepsilon(\lambda,x)\phi\left(\lambda,x,\frac{x}{\varepsilon}\right)dxd\lambda=\int_\Lambda\int_\Omega\int_Z u_0(\lambda,x,y)\phi(\lambda,x,y)dxdyd\lambda.$$

THEOREM 6.2. *From each bounded sequence (u_ε) in $L^2(\Lambda\times\Omega)$ we can extract a subsequence which two-scale converges to $u_0\in L^2(\Lambda\times\Omega\times Z)$.*

THEOREM 6.3. 1. *Let (u_ε) be a bounded sequence in $L^2(\Lambda, H^1(\Omega))$, which converges weakly to a limit function $u\in L^2(\Lambda,H^1(\Omega))$. Then there exists $u_1\in L^2(\Lambda\times\Omega, H^1_{per}(Z))$ such that, up to a subsequence, u_ε two-scale converges to u and ∇u_ε two-scale converges to $\nabla u(\lambda,x)+\nabla_y u_1(\lambda,x,y)$.*

2. *Let (u_ε) and $(\varepsilon\nabla u_\varepsilon)$ be bounded sequences in $L^2(\Lambda\times\Omega))$. Then there exists $u_0\in L^2(\Lambda\times\Omega,H^1_{per}(Z))$ such that, up to a subsequence, u_ε and $\varepsilon\nabla u_\varepsilon$ two-scale converge to $u_0(\lambda,x,y)$ and $\nabla_y u_0(\lambda,x,y)$, respectively.*

Now, we transfer the compactness results to the case of a sequence u_ε defined on an $(n-1)$-dimensional ε-periodic manifold $\Gamma^\varepsilon \in \Omega$. Let $\Gamma \in Z$ be a smooth $(n-1)$-dimensional manifold (in our application a sphere, $n=3$). Then Γ^ε is the union of all $\varepsilon\Gamma$. For each Γ^ε we consider the space $L^2(\Gamma^\varepsilon)$ equipped with the scalar product $(u,v)_{\Gamma^\varepsilon} := \varepsilon \int_{\Gamma^\varepsilon} u(x)v(x)dx$.

DEFINITION 6.4 (see [37]). *A sequence of functions $(w_\varepsilon) \in L^2(\Lambda \times \Gamma^\varepsilon)$ is said to two-scale converge to a limit $w \in L^2(\Lambda \times \Omega \times \Gamma)$ iff for any $\psi \in \mathcal{D}(\Lambda \times \Omega, C^\infty_{per}(\Gamma))$ we have*

$$\lim_{\varepsilon \to 0} \varepsilon \int_\Lambda \int_{\Gamma^\varepsilon} w^\varepsilon(\lambda,x)\psi\left(\lambda, x, \frac{x}{\varepsilon}\right) d\gamma_x d\lambda = \int_\Lambda \int_\Omega \int_\Gamma w(\lambda,x,y)\psi(\lambda,x,y) dx d\gamma_y d\lambda.$$

THEOREM 6.5. 1. *From each bounded sequence (w_ε) in $L^2(\Lambda \times \Gamma^\varepsilon)$ we can extract a subsequence which two-scale converges to $w \in L^2(\Lambda \times \Omega \times \Gamma)$.*

2. *If the sequence (w_ε) is bounded in $L^\infty(\Lambda \times \Gamma^\varepsilon)$, then the limit w belongs to $L^\infty(\Lambda \times \Omega \times \Gamma)$.*

Proof. For the proof of 1, see [37].

2. We know that if w^ε is bounded in $L^2((0,T) \times \Gamma^\varepsilon)$, then there exists $w \in L^2((0,T) \times \Omega \times \Gamma)$ such that $w^\varepsilon \to w$ two-scale [37]. Now we use the proof of that theorem and show that if w^ε is bounded in $L^\infty((0,T) \times \Gamma^\varepsilon)$, then $w^\varepsilon \to w$ two-scale and $w \in L^\infty((0,T) \times \Omega \times \Gamma)$. We define $\mu_\varepsilon(\phi) = \varepsilon \int_0^T \int_{\Gamma^\varepsilon} w^\varepsilon(t,x)\phi(t,x,\frac{x}{\varepsilon})\, d\gamma_x^\varepsilon\, dt$ and obtain

$$|\mu_\varepsilon(\phi)| \le ||w^\varepsilon||_{L^2((0,T)\times\Gamma^\varepsilon)} \Big(\int_0^T \int_{\Gamma^\varepsilon} \varepsilon \left|\phi\left(x, \frac{x}{\varepsilon}\right)\right|^2 d\gamma_x^\varepsilon\, dt\Big)^{\frac{1}{2}} \le c||\phi||^2_{C^0([0,T]\times\bar{\Omega}; C^0_{per}(\Gamma))}.$$

Therefore, $\{\mu_\varepsilon\}$ is a bounded sequence of functionals on $C^0([0,T] \times \bar{\Omega}; C^0_{per}(\Gamma))$. Since this space is a separable Banach space, there exists a subsequence of μ_ε that converges weakly* to μ. Using the boundedness of w^ε and a variant of the oscillation lemma [2], we obtain

$$|\mu(\phi)| = \lim_{\varepsilon\to 0} |\mu_\varepsilon(\phi)| \le C \lim_{\varepsilon \to 0}\Big(\int_0^T \int_{\Gamma^\varepsilon} \varepsilon \left|\phi\left(x, \frac{x}{\varepsilon}\right)\right|^2 d\gamma_x^\varepsilon\, dt\Big)^{\frac{1}{2}} = c||\phi||_{L^2((0,T)\times\Omega\times\Gamma)}.$$

Therefore, μ is a bounded functional on $L^2((0,T) \times \Omega \times \Gamma)$. The Riesz representation theorem implies the existence of a function $w \in L^2((0,T) \times \Omega \times \Gamma)$. Furthermore, $||w^\varepsilon||_{L^\infty((0,T)\times\Gamma^\varepsilon)} \le C$ yields

$$|\mu(\phi)| = \lim |\mu_\varepsilon(\phi)| \le C \lim_{\varepsilon\to 0} \int_0^T \int_{\Gamma^\varepsilon} \varepsilon \left|\phi\left(x, \frac{x}{\varepsilon}\right)\right| d\gamma_x^\varepsilon\, dt = c||\phi||_{L^1((0,T)\times\Omega\times\Gamma)}.$$

Finally, we conclude

$$\begin{aligned} ||w||_{L^\infty((0,T)\times\Omega\times\Gamma)} &= \frac{\langle w,\phi\rangle}{||\phi||_{L^1((0,T)\times\Omega\times\Gamma)}} \\ &= \frac{|\mu(\phi)|}{||\phi||_{L^1((0,T)\times\Omega\times\Gamma)}} \le \frac{C||\phi||_{L^1((0,T)\times\Omega\times\Gamma)}}{||\phi||_{L^1((0,T)\times\Omega\times\Gamma)}} = C. \qquad \square \end{aligned}$$

THEOREM 6.6 (see [37]). *Let (u_ε) and $(\varepsilon\nabla u_\varepsilon)$ be bounded sequences in $L^2(\Lambda \times \Gamma^\varepsilon))$. Then there exists $u_0 \in L^2(\Lambda \times \Omega, H^1_{per}(\Gamma))$ such that, up to a subsequence, u_ε and $\varepsilon\nabla u_\varepsilon$, two-scale converge to $u_0(\lambda,x,y)$ and $\nabla_y u_0(\lambda,x,y)$, respectively.*

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