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DIFFUSION ON SURFACES AND THE BOUNDARY PERIODIC UNFOLDING OPERATOR WITH AN APPLICATION TO CARCINOGENESIS IN HUMAN CELLS*

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Abstract. In the context of periodic homogenization based on the periodic unfolding method, we extend the existing convergence results for the boundary periodic unfolding operator to gradients defined on manifolds. These general results are then used to homogenize a system of five coupled reaction-diffusion equations, three of which are defined on a manifold. The system describes 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. The diffusion on the endoplasmic reticulum, modeled as a Riemannian manifold, is described by the Laplace–Beltrami operator. The binding process to the surface of the endoplasmic reticulum is modeled in a nonlinear way taking into account the number of free receptors.

Key words. periodic homogenization, periodic unfolding method, carcinogenesis, reaction-diffusion system, surface diffusion

AMS subject classifications. 35B27, 35K51, 35K58, 92C37

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1. Introduction.

Periodic homogenization is a method for upscaling rigorously mathematical models of multiscale processes. In many cases, the multiscale nature of the problem is due to a microstructure of the material under consideration. While it is infeasible to resolve the microstructure in detail in numerical simulations (and often unnecessary), upscaled models describing the processes on an observation scale much larger than the characteristic size of the microstructure are required. In periodic homogenization, such upscaled models are obtained by assuming the microstructure of the material to be periodic with respect to a reference cell and considering the limit as the periodicity length $\varepsilon > 0$ approaches zero. Monographs on the subject include [3, 28, 24, 21, 8, 22].

An elegant technique for performing periodic homogenization is the periodic unfolding method developed in [9, 7, 6, 11, 5]. In these articles, many assertions, which are useful for homogenizing partial differential equations, are proved, for instance, convergence results for the periodic unfolding operator involving gradients defined in the domain (summarized in Theorem 2.2) and basic properties of the boundary periodic unfolding operator (Lemma 2.4).

We extend the theory of the periodic unfolding operator acting on hypersurfaces to results for gradients of functions defined on a smooth periodic manifold. In Lemma 2.5, the weak convergence of a product of functions on a periodic manifold is stated. A connection between the gradient with respect to Γ_ε and with respect to Γ is deduced in Lemma 2.6. In Theorem 2.9 we give a convergence result for gradients defined on manifolds.

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In the second part of the paper, we apply the general results to homogenize a model for carcinogenesis of a human cell, where carcinogenic molecules invade a cell, undergo chemical reactions to more aggressive molecules and enter the nucleus to bind to the DNA. The transformations to the aggressive molecules happen at the surface of the endoplasmic reticulum. Binding to the surface of the endoplasmic reticulum works as connecting to receptors, which are part of the endoplasmic reticulum. Natural cleaning mechanisms render the carcinogenic molecules harmless. These cleaning enzymes mainly occur in the cytosol. We refer to [13, 27, 30, 25] for this information and further details on the subject.

This mechanism is modeled by a system of five coupled partial differential equations. We emphasize the binding process to the endoplasmic reticulum by including a function that describes the relative concentration of free receptors. To bind to the surface, molecules need to find a free receptor [14], which is modeled by the product of concentration of molecules and receptors based on the law of mass action. This product makes the binding term nonlinear. Other nonlinear terms are the cleaning of molecules in cytosol and the transformations of the molecules on the surface. Much simpler carcinogenesis models taking into account the main subprocesses are found in [4, 16].

The endoplasmic reticulum is a bilayered membrane, which pervades the whole cytoplasm of the cell; cf. [14]. 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 the periodic unfolding method, which requires the use of results of the first part of this article.

As the biochemical processes in the cell contributing to carcinogenesis take place on the microscopic scale, it is expected that multiscale models taking into account this microstructure, such as the one developed here, allow for a much better representation of the overall process than conventional (purely macroscopic) compartment models. In turn, this enables a better understanding of the process and, in particular, models and model assumptions can be tested in much more detail. Moreover, medical interventions often involve the microstructure, e.g., blocking of receptors, and it is thus expected that such multiscale models will be helpful in this direction as well.

This paper is organized as follows. In section 2, we recall the definitions and some results of the periodic unfolding method and prove the new statements required for the homogenization process, which follows. It is important to note that these results are general in the sense that they could be useful in the homogenization of related problems. In section 3, the system of reaction-diffusion equations is introduced and its relation to carcinogenesis in a human cell is discussed. Further, we show the a priori estimates and the existence of a solution for every $\varepsilon > 0$ in section 4, the technical details of which are relegated to the appendix. The limit for ε tending to zero is characterized in section 5, where the main result of convergence of solutions of the microscopic model to solutions of the homogenized system is found in Theorem 5.1. We show uniqueness of the limit model in section 6 and give some concluding remarks in section 7.

2. The periodic unfolding method.

Let $\Omega \subset \mathbf{R}^n$ be open and bounded and $Y = [0,1)^n$ be the unit cell. Further, let $\Omega_\varepsilon = \bigcup_{k \in \mathbf{Z}^n} \varepsilon(k+Y)$. We recall the definition of the periodic unfolding operator and a compactness result for H^1 from [9]. Here and in what follows we denote

$$L^2(\Omega) = \left\{ u : \Omega \to \mathbf{R} |\ u \text{ measurable and } \int_\Omega u^2 \,\mathrm{d}x < \infty \right\},$$
$$H^1(\Omega) = \left\{ u \in L^2(\Omega) |\ \int_\Omega |\nabla u|^2 \,\mathrm{d}x < \infty \right\},$$

where ∇u is the weak derivative; see [12] for this notation.

Let $\Xi_\varepsilon := \{\xi \in \mathbf{Z}^n |\ \varepsilon(\xi + Y) \subset \Omega\}$ and $\hat{\Omega}_\varepsilon := \text{interior}\{\bigcup_{\xi \in \Xi_\varepsilon} \varepsilon(\xi + \overline{Y})\}$. For every $z \in \mathbf{R}^n$, $[z]_Y$ is defined as the unique integer combination $\sum_{i=1}^n k_i e_i$ of the periods such that $\{z\}_Y = z - [z]_Y \in Y$. The periodic unfolding operator $\mathcal{T}_\varepsilon$ is then defined as follows; see [6].

Definition 2.1. *Let $\varepsilon > 0$, $\varphi \in L^p(\Omega_\varepsilon)$, and $p \in [1, \infty]$. Then, the periodic unfolding operator $\mathcal{T}_\varepsilon : L^p(\Omega_\varepsilon) \to L^p(\mathbf{R}^n \times Y)$ is defined as*

$$[\mathcal{T}_\varepsilon(\varphi)](x, y) = \varphi\left(\varepsilon \left[\frac{x}{\varepsilon}\right]_Y + \varepsilon y\right) \text{ a.e. for } (x, y) \in \hat{\Omega}_\varepsilon \times Y,$$
$$[\mathcal{T}_\varepsilon(\varphi)](x, y) = 0 \text{ a.e. for } (x, y) \in \Omega \backslash \hat{\Omega}_\varepsilon \times Y.$$

Theorem 2.2. *For every $\varepsilon > 0$, let φ_ε be in $H^1(\Omega_\varepsilon)$ with $\|\varphi_\varepsilon\|_{H^1(\Omega_\varepsilon)}$ bounded independently of ε. Then, there exists $\varphi \in H^1(\Omega)$ and $\hat{\varphi} \in L^2(\Omega, H^1_\#(Y))$ such that, up to a subsequence,*

$$\mathcal{T}_\varepsilon(\varphi_\varepsilon) \rightharpoonup \varphi \qquad \text{weakly in } L^2_{\text{loc}}(\Omega, H^1_\#(Y)),$$
$$\mathcal{T}_\varepsilon(\nabla_x \varphi_\varepsilon) \rightharpoonup \nabla_x \varphi + \nabla_y \hat{\varphi} \qquad \text{weakly in } L^2_{\text{loc}}(\Omega, L^2(Y)).$$

Functions $\varphi \in L^2(\Omega, H^1_\#(Y))$ are Y-periodic in their second argument.

Further, let $\Gamma \subset Y$ and $\Gamma_\varepsilon = \bigcup_{k \in \mathbf{Z}^n} \varepsilon(k + \Gamma)$ be smooth manifolds. The definition of the boundary periodic unfolding operator $\mathcal{T}^b_\varepsilon$ is given as follows; see [9].

Definition 2.3. *Let $\varphi \in L^p(\Gamma_\varepsilon)$, $p \in [1, \infty]$. Then, the boundary periodic unfolding operator $\mathcal{T}^b_\varepsilon : L^p(\Gamma_\varepsilon) \to L^p(\Omega \times \Gamma)$ is defined as*

$$\mathcal{T}^b_\varepsilon(\varphi)(x, y) = \varphi\left(\varepsilon \left[\frac{x}{\varepsilon}\right] + \varepsilon y\right) \text{ a.e. for } (x, y) \in \hat{\Omega}_\varepsilon \times \Gamma,$$
$$\mathcal{T}^b_\varepsilon(\varphi)(x, y) = 0 \text{ a.e. for } (x, y) \in \Omega \backslash \hat{\Omega}_\varepsilon \times \Gamma.$$

The boundary periodic unfolding operator has some important properties, summarized in the following lemma, the proofs of which can be found in [9].

Lemma 2.4. *For the periodic unfolding operator $\mathcal{T}^b_\varepsilon$ as defined in Definition 2.3, the following assumptions hold true:*

1. *$\mathcal{T}^b_\varepsilon$ is linear.*
2. *$\mathcal{T}^b_\varepsilon(\varphi\psi) = \mathcal{T}^b_\varepsilon(\varphi)\mathcal{T}^b_\varepsilon(\psi)$ for all $\varphi, \psi \in L^p(\Gamma_\varepsilon)$.*
3. *For every $\varphi \in L^1(\Gamma_\varepsilon)$, we have the integration formula*

$$\int_{\Gamma_\varepsilon} \varphi(x) \,\mathrm{d}\sigma_x = \frac{1}{\varepsilon|Y|} \int_{\Omega \times \Gamma} \mathcal{T}^b_\varepsilon(\varphi)(x, y) \,\mathrm{d}x \,\mathrm{d}\sigma_y.$$

The remaining five results of this section for the boundary periodic unfolding operator are new. The first one considers the limit of a product of functions using the periodic unfolding method.

Lemma 2.5. *Let u_ε, $v_\varepsilon \in L^2(\Gamma_\varepsilon)$. Let $\mathcal{T}^b_\varepsilon(u_\varepsilon)$ converge to u_0 weakly in $L^2(\Omega \times \Gamma)$ and let $\mathcal{T}^b_\varepsilon(v_\varepsilon)$ converge to v_0 strongly in $L^2(\Omega \times \Gamma)$. Then,*

$$\mathcal{T}^b_\varepsilon(u_\varepsilon)\mathcal{T}^b_\varepsilon(v_\varepsilon) \rightharpoonup u_0 v_0$$

weakly in $L^2(\Omega \times \Gamma)$.

Proof. We have for test functions $\varphi \in C^\infty(\Omega \times \Gamma)$ that

$$\begin{aligned}
&\lim_{\varepsilon\to 0}\int_{\Omega\times\Gamma}(\mathcal{T}_\varepsilon^b(u_\varepsilon)\mathcal{T}_\varepsilon^b(v_\varepsilon)-u_0v_0)\varphi\,\mathrm{d}\sigma_y\,\mathrm{d}x\\
&\quad=\lim_{\varepsilon\to 0}\int_{\Omega\times\Gamma}(\mathcal{T}_\varepsilon^b(u_\varepsilon)\mathcal{T}_\varepsilon^b(v_\varepsilon)-\mathcal{T}_\varepsilon^b(u_\varepsilon)v_0+\mathcal{T}_\varepsilon^b(u_\varepsilon)v_0-u_0v_0)\varphi\,\mathrm{d}\sigma_y\,\mathrm{d}x\\
&\quad=\lim_{\varepsilon\to 0}\int_{\Omega\times\Gamma}\mathcal{T}_\varepsilon^b(u_\varepsilon)(\mathcal{T}_\varepsilon^b(v_\varepsilon)-v_0)\varphi\,\mathrm{d}\sigma_y\,\mathrm{d}x+\lim_{\varepsilon\to 0}\int_{\Omega\times\Gamma}(\mathcal{T}_\varepsilon^b(u_\varepsilon)-u_0)\underbrace{v_0\varphi}_{\tilde\varphi}\,\mathrm{d}\sigma_y\,\mathrm{d}x\\
&\quad=\lim_{\varepsilon\to 0}\int_{\Omega\times\Gamma}\mathcal{T}_\varepsilon^b(u_\varepsilon)(\mathcal{T}_\varepsilon^b(v_\varepsilon)-v_0)\varphi\,\mathrm{d}\sigma_y\,\mathrm{d}x.
\end{aligned}$$

Here, we used that $\tilde\varphi := v_0\varphi \in L^2(\Omega\times\Gamma)$ can be used as test function as well. We continue with the absolute values of the limits:

$$\begin{aligned}
&\lim_{\varepsilon\to 0}\left|\int_{\Omega\times\Gamma}(\mathcal{T}_\varepsilon^b(u_\varepsilon)\mathcal{T}_\varepsilon^b(v_\varepsilon)-u_0v_0)\varphi\,\mathrm{d}\sigma_y\,\mathrm{d}x\right|\\
&\quad=\lim_{\varepsilon\to 0}\left|\int_{\Omega\times\Gamma}\mathcal{T}_\varepsilon^b(u_\varepsilon)(\mathcal{T}_\varepsilon^b(v_\varepsilon)-v_0)\varphi\,\mathrm{d}\sigma_y\,\mathrm{d}x\right|\\
&\quad\le\lim_{\varepsilon\to 0}\underbrace{\|\mathcal{T}_\varepsilon^b(u_\varepsilon)\varphi\|_{L^2(\Omega\times\Gamma)}}_{\text{bounded}}\underbrace{\|\mathcal{T}_\varepsilon^b(v_\varepsilon)-v_0\|_{L^2(\Omega\times\Gamma)}}_{\to 0}\\
&\quad=0
\end{aligned}$$

for every $\varphi \in C^\infty(\Omega\times\Gamma)$ and the assertion holds true. ∎

The most useful new result is Theorem 2.9. It allows us to apply the boundary periodic unfolding operator for diffusion equations defined on smooth manifolds. For linear reaction-diffusion equations defined on manifolds it is also possible to use two-scale convergence for the homogenization process; see [23, 2], and we also refer to [15] for results on fast diffusion on manifolds. But if there are nonlinear reaction terms in the equation, strong convergence of the functions typically is required. This is not straightforward on manifolds but an elegant way is by using the boundary periodic unfolding operator, as done in [11]. For nonlinear reaction-diffusion equations on smooth manifolds, Theorem 2.9 can be used, such as in Lemma 4.3 below.

Before we can formulate and prove Theorem 2.9, we first describe a suitable setting. Let $\Gamma \subset \mathbf{R}^n$ be a k-dimensional compact C^∞-Riemannian manifold with Riemannian metric g. This means we have an atlas $\{(U_\lambda, \alpha_\lambda) \mid \lambda \in \Lambda\}$ of charts on Γ such that $\Gamma = \bigcup_\lambda U_\lambda$ and

$$\alpha_\lambda : U_\lambda \to V_\lambda \subset \mathbf{R}^k, \qquad \lambda \in \Lambda.$$

Further, we require that $\Gamma_\varepsilon = \bigcup_{\xi\in\mathbf{Z}^n} \varepsilon(\Gamma+\xi)$ also is a Riemannian manifold with atlas $\{(U^\varepsilon_{\lambda,\xi}, \alpha^\varepsilon_{\lambda,\xi}) \mid \lambda \in \Lambda, \xi \in \mathbf{Z}^n\}$, where $U^\varepsilon_{\lambda,\xi} := \varepsilon(U_\lambda + \xi)$. This means $\Gamma_\varepsilon = \bigcup_{\lambda,\xi} U^\varepsilon_{\lambda,\xi}$ and

$$\begin{aligned}
\alpha^\varepsilon_{\lambda,\xi} &: U^\varepsilon_{\lambda,\xi} \to V_\lambda,\\
\alpha^\varepsilon_{\lambda,\xi}(p) &:= \alpha_\lambda\left(\frac{1}{\varepsilon}p - \xi\right), \qquad p \in U^\varepsilon_{\lambda,\xi}, \quad \forall\ \lambda \in \Lambda,\ \xi \in \mathbf{Z}^n,\ \varepsilon > 0.
\end{aligned}$$

Obviously we have

$$\alpha^{\varepsilon}_{\lambda,\xi}(p) = \alpha_\lambda\left(\left\{\frac{p}{\varepsilon}\right\}_Y\right) = \alpha_\lambda(y_p), \qquad p \in U^{\varepsilon}_{\lambda,\xi}, \quad \forall\, \lambda \in \Lambda,\ \xi \in \mathbf{Z}^n,$$

where $y_p := \left\{\frac{p}{\varepsilon}\right\}_Y$. For the inverse of α_λ we have $\alpha_\lambda^{-1} : V_\lambda \to U_\lambda$ and $\alpha^{-1,\varepsilon}_{\lambda,\xi} : V_\lambda \to U^{\varepsilon}_{\lambda,\xi}$ given by

$$\alpha^{-1,\varepsilon}_{\lambda,\xi}(z) = \varepsilon(\alpha_\lambda^{-1}(z) + \xi) = \pi^{\varepsilon}_{\xi}(\alpha_\lambda^{-1}(z))$$

with the function π_ξ defined as

$$\pi^{\varepsilon}_{\xi} : \Gamma \to \Gamma_\varepsilon, \qquad \pi^{\varepsilon}_{\xi}(y) := \varepsilon(y + \xi), \qquad \xi \in \mathbf{Z}^n.$$

For any function $\varphi \in L^p(\Gamma_\varepsilon)$ the relation between π_ξ and $\mathcal{T}^b_\varepsilon$ is given by

$$\varphi(\pi^{\varepsilon}_{\xi}(y)) = \mathcal{T}^b_\varepsilon(\varphi)(\xi, y).$$

Now, let us have a look at the tangential vectors $\frac{\mathrm{d}}{\mathrm{d}x^{i,\varepsilon}}$ on Γ_ε. Let e_i be the ith basis vector in $\mathbf{R}^k$, $z = \alpha^{\varepsilon}_{\lambda,\xi}(p) \in V_\lambda$ and $t \in [-\delta, \delta]$, $\delta > 0$ small. Then, $z = \alpha_\lambda(y_p)$ and

$$t \mapsto z + te_i$$

is a curve in V_λ. The relationship between tangential vectors on Γ_ε and on Γ in the point p is given by

$$\frac{\mathrm{d}}{\mathrm{d}x^{i,\varepsilon}}(p) := \frac{\mathrm{d}}{\mathrm{d}t}_{|t=0}\alpha^{-1,\varepsilon}_{\lambda,\xi}(z + te_i) = \frac{\mathrm{d}}{\mathrm{d}t}_{|t=0}\varepsilon\alpha_\lambda^{-1}(z + te_i) = \varepsilon\frac{\mathrm{d}}{\mathrm{d}x^i}(y_p).$$

Next, we have a look at the Riemannian metrics g_{ij} and g^{ε}_{ij}. We have

$$g^{\varepsilon}_{ij}(p) = \left\langle \frac{\mathrm{d}}{\mathrm{d}x^{i,\varepsilon}}(p), \frac{\mathrm{d}}{\mathrm{d}x^{j,\varepsilon}}(p) \right\rangle = \left\langle \varepsilon\frac{\mathrm{d}}{\mathrm{d}x^i}(y_p), \varepsilon\frac{\mathrm{d}}{\mathrm{d}x^j}(y_p) \right\rangle = \varepsilon^2 g_{ij}(y_p),$$

$$\text{which yields} \qquad g^{ij,\varepsilon}(p) = \frac{1}{\varepsilon^2}g^{ij}(y_p)$$

for $i, j = 1, \ldots, k$. Within this setting, we want to deduce some assertions. The first one is an extension of the fact that $\nabla_y\mathcal{T}_\varepsilon(\varphi_\varepsilon) = \varepsilon\mathcal{T}_\varepsilon(\nabla_x\varphi_\varepsilon)$ for functions $\varphi_\varepsilon \in H^1(\Omega_\varepsilon)$ (see [9]) to functions on $H^1(\Gamma_\varepsilon)$.

Lemma 2.6. *Let φ be in $H^1(\Gamma_\varepsilon)$. Then,*

$$\varepsilon\mathcal{T}^b_\varepsilon(\nabla_x\varphi) = \nabla_y\mathcal{T}^b_\varepsilon(\varphi).$$

Proof. In the proof we suppress the λ or ξ dependence of the charts α_λ and $\alpha^{\varepsilon}_{\lambda,\xi}$. We just take the appropriate chart for any subset $U_\lambda \subset \Gamma$ and $U^{\varepsilon}_{\lambda,\xi} \subset \Gamma_\varepsilon$, respectively. In the setting of Riemannian manifolds the gradient $\nabla_x\varphi$ is defined as

$$\nabla_x\varphi(p) = \sum_{ij} g^{ij\varepsilon}(p)\frac{\partial\varphi}{\partial x^{j,\varepsilon}}(p)\frac{\mathrm{d}}{\mathrm{d}x^{i,\varepsilon}}(p) \tag{2.1}$$

with

$$\frac{\partial \varphi}{\partial x^{i,\varepsilon}}(p) := \frac{\partial(\varphi \circ \alpha^{-1,\varepsilon})}{\partial x_i}(\alpha^{\varepsilon}(p)).$$

Here $x_i,\ i = 1, \ldots, k$, denote the components of $\mathbf{R}^k$. Applying $\mathcal{T}_\varepsilon^b$ to $\frac{\partial \varphi}{\partial x^{j,\varepsilon}}$ leads to

$$\begin{aligned}\mathcal{T}_\varepsilon^b\left(\frac{\partial \varphi}{\partial x^{j,\varepsilon}}\right)(p, y_p) &= \left(\frac{\partial(\varphi \circ \alpha^{-1,\varepsilon})}{\partial x_j} \circ \alpha^{\varepsilon}\right)([p]_Y + \varepsilon y_p) \\ &= \frac{\partial(\varphi \circ \pi \circ \alpha^{-1})}{\partial x_j}\alpha(y_p) = \frac{\partial_y(\mathcal{T}_\varepsilon^b(\varphi) \circ \alpha^{-1})}{\partial x_j}\alpha(y_p) \\ &= \frac{\partial_y \mathcal{T}_\varepsilon^b(\varphi)}{\partial x^j}(p, y_p).\end{aligned}$$

Putting the pieces together we get

$$\begin{aligned}\mathcal{T}_\varepsilon^b(\nabla_x \varphi)(p, y_p) &= \mathcal{T}_\varepsilon^b\left(\sum_{ij} g^{ij\varepsilon}\frac{\partial \varphi}{\partial x^{j,\varepsilon}}\frac{\mathrm{d}}{\mathrm{d}x^{i,\varepsilon}}\right)(p, y_p) \\ &= \sum_{ij}\frac{1}{\varepsilon^2}g^{ij}(y_p)\mathcal{T}_\varepsilon^b\left(\frac{\partial \varphi}{\partial x^{j,\varepsilon}}\right)(p, y_p)\varepsilon\frac{\mathrm{d}}{\mathrm{d}x^i}(y_p) = \frac{1}{\varepsilon}\nabla_y(\mathcal{T}_\varepsilon^b(\varphi))(p, y_p).\end{aligned}$$

Thus, $\nabla_y(\mathcal{T}_\varepsilon^b(\varphi)) = \varepsilon\mathcal{T}_\varepsilon^b(\nabla_x\varphi)$. ∎

Having established this result, the following two lemmas easily follow.

LEMMA 2.7. *Let φ be in $H^1(\Gamma_\varepsilon)$. Then,*

$$\|\nabla_y \mathcal{T}_\varepsilon^b(\varphi)\|^2_{L^2(\mathbf{R}^n \times \Gamma)} = |Y|\varepsilon^3\|\nabla_x\varphi\|^2_{L^2(\Gamma_\varepsilon)}.$$

Proof. With assertion 3 of Lemma 2.4 we have

$$\begin{aligned}\|\nabla_x\varphi\|^2_{L^2(\Gamma_\varepsilon)} &= \frac{1}{\varepsilon|Y|}\int_{\mathbf{R}^n\times\Gamma}\mathcal{T}_\varepsilon^b(\nabla_x\varphi)\mathcal{T}_\varepsilon^b(\nabla_x\varphi)\,\mathrm{d}x\,\mathrm{d}\sigma_y \\ &= \frac{1}{\varepsilon|Y|}\int_{\mathbf{R}^n\times\Gamma}\frac{1}{\varepsilon}\nabla_y\mathcal{T}_\varepsilon^b(\varphi)\frac{1}{\varepsilon}\nabla_y\mathcal{T}_\varepsilon^b(\varphi)\,\mathrm{d}x\,\mathrm{d}\sigma_y = \frac{1}{\varepsilon^3|Y|}\|\nabla_y\mathcal{T}_\varepsilon^b(\varphi)\|^2_{L^2(\mathbf{R}^n\times\Gamma)}\end{aligned}$$

and the claim follows. ∎

LEMMA 2.8. *If $\varphi_\varepsilon \in H^1(\Gamma_\varepsilon)$, then $\mathcal{T}_\varepsilon^b(\varphi_\varepsilon) \in L^2(\Omega, H^1(\Gamma))$.*

Proof. Since $\varphi_\varepsilon \in H^1(\Gamma_\varepsilon)$, it holds that

$$\varepsilon\|\varphi_\varepsilon\|^2_{L^2(\Gamma_\varepsilon)} + \varepsilon\|\nabla_x\varphi_\varepsilon\|^2_{L^2(\Gamma_\varepsilon)} \le C(\varepsilon)$$

for a $C(\varepsilon) > 0$. Because $\nabla_y\mathcal{T}_\varepsilon^b(\varphi_\varepsilon) = \varepsilon\mathcal{T}_\varepsilon^b(\nabla_x\varphi_\varepsilon)$ we have for small $\varepsilon < 1$

$$\begin{aligned}\|\mathcal{T}_\varepsilon^b(\varphi_\varepsilon)\|^2_{L^2(\Omega,H^1(\Gamma))} &= \int_{\Omega\times\Gamma}\mathcal{T}_\varepsilon^b(\varphi_\varepsilon)^2\,\mathrm{d}\sigma_y\,\mathrm{d}x + \int_{\Omega\times\Gamma}(\nabla_y\mathcal{T}_\varepsilon^b(\varphi_\varepsilon))^2\,\mathrm{d}\sigma_y\,\mathrm{d}x \\ &= |Y|\varepsilon\|\varphi_\varepsilon\|^2_{L^2(\Gamma_\varepsilon)} + |Y|\varepsilon^3\|\nabla_x\varphi_\varepsilon\|^2_{L^2(\Gamma_\varepsilon)} \le |Y|C(\varepsilon).\end{aligned}$$ ∎

The main Theorem 2.9 is a compactness result and deduces a limit function in $L^2(\Omega, H^1_\#(\Gamma))$ of a bounded sequence in $H^1(\Gamma_\varepsilon)$.

THEOREM 2.9. *Let $\varphi_\varepsilon \in H^1(\Gamma_\varepsilon)$ be bounded for every ε such that*

$$\varepsilon\|\varphi_\varepsilon\|^2_{L^2(\Gamma_\varepsilon)} \le C \quad \text{and} \quad \varepsilon^3\|\nabla_x\varphi_\varepsilon\|^2_{L^2(\Gamma_\varepsilon)} \le C$$

for $C > 0$ independent of ε. Then, there exists a $\hat{\varphi} \in L^2(\mathbf{R}^n, H^1_\#(\Gamma))$ such that, up to a subsequence,

$$\mathcal{T}^b_\varepsilon(\varphi_\varepsilon) \rightharpoonup \hat{\varphi} \quad \textit{weakly in } L^2(\mathbf{R}^n, H^1(\Gamma))$$

and

$$\varepsilon\mathcal{T}^b_\varepsilon(\nabla_x\varphi_\varepsilon) \rightharpoonup \nabla_y\hat{\varphi} \quad \textit{weakly in } L^2(\mathbf{R}^n \times \Gamma).$$

Proof. We use the statement that, in a reflexive Banach space, a bounded sequence contains a weakly converging subsequence. Hence, we need to show that $\mathcal{T}^b_\varepsilon(\varphi_\varepsilon)$ is bounded in $L^2(\mathbf{R}^n, H^1(\Gamma))$.

With assertion 3 of Lemma 2.4 we get

$$\frac{1}{|Y|}\|\mathcal{T}^b_\varepsilon(\varphi_\varepsilon)\|^2_{L^2(\mathbf{R}^n\times\Gamma)} = \varepsilon\|\varphi_\varepsilon\|^2_{L^2(\Gamma_\varepsilon)} \le C$$

and with Lemma 2.7

$$\frac{1}{|Y|}\|\nabla_y\mathcal{T}^b_\varepsilon(\varphi_\varepsilon)\|^2_{L^2(\mathbf{R}^n\times\Gamma)} = \varepsilon^3\|\nabla_x\varphi_\varepsilon\|^2_{L^2(\Gamma_\varepsilon)} \le C.$$

Hence, $\mathcal{T}^b_\varepsilon(\varphi_\varepsilon)$ is bounded in $L^2(\mathbf{R}^n \times \Gamma)$ and $\nabla_y\mathcal{T}^b_\varepsilon(\varphi)$ is bounded in $L^2(\mathbf{R}^n \times \Gamma)$. It follows that $\mathcal{T}^b_\varepsilon(\varphi_\varepsilon)$ is bounded in $L^2(\mathbf{R}^n, H^1(\Gamma))$ and there exists $\hat{\varphi} \in L^2(\mathbf{R}^n, H^1(\Gamma))$ such that

$$\mathcal{T}^b_\varepsilon(\varphi_\varepsilon) \rightharpoonup \hat{\varphi} \quad \text{weakly in } L^2(\mathbf{R}^n, H^1(\Gamma)).$$

With Lemma 2.6 we conclude

$$\varepsilon\mathcal{T}^b_\varepsilon(\nabla_x\varphi_\varepsilon) = \nabla_y\mathcal{T}^b_\varepsilon(\varphi_\varepsilon) \rightharpoonup \nabla_y\hat{\varphi} \quad \text{weakly in } L^2(\mathbf{R}^n \times \Gamma).$$

It is left to show that $\hat{\varphi}$ is Y-periodic. To this end, let $\psi \in C^\infty(\mathbf{R}^n \times \Gamma)$ be periodic in its second argument. Then, for $\xi \in \mathbf{Z}^n$

$$\begin{aligned}
&\int_{\mathbf{R}^n\times\Gamma}(\mathcal{T}^b_\varepsilon(\varphi_\varepsilon)(x, y+\xi) - \mathcal{T}^b_\varepsilon(\varphi_\varepsilon)(x,y))\psi(x,y)\,\mathrm{d}x\,\mathrm{d}\sigma_y \\
&\quad = \int_{\mathbf{R}^n\times\Gamma}\left(\varphi_\varepsilon\left(\varepsilon\left(\left[\frac{x}{\varepsilon}\right]_Y + \xi\right) + \varepsilon y\right) - \varphi_\varepsilon\left(\varepsilon\left[\frac{x}{\varepsilon}\right]_Y + \varepsilon y\right)\right)\psi(x,y)\,\mathrm{d}x\,\mathrm{d}\sigma_y \\
&\quad = \int_{\mathbf{R}^n\times\Gamma}\varphi_\varepsilon\left(\varepsilon\left[\frac{x}{\varepsilon}\right]_Y + \varepsilon y\right)(\psi(x-\varepsilon\xi, y) - \psi(x,y))\,\mathrm{d}x\,\mathrm{d}\sigma_y.
\end{aligned}$$

Since $\psi(x - \varepsilon\xi, y) \to \psi(x, y)$ for ε tending to zero, we finally conclude that

$$\int_{\mathbf{R}^n\times\Gamma}\mathcal{T}^b_\varepsilon(\varphi_\varepsilon)(x, y+\xi)\psi(x,y)\,\mathrm{d}x\,\mathrm{d}\sigma_y - \int_{\mathbf{R}^n\times\Gamma}\mathcal{T}^b_\varepsilon(\varphi_\varepsilon)(x,y)\psi(x,y)\,\mathrm{d}x\,\mathrm{d}\sigma_y \overset{\varepsilon\to 0}{\longrightarrow} 0. \qquad \square$$

3. Nonlinear carcinogenesis problem. With the tools introduced in the previous section, we are prepared to pass to the homogenization limit of a system of equations including diffusion on a biological membrane using the periodic unfolding method. One of the longest known and best understood causes of carcinogenesis is the molecule Benzo[a]pyrene (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 BP. Often chimney sweepers are affected because of the frequent exposure to coal (see [20, 14]).

The molecule itself is not dangerous. But chemical reactions in the human cell can transform it to the molecule Benzo[a]pyrene-7,8-diol-9,10-epoxide (DE), which can bind to and damage the human DNA (see [14]). The chemical reactions mostly take place on the surface of the endoplasmic reticulum.

In the cytosol of a human cell, there are molecules which can bind to BP or DE and render them harmless. Examples of such molecules are glutathione epoxide transferase or sulfo transferase (transferase is an enzyme); see [13]. They bind to potentially dangerous and alien molecules and render them water soluble.

Hence, 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 and can be removed by cleaning mechanisms of the cell. They can bind to the surface of the endoplasmic reticulum by connecting to receptors. There, a series of chemical reactions takes place summarized to just one metabolism from BP to DE. Newly created DE molecules unbind from the surface of the endoplasmic reticulum by uncoupling from the receptor and diffuse again in the cytosol of the cell, where they can be removed by cleaning mechanisms. There, they may enter the nucleus. For simplicity, we restrict BP not to pass the nuclear membrane, whereas DE cannot pass the plasma membrane, which describes a worst-case scenario.

3.1. Microscopic model. Let $\Omega \subset \mathbf{R}^n$ be a human cell with a Lipschitz boundary $\partial\Omega$ and which we assume to be representable by a finite union of axis-parallel cuboids with corner coordinates in $\mathbb{Q}^n$. Furthermore, let $Y = [0,1)^n$ be a unit cell with an open subset $Y_0 \subset Y$ with smooth boundary Γ, where Γ does not touch the boundary of Y. The sets $Y^* = Y \backslash \overline{Y_0}$ and Γ form characteristic parts of the cytosol and the surface of the endoplasmic reticulum, respectively. Let $\varepsilon > 0$; then $\Omega_\varepsilon := \bigcup_{k\in\mathbf{Z}^n} \varepsilon(k + Y^*) \cap \Omega$ is ε-periodic and $\Gamma_\varepsilon := \bigcup_{k\in\mathbf{Z}^n} \varepsilon(k + \Gamma) \cap \Omega$ a periodic and smooth surface. The process is considered in the time interval $[0,T]$ for fixed $0 < T < \infty$. Further, the concentration of BP molecules in cytosol is denoted by $u_\varepsilon : [0,T] \times \Omega_\varepsilon \to \mathbf{R}$ and the concentration of DE molecules in cytosol is $v_\varepsilon : [0,T] \times \Omega_\varepsilon \to \mathbf{R}$. The concentration of BP molecules bound to the surface of the endoplasmic reticulum is denoted by $s_\varepsilon : [0,T] \times \Gamma_\varepsilon \to \mathbf{R}$ and the concentration of DE molecules bound to the surface of the endoplasmic reticulum is denoted by $w_\varepsilon : [0,T] \times \Gamma_\varepsilon \to \mathbf{R}$. The relative concentration of free receptors on the surface of the endoplasmic reticulum is given by $R_\varepsilon : [0,T] \times \Gamma_\varepsilon \to [0,1]$. Molecules bind to a membrane by connecting to receptors, which are attached to the membrane. BP molecules in the cytosol (u_ε) can transform to BP molecules bound to the surface of the ER (s_ε) only when they find a free receptor (R_ε). The maximal relative amount of free receptors is denoted by $\overline{R} = 1$.

This consideration leads to the following microscopic model for carcinogenesis of a human cell in the context described above. BP molecules diffuse freely in the cytosol with diffusion coefficient $D_u > 0$ and the cleaning mechanism is taken care of by the function f,

$$\partial_t u_\varepsilon - D_u \Delta u_\varepsilon = -f(u_\varepsilon) \quad \text{in } \Omega_\varepsilon.$$

The enzymes necessary for cleaning are available only in limited quantities. If only a few BP molecules are present, we assume that the cleaning is almost linear. If there are many molecules the cleaning rate will reach a threshold. The following function is suitable to describe this behavior:

$$f: \mathbf{R} \to \mathbf{R}_0^+, \qquad f(x) = \begin{cases} \frac{x}{x+M} Ma & \text{for } x \geq 0, \\ 0 & \text{for } x < 0, \end{cases}$$

where $M, a > 0$. This function f is nonlinear, nonnegative, bounded, and Lipschitz-continuous. At the surface of the endoplasmic reticulum, BP molecules can bind to receptors. With the law of mass action, the binding is modeled by the product $k_u u_\varepsilon R_\varepsilon$, since one BP molecule and one receptor are needed, with constant rate $k_u > 0$. Bound BP molecules are denoted by s_ε and unbind with rate $l_s > 0$. This Robin-boundary term is multiplied by ε to compensate the growth of the surface by shrinking ε (see [23] for details),

$$-D_u \nabla u_\varepsilon \cdot n = \varepsilon(k_u R_\varepsilon u_\varepsilon - l_s s_\varepsilon) \quad \text{on } \Gamma_\varepsilon.$$

At the plasma membrane, u_ε satisfies a Dirichlet boundary condition and at the nuclear membrane a no-flux Neumann boundary condition,

$$\begin{aligned} u_\varepsilon &= u_{\text{Boundary}} && \text{on } \Gamma_{\text{C}}, \\ -D_u \nabla u_\varepsilon \cdot n &= 0 && \text{on } \Gamma_{\text{N}}. \end{aligned}$$

DE molecules have a similar behavior, diffuse freely in the cytosol with diffusion coefficient $D_v > 0$ and cleaning function g, which has the same form as f but with different parameters. At the plasma membrane DE molecules satisfy a no-flux Neumann boundary condition and at the nuclear membrane a Dirichlet boundary condition,

$$\begin{aligned} \partial_t v_\varepsilon - D_v \Delta v_\varepsilon &= -g(v_\varepsilon) && \text{in } \Omega_\varepsilon, \\ -D_v \nabla v_\varepsilon \cdot n &= \varepsilon(k_v R_\varepsilon v_\varepsilon - l_w w_\varepsilon) && \text{on } \Gamma_\varepsilon, \\ -D_v \nabla v_\varepsilon \cdot n &= 0 && \text{on } \Gamma_{\text{C}}, \\ v_\varepsilon &= 0 && \text{on } \Gamma_{\text{N}}, \end{aligned}$$

with binding and unbinding rates k_v and l_w, respectively. Bound to the endoplasmic reticulum, the molecules diffuse on the surface modeled by the Laplace–Beltrami operator Δ_Γ. For the transformation from BP molecules to DE molecules bound to the surface of the endoplasmic reticulum, a function h of the same form as f or g is used, since the enzymes necessary for the transformation are available only in limited quantities,

$$\begin{aligned} \partial_t s_\varepsilon - \varepsilon^2 D_s \Delta_\Gamma s_\varepsilon &= -h(s_\varepsilon) + k_u R_\varepsilon u_\varepsilon - l_s s_\varepsilon && \text{on } \Gamma_\varepsilon, \\ \partial_t w_\varepsilon - \varepsilon^2 D_w \Delta_\Gamma w_\varepsilon &= h(s_\varepsilon) + k_v R_\varepsilon v_\varepsilon - l_w w_\varepsilon && \text{on } \Gamma_\varepsilon. \end{aligned}$$

If BP molecules u_ε or DE molecules v_ε bind to the surface of the endoplasmic reticulum with rate k_u or k_v, the number of free receptors R_ε decreases. If BP molecules s_ε or DE molecules w_ε leave the surface of the endoplasmic reticulum with rate l_s or l_w, then R_ε increases. Receptors do not move on the surface of the endoplasmic reticulum but are fixed. Hence the equation for R_ε is given by

$$\partial_t R_\varepsilon = -R_\varepsilon |k_u u_\varepsilon + k_v v_\varepsilon| + (\overline{R} - R_\varepsilon)|k_s s_\varepsilon + k_w w_\varepsilon| \quad \text{on } \Gamma_\varepsilon. \tag{3.1}$$

The factors $k_s > 0$ and $k_w > 0$ are multiples of l_s, l_w, respectively, and ensure that $k_s(\overline{R} - R_\varepsilon)$ and $k_w(\overline{R} - R_\varepsilon)$ are rates.

Here, we remark on a simplifying assumption of this formulation of the model. On the surface of the membrane, the molecules diffuse by moving from one free receptor to the next free one. This means that for parts of the membrane, which are crowded with molecules, diffusion of these molecules becomes more difficult because of the lack of free receptors. We neglect this aggregation effect in this model.

The initial values

$$(u_I, v_I, s_I, w_I, R_I) = (u_\varepsilon(0), v_\varepsilon(0), s_\varepsilon(0), w_\varepsilon(0), \overline{R}) \tag{3.2a}$$

are smooth, bounded, and nonnegative.

For the weak formulation, we take the function spaces

$$\begin{aligned}
\mathcal{V}_{\mathrm{N}}(\Omega_\varepsilon) &= \{u \in L^2([0,T], H^1(\Omega_\varepsilon))|\ u = 0 \text{ on } \Gamma_{\mathrm{N}},\ \partial_t u \in L^2([0,T], H^1(\Omega_\varepsilon)')\},\\
\mathcal{V}_{\mathrm{C}}(\Omega_\varepsilon) &= \{u \in L^2([0,T], H^1(\Omega_\varepsilon))|\ u = u_{\mathrm{Boundary}} \text{ on } \Gamma_{\mathrm{C}},\ \partial_t u \in L^2([0,T], H^1(\Omega_\varepsilon)')\},\\
\mathcal{V}(\Gamma_\varepsilon) &= \{u \in L^2([0,T], H^1(\Gamma_\varepsilon))|\ \partial_t u \in L^2([0,T], H^1(\Gamma_\varepsilon)')\},\\
\mathcal{V}_R(\Gamma_\varepsilon) &= \{u \in L^2([0,T], L^2(\Gamma_\varepsilon))|\ \partial_t u \in L^2([0,T], L^2(\Gamma_\varepsilon))\}
\end{aligned}$$

and we use the notation $(\varphi, \psi)_{\Omega_\varepsilon} = \int_{\Omega_\varepsilon} \varphi\psi \,\mathrm{d}x$, $(\varphi, \psi)_{\Omega_\varepsilon, t} = \int_0^t (\varphi(\tau), \psi(\tau))_{\Omega_\varepsilon} \,\mathrm{d}\tau$, and $\langle \varphi, \psi \rangle_{\Gamma_\varepsilon} = \int_{\Gamma_\varepsilon} g_\varepsilon \varphi\psi \,\mathrm{d}\sigma_x$ with Riemannian metric g_ε. For the test functions, we need the spaces

$$\begin{aligned}
V_{\mathrm{C}0}(\Omega_\varepsilon) &= \{u \in H^1(\Omega_\varepsilon)|\ u = 0 \text{ on } \Gamma_C\},\\
V_{\mathrm{N}}(\Omega_\varepsilon) &= \{u \in H^1(\Omega_\varepsilon)|\ u = 0 \text{ on } \Gamma_N\},\\
V(\Gamma_\varepsilon) &= H^1(\Gamma_\varepsilon).
\end{aligned}$$

Then, the weak formulation is as follows: Find $u_\varepsilon \in \mathcal{V}_{\mathrm{C}}(\Omega_\varepsilon)$, $v_\varepsilon \in \mathcal{V}_{\mathrm{N}}(\Omega_\varepsilon)$, $s_\varepsilon, w_\varepsilon \in \mathcal{V}(\Gamma_\varepsilon)$, and $R_\varepsilon \in \mathcal{V}_R(\Gamma_\varepsilon)$ satisfying the initial condition (3.2a) and

$$\begin{aligned}
&(\partial_t u_\varepsilon, \varphi_1)_{\Omega_\varepsilon} + D_u(\nabla u_\varepsilon, \nabla\varphi_1)_{\Omega_\varepsilon} + \varepsilon\langle k_u u_\varepsilon R_\varepsilon - l_s s_\varepsilon, \varphi_1\rangle_{\Gamma_\varepsilon} = -(f(u_\varepsilon), \varphi_1)_{\Omega_\varepsilon},\\
&(\partial_t v_\varepsilon, \varphi_2)_{\Omega_\varepsilon} + D_v(\nabla v_\varepsilon, \nabla\varphi_2)_{\Omega_\varepsilon} + \varepsilon\langle k_v v_\varepsilon R_\varepsilon - l_w w_\varepsilon, \varphi_2\rangle_{\Gamma_\varepsilon} = -(g(v_\varepsilon), \varphi_2)_{\Omega_\varepsilon},\\
&\langle \partial_t s_\varepsilon, \psi\rangle_{\Gamma_\varepsilon} + \varepsilon^2 D_s\langle \nabla_\Gamma s_\varepsilon, \nabla_\Gamma\psi\rangle_{\Gamma_\varepsilon} = \langle k_u u_\varepsilon R_\varepsilon - l_s s_\varepsilon, \psi\rangle_{\Gamma_\varepsilon} - \langle h(s_\varepsilon), \psi\rangle_{\Gamma_\varepsilon},\\
&\langle \partial_t w_\varepsilon, \psi\rangle_{\Gamma_\varepsilon} + \varepsilon^2 D_w\langle \nabla_\Gamma w_\varepsilon, \nabla_\Gamma\psi\rangle_{\Gamma_\varepsilon} = \langle k_v v_\varepsilon R_\varepsilon - l_w w_\varepsilon, \psi\rangle_{\Gamma_\varepsilon} + \langle h(s_\varepsilon), \psi\rangle_{\Gamma_\varepsilon},\\
&\langle \partial_t R_\varepsilon, \psi\rangle_{\Gamma_\varepsilon} + \langle R_\varepsilon|k_u u_\varepsilon + k_v v_\varepsilon|, \psi\rangle_{\Gamma_\varepsilon} = \langle(\overline{R} - R_\varepsilon)|k_s s_\varepsilon + k_w w_\varepsilon|, \psi\rangle_{\Gamma_\varepsilon}
\end{aligned} \tag{3.2b}$$

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

We show in what follows that the solution of (3.2) converges to the solution of the homogenized macroscopic system (5.5) in the limit as $\varepsilon \to 0$, cf. Theorem 5.1.

4. A priori estimates and existence of solutions of the microscopic problem. In this section, we show that the functions u_ε, v_ε, s_ε, w_ε, and R_ε are bounded independently of ε in $L^2([0,T], H^1(\Omega_\varepsilon))$ and $L^2([0,T], H^1(\Gamma_\varepsilon))$ and $L^2([0,T] \times \Gamma_\varepsilon)$, respectively. This is necessary to use the periodic unfolding operator for the convergence. Furthermore, we prove that u_ε and v_ε are elements of $L^\infty([0,T] \times \Omega_\varepsilon) \cap H^1([0,T], H_0^1(\Omega_\varepsilon)')$ bounded independently of ε and that $\mathcal{T}_\varepsilon^b(s_\varepsilon), \mathcal{T}_\varepsilon^b(w_\varepsilon)$ and $\mathcal{T}_\varepsilon^b(R_\varepsilon)$ are Cauchy-sequences in $L^2([0,T] \times \Omega \times \Gamma)$. This yields strong convergence of the function sequences. Finally, existence of solutions of the microscopic problem is established.

LEMMA 4.1. *A function R_ε, satisfying* (3.2)*, is nonnegative and bounded by $\overline{R} > 0$ almost everywhere in $x \in \Gamma_\varepsilon$ and $t \in [0,T]$.*

Proof. First the nonnegativity of R_ε is proved: The weak formulation of R_ε is tested with the function $R_{\varepsilon-} = -R_\varepsilon$ for $R_\varepsilon \leq 0$ and 0 otherwise, and it is found that

$$\langle \partial_t R_{\varepsilon-}, R_{\varepsilon-}\rangle_{\Gamma_\varepsilon} + \langle R_{\varepsilon-}|k_u u_\varepsilon + k_v v_\varepsilon|, R_{\varepsilon-}\rangle_{\Gamma_\varepsilon} + \langle(\overline{R} + R_{\varepsilon-})|k_s s_\varepsilon + k_w w_\varepsilon|, R_{\varepsilon-}\rangle_{\Gamma_\varepsilon} = 0.$$

Integration from 0 to t and observing $R_\varepsilon(0) \geq 0$ yields

$$\frac{1}{2}\|R_{\varepsilon-}\|^2_{\Gamma_\varepsilon} + \underbrace{\|R_{\varepsilon-}\sqrt{|k_u u_\varepsilon + k_v v_\varepsilon|}\|^2_{\Gamma_\varepsilon,t}}_{\geq 0} + \underbrace{\langle(\overline{R} + R_{\varepsilon-})|k_s s_\varepsilon + k_w w_\varepsilon|, R_{\varepsilon-}\rangle_{\Gamma_\varepsilon,t}}_{\geq 0} = 0.$$

We deduce $\|R_{\varepsilon-}\|^2_{\Gamma_\varepsilon} \leq 0$ for almost every $t \in [0,T]$. This implies $R_\varepsilon \geq 0$ for almost every $x \in \Gamma_\varepsilon$ and $t \in [0,T]$. To show boundedness of R_ε, we test the weak formulation with $(R_\varepsilon - \overline{R})_+ = R_\varepsilon - \overline{R}$ for $R_\varepsilon - \overline{R} \geq 0$ and 0 otherwise and obtain

$$\begin{aligned}\langle \partial_t R_\varepsilon, (R_\varepsilon - \overline{R})_+\rangle_{\Gamma_\varepsilon} &+ \underbrace{\langle R_\varepsilon|k_u u_\varepsilon + k_v v_\varepsilon|, (R_\varepsilon - \overline{R})_+\rangle_{\Gamma_\varepsilon}}_{\geq 0} \\ &- \langle(\overline{R} - R_\varepsilon)|k_s s_\varepsilon + k_w w_\varepsilon|, (R_\varepsilon - \overline{R})_+\rangle_{\Gamma_\varepsilon} = 0.\end{aligned}$$

Since $\partial_t \overline{R} = 0$, it yields

$$\langle \partial_t (R_\varepsilon - \overline{R})_+, (R_\varepsilon - \overline{R})_+\rangle_{\Gamma_\varepsilon} + \langle (R_\varepsilon - \overline{R})_+|k_s s_\varepsilon + k_w w_\varepsilon|, (R_\varepsilon - \overline{R})_+\rangle_{\Gamma_\varepsilon} \leq 0.$$

Integrating from 0 to t and using $R_I \leq \overline{R}$ leads to

$$\frac{1}{2}\|(R_\varepsilon - \overline{R})_+\|^2_{\Gamma_\varepsilon} + \|(R_\varepsilon - \overline{R})_+\sqrt{|k_s s_\varepsilon + k_w w_\varepsilon|}\|^2_{\Gamma_\varepsilon,t} \leq 0.$$

We conclude that $R_\varepsilon < \overline{R}$ for almost every $x \in \Gamma_\varepsilon$ and $t \in [0,T]$. ∎

The required a priori estimates for the other unknowns are proved in Appendix A.1. They are summarized in the following lemma.

LEMMA 4.2. *The following statements hold:*

1. *The functions u_ε, v_ε, s_ε, and w_ε are nonnegative for almost every $x \in \Omega_\varepsilon$, $x \in \Gamma_\varepsilon$, respectively, and $t \in [0,T]$.*
2. *There exists a constant $C > 0$, independent of ε, such that*

$$\begin{aligned}&\|u_\varepsilon\|^2_{\Omega_\varepsilon} + \|v_\varepsilon\|^2_{\Omega_\varepsilon} + \varepsilon\|s_\varepsilon\|^2_{\Gamma_\varepsilon} + \varepsilon\|w_\varepsilon\|^2_{\Gamma_\varepsilon} + \|\nabla u_\varepsilon\|^2_{\Omega_\varepsilon,t} + \|\nabla v_\varepsilon\|^2_{\Omega_\varepsilon,t} \\ &\quad + \varepsilon^3\|\nabla_\Gamma s_\varepsilon\|^2_{\Gamma_\varepsilon,t} + \varepsilon^3\|\nabla_\Gamma w_\varepsilon\|^2_{\Gamma_\varepsilon,t} + \varepsilon\|k_u u_\varepsilon R_\varepsilon - l_s s_\varepsilon\|^2_{\Gamma_\varepsilon,t} \\ &\quad + \varepsilon\|k_v v_\varepsilon R_\varepsilon - l_w w_\varepsilon\|^2_{\Gamma_\varepsilon,t} \leq C.\end{aligned}$$

3. *The functions u_ε, v_ε, s_ε, and w_ε are bounded independently of ε almost everywhere in $\Omega_\varepsilon \times [0,T]$ and $\Gamma_\varepsilon \times [0,T]$, respectively.*
4. *There exists a $C > 0$, independent of ε, such that*

$$\|\partial_t u_\varepsilon\|_{L^2([0,T],H^1_0(\Omega_\varepsilon)')} + \|\partial_t v_\varepsilon\|_{L^2([0,T],H^1_0(\Omega_\varepsilon)')} < C.$$

Now we know that $u_\varepsilon, v_\varepsilon \in L^2([0,T], H^1(\Omega_\varepsilon)) \cap H^1([0,T], H^1_0(\Omega_\varepsilon)') \cap L^\infty(\Omega_\varepsilon \times [0,T])$. Using the extension lemma from [18], we extend the functions u_ε and v_ε from Ω_ε to the whole domain Ω and know now that $u_\varepsilon, v_\varepsilon \in L^2([0,T], H^1(\Omega)) \cap H^1([0,T], H^1_0(\Omega)') \cap L^\infty(\Omega \times [0,T])$ with bounds independent of ε. Applying Lemma 5.6 from article [17] u_ε, v_ε converge strongly to limit functions u_0, v_0 in $L^2([0,T], L^2(\Omega))$, respectively.

We cannot prove strong convergence of the functions s_ε, w_ε, and R_ε using extensions to Ω, because they are defined on the ε-dependent manifold Γ_ε, which has a smaller dimension than Ω. Hence, we use the boundary unfolding operator $\mathcal{T}_\varepsilon^b$, because it is already defined on a fixed domain $\Omega \times \Gamma$ and show that $\mathcal{T}_\varepsilon^b(s_\varepsilon)$, $\mathcal{T}_\varepsilon^b(w_\varepsilon)$, and $\mathcal{T}_\varepsilon^b(R_\varepsilon)$ are Cauchy-sequences, the proof of which is found in Appendix A.2. This procedure is similar to that in [11], where a nonlinear ordinary differential equation defined on a surface was homogenized.

LEMMA 4.3 (s_ε, w_ε, R_ε are Cauchy-sequences). *For all $\delta > 0$ there exists $\tilde{\varepsilon} > 0$ such that for all $0 < \varepsilon_1, \varepsilon_2 < \tilde{\varepsilon}$ it holds that*

$$\|\mathcal{T}_{\varepsilon_1}^b(s_{\varepsilon_1}) - \mathcal{T}_{\varepsilon_2}^b(s_{\varepsilon_2})\|^2_{[0,T]\times\Omega\times\Gamma} + \|\mathcal{T}_{\varepsilon_1}^b(w_{\varepsilon_1}) - \mathcal{T}_{\varepsilon_2}^b(w_{\varepsilon_2})\|^2_{[0,T]\times\Omega\times\Gamma}$$
$$+ \|\mathcal{T}_{\varepsilon_1}^b(R_{\varepsilon_1}) - \mathcal{T}_{\varepsilon_2}^b(R_{\varepsilon_2})\|^2_{[0,T]\times\Omega\times\Gamma} < \delta.$$

This means that s_ε, w_ε, and R_ε are Cauchy-sequences in $L^2([0,T] \times \Omega \times \Gamma)$.

Now, we need to ensure that, for every $\varepsilon > 0$, there exists a solution of the system of equations (3.2). The following assertion is proved in Appendix B.

THEOREM 4.4 (existence of u_ε, v_ε, s_ε, w_ε, and R_ε). *For every small $\varepsilon > 0$ there exists at least one solution $(u_\varepsilon, v_\varepsilon, s_\varepsilon, w_\varepsilon, R_\varepsilon) \in \mathcal{V}_\mathrm{C} \times \mathcal{V}_\mathrm{N} \times \mathcal{V}(\Gamma_\varepsilon)^2 \times \mathcal{V}_R(\Gamma_\varepsilon)$ of the system* (3.2).

Having established these results, we use the results of section 2 to deduce convergence of the solutions of system (3.2) to some limit functions.

THEOREM 4.5. *There exist $u_0, v_0 \in L^2([0,T], H^1(\Omega))$, $u_1, v_1 \in L^2([0,T] \times \Omega, H^1_\#(Y^*))$, $s_0, w_0 \in L^2([0,T] \times \Omega, H^1_\#(\Gamma))$ and $R_0 \in L^2([0,T] \times \Omega, L^2_\#(\Gamma))$ such that the sequence of solutions $(u_\varepsilon, v_\varepsilon, s_\varepsilon, w_\varepsilon, R_\varepsilon)$ of* (3.2) *converges as $\varepsilon \to 0$, up to a subsequence, as follows:*

1. *$\mathcal{T}_\varepsilon(u_\varepsilon) \rightharpoonup u_0$ and $\mathcal{T}_\varepsilon(v_\varepsilon) \rightharpoonup v_0$ weakly in $L^2([0,T] \times \Omega, H^1(Y^*))$,*
2. *$\mathcal{T}_\varepsilon(\nabla_x u_\varepsilon) \rightharpoonup \nabla_x u_0 + \nabla_y u_1$ and $\mathcal{T}_\varepsilon(\nabla_x v_\varepsilon) \rightharpoonup \nabla_x v_0 + \nabla_y v_1$ weakly in $L^2([0,T] \times \Omega \times Y^*)$,*
3. *$\mathcal{T}_\varepsilon^b(s_\varepsilon) \rightharpoonup s_0$ and $\mathcal{T}_\varepsilon^b(w_\varepsilon) \rightharpoonup w_0$ weakly in $L^2([0,T] \times \Omega, H^1(\Gamma))$,*
4. *$\mathcal{T}_\varepsilon^b(R_\varepsilon) \rightharpoonup R_0$ weakly in $L^2([0,T] \times \Omega \times \Gamma)$,*
5. *$u_\varepsilon \to u_0$ and $v_\varepsilon \to v_0$ strongly in $L^2([0,T] \times \Omega)$,*
6. *$\mathcal{T}_\varepsilon^b(s_\varepsilon) \to s_0$, $\mathcal{T}_\varepsilon^b(w_\varepsilon) \to w_0$, and $\mathcal{T}_\varepsilon^b(R_\varepsilon) \to R_0$ strongly in $L^2([0,T] \times \Omega \times \Gamma)$.*

Proof. Existence of $(u_\varepsilon, v_\varepsilon, s_\varepsilon, w_\varepsilon, R_\varepsilon)$ satisfying system (3.2) is provided by Theorem 4.4. The convergences 1–4 follow from the estimates of Lemma 4.2 by applying Theorems 2.2 and 2.9. Furthermore, 5 is deduced by applying Lemma 5.6 of [17] using the estimates of Lemmas 4.1 and 4.2 as described above, while 6 directly follows from Lemma 4.3. ∎

To find the system of equations satisfied by the limit functions of Theorem 4.5, we pass to the limit in system (3.2) in the next section.

5. Identification of the limit model for the nonlinear carcinogenesis model.

First, we consider the ε-limits of the nonlinear terms. Afterward, we derive the complete limit system.

5.1. The nonlinear terms.

First, we consider the nonlinear terms $f(u_\varepsilon)$ and $g(v_\varepsilon)$ in the equations for u_ε and v_ε, respectively, in the system (3.2). Using the periodic unfolding operator $\mathcal{T}_\varepsilon$, the Nemytskii operator for the bounded and continuous functions f and g (see [29]), and the strong convergences of u_ε and v_ε (see Theorem 4.5), it follows that

$$f(\mathcal{T}_\varepsilon(u_\varepsilon)) \to f(u_0) \quad \text{strongly in } L^2([0,T] \times \Omega \times Y^*),$$
$$g(\mathcal{T}_\varepsilon(v_\varepsilon)) \to g(v_0) \quad \text{strongly in } L^2([0,T] \times \Omega \times Y^*).$$

Analogously it holds that

$$h(\mathcal{T}_\varepsilon^b(s_\varepsilon)) \to h(s_0) \quad \text{strongly in } L^2([0,T] \times \Omega \times \Gamma),$$

since $\mathcal{T}_\varepsilon^b(s_\varepsilon)$ converges strongly to the function $s_0 \in L^2([0,T] \times \Omega \times \Gamma)$ using Theorem 4.5 and noting that h is continuous and bounded.

Second, we calculate the limits of the nonlinear Robin-boundary terms $k_u u_\varepsilon R_\varepsilon$ and $k_v v_\varepsilon R_\varepsilon$ at the surface of the ER. With Theorem 4.5 we know that $\mathcal{T}_\varepsilon^b(R_\varepsilon)$ converges strongly to the function R_0 in $L^2([0,T] \times \Omega \times \Gamma)$. Then, we use Lemma 2.5 to deduce that

$$\lim_{\varepsilon \to 0} \int_{\Omega \times \Gamma} (\mathcal{T}_\varepsilon^b(u_\varepsilon)\mathcal{T}_\varepsilon^b(R_\varepsilon) - u_0 R_0)\varphi \, \mathrm{d}\sigma_y \, \mathrm{d}x = 0$$

and

$$\lim_{\varepsilon \to 0} \int_{\Omega \times \Gamma} (\mathcal{T}_\varepsilon^b(v_\varepsilon)\mathcal{T}_\varepsilon^b(R_\varepsilon) - v_0 R_0)\varphi \, \mathrm{d}\sigma_y \, \mathrm{d}x = 0$$

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

Now, we perform the limit derivation for the equations u_ε, v_ε, s_ε, w_ε, and R_ε and use the just calculated ε-limits of the nonlinear terms.

We test these equations with admissible test functions $\varphi_\varepsilon \in C^\infty(\Omega, C^\infty_\#(Y))$. As test functions $\varphi_\varepsilon \in C^\infty(\Omega, C^\infty_\#(Y))$, we choose functions of the form

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

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

5.2. Calculation of the ε-limits. We use assertion 2 of Lemma 2.4 for the first term on Γ_ε in the equation for u_ε in system (3.2) and the integration formula of the periodic unfolding operator,

$$\begin{aligned}\int_{\Omega \times Y^*} \partial_t \mathcal{T}_\varepsilon(u_\varepsilon)\varphi_\varepsilon \, \mathrm{d}y \, \mathrm{d}x + D_u \int_{\Omega \times Y^*} \mathcal{T}_\varepsilon(\nabla_x u_\varepsilon)\nabla_x \varphi_\varepsilon \, \mathrm{d}y \, \mathrm{d}x \\ + \int_{\Omega \times \Gamma} k_u \mathcal{T}_\varepsilon^b(u_\varepsilon)\mathcal{T}_\varepsilon^b(R_\varepsilon)\varphi_\varepsilon \, \mathrm{d}\sigma_y \, \mathrm{d}x - \int_{\Omega \times \Gamma} l_s \mathcal{T}_\varepsilon^b(s_\varepsilon)\varphi_\varepsilon \, \mathrm{d}\sigma_y \, \mathrm{d}x \\ = -\int_{\Omega \times Y^*} f(\mathcal{T}_\varepsilon(u_\varepsilon))\varphi_\varepsilon \, \mathrm{d}y \, \mathrm{d}x.\end{aligned}$$

With Theorem 2.2, Lemma 2.5, and the considerations for the nonlinear terms we find for $\varepsilon \to 0$

$$\begin{aligned}\int_{\Omega \times Y^*} \partial_t u_0 \varphi_0 \, \mathrm{d}x \, \mathrm{d}y + D_u \int_{\Omega \times Y^*} [\nabla_x u_0 + \nabla_y u_1][\nabla_x \varphi_0 + \nabla_y \varphi_1] \, \mathrm{d}x \, \mathrm{d}y \\ + \int_{\Omega \times \Gamma} (k_u u_0 R_0 - l_s s_0)\varphi_0 \, \mathrm{d}x \, \mathrm{d}\sigma_y = -\int_{\Omega \times Y^*} f(u_0)\varphi_0 \, \mathrm{d}x \, \mathrm{d}y\end{aligned} \tag{5.1}$$

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

Analogously we obtain for the equation for v_ε and $\varepsilon \to 0$ that

$$\begin{aligned}(5.2)\qquad &\int_{\Omega\times Y^*} \partial_t v_0 \varphi_0 \,\mathrm{d}x\,\mathrm{d}y + D_v \int_{\Omega\times Y^*} [\nabla_x v_0 + \nabla_y v_1][\nabla_x \varphi_0 + \nabla_y \varphi_1] \,\mathrm{d}x\,\mathrm{d}y \\ &+ \int_{\Omega\times\Gamma} (k_v v_0 R_0 - l_w w_0)\varphi_0 \,\mathrm{d}x\,\mathrm{d}\sigma_y = -\int_{\Omega\times Y^*} g(v_0)\varphi_0 \,\mathrm{d}x\,\mathrm{d}y\end{aligned}$$

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

Again with Lemma 2.5 for the function products and the considerations of the nonlinear terms, we calculate the limit equation for R_ε,

$$\begin{aligned}&\int_{\Omega\times\Gamma} \partial_t \mathcal{T}^b_\varepsilon(R_\varepsilon)\psi_\varepsilon \,\mathrm{d}\sigma_y\,\mathrm{d}x + \int_{\Omega\times\Gamma} \mathcal{T}^b_\varepsilon(R_\varepsilon)(k_u \mathcal{T}^b_\varepsilon(u_\varepsilon) + k_v \mathcal{T}^b_\varepsilon(v_\varepsilon) \\ &\quad + l_s \mathcal{T}^b_\varepsilon(s_\varepsilon) + l_w \mathcal{T}^b_\varepsilon(w_\varepsilon))\psi_\varepsilon \,\mathrm{d}\sigma_y\,\mathrm{d}x \\ &\quad = \int_{\Omega\times\Gamma} \overline{R}(l_s \mathcal{T}^b_\varepsilon(s_\varepsilon) + l_w \mathcal{T}^b_\varepsilon(w_\varepsilon))\psi_\varepsilon \,\mathrm{d}\sigma_y\,\mathrm{d}x.\end{aligned}$$

We find for $\varepsilon \to 0$

$$\begin{aligned}&\int_{\Omega\times\Gamma} \partial_t R_0 \psi_0 \,\mathrm{d}x\,\mathrm{d}\sigma_y + \int_{\Omega\times\Gamma} R_0(k_u u_0 + k_v v_0 + l_s s_0 + l_w w_0)\psi_0 \,\mathrm{d}x\,\mathrm{d}\sigma_y \\ &\quad = \int_{\Omega\times\Gamma} \overline{R}(l_s s_0 + l_w w_0)\psi_0 \,\mathrm{d}x\,\mathrm{d}\sigma_y\end{aligned}$$

for all $\psi_0 \in C^\infty(\Omega, C^\infty_\#(\Gamma))$.

Now, we calculate the limit equations for s_ε and w_ε,

$$\begin{aligned}&\int_{\Omega\times\Gamma} \partial_t \mathcal{T}^b_\varepsilon(s_\varepsilon)\psi_\varepsilon \,\mathrm{d}\sigma_y\,\mathrm{d}x + D_s \int_{\Omega\times\Gamma} \nabla_y \mathcal{T}^b_\varepsilon(s_\varepsilon)\nabla_y \psi_\varepsilon \,\mathrm{d}\sigma_y\,\mathrm{d}x \\ &\quad = \int_{\Omega\times\Gamma} (k_u \mathcal{T}^b_\varepsilon(u_\varepsilon)\mathcal{T}^b_\varepsilon(R_\varepsilon) - l_s \mathcal{T}^b_\varepsilon(s_\varepsilon))\psi_\varepsilon \,\mathrm{d}\sigma_y\,\mathrm{d}x - \int_{\Omega\times\Gamma} \mathcal{T}^b_\varepsilon(h(s_\varepsilon)\psi_\varepsilon \,\mathrm{d}\sigma_y\,\mathrm{d}x.\end{aligned}$$

For this purpose, we use Lemma 2.6 and Theorem 2.9 to deduce for $\varepsilon \to 0$ that

$$\begin{aligned}&\int_{\Omega\times\Gamma} \partial_t s_0 \psi_0 \,\mathrm{d}x\,\mathrm{d}\sigma_y + D_s \int_{\Omega\times\Gamma} \nabla_y s_0 \nabla_y \psi_0 \,\mathrm{d}x\,\mathrm{d}\sigma_y \\ &\quad = \int_{\Omega\times\Gamma} (k_u u_0 R_0 - l_s s_0)\psi_0 \,\mathrm{d}x\,\mathrm{d}\sigma_y - \int_{\Omega\times\Gamma} h(s_0)\psi_0 \,\mathrm{d}x\,\mathrm{d}\sigma_y\end{aligned}$$

for all $\psi_0 \in C^\infty(\Omega, C^\infty_\#(\Gamma))$. Analogously we get

$$\begin{aligned}&\int_{\Omega\times\Gamma} \partial_t w_0 \psi_0 \,\mathrm{d}x\,\mathrm{d}\sigma_y + D_w \int_{\Omega\times\Gamma} \nabla_\Gamma w_0 \nabla_\Gamma \psi_0 \,\mathrm{d}x\,\mathrm{d}\sigma_y \\ &\quad = \int_{\Omega\times\Gamma} (k_v v_0 R_0 - l_w w_0)\psi_0 \,\mathrm{d}x\,\mathrm{d}\sigma_y + \int_{\Omega\times\Gamma} h(s_0)\psi_0 \,\mathrm{d}x\,\mathrm{d}\sigma_y\end{aligned}$$

for all $\psi_0 \in C^\infty(\Omega, C^\infty_\#(\Gamma))$.

5.3. Identification of $u_1(x,y,t)$ and $v_1(x,y,t)$. For (5.1) and (5.2) we obtain the standard cell problem

$$\begin{aligned}(5.3)\qquad \nabla_y \cdot (e_j + \nabla_y \mu_j) &= 0 \qquad \text{in } Y^*, \\ (e_j + \nabla_y \mu_j) \cdot n &= 0 \qquad \text{on } \partial Y^*,\end{aligned}$$

where μ_j must be Y-periodic for all $j = 1, \ldots, n$. This can be found by setting $\varphi_0 = 0$ in (5.1) and is deduced in detail in [19, Chapter 1]. The elements of the diffusion tensors P^u and P^v are found by setting $\varphi_1 = 0$ and are given by

$$P^u_{ij} = D_u \int_{Y^*} (\delta_{ij} + \partial_{y_i}\mu_j)\,\mathrm{d}y \quad \text{and} \quad P^v_{ij} = D_v \int_{Y^*} (\delta_{ij} + \partial_{y_i}\mu_j)\,\mathrm{d}y. \tag{5.4}$$

5.4. Limit system. Now, we know all equations satisfied by the ε-limits of the solutions of (3.2) as given by Theorem 4.5. For convenience we denote the limit $(u_0, v_0, s_0, w_0, R_0)$ by (u, v, s, w, R). We use that u and v are y-independent and, before summarizing the homogenized limit problem in the following theorem, we note that every convergent subsequence of the sequence $(u_\varepsilon, v_\varepsilon, s_\varepsilon, w_\varepsilon, R_\varepsilon)$ converges to a limit, which satisfies the equations derived above. Because this system of equations has a unique solution, as proved in Theorem 6.1 below, the whole sequence $(u_\varepsilon, v_\varepsilon, s_\varepsilon, w_\varepsilon, R_\varepsilon)$ must converge to the solution of this limit problem.

THEOREM 5.1. *The homogenized limit problem of model* (3.2)*, satisfied by the limit functions of Theorem* 4.5*, reads as follows: Find* $(u, v, s, w, R) \in \mathcal{V}_{\mathrm{C}}(\Omega) \times \mathcal{V}_{\mathrm{N}}(\Omega) \times \mathcal{V}(\Omega, \Gamma)^2 \times \mathcal{V}_R(\Omega, \Gamma)$ *satisfying*

$$(u(0), v(0), s(0), w(0), R) = (u_I, v_I, s_I, w_I, R_I) \tag{5.5a}$$

and

(5.5b)
$$\begin{aligned}
|Y^*|(\partial_t u, \varphi_1)_\Omega + (P^u \nabla u, \nabla\varphi_1)_\Omega + (k_u uR - l_s s, \varphi_1)_{\Omega\times\Gamma} &= -|Y^*|(f(u), \varphi_1)_\Omega,\\
|Y^*|(\partial_t v, \varphi_2)_\Omega + (P^v \nabla v, \nabla\varphi_2)_\Omega + (k_v vR - l_w w, \varphi_2)_{\Omega\times\Gamma} &= -|Y^*|(g(v), \varphi_2)_\Omega,\\
(\partial_t s, \psi)_{\Omega\times\Gamma} + D_s(\nabla_\Gamma s, \nabla_\Gamma\psi)_{\Omega\times\Gamma} - (k_u uR - l_s s, \psi)_{\Omega\times\Gamma} &= -(h(s), \psi)_{\Omega\times\Gamma},\\
(\partial_t w, \psi)_{\Omega\times\Gamma} + D_w(\nabla_\Gamma w, \nabla_\Gamma\psi)_{\Omega\times\Gamma} - (k_v vR - l_w w, \psi)_{\Omega\times\Gamma} &= (h(s), \psi)_{\Omega\times\Gamma},\\
(\partial_t R, \psi)_{\Omega\times\Gamma} + (R(k_u u + k_v v + l_s s + l_w w), \psi)_{\Omega\times\Gamma} &= (\overline{R}(l_s s + l_w w), \psi)_{\Omega\times\Gamma},
\end{aligned}$$

for all $(\varphi_1, \varphi_2, \psi) \in V_{\mathrm{C0}}(\Omega) \times V_{\mathrm{N}}(\Omega) \times V(\Omega, \Gamma)$*, where the effective diffusion tensors* P^u *and* P^v *are given by* (5.4).

For the reader's convenience, we also state the strong form of the limit system (5.5): Find (u, v, s, w, R) satisfying (5.5a) as well as

(5.6a)
$$\begin{aligned}
|Y^*|\partial_t u - \nabla\cdot P^u\nabla u + \int_\Gamma (k_u uR - l_s s)\,\mathrm{d}\sigma_y &= -|Y^*| f(u) && \text{in } \Omega,\\
|Y^*|\partial_t v - \nabla\cdot P^v\nabla v + \int_\Gamma (k_v vR - l_w w)\,\mathrm{d}\sigma_y &= -|Y^*| g(v) && \text{in } \Omega,\\
\partial_t s + \nabla_\Gamma\cdot(D_s\nabla_\Gamma s) - (k_u uR - l_s s) &= -h(s) && \text{in } \Omega\times\Gamma,\\
\partial_t w - \nabla_\Gamma\cdot(D_w\nabla_\Gamma w) - (k_v vR - l_w w) &= h(s) && \text{in } \Omega\times\Gamma,\\
\partial_t R + R(k_u u + k_v v + l_s s + l_w w) &= \overline{R}(l_s s + l_w w) && \text{in } \Omega\times\Gamma.
\end{aligned}$$

and

(5.6b)
$$\begin{aligned}
u &= u_{\mathrm{Boundary}} && \text{on } \Gamma_{\mathrm{C}},\\
-P^u\nabla u\cdot n &= 0 && \text{on } \Gamma_{\mathrm{N}},\\
-P^v\nabla v\cdot n &= 0 && \text{on } \Gamma_{\mathrm{C}},\\
v &= 0 && \text{on } \Gamma_{\mathrm{N}}.
\end{aligned}$$

To conclude the analysis, we show the uniqueness of the solution of (5.5) in section 6.

6. Uniqueness of the limit model. In this section we show that the solution of system (5.5) is unique.

THEOREM 6.1. *There is at most one solution of problem* (5.5).

Proof. To prove uniqueness of the homogenized limit model, we need to show uniqueness of the cell problem (5.3) and the macroscopic system of (5.5).

Uniqueness up to a constant of the solution of the cell problem (5.3) is proved in [19] and it is left to show uniqueness of the macroscopic system of equations. Let us suppose that there exist two solutions $(u_1, v_1, s_1, w_1, R_1)$ and $(u_2, v_2, s_2, w_2, R_2)$ of the weak problem (5.5) with the same given initial values. We want to show that $(u_1, v_1, s_1, w_1, R_1) = (u_2, v_2, s_2, w_2, R_2)$ almost everywhere.

Now, we take the equations for u_1 and u_2, subtract them from each other, and test with $\varphi = u_1 - u_2$. Integration from 0 to t yields

$$\begin{aligned}|Y|\frac{1}{2}\|u_1 - u_2\|_\Omega^2 &+ \|\sqrt{P^u}\nabla(u_1 - u_2)\|^2_{\Omega\times[0,t]}\\ &+ (k_u(u_1R_1 - u_2R_2) - l_s(s_1 - s_2), u_1 - u_2)_{\Omega\times\Gamma}\\ &= -|Y|(f(u_1) - f(u_2), u_1 - u_2)_\Omega \le 0\end{aligned}$$

since f is monotone. Adding and subtracting u_1R_2 in the third term, we obtain with the binomial theorem that

$$\begin{aligned}|Y|\frac{1}{2}\|u_1 - u_2\|_\Omega^2 &+ \|\sqrt{P^u}\nabla(u_1 - u_2)\|^2_{\Omega,t}\\ &\le |\Gamma|\left(k_u\|u\|_{L^\infty} + k_u\overline{R} + l_s\right)\|u_1 - u_2\|^2_{\Omega,t} + k_u\|u\|_{L^\infty}\|R_1 - R_2\|^2_{\Omega\times\Gamma,t}\\ &\quad + l_s\|s_1 - s_2\|^2_{\Omega\times\Gamma,t}.\end{aligned}$$

Analogously, we find similar estimations for the equations for v, s, w, and R. We add them up and obtain

$$\begin{aligned}&\|u_1 - u_2\|_\Omega^2 + \|v_1 - v_2\|_\Omega^2 + \|s_1 - s_2\|^2_{\Omega\times\Gamma} + \|w_1 - w_2\|^2_{\Omega\times\Gamma} + \|R_1 - R_2\|^2_{\Omega\times\Gamma}\\ &\quad \le c_1\big(\|u_1 - u_2\|^2_{\Omega,t} + \|v_1 - v_2\|^2_{\Omega,t} + \|s_1 - s_2\|^2_{\Omega\times\Gamma,t} + \|w_1 - w_2\|^2_{\Omega\times\Gamma,t}\\ &\qquad + \|R_1 - R_2\|^2_{\Omega\times\Gamma,t}\big)\end{aligned}$$

for a constant $c_1 > 0$.

Gronwall's lemma implies

$$\|u_1 - u_2\|_\Omega^2 + \|v_1 - v_2\|_\Omega^2 + \|s_1 - s_2\|^2_{\Omega\times\Gamma} + \|w_1 - w_2\|^2_{\Omega\times\Gamma} + \|R_1 - R_2\|^2_{\Omega\times\Gamma} \le 0$$

and we obtain that $u_1 = u_2$ and $v_1 = v_2$ almost everywhere in Ω and $s_1 = s_2$, $w_1 = w_2$ and $R_1 = R_2$ almost everywhere in $\Omega \times \Gamma$ and for almost every $t \in [0, T]$. ∎

7. Conclusions. The limit model (5.5) (or, in its strong form, (5.6)) for carcinogenesis obtained in the homogenization process is of distributed-microstructure type. It consists of two partial differential equations involving global diffusion for the two species defined in the cytosol coupled to two partial differential equations involving local diffusion on the surface of the endoplasmic reticulum in a representative unit cell *attached* to each macroscopic point in space. Moreover, the number of free receptors in each representative unit cell is accounted for by an ordinary differential equation for this quantity. All parameters of the homogenized model are explicitly related to those of the microscopic model. In the future, it would be of great interest to test the model qualitatively and quantitatively, for which corresponding experimental data is required. In this context, it might be useful to look into different scalings as well (as in [16, 26]) or to include more complex exchange mechanisms through membranes (as in [31]).

From a homogenization point of view, the compactness result in Theorem 2.9 is worth highlighting as this result should be useful whenever systems involving slow diffusion on hypersurfaces are to be homogenized using the periodic unfolding method.

Appendix A. Estimates.

A.1. A priori estimates.

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

Proof. We start with the equations for u_ε and s_ε and test the weak formulation with $u_{\varepsilon-}$ and $s_{\varepsilon-}$, respectively, and add them up,

$$\begin{aligned}&(\partial_t u_\varepsilon, u_{\varepsilon-})_{\Omega_\varepsilon} + \varepsilon\langle \partial_t s_\varepsilon, s_{\varepsilon-}\rangle_{\Gamma_\varepsilon} + D_u(\nabla u_\varepsilon, \nabla u_{\varepsilon-})_{\Omega_\varepsilon} + D_s\varepsilon^3\langle \nabla_\Gamma s_\varepsilon, \nabla_\Gamma s_{\varepsilon-}\rangle_{\Gamma_\varepsilon}\\ &\quad + \varepsilon\langle k_u u_\varepsilon R_\varepsilon - l_s s_\varepsilon, u_{\varepsilon-} - s_{\varepsilon-}\rangle_{\Gamma_\varepsilon} = -(f(u_\varepsilon), u_{\varepsilon-})_{\Omega_\varepsilon} - \varepsilon\langle h(s_\varepsilon), s_{\varepsilon-}\rangle_{\Gamma_\varepsilon} = 0.\end{aligned}$$

Multiplying with -1 leads to

$$\begin{aligned}&(\partial_t u_{\varepsilon-}, u_{\varepsilon-})_{\Omega_\varepsilon} + \varepsilon\langle \partial_t s_{\varepsilon-}, s_{\varepsilon-}\rangle_{\Gamma_\varepsilon} + D_u(\nabla u_{\varepsilon-}, \nabla u_{\varepsilon-})_{\Omega_\varepsilon} + D_s\varepsilon^3\langle \nabla_\Gamma s_{\varepsilon-}, \nabla_\Gamma s_{\varepsilon-}\rangle_{\Gamma_\varepsilon}\\ &\quad + \varepsilon\langle k_u u_{\varepsilon-} R_\varepsilon, u_{\varepsilon-}\rangle_{\Gamma_\varepsilon} + \varepsilon\langle l_s s_{\varepsilon-}, s_{\varepsilon-}\rangle_{\Gamma_\varepsilon}\\ &\quad = \underbrace{-\varepsilon\langle k_u u_{\varepsilon+} R_\varepsilon, s_{\varepsilon-}\rangle_{\Gamma_\varepsilon} - \varepsilon\langle l_s s_{\varepsilon+}, u_{\varepsilon-}\rangle_{\Gamma_\varepsilon}}_{\le 0} + \varepsilon\langle k_u u_{\varepsilon-} R_\varepsilon, s_{\varepsilon-}\rangle_{\Gamma_\varepsilon} + \varepsilon\langle l_s s_{\varepsilon-}, u_{\varepsilon-}\rangle_{\Gamma_\varepsilon}.\end{aligned}$$

We drop the negative term on the right-hand side and integrate from 0 to t. The trace inequality and the Cauchy–Schwarz inequality yield

$$\begin{aligned}&\frac{1}{2}\|u_{\varepsilon-}\|^2_{\Omega_\varepsilon} + \frac{1}{2}\varepsilon\|s_{\varepsilon-}\|^2_{\Gamma_\varepsilon} + (D_u - \varepsilon^2(l_s + k_u\overline{R})c_0)\|\nabla u_{\varepsilon-}\|^2_{\Omega_\varepsilon,t} + D_s\varepsilon^3\|\nabla_\Gamma s_{\varepsilon-}\|^2_{\Gamma_\varepsilon,t}\\ &\quad + k_u\varepsilon\|u_{\varepsilon-}\sqrt{R_\varepsilon}\|^2_{\Gamma_\varepsilon,t} + \varepsilon l_s\|s_{\varepsilon-}\|^2_{\Gamma_\varepsilon,t} \le (l_s + k_u\overline{R})\left(\varepsilon\|s_{\varepsilon-}\|^2_{\Gamma_\varepsilon,t} + c_0\|u_{\varepsilon-}\|^2_{\Omega_\varepsilon,t}\right).\end{aligned}$$

After merging the constants, for ε small and with Gronwall's lemma we deduce that $\|u_{\varepsilon-}\|^2_{\Omega_\varepsilon} + \|s_{\varepsilon-}\|^2_{\Gamma_\varepsilon} \le 0$ and therefore u_ε and s_ε are greater than or equal to zero for almost every $x \in \Omega_\varepsilon$ or $x \in \Gamma_\varepsilon$ and $t \in [0,T]$. With similar estimations we also obtain that v_ε and w_ε are nonnegative for almost every $x \in \Omega_\varepsilon$ or $x \in \Gamma_\varepsilon$ and $t \in [0,T]$. ∎

LEMMA A.2 (boundedness in L^2). *There exists a constant $C > 0$, independent of ε, such that*

$$\begin{aligned}&\|u_\varepsilon\|^2_{\Omega_\varepsilon} + \|v_\varepsilon\|^2_{\Omega_\varepsilon} + \varepsilon\|s_\varepsilon\|^2_{\Gamma_\varepsilon} + \varepsilon\|w_\varepsilon\|^2_{\Gamma_\varepsilon}\\ &\quad + \|\nabla u_\varepsilon\|^2_{\Omega_\varepsilon,t} + \|\nabla v_\varepsilon\|^2_{\Omega_\varepsilon,t} + \varepsilon^3\|\nabla_\Gamma s_\varepsilon\|^2_{\Gamma_\varepsilon,t} + \varepsilon^3\|\nabla_\Gamma w_\varepsilon\|^2_{\Gamma_\varepsilon,t}\\ &\quad + \varepsilon\|k_u u_\varepsilon R_\varepsilon - l_s s_\varepsilon\|^2_{\Gamma_\varepsilon,t} + \varepsilon\|k_v v_\varepsilon R_\varepsilon - l_w w_\varepsilon\|^2_{\Gamma_\varepsilon,t} \le C.\end{aligned}$$

Proof. We perform the proof for u_ε and s_ε. The estimations for v_ε and w_ε are analogous. For that purpose we test the weak formulations for u_ε and s_ε with $k_u\overline{R}u_\varepsilon$ and $l_s s_\varepsilon$, respectively,

$$\begin{aligned}&k_u\overline{R}(\partial_t u_\varepsilon, u_\varepsilon)_{\Omega_\varepsilon} + \varepsilon l_s\langle \partial_t s_\varepsilon, s_\varepsilon\rangle_{\Gamma_\varepsilon} + D_u k_u\overline{R}(\nabla u_\varepsilon, \nabla u_\varepsilon)_{\Omega_\varepsilon} + \varepsilon^3 D_s l_s\langle \nabla_\Gamma s_\varepsilon, \nabla_\Gamma s_\varepsilon\rangle_{\Gamma_\varepsilon}\\ &\quad + \varepsilon\langle R_\varepsilon u_\varepsilon k_u - l_s s_\varepsilon, k_u\overline{R}u_\varepsilon - l_s s_\varepsilon\rangle_{\Gamma_\varepsilon} = -k_u\overline{R}(f(u_\varepsilon), u_\varepsilon)_{\Omega_\varepsilon} - \varepsilon l_s\langle h(s_\varepsilon), s_\varepsilon\rangle_{\Gamma_\varepsilon} \le 0.\end{aligned}$$

We add $\varepsilon\langle k_u R_\varepsilon u_\varepsilon - l_s s_\varepsilon, R_\varepsilon k_u u_\varepsilon - \overline{R} k_u u_\varepsilon\rangle_{\Gamma_\varepsilon}$ on the left-hand and on the right-hand side and compute

$$\begin{aligned} k_u\overline{R}(\partial_t u_\varepsilon, u_\varepsilon)_{\Omega_\varepsilon} + \varepsilon l_s \langle \partial_t s_\varepsilon, s_\varepsilon\rangle_{\Gamma_\varepsilon} + D_u k_u \overline{R}(\nabla u_\varepsilon, \nabla u_\varepsilon)_{\Omega_\varepsilon} + \varepsilon^3 D_s l_s \langle \nabla_\Gamma s_\varepsilon, \nabla_\Gamma s_\varepsilon\rangle_{\Gamma_\varepsilon} \\ + \varepsilon\langle R_\varepsilon u_\varepsilon k_u - l_s s_\varepsilon, k_u R u_\varepsilon - l_s s_\varepsilon\rangle_{\Gamma_\varepsilon} \le \varepsilon\langle k_u R_\varepsilon u_\varepsilon - l_s s_\varepsilon, R_\varepsilon k_u u_\varepsilon - \overline{R} k_u u_\varepsilon\rangle_{\Gamma_\varepsilon}. \end{aligned}$$

With integration from 0 to t we obtain

$$\begin{aligned} &\frac{1}{2}k_u\overline{R}\|u_\varepsilon\|^2_{\Omega_\varepsilon} + D_u k_u\overline{R}\|\nabla u_\varepsilon\|^2_{\Omega_\varepsilon,t} + \frac{1}{2}\varepsilon l_s\|s_\varepsilon\|^2_{\Gamma_\varepsilon} \\ &\quad + \varepsilon^3 D_s l_s\|\nabla_\Gamma s_\varepsilon\|^2_{\Gamma_\varepsilon,t} + \varepsilon\|k_u R_\varepsilon u_\varepsilon - l_s s_\varepsilon\|^2_{\Gamma_\varepsilon,t} \\ &= \varepsilon\langle k_u R_\varepsilon u_\varepsilon - l_s s_\varepsilon, k_u u_\varepsilon(R_\varepsilon - \overline{R})\rangle_{\Gamma_\varepsilon,t} + \underbrace{\frac{1}{2}k_u\overline{R}\|u_\varepsilon(0)\|^2_{\Omega_\varepsilon} + \frac{1}{2}\varepsilon l_s\|s_\varepsilon(0)\|^2_{\Gamma_\varepsilon}}_{=c_1}. \end{aligned}$$

Using the binomial theorem for a $\lambda > 0$ and the trace inequality gives

$$\begin{aligned} &\frac{1}{2}k_u\overline{R}\|u_\varepsilon\|^2_{\Omega_\varepsilon} + D_u k_u\overline{R}\|\nabla u_\varepsilon\|^2_{\Omega_\varepsilon,t} + \frac{1}{2}\varepsilon l_s\|s_\varepsilon\|^2_{\Gamma_\varepsilon} \\ &\quad + \varepsilon^3 D_s l_s\|\nabla_\Gamma s_\varepsilon\|^2_{\Gamma_\varepsilon,t} + \varepsilon\|R_\varepsilon u_\varepsilon k_u - l_s s_\varepsilon\|^2_{\Gamma_\varepsilon,t} \\ &\le c_1 + \frac{1}{2\lambda}\varepsilon\|k_u R_\varepsilon u_\varepsilon - l_s s_\varepsilon\|^2_{\Gamma_\varepsilon,t} + \frac{\lambda}{2}\varepsilon k_u^2\overline{R}^2\|u_\varepsilon\|^2_{\Gamma_\varepsilon,t} \\ &\le c_1 + \frac{1}{2\lambda}\varepsilon\|k_u R_\varepsilon u_\varepsilon - l_s s_\varepsilon\|^2_{\Gamma_\varepsilon,t} + \frac{\lambda}{2}k_u^2\overline{R}^2 c_0\left(\|u_\varepsilon\|^2_{\Omega_\varepsilon,t} + \varepsilon^2\|\nabla u_\varepsilon\|^2_{\Omega_\varepsilon,t}\right). \end{aligned}$$

Hence,

$$\begin{aligned} &\frac{1}{2}k_u\overline{R}\|u_\varepsilon\|^2_{\Omega_\varepsilon} + \left(D_u k_u\overline{R} - \frac{\lambda}{2}k_u^2\overline{R}^2 c_0\varepsilon^2\right)\|\nabla u_\varepsilon\|^2_{\Omega_\varepsilon,t} \\ &\quad + \frac{1}{2}\varepsilon l_s\|s_\varepsilon\|^2_{\Gamma_\varepsilon} + \varepsilon^3 D_s l_s\|\nabla_\Gamma s_\varepsilon\|^2_{\Gamma_\varepsilon,t} + \varepsilon\left(1 - \frac{1}{2\lambda}\right)\|R_\varepsilon u_\varepsilon k_u - l_s s_\varepsilon\|^2_{\Gamma_\varepsilon,t} \\ &\le c_1 + \frac{\lambda}{2}k_u^2\overline{R}^2 c_0\|u_\varepsilon\|^2_{\Omega_\varepsilon,t}. \end{aligned}$$

With $\lambda > \frac{1}{2}$ and ε small, we can merge the constants and use Gronwall's lemma to deduce the assertion. ∎

To prove strong convergence it is necessary to show that u_ε, $v_\varepsilon \in L^\infty(\Omega_\varepsilon)$ and $s_\varepsilon, w_\varepsilon \in L^\infty(\Gamma_\varepsilon)$. We already know that $u_\varepsilon, v_\varepsilon, s_\varepsilon, w_\varepsilon$ are nonnegative and, hence, bounded from below. It is left to show boundedness from above. We make use of the fact that $R_\varepsilon \in L^\infty(\Gamma_\varepsilon)$, which we established in Lemma 4.1.

LEMMA A.3 (boundedness in L^∞). *The functions u_ε, v_ε, s_ε, and w_ε are bounded independently of ε almost everywhere in $\Omega_\varepsilon \times [0,T]$ and $\Gamma_\varepsilon \times [0,T]$, respectively.*

Proof. Let $M(t) = \max\{\|u_I\|_{L^\infty(\Omega_\varepsilon)}, \|v_I\|_{L^\infty(\Omega_\varepsilon)}, \|s_I\|_{L^\infty(\Gamma_\varepsilon)}, \|w_I\|_{L^\infty(\Gamma_\varepsilon)}\}e^{kt}$ for a constant $k \in \mathbf{R}$. The function M exists because the initial conditions are bounded. At first we prove the assertion for u_ε and s_ε. We test the weak formulation for u_ε, s_ε with $(\overline{R}k_u u_\varepsilon - M)_+$ and $(l_s s_\varepsilon - M)_+$, respectively. Then, we add the two equations,

$$\begin{aligned}&(\partial_t u_\varepsilon, (\overline{R}k_u u_\varepsilon - M)_+)_{\Omega_\varepsilon} + \varepsilon\langle \partial_t s_\varepsilon, (l_s s_\varepsilon - M)_+\rangle_{\Gamma_\varepsilon} + (D_u \nabla u_\varepsilon, \nabla(\overline{R}k_u u_\varepsilon - M)_+)_{\Omega_\varepsilon}\\
&\quad + \varepsilon^3 \langle D_s \nabla_\Gamma s_\varepsilon, \nabla_\Gamma (l_s s_\varepsilon - M)_+\rangle_{\Gamma_\varepsilon} + \varepsilon\langle k_u R_\varepsilon u_\varepsilon - l_s s_\varepsilon, (\overline{R}k_u u_\varepsilon - M)_+\rangle_{\Gamma_\varepsilon}\\
&\quad = \underbrace{(-f(u_\varepsilon), (\overline{R}k_u u_\varepsilon - M)_+)_{\Omega_\varepsilon}}_{\leq 0} + \varepsilon\langle k_u R_\varepsilon u_\varepsilon - l_s s_\varepsilon, (l_s s_\varepsilon - M)_+\rangle_{\Gamma_\varepsilon}\\
&\quad + \underbrace{\langle -h(s_\varepsilon), (l_s s_\varepsilon - M)_+\rangle_{\Gamma_\varepsilon}}_{\leq 0}\end{aligned}$$

and estimate

$$\begin{aligned}&\frac{1}{\overline{R}k_u}(\partial_t(\overline{R}k_u u_\varepsilon - M)_+, (\overline{R}k_u u_\varepsilon - M)_+)_{\Omega_\varepsilon} + \frac{1}{l_s}\varepsilon\langle \partial_t (l_s s_\varepsilon - M)_+, (l_s s_\varepsilon - M)_+\rangle_{\Gamma_\varepsilon}\\
&\qquad + \frac{D_u}{\overline{R}k_u}\|\nabla(\overline{R}k_u u_\varepsilon - M)_+\|^2_{\Omega_\varepsilon} + \frac{D_s}{l_s}\varepsilon^3\|\nabla_\Gamma(l_s s_\varepsilon - M)_+\|^2_{\Gamma_\varepsilon}\\
&\qquad + \varepsilon\langle k_u R_\varepsilon u_\varepsilon - l_s s_\varepsilon, (\overline{R}k_u u_\varepsilon - M)_+ - (l_s s_\varepsilon - M)_+\rangle_{\Gamma_\varepsilon}\\
&\quad \leq -\frac{1}{\overline{R}k_u}(Mk, (\overline{R}k_u u_\varepsilon - M)_+)_{\Omega_\varepsilon} - \frac{1}{l_s}\varepsilon\langle Mk, (l_s s_\varepsilon - M)_+\rangle_{\Gamma_\varepsilon}.\end{aligned}$$

We add $\varepsilon\langle k_u\overline{R}u_\varepsilon - k_u R_\varepsilon u_\varepsilon, (\overline{R}k_u u_\varepsilon - M)_+ - (l_s s_\varepsilon - M)_+\rangle_{\Gamma_\varepsilon}$ on each side of the inequality, integrate from 0 to t, and use the binomial theorem for any $\lambda > 0$

$$\begin{aligned}&\frac{1}{2\overline{R}k_u}\|(\overline{R}k_u u_\varepsilon - M)_+\|^2_{\Omega_\varepsilon} + \frac{1}{2l_s}\varepsilon\|(l_s s_\varepsilon - M)_+\|^2_{\Gamma_\varepsilon} + \frac{D_u}{\overline{R}k_u}\|\nabla(\overline{R}k_u u_\varepsilon - M)_+\|^2_{\Omega_\varepsilon,t}\\
&\qquad + \frac{D_s}{l_s}\varepsilon^3\|\nabla_\Gamma(l_s s_\varepsilon - M)_+\|^2_{\Gamma_\varepsilon,t} + \varepsilon\|(\overline{R}k_u u_\varepsilon - M)_+ - (l_s s_\varepsilon - M)_+\|^2_{\Gamma_\varepsilon,t}\\
&\quad \leq \lambda\overline{R}^2 k_u^2\varepsilon\|u_\varepsilon\|^2_{\Gamma_\varepsilon} + \frac{1}{2\lambda}\varepsilon\|(\overline{R}k_u u_\varepsilon - M)_+ - (l_s s_\varepsilon - M)_+\|^2_{\Gamma_\varepsilon,t}\\
&\qquad - \frac{1}{\overline{R}k_u}(Mk, (\overline{R}k_u u_\varepsilon - M)_+)_{\Omega_\varepsilon,t} - \frac{1}{l_s}\varepsilon\langle Mk, (l_s s_\varepsilon - M)_+\rangle_{\Gamma_\varepsilon,t}.\end{aligned}$$

Simplifying further yields

$$\begin{aligned}&\frac{1}{2\overline{R}k_u}\|(\overline{R}k_u u_\varepsilon - M)_+\|^2_{\Omega_\varepsilon} + \frac{1}{2l_s}\varepsilon\|(l_s s_\varepsilon - M)_+\|^2_{\Gamma_\varepsilon} + \frac{D_u}{\overline{R}k_u}\|\nabla(\overline{R}k_u u_\varepsilon - M)_+\|^2_{\Omega_\varepsilon,t}\\
&\qquad + \frac{D_s}{l_s}\varepsilon^3\|\nabla_\Gamma(l_s s_\varepsilon - M)_+\|^2_{\Gamma_\varepsilon,t} + \left(1 - \frac{1}{2\lambda}\right)\varepsilon\|(\overline{R}k_u u_\varepsilon - M)_+ - (l_s s_\varepsilon - M)_+\|^2_{\Gamma_\varepsilon,t}\\
&\quad \leq c_1 - \frac{1}{\overline{R}k_u}(Mk, (\overline{R}k_u u_\varepsilon - M)_+)_{\Omega_\varepsilon,t} - \frac{1}{l_s}\varepsilon\langle Mk, (l_s s_\varepsilon - M)_+\rangle_{\Gamma_\varepsilon,t},\end{aligned}$$

where we choose $\lambda > \frac{1}{2}$. Now we distinguish two cases:

(a) Either $\overline{R}k_u u_\varepsilon - M \leq 0$ and $l_s s_\varepsilon - M \leq 0$ almost everywhere in Ω_ε and Γ_ε, respectively. Then, $u_\varepsilon \in L^\infty(\Omega_\varepsilon)$ and $s_\varepsilon \in L^\infty(\Gamma_\varepsilon)$ for almost every $t \in [0,T]$ and the assertion holds true.

(b) Or there exists $V \subset \Omega_\varepsilon$ (not a null set) with $\overline{R}k_u u_\varepsilon - M > 0$ in V or there exists $V \subset \Gamma_\varepsilon$ (not a null set) with $l_s s_\varepsilon - M > 0$ in V. Then, we choose k such that the right-hand side is smaller than or equal to zero and we conclude

$$\begin{aligned}&\frac{1}{2\overline{R}k_u}\|(\overline{R}k_u u_\varepsilon - M)_+\|^2_{\Omega_\varepsilon} + \frac{1}{2l_s}\varepsilon\|(l_s s_\varepsilon - M)_+\|^2_{\Gamma_\varepsilon} + \frac{D_u}{\overline{R}k_u}\|\nabla(\overline{R}k_u u_\varepsilon - M)_+\|^2_{\Omega_\varepsilon,t}\\
&\quad + \frac{D_s}{l_s}\varepsilon^3\|\nabla_\Gamma(l_s s_\varepsilon - M)_+\|^2_{\Gamma_\varepsilon,t} + c_1\varepsilon\|(\overline{R}k_u u_\varepsilon - M)_+ - (l_s s_\varepsilon - M)_+\|^2_{\Gamma_\varepsilon,t} \leq 0.\end{aligned}$$

This yields $\overline{R}k_u u_\varepsilon - M < 0$ and $l_s s_\varepsilon - M < 0$ almost everywhere in Ω_ε and Γ_ε, respectively, and for almost every $t \in [0,T]$.

The proof for v_ε and w_ε is very similar. With corresponding estimates as before we get that $\overline{R}k_v v_\varepsilon - M \leq 0$ and $l_w w_\varepsilon - M \leq 0$ almost everywhere in Ω_ε and Γ_ε, respectively, and for almost every $t \in [0,T]$. ∎

Next, we show that the time derivatives of u_ε and v_ε are elements of $H_0^1(\Omega_\varepsilon)'$.

LEMMA A.4 (time-estimation in $(H_0^1)'$). *There exists a $C > 0$, independent of ε, such that*

$$\|\partial_t u_\varepsilon\|_{L^2([0,T],H_0^1(\Omega_\varepsilon)')} + \|\partial_t v_\varepsilon\|_{L^2([0,T],H_0^1(\Omega_\varepsilon)')} < C.$$

Proof. We start by writing the $H_0^1(\Omega_\varepsilon)'$-Norm in full for $\partial_t u_\varepsilon$. In the following we use that test functions φ in $H_0^1(\Omega_\varepsilon)$ are zero on the boundary Γ_ε:

$$\begin{aligned}
&\|\partial_t u_\varepsilon\|_{H_0^1(\Omega_\varepsilon)'} \\
&\quad= \sup_{\varphi\in H_0^1(\Omega_\varepsilon), \|\varphi\|=1} (\partial_t u_\varepsilon, \varphi)_{H_0^1(\Omega_\varepsilon)'\times H_0^1(\Omega_\varepsilon)} \\
&\quad= \sup_{\varphi\in H_0^1(\Omega_\varepsilon), \|\varphi\|=1} ((-D_u \nabla u_\varepsilon, \nabla\varphi)_{H_0^1(\Omega_\varepsilon)'\times H_0^1(\Omega_\varepsilon)} - \underbrace{\varepsilon\langle k_u R u_\varepsilon - l_s s_\varepsilon, \varphi\rangle_{\Gamma_\varepsilon}}_{=0} \\
&\qquad - (f(u_\varepsilon), \varphi)_{H_0^1(\Omega_\varepsilon)'\times H_0^1(\Omega_\varepsilon)}) \\
&\quad\leq \sup_{\varphi\in H_0^1(\Omega_\varepsilon), \|\varphi\|=1} \left(c_1\|\nabla u_\varepsilon\|_{L^2(\Omega_\varepsilon)}\|\nabla\varphi\|_{L^2(\Omega)} + c_2\|f(u_\varepsilon)\|_{L^2(\Omega_\varepsilon)}\|\varphi\|_{L^2(\Omega_\varepsilon)}\right) \\
&\quad\leq c_1\left(\|\nabla u_\varepsilon\|_{\Omega_\varepsilon} + \|f(u_\varepsilon)\|_{\Omega_\varepsilon}\right).
\end{aligned}$$

Integration with respect to time yields

$$\|\partial_t u_\varepsilon\|^2_{L^2([0,T],H_0^1(\Omega_\varepsilon)')} \leq c_1\left(\|\nabla u_\varepsilon\|^2_{\Omega_\varepsilon,t} + \|f(u_\varepsilon)\|^2_{\Omega_\varepsilon,t}\right) < c_2,$$

where the boundedness holds because of Lemma A.2.

The proof for $\|\partial_t v_\varepsilon\|_{L^2([0,T],H_0^1(\Omega_\varepsilon)')}$ works analogously. ∎

A.2. Proof of Lemma 4.3. We apply parts 2 and 3 of Lemma 2.4 to the weak equation of s_ε and find

$$\begin{aligned}
&(\partial_t \mathcal{T}_\varepsilon^b(s_\varepsilon), \psi)_{\Omega\times\Gamma} + D_s(\varepsilon\mathcal{T}_\varepsilon^b(\nabla_\Gamma s_\varepsilon), \nabla_\Gamma\psi)_{\Omega\times\Gamma} \\
&\quad= (k_u\mathcal{T}_\varepsilon^b(u_\varepsilon)\mathcal{T}_\varepsilon^b(R_\varepsilon) - l_s\mathcal{T}_\varepsilon^b(s_\varepsilon), \psi)_{\Omega\times\Gamma} - (\mathcal{T}_\varepsilon^b(h(s_\varepsilon)), \psi)_{\Omega\times\Gamma}
\end{aligned}$$

for all $\psi \in L^2(\Omega, H^1_\#(\Gamma))$. Now we write this equation for two epsilons ε_1 and ε_2 and subtract the equations from each other. As test function ψ we take $\psi = \mathcal{T}_{\varepsilon_1}^b(s_{\varepsilon_1}) - \mathcal{T}_{\varepsilon_2}^b(s_{\varepsilon_2})$. Adding and subtracting the term $k_u\mathcal{T}_{\varepsilon_2}^b(u_{\varepsilon_2})\mathcal{T}_{\varepsilon_1}^b(R_{\varepsilon_1})$ yields

$$\begin{aligned}
&(\partial_t(\mathcal{T}_{\varepsilon_1}^b(s_{\varepsilon_1}) - \mathcal{T}_{\varepsilon_2}^b(s_{\varepsilon_2})), \mathcal{T}_{\varepsilon_1}^b(s_{\varepsilon_1}) - \mathcal{T}_{\varepsilon_2}^b(s_{\varepsilon_2}))_{\Omega\times\Gamma} \\
&\qquad + D_s\|\varepsilon_1\mathcal{T}_{\varepsilon_1}^b(\nabla_\Gamma s_{\varepsilon_1}) - \varepsilon_2\mathcal{T}_{\varepsilon_2}^b(\nabla_\Gamma s_{\varepsilon_2})\|^2_{\Omega\times\Gamma} + l_s\|\mathcal{T}_{\varepsilon_1}^b(s_{\varepsilon_1}) - \mathcal{T}_{\varepsilon_2}^b(s_{\varepsilon_2})\|^2_{\Omega\times\Gamma} \\
&\quad= (k_u\mathcal{T}_{\varepsilon_1}^b(u_{\varepsilon_1})\mathcal{T}_{\varepsilon_1}^b(R_{\varepsilon_1}) - k_u\mathcal{T}_{\varepsilon_2}^b(u_{\varepsilon_2})\mathcal{T}_{\varepsilon_1}^b(R_{\varepsilon_1}) \\
&\qquad + k_u\mathcal{T}_{\varepsilon_2}^b(u_{\varepsilon_2})\mathcal{T}_{\varepsilon_1}^b(R_{\varepsilon_1}) - k_u\mathcal{T}_{\varepsilon_2}^b(u_{\varepsilon_2})\mathcal{T}_{\varepsilon_2}^b(R_{\varepsilon_2}), \mathcal{T}_{\varepsilon_1}^b(s_{\varepsilon_1}) - \mathcal{T}_{\varepsilon_2}^b(s_{\varepsilon_2}))_{\Omega\times\Gamma} \\
&\qquad - (\mathcal{T}_{\varepsilon_1}^b(h(s_{\varepsilon_1})) - \mathcal{T}_{\varepsilon_2}^b(h(s_{\varepsilon_2})), \mathcal{T}_{\varepsilon_1}^b(s_{\varepsilon_1}) - \mathcal{T}_{\varepsilon_2}^b(s_{\varepsilon_2}))_{\Omega\times\Gamma} \\
&\quad\leq k_u\overline{R}\|\mathcal{T}_{\varepsilon_1}^b(u_{\varepsilon_1}) - \mathcal{T}_{\varepsilon_2}^b(u_{\varepsilon_2})\|^2_{\Omega\times\Gamma} + k_u\overline{R}\|\mathcal{T}_{\varepsilon_1}^b(s_{\varepsilon_1}) - \mathcal{T}_{\varepsilon_2}^b(s_{\varepsilon_2})\|^2_{\Omega\times\Gamma} \\
&\qquad + k_u\|u_\varepsilon\|_{L^\infty}\|\mathcal{T}_{\varepsilon_1}^b(R_{\varepsilon_1}) - \mathcal{T}_{\varepsilon_2}^b(R_{\varepsilon_2})\|^2_{\Omega\times\Gamma} \\
&\qquad + k_u\|u_\varepsilon\|_{L^\infty}\|\mathcal{T}_{\varepsilon_1}^b(s_{\varepsilon_1}) - \mathcal{T}_{\varepsilon_2}^b(s_{\varepsilon_2})\|^2_{\Omega\times\Gamma} + L_h\|\mathcal{T}_{\varepsilon_1}^b(s_{\varepsilon_1}) - \mathcal{T}_{\varepsilon_2}^b(s_{\varepsilon_2})\|^2_{\Omega\times\Gamma}.
\end{aligned}$$

Here we used that the function h is Lipschitz-continuous with constant L_h. We integrate from 0 to t and merge the constants to a single constant $c_1 > 0$,

$$\begin{aligned}
&\|\mathcal{T}^b_{\varepsilon_1}(s_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(s_{\varepsilon_2})\|^2_{\Omega\times\Gamma} + \|\varepsilon_1\mathcal{T}^b_{\varepsilon_1}(\nabla_\Gamma s_{\varepsilon_1}) - \varepsilon_2\mathcal{T}^b_{\varepsilon_2}(\nabla_\Gamma s_{\varepsilon_2})\|^2_{\Omega\times\Gamma,t}\\
&\qquad + \|\mathcal{T}^b_{\varepsilon_1}(s_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(s_{\varepsilon_2})\|^2_{\Omega\times\Gamma,t}\\
&\quad \le c_1\big(\|\mathcal{T}^b_{\varepsilon_1}(s_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(s_{\varepsilon_2})\|^2_{\Omega\times\Gamma,t}\\
&\qquad + \|\mathcal{T}^b_{\varepsilon_1}(u_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(u_{\varepsilon_2})\|^2_{\Omega\times\Gamma,t} + \|\mathcal{T}^b_{\varepsilon_1}(R_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(R_{\varepsilon_2})\|^2_{\Omega\times\Gamma,t}\big).
\end{aligned}$$

With similar estimations we find

$$\begin{aligned}
&\|\mathcal{T}^b_{\varepsilon_1}(R_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(R_{\varepsilon_2})\|^2_{\Omega\times\Gamma}\\
&\quad \le c_1\big(\|\mathcal{T}^b_{\varepsilon_1}(R_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(R_{\varepsilon_2})\|^2_{\Omega\times\Gamma,t} + \|\mathcal{T}^b_{\varepsilon_1}(s_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(s_{\varepsilon_2})\|^2_{\Omega\times\Gamma,t}\\
&\qquad + \|\mathcal{T}^b_{\varepsilon_1}(w_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(w_{\varepsilon_2})\|^2_{\Omega\times\Gamma,t} + \|\mathcal{T}^b_{\varepsilon_1}(u_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(u_{\varepsilon_2})\|^2_{\Omega\times\Gamma,t}\\
&\qquad + \|\mathcal{T}^b_{\varepsilon_1}(v_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(v_{\varepsilon_2})\|^2_{\Omega\times\Gamma,t}\big)
\end{aligned}$$

and

$$\begin{aligned}
&\|\mathcal{T}^b_{\varepsilon_1}(w_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(w_{\varepsilon_2})\|^2_{\Omega\times\Gamma} + \|\varepsilon_1\mathcal{T}^b_{\varepsilon_1}(\nabla_\Gamma w_{\varepsilon_1}) - \varepsilon_2\mathcal{T}^b_{\varepsilon_2}(\nabla_\Gamma w_{\varepsilon_2})\|^2_{\Omega\times\Gamma,t}\\
&\qquad + \|\mathcal{T}^b_{\varepsilon_1}(w_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(w_{\varepsilon_2})\|^2_{\Omega\times\Gamma,t}\\
&\quad \le c_1\|\mathcal{T}^b_{\varepsilon_1}(s_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(s_{\varepsilon_2})\|^2_{\Omega\times\Gamma,t} + \|\mathcal{T}^b_{\varepsilon_1}(w_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(w_{\varepsilon_2})\|^2_{\Omega\times\Gamma,t}\\
&\qquad + \|\mathcal{T}^b_{\varepsilon_1}(v_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(v_{\varepsilon_2})\|^2_{\Omega\times\Gamma,t} + \|\mathcal{T}^b_{\varepsilon_1}(R_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(R_{\varepsilon_2})\|^2_{\Omega\times\Gamma,t}.
\end{aligned}$$

Adding all three inequalities, using Gronwall's lemma and the trace inequality gives

$$\begin{aligned}
&\|\mathcal{T}^b_{\varepsilon_1}(s_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(s_{\varepsilon_2})\|^2_{\Omega\times\Gamma} + \|\mathcal{T}^b_{\varepsilon_1}(w_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(w_{\varepsilon_2})\|^2_{\Omega\times\Gamma} + \|\mathcal{T}^b_{\varepsilon_1}(R_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(R_{\varepsilon_2})\|^2_{\Omega\times\Gamma}\\
&\quad \le c_1\left(\|\mathcal{T}^b_{\varepsilon_1}(u_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(u_{\varepsilon_2})\|^2_{\Omega\times\Gamma} + \|\mathcal{T}^b_{\varepsilon_1}(v_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(v_{\varepsilon_2})\|^2_{\Omega\times\Gamma}\right)\\
&\quad \le c_1c_0\left(\|\mathcal{T}_{\varepsilon_1}(u_{\varepsilon 1}) - \mathcal{T}_{\varepsilon_2}(u_{\varepsilon_2})\|^2_{\Omega\times Y} + \|\varepsilon_1\mathcal{T}_{\varepsilon_1}(\nabla_x u_{\varepsilon 1}) - \varepsilon_2\mathcal{T}_{\varepsilon_2}(\nabla_x u_{\varepsilon_2})\|^2_{\Omega\times Y}\right.\\
&\qquad \left. + \|\mathcal{T}_{\varepsilon_1}(v_{\varepsilon 1}) - \mathcal{T}_{\varepsilon_2}(v_{\varepsilon_2})\|^2_{\Omega\times Y} + \|\varepsilon_1\mathcal{T}_{\varepsilon_1}(\nabla_x v_{\varepsilon 1}) - \varepsilon_2\mathcal{T}_{\varepsilon_2}(\nabla_x v_{\varepsilon_2})\|^2_{\Omega\times Y}\right),
\end{aligned}$$

where we used that $\nabla_y\mathcal{T}_\varepsilon(u_\varepsilon) = \varepsilon\mathcal{T}_\varepsilon(\nabla_x u_\varepsilon)$; see [9]. With integration with respect to time we find

$$\begin{aligned}
&\|\mathcal{T}^b_{\varepsilon_1}(u_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(u_{\varepsilon_2})\|^2_{\Omega\times\Gamma,t} + \|\mathcal{T}^b_{\varepsilon_1}(v_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(v_{\varepsilon_2})\|^2_{\Omega\times\Gamma,t}\\
&\quad \le c_1|Y|(\underbrace{\|u_{\varepsilon_1} - u_{\varepsilon_2}\|^2_{\Omega,t} + \|v_{\varepsilon_1} - v_{\varepsilon_2}\|^2_{\Omega,t}}_{<\tilde\delta}\\
&\qquad + \underbrace{\max\{\varepsilon_1,\varepsilon_2\}^2}_{\overset{\varepsilon\to 0}{\longrightarrow} 0}\underbrace{(\|\nabla_x u_{\varepsilon_1}\|^2_{\Omega,t} + \|\nabla_x u_{\varepsilon_2}\|^2_{\Omega,t} + \|\nabla_x v_{\varepsilon_1}\|^2_{\Omega,t} + \|\nabla_x v_{\varepsilon_2}\|^2_{\Omega,t})}_{<C,\text{bounded}}).
\end{aligned}$$

Because u_ε and v_ε converge strongly in $L^2([0,T]\times\Omega)$, there exists a $\tilde\varepsilon > 0$ such that the first estimate holds true for $\varepsilon_1, \varepsilon_2 < \tilde\varepsilon$. Hence, we deduce

$$\begin{aligned}
&\|\mathcal{T}^b_{\varepsilon_1}(s_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(s_{\varepsilon_2})\|^2_{\Omega\times\Gamma,t} + \|\mathcal{T}^b_{\varepsilon_1}(w_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(w_{\varepsilon_2})\|^2_{\Omega\times\Gamma,t}\\
&\qquad + \|\mathcal{T}^b_{\varepsilon_1}(R_{\varepsilon_1}) - \mathcal{T}^b_{\varepsilon_2}(R_{\varepsilon_2})\|^2_{\Omega\times\Gamma,t} \le c_1(\tilde\delta + \tilde\varepsilon C) \le \delta
\end{aligned}$$

for $\varepsilon_1, \varepsilon_2 < \tilde{\varepsilon}$ and δ dependent on $\tilde{\varepsilon}$. This means that s_ε, w_ε, and R_ε converge strongly in $L^2([0,T] \times \Omega \times \Gamma)$.

Appendix B. Existence of solutions of the microscopic problem: Proof of Theorem 4.4. We show existence of the solution $(u_\varepsilon, v_\varepsilon, s_\varepsilon, w_\varepsilon, R_\varepsilon)$ of the system of equations (3.2) for every $\varepsilon > 0$. This is done in two steps. First we prove existence of the function $R_\varepsilon \in L^2([0,T] \times \Gamma_\varepsilon)$ when we assume the existence of $s_\varepsilon, w_\varepsilon, u_\varepsilon, v_\varepsilon \in L^2([0,T] \times \Gamma_\varepsilon)$. Then, we show by using Schauder's theorem (see [29]) the existence of the solutions u_ε, v_ε, s_ε, and w_ε.

B.1. Existence for $\boldsymbol{R_\varepsilon}$. We start with considering the ordinary differential equation for R_ε given in (3.1).

LEMMA B.1 (existence of R_ε). *Let $\varepsilon > 0$ and $s_\varepsilon, w_\varepsilon, u_\varepsilon, v_\varepsilon \in L^2([0,T] \times \Gamma_\varepsilon)$. Then, there exists a solution $R_\varepsilon \in \{u \in L^2([0,T] \times \Gamma_\varepsilon) |\ \partial_t u \in L^2([0,T] \times \Gamma_\varepsilon)\}$ of the ordinary differential equation* (3.1).

Proof. We use Carathéodory's existence theorem (see [10]). For this purpose, we define for almost every $x \in \Gamma_\varepsilon$ the function $j_x : [0,T] \times [0, \overline{R}] \to \mathbf{R}$ as

$$j_x(t, R_\varepsilon) := -R_\varepsilon |k_u u_\varepsilon(t) + k_v v_\varepsilon(t)| + (\overline{R} - R_\varepsilon)|k_s s_\varepsilon(t) + k_w w_\varepsilon(t)|.$$

Carathéodory's existence theorem states, if the following conditions hold for the function j_x for almost every $x \in \Gamma_\varepsilon$, then there exists a solution $R_\varepsilon(\cdot, x) \in C([0,T])$ for almost every $x \in \Gamma_\varepsilon$:

(a) The function j_x is defined on a rectangle $[0,T] \times [0, \overline{R}]$.
(b) The function j_x is measurable in t for all fixed $R_\varepsilon \in [0, \overline{R}]$.
(c) The function j_x is continuous in R_ε for all fixed $t \in [0,T]$.
(d) There exists a Lebesgue-integrable function $m : [0,T] \to \mathbf{R}$ such that $|j_x(t, R_\varepsilon)| \le m(t)$ for all $(t, R_\varepsilon) \in [0,T] \times [0, \overline{R}]$.

Conditions (a) and (c) are easily verified. Condition (b) is true because $u_\varepsilon, v_\varepsilon, s_\varepsilon, w_\varepsilon$ are L^2-functions and $|\cdot|$ is continuous. For (d) we use that $u_\varepsilon(x)$, $v_\varepsilon(x)$, $s_\varepsilon(x)$, and $w_\varepsilon(x)$ are elements of $L^2([0,T])$ thus Lebesgue-integrable for almost every $x \in \Gamma_\varepsilon$. It follows that j_x is Lebesgue-integrable itself and condition (d) is fulfilled. Hence, there exists a solution $R_\varepsilon(\cdot, x) \in C([0,T])$ for almost every $x \in L^2(\Gamma_\varepsilon)$.

We note that $R_\varepsilon(t,x) \in [0, \overline{R}]$ for almost every $t, x \in [0,T] \times \Gamma_\varepsilon$. The function $R : [L^2((0,T) \times \Gamma_\varepsilon)]^4 \to C([0,T], L^2(\Gamma_\varepsilon)) \subset L^2([0,T] \times \Gamma_\varepsilon)$ with $R(u_\varepsilon, v_\varepsilon, s_\varepsilon, w_\varepsilon) = R_\varepsilon$ is bounded and continuous. ∎

It is easily checked that the functions f, g, and h are continuous and satisfy the growth condition $|\varphi(x)| \le C|x|^{\frac{p}{q}}$ for $p = q = 2$ and a $C > 0$ for $\varphi = f,\ g$, and h. Then, with the theorem of Nemytskii (see [29]) it holds that the operators

$$\begin{aligned} F, G : L^2([0,T], L^2(\Omega_\varepsilon)) &\to L^2([0,T], L^2(\Omega_\varepsilon)), \\ F(u)(t) &= f(u(t)), \\ G(v)(t) &= g(v(t)), \\ &\text{and} \\ H : L^2([0,T], L^2(\Gamma_\varepsilon)) &\to L^2([0,T], L^2(\Gamma_\varepsilon)), \\ H(s)(t) &= h(s(t)) \end{aligned} \tag{B.1}$$

are continuous and bounded for fixed ε.

B.2. Main part of the proof of Theorem 4.4. To complete the proof of the theorem, we use Schauder's theorem and Lemma B.1. We show that there exists a solution for a small time step $[0, \tau]$. To find the solution on the whole interval $[0,T]$

the solution parts must be linked together bit by bit. We define for a $\delta \in (0, \frac{1}{2})$ the function space $V = L^2([0,\tau], H^{1-\delta}(\Omega_\varepsilon))$ and $W := L^2([0,\tau], L^2(\Gamma_\varepsilon))$. Furthermore we define the mapping

$$\begin{aligned} S : V^2 \times W^2 \to \{u \in L^2([0,\tau], H^1(\Omega_\varepsilon))|\ \partial_t u \in L^2([0,\tau], H^1(\Omega_\varepsilon)')\}^2 \\ \times \{u \in L^2([0,\tau], H^1(\Gamma_\varepsilon))|\ \partial_t u \in L^2([0,\tau], H^1(\Gamma_\varepsilon)')\}^2 \end{aligned}$$

given by

$$S(\hat{u}_\varepsilon, \hat{v}_\varepsilon, \hat{s}_\varepsilon, \hat{w}_\varepsilon) = (u_\varepsilon, v_\varepsilon, s_\varepsilon, w_\varepsilon),$$

where $(u_\varepsilon, v_\varepsilon, s_\varepsilon, w_\varepsilon)$ is given by

$$\text{(B.2)} \qquad \begin{aligned} \partial_t u_\varepsilon - D_u \Delta u_\varepsilon &= f(\hat{u}_\varepsilon) && \text{in } \Omega_\varepsilon, \\ \partial_t v_\varepsilon - D_v \Delta v_\varepsilon &= g(\hat{v}_\varepsilon) && \text{in } \Omega_\varepsilon, \\ -D_u \nabla u_\varepsilon \cdot n &= \varepsilon(k_u u_\varepsilon R(\hat{u}_\varepsilon, \hat{v}_\varepsilon, \hat{s}_\varepsilon, \hat{w}_\varepsilon) - l_s \hat{s}_\varepsilon) && \text{on } \Gamma_\varepsilon, \\ -D_v \nabla v_\varepsilon \cdot n &= \varepsilon(k_v v_\varepsilon R(\hat{u}_\varepsilon, \hat{v}_\varepsilon, \hat{s}_\varepsilon, \hat{w}_\varepsilon) - l_w \hat{w}_\varepsilon) && \text{on } \Gamma_\varepsilon, \\ \partial_t s_\varepsilon - \varepsilon^2 D_s \Delta_\Gamma s_\varepsilon &= -l_s s_\varepsilon - h(\hat{s}_\varepsilon) + k_u u_\varepsilon R(\hat{u}_\varepsilon, \hat{v}_\varepsilon, \hat{s}_\varepsilon, \hat{w}_\varepsilon) && \text{on } \Gamma_\varepsilon, \\ \partial_t w_\varepsilon - \varepsilon^2 D_w \Delta_\Gamma w_\varepsilon &= -l_w w_\varepsilon + h(\hat{s}_\varepsilon) + k_v v_\varepsilon R(\hat{u}_\varepsilon, \hat{v}_\varepsilon, \hat{s}_\varepsilon, \hat{w}_\varepsilon) && \text{on } \Gamma_\varepsilon. \end{aligned}$$

The system of partial differential equations (B.2) is linear and has a unique solution (see [12]) and the mapping S is continuous. With the lemma of Lions–Aubin (see [29]) we know that $\{u \in L^2([0,\tau], H^1(\Omega_\varepsilon))|\ \partial_t u \in L^2([0,\tau], H^1(\Omega_\varepsilon)')\}$ is compactly embedded in V and $\{u \in L^2([0,\tau], H^1(\Gamma_\varepsilon))|\ \partial_t u \in L^2([0,\tau], H^1(\Gamma_\varepsilon)')\}$ is compactly embedded in W. We deduce that the operator which maps $(\hat{u}_\varepsilon, \hat{v}_\varepsilon, \hat{s}_\varepsilon, \hat{w}_\varepsilon) \in V^2 \times W^2$ to $(u_\varepsilon, v_\varepsilon, s_\varepsilon, w_\varepsilon) \in V^2 \times W^2$ is continuous and compact.

Now, in order to apply Schauder's theorem, it is left to show that

$$\begin{aligned} \left(\|\hat{u}_\varepsilon\|_V^2 + \|\hat{v}_\varepsilon\|_V^2 + \|\hat{s}_\varepsilon\|_W^2 + \|\hat{w}_\varepsilon\|_W^2\right) \le r \quad \text{implies} \\ \left(\|u_\varepsilon\|_V^2 + \|v_\varepsilon\|_V^2 + \|s_\varepsilon\|_W^2 + \|w_\varepsilon\|_W^2\right) \le r \end{aligned}$$

for some $r > 0$, where we may assume that the norms of the initial conditions are smaller than r. We test the equation for u_ε of system (B.2) with u_ε and integrate from 0 to $t < \tau$. Using standard estimations such as trace inequality, the Cauchy–Schwarz inequality, and the binomial theorem we find

$$\begin{aligned} \|u_\varepsilon\|_{\Omega_\varepsilon}^2 + D_u \|\nabla u_\varepsilon\|_{\Omega_\varepsilon,t}^2 &\le c_1 \|u_\varepsilon\|_{\Omega_\varepsilon,t}^2 + \varepsilon^2 c_2 \|\nabla u_\varepsilon\|_{\Omega_\varepsilon,t}^2 + c_3 r, \\ \|v_\varepsilon\|_{\Omega_\varepsilon}^2 + D_v \|\nabla v_\varepsilon\|_{\Omega_\varepsilon,t}^2 &\le c_1 \|v_\varepsilon\|_{\Omega_\varepsilon,t}^2 + \varepsilon^2 c_2 \|\nabla v_\varepsilon\|_{\Omega_\varepsilon,t}^2 + c_3 r, \\ \varepsilon \|s_\varepsilon\|_{\Gamma_\varepsilon}^2 + \varepsilon^3 D_s \|\nabla_\Gamma s_\varepsilon, t\|_{\Gamma_\varepsilon}^2 &\le c_1 \varepsilon \|s_\varepsilon\|_{\Gamma_\varepsilon,t}^2 + c_2 \|u_\varepsilon\|_{\Omega_\varepsilon,t}^2 + c_3 \varepsilon^2 \|\nabla u_\varepsilon\|_{\Omega_\varepsilon,t}^2 + c_4 r, \\ \varepsilon \|w_\varepsilon\|_{\Gamma_\varepsilon}^2 + \varepsilon^3 D_w \|\nabla_\Gamma w_\varepsilon\|_{\Gamma_\varepsilon,t}^2 &\le c_1 \varepsilon \|w_\varepsilon\|_{\Gamma_\varepsilon,t}^2 + c_2 \|v_\varepsilon\|_{\Omega_\varepsilon,t}^2 + c_3 \varepsilon^2 \|\nabla v_\varepsilon\|_{\Omega_\varepsilon,t}^2 + c_4 r \end{aligned}$$

for some constants $c_1, c_2, c_3, c_4 > 0$. We add the results above and with ε small we find

$$\begin{aligned} &\frac{1}{2}\left(\|u_\varepsilon\|_{\Omega_\varepsilon}^2 + \|v_\varepsilon\|_{\Omega_\varepsilon}^2 + \varepsilon \|s_\varepsilon\|_{\Gamma_\varepsilon}^2 + \varepsilon \|w_\varepsilon\|_{\Gamma_\varepsilon}^2\right) + (D_u - \varepsilon^2 c_2) \|\nabla u_\varepsilon\|_{\Omega_\varepsilon,t}^2 \\ &\quad + (D_v - \varepsilon^2 c_2) \|\nabla v_\varepsilon\|_{\Omega_\varepsilon,t}^2 + \varepsilon^3 D_s \|\nabla_\Gamma s_\varepsilon\|_{\Gamma_\varepsilon,t}^2 + \varepsilon^3 D_s \|\nabla_\Gamma w_\varepsilon\|_{\Gamma_\varepsilon,t}^2 \\ &\le c_1 (\|u_\varepsilon\|_{\Omega_\varepsilon,t}^2 + \|v_\varepsilon\|_{\Omega_\varepsilon,t}^2 + \varepsilon \|s_\varepsilon\|_{\Gamma_\varepsilon,t}^2 + \varepsilon \|w_\varepsilon\|_{\Gamma_\varepsilon,t}^2) + 4 c_4 r. \end{aligned}$$

With Gronwall's lemma we conclude

$$\begin{aligned}\text{(B.3)}\qquad &\|u_\varepsilon\|^2_{\Omega_\varepsilon} + \|v_\varepsilon\|^2_{\Omega_\varepsilon} + \varepsilon\|s_\varepsilon\|^2_{\Gamma_\varepsilon} + \varepsilon\|w_\varepsilon\|^2_{\Gamma_\varepsilon}\\ &\quad + \|\nabla u_\varepsilon\|^2_{\Omega_\varepsilon,t} + \|\nabla v_\varepsilon\|^2_{\Omega_\varepsilon,t} + \varepsilon\|\nabla_\Gamma s_\varepsilon\|^2_{\Gamma_\varepsilon,t} + \varepsilon\|\nabla_\Gamma w_\varepsilon\|^2_{\Gamma_\varepsilon,t} \le c_1 r.\end{aligned}$$

This inequality (B.3) implies

$$\begin{aligned}&\|u_\varepsilon\|^2_{L^2((0,\tau),H^1(\Omega_\varepsilon))} + \|v_\varepsilon\|^2_{L^2((0,\tau),H^1(\Omega_\varepsilon))}\\ &\quad + \|s_\varepsilon\|^2_{L^2((0,\tau),H^1(\Gamma_\varepsilon))} + \|w_\varepsilon\|^2_{L^2((0,\tau),H^1(\Gamma_\varepsilon))} \le c_1 r.\end{aligned}$$

Integration from 0 to τ of inequality (B.3) gives

$$\begin{aligned}&\|u_\varepsilon\|^2_{L^2((0,\tau),L^2(\Omega_\varepsilon))} + \|v_\varepsilon\|^2_{L^2((0,\tau),L^2(\Omega_\varepsilon))}\\ &\quad + \varepsilon\|s_\varepsilon\|^2_{L^2((0,\tau),L^2(\Gamma_\varepsilon))} + \varepsilon\|w_\varepsilon\|^2_{L^2((0,\tau),L^2(\Gamma_\varepsilon))} \le c_1 r\tau.\end{aligned}$$

With the interpolation inequality (see [1])

$$\|\cdot\|_V \le \tilde{c}\|\cdot\|^{\delta}_{L^2((0,\tau),L^2(\Omega_\varepsilon))}\|\cdot\|^{1-\delta}_{L^2((0,\tau),H^1(\Omega_\varepsilon))}$$

we get

$$\|u_\varepsilon\|^2_V + \|v_\varepsilon\|^2_V + \|s_\varepsilon\|^2_W + \|w_\varepsilon\|^2_W \le \tilde{c}(c_1 r\tau)^{\delta}(c_1 r)^{1-\delta} \le r.$$

The last inequality is correct if τ is chosen smaller than $\frac{1}{(\tilde{c}c_1)^{\frac{1}{\delta}}}$. Hence, the embedding composed with the mapping S has at least one fixed point in $\{u \in L^2([0,\tau];H^1(\Omega_\varepsilon))|\ \partial_t u \in H^1(\Omega_\varepsilon)'\}^2 \times \{u \in L^2([0,\tau],H^1(\Gamma_\varepsilon))|\ \partial_t u \in H^1(\Gamma_\varepsilon)'\}^2$.

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