MULTISCALE ANALYSIS OF SIGNALLING PROCESSES IN TISSUES WITH NON-PERIODIC DISTRIBUTION OF CELLS.

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Abstract. In this paper a microscopic model for a signalling process in the cardiac muscle tissue of the left ventricular wall, comprising non-periodic fibrous microstructure is considered. To derive the macroscopic equations we approximate the non-periodic microstructure by the corresponding locally-periodic microstructure. Then applying the methods of the locally-periodic (l-p) unfolding operator, locally-periodic two-scale (l-t-s) convergence on oscillating surfaces and l-p boundary unfolding operator we obtain the macroscopic problem for a signalling process in the heart muscle tissue.

Key words: non-periodic microstructures, plywood-like microstructures, signalling processes, domains with non-periodic perforations, locally-periodic homogenization, unfolding operator

1. Introduction

In this paper we consider the multiscale analysis of microscopic problems posed in domains with non-periodic microstructures. We consider a model for a signalling process in the cardiac muscle tissue of the left ventricular wall, comprising plywood-like structure. The plywood-like structure is given by the superposition of planes of parallel aligned fibres, gradually rotated with a rotation angle $\gamma$, see Fig. 1.1. It was observed that cardiac muscle fibre orientations vary continuously through the left ventricular wall from a negative angle at the epicardium to positive values toward the endocardium [19, 22]. In the microscopic model we consider the diffusion of signalling molecules in the intercellular space between muscle fibres and their interaction with receptors located on the surface of the fibres. There are two main difficulties in the multiscale analysis of a microscopic problem posed in a domain with non-periodic perforations: (i) the approximation of the non-periodic microstructure by a locally-periodic and (ii) derivation of limit equations for the non-linear equations defined on oscillating surfaces of the microstructure. Thus, as first we define the locally-periodic microstructure which approximates the original non-periodic microstructure. Then, applying techniques of locally-periodic homogenization (locally-periodic (l-p) two-scale convergence and l-p unfolding operator) to the locally-periodic approximation we derive macroscopic equations for the original microscopic model. The l-p two-scale convergence on oscillating surfaces and l-p boundary unfolding operator allow us to pass to the limit in the non-linear equations defined on surfaces of the locally-periodic microstructure. In this paper we consider a simplest model describing interactions between processes defined in a perforated domains and the dynamics on surfaces of the microstructure. However the techniques presented here can be applied also to more general microscopic models as well as to other non-periodic microstructures.

Previous results on homogenization in locally periodic media constitute the multiscale analysis of a heat-conductivity problem defined in domains with non-periodically distributed spherical balls [1, 5, 23], and elliptic and Stokes equations in non-periodic fibrous materials [4, 5, 2, 23]. Formal asymptotic expansion and two-scale convergence defined for periodic test functions, [20], were used to derive macroscopic equations for models posed in domains with locally periodic perforations, i.e. domains consisting of periodic cells with smoothly changing perforations [3, 8, 9, 16, 18, 21].

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The paper is organized as follows. In Section 2 the microscopic model for a signalling process in a tissue with non-periodic plywood-like microstructure is formulated. In Section 3 we prove the existence and uniqueness results for the microscopic model and derive a priori estimates for solutions of the microscopic model. The approximation of the microscopic equations posed in the domain with non-periodic microstructure by a corresponding problem defined in a domain with locally-periodic microstructure is given in Section 4. Then, applying the l-p unfolding operator, l-t-s convergence on oscillating surfaces, and l-p boundary unfolding operator we derive the macroscopic model for a signalling process in the heart muscle tissue. In Appendix we summarise the definitions and main compactness results for l-t-s convergence and l-p unfolding operator.

2. MICROSCOPIC MODEL FOR A SIGNALING PROCESS IN A TISSUE WITH NON-PERIODIC DISTRIBUTION OF CELLS.

We consider a signalling processes in a tissue with non-periodic distribution of cells. As an example of a non-periodic microstructure of a cell tissue we consider the plywood-like structure of the cardiac muscle tissue of the left ventricular wall, with gradually rotating layers of the height $\varepsilon$ of fibres aligned in the same direction.

We consider an open, bounded subdomain $\Omega \subset \mathbb{R}^3$ representing a part of a tissue. Similarly to [23], we define the non-periodic distribution of rotating fibres by considering a rotation matrix $R$. For a given function $\gamma \in C^2(\mathbb{R})$, with $0 \leq \gamma(x) \leq \pi$ for $x \in \mathbb{R}$, we define the rotation matrix around the $x_3$-axis with rotation angle $\gamma(x)$ with the $x_1$-axis as

$$R(\gamma(x)) = \begin{pmatrix} \cos(\gamma(x)) & -\sin(\gamma(x)) & 0 \\ \sin(\gamma(x)) & \cos(\gamma(x)) & 0 \\ 0 & 0 & 1 \end{pmatrix}.$$ 

and the characteristic function of a fibre of radius $\rho(x)a$ is given by

$$\vartheta(x,y) = \begin{cases} 1, & |\hat{y}| \leq \rho(x)a, \\ 0, & |\hat{y}| > \rho(x)a, \end{cases}$$

where $\hat{y} = (y_2, y_3)$, $\rho \in C^1(\overline{\Omega})$ and $\rho(x)a \leq 2/5$, with $0 < \rho_0 \leq \rho(x) \leq \rho_1 < \infty$ for all $x \in \overline{\Omega}$.

For $k \in \mathbb{Z}^3$ we define $x_k^\varepsilon = R_{x_k^\varepsilon}\xi k$ with $R_{x_k^\varepsilon} := R(\gamma(x_k^\varepsilon,3))$. Notice that $x_k^\varepsilon_{k,3} = \varepsilon k_3$ and the third variable is invariant under the rotation $R_{x_k^\varepsilon}$. This ensure that for each fixed $\varepsilon k_3$ we obtain a layer of parallel aligned fibres. Then the characteristic function of fibres in the non-periodic plywood-like microstructure reads

$$\chi_{\Omega^\varepsilon_j}(x) = \chi_{\Omega}(x) \sum_{k \in \mathbb{Z}^3} \vartheta(x_k^\varepsilon, R_k^{-1}(x - x_k^\varepsilon)/\varepsilon)$$

and the inter-cellular space in the tissue is characterized by

$$\chi_{\Omega^\varepsilon} = (1 - \chi_{\Omega^\varepsilon_j})\chi_{\Omega},$$
We define the non-periodic perforated domain $\Omega_\varepsilon^*$ as

$$\Omega_\varepsilon^* = \Omega \setminus \Omega_\varepsilon^0,$$

with $\Omega_\varepsilon^0 = \bigcup_{k \in \Xi_\varepsilon^0} (\varepsilon R_{x_k}^\varepsilon K_{x_k} Y_0 + x_k^\varepsilon) = \bigcup_{k \in \Xi_\varepsilon^0} \varepsilon R_{x_k}^\varepsilon (K_{x_k} Y_0 + k)$

where $\Xi_\varepsilon = \{ k \in \mathbb{Z}^3 : \varepsilon R_{x_k}^\varepsilon (Y_1 + k) \subset \Omega \}$, $Y_{x_k}^\varepsilon = R_{x_k}^\varepsilon Y_1$, and $Y_{x_k}^\varepsilon, K = R_{x_k}^\varepsilon (Y_1 \setminus K_{x_k} Y_0)$, with

$$Y_1 = \left( -\frac{1}{2}, \frac{1}{2} \right)^3$$

and

$$Y_0 = \{ y \in \mathbb{R}^3 : |\bar{y}| \leq a \}.$$

The assumptions on $\rho$ and $a$ ensure that $K_{x} Y_0 \subset Y_1$ for all $x \in \Gamma$. Here

$$K_{x} = K(x) \quad \text{and} \quad K(x) = \begin{pmatrix} 1 & 0 & 0 \\ 0 & \rho(x) & 0 \\ 0 & 0 & \rho(x) \end{pmatrix}.$$

Notice that since $R$ is a rotation matrix and $K_{x} Y_0 \subset Y_1$ for all $x \in \Gamma$, we have that $(\varepsilon R_{x_k}^\varepsilon K_{x_k} \bar{Y}_0 + x_k^\varepsilon) \cap (\varepsilon R_{x_k}^\varepsilon R_{x_m}^\varepsilon \bar{Y}_0 + x_m^\varepsilon) = \emptyset$ for any $m, n \in \mathbb{Z}^3$ with $n \neq m$, and $\Omega_\varepsilon^*$ is connected.

The surfaces of cells, i.e., boundaries of the microstructure, are denoted by

$$\Gamma^\varepsilon = \sum_{k \in \Xi_\varepsilon} (\varepsilon R_{x_k}^\varepsilon K_{x_k} \Gamma + x_k^\varepsilon) = \bigcup_{k \in I^\varepsilon} \varepsilon R_{x_k}^\varepsilon (K_{x_k} \Gamma + k),$$

where $\Gamma = \partial Y_0$.

Notice that the changes in the microstructure of $\Omega_\varepsilon^*$ are defined by changes in the periodicity given by a linear transformation (rotation) $R(x)$ and by changes in the shape of the microstructure (changes in the radius of fibres) given by $K(x)$, for $x \in \Omega$.

To define the non-constant reaction rates for binding and dissociation processes on cell membranes we consider $\alpha, \beta \in C^1(\bar{\Omega}; C_0^1(Y_1))$, extended in $y$-variable by zero to $\mathbb{R}^3$, and define

$$\alpha^\varepsilon(x) = \sum_{k \in \Xi_\varepsilon} \alpha(x, R_{x_k}^{-1}(x - x_k^\varepsilon)/\varepsilon) \chi_{(\varepsilon Y_{x_k}^\varepsilon + x_k^\varepsilon)}(x),$$

$$\beta^\varepsilon(x) = \sum_{k \in \Xi_\varepsilon} \beta(x, R_{x_k}^{-1}(x - x_k^\varepsilon)/\varepsilon) \chi_{(\varepsilon Y_{x_k}^\varepsilon + x_k^\varepsilon)}(x).$$

In the microscopic model for a signalling process in a cell tissue we consider the diffusion of signaling molecules $c^\varepsilon$ in the inter-cellular space and their interaction with free and bound receptors $r_{f}^\varepsilon$ and $r_{b}^\varepsilon$ located on surfaces of cells. Then the microscopic problem reads

$$\partial_t c^\varepsilon - \text{div}(A \nabla c^\varepsilon) = F^\varepsilon(x, c^\varepsilon) \quad \text{in} \quad (0, T) \times \Omega_\varepsilon^*, \tag{2.2}$$

$$-A \nabla c^\varepsilon \cdot n = \varepsilon [\alpha^\varepsilon(x) c^\varepsilon r_{f}^\varepsilon - \beta^\varepsilon(x) r_{b}^\varepsilon] \quad \text{on} \quad (0, T) \times \Gamma^\varepsilon,$$

$$A \nabla c^\varepsilon \cdot n = 0 \quad \text{on} \quad (0, T) \times (\partial \Omega \cap \partial \Omega_\varepsilon^*),$$

$$c^\varepsilon(0, x) = c_0(x) \quad \text{in} \quad \Omega_\varepsilon^*,$$

where the dynamics in the concentrations of free and bound receptors on cell surfaces is determined by two ordinary differential equations

$$\partial_t r_{f}^\varepsilon = p^\varepsilon(x, r_{f}^\varepsilon) - \alpha^\varepsilon(x) c^\varepsilon r_{f}^\varepsilon + \beta^\varepsilon(x) r_{b}^\varepsilon - d_{f}^\varepsilon(x) r_{f}^\varepsilon \quad \text{on} \quad (0, T) \times \Gamma^\varepsilon, \tag{2.3}$$

$$\partial_t r_{b}^\varepsilon = \alpha^\varepsilon(x) c^\varepsilon r_{f}^\varepsilon - \beta^\varepsilon(x) r_{b}^\varepsilon - d_{b}^\varepsilon(x) r_{b}^\varepsilon \quad \text{on} \quad (0, T) \times \Gamma^\varepsilon,$$

$$r_{f}^\varepsilon(0, x) = r_{f0}(x), \quad r_{b}^\varepsilon(0, x) = r_{b0}(x) \quad \text{on} \quad \Gamma^\varepsilon,$$

where

$$r_{f0}(x) = r_{f0}(x) \sum_{k \in \Xi_\varepsilon} r_{j0}^2(R_{x_k}^{-1}(x - x_k^\varepsilon)/\varepsilon) \chi_{(\varepsilon Y_{x_k}^\varepsilon + x_k^\varepsilon)}(x), \quad j = f, b.$$

For simplicity of the presentation we shall assume that the diffusion coefficient $A$ and the decay rates $d_{f}^\varepsilon, d_{b}^\varepsilon$ are constant. We also assume that the functions $F^\varepsilon(x, c^\varepsilon) = F(c^\varepsilon)$ and $p^\varepsilon(x, r_{f}^\varepsilon) = p(r_{f}^\varepsilon)$ are
independent of $x \in \Omega$. The dependence of $A$, $d_j$, $F$ and $p$ on the microscopic and macroscopic variables can be analysed in the same way as for $\alpha^\varepsilon$ and $\beta^\varepsilon$.

**Assumption 1.**

- $(A\xi, \xi) > A_0|\xi|^2$ for $\xi \in \mathbb{R}^3$, $A_0 > 0$, $d_j \geq 0$, $j = f, b$.
- $F : \mathbb{R} \to \mathbb{R}$ Lipschitz continuous, $F(\xi)\xi_\varepsilon \leq C|\xi_\varepsilon|^2$, where $\xi_\varepsilon = \min\{0, \xi\}$.
- $p : \mathbb{R} \to \mathbb{R}$ Lipschitz continuous and $p(\xi)$ is nonnegative for nonnegative $\xi$.
- $\alpha, \beta \in C^1(\overline{\Omega}; \mathbb{C}^1(0, Y))$ are nonnegative.
- $c_0 \in H^1(\Omega) \cap L^\infty(\Omega)$, $r^f_j \in C^1(\Omega)$, and $r^b_j \in C^1(0, Y)$ extended by zero to $\mathbb{R}^3$, and $c_0$, $r^f_j$ are nonnegative, for $j = f, b$ and $l = 1, 2$.

We shall use the following notations $\Omega^\varepsilon_{,T} = (0, T) \times \Omega^\varepsilon$, $\Gamma^\varepsilon_T = (0, T) \times \Gamma^\varepsilon$, $\Omega_T = (0, T) \times \Omega$, $\Gamma_T = (0, T) \times \Gamma$, and $\Gamma_{x,T} = (0, T) \times \Gamma_x$. For $u \in L^3(0, \tau; L^p(G))$ and $v \in L^q(0, \tau; L^p(G))$ we denote by $\langle u, v \rangle_{G_T} = \int_0^T \int_{G_T} u v \, dx dt$.

**Definition 2.** A weak solution of the microscopic problem (2.2)–(2.3) are functions $c^\varepsilon, r^f_j, r^b_j$ such that

$$c^\varepsilon \in L^2(0, T; H^1(\Omega^\varepsilon)), \quad r^f_j \in H^1(0, T; L^2(\Omega^\varepsilon)), \quad r^b_j \in L^\infty(\Gamma^\varepsilon), \quad j = f, b,$$

satisfying the equation (2.2) in the weak form

$$(2.4) \quad \langle \partial_t c^\varepsilon, \phi \rangle_{\Omega^\varepsilon_{,T}} + \langle A \nabla c^\varepsilon, \nabla \phi \rangle_{\Omega^\varepsilon_{,T}} = \langle F(c^\varepsilon), \phi \rangle_{\Omega^\varepsilon_{,T}} + \varepsilon \langle \beta r^b_j - \alpha^\varepsilon c^\varepsilon r^f_j, \phi \rangle_{\Gamma^\varepsilon_T},$$

for all $\phi \in L^2(0, T; H^1(\Omega^\varepsilon))$, the equations (2.3) are satisfied a.e. on $\Gamma^\varepsilon_T$, and $c^\varepsilon \to c_0$ in $L^2(\Omega^\varepsilon)$, $r^f_j \to r^f_j$ in $L^2(\Gamma^\varepsilon)$ as $t \to 0$.

3. **Existence and uniqueness result and a priori estimates for a weak solution of the microscopic problem.**

In a similar way as in [7, 15, 24] we can proof the existence and uniqueness results and a priori estimates for a weak solution of the problem (2.2)–(2.3).

**Lemma 3.** Under Assumption 7 there exists a unique non-negative weak solution of the microscopic problem (2.2)–(2.3) satisfying the a priori estimates

$$(3.1) \quad \|c^\varepsilon\|_{L^\infty(0,T;L^2(\Omega))} + \|\nabla c^\varepsilon\|_{L^2(\Omega^\varepsilon_{,T})} + \|\partial_t c^\varepsilon\|_{L^2(\Omega^\varepsilon_{,T})} + \varepsilon^{\frac{1}{2}}\|c^\varepsilon\|_{L^2(\Gamma^\varepsilon_T)} \leq \mu,$$

$$(3.2) \quad \|(c^\varepsilon - M_1 e^{M_2 t})^+\|_{L^\infty(0,T;L^2(\Omega))} + \|\nabla(c^\varepsilon - M_1 e^{M_2 t})^+\|_{L^2(\Omega^\varepsilon_{,T})} \leq \mu e^t,$$

where the constant $\mu$ is independent of $\varepsilon$ and

where $M_1 \geq \|c_0\|_{L^\infty(\Omega)}$, $M_1 M_2 \geq |F(0)| + |F(1)| + \mu\|\beta\|_{L^\infty(\Omega \times Y)}$ and $\mu$ is independent of $\varepsilon$.

**Sketch.** As in [24] the existence of a solution of the microscopic problem (2.2)–(2.3) for each fixed $\varepsilon > 0$ is obtained by applying fixed point arguments. To derive a priori estimate we consider the structure of the microscopic equations. For non-negative solutions, by adding the equations for $r^f_j$ and $r^b_j$, we obtain

$$\partial_t (r^f_j + r^b_j) + p(r^f_j) = d_r r^b_j - d_f r^f_j.$$

Then the Lipschitz continuity of $p$, the non-negativity of $r^f_j$, and the boundedness of $d_j$, with $j = f, b$, imply the boundedness of $r^f_j$ and $r^b_j$ on $\Gamma^\varepsilon$. Using $K_x Y_0 \subset Y_1$ for all $x \in \overline{\Omega}$ and the uniform bounds for $K$, i.e., $0 < \rho_0^2 < |\det K(x)| \leq \rho_1^2 < \infty$, we obtain the trace estimate

$$\|\phi\|_{L^p(K_{x_h} \Gamma)} \leq C \left[ \|\phi\|_{L^p(Y_1 \setminus K_{x_h} Y_0)} + \|\nabla y \phi\|_{L^p(Y_1 \setminus K_{x_h} Y_0)} \right].$$
where the constant $C$ depends on $Y_1$, $Y_0$, $K$ and is independent of $\varepsilon$ and $k$. Considering the change of variables $x = \varepsilon R_{x_k} y + x_k^e$ and summing up over $k \in \Xi$ yield for $\phi \in W^{1,p}(\Omega^e)$, with $p \in [1, \infty)$,

\begin{equation}
(3.3) \quad \varepsilon \| \phi \|_{L^p(\Omega^e)}^p \leq \mu \left[ \| \phi \|_{L^p(\Omega^e)}^p + \varepsilon \| \nabla \phi \|_{L^p(\Omega^e)}^p \right],
\end{equation}

where the constant $\mu$ depends on $Y_1$, $Y_0$, $R$ and $K$ and is independent of $\varepsilon$.

Taking $c^e$ as a test function in (2.4) and using the trace estimate (3.3) we obtain the estimates for $c^e$. Testing the equations (2.3) by $\partial_t r^e_j$ and $\partial_t r^e_b$, respectively, yields the estimates for the time derivatives of $r^e_j$, $j = f, b$. In the derivation of the a priori estimate for $\partial_t c^e$, we use the equation for $\partial_t r^e_j$ to estimate the non-linear term on the boundary $\Gamma^e$:

\[- \int_{\Gamma^e} \alpha^e r^e_j c^e \partial_t c^e \, d\gamma_x = \frac{1}{2} \frac{d}{dt} \int_{\Gamma^e} \alpha^e r^e_j |c^e|^2 \, d\gamma_x + \frac{1}{2} \frac{d}{dt} \int_{\Gamma^e} \alpha^e \varepsilon r^e_j |c^e|^2 \, d\gamma_x \leq \frac{1}{2} \frac{d}{dt} \int_{\Gamma^e} \alpha^e \varepsilon r^e_j |c^e|^2 \, d\gamma_x.
\]

Considering $(c^e - M_1 e^{M_2 t})^+$ as a test function in (2.4) we obtain

\[\int_{\Omega^e} (c^e(\tau) - M_1 e^{M_2 t})^+ \, dx \leq \mu \int_{\Omega^e} \alpha^e |c^e|^2 \, dx + \mu \int_{\Omega^e} \varepsilon |c^e|^2 \, dx + \mu \int_{\Omega^e} \beta^e r^e_j (c^e - M_1 e^{M_2 t})^+ \, dx dt\]

Using the non-negativity and boundedness of $\beta^e$ and $r^e_j$, along with the trace estimate (3.3), the last integral we can be estimated as

\[\varepsilon \int_{0}^{T} \int_{\Omega^e} \beta^e r^e_j (c^e - M_1 e^{M_2 t})^+ \, dx dt \leq \mu \int_{0}^{T} \int_{\Omega^e} (c^e - M_1 e^{M_2 t})^+ \, dx dt + \mu \int_{0}^{T} \int_{\Omega^e} \beta^e r^e_j (c^e - M_1 e^{M_2 t})^+ \, dx dt + \mu \int_{0}^{T} \int_{\Omega^e} \beta^e r^e_j (c^e - M_1 e^{M_2 t})^+ \, dx dt + \mu \int_{0}^{T} \int_{\Omega^e} \beta^e r^e_j (c^e - M_1 e^{M_2 t})^+ \, dx dt\]

for any $\delta > 0$, where the constants $\mu_1$, $\mu_2$ and $\mu_3$ depend on $\|\beta\|_{L^\infty(\Omega \times Y)}$, $\|r^e_b\|_{L^\infty(\Gamma^e)}$ and on the transformation matrices $R$ and $K$, but are independent of $\varepsilon$. Using Lipschitz continuity of $F$ and applying the Gronwall inequality yield estimate (3.2).

To show the uniqueness of a solution of the microscopic problem (2.2)–(2.3) we considering the equations for the difference of two solutions. Especially, the non-negativity of $\alpha^e$, $r^e_j$ and $c^e$ along with the boundedness of $r^e_j$ ensures

\[\|r^e_{f,1}(\tau) - r^e_{f,2}(\tau)\|_{L^2(\Gamma^e)}^2 \leq \mu \int_{0}^{T} \sum_{j=f,b} \|r^e_{j,1} - r^e_{j,2}\|_{L^2(\Gamma^e)}^2 dt + \|c^e_1 - c^e_2\|_{L^2(\Gamma^e)}^2 dt.\]
Testing the sum of the equations for $r^e_{j,1} - r^e_{j,2}$ and $r^e_{b,1} - r^e_{b,2}$ by $r^e_{j,1} + r^e_{j,2} - r^e_{b,1}$ and using the estimate from above yield

$$
\| r^e_{b,1}(\tau) - r^e_{b,2}(\tau) \|_{L^2(\Gamma^c)}^2 \leq \| r^e_{b,1}(\tau) + r^e_{j,1}(\tau) - r^e_{j,2}(\tau) \|_{L^2(\Gamma^c)}^2 + \| r^e_{j,1}(\tau) - r^e_{j,2}(\tau) \|_{L^2(\Gamma^c)}^2 \\
\leq \mu_1 \int_0^T \sum_{j=f,b} \| r^e_{j,1} - r^e_{j,2} \|_{L^2(\Gamma^c)}^2 \, dt + \mu_2 \int_0^T \| c^e_i - c^e_2 \|_{L^2(\Gamma^c)}^2 \, dt.
$$

Combining last two inequalities and applying the Gronwall inequality imply the estimates for $\| r^e_{j,1}(\tau) - r^e_{j,2}(\tau) \|_{L^2(\Gamma^c)}^2$, with $\tau \in (0, T)$ and $j = f, b$, in terms of $\| c^e_i - c^e_2 \|_{L^2(\Gamma^c)}^2$. Considering $(c^e - S)^+$ as a test function in (2.4), using the boundedness of $r^e_{j,1}$ and applying Theorem II.6.1 in [14] yield the boundedness of $c^e$ for every fixed $\varepsilon$. Then considering (2.4) for $c^e_1$ and $c^e_2$ we obtain the estimate for $\| c^e_1 - c^e_2 \|_{L^2(\Omega_{\varepsilon, T}^c)}$ and $\varepsilon^{1/2} \| c^e_1 - c^e_2 \|_{L^2(\Gamma^c)}$ in terms of $\varepsilon^{1/2} \| r^e_{j,1} - r^e_{j,2} \|_{L^2(\Gamma^c)}$, with $j = f, b$. Hence, using the estimates for $\| r^e_{j,1} - r^e_{j,2} \|_{L^2(\Gamma^c)}$ we obtain that $c^e_1 = c^e_2$ a.e. in $\Omega_{\varepsilon, T}$ and $r^e_{j,1} = r^e_{j,2}$ a.e. in $\Gamma^c_T$, where $j = f, b$.  

The assumptions on the microstructure of the non-periodic domain and the regularity of the transformation matrices $R$ and $K$ ensure the following extension result.

**Lemma 4.** For $x^e_k \in \Omega$, and $u \in W^{1,p}(Y^*_{x^e_k, K})$, with $p \in (1, \infty)$, there exists an extension $\tilde{u} \in W^{1,p}(Y^*_{x^e_k})$ from $Y^*_{x^e_k, K}$ to $Y^*_{x^e_k}$ such that

$$
\left\| \tilde{u} \right\|_{W^{1,p}(Y^*_{x^e_k})} \leq \mu \| u \|_{W^{1,p}(Y^*_{x^e_k, K})}, \quad \left\| \nabla \tilde{u} \right\|_{W^{1,p}(Y^*_{x^e_k})} \leq \mu \| \nabla u \|_{W^{1,p}(Y^*_{x^e_k, K})},
$$

where $\mu$ depends on $Y_1$, $Y_0$, $R$ and $K$ and is independent of $\varepsilon$ and $k \in \Xi_\varepsilon$. For $u \in W^{1,p}(\Omega^*_\varepsilon)$ we have an extension $\tilde{u} \in W^{1,p}(\Omega)$ from $\Omega^*_\varepsilon$ to $\Omega$ such that

$$
\left\| \tilde{u} \right\|_{W^{1,p}(\Omega)} \leq \mu \| u \|_{W^{1,p}(\Omega^*_\varepsilon)}, \quad \left\| \nabla \tilde{u} \right\|_{W^{1,p}(\Omega)} \leq \mu \| \nabla u \|_{W^{1,p}(\Omega^*_\varepsilon)},
$$

where $\mu$ depends on $Y_1$, $Y_0$, $D$ and $K$ and is independent of $\varepsilon$.

**Sketch.** The proof follows the same lines as in the periodic case [13]. The only difference is that the extension depends on the Lipschitz continuity of $K$ and $R$ and the uniform boundedness from above and below of $| \det K(x) |$ and $| \det R(x) |$ for all $x \in \overline{\Omega}$. To show (3.4) we consider first the extension from $R^e_{x^e_k}(k + Y^*_{1,K_{x^e_k}})$ into $R^e_{x^e_k}(k + Y_1)$, where $Y^*_{1,K_{x^e_k}} = Y_1 \setminus K_{x^e_k} Y_0$, and obtain the estimates in (3.4). Then scaling by $\varepsilon$ and summing up over $k \in \Xi_\varepsilon$ imply (3.5). Notice that in the definition of $\Omega^*_\varepsilon$ we consider only those $R^e_{x^e_k}(k + Y_0)$ that $R^e_{x^e_k}(k + Y_1) \subset \Omega$, and hence near $\partial \Omega$ we need to extend only in the directions parallel to $\partial \Omega$. In general we would obtain a local extension to a subdomain $\Omega^\delta = \{ x \in \Omega : \text{dist}(x, \partial \Omega) > \delta \}$ for any fixed $\delta > 0$.  

4. **Derivation of macroscopic equations.**

To derive the macroscopic equations for the microscopic problem posed in a domain with non-periodic microstructure we shall approximate it by a locally-periodic problem and apply the methods of locally-periodic two-scale convergence and $l$-$p$ unfolding operator, see Appendix for the definitions and convergence results for $l$-$t$-$s$ convergence and $l$-$p$ unfolding operator.

To define the locally-periodic microscopic structure related to the original non-periodic one, we consider, similarly to [6, 23], the partition covering of $\Omega$ by a family of open non-intersecting cubes $\{ \Omega^*_n \}_{1 \leq n \leq N_\varepsilon}$ of side $\varepsilon^r$, with $0 < r < 1$, such that

$$
\Omega \subset \bigcup_{n=1}^{N_\varepsilon} \overline{\Omega^*_n} \quad \text{and} \quad \Omega^*_n \cap \Omega \neq \emptyset.
$$
For each \( x \in \mathbb{R}^3 \) we consider a transformation matrix \( D(x) \in \mathbb{R}^{3 \times 3} \) and assume that \( D, D^{-1} \in \text{Lip}(\mathbb{R}^3; \mathbb{R}^{3 \times 3}) \) and \( 0 < D_1 \leq |\det D(x)| \leq D_2 < \infty \) for all \( x \in \overline{\Omega} \). The matrix \( D \) will be defined by the rotation matrix \( R \) and its derivatives and the specific formula of \( D \) will be given later.

The locally-periodic microstructure is defined by considering for \( x_n^\varepsilon, \tilde{x}_n^\varepsilon \in \Omega_n^\varepsilon \), arbitrary chosen fixed points, \( n = 1, \ldots, N_\varepsilon \), a covering of \( \Omega_n^\varepsilon \) by parallelepipeds \( D_{x_n}Y \)

\[
\Omega_n^\varepsilon \subset \tilde{x}_n^\varepsilon + \bigcup_{\xi \in \Xi_n^\varepsilon} \varepsilon D_{x_n^\varepsilon}(\overline{Y} + \xi), \quad \text{where } \Xi_n^\varepsilon = \{ \xi \in \mathbb{Z}^3 : \varepsilon D_{x_n^\varepsilon}(Y + \xi) \cap \Omega_n^\varepsilon \neq \emptyset \},
\]

with \( Y = (0,1)^3, D_x := D(x), D_{x_n^\varepsilon} = D(x_n^\varepsilon), \) and \( 1 \leq n \leq N_\varepsilon \).

The perforated domain with locally-periodic microstructure is given by

\[
\tilde{\Omega}_\varepsilon^* = \text{Int}(\bigcup_{n=1}^{N_\varepsilon} \Omega_n^* \cap \Omega), \quad \text{with } \Omega_n^* = \left( \tilde{x}_n^\varepsilon + \bigcup_{\xi \in \Xi_n^\varepsilon} \varepsilon D_{x_n^\varepsilon}(\overline{Y}_K^* + \xi) \right) \cap \Omega_n^\varepsilon,
\]

where \( \overline{Y}_K^* = Y \setminus \bigcup_{k \in \{0,1\}^3, \tilde{K}} \bigcup_{n=1}^{N_\varepsilon} (\tilde{K}_{x_n^\varepsilon} Y_0 + k), \) with \( \tilde{K}_{x_n^\varepsilon} = \tilde{K}(x_n^\varepsilon), \) for \( n = 1, \ldots, N_\varepsilon \), where the transformation matrix \( \tilde{K} \) will be specified later. We shall also denote

\[
\hat{\Omega}_\varepsilon^* = \tilde{x}_n^\varepsilon + \text{Int}\left( \bigcup_{\xi \in \Xi_n^\varepsilon} \varepsilon D_{x_n^\varepsilon}(\overline{Y} + \xi) \right), \quad \Lambda_n^\varepsilon = \hat{\Omega}_\varepsilon^* \setminus \bigcup_{n=1}^{N_\varepsilon} \hat{\Omega}_n^\varepsilon,
\]

where \( \hat{\Xi}_n^\varepsilon = \{ \xi \in \Xi_n^\varepsilon : \varepsilon D_{x_n^\varepsilon}(Y + \xi) \subset (\Omega_n^\varepsilon \cap \Omega) \} \). The boundaries of the locally-periodic microstructure are defined as

\[
\tilde{\Gamma}_n^\varepsilon = \bigcup_{n=1}^{N_\varepsilon} \Gamma_n^\varepsilon \cap \Omega, \quad \text{where } \Gamma_n^\varepsilon = \left( \tilde{x}_n^\varepsilon + \bigcup_{\xi \in \Xi_n^\varepsilon} \varepsilon D_{x_n^\varepsilon}(\overline{\tilde{\Gamma}_{x_n^\varepsilon}^*, K} + \xi) \right) \cap \Omega_n^\varepsilon,
\]

and

\[
\tilde{\Gamma}_n^\varepsilon = \bigcup_{n=1}^{N_\varepsilon} \left( \tilde{x}_n^\varepsilon + \bigcup_{\xi \in \Xi_n^\varepsilon} \varepsilon D_{x_n^\varepsilon}(\overline{\tilde{\Gamma}_{x_n^\varepsilon}^*, K} + \xi) \right),
\]

where \( \tilde{\Gamma}_{x_n^\varepsilon, K} = \tilde{K}_{x_n^\varepsilon} \Gamma \) and \( \Gamma = \partial Y_0 \). For the problem analysed here we shall consider \( \tilde{x}_n^\varepsilon = x_n^\varepsilon \).

The following calculations illustrate the motivation for the locally-periodic approximation and determine formulas for the transformation matrices \( D \) and \( \tilde{K} \). For \( n = 1, \ldots, N_\varepsilon \) we choose such \( \kappa_n \in \mathbb{Z}^3 \) that for \( x_n^\varepsilon = R_{\kappa_n} \varepsilon \kappa_n \) we have \( x_n^\varepsilon \in \Omega_n^\varepsilon \). In the definition of covering of \( \Omega_n^\varepsilon \) by shifted parallelepipeds we consider a numbering of \( \xi \in \Xi_n^\varepsilon \) and write

\[
\Omega_n^\varepsilon \subset x_n^\varepsilon + \bigcup_{j=1}^{I_n^\varepsilon} \varepsilon D_{x_n^\varepsilon}(Y + \xi_j) \quad \text{for} \quad \xi_j \in \Xi_n^\varepsilon.
\]

Then for \( 1 \leq j \leq I_n^\varepsilon \) we consider \( k_j^n = \kappa_n + \xi_j \) and \( x_n^\varepsilon = R_{k_j^n} \varepsilon k_j^n \).

Using the regularity assumptions on the function \( \gamma \), determining the macroscopic changes of the rotation angle, and considering the Taylor expansion for \( R^{-1} \) around \( x_{\kappa_n} \), i.e. around \( \varepsilon \kappa_n 3 \), we obtain

\[
R_{k_j^n}^{-1}(x - x_{k_j^n}) = R_{k_j^n}^{-1} x - \varepsilon k_j^n = R_{\kappa_n}^{-1} x
\]

\[
+ (R_{\kappa_n}^{-1} + (R_{\kappa_n}^{-1})' (x - x_{\kappa_n}) \varepsilon + (R_{\kappa_n}^{-1})' (x - x_{\kappa_n}) \varepsilon \xi_{j,3} \varepsilon + b(|\xi_{j,3} \varepsilon|^2) x - \varepsilon (\kappa_n + \xi_j))
\]

\[
= R_{\kappa_n}^{-1} x - \varepsilon x_{\kappa_n} - \tilde{W}_{x_{\kappa_n}} \varepsilon \xi_j + (R_{\kappa_n}^{-1})' (x - x_{\kappa_n}) \varepsilon \xi_{j,3} \varepsilon + b(|\xi_{j,3} \varepsilon|^2) x,
\]

where \( \tilde{W}_{x_{\kappa_n}} = \tilde{W}(x_{\kappa_n}) \) with \( \tilde{W}(x) = (I - \nabla R^{-1}(\gamma(x_3))) x \). The notation of the gradient is understood as \( \nabla R^{-1}(\gamma(x)) = \nabla_x (R^{-1}(\gamma(x)) x) |_{x=x} \). Thus for \( x \in \Omega_n^\varepsilon \) the distance between \( R_{\kappa_n}^{-1}(x - x_{\kappa_n}) - \tilde{W}_{x_{\kappa_n}} \varepsilon \xi_j \varepsilon \) and \( R_{k_j^n}^{-1}(x - x_{k_j^n}) \) is of the order \( \sup_{1 \leq j \leq I_n^\varepsilon} |\xi_j \varepsilon|^2 \sim \varepsilon^{2r} \).
This calculations together with the estimates below will show that the non-periodic plywood-like microstructure can by approximated by locally-periodic one, comprising $\tilde{Y}_x^{e}$-periodic structure in each $\Omega_n^e$ of side $\varepsilon^r$, $n = 1, \ldots, N_\varepsilon$, with an appropriately chosen $r \in (0, 1)$.

Here $\tilde{Y}_x = D(x)Y$ and $\tilde{\Gamma}_x = D(x)\tilde{K}(x)\Gamma = R_x K(x)\Gamma$, with $R_x = R(\gamma(x_3))$, $D(x) = R_x W(x)$, $\tilde{K}(x) = W^{-1}(x)K(x)$, and

\[
W(x) = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & w(x) \\ 0 & 0 & 1 \end{pmatrix},
\]

where $w(x) = \gamma'(x_3)(\cos(\gamma(x_3))x_1 + \sin(\gamma(x_3))x_2)$.

The definitions of $R$, $W$ and $\gamma$ ensure that the transformation matrices $D$ and $\tilde{K}$ are Lipschitz continuous and $0 < d_0 \leq |\det D(x)| \leq d_1 < \infty$, $0 < \rho_0 \leq |\det \tilde{K}(x)| \leq \rho_1 < 0$, for all $x \in \overline{\Omega}$. Since $\gamma$ is independent of the first variable, we consider in $W(x)$ the shift only for the second variable. Notice that if the microscopic structure would be locally-periodic, then the matrix $R$ would be constant in each $\Omega_n^e$ and we would obtain $D(x) = R_x$.

In the estimates for the approximation of the non-periodic problem by locally-periodic we shall use Lemma, proven in [4], facilitating the estimate for the difference between the values of the characteristic function at two different points.

**Lemma 5** ([4]). For the characteristic function of a fibre system yields

\[
||\vartheta_r(x + \tau) - \vartheta_r(x)||^2_{L^2(\Omega)} \leq CrL|\tau|,
\]

where $L$ is the length and $r$ is the radius of fibres.

We obtain the following macroscopic equations for the microscopic problem (2.2)–(2.3).

**Theorem 6.** A sequence of solutions of the microscopic model (2.2)–(2.3) converges to a solution $c \in L^2(0, T; H^1(\Omega)) \cap H^1(0, T; L^2(\Omega))$ and $r_j \in H^1(0, T; L^2(\Omega; L^2(\Gamma_x)))$ of the macroscopic equations

\[
\left. \begin{array}{ll}
\begin{align*}
\theta(x)\partial_t c - \text{div}(A(x)\nabla c) &= \theta(x)F(c) + \frac{1}{|Y_x|} \int_{\tilde{\Gamma}_x} [\tilde{\beta}(x, y)r_b - \tilde{\alpha}(x, y)r_f c] d\sigma_y, \\
A(x)\nabla c \cdot n &= 0 \quad \text{on } \partial \Omega \times (0, T), \\
\partial_t r_f &= p(r_b) - \tilde{\alpha}(x, y)r_f c + \tilde{\beta}(x, y)r_b - df r_f, \\
\partial_t r_b &= \tilde{\alpha}(x, y)r_f c - \tilde{\beta}(x, y)r_b - db r_b,
\end{align*}
\end{array} \right\}
\]

for $(t, x) \in (0, T) \times \Omega$ and $y \in \tilde{\Gamma}_x$, where the macroscopic diffusion coefficient $A$ is defined as

\[
A_{ij}(x) = \frac{1}{|Y_x|} \int_{\tilde{Y}_x^{e,K}} (A_{ij} + A_{ik}\partial_y w^j(x, y))dy,
\]

with $w^j$, for $j = 1, 2, 3$, are solutions of the unit cell problems

\[
\begin{array}{ll}
\text{div}(A(\nabla y w^j + e_j)) = 0 & \text{in } \tilde{Y}_x^{e,K}, \\
A(\nabla y w^j + e_j) \cdot n = 0 & \text{on } \tilde{\Gamma}_x, \quad w^j \text{ - } \tilde{Y}_x \text{ - periodic.}
\end{array}
\]

Here

\[
\tilde{Y}_x^{e,K} = D_x(Y \setminus \bigcup_{k \in \{0, 1\}^3} (\tilde{K}_x Y_0 + k)), \quad \tilde{Y}_x = D_x Y,
\]

\[
\tilde{\Gamma}_x = \bigcup_{k \in \{0, 1\}^3} D_x(\tilde{K}_x \Gamma + k) \cap \tilde{Y}_x, \quad \theta(x) = \frac{|\tilde{Y}_x^{e,K}|}{|Y_x|},
\]
where \( Y = (0,1)^3 \), \( R_x = R(\gamma(x_3)) \), \( D_x = R_x W_x \), \( \tilde{K}_x = W_x^{-1} K_x \), with \( W_x = W(x) \) defined by (4.2), and

\[
\tilde{\alpha}(x,y) = \sum_{k \in \mathbb{Z}^3} \alpha(x, R_x^{-1}(y - D_x k)), \quad \tilde{\beta}(x,y) = \sum_{k \in \mathbb{Z}^3} \beta(x, R_x^{-1}(y - D_x k)).
\]

**Proof.** To derive macroscopic equations for the microscopic problem posed in a domain with non-periodic microstructure we shall approximate it by equations posed in a domain with locally-periodic microstructure and then apply methods of locally-periodic homogenization.

Using calculations from above we consider a domain with a locally-periodic microstructure characterised by the periodicity cell \( \tilde{Y}_\varepsilon = D_{x_n^\varepsilon} Y \) in each \( \tilde{\Omega}_n^\varepsilon \), with \( n = 1, \ldots, N_\varepsilon \). We consider the shift \( x_n^\varepsilon \) in the covering of \( \tilde{\Omega}_n^\varepsilon \) by \( D_{x_n^\varepsilon}(Y + \xi) \), with \( \xi \in \Xi_\varepsilon \).

Then the characteristic function of the inter-cellular space \( \tilde{\Omega}_n^\varepsilon \) in a tissue with the locally-periodic plywood-like microstructure is defined by \( \chi_{\tilde{\Omega}_n^\varepsilon} = (1 - \chi_{\tilde{\Omega}_f^\varepsilon}) \chi_\Omega \), where \( \chi_{\tilde{\Omega}_f^\varepsilon} \) denotes the characteristic function of fibres

\[
\chi_{\tilde{\Omega}_f^\varepsilon} = \sum_{n=1}^{N_\varepsilon} \chi_{\tilde{\Omega}_{n,f}^\varepsilon}, \quad \chi_{\tilde{\Omega}_{n,f}^\varepsilon} = \sum_{\xi \in \Xi_\varepsilon} \theta(x_n^\varepsilon, R_x^{-1}(x - x_n^\varepsilon - \varepsilon D_x^\varepsilon \xi)/\varepsilon) \chi_{\Omega_n^\varepsilon}.
\]

The boundaries of the locally-periodic microstructure are denoted by

\[
\tilde{\Gamma}^\varepsilon = \bigcup_{n=1}^{N_\varepsilon} \bigcup_{\xi \in \Xi_\varepsilon} (x_n^\varepsilon + \varepsilon R_x^\varepsilon K_x^\varepsilon \Gamma + \varepsilon D_x^\varepsilon \xi) \cap \Omega.
\]

Notice that non-periodic changed in the shape of the perforations can be approximated locally-periodic by the same function. This is consistent with the results obtained in [8, 9, 18, 21]. However spatial changes in the periodicity are approximated with a different spatially-dependent periodicity in the locally-periodic microstructure.

We define the reaction rates in term of locally-periodic microstructure

\[
\bar{\alpha}^\varepsilon(x) = \sum_{n=1}^{N_\varepsilon} \sum_{\xi \in \Xi_\varepsilon} \alpha(x, (R_x^{-1}(x - x_n^\varepsilon) - W_x^\varepsilon \varepsilon \xi)/\varepsilon) \chi_{\Omega_n^\varepsilon},
\]

\[
\bar{\beta}^\varepsilon(x) = \sum_{n=1}^{N_\varepsilon} \sum_{\xi \in \Xi_\varepsilon} \beta(x, (R_x^{-1}(x - x_n^\varepsilon) - W_x^\varepsilon \varepsilon \xi)/\varepsilon) \chi_{\Omega_n^\varepsilon}.
\]

To show that we can approximate the problem (2.2)-(2.3) considered in the tissue with the non-periodic microstructure by a locally-periodic one, we have to prove that the difference between the characteristic function of the original domain with non-periodic microstructure \( \chi_{\Omega_f^\varepsilon} \) and of the locally-periodic perforated domain \( \chi_{\tilde{\Omega}_f^\varepsilon} \) converges to zero strongly in \( L^2(\Omega) \) as \( \varepsilon \to 0 \). Also we have to show that the difference between boundary integrals and their locally-periodic approximations converges to zero as \( \varepsilon \to 0 \). This will ensure that as \( \varepsilon \) the sequence of solutions of the microscopic non-periodic problem will converge to a solution of the same macroscopic equations as the sequence of solutions of the locally-periodic microscopic problem. Then applying the techniques of locally-periodic homogenization, i.e. \( 1-t-s \) convergence and \( 1-p \) unfolding operator to the microscopic equations posed in the perforated domain with locally-periodic microstructure we derive the macroscopic equations for the original non-periodic problem.
For the difference between two characteristic functions we have
\[
\int_{\Omega} |\chi_{\Omega^\varepsilon} - \chi_{\Omega^\varepsilon}|^2 \, dx = I_1 + I_2 \\
= \sum_{n=1}^{N_\varepsilon} \int_{\Omega^\varepsilon_n} \sum_{j \in J^\varepsilon_n} \left| \partial (x^\varepsilon_{k_j} (R_{x^\varepsilon_{k_j}}^{-1} (x - x^\varepsilon_{k_j}) / \varepsilon) - \partial (x^\varepsilon_n R_{x^\varepsilon_{k_j}}^{-1} (x - x^\varepsilon_{k_j}) / \varepsilon) \right|^2 \, dx \\
+ \sum_{n=1}^{N_\varepsilon} \int_{\Omega^\varepsilon_n} \sum_{j \in J^\varepsilon_n} \left| \partial (x^\varepsilon_n R_{x^\varepsilon_{k_j}}^{-1} (x - x^\varepsilon_{k_j}) / \varepsilon) - \partial (x^\varepsilon_n (R_{x^\varepsilon_{k_j}}^{-1} (x - x^\varepsilon_{k_j}) - \varepsilon W_{x^\varepsilon_{k_j}}) / \varepsilon) \right|^2 \, dx,
\]
where \( x^\varepsilon_{k_j} = R_{x^\varepsilon_{k_j}} \varepsilon_{k_j}, \) with \( k_j = \kappa_n + j, \) \( x^\varepsilon_n = R_{x^\varepsilon_{k_j}} \varepsilon_{k_n}, \) and
\[
J^\varepsilon_n = \{ j \in \mathbb{Z}^3 : [(x^\varepsilon_{k_j} + \varepsilon R_{x^\varepsilon_{k_j}} Y_1) \cup (x^\varepsilon_n + \varepsilon R_{x^\varepsilon_{k_j}} Y_1 + \varepsilon D_{x^\varepsilon_{k_j}}) \cap \Omega^\varepsilon_n \neq \emptyset \}.
\]
We notice that \( \varepsilon^3 |J^\varepsilon_n| \leq C \varepsilon^{3r} \) and \( |N_{\varepsilon}| \leq C \varepsilon^{-3r} \). For the first integral we have
\[
\mathcal{I}_1 \leq \sum_{n=1}^{N_\varepsilon} \varepsilon^3 |J^\varepsilon_n| \sup_{j \in J^\varepsilon_n} |x^\varepsilon_n - x^\varepsilon_{k_j}| \leq C \varepsilon^r.
\]
To estimate the second term we use Lemma [5]. Since in each \( \Omega^\varepsilon_n \) the length of fibres is of order \( \varepsilon^r \), applying estimate in Lemma [5] equality \([4,1]\), and the estimates \( N_{\varepsilon} \leq C \varepsilon^{-3r} \) and \( |J^\varepsilon_n| \leq C \varepsilon^{3(r-1)} \) we conclude that
\[
\mathcal{I}_2 \leq C \varepsilon^3 \varepsilon^{-2r - 3}.
\]
Thus for \( r \in (2/3, 1) \) we have \( \mathcal{I}_1 \to 0 \) and \( \mathcal{I}_2 \to 0 \) as \( \varepsilon \to 0 \).

To estimate the difference between boundary integral we have to extend \( \varepsilon^\omega \) and \( r^\varepsilon_j \), with \( j = f, b \) from \( \Omega^\varepsilon \) to \( \Omega \). For \( \varepsilon^\omega \) we can consider the extension as in Lemma [4]. Then using the extended \( \varepsilon^\omega \) and the fact that the reaction rates and the initial data are defined on whole \( \Omega \) we can extend \( r^\varepsilon_f \) and \( r^\varepsilon_b \) to \( \Omega \) by considering solutions of ordinary differential equations with \( \varepsilon^\omega \) instead of \( \varepsilon^\omega \)

\[
\begin{align*}
\partial_t \tilde{r}^\varepsilon_f &= p(\tilde{r}^\varepsilon_f) - \alpha^\varepsilon (x, \tilde{r}^\varepsilon_f) \tilde{r}^\varepsilon_f - \beta^\varepsilon (x) \tilde{r}^\varepsilon_f - d_f \tilde{r}^\varepsilon_f \quad \text{in } (0, T) \times \Omega, \\
\partial_t \tilde{r}^\varepsilon_b &= \alpha^\varepsilon (x, \tilde{r}^\varepsilon_f) \tilde{r}^\varepsilon_f - \beta^\varepsilon (x, \tilde{r}^\varepsilon_f) \tilde{r}^\varepsilon_b - d_b \tilde{r}^\varepsilon_f \quad \text{in } (0, T) \times \Omega, \\
\tilde{r}^\varepsilon_f (0, x) &= r^\varepsilon_{f0} (x), \quad \tilde{r}^\varepsilon_b (0, x) = r^\varepsilon_{b0} (x) \quad \text{in } \Omega.
\end{align*}
\]

The non-negativity of \( \varepsilon^\omega \) and the construction of the extension ensure that \( \varepsilon^\omega \) is non-negative. Then in the same way as for \( r^\varepsilon_j \), using the properties of \( p \) and the non-negativity of the coefficients and initial data we obtain the non-negativity of \( \tilde{r}^\varepsilon_j \). Thus adding the equations for \( \tilde{r}^\varepsilon_f \) and \( \tilde{r}^\varepsilon_b \) we obtain the boundedness of \( \tilde{r}^\varepsilon_j \) in \( \Omega_T \), i.e.

\[
\| \tilde{r}^\varepsilon_f \|_{L^\infty(\Omega_T)} + \| \tilde{r}^\varepsilon_b \|_{L^\infty(\Omega_T)} \leq C.
\]

Differentiating equations in \([4,5]\) with respect to \( x \) and using the estimate \( \| \nabla \tilde{r}^\varepsilon_b \|_{L^2(\Omega)} \leq \| \nabla \tilde{r}^\varepsilon_f + \nabla \tilde{r}^\varepsilon_f \|_{L^2(\Omega)} + \| \nabla \tilde{r}^\varepsilon_f \|_{L^2(\Omega)} \) we obtain

\[
\| \nabla \tilde{r}^\varepsilon_j \|_{L^\infty(0, T; L^2(\Omega))} \leq \mu_1 \| \nabla \tilde{r}^\varepsilon_j \|_{L^2(\Omega_T)} + \varepsilon^{-1} |\mu_2| \| \tilde{r}^\varepsilon_j \|_{L^2(\Omega_T)}
\]
\[
+ \varepsilon^{-1} |\mu_3| [ \| \tilde{r}^\varepsilon_f \|_{L^\infty(\Omega_T)} + \| \tilde{r}^\varepsilon_b \|_{L^\infty(\Omega_T)} ] \leq \mu_4 (1 + 1 / \varepsilon),
\]
where the constants \( \mu_j \), with \( j = 2, 3, 4 \), depend on the derivatives of \( \alpha, \beta, \mu_j \), with \( j = 1, 2, 3, 4 \), are independent of \( \varepsilon \). Hence the extensions \( \tilde{r}^\varepsilon_j \) and \( \tilde{r}^\varepsilon \) are well-defined on the boundaries \( \Gamma_{\varepsilon} \) of the locally-periodic microstructure. In what follows we shall use the same notation for a function and for its extension. Notice that \( \varepsilon^{-1} \) in the estimates for \( \nabla r^\varepsilon \) will be compensated by \( \varepsilon \) in the estimate for the difference between neighbouring points in periodic and locally-periodic domains, respectively, i.e.

\[
|\varepsilon R_{x^\varepsilon_{k_j}} K_{x^\varepsilon_{k_j}} y - \varepsilon R_{x^\varepsilon_n} K_{x^\varepsilon_n} y| \leq C \varepsilon^{1+r} (1 + \gamma') L^\infty(\Omega) (1 + \| \nabla K \|_{L^\infty(\Omega)}).
\]
we have
\[
\varepsilon \left| \int_{\Gamma^\varepsilon} \alpha^\varepsilon r^\varepsilon f r^\varepsilon \psi \, d\sigma^\varepsilon_x - \int_{\Gamma^\varepsilon} \bar{\alpha}^\varepsilon r^\varepsilon f c^\varepsilon \psi \, d\sigma^\varepsilon_x \right| = I_3 + I_4
\]
\[
= \varepsilon \sum_{n=1}^{N_\varepsilon} \sum_{j \in J_n^\varepsilon} \left| \int_{\varepsilon K_{x_n^j}^\varepsilon x_n^j + x_n^j} \alpha^\varepsilon r^\varepsilon f \bar{c}^\varepsilon \psi \, d\sigma^\varepsilon_x - \int_{\varepsilon K_{x_n^j}^\varepsilon x_n^j + x_n^j} \alpha^\varepsilon r^\varepsilon f c^\varepsilon \psi \, d\sigma^\varepsilon_x \right|
\]
\[
+ \varepsilon \sum_{n=1}^{N_\varepsilon} \sum_{j \in J_n^\varepsilon} \left| \int_{\varepsilon K_{x_n^j}^\varepsilon x_n^j + x_n^j} \alpha^\varepsilon r^\varepsilon f c^\varepsilon \psi \, d\sigma^\varepsilon_x - \int_{\varepsilon K_{x_n^j}^\varepsilon x_n^j + x_n^j + \varepsilon D_{x_n^j}} \bar{\alpha}^\varepsilon r^\varepsilon f c^\varepsilon \psi \, d\sigma^\varepsilon_x \right|
\]
for \( \psi \in C^\infty(\overline{\Omega_T}) \), where \( K^R(x) = R(x)K(x) \). Considering the regularity of \( K \) and \( R \) and the uniform boundedness from below and above of \( |\det K| \), and using the trace estimate for the \( L^2(\Gamma) \)-norm of a \( H^s(Y) \)-function, with \( \varsigma \in (1/2, 1) \), the first integral can we estimate as
\[
I_3 \leq C_1 \varepsilon^d \sum_{n=1}^{N_\varepsilon} \sum_{j \in J_n^\varepsilon} \left| \int_{\Gamma^\varepsilon} \left| \alpha^\varepsilon r^\varepsilon f(t, y_n^j) \bar{c}^\varepsilon(t, y_n^j) - \alpha^\varepsilon r^\varepsilon f(t, y_n^j) c^\varepsilon(t, y_n^j) \right| \, ds \right|
\]
\[
+ C_2 \varepsilon^r \leq C_3 \left[ \frac{d + d}{2} \sum_{n=1}^{N_\varepsilon} \sum_{j \in J_n^\varepsilon} \left| \int_{T^\varepsilon} \left| c^\varepsilon(t, y_n^j) - \alpha^\varepsilon(y_n^j) \right|^2 \right| \right]^{\frac{1}{2}}
\]
\[
+ C_4 \varepsilon^d \sum_{n=1}^{N_\varepsilon} \sum_{j \in J_n^\varepsilon} \left| \int_{\Gamma^\varepsilon} \left| r^\varepsilon f(t, y_n^j) - r^\varepsilon f(t, y_n^j) \right|^2 \right| \, ds \leq C_5 \varepsilon^r,
\]
where \( d = \dim(\Omega) = 3 \) and \( \Gamma_n^\varepsilon \ni x_n^j + \varepsilon R_{x_n^j} \Gamma = x_n^j + \varepsilon R(y_n^j)K(x_n^j) \Gamma \), with \( j \in J_n^\varepsilon \) and \( n = 1, \ldots, N_\varepsilon \).

Here we used the short notations \( y_n^j = x_n^j + \varepsilon R_{x_n^j} y_n^j \) and \( x_n^j = x_n^j + \varepsilon R_{x_n^j} y_n^j \), respectively. Using the regularity of \( \gamma, K, \) and \( \alpha \), and applying a priori estimates for \( c^\varepsilon \) and \( r^\varepsilon f \), together with (4.6), we obtain for \( 0 < \varsigma < 1/2 \), with \( \varsigma + \varsigma_1 = 1 \),
\[
\int_0^T I_3 \, dt \leq \mu_1 \sum_{n=1}^{N_\varepsilon} \sum_{j \in J_n^\varepsilon} \left| \int_0^T \left( \| \nabla r^\varepsilon f \|_{L^2(Y_n^j)} + \| \nabla c^\varepsilon \|_{L^2(Y_n^j)} + \| \nabla \alpha^\varepsilon \|_{C(Y_n^j)} \right) \, dt \right|
\]
\[
\times \left( \sup_{j \in J_n^\varepsilon} \left| x_n^j - x_n^j \right| + \sup_{j \in J_n^\varepsilon} \left| x_n^j - x_n^j \right| \right) + \mu_1 \varepsilon^r \leq \mu_1 \varepsilon^{\varsigma \varsigma_1},
\]
where \( Y_n^j = x_n^j + \varepsilon R_{x_n^j} Y_n^j \). Combining the estimates for \( I_3 \) and \( I_4 \) we conclude that for \( r > 1/2 \) the difference between the boundary integrals for non-periodic and locally-periodic...
microstructures converges to zero as $\varepsilon \to 0$. In a similar way we obtain the estimates for other boundary integrals.

We rewrite the weak formulation of the microscopic equations as

$$
\langle \partial_t c^\varepsilon - F(c^\varepsilon), \phi \chi_{\Omega^\varepsilon} \rangle_{\Omega^T} + \langle A \nabla c^\varepsilon, \nabla \phi \chi_{\Omega^\varepsilon} \rangle_{\Omega^T} - \varepsilon \langle \beta^\varepsilon r_b^\varepsilon - \alpha^\varepsilon c^\varepsilon r_f^\varepsilon, \phi \rangle_{\Gamma_T^T}
= \left[ \langle \partial_t c^\varepsilon - F(c^\varepsilon), \phi \chi_{\Omega^\varepsilon} \rangle_{\Omega^T} + \langle A \nabla c^\varepsilon, \nabla \phi \chi_{\Omega^\varepsilon} \rangle_{\Omega^T} - \varepsilon \langle \beta^\varepsilon r_b^\varepsilon - \alpha^\varepsilon c^\varepsilon r_f^\varepsilon, \phi \rangle_{\Gamma_T^T} \right]
+ \left[ \langle \partial_t c^\varepsilon - F(c^\varepsilon), \phi (\chi_{\Omega^\varepsilon} - \chi_{\Omega^\varepsilon}) \rangle_{\Omega^T} + \langle A \nabla c^\varepsilon, \nabla \phi (\chi_{\Omega^\varepsilon} - \chi_{\Omega^\varepsilon}) \rangle_{\Omega^T} \right]
- \varepsilon \left[ \langle \beta^\varepsilon r_b^\varepsilon - \alpha^\varepsilon c^\varepsilon r_f^\varepsilon, \phi \rangle_{\Gamma_T^T} - \langle \beta^\varepsilon r_b^\varepsilon - \alpha^\varepsilon c^\varepsilon r_f^\varepsilon, \phi \rangle_{\Gamma_T^T} \right] = I_1 + I_2 + I_3.
$$

for $\phi \in C^\infty(\overline{\Omega_T})$. Due to the estimates for $I_1$, $I_2$, $I_3$, and $I_4$, shown above, we have that $I_2 \to 0$ and $I_3 \to \varepsilon \to 0$. Thus we obtain

$$
\lim_{\varepsilon \to 0} \left[ \langle \partial_t c^\varepsilon - F(c^\varepsilon), \phi \chi_{\Omega^\varepsilon} \rangle_{\Omega^T} + \langle A \nabla c^\varepsilon, \nabla \phi \chi_{\Omega^\varepsilon} \rangle_{\Omega^T} - \varepsilon \langle \beta^\varepsilon r_b^\varepsilon - \alpha^\varepsilon c^\varepsilon r_f^\varepsilon, \phi \rangle_{\Gamma_T^T} \right] = \lim_{\varepsilon \to 0} \left[ \langle \partial_t c^\varepsilon - F(c^\varepsilon), \phi \chi_{\Omega^\varepsilon} \rangle_{\Omega^T} + \langle A \nabla c^\varepsilon, \nabla \phi \chi_{\Omega^\varepsilon} \rangle_{\Omega^T} - \varepsilon \langle \beta^\varepsilon r_b^\varepsilon - \alpha^\varepsilon c^\varepsilon r_f^\varepsilon, \phi \rangle_{\Gamma_T^T} \right]
$$

The definition of $\tilde{\Omega}^\varepsilon$, $\tilde{\Gamma}^\varepsilon$, $\tilde{\alpha}^\varepsilon$, and $\tilde{\beta}^\varepsilon$ implies that the original non-periodic problem is approximated by equations posed in a domain with locally-periodic microstructure. Hence we can apply the locally-periodic two-scale convergence (l-t-s) and the l-p unfolding operator method to derive the limit equations.

The coefficients $\tilde{A}^\varepsilon$, $\tilde{\alpha}^\varepsilon$, $\tilde{\beta}^\varepsilon$ can be defined as locally-periodic approximations

$$
A_{\chi_{\tilde{\Omega}^\varepsilon}} = L_0(\tilde{A}), \quad \tilde{\alpha}^\varepsilon = L_0(\tilde{\alpha}), \quad \tilde{\beta}^\varepsilon = L_0(\tilde{\beta}) \quad \text{with} \quad \tilde{x}_n = x_n^\varepsilon,
$$

where $\tilde{A}(x, y) = A(1 - \tilde{\vartheta}(x, y))$ and $\tilde{\vartheta}(x, y) = \sum_{k \in \mathbb{Z}^3} \vartheta(x, R^{-1}(x)(y - D_x k))$, and $\tilde{\alpha}, \tilde{\beta}$ are given by [4.3] (see Appendix for the definition of locally-periodic approximation $L_0^\varepsilon$). The regularity assumptions on $\alpha, \beta, K,$ and $R$ ensure that $\tilde{A} \in L^\infty(\bigcup_{x \in \Omega} \{x\} \times \tilde{Y}_x)$, $\tilde{A} \in C(\overline{\Omega}; L^p_{\text{per}}(\tilde{Y}_x))$, for $1 \leq p < \infty$, and $\tilde{\alpha}, \tilde{\beta} \in C(\overline{\Omega}; C_{\text{per}}(\overline{\tilde{Y}_x}))$.

Using the extension of $c^\varepsilon$ we have that the sequences $\{c^\varepsilon\}, \{\nabla c^\varepsilon\}$ and $\{\partial_t c^\varepsilon\}$ are defined on $\Omega_T$ and we can determine $T_{\tilde{E}}(c^\varepsilon), T_{\tilde{E}}(\nabla c^\varepsilon), \partial_t T_{\tilde{E}}(c^\varepsilon), \text{and} T_{\tilde{E}}^{\varepsilon,b}(c^\varepsilon)$. The properties of $T_{\tilde{E}}$ and $T_{\tilde{E}}^{\varepsilon,b}$ together with the estimates ensure

$$
\|T_{\tilde{E}}(c^\varepsilon)\|_{L^2(\Omega_T \times Y)} + \|T_{\tilde{E}}(\nabla c^\varepsilon)\|_{L^2(\Omega_T \times Y)} + \|\partial_t T_{\tilde{E}}(c^\varepsilon)\|_{L^2(\Omega_T \times Y)} \leq C,
\|T_{\tilde{E}}^{\varepsilon,b}(c^\varepsilon)\|_{L^2(\Omega_T \times \Gamma)} + \sum_{j=f,b} \|T_{\tilde{E}}^{\varepsilon,b}(r_j^\varepsilon)\|_{H^1(\Omega; L^2(\Omega \times \Gamma))} \leq C.
$$

Then, the convergence results for l-s-t convergence and l-p unfolding operator, see [23, 24] or Appendix, imply that there exist subsequences (denoted again by $c^\varepsilon, r_j^\varepsilon$ and $r_j^\varepsilon$) and the functions $c \in L^2(0, T; H^1(\Omega))$, $\partial_t c \in L^2(\Omega_T), c_1 \in L^2(\Omega_T; H^1_{\text{per}}(\tilde{Y}_x)), r_j \in H^1(0, T; L^2(\Omega; L^2(\tilde{\Gamma}_x)))$ such that

(4.7)

$$
\begin{align*}
T_{\tilde{E}}(c^\varepsilon) &\to c & \text{strongly in} & L^2(\Omega_T; H^1(\Gamma)),\\
\partial_t T_{\tilde{E}}(c^\varepsilon) &\to \partial_t c & \text{weakly in} & L^2(\Omega_T \times Y),\\
T_{\tilde{E}}(\nabla c^\varepsilon) &\to \nabla c + D_x^{-T} \nabla \vartheta \varphi c_1(\cdot, D_x \cdot) & \text{weakly in} & L^2(\Omega_T \times Y),\\
T_{\tilde{E}}^{\varepsilon,b}(c^\varepsilon) &\to c & \text{strongly in} & L^2(\Omega_T; L^2(\Gamma)),\\
r_j^\varepsilon &\to r_j, & \partial_t r_j^\varepsilon \to \partial_t r_j & \text{l-s-t,} & r_j, \partial_t r_j \in L^2(\Omega_T; L^2(\tilde{\Gamma}_x)),\\
T_{\tilde{E}}^{\varepsilon,b}(r_j^\varepsilon) &\to r_j(\cdot, \cdot, D_x \tilde{K}_x), & \text{weakly in} & L^2(\Omega_T \times \Gamma),\\
\partial_t T_{\tilde{E}}^{\varepsilon,b}(r_j^\varepsilon) &\to \partial_t r_j(\cdot, \cdot, D_x \tilde{K}_x), & \text{weakly in} & L^2(\Omega_T \times \Gamma), & j = f, b.
\end{align*}
$$

Considering $\psi^\varepsilon(x) = \psi_1(x) + \varepsilon L^\varepsilon_0(\psi_2)(x)$ with $\psi_1 \in C^1(\overline{\Omega})$ and $\psi_2 \in C^0(\Omega; C^1_{\text{per}}(\tilde{Y}_x))$ as a test function in (2.4) (see Appendix for the definition of $L^\varepsilon_0$) and applying l-p unfolding operator and l-p boundary
unfolding operator imply
\[ \langle \mathcal{T}_L^\varepsilon(\chi_{\tilde{\Omega}_x}^\varepsilon), D \mathcal{T}_L^\varepsilon(c^\varepsilon) \rangle_{\Omega_T \times Y} + \langle \mathcal{T}_L^\varepsilon(A \chi_{\tilde{\Omega}_x}^\varepsilon), D \mathcal{T}_L^\varepsilon(\nabla c^\varepsilon) \rangle_{\Omega_T \times Y} = \langle \mathcal{T}_L^\varepsilon(\chi_{\tilde{\Omega}_x}^\varepsilon), D \mathcal{T}_L^\varepsilon(\nabla \psi^\varepsilon) \rangle_{\Omega_T \times Y} \]
\[ + \left( \sum_{n=1}^{N_x} \frac{\sqrt{g|Y_{x_n}|}}{\sqrt{g}} \right) \left[ \mathcal{T}_L^{b,\varepsilon}(\beta^\varepsilon r^\varepsilon_h) - \mathcal{T}_L^{b,\varepsilon}(\alpha^\varepsilon) \mathcal{T}_L^{b,\varepsilon}(c^\varepsilon) \mathcal{T}_L^{b,\varepsilon}(r^\varepsilon_f) \right] \chi_{\tilde{\Omega}_x}^\varepsilon, \mathcal{T}_L^{b,\varepsilon}(\psi^\varepsilon) \rightangle_{\Omega_T \times \Gamma} \]
\[ - \langle D \psi^\varepsilon, \psi^\varepsilon \rangle_{\Lambda^*_T, T} - \langle A \nabla c^\varepsilon, \nabla \psi^\varepsilon \rangle_{\Lambda^*_T, T} + \langle F(c^\varepsilon), \psi^\varepsilon \rangle_{\Lambda^*_T, T} \]
where \( \chi_{\tilde{\Omega}_x}^\varepsilon = \mathcal{L}^\varepsilon(\chi_{\tilde{\Omega}_x}^\varepsilon) \) and \( \chi_{\tilde{\Omega}_x}^\varepsilon \) is the characteristic function of \( \tilde{\Omega}_x \)-periodically extended \( \tilde{\Omega}_x \) to \( \mathbb{R}^3 \).

Applying the results shown in [23] implies \( \mathcal{T}_L^\varepsilon(\chi_{\tilde{\Omega}_x}^\varepsilon)(x, \tilde{y}) \rightarrow \chi_{\tilde{\Omega}_x}^\varepsilon(x, D_x \tilde{y}) \) in \( L^p(\Omega_T \times Y) \) as well as
\[ \mathcal{T}_L^{b,\varepsilon}(\beta^\varepsilon)(x, \tilde{y}) \rightarrow \beta(x, D_x \tilde{K}_x \tilde{y}) \quad \text{and} \quad \mathcal{T}_L^{b,\varepsilon}(\alpha^\varepsilon)(x, \tilde{y}) \rightarrow \alpha(x, D_x \tilde{K}_x \tilde{y}) \] in \( L^p(\Omega \times \Gamma) \), as \( \varepsilon \rightarrow 0 \).

Using the a priori estimates for \( c^\varepsilon \) and \( \varepsilon_f \), the strong convergence of \( \mathcal{T}_L^\varepsilon(c^\varepsilon) \) in \( L^2(\Omega_T; H^1(Y)) \), the strong convergence and the boundedness of \( \mathcal{T}_L^{b,\varepsilon}(\alpha^\varepsilon) \), the weak convergence and the boundedness of \( \mathcal{T}_L^{b,\varepsilon}(r^\varepsilon_f) \), together with the regularity of \( D, R, \) and \( K \), and the strong convergence of \( \mathcal{T}_L^{b,\varepsilon}(\psi^\varepsilon) \) we obtain
\[ \lim_{\varepsilon \rightarrow 0} \left( \sum_{n=1}^{N_x} \frac{\sqrt{g|Y_{x_n}|}}{\sqrt{g}} \mathcal{T}_L^{b,\varepsilon}(\alpha^\varepsilon) \mathcal{T}_L^{b,\varepsilon}(c^\varepsilon) \mathcal{T}_L^{b,\varepsilon}(r^\varepsilon_f) \chi_{\tilde{\Omega}_x}^\varepsilon, \mathcal{T}_L^{b,\varepsilon}(\psi^\varepsilon) \right)_{\Omega_T \times \Gamma} \]
\[ = \left( \frac{\sqrt{g|Y_x|}}{\sqrt{g}} \alpha(x, D_x \tilde{K}_x \tilde{y}) c(t, x) \mathcal{F}_x^\varepsilon(t, x, D_x \tilde{K}_x \tilde{y}), \psi_1(x) \right)_{\Omega_T \times \Gamma}. \]

Similar arguments along with the Lipschitz continuity of \( F \) and the strong convergence of \( \mathcal{T}_L^\varepsilon(\chi_{\tilde{\Omega}_x}^\varepsilon) \) ensure the convergence
\[ \langle \mathcal{T}_L^\varepsilon(\chi_{\tilde{\Omega}_x}^\varepsilon), D \mathcal{T}_L^\varepsilon(\psi^\varepsilon) \rangle_{\Omega_T \times Y} \rightarrow \langle \chi_{\tilde{\Omega}_x}^\varepsilon(x, D_x \tilde{y}) F(c), \psi_1 \rangle_{\Omega_T \times Y} \]
as \( \varepsilon \rightarrow 0 \). Using the convergences results [4], the strong convergence of \( \mathcal{T}_L^\varepsilon(\psi^\varepsilon) \) and \( \mathcal{T}_L^\varepsilon(\nabla \psi^\varepsilon) \) and the fact that \( |\Lambda^*_x| \rightarrow 0 \) as \( \varepsilon \rightarrow 0 \), taking the limit as \( \varepsilon \rightarrow 0 \), and considering the transformation of variables \( y = D_x \tilde{y} \) for \( \tilde{y} \in Y \) and \( y = D_x \tilde{K}_x \tilde{y} \) for \( \tilde{y} \in \Gamma \) we obtain
\[ \langle |\tilde{Y}_x|^{-1} c, \psi_1 \rangle_{\tilde{\Omega}_x,K \times \Omega_T} + \langle |\tilde{Y}_x|^{-1} A(\nabla c + \nabla_y c_1), \nabla \psi_1 + \nabla_y \psi_2 \rangle_{\tilde{\Omega}_x,K \times \Omega_T} \]
\[ + \langle |\tilde{Y}_x|^{-1} \alpha(x, y) r_f c - \beta(x, y) r_b, \psi_1 \rangle_{\tilde{\Omega}_x,K \times \Omega_T} = \langle |\tilde{Y}_x|^{-1} F(c), \psi_1 \rangle_{\tilde{\Omega}_x,K \times \Omega_T}. \]

Considering \( \psi_1(t, x) = 0 \) for \( (t, x) \in \Omega_T \) we obtain
\[ c_1(t, x, y) = \sum_{j=1}^{3} \partial_j c(t, x, y) w^j(x, y), \]
where \( w^j \) are solutions of (4.3). Choosing \( \psi_2(t, x, y) = 0 \) for \( (t, x) \in \Omega_T \) and \( y \in \tilde{\Omega}_x \) yields the macroscopic equation for \( c \).

Using the strong convergence of \( \mathcal{T}_L^{b,\varepsilon}(c^\varepsilon) \) in \( L^2(\Omega_T; L^2(\Gamma)) \)), the estimates (3.1) and (3.2), and the Lipschitz continuity of \( p \) we prove that \( \{ \mathcal{T}_L^{b,\varepsilon}(r^\varepsilon_f) \} \) is a Cauchy sequence in \( L^2(\Omega_T; L^2(\Gamma)) \)), for \( j = f, b \), and hence up to a subsequence, \( \mathcal{T}_L^{b,\varepsilon}(r^\varepsilon_f) \rightarrow r_f(\cdot, \cdot; D_x \tilde{K}_x) \) strongly in \( L^2(\Omega_T; L^2(\Gamma)) \)). Then applying the l-p boundary unfolding operator to the equations on \( \tilde{\Omega}_x \) and taking the limit as \( \varepsilon \rightarrow 0 \) we obtain the equations for \( r_f \) and \( r_b \). \( \Box \)

**Remark.** Notice that for the proof of the homogenization results it is sufficient to have a local extension of \( c^\varepsilon \) from \( \tilde{\Omega}_x \) to \( \tilde{\Omega}_x^\delta \), with \( \Omega^\delta = \{ x \in \Omega : \text{dist}(x, \partial \Omega) > \delta \} \) for any fixed \( \delta > 0 \), and, hence, the local strong convergence of \( \mathcal{T}_L^\varepsilon(c^\varepsilon) \) in \( L^2(0, T; L^2_{\text{loc}}(\Omega; H^1(Y))) \).
5. Appendix: Definition and convergence results for the l-t-s convergence and l-p unfolding operator.

We shall consider the space \( C(\Omega; C_{\text{per}}(\tilde{Y}_x)) \) given in a standard way, i.e. for any \( \tilde{\psi} \in C(\Omega; C_{\text{per}}(Y)) \) the relation \( \psi(x,y) = \tilde{\psi}(x, D_x^{-1} y) \) with \( x \in \Omega \) and \( y \in \tilde{Y}_x \) yields \( \psi \in C(\Omega; C_{\text{per}}(\tilde{Y}_x)) \). In the same way the spaces \( L^p(\Omega; C_{\text{per}}(\tilde{Y}_x)) \), \( L^p(\Omega; L^q_{\text{per}}(\tilde{Y}_x)) \) and \( C(\Omega; L^q_{\text{per}}(\tilde{Y}_x)) \), for \( 1 \leq p \leq \infty, 1 \leq q < \infty \), are given.

Consider \( \psi \in C(\Omega; C_{\text{per}}(\tilde{Y}_x)) \) and corresponding \( \tilde{\psi} \in C(\Omega; C_{\text{per}}(Y)) \). As a locally periodic (l-p) approximation of \( \psi \) we name \( \mathcal{L}^\epsilon : C(\Omega; C_{\text{per}}(\tilde{Y}_x)) \to \mathcal{L}^{\infty}(\Omega) \) given by, see [23],

\[
(\mathcal{L}^\epsilon \psi)(x) = \sum_{n=1}^{N} \tilde{\psi}(x, \frac{D_x^{-1} (x - x_n^\epsilon)}{\epsilon}) \chi_{\Omega_n^\epsilon}(x) \quad \text{for} \ x \in \Omega.
\]

We consider also the map \( \mathcal{L}^\epsilon_0 : C(\Omega; C_{\text{per}}(\tilde{Y}_x)) \to \mathcal{L}^{\infty}(\Omega) \) defined for \( x \in \Omega \) as

\[
(\mathcal{L}^\epsilon_0 \psi)(x) = \sum_{n=1}^{N} \tilde{\psi}(x, \frac{x_n^\epsilon - x_n^\epsilon k}{\epsilon}) \chi_{\Omega_n^\epsilon}(x) = \sum_{n=1}^{N} \tilde{\psi}(x_n^\epsilon, \frac{D_x^{-1} (x - x_n^\epsilon)}{\epsilon}) \chi_{\Omega_n^\epsilon}(x).
\]

If we choose \( x_n^\epsilon = D_x^{-1} \epsilon \) for some \( k \in \mathbb{Z}^3 \), then the periodicity of \( \tilde{\psi} \) implies

\[
(\mathcal{L}^\epsilon \psi)(x) = \sum_{n=1}^{N} \tilde{\psi}(x, \frac{D_x^{-1} x}{\epsilon}) \chi_{\Omega_n^\epsilon}(x), \quad (\mathcal{L}^\epsilon_0 \psi)(x) = \sum_{n=1}^{N} \tilde{\psi}(x_n^\epsilon, \frac{D_x^{-1} x}{\epsilon}) \chi_{\Omega_n^\epsilon}(x)
\]

for \( x \in \Omega \), see e.g. [23] for more details. In the similar way we define \( \mathcal{L}^\epsilon \psi \) and \( \mathcal{L}^\epsilon_0 \psi \) for \( \psi \in C(\Omega; L^p_{\text{per}}(\tilde{Y}_x)) \) or \( L^p(\Omega; C_{\text{per}}(\tilde{Y}_x)) \).

We define also regular approximation of \( \mathcal{L}^\epsilon \psi \)

\[
(\mathcal{L}^\epsilon_\rho \psi)(x) = \sum_{n=1}^{N} \tilde{\psi}(x, \frac{D_x^{-1} x}{\epsilon}) \phi_{\Omega_n^\epsilon}(x) \quad \text{for} \ x \in \Omega,
\]

where \( \phi_{\Omega_n^\epsilon} \) are approximations of \( \chi_{\Omega_n^\epsilon} \) such that \( \phi_{\Omega_n^\epsilon} \in C^0(\Omega_n^\epsilon) \) and

\[
\sum_{n=1}^{N} |\phi_{\Omega_n^\epsilon} - \chi_{\Omega_n^\epsilon}| \to 0 \text{ in } L^2(\Omega), \quad \|\nabla^m \phi_{\Omega_n^\epsilon}\|_{L^\infty(\mathbb{R}^d)} \leq C \epsilon^{-\rho m} \text{ for } 0 < r < \rho < 1.
\]

We recall here the definition of locally periodic two-scale (l-t-s) convergence and l-p unfolding operator, see [23] for details.

**Definition 7** ([23]). Let \( u^\epsilon \in L^p(\Omega) \) for all \( \epsilon > 0 \) and \( 1 < p < \infty \). We say the sequence \( \{u^\epsilon\} \) converges l-t-s to \( u \in L^p(\Omega; L^p(\tilde{Y}_x)) \) as \( \epsilon \to 0 \) if \( \|u^\epsilon\|_{L^p(\Omega)} \leq C \) and for any \( \psi \in L^q(\Omega; C_{\text{per}}(\tilde{Y}_x)) \)

\[
\lim_{\epsilon \to 0} \int_\Omega u^\epsilon(x) \mathcal{L}^\epsilon \psi(x) dx = \int_\Omega \int_{\tilde{Y}_x} u(x,y) \psi(x,y) dy dx,
\]

where \( \mathcal{L}^\epsilon \) is the l-p approximation of \( \psi \) and \( 1/p + 1/q = 1 \).

**Definition 8** ([24]). A sequence \( \{u^\epsilon\} \subset L^p(\tilde{\Gamma}^\epsilon) \), with \( 1 < p < \infty \), is said to converge locally periodic two-scale (l-t-s) to \( u \in L^p(\Omega; L^p(\tilde{Y}_x)) \) if \( \|u^\epsilon\|_{L^p(\tilde{\Gamma}^\epsilon)} \leq C \) and for any \( \psi \in C(\tilde{\Omega}; C_{\text{per}}(\tilde{Y}_x)) \)

\[
\lim_{\epsilon \to 0} \epsilon \int_{\Gamma^\epsilon} u^\epsilon(x) \mathcal{L}^\epsilon \psi(x) d\sigma_x = \int_\Omega \int_{\tilde{\Gamma}_x} \frac{1}{|Y_x|} u(x,y) \psi(x,y) d\sigma_y dx,
\]

where \( \mathcal{L}^\epsilon \) is the l-p approximation of \( \psi \) defined in (5.1).

**Lemma 9** ([24]). For \( \psi \in C(\tilde{\Omega}; C_{\text{per}}(\tilde{Y}_x)) \) and \( 1 \leq p < \infty \), we have that

\[
\lim_{\epsilon \to 0} \int_{\Gamma^\epsilon} |\mathcal{L}^\epsilon \psi(x)|^p d\sigma_x = \int_\Omega \int_{\tilde{\Gamma}_x} |\psi(x,y)|^p d\sigma_y dx.
\]
Theorem 12 (\cite{24}). For any Lebesgue-measurable on $\Omega$ function $\psi$ the locally periodic unfolding operator (l-p unfolding operator) $T^\varepsilon_L : \Omega \to \Omega \times Y$ is defined as

$$T^\varepsilon_L(\psi)(x, y) = \sum_{n=1}^{N_\varepsilon} \psi(\varepsilon D_{x_n}[D_{x_n^{-1}}x/\varepsilon]_Y + \varepsilon D_{x_n}y) \chi_{\Omega_n}(x)$$

for $x \in \Omega$ and $y \in Y$.

The definition implies that $T^\varepsilon_L(\phi)$ is Lebesgue-measurable on $\Omega \times Y$ and is zero for $x \in \Lambda^\varepsilon$, where $\Lambda^\varepsilon = \bigcup_{n=1}^{N_\varepsilon} (\Omega^\varepsilon_n \setminus \hat{\Omega}_n^\varepsilon) \cap \Omega$.

Definition 11 (\cite{24}). For any Lebesgue-measurable on $\tilde{\Gamma}^\varepsilon$ function $\psi$ the l-p boundary unfolding operator $T^\varepsilon_{b,L} : \Omega \to \Omega \times \Gamma$ is defined as

$$T^\varepsilon_{b,L}(\psi)(x, y) = \sum_{n=1}^{N_\varepsilon} \psi(\varepsilon D_{x_n}[D_{x_n^{-1}}x/\varepsilon]_Y + \varepsilon D_{x_n}\tilde{K}_{x_n}y) \chi_{\hat{\Omega}_n}(x)$$

for $x \in \Omega$ and $y \in \Gamma$.

There definitions give a generalization of the periodic boundary unfolding operator introduced in \cite{11 12} to locally-periodic microstructures.

Theorem 13 (\cite{24}). For a sequence $\{w^\varepsilon\} \subset L^p(\Omega)$, with $p \in (1, \infty)$, satisfying

$$\|w^\varepsilon\|_{L^p(\Omega)} + \varepsilon \|
abla w^\varepsilon\|_{L^p(\Omega)} \leq C$$

there exist a subsequence (denoted again by $\{w^\varepsilon\}$) and $w \in L^p(\Omega; W^{1,p}(\tilde{\Gamma}_x))$ such that

$$T^\varepsilon_L(w^\varepsilon) \rightharpoonup w(\cdot, D_x) \quad \text{weakly in } L^p(\Omega; W^{1,p}(Y)),$n

$$\varepsilon T^\varepsilon_L(\nabla w^\varepsilon) \rightharpoonup D_x T \nabla_y w(\cdot, D_x) \quad \text{weakly in } L^p(\Omega \times Y).$$

Theorem 14 (\cite{24}). For a sequence $\{w^\varepsilon\} \subset W^{1,p}(\Omega)$, with $p \in (1, \infty)$, that converges weakly to $w$ in $W^{1,p}(\Omega)$, there exist a subsequence (denoted again by $\{w^\varepsilon\}$) and a function $w_1 \in L^p(\Omega; W^{1,p}(\tilde{\Gamma}_x))$ such that

$$T^\varepsilon_L(w^\varepsilon) \rightharpoonup w \quad \text{weakly in } L^p(\Omega; W^{1,p}(Y)),$n

$$T^\varepsilon_L(\nabla w^\varepsilon)(\cdot, \cdot) \rightharpoonup \nabla_x w(\cdot) + D_x T \nabla_y w_1(\cdot, D_x) \quad \text{weakly in } L^p(\Omega \times Y).$$

Theorem 15 (\cite{24}). Let $\{w^\varepsilon\} \subset L^p(\tilde{\Gamma}^\varepsilon)$ with $\varepsilon \|w^\varepsilon\|_{L^p(\tilde{\Gamma}^\varepsilon)} \leq C$, where $p \in (1, \infty)$. The following assertions are equivalent

(i) \quad $w^\varepsilon \rightharpoonup w$ \quad l-t-s, \quad w \in L^p(\Omega; L^p(\tilde{\Gamma}_x)).$

(ii) \quad $T^\varepsilon_{b,L}(w^\varepsilon) \rightharpoonup w(\cdot, D_x \tilde{K}_x)$ \quad weakly in $L^p(\Omega \times \Gamma)$.

Theorems 14 and 15 imply that for $\{w^\varepsilon\} \subset L^p(\tilde{\Gamma}^\varepsilon)$ with $\varepsilon \|w^\varepsilon\|_{L^p(\tilde{\Gamma}^\varepsilon)} \leq C$ we have the weak convergence of $\{T^\varepsilon_{b,L}(w^\varepsilon)\}$ in $L^p(\Omega \times \Gamma)$, where $p \in (1, \infty)$.
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