From a Microscopic to a Macroscopic Model for Alzheimer Disease:

Two-Scale Homogenization of the Smoluchowski Equation

in Perforated Domains

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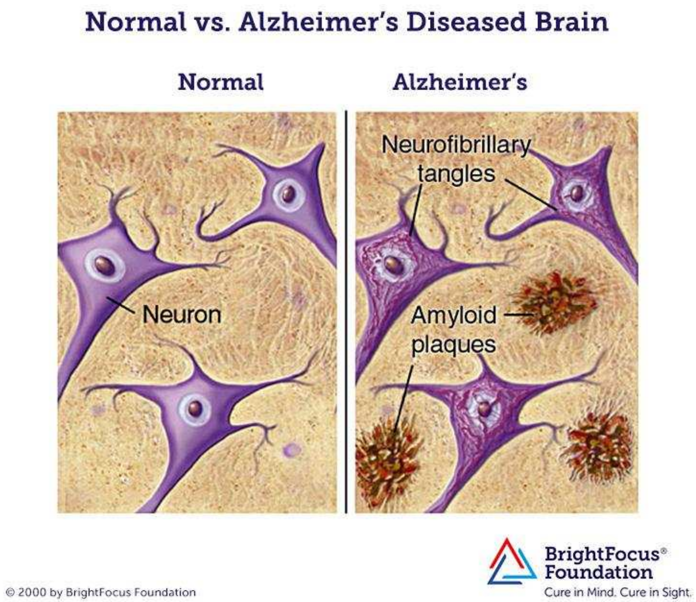
Alzheimer Disease (AD)



Alzheimer disease is characterized pathologically by the formation of senile plaques composed of β-amyloid peptide (Aβ). Aβ is naturally present in the brain and cerebrospinal fluid of humans throughout life. By unknown reasons (partially genetic), some neurons start to present an imbalance between production and clearance of Aβ amyloid during aging. Therefore, neuronal injury is the result of ordered Aβ self-association.

The Smoluchowski Equation

For $k \in \mathbb{N}$, let P_k denote a polymer of size k, that is a set of k identical particles (monomers). As time advances, the polymers evolve and, if they approach each other sufficiently close, there is some chance that they merge into a single polymer whose size equals the sum of the sizes of the two polymers which take part in this reaction.

By convention, we admit only binary reactions. This phenomenon is called coalescence and we write formally

$$P_k + P_j \longrightarrow P_{k+j},$$

for the coalescence of a polymer of size k with a polymer of size j.

We restrict ourselves to the following physical situation: the approach of two clusters leading to aggregation is assumed to result only from Brownian movement or diffusion (thermal coagulation).

Under these assumptions, the discrete diffusive coagulation equations read

$$\frac{\partial u_i}{\partial t}(t,x) - d_i \, \triangle_x u_i(t,x) = Q_i(u) \quad \text{in } [0,T] \times \Omega, \tag{1}$$

with appropriate initial and boundary conditions.

The variable $u_i(t,x) \geq 0$ (for $i \geq 1$) represents the concentration of i-clusters, that is, clusters consisting of i identical elementary particles, and

$$Q_i(u) = Q_{g,i}(u) - Q_{l,i}(u) \qquad i \geq 1 \tag{2}$$

with the gain ($Q_{g,i}$) and loss ($Q_{l,i}$) terms given by

$$Q_{g,i} = \frac{1}{2} \sum_{j=1}^{i-1} a_{i-j,j} \, u_{i-j} \, u_j \tag{3}$$

$$Q_{l,i} = u_i \sum_{j=1}^{\infty} a_{i,j} \, u_j \tag{4}$$

where $u = (u_i)_{i \geq 1}$.

A Mathematical Model for the Aggregation and Diffusion of β-Amyloid Peptide

We define a periodically perforated domain obtained by removing from the fixed domain Ω (the cerebral tissue) infinitely many small holes of size ϵ (the neurons), which support a non-homogeneous Neumann boundary condition describing the production of Aβ by the neuron membranes.

- Let Ω be a bounded open set in $\mathbb{R}^3$ with a smooth boundary $\partial\Omega$.
- Let Y be the unit periodicity cell $[0, 1[^3$ having the paving property.
- Let us denote by T an open subset of Y with a smooth boundary Γ, such that $\overline{T} \subset \mathrm{Int}\, Y$.
- Set $Y^* = Y \setminus T$ which is called in the literature the solid or material part.
- We define $\tau(\epsilon\overline{T})$ to be the set of all translated images of $\epsilon\overline{T}$ of the form $\epsilon(k + \overline{T})$, $k \in \mathbb{Z}^3$.

Then, $T_\epsilon := \Omega \cap \tau(\epsilon\overline{T})$.

Introduce now the periodically perforated domain Ω_ϵ defined by

$$\Omega_\epsilon = \Omega \setminus \overline{T}_\epsilon.$$

We make the following standard assumption on the holes: there exists a ‘security’ zone around $\partial\Omega$ without holes, i.e.,

$$\exists\, \delta > 0 \text{ such that } \mathrm{dist}\,(\partial\Omega, T_\epsilon) \geq \delta. \tag{5}$$

Therefore, Ω_ϵ is a connected set.

The boundary $\partial\Omega_\epsilon$ of Ω_ϵ is then composed of two parts:

- the union of the boundaries of the holes strictly contained in Ω:
  $\Gamma_\epsilon := \cup\left\{\partial(\epsilon(k+\overline{T})) \mid \epsilon(k+\overline{T}) \subset \Omega\right\}; \quad \lim_{\epsilon\to 0} \epsilon \mid \Gamma_\epsilon|_{N-1} =| \Gamma|_{N-1} \frac{|\,\Omega\,|_N}{|\,Y\,|_N}$
- the fixed exterior boundary denoted by $\partial\Omega$.

We introduce the vector-valued function $u^\epsilon : [0,T] \times \Omega_\epsilon \to \mathbb{R}^M$, $u^\epsilon = (u_1^\epsilon, \ldots, u_M^\epsilon)$ where the variable $u_m^\epsilon \geq 0$ ($1 \leq m < M$) represents the concentration of m-clusters, that is, clusters consisting of m identical elementary particles (monomers), while $u_M^\epsilon \geq 0$ takes into account aggregations of more than $M-1$ monomers.

We assume that the only reaction allowing clusters to coalesce to form larger clusters is a binary coagulation mechanism, while the movement of clusters leading to aggregation results only from a diffusion process described by constant coefficients $d_m > 0$, ($m = 1, \ldots, M$).

Under these assumptions, the mathematical model based on the discrete Smoluchowski equation, describing the aggregation and diffusion of β-amyloid peptide (Aβ) in the brain affected by Alzheimer's disease (AD), can be written as a family of equations in Ω_ϵ:

$$
\begin{cases}
\frac{\partial u_1^\epsilon}{\partial t} - \mathrm{div}(d_1 \nabla_x u_1^\epsilon) + u_1^\epsilon \sum_{j=1}^{M} a_{1,j} u_j^\epsilon = 0 & \text{in } [0,T] \times \Omega_\epsilon \\
\frac{\partial u_1^\epsilon}{\partial \nu} \equiv \nabla_x u_1^\epsilon \cdot n = 0 & \text{on } [0,T] \times \partial\Omega \\
\frac{\partial u_1^\epsilon}{\partial \nu} \equiv \nabla_x u_1^\epsilon \cdot n = \epsilon\, \psi(t, x, \frac{x}{\epsilon}) & \text{on } [0,T] \times \Gamma_\epsilon \\
u_1^\epsilon(0,x) = U_1 & \text{in } \Omega_\epsilon
\end{cases}
\tag{6}
$$

where ψ is a given bounded function satisfying the following conditions:

(i) $\psi(t, x, \frac{x}{\epsilon}) \in C^1(0,T;B)$ with $B = C^1[\overline{\Omega}; C^1_\#(Y)]$, where $C^1_\#(Y)$ is the subset of $C^1(\mathbb{R}^N)$ of Y-periodic functions;

(ii) $\psi(t = 0, x, \frac{x}{\epsilon}) = 0$

and U_1 is a positive constant such that

$$
U_1 \leq \|\psi\|_{L^\infty(0,T;B)}. \tag{7}
$$

In addition, if $1 < m < M$,

$$
\begin{cases}
\dfrac{\partial u_m^\epsilon}{\partial t} - \text{div}(d_m \, \nabla_x u_m^\epsilon) + u_m^\epsilon \, \sum_{j=1}^{M} a_{m,j} u_j^\epsilon = f^\epsilon & \text{in } [0,T] \times \Omega_\epsilon \\[2ex]
\dfrac{\partial u_m^\epsilon}{\partial \nu} \equiv \nabla_x u_m^\epsilon \cdot n = 0 & \text{on } [0,T] \times \partial\Omega \\[2ex]
\dfrac{\partial u_m^\epsilon}{\partial \nu} \equiv \nabla_x u_m^\epsilon \cdot n = 0 & \text{on } [0,T] \times \Gamma_\epsilon \\[2ex]
u_m^\epsilon(0,x) = 0 & \text{in } \Omega_\epsilon
\end{cases}
\tag{8}
$$

where the gain term f^ϵ is given by

$$
f^\epsilon = \frac{1}{2} \sum_{j=1}^{m-1} a_{j,m-j} \, u_j^\epsilon \, u_{m-j}^\epsilon \tag{9}
$$

and

$$\begin{cases} \dfrac{\partial u_M^\epsilon}{\partial t} - \text{div}(d_M \nabla_x u_M^\epsilon) = g^\epsilon & \text{in } [0,T] \times \Omega_\epsilon \\[2ex] \dfrac{\partial u_M^\epsilon}{\partial \nu} \equiv \nabla_x u_M^\epsilon \cdot n = 0 & \text{on } [0,T] \times \partial\Omega \\[2ex] \dfrac{\partial u_M^\epsilon}{\partial \nu} \equiv \nabla_x u_M^\epsilon \cdot n = 0 & \text{on } [0,T] \times \Gamma_\epsilon \\[2ex] u_M^\epsilon(0,x) = 0 & \text{in } \Omega_\epsilon \end{cases} \tag{10}$$

where the gain term g^ϵ is given by

$$g^\epsilon = \frac{1}{2} \sum_{\substack{j+k \geq M \\ k < M \\ j < M}} a_{j,k}\, u_j^\epsilon\, u_k^\epsilon. \tag{11}$$

Theorem 1. *If $\epsilon > 0$, the system* (6) - (11) *has a unique solution*

$$(u_1^\epsilon, \ldots, u_M^\epsilon) \in C^{1+\alpha/2, 2+\alpha}([0,T] \times \Omega_\epsilon) \quad (\alpha \in (0,1))$$

such that

$$u_j^\epsilon(t,x) > 0 \quad \textit{for } (t,x) \in (0,T) \times \Omega_\epsilon, j = 1, \ldots, M.$$

Our aim is to study the homogenization of the set of Eqs. (6)-(11) as $\epsilon \to 0$, i.e., to study the behavior of $u_j^\epsilon (1 \leq j \leq M)$ as $\epsilon \to 0$ and obtain the equations satisfied by the limit.

There is no clear notion of convergence for the sequence $u_j^\epsilon (1 \leq j \leq M)$ which is defined on a varying set Ω_ϵ.

This difficulty is specific to the case of perforated domains. A natural way to get rid of this difficulty is given by Nguetseng-Allaire two-scale convergence (Allaire 1992; Nguetseng 1989).

Homogenization Theory

Passing from a microscopic model to a macroscopic one has always been a common issue in mathematical modeling. As a matter of fact, while being closer to the actual physical nature, a mathematical model for a physical system that resolves smaller scales is usually more complicated and sometimes even virtually impossible to solve. Moreover, experimental data are often available for macroscale quantities only, but not for the microscale.

Therefore, for quite a long time, the key issue has been how to formulate laws on a scale that is larger than the microscale and to justify these laws on the basis of a microscopic approach.

In practice, one wants to start from differential equations that are assumed to hold on the microscale and to transform them into equations on the macroscale, by performing a sort of 'averaging process'. To do that, in the seventies, mathematicians have developed a new method called homogenization.

From a mathematical point of view, we have a family of partial differential operators L_ϵ and a family of solutions u^ϵ which, for given varying set Ω_ϵ and a source term f, satisfy

$$L_\epsilon \, u^\epsilon = f \quad \text{in} \quad \Omega_\epsilon, \tag{12}$$

complemented by appropriate boundary conditions.

Assuming that the sequence u^ϵ converges, in some sense, to a limit u, we look for a so-called homogenized operator $\overline{L}$ such that u is a solution of

$$\overline{L} \, u = f \quad \text{in} \quad \Omega. \tag{13}$$

Passing from (12) to (13) is the homogenization process.

The wording is self-explaining: the limit model has no microstructure any more since it was eliminated by letting its 'size' ϵ tend to zero.

Two-Scale Convergence Method

Definition 1. *A sequence of functions v^ϵ in $L^2([0,T]\times\Omega)$ two-scale converges to $v_0 \in L^2([0,T]\times\Omega\times Y)$ if*

$$\lim_{\epsilon\to 0}\int_0^T\int_\Omega v^\epsilon(t,x)\,\phi\left(t,x,\frac{x}{\epsilon}\right)dt\,dx = \int_0^T\int_\Omega\int_Y v_0(t,x,y)\,\phi(t,x,y)\,dt\,dx\,dy \tag{14}$$

for all $\phi \in C^1([0,T]\times\overline{\Omega}; C^\infty_\#(Y))$.

The notion of 'two-scale convergence' makes sense because of the next compactness theorem.

Theorem 2. *If v^ϵ is a bounded sequence in $L^2([0,T]\times\Omega)$, then there exists a function $v_0(t,x,y)$ in $L^2([0,T]\times\Omega\times Y)$ such that, up to a subsequence, v^ϵ two-scale converges to v_0.*

The following theorem is useful in obtaining the limit of the product of two two-scale convergent sequences.

Theorem 3. *Let v^ϵ be a sequence of functions in $L^2([0,T]\times\Omega)$ which two-scale converges to a limit $v_0 \in L^2([0,T]\times\Omega\times Y)$. Suppose furthermore that*

$$\lim_{\epsilon\to 0}\int_0^T \int_\Omega |v^\epsilon(t,x)|^2\,dt\,dx = \int_0^T \int_\Omega \int_Y |v_0(t,x,y)|^2\,dt\,dx\,dy \tag{15}$$

Then, for any sequence w^ϵ in $L^2([0,T]\times\Omega)$ that two-scale converges to a limit $w_0 \in L^2([0,T]\times\Omega\times Y)$, we have

$$\begin{aligned}\lim_{\epsilon\to 0}\int_0^T \int_\Omega v^\epsilon(t,x)\,w^\epsilon(t,x)\,\phi\left(t,x,\frac{x}{\epsilon}\right)dt\,dx \\ = \int_0^T \int_\Omega \int_Y v_0(t,x,y)\,w_0(t,x,y)\,\phi(t,x,y)\,dt\,dx\,dy\end{aligned} \tag{16}$$

for all $\phi \in C^1([0,T]\times\overline{\Omega}; C^\infty_\#(Y))$.

The next theorem yields a characterization of the two-scale limit of the gradients of bounded sequences v^ϵ.

We identify $H^1(\Omega) = W^{1,2}(\Omega)$, where the Sobolev space $W^{1,p}(\Omega)$ is defined by

$$W^{1,p}(\Omega) = \left\{ v | v \in L^p(\Omega), \frac{\partial v}{\partial x_i} \in L^p(\Omega), i = 1, \ldots, N \right\}$$

and we denote by $H^1_\#(Y)$ the closure of $C^\infty_\#(Y)$ for the H^1-norm.

Theorem 4. *Let v^ϵ be a bounded sequence in $L^2(0,T;H^1(\Omega))$ that converges weakly to a limit $v(t,x)$ in $L^2(0,T;H^1(\Omega))$.*

Then, v^ϵ two-scale converges to $v(t,x)$, and there exists a function $v_1(t,x,y)$ in $L^2([0,T] \times \Omega; H^1_\#(Y)/\mathbb{R})$ such that, up to a subsequence, ∇v^ϵ two-scale converges to $\nabla_x v(t,x) + \nabla_y v_1(t,x,y)$.

The main result of two-scale convergence can be generalized to the case of sequences defined in $L^2([0,T]\times\Gamma_\epsilon)$.

Theorem 5. *Let v^ϵ be a sequence in $L^2([0,T]\times\Gamma_\epsilon)$ such that*

$$\epsilon \int_0^T \int_{\Gamma_\epsilon} |v^\epsilon(t,x)|^2 \, dt \, d\sigma_\epsilon(x) \leq C \tag{17}$$

where C is a positive constant, independent of ϵ. There exist a subsequence (still denoted by ϵ) and a two-scale limit $v_0(t,x,y) \in L^2([0,T]\times\Omega; L^2(\Gamma))$ such that $v^\epsilon(t,x)$ two-scale converges to $v_0(t,x,y)$ in the sense that

$$\lim_{\epsilon\to 0} \epsilon \int_0^T \int_{\Gamma_\epsilon} v^\epsilon(t,x)\, \phi\left(t,x,\frac{x}{\epsilon}\right) dt\, d\sigma_\epsilon(x) = \int_0^T \int_\Omega \int_\Gamma v_0(t,x,y)\, \phi(t,x,y)\, dt\, dx\, d\sigma(y) \tag{18}$$

for any function $\phi \in C^1([0,T]\times\overline{\Omega}; C^\infty_\#(Y))$.

Preliminary a Priori Estimates

Since the homogenization will be carried out in the framework of two-scale convergence, we first need to obtain the a priori estimates for the sequences u_j^ϵ, ∇u_j^ϵ, $\partial_t u_j^\epsilon$ in $[0,T] \times \Omega_\epsilon$, that are independent of ϵ.

Lemma 1. *Let $T > 0$ be arbitrary and u_1^ϵ be a classical solution of (6). Then,*

$$\|u_1^\epsilon\|_{L^\infty(0,T;L^\infty(\Omega_\epsilon))} \leq |U_1| + \|u_1^\epsilon\|_{L^\infty(0,T;L^\infty(\Gamma_\epsilon))}. \tag{19}$$

The boundedness of $u_1^\epsilon(t,x)$ in $L^\infty([0,T] \times \Gamma_\epsilon)$, uniformly in ϵ, can be immediately deduced from Lemma 2 below.

Lemma 2. *Let $T > 0$ be arbitrary and u_1^ϵ be a classical solution of (6). Then,*

$$\|u_1^\epsilon\|_{L^\infty(0,T;L^\infty(\Gamma_\epsilon))} \leq c\,\|\psi\|_{L^\infty(0,T;B)} \tag{20}$$

where c is independent of ϵ.

Lemma 3. *Let* $u_m^\epsilon(t,x)$ *(*$1 < m < M$*) be a classical solution of (8). Then*

$$\|u_m^\epsilon\|_{L^\infty(0,T;L^\infty(\Omega_\epsilon))} \leq K_m \tag{21}$$

uniformly with respect to ϵ*, where*

$$K_m = 1 + \frac{\left[\displaystyle\sum_{j=1}^{m-1} a_{j,m-j} K_j K_{m-j}\right]}{a_{m,m}} \tag{22}$$

Lemma 4. *Let* $u_M^\epsilon(t,x)$ *be a classical solution of (10). Then*

$$\|u_M^\epsilon\|_{L^\infty(0,T;L^\infty(\Omega_\epsilon))} \leq K_M \tag{23}$$

uniformly with respect to ϵ*, where*

$$K_M = e^T \sum_{\substack{j+k\geq M\\ k<M\\ j<M}} a_{j,k}\, K_j\, K_k \tag{24}$$

with the constants K_j *(*$1 < j < M$*) given by (22).*

Lemma 5. *The sequences* $\nabla_x u_m^\epsilon$ *and* $\partial_t u_m^\epsilon$ *(*$1 \le m \le M$*) are bounded in* $L^2([0,T] \times \Omega_\epsilon)$*, uniformly in* ϵ*.*

The proofs of the previous Lemmas rely on a generalization to perforated domains of the main inequalities valid in Ω, through the following extension Lemma:

Lemma 6. *Suppose that the domain* Ω_ϵ *is such that assumption (5) is satisfied. Then, there exists a family of linear continuous extension operators*

$$P_\epsilon : W^{1,p}(\Omega_\epsilon) \to W^{1,p}(\Omega)$$

and a constant $C > 0$ *independent of* ϵ *such that:* $P_\epsilon v = v$ *in* Ω_ϵ*, and*

$$\int_\Omega |P_\epsilon v|^p dx \le C \int_{\Omega_\epsilon} |v|^p dx, \quad \int_\Omega |\nabla(P_\epsilon v)|^p dx \le C \int_{\Omega_\epsilon} |\nabla v|^p dx \tag{25}$$

for each $v \in W^{1,p}(\Omega_\epsilon)$ *and for any* $p \in (1, +\infty)$*.*

Homogenization: Main Results

Theorem 6. *Let* $u_m^\epsilon(t,x)$ *(*$1 \le m \le M$*) be a family of classical solutions to problems (6)-(10). The sequences* $\widetilde{u_m^\epsilon}$ *and* $\widetilde{\nabla_x u_m^\epsilon}$ *(*$1 \le m \le M$*) two-scale converge to:*

$[\chi(y)\, u_m(t,x)]$ *and*

$[\chi(y)(\nabla_x u_m(t,x) + \nabla_y u_m^1(t,x,y))]$ *(*$1 \le m \le M$*), respectively, where tilde denotes the extension by zero outside* Ω_ϵ *and* $\chi(y)$ *represents the characteristic function of* Y^**.*

The limiting functions $(u_m(t,x), u_m^1(t,x,y))$ *(*$1 \le m \le M$*) are the unique solutions in*

$L^2(0,T;H^1(\Omega)) \times L^2([0,T] \times \Omega; H^1_\#(Y)/\mathbb{R})$

of the following two-scale homogenized systems.

If $m = 1$ we have:

$$\begin{cases} \theta \, \frac{\partial u_1}{\partial t}(t,x) - \mathrm{div}_x \left[d_1 \, A \, \nabla_x u_1(t,x) \right] + \theta \, u_1(t,x) \sum_{j=1}^{M} a_{1,j} \, u_j(t,x) \\ = d_1 \, \int_{\Gamma} \psi(t,x,y) \, d\sigma(y) & \text{in } [0,T] \times \Omega \\ \\ [A \, \nabla_x u_1(t,x)] \cdot n = 0 & \text{on } [0,T] \times \partial\Omega \\ \\ u_1(0,x) = U_1 & \text{in } \Omega \end{cases} \tag{26}$$

if $1 < m < M$ we have:

$$\begin{cases} \theta \, \frac{\partial u_m}{\partial t}(t,x) - \mathrm{div}_x \left[d_m \, A \, \nabla_x u_m(t,x) \right] + \theta \, u_m(t,x) \sum_{j=1}^{M} a_{m,j} \, u_j(t,x) \\ = \frac{\theta}{2} \sum_{j=1}^{m-1} a_{j,m-j} u_j(t,x) \, u_{m-j}(t,x) & \text{in } [0,T] \times \Omega \\ \\ [A \, \nabla_x u_m(t,x)] \cdot n = 0 & \text{on } [0,T] \times \partial\Omega \\ \\ u_m(0,x) = 0 & \text{in } \Omega \end{cases} \tag{27}$$

if $m = M$ we have:

$$\begin{cases} \theta \, \frac{\partial u_M}{\partial t}(t,x) - \text{div}_x \left[d_M \, A \, \nabla_x u_M(t,x) \right] \\ = \frac{\theta}{2} \sum_{\substack{j+k \geq M \\ k < M \\ j < M}} a_{j,k} \, u_j(t,x) \, u_k(t,x) & \text{in } [0,T] \times \Omega \\ \\ [A \, \nabla_x u_M(t,x)] \cdot n = 0 & \text{on } [0,T] \times \partial\Omega \\ \\ u_M(0,x) = 0 & \text{in } \Omega \end{cases} \tag{28}$$

where

$$u_m^1(t,x,y) = \sum_{i=1}^{N} w_i(y) \, \frac{\partial u_m}{\partial x_i}(t,x) \quad (1 \leq m \leq M),$$

and

$$\theta = \int_Y \chi(y) dy = |Y^*|$$

is the volume fraction of material.

A is a matrix with constant coefficients defined by

$$A_{ij} = \int_{Y^*} (\nabla_y w_i + \hat{e}_i) \cdot (\nabla_y w_j + \hat{e}_j)\, dy$$

with $\hat{e}_i$ being the i-th unit vector in $\mathbb{R}^N$, and $(w_i)_{1 \leq i \leq N}$ the family of solutions of the cell problem

$$\begin{cases} -div_y[\nabla_y w_i + \hat{e}_i] = 0 & \text{in } Y^* \\ (\nabla_y w_i + \hat{e}_i) \cdot n = 0 & \text{on } \Gamma \\ y \to w_i(y) \quad Y-\text{periodic} & \end{cases} \tag{29}$$

When $\epsilon \longrightarrow 0$, the solution of the micromodel two-scale converges to the solution of a macromodel, where the information given on the microscale by the non-homogeneous Neumann boundary condition is transferred into a global source term in the limiting (homogenized) evolution equation for the concentration of monomers.

Moreover, at the macroscale, the geometric structure of the perforated domain induces a correction in the scalar diffusion coefficients that are indeed replaced by a tensorial quantity with constant coefficients.

Proof

The sequences $\widetilde{u_m^\epsilon}$ and $\widetilde{\nabla_x u_m^\epsilon}$ $(1 \leq m \leq M)$ are bounded in $L^2([0,T] \times \Omega)$.

Therefore, they two-scale converge, up to a subsequence, to: $[\chi(y)\, u_m(t,x)]$ and $[\chi(y)(\nabla_x u_m(t,x) + \nabla_y u_m^1(t,x,y))]$ $(1 \leq m \leq M)$.

Similarly, the sequence $\left(\widetilde{\dfrac{\partial u_m^\epsilon}{\partial t}}\right)$ $(1 \leq m \leq M)$ two-scale converges to: $\left[\chi(y)\, \dfrac{\partial u_m}{\partial t}(t,x)\right]$ $(1 \leq m \leq M)$.

Case $m = 1$:

Let us multiply the first equation of (6) by the test function

$$\phi_\epsilon \equiv \phi(t,x) + \epsilon\, \phi_1\left(t, x, \frac{x}{\epsilon}\right)$$

where $\phi \in C^1([0,T] \times \overline{\Omega})$ and $\phi_1 \in C^1([0,T] \times \overline{\Omega}; C^\infty_\#(Y))$.

Integrating, the divergence theorem yields

$$\int_0^T \int_{\Omega_\epsilon} \frac{\partial u_1^\epsilon}{\partial t} \phi_\epsilon(t, x, \frac{x}{\epsilon})\, dt\, dx + d_1 \int_0^T \int_{\Omega_\epsilon} \nabla_x u_1^\epsilon \cdot \nabla \phi_\epsilon \, dt\, dx$$
$$+ \int_0^T \int_{\Omega_\epsilon} u_1^\epsilon \sum_{j=1}^{M} a_{1,j}\, u_j^\epsilon\, \phi_\epsilon \, dt\, dx = \epsilon\, d_1 \int_0^T \int_{\Gamma_\epsilon} \psi\left(t, x, \frac{x}{\epsilon}\right) \phi_\epsilon \, dt\, d\sigma_\epsilon(x) \tag{30}$$

Passing to the two-scale limit, we get

$$\int_0^T \int_\Omega \int_{Y^*} \frac{\partial u_1}{\partial t}(t,x)\, \phi(t,x)\, dt\, dx\, dy$$
$$+ d_1 \int_0^T \int_\Omega \int_{Y^*} [\nabla_x u_1(t,x) + \nabla_y u_1^1(t,x,y)] \cdot [\nabla_x \phi(t,x) + \nabla_y \phi_1(t,x,y)]\, dt\, dx\, dy$$
$$+ \int_0^T \int_\Omega \int_{Y^*} u_1(t,x) \sum_{j=1}^{M} a_{1,j}\, u_j(t,x)\, \phi(t,x)\, dt\, dx\, dy \tag{31}$$
$$= d_1 \int_0^T \int_\Omega \int_\Gamma \psi(t,x,y)\, \phi(t,x)\, dt\, dx\, d\sigma(y).$$

An integration by parts shows that (31) is a variational formulation associated with the following homogenized system:

$$-\mathrm{div}_y[d_1(\nabla_x u_1(t,x) + \nabla_y u_1^1(t,x,y))] = 0 \qquad \text{in } [0,T]\times\Omega\times Y^* \tag{32}$$

$$[\nabla_x u_1(t,x) + \nabla_y u_1^1(t,x,y)]\cdot n = 0 \qquad \text{on } [0,T]\times\Omega\times\Gamma \tag{33}$$

$$\begin{aligned} &\theta\,\frac{\partial u_1}{\partial t}(t,x) - \mathrm{div}_x\left[d_1\int_{Y^*}(\nabla_x u_1(t,x) + \nabla_y u_1^1(t,x,y))dy\right] \\ &+\theta\,u_1(t,x)\sum_{j=1}^{M} a_{1,j}\,u_j(t,x) - d_1\int_\Gamma \psi(t,x,y)\,d\sigma(y) = 0 \qquad \text{in } [0,T]\times\Omega \end{aligned} \tag{34}$$

$$\left[\int_{Y^*}(\nabla_x u_1(t,x) + \nabla_y u_1^1(t,x,y))\,dy\right]\cdot n = 0 \qquad \text{on } [0,T]\times\partial\Omega \tag{35}$$

where $\theta = \int_Y \chi(y)dy = |Y^*|$ is the volume fraction of material and by continuity: $u_1(0,x) = U_1$ in Ω.

Taking advantage of the constancy of the diffusion coefficient d_1, Eqs. (32) and (33) can be reexpressed as follows

$$\triangle_y u_1^1(t,x,y) = 0 \qquad \text{in } [0,T]\times\Omega\times Y^* \tag{36}$$

$$\nabla_y u_1^1(t,x,y)\cdot n = -\nabla_x u_1(t,x)\cdot n \qquad \text{on } [0,T]\times\Omega\times\Gamma \tag{37}$$

Then, $u_1^1(t,x,y)$ satisfying (36)-(37) can be written as

$$u_1^1(t,x,y) = \sum_{i=1}^{N} w_i(y)\,\frac{\partial u_1}{\partial x_i}(t,x) \tag{38}$$

where $(w_i)_{1\le i\le N}$ is the family of solutions of the cell problem

$$\begin{cases} -\text{div}_y[\nabla_y w_i + \hat{e}_i] = 0 & \text{in } Y^* \\ (\nabla_y w_i + \hat{e}_i)\cdot n = 0 & \text{on } \Gamma \\ y \to w_i(y) \quad Y-\text{periodic} & \end{cases} \tag{39}$$

By using the relation (38) in Eqs. (34) and (35), we get

$$\theta \frac{\partial u_1}{\partial t}(t,x) - \mathrm{div}_x \left[d_1 \, A \, \nabla_x u_1(t,x) \right] + \theta \, u_1(t,x) \sum_{j=1}^{M} a_{1,j} \, u_j(t,x)$$
$$- \, d_1 \int_\Gamma \psi(t,x,y) \, d\sigma(y) = 0 \qquad \text{in } [0,T] \times \Omega \tag{40}$$

$$[A \, \nabla_x u_1(t,x)] \cdot n = 0 \qquad \text{on } [0,T] \times \partial\Omega \tag{41}$$

where A is a matrix with constant coefficients defined by

$$A_{ij} = \int_{Y^*} (\nabla_y w_i + \hat{e}_i) \cdot (\nabla_y w_j + \hat{e}_j) \, dy.$$

The proof for the case $1 < m \leq M$ is achieved by applying exactly the same arguments considered when $m = 1$.

Appendix: Some properties of L^p spaces

Definition 2. *Let* $p \in \mathbb{R}$ *with* $1 \leq p < +\infty$. *Define*

$$L^p(\mathcal{O}) = \left\{ f | \, f : \mathcal{O} \mapsto \mathbb{R}, f \text{ measurable and such that } \int_{\mathcal{O}} |f(x)|^p \, dx < +\infty \right\}$$

$$L^\infty(\mathcal{O}) = \Big\{ f | \, f : \mathcal{O} \mapsto \mathbb{R}, f \text{ measurable and such that there exists } C \in \mathbb{R}$$
$$\text{with } |f| \leq C, \text{a.e. on } \mathcal{O} \Big\}.$$

Proposition 1. *Let* $p \in \mathbb{R}$ *with* $1 \leq p \leq +\infty$. *The set* $L^p(\mathcal{O})$ *is a Banach space for the norm*

$$\|f\|_{L^p(\mathcal{O})} = \begin{cases} [\int_{\mathcal{O}} |f(x)|^p dx]^{1/p} & \text{if } p < +\infty \\ \\ \inf \{C, |f| \leq C \text{ a.e. on } \mathcal{O}\} & \text{if } p = +\infty. \end{cases}$$

Definition 3. *Let Y be the interval in $\mathbb{R}^N$ defined by*

$$Y =]0, l_1[\times \ldots \times]0, l_N[$$

(where $l_1, \ldots, l_N$ are given positive numbers) and f a function defined a.e. on $\mathbb{R}^N$. The function f is called Y-periodic iff

$$f(x + kl_i e_i) = f(x) \text{ a.e. on } \mathbb{R}^N, \ \forall k \in \mathbb{Z}, \forall i \in \{1, \ldots, N\},$$

where $\{e_1, \ldots, e_N\}$ is the canonical basis of $\mathbb{R}^N$.

Definition 4. *We denote by*

- $C_\#(Y)$*, the subspace of $C(\mathbb{R}^N)$ of Y-periodic functions;*
- $C_\#^\infty(Y)$*, the subspace of $C^\infty(\bar{Y})$ of Y-periodic functions;*
- $L_\#^p(Y)$*, the subspace of $L^p(Y)$ of Y-periodic functions in the sense of Definition 3.*

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