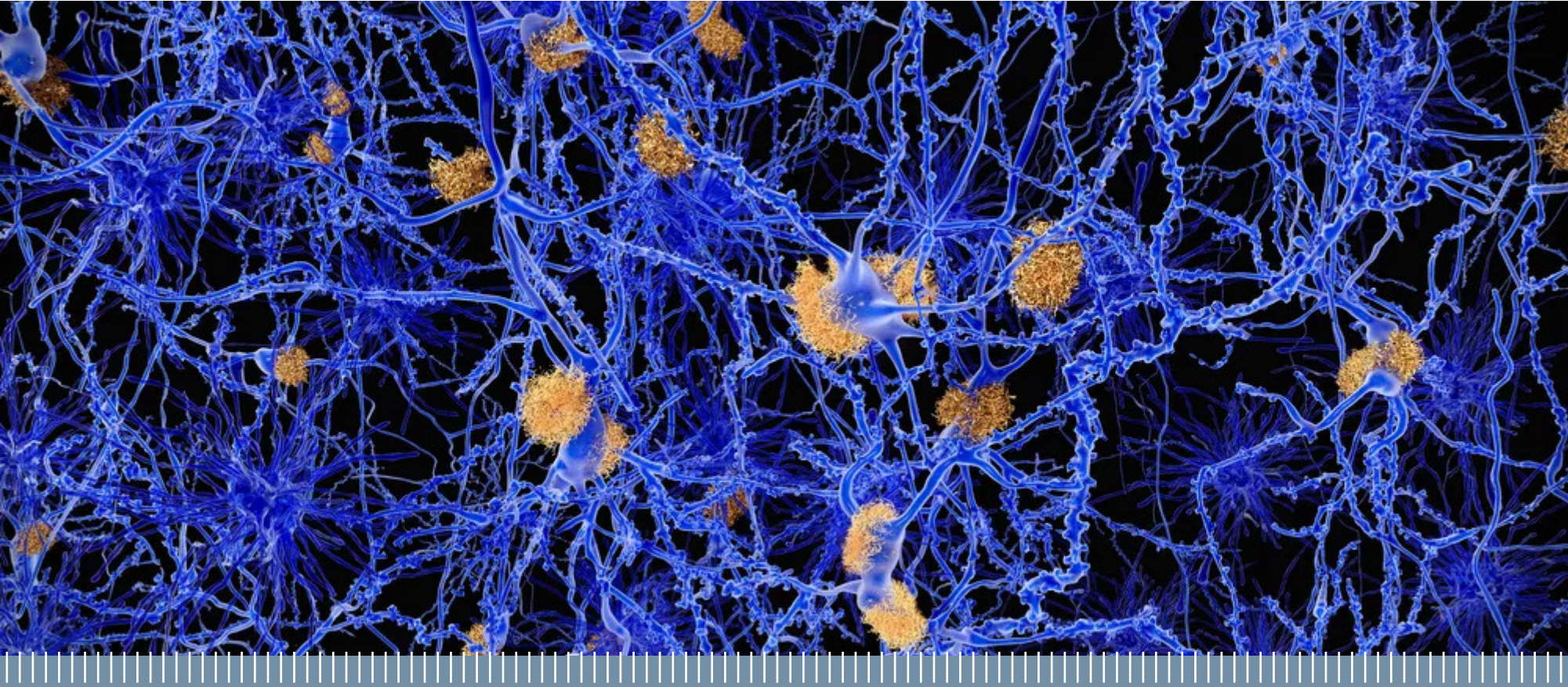

A mathematical model for Alzheimer's disease:

from a microscopic to a macroscopic model using the Two-Scale Homogenization Theory

Andrea Bonifacio

A brief introduction to Alzheimer's disease

- Alzheimer's disease (AD) is a neurodegenerative disease that usually **starts slowly and progressively worsens**. It is the most common form of senile dementia but the cause of it is still poorly understood.
- Inside the brain exists a protein called β-peptide,which has a substantial role in the process of synaptic degeneration. **This protein is produced in monomeric form by every healthy brain**, but some problems arise when, by unknown reasons (partially genetic), some neurons start to present an imbalance between production and clearance of $\mathrm{A}\beta$ amyloid during aging.

The idea

- Having a mathematical model for Alzheimer's disease is crucial because the **highly toxic polymers** involved in the disease **have a short lifespan and cannot be easily studied experimentally**. Therefore, a mathematical model provides the only means to investigate the behavior of amyloid in this context.
- The modeling process carried out here starts from the **Smoluchowski equation**: a system of PDEs which describes the evolving densities of diffusing particles that coagulate in pairs. In this report it will be studied the application of the Smoluchowski equation to the description of agglomeration of $\mathrm{A}\beta$ peptide.

The idea

- The main objective is **to derive a macroscopic model starting from a microscopic one.**
- In Bertsch et al. (2016) the authors present a model for the evolution of AD at a macroscopic scale and over the entire lifetime of the patient. In this case, the process of diffusion and aggregation of $\mathrm{A}\beta$ is modeled by a **Smoluchowski system with a source term**, coupled with a kinetic-type transport equation that keeps into account the spreading of the disease. Clearly, at this scale, neurons are no more visible so that they can be described mathematically as points.

The problem

- Passing from the microscopic to the macroscopic scale is not trivial. It involves a sort of **"averaging process" and it is done using a method called homogenization**. It consists in performing the limits of the solutions of PDEs and finding the set of equations of which these limits are solutions.
- To do so, will be used the **two-scale convergence theory**, which is a powerful tool to pass from the microscopic to the macroscopic scale.

The Smoluchowski equation

The Smoluchowski equation is a system of PDEs which describes the evolving densities of **diffusing particles that coagulate in pairs**. It has been used to describe a lot of phenomena. In this case, it will be used to describe the agglomeration of $\mathrm{A}\beta$ peptide, starting from monomers.
This phenomenon is called **coalescence** and can be written formally as

$$P_i + P_j \to P_{i+j}$$

which means that two polymers of length i and j coagulate to form a polymer of length $i + j$.

The Smoluchowski equation

Under the assumption that the aggregation of cluster is the result of only Brownian motion or diffusion, the equations can be written as:

$$\frac{\partial u_i}{\partial t}(t,x) - d_i \Delta_x u_i(t,x) = Q_i(u) \quad \text{in } [0,T] \times \Omega, \tag{2.1}$$

where u_i is the concentration of the cluster of length i, d_i is the diffusion coefficient, Ω is the domain of the system and $Q_i(u)$ is the gain term minus the loss term which are defined in this way:

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

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

The Smoluchowski equation

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

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

$Q_{g,i}$ describes the increasing of concentrations of the cluster of length i, $Q_{l,i}$ describes the depletion of the polymers of size i. An important role is played by the coagulation coefficients $a_{i-j,j}$ which describe a situation where a polymer of length $i-j$ coagulates with a polymer of length j to form one of length i. These coefficients are symmetric, indeed $a_{i,j} = a_{j,i}$.

The domain

A piece of cerebral tissue is considered as the domain Ω. Inside this domain it is necessary to **find a way to represent the presence of neurons**, which is not so straightforward as it may seem.
The idea is to represent the neurons as a set of holes in the domain.

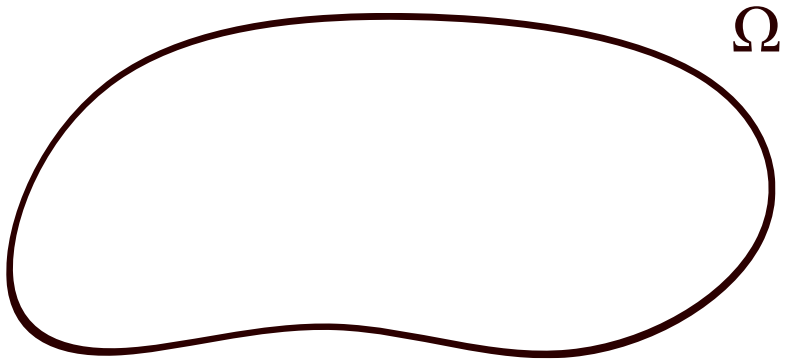

Figure: The domain Ω representing the cerebral tissue.

The periodic neuron

Let Y be the unit periodicity cell $\left[0,1\right[^3$ shown here.
To represent the neurons, it is necessary to consider them as **holes inside the cell**.
Denote by T an open subset of Y with a smooth boundary Γ, such that $\overline{T} \subset \mathrm{Int}(Y)$.
Now call with $Y^* = Y \setminus T$ the material part, the "solid part" of the brain.

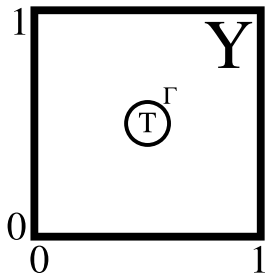

Figure: The periodic neuron

The periodic neuron

- The set T represents a generic neuron, and Y^* the supporting cerebral tissue.
- Define $\tau(\varepsilon\overline{T})$ to be the set of all translated images $\varepsilon\overline{T}$ of the form $\varepsilon(k+\overline{T}), k \in \mathbb{Z}^3$.
- Now are defined both the cerebral tissue domain Ω and the set of all neurons $\tau(\varepsilon\overline{(}T))$, so it's possible to define **the set of neurons inside the domain** as

$$T_\varepsilon := \Omega \cap \tau(\varepsilon\overline{T}).$$

The perforated domain

Define the perforated domain Ω_ε as

$$\Omega_\varepsilon := \Omega \setminus T_\varepsilon.$$

Ensure that there exists a "security zone" where the neurons cannot touch the boundary of Ω.

$$\exists \delta > 0 : \text{dist}\,(\partial\Omega, T_\varepsilon) \geq \delta. \quad (3.1)$$

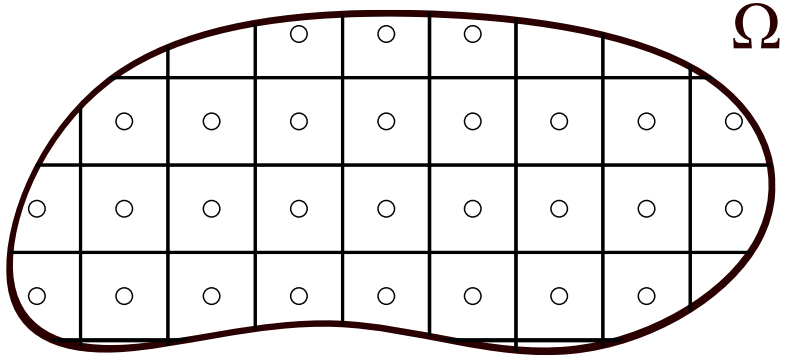

Figure: The perforated domain Ω_ε representing the cerebral tissue full of neurons.

Boundaries

The boundaries of the domain are divided into two parts:

- $\partial\Omega$ is the boundary of the external domain Ω.
- Γ_ε is the boundary of the set of neurons T_ε defined as

$$\Gamma_\varepsilon := \bigcup \left\{ \partial(\varepsilon(k + \overline{T})) \mid \varepsilon(k + \overline{T}) \subset \Omega \right\}.$$

- $\partial\Omega_\varepsilon := \partial\Omega + \Gamma_\varepsilon$.

ε will denote the general term of a sequence of real numbers converging to zero.

The Smoluchowski equation in the perforated domain

- Consider the vector-valued function $u = (u_1, \ldots, u_M)$, where $u_j = u_j(t, x)$ ($t \geq 0, t \in \mathbb{R}$ and $x \in \Omega$) is the molar concentration at the point x and at the time t of an assembly of j monomers.
- With the definition of u_M it is assumed that **'large' assemblies do not aggregate to each other**.
- The model is built assuming only **binary coagulation**.

The Smoluchowski equation in the perforated domain

The model is given by a system of PDEs:

- The first equation describes the evolution of monomers:

$$
\begin{cases}
\dfrac{\partial u_1^\varepsilon}{\partial t}(t,x) - d_1 \Delta_x u_1^\varepsilon(t,x) & \\
+u_1^\varepsilon(t,x) \displaystyle\sum_{j=1}^{M} a_{1,j} u_j^\varepsilon(t,x) = 0, & \text{in } [0,T] \times \Omega_\varepsilon, \\
\dfrac{\partial u_1^\varepsilon}{\partial \nu} \equiv \nabla_x u_1^\varepsilon \cdot n = 0, & \text{on } [0,T] \times \partial\Omega, \\
\dfrac{\partial u_1^\varepsilon}{\partial \nu} \equiv \nabla_x u_1^\varepsilon \cdot n = \varepsilon \psi\left(t, x, \dfrac{x}{\varepsilon}\right), & \text{on } [0,T] \times \Gamma_\varepsilon, \\
u_1^\varepsilon(0,x) = U_1, & \text{in } \Omega_\varepsilon.
\end{cases}
\tag{3.2}
$$

The Smoluchowski equation in the perforated domain

- The second system of equation describes the evolution of the clusters with size $1 < m < M$:

$$
\begin{cases}
\dfrac{\partial u_m^\varepsilon}{\partial t}(t,x) - d_m \Delta_x u_m^\varepsilon(t,x) & \\
\quad + u_m^\varepsilon(t,x) \displaystyle\sum_{j=1}^{M} a_{m,j} u_j^\varepsilon(t,x), & \text{in } [0,T] \times \Omega_\varepsilon, \\
\quad = \dfrac{1}{2} \displaystyle\sum_{j=1}^{m-1} a_{j,m-j} u_j^\varepsilon u_{m-j}^\varepsilon & \\
\dfrac{\partial u_m^\varepsilon}{\partial \nu} \equiv \nabla_x u_m^\varepsilon \cdot n = 0, & \text{on } [0,T] \times \partial\Omega_\varepsilon, \\
u_m^\varepsilon(0,x) = 0, & \text{in } \Omega_\varepsilon.
\end{cases}
\tag{3.3}
$$

The Smoluchowski equation in the perforated domain

- The last system of equation describes the evolution of the clusters with size M:

$$\begin{cases} \dfrac{\partial u_M^\varepsilon}{\partial t}(t,x) - d_M \Delta_x u_M^\varepsilon(t,x) \\ \qquad\qquad = \dfrac{1}{2} \displaystyle\sum_{\substack{j+k \geq M \\ j,k<M}} a_{j,k} u_j^\varepsilon u_k^\varepsilon, & \text{in } [0,T] \times \Omega_\varepsilon, \\ \dfrac{\partial u_M^\varepsilon}{\partial \nu} \equiv \nabla_x u_M^\varepsilon \cdot n = 0, & \text{on } [0,T] \times \partial\Omega_\varepsilon, \\ u_M^\varepsilon(0,x) = 0, & \text{in } \Omega_\varepsilon. \end{cases} \tag{3.4}$$

The Smoluchowski equation in the perforated domain

In (3.2) ε is put in front of ψ to prevent the divergence of the integral in a further passage, in order to avoid singularities. The variable x is called the **slow scale** variable, while the variable $\frac{x}{\varepsilon}$ is called the **fast scale** variable, which represents the microscopic scale.
It's assumed that for $t > 0$ the brain becomes sick. For technical reasons some regularity is needed on ψ and U_1:

1. $\psi\left(t, x, \frac{x}{\varepsilon}\right) \in C^1(0, T; B)$ with $B = C^1\left[\bar{\Omega}; C^1_{\#}(Y)\right]$, where $C^1_{\#}(Y)$ is the subset of $C^1\left(\mathbb{R}^N\right)$ of Y-periodic functions;
2. $\psi\left(t = 0, x, \frac{x}{\varepsilon}\right) = 0$
3. U_1 is a positive constant such that

$$U_1 \leq \|\psi\|_{L^\infty(0,T;B)}. \tag{3.5}$$

Convergence to the macroscopic model

At this point the idea is to go **from microscopic to macroscopic**, by a sort of "averaging process". Indeed, the objective is to perform the homogenization on the set (3.2)-(3.3) of equations as $\varepsilon \to 0$, however there is not a clear notion of convergence for the sequence u_j^ε $1 \geq j \geq M$ which is defined on a varying set Ω_ε, which also is **perforated**.

Convergence to the macroscopic model

Theorem 1

If $\varepsilon > 0$, *the system* (3.2)-(3.3) *has a unique solution*

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

such that

$$u_j^\varepsilon(t, x) > 0 \text{ for } (t, x) \in (0, T) \times \Omega_\varepsilon, j = 1, \dots, M.$$

Two-scale convergence definition

Two-scale convergence is a powerful tool that can help the **study of functions in perforated domains**.

Definition 2 (Two-scale convergence)

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

$$\lim_{\varepsilon\to 0}\int_0^T\int_\Omega v^\varepsilon(t,x)\psi\left(t,x,\frac{x}{\varepsilon}\right)\,dxdt$$
$$=\int_0^T\int_\Omega\int_Y v(t,x,y)\psi(t,x,y)\,dydxdt$$

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

Compactness theorem

This definition makes sense because of the next **compactness theorem**

Theorem 3 (Compactness Theorem)

If v^ε is a bounded sequence in $L^2([0,T]\times\Omega)$, then there exist a function $v_0(t,x,y)\in L^2([0,T]\times\Omega\times Y)$ s.t. v^ε two-scale converges to v_0, we write: $v^\varepsilon \overset{2s}{\rightharpoonup} v_0$.

This theorem is important because it shows that the minimal requirement to have two-scale convergence is that v must be **bounded**.

Relation with weak convergence

Remark (Remark, relation with weak convergence)

If it is assumed that ψ is independent of y, it will be obtained:

$$\lim_{\varepsilon \to 0} \int_\Omega v^\varepsilon(x)\psi(x)dx = \int_\Omega \int_Y v(x,y)\psi(x)dy\,dx$$
$$= \int_\Omega \left[\int_Y v(x,y)dy \right] \psi(x)dx.$$

*This shows that, in this specific case, the **two-scale convergence coincides with the weak convergence**. Therefore, the two-scale convergence and the weak convergence are strictly related: the main difference between them is that in the first one the oscillations are captured due to the extra variable y.*

Two-scale convergence of products I

The next theorems yield a characterization of the two-scale limit of the gradients of bounded sequences v^ε which is a critical result in order to apply the homogenization on problems. This theorem shows that, under specific hypotheses, **the limit of the product coincides with the product of the limits**.

Two-scale convergence of products II

Theorem 4

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

$$\lim_{\varepsilon\to 0}\int_0^T\int_\Omega |v^\varepsilon(t,x)|^2\,dxdt = \int_0^T\int_\Omega\int_Y |v_0(t,x,y)|^2\,dydxdt.$$

$\downarrow$

Two-scale convergence of products III

Theorem 4

↳ *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*

$$\lim_{\varepsilon\to 0}\int_0^T\int_\Omega v^\varepsilon(t,x)w^\varepsilon(t,x)\phi\left(t,x,\frac{x}{\varepsilon}\right)\,dxdt = \int_0^T\int_\Omega\int_Y v_0(t,x,y)w_0(t,x,y)\phi(t,x,y)\,dydxdt$$

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

Sobolev spaces

Here's a brief introduction to the **Sobolev spaces**, which can be "improperly" defined as L^p spaces with L^p derivatives. Formally

Definition 5

The Sobolev space $W^{1,p}(\Omega)$ is defined by

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

Identify $H^1(\Omega) = W^{1,2}(\Omega)$, where and denote by $H^1_\#(Y)$ the closure of $C^\infty_\#(Y)$ for the H^1-norm.
Now it's possible to introduce the next useful results.

Managing gradients I

When the limit is performed it appears an **extra variable** and one needs a theorem that defines **how to manage the gradient of this variable**.

Theorem 6

Let v^ε be a bounded sequence belonging in $L^2\left(0,T;H^1(\Omega)\right)$ such that $v_\varepsilon(t,x) \rightharpoonup v(t,x)$ in $L^2\left(0,T;H^1(\Omega)\right)$. Then $v^\varepsilon \overset{2s}{\rightharpoonup} v(t,x)$, and there exists a function $v_1(t,x,y)$ in $L^2\left([0,T]\times\Omega;H^1_\#(Y)/\mathbb{R}\right)$ such that, up to a subsequence, $\nabla v^\varepsilon \overset{2s}{\rightharpoonup} (\nabla_x v(t,x)+\nabla_y v_1(t,x,y))$.

Managing gradients II

Theorem 7

Let v^ε and $\varepsilon\nabla v^\varepsilon$ be two bounded sequences in $L^2([0,T]\times\Omega)$. Then, there exists a function $v_1(t,x,y)$ in $L^2\left([0,T]\times\Omega; H^1_\#(Y)/\mathbb{R}\right)$ such that, up to a subsequence, v^ε and $\varepsilon\nabla v^\varepsilon$ two-scale converge to $v_1(t,x,y)$ and $\nabla_y v_1(t,x,y)$, respectively.

Generalization to the boundary I

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

Theorem 8

Let v^ε be a sequence in $L^2([0,T]\times\Gamma_\varepsilon)$ such that

$$\varepsilon\int_0^T\int_{\Gamma_\varepsilon}|v^\varepsilon(t,x)|^2\,d\sigma_\varepsilon(x)dt\le C,$$

where C is a positive constant, independent of ε. $\downarrow$

Generalization to the boundary II

Theorem 8

↳ *Then there exists a subsequence (still denoted by ε) and a two-scale limit $v_0(t,x,y) \in L^2\left([0,T]\times\Omega; L^2(\Gamma)\right)$ such that $v^\varepsilon(t,x)$ two-scale converges to $v_0(t,x,y)$ in the sense that*

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

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

Estimates on $u_m^\varepsilon, \nabla_x u_m^\varepsilon$ I

Since the homogenization will be carried out in the framework of two-scale convergence, the first necessary step is to obtain the a priori estimates for the sequences $u_j^\varepsilon, \nabla u_j^\varepsilon, \partial_t u_j^\varepsilon$ in $[0, T] \times \Omega_\varepsilon$. Here will be presented the estimate on the solution and its gradient.

Lemma 9

Let $T > 0$ be arbitrary and u_1^ε be a classical solution of (3.2). Then,

$$\|u_1^\varepsilon\|_{L^\infty(0,T;L^\infty(\Omega_\varepsilon))} \leq |U_1| + \|u_1^\varepsilon\|_{L^\infty(0,T;L^\infty(\Gamma_\varepsilon))}. \tag{5.1}$$

Estimates on $u_m^\varepsilon, \nabla_x u_m^\varepsilon$ II

Lemma 10

Let $T > 0$ be arbitrary and u_1^ε be a classical solution of (3.2). Then,

$$\|u_1^\varepsilon\|_{L^\infty(0,T;L^\infty(\Gamma_\varepsilon))} \leq c\|\psi\|_{L^\infty(0,T;B)}, \tag{5.2}$$

where c is independent of ε.

Thus, the boundedness of $u_1^\varepsilon(t,x)$ in $L^\infty([0,T]\times\Gamma_\varepsilon)$, uniformly in ε, can be immediately deduced from Lemma (10) applying Lemma (9).

Lemma 11

The sequence $\nabla_x u_1^\varepsilon$ is bounded in $L^2([0,T]\times\Omega_\varepsilon)$, uniformly in ε.

Estimates on $u_m^\varepsilon, \nabla_x u_m^\varepsilon$ III

The lemmas considered show the boundedness of the term $u_1^\varepsilon(t,x)$ and $\nabla_x u_1^\varepsilon(t,x)$. With a similar procedure one can show the boundedness of the generic term u_m and of its gradient.

Estimate on ∂u_m^ε

Lemma 12

The sequence $\partial_t u_j^\varepsilon (1 \leq j \leq M)$ is bounded in $L^2([0,T] \times \Omega_\varepsilon)$, uniformly in ε.

Estimate on ∂u_m^ε

Proof.

Case $j = 1$: multiply the first equation in (3.2) by the function $\partial_t u_1^\varepsilon(t,x)$. By the divergence theorem, by Hölder's and Young's inequalities, following the same arguments of the previous proofs and exploiting the boundedness of $u_j^\varepsilon(t,x)(1 \le j \le M)$ in $L^\infty(0,T;L^\infty(\Omega_\varepsilon))$, one can get

$$\begin{aligned} &\int_{\Omega_\varepsilon} \left|\frac{\partial u_1^\varepsilon}{\partial t}\right|^2 dx + d_1 \frac{\partial}{\partial t}\int_{\Omega_\varepsilon} |\nabla_x u_1^\varepsilon|^2 \, dx \\ &\le C_1 + 2\varepsilon d_1 \int_{\Gamma_\varepsilon} \psi\left(t,x,\frac{x}{\varepsilon}\right)\frac{\partial u_1^\varepsilon}{\partial t}\, d\sigma_\varepsilon(x). \end{aligned} \tag{5.3}$$

Estimate on ∂u_m^ε

Integrating over $[0, t]$ with $t \in [0, T]$, it is possible to obtain

$$\int_0^t ds \int_{\Omega_\varepsilon} \left| \frac{\partial u_1^\varepsilon}{\partial s} \right|^2 dx + d_1 \left(1 - \varepsilon^2 C_3\right) \int_{\Omega_\varepsilon} |\nabla_x u_1^\varepsilon|^2 \, dx \leq C_1 T + C_4 + C_7, \tag{5.4}$$

where the positive constants C_1, C_3, C_4, C_7 are independent of ε, since $\psi \in L^\infty(0, T; B)$, u_1^ε is bounded in $L^\infty\left(0, T; L^\infty\left(\Omega_\varepsilon\right)\right)$, $\nabla_x u_1^\varepsilon$ is bounded in $L^2(0, T; L^2\left(\Omega_\varepsilon\right))$ and the following inequality holds

Estimate on ∂u_m^ε

$$\varepsilon \int_{\Gamma_\varepsilon} \left| \partial_t \psi \left(t, x, \frac{x}{\varepsilon} \right) \right|^2 d\sigma_\varepsilon(x) \leq \tilde{C} \left\| \partial_t \psi(t) \right\|_B^2 \leq C_5$$

with $\tilde{C}$ and C_5 independent of ε. For a sequence ε of positive numbers going to zero: $\left(1 - \varepsilon^2 C_3\right) \geq 0$. Then, the second term on the left-hand side of (5.4) is nonnegative, and one has

$$\left\| \partial_t u_1^\varepsilon \right\|_{L^2(0,T;L^2(\Omega_\varepsilon))}^2 \leq C, \tag{5.5}$$

where $C \geq 0$ is a constant independent of ε. A similar procedure can be applied to the generic term u_m. □

Extension lemma I

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 13

Suppose that the domain Ω_ε is such that assumption (3.1) *is satisfied. Then, there exists a family of linear continuous extension operators*

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

$\downarrow$

Extension lemma II

Lemma 13

↳*and a constant* $C > 0$ *independent of* ε *such that*

$$P_\varepsilon v = v \quad \text{in } \Omega_\varepsilon$$

and

$$\int_\Omega |P_\varepsilon v|^p \, dx \leq C \int_{\Omega_\varepsilon} |v|^p \, dx, \tag{5.6}$$

$$\int_\Omega |\nabla (P_\varepsilon v)|^p \, dx \leq C \int_{\Omega_\varepsilon} |\nabla v|^p \, dx \tag{5.7}$$

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

Statement of the main theorem I

- Now that all the necessary result are obtained, it's possible to state the main theorem of the homogenization of the Smoluchowski equation in perforated domains.
- Theorem (14) shows that the macroscale (homogenized) model, obtained from Eqs. (3.2)-(3.4) as $\varepsilon \to 0$, is **asymptotically consistent** with the original model and resolves both the coarse and the small scale.
- The information given on the microscale, by the non-homogeneous Neumann boundary condition in (3.2), is transferred into the source term in the first equation of (6.1), describing the limit model.

Statement of the main theorem II

Theorem 14

Let $u_m^\varepsilon(t,x)(1 \le m \le M)$ *be a family of classical solutions to problems* (3.2)-(3.4). *The sequences* $\widetilde{u_m^\varepsilon}$ *and* $\widetilde{\nabla_x u_m^\varepsilon}(1 \le m \le M)$ *two-scale converge to:* $[\chi(y)u_m(t,x)]$ *and* $\left[\chi(y)\left(\nabla_x u_m(t,x) + \nabla_y u_m^1(t,x,y)\right)\right](1 \le m \le M)$, *respectively, where tilde denotes the extension by zero outside* Ω_ε *and* $\chi(y)$ *represents the characteristic function of* Y^*. *The limiting functions* $\left(u_m(t,x), u_m^1(t,x,y)\right)(1 \le m \le M)$ *are the unique solutions in* $L^2\left(0,T;H^1(\Omega)\right) \times L^2\left([0,T]\times\Omega; H^1_\#(Y)/\mathbb{R}\right)$ *of the following two-scale homogenized systems.*

Statement of the main theorem III

If $m = 1$:

$$\begin{cases} \theta \dfrac{\partial u_1}{\partial t}(t,x) - \operatorname{div}_x \left[d_1 A \nabla_x u_1(t,x) \right] & \\ \qquad + \theta u_1(t,x) \displaystyle\sum_{j=1}^{M} a_{1,j} u_j(t,x) & \text{in } [0,T] \times \Omega, \\ \qquad = d_1 \displaystyle\int_\Gamma \psi(t,x,y)\, d\sigma(y), & \\ \left[A \nabla_x u_1(t,x) \right] \cdot n = 0, & \text{on } [0,T] \times \partial\Omega, \\ u_1(0,x) = U_1, & \text{in } \Omega. \end{cases} \tag{6.1}$$

Statement of the main theorem IV

If $1 < m < M$:

$$
\begin{cases}
\theta \dfrac{\partial u_m}{\partial t}(t,x) - \operatorname{div}_x \left[d_m A \nabla_x u_m(t,x) \right] \\
\qquad\qquad + \theta u_m(t,x) \displaystyle\sum_{j=1}^{M} a_{m,j} u_j(t,x) & \text{in } [0,T] \times \Omega, \\
\quad = \dfrac{\theta}{2} \displaystyle\sum_{j=1}^{m-1} a_{j,m-j} u_j(t,x) u_{m-j}(t,x), & \\
\left[A \nabla_x u_m(t,x) \right] \cdot n = 0, & \text{on } [0,T] \times \partial\Omega, \\
u_m(0,x) = 0, & \text{in } \Omega.
\end{cases}
\tag{6.2}
$$

Statement of the main theorem V

If $m = M$:

$$\begin{cases} \theta \dfrac{\partial u_M}{\partial t}(t,x) - div_x \left[d_M A \nabla_x u_M(t,x) \right] \\ \qquad = \dfrac{\theta}{2} \displaystyle\sum_{\substack{j+k \geq M \\ j,k<M}} a_{j,k} u_j(t,x) u_k(t,x), & \text{in } [0,T] \times \Omega, \\ [A \nabla_x u_M(t,x)] \cdot n = 0, & \text{on } [0,T] \times \partial\Omega, \\ u_M(0,x) = 0, & \text{in } \Omega. \end{cases} \tag{6.3}$$

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

Statement of the main theorem VI

and $\theta = \int_Y \chi(y)\, dy = |Y^*|$ is the volume fraction of material, and 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 *ith* unit vector in $\mathbb{R}^n$ and $(w_i)_1 \leq i \leq N$ the family of solutions of the cell problem

$$\begin{cases} -\operatorname{div}_y [\nabla_y w_i + \hat{e}_i] = 0, & \text{in } Y^*, \\ (\nabla_y w_i + \hat{e}_i) \cdot n = 0, & \text{on } \Gamma, \\ y \to w_i(y), & Y - \text{periodic}. \end{cases} \tag{6.4}$$

Proof for $m = 1$ I

Proof.

In view of Lemmas (9)-(10) and (11), the sequences $\widetilde{u_m^\varepsilon}$ and $\widetilde{\nabla_x u_m^\varepsilon}(1 \leq m \leq M)$ are bounded in $L^2([0,T] \times \Omega)$, and by application of Theorem (3) and Theorem (6), and so:

$$\widetilde{u_m^\varepsilon} \overset{2s}{\rightharpoonup} [\chi(y) u_m(t,x)], \tag{6.5}$$

$$\widetilde{\nabla_x u_m^\varepsilon} \overset{2s}{\rightharpoonup} [\chi(y) (\nabla_x u_m(t,x) + \nabla_y u_m^1(t,x,y))], \quad (1 \leq m \leq M). \tag{6.6}$$

Proof for $m = 1$ II

Similarly, in view of Lemma (12), it is possible to prove that

$$\left(\widetilde{\frac{\partial u_m^\varepsilon}{\partial t}}\right) \overset{2s}{\rightharpoonup} \left[\chi(y)\frac{\partial u_m}{\partial t}(t,x)\right], \quad (1 \le m \le M). \tag{6.7}$$

One can now find the homogenized equations satisfied by $u_m(t,x)$ and $u_m^1(t,x,y)$ $(1 \le m \le M)$. In the case $m = 1$, multiply the first equation of (3.2) by the test function to obtain the weak formulation of the problem

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

Proof for $m = 1$ III

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

$$\frac{\partial u_1^\varepsilon}{\partial t}\phi_\varepsilon - \operatorname{div}\left(d_1 \nabla_x u_1^\varepsilon\right)\phi_\varepsilon + u_1^\varepsilon \sum_{j=1}^{M} a_{1,j} u_1^\varepsilon \phi_\varepsilon = 0.$$

Proof for $m = 1$ IV

Integrating, the divergence theorem yields

$$\begin{aligned}
&\int_0^T \int_{\Omega_\varepsilon} \frac{\partial u_1^\varepsilon}{\partial t} \phi_\varepsilon \left(t, x, \frac{x}{\varepsilon}\right) \, dt \, dx \\
&+ d_1 \int_0^T \int_{\Omega_\varepsilon} \nabla_x u_1^\varepsilon \cdot \nabla \phi_\varepsilon \, dt \, dx \\
&+ \int_0^T \int_{\Omega_\varepsilon} u_1^\varepsilon \sum_{j=1}^M a_{1,j} u_j^\varepsilon \phi_\varepsilon \, dt \, dx \\
&= \varepsilon d_1 \int_0^T \int_{\Gamma_\varepsilon} \psi \left(t, x, \frac{x}{\varepsilon}\right) \phi_\varepsilon \, dt \, d\sigma_\varepsilon(x).
\end{aligned} \tag{6.8}$$

Proof for $m = 1$ V

Passing to the two-scale limit, one can get

$$\begin{aligned}
&\int_0^T \int_\Omega \int_{Y^*} \frac{\partial u_1}{\partial t}(t,x)\phi(t,x)\,dt\,dx\,dy \\
&\quad + d_1 \int_0^T \int_\Omega \int_{Y^*} [\nabla_x u_1(t,x) + \\
&\qquad \nabla_y u_1^1\,(t,x,y)] \cdot [\nabla_x \phi(t,x) + \nabla_y \phi_1(t,x,y)]\,dt\,dx\,dy \\
&+ \int_0^T \int_\Omega \int_{Y^*} u_1(t,x) \sum_{j=1}^{M} a_{1,j} u_j(t,x)\phi(t,x)\,dt\,dx\,dy \\
&= d_1 \int_0^T \int_\Omega \int_\Gamma \psi(t,x,y)\phi(t,x)\,dt\,dx\,d\sigma(y).
\end{aligned} \tag{6.9}$$

Proof for $m = 1$ VI

The last term on the left-hand side of (6.9) has been obtained by using Theorem (4), while the term on the right-hand side has been attained by application of Theorem (8). An integration by parts shows that (6.9) is a variational formulation associated with the following homogenized system:

Proof for $m = 1$ VII

$$-\operatorname{div}_y \left[d_1 \left(\nabla_x u_1(t,x) + \nabla_y u_1^1(t,x,y) \right) \right] = 0, \quad \text{in } [0,T] \times \Omega \times Y^*, \tag{6.10}$$

$$\left[\nabla_x u_1(t,x) + \nabla_y u_1^1(t,x,y) \right] \cdot n = 0, \quad \text{on } [0,T] \times \Omega \times \Gamma, \tag{6.11}$$

Proof for $m = 1$ VIII

$$\theta \frac{\partial u_1}{\partial t}(t,x) - \operatorname{div}_x \left[d_1 \int_{Y^*} \left(\nabla_x u_1(t,x) + \nabla_y u_1^1(t,x,y) \right) \, dy \right]$$
$$+\theta u_1(t,x) \sum_{j=1}^{M} a_{1,j} u_j(t,x) - d_1 \int_{\Gamma} \psi(t,x,y) \, d\sigma(y) = 0, \quad (6.12)$$
$$\text{in } [0,T] \times \Omega,$$
$$\left[\int_{Y^*} \left(\nabla_x u_1(t,x) + \nabla_y u_1^1(t,x,y) \right) \, dy \right] \cdot n = 0, \quad (6.13)$$
$$\text{on } [0,T] \times \partial\Omega.$$

Proof for $m = 1$ IX

To conclude, by continuity, one can have that

$$u_1(0, x) = U_1 \quad \text{in } \Omega.$$

Taking advantage of the constancy of the diffusion coefficient d_1, Eqs. (6.10) and (6.11) can be rewritten as follows

$$\Delta_y u_1^1(t, x, y) = 0, \quad \text{in } [0, T] \times \Omega \times Y^*, \tag{6.14}$$

$$\nabla_y u_1^1(t, x, y) \cdot n = -\nabla_x u_1(t, x) \cdot n, \quad \text{on } [0, T] \times \Omega \times \Gamma. \tag{6.15}$$

Proof for $m = 1$ X

Then, $u_1^1(t, x, y)$ satisfying (92)-(93) can be written as

$$u_1^1(t, x, y) = \sum_{i=1}^{N} w_i(y) \frac{\partial u_1}{\partial x_i}(t, x), \tag{6.16}$$

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

$$\begin{cases} -\operatorname{div}_y [\nabla_y w_i + \hat{e}_i] = 0, & \text{in } Y^*, \\ (\nabla_y w_i + \hat{e}_i) \cdot n = 0, & \text{on } \Gamma, \\ y \to w_i(y), & Y - \text{periodic}. \end{cases} \tag{6.17}$$

Proof for $m = 1$ XI

By using the relation (6.16) in Eqs. (6.12) and (6.13), it is possible to get

$$\theta \frac{\partial u_1}{\partial t}(t,x) - \operatorname{div}_x \left[d_1 A \nabla_x u_1(t,x) \right] + \theta u_1(t,x) \sum_{j=1}^{M} a_{1,j} u_j(t,x) - d_1 \int_\Gamma \psi(t,x,y)\, d\sigma(y) = 0, \quad \text{in } [0,T] \times \Omega, \tag{6.18}$$

$$\left[A \nabla_x u_1(t,x) \right] \cdot n = 0, \quad \text{on } [0,T] \times \partial\Omega, \tag{6.19}$$

Proof for $m = 1$ XII

where A is a matrix with constant coefficients defined by

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

Some conclusions

- The model presented here can be related to the one introduced in Bertsch et. al. (2016), where the process of diffusion and agglomeration of $\mathrm{A}\beta$ is described on the macroscale by a Smoluchowski system with a source term.
- Performed a **formal derivation**, starting from the microscale, of the source term $\mathcal{F}$.
- It's good to notice that the homogenization theory works in every perforated domain so one can follow the previous arguments to homogenize every system in a random perforated domain.

Thanks for your attention!

References

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