A mathematical model for Alzheimer's disease:

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

- 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-**amyloid 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 $A\beta$ amyloid during aging.

- 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 $A\beta$ peptide.

- 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 $A\beta$ 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.

- 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 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 $A\beta$ peptide, starting from monomers.

This phenomenon is called **coalescence** and can be written formally as

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

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

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

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

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:

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

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

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

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

$Q_{g,i}$ 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 $a_{i,j} = a_{j,i}$.

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.
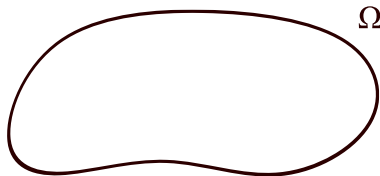
Figure: The domain Ω representing the cerebral tissue.

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 $\overline{T} \subset \text{Int}(Y)$.
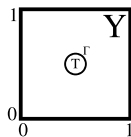Now call with $Y^* = Y \backslash T$ the material part, the
"solid part" of the brain.

Figure: The periodic
neuron

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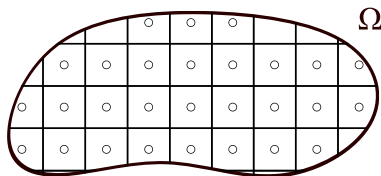
$$T_\varepsilon := \Omega \cap \tau(\varepsilon\overline{T}).$$

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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.

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.

- 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 model is given by a system of PDEs:

- The first equation describes the evolution of monomers:

$$
\begin{cases}
\dfrac{\partial u_1^\varepsilon}{\partial t}(t,x) - d_1 \Delta_x u_1^\varepsilon(t,x) \\
+ u_1^\varepsilon(t,x) \displaystyle\sum_{j=1}^{M} a_{1,j} u_j^\varepsilon(t,x) = 0, & \text{in } [0,T] \times \Omega_\varepsilon, \\[2mm]
\dfrac{\partial u_1^\varepsilon}{\partial v} \equiv \nabla_x u_1^\varepsilon \cdot n = 0, & \text{on } [0,T] \times \partial\Omega, \\[2mm]
\dfrac{\partial u_1^\varepsilon}{\partial v} \equiv \nabla_x u_1^\varepsilon \cdot n = \varepsilon \psi\left(t,x,\dfrac{x}{\varepsilon}\right), & \text{on } [0,T] \times \Gamma_\varepsilon, \\[2mm]
u_1^\varepsilon(0,x) = U_1, & \text{in } \Omega_\varepsilon.
\end{cases}
\tag{3.2}
$$

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

$$
\begin{cases}
\dfrac{\partial u_m^\varepsilon}{\partial t}(t,x) - d_m \Delta_x u_m^\varepsilon(t,x) \\[2mm]
\quad + u_m^\varepsilon(t,x) \displaystyle\sum_{j=1}^{M} a_{m,j} u_j^\varepsilon(t,x), \quad \text{in } [0,T] \times \Omega_\varepsilon, \\[2mm]
\quad = \dfrac{1}{2} \displaystyle\sum_{j=1}^{m-1} a_{j,m-j} u_j^\varepsilon u_{m-j}^\varepsilon \\[4mm]
\dfrac{\partial u_m^\varepsilon}{\partial v} \equiv \nabla_x u_m^\varepsilon \cdot n = 0, \quad\quad \text{on } [0,T] \times \partial\Omega_\varepsilon, \\[2mm]
u_m^\varepsilon(0,x) = 0, \quad\quad\quad\quad\quad \text{in } \Omega_\varepsilon.
\end{cases}
\tag{3.3}
$$

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

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

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

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

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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 $u_j^\varepsilon \ 1 \geq j \geq M$ which is defined on a varying set Ω_ε, which also is **perforated**.

Theorem 1

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

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

such that

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

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

$$\lim_{\varepsilon \to 0} \int_0^T \int_\Omega v^\varepsilon(t, x) \psi \left(t, x, \frac{x}{\varepsilon} \right) \, dx dt$$

$$= \int_0^T \int_\Omega \int_Y v_0(t, x, y) \psi(t, x, y) \, dy dx dt$$

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

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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: $v^\varepsilon \xrightarrow{2s} v_0$.

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

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.*

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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**.

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

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

↓

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Theorem 4

$\hookrightarrow$ *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*

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

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

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

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Definition 5

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

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

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.

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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 $v^{\varepsilon} \stackrel{2s}{\rightharpoonup} v(t,x)$, 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, $\nabla v^{\varepsilon} \stackrel{2s}{\rightharpoonup} \left(\nabla_x v(t,x) + \nabla_y v_1(t,x,y)\right)$.*

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.

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

Theorem 8

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

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

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

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

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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,

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

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.

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.

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.

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 $u_j^\varepsilon(t, x)(1 \leq j \leq M)$ in $L^\infty(0, T; L^\infty(\Omega_\varepsilon))$, one can get

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

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

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

where the positive constants C_1, C_3, C_4, C_7 are independent of ε, since $\psi \in L^\infty(0, T; B), u_1^\varepsilon$ 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

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

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

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

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

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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*

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

$\downarrow$

Lemma 13

$\hookrightarrow$and a constant $C > 0$ independent of ε such that

$$P_\varepsilon v = v \quad in \; \Omega_\varepsilon$$

and

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

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

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

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- 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.

Theorem 14

Let $u_m^\varepsilon(t,x)(1 \leq m \leq M)$ be a family of classical solutions to problems (3.2)-(3.4). The sequences $\widetilde{u_m^\varepsilon}$ and $\widetilde{\nabla_x u_m^\varepsilon}(1 \leq m \leq M)$ two-scale converge to: $[\chi(y)u_m(t,x)]$ and $\left[\chi(y)\left(\nabla_x u_m(t,x) + \nabla_y u_m^1(t,x,y)\right)\right](1 \leq m \leq M)$, respectively, where tilde denotes the extension by zero outside Ω_ε and $\chi(y)$ represents the characteristic function of Y^*. The limiting functions $\left(u_m(t,x), u_m^1(t,x,y)\right)(1 \leq m \leq M)$ 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.

If $m = 1$:

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

If $1 < m < M$:

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

If $m = M$:

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

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

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.

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:

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

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

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

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

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

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

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

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

Andrea Bonifacio   **POLITECNICO** MILANO 1863

Integrating, the divergence theorem yields

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

Passing to the two-scale limit, one can get

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

Andrea Bonifacio

POLITECNICO MILANO 1863

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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:

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

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

$$\theta \frac{\partial u_1}{\partial t}(t,x) - \text{div}_x \left[d_1 \int_{Y^*} \left(\nabla_x u_1(t,x) + \nabla_y u_1^1(t,x,y) \right) \, dy \right]$$

$$+ \theta u_1(t,x) \sum_{j=1}^{M} a_{1,j} u_j(t,x) - d_1 \int_{\Gamma} \psi(t,x,y) \, d\sigma(y) = 0, \quad (6.12)$$

$$\text{in } [0,T] \times \Omega,$$

$$\left[\int_{Y^*} \left(\nabla_x u_1(t,x) + \nabla_y u_1^1(t,x,y) \right) \, dy \right] \cdot n = 0, \quad (6.13)$$

$$\text{on } [0,T] \times \partial\Omega.$$

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

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

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

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

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

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

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

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

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

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

Andrea Bonifacio

POLITECNICO MILANO 1863

where A is a matrix with constant coefficients defined by

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

$\square$

- The model presented here can be related to the one introduced in Bertsch et. al. (2016), where the process of diffusion and agglomeration of $A\beta$ 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!

POLITECNICO MILANO 1863

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