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Mathematical models in medicine:

An approach via stochastic homogenization of the

Smoluchowski equation

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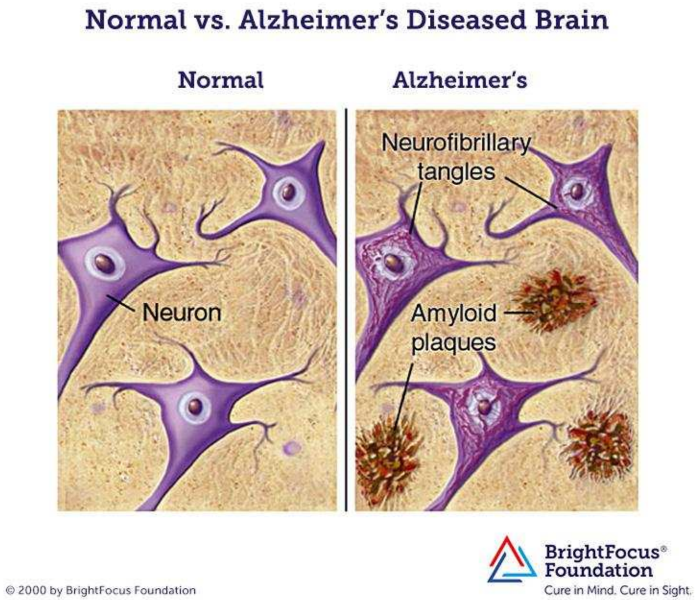
Alzheimer Disease (AD)



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

$$\frac{\partial u_i}{\partial t}(t,x) - d_i \, \triangle_x u_i(t,x) = \mathcal{Q}_i(u) \qquad \text{in } [0,T] \times \mathbf{Q}, \tag{1}$$

where $\mathbf{Q}$ is the spatial domain and $[0,T]$ a time interval.

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

$$\mathcal{Q}_i(u) = \mathcal{Q}_{g,i}(u) - \mathcal{Q}_{l,i}(u) \qquad\qquad i \geq 1 \tag{2}$$

with the gain ($\mathcal{Q}_{g,i}$) and loss ($\mathcal{Q}_{l,i}$) terms given by

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

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

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

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

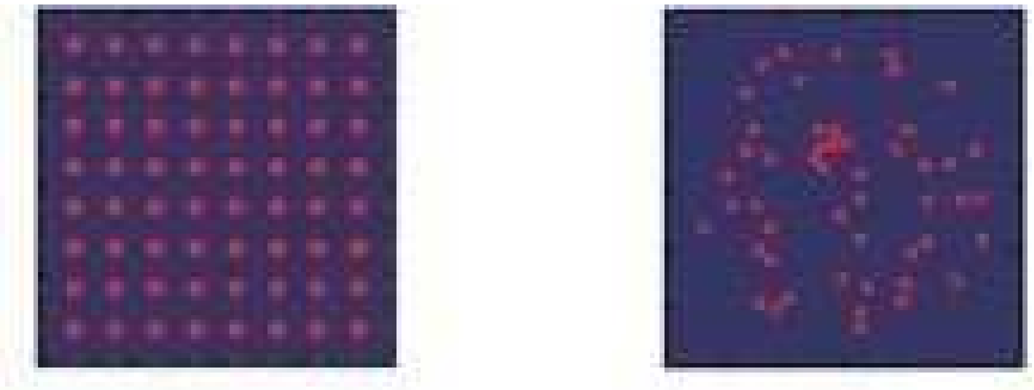


Figure 1: Periodically (left) and randomly (right) perforated domains.

In the present work, we account for the non-periodic cellular structure of the brain.

The distribution of neurons is modeled in the following way: there exists a family of predominantly genetic causes, not wholly deterministic, which influences the position of neurons and the microscopic structure of the parenchyma in a portion of the brain tissue $\mathbf{Q}$.

We consider non-periodic random diffusion coefficients and a random production of Aβ in the monomeric form at the level of neuronal membranes.

This together defines a probability space $(\Omega, \mathcal{F}, \mathbb{P})$.

Denoting by $\omega \in \Omega$ the random variable in our model, the set of random holes in $\mathbb{R}^m$ (representing the neurons) is labeled by $G(\omega)$.

The production of β-amyloid at the boundary $\Gamma(\omega)$ of $G(\omega)$ is described by a random scalar function $\eta(x, \omega)$.

The diffusivity, in the brain parenchyma, of clusters of different sizes s is modeled by random matrices $D_s(x, \omega)$ on Ω.

We assume that the randomness of the medium is stationary, that is, the probability distribution of the random variables is shift invariant.

The assumption of stationarity provides a family of mappings $(\tau_x)_{x\in\mathbb{R}^m} : \Omega \to \Omega$ such that $\eta(x, \omega) = \eta(\tau_x \omega)$, $D_s(x, \omega) = D_s(\tau_x \omega)$.

The stationarity of the coefficients and the resulting dynamical system τ_x transfer some structural properties from $\mathbb{R}^m$ to Ω such that we could formally identify $\Omega \approx \mathbb{R}^m$.

In the following, ε will denote the general term of a sequence of positive reals which converges to zero.

We introduce the vector-valued random function $u^\varepsilon : [0,T] \times \mathbf{Q}^\varepsilon \to \mathbb{R}^M$, $u^\varepsilon = (u_1^\varepsilon, \ldots, u_M^\varepsilon)$ (with $M \in \mathbb{N}$ being fixed) where the variable $u_s^\varepsilon \geq 0$ ($1 \leq s < M$) represents the concentration of s-clusters, while $u_M^\varepsilon \geq 0$ takes into account aggregations of more than $M-1$ monomers.

With these notations, our system reads:

$$\begin{cases} \dfrac{\partial u_1^\varepsilon}{\partial t} - div(D_1(t,x,\tau_{\frac{x}{\varepsilon}}\omega)\,\nabla_x u_1^\varepsilon) + u_1^\varepsilon \sum_{j=1}^M a_{1,j} u_j^\varepsilon = 0 & \text{in } [0,T] \times \mathbf{Q}^\varepsilon \\ [D_1(t,x,\tau_{\frac{x}{\varepsilon}}\omega)\,\nabla_x u_1^\varepsilon] \cdot n = 0 & \text{on } [0,T] \times \partial\mathbf{Q} \\ [D_1(t,x,\tau_{\frac{x}{\varepsilon}}\omega)\,\nabla_x u_1^\varepsilon] \cdot \nu_{\Gamma_{\mathbf{Q}}^\varepsilon} = \varepsilon\,\eta(t,x,\tau_{\frac{x}{\varepsilon}}\omega) & \text{on } [0,T] \times \Gamma_{\mathbf{Q}}^\varepsilon \\ u_1^\varepsilon(0,x) = U_1 & \text{in } \mathbf{Q}^\varepsilon \end{cases} \tag{5}$$

if $1 < s < M$

$$\begin{cases} \frac{\partial u_s^\varepsilon}{\partial t} - div(D_s(t,x,\tau_{\frac{x}{\varepsilon}}\omega)\,\nabla_x u_s^\varepsilon) + u_s^\varepsilon \sum_{j=1}^{M} a_{s,j} u_j^\varepsilon = \frac{1}{2}\sum_{j=1}^{s-1} a_{j,s-j}\, u_j^\varepsilon\, u_{s-j}^\varepsilon & \text{in } [0,T]\times \mathbf{Q}^\varepsilon \\ [D_s(t,x,\tau_{\frac{x}{\varepsilon}}\omega)\,\nabla_x u_s^\varepsilon]\cdot n = 0 & \text{on } [0,T]\times \partial\mathbf{Q} \\ [D_s(t,x,\tau_{\frac{x}{\varepsilon}}\omega)\,\nabla_x u_s^\varepsilon]\cdot \nu_{\Gamma_{\mathbf{Q}}^\varepsilon} = 0 & \text{on } [0,T]\times \Gamma_{\mathbf{Q}}^\varepsilon \\ u_s^\varepsilon(0,x) = 0 & \text{in } \mathbf{Q}^\varepsilon \end{cases} \tag{6}$$

and eventually

$$\begin{cases} \frac{\partial u_M^\varepsilon}{\partial t} - div(D_M(t,x,\tau_{\frac{x}{\varepsilon}}\omega)\,\nabla_x u_M^\varepsilon) = \frac{1}{2}\sum_{\substack{j+k\geq M \\ k<M\,(\text{if } j=M) \\ j<M\,(\text{if } k=M)}} a_{j,k}\, u_j^\varepsilon\, u_k^\varepsilon & \text{in } [0,T]\times \mathbf{Q}^\varepsilon \\ [D_M(t,x,\tau_{\frac{x}{\varepsilon}}\omega)\,\nabla_x u_M^\varepsilon]\cdot n = 0 & \text{on } [0,T]\times \partial\mathbf{Q} \\ [D_M(t,x,\tau_{\frac{x}{\varepsilon}}\omega)\,\nabla_x u_M^\varepsilon]\cdot \nu_{\Gamma_{\mathbf{Q}}^\varepsilon} = 0 & \text{on } [0,T]\times \Gamma_{\mathbf{Q}}^\varepsilon \\ u_M^\varepsilon(0,x) = 0 & \text{in } \mathbf{Q}^\varepsilon \end{cases} \tag{7}$$

We assume that the movement of clusters results only from a diffusion process described by a stationary ergodic random matrix

$$\left(d^s_{i,j}(t, x, \tau_{\frac{x}{\varepsilon}}\omega)\right)_{i,j=1,\dots,m} =: D_s(t, x, \tau_{\frac{x}{\varepsilon}}\omega) \qquad 1 \leq s \leq M$$

where $(t, x) \in [0, T] \times \mathbf{Q}$.

The production of β-amyloid peptide by the malfunctioning neurons is described imposing a non-homogeneous Neumann condition on the boundary of the holes, randomly selected within our domain.

To this end, we consider on $\Gamma^\varepsilon_{\mathbf{Q}}$ a stationary ergodic random function

$$\eta : [0, T] \times \overline{\mathbf{Q}} \times \Omega \to [0, 1] \tag{8}$$

where the value '0' is assigned to 'healthy' neurons while all the other values in $]0, 1]$ indicate different degrees of malfunctioning.

Moreover, we assume that η is an increasing function of time, since once the neuron has become 'ill', it can no longer regain its original state of health.

Stationary ergodic dynamical systems

Definition 1 (Dynamical system). *Let $(\Omega, \mathcal{F}, \mathbb{P})$ be a probability space. An m-dimensional dynamical system is defined as a family of measurable bijective mappings $\tau_x : \Omega \to \Omega$, $x \in \mathbb{R}^m$, satisfying the following conditions:*

(i) the group property: $\tau_0 = \mathbb{1}$ ($\mathbb{1}$ is the identity mapping), $\tau_{x+y} = \tau_x \circ \tau_y \quad \forall x, y \in \mathbb{R}^m$;

(ii) the mappings $\tau_x : \Omega \to \Omega$ preserve the measure $\mathbb{P}$ on Ω, i.e., for every $x \in \mathbb{R}^m$, and every $\mathbb{P}$-measurable set $F \in \mathcal{F}$, we have $\mathbb{P}(\tau_x F) = \mathbb{P}(F)$;

(iii) the map $\mathcal{T} : \Omega \times \mathbb{R}^m \to \Omega$: $(\omega, x) \mapsto \tau_x \omega$ is measurable (for the standard σ-algebra on the product space, where on $\mathbb{R}^m$ we take the Borel σ-algebra).

Definition 2 (Ergodicity). *A dynamical system is called ergodic if one of the following equivalent conditions is fulfilled:*

(i) given a measurable and invariant function f in Ω, that is

$$\forall x \in \mathbb{R}^m \quad f(\omega) = f(\tau_x \omega)$$

almost everywhere in Ω, then

$$f(\omega) = \text{const.} \quad \text{for} \quad \mathbb{P} - a.e. \ \omega \in \Omega;$$

(ii) if $F \in \mathcal{F}$ is such that $\tau_x F = F \quad \forall x \in \mathbb{R}^m$, then $\mathbb{P}(F) = 0$ or $\mathbb{P}(F) = 1$.

Definition 3 (Stationarity). *Given a probability space $(\Omega, \mathcal{F}, \mathbb{P})$, a real valued process is a measurable function $f : \mathbb{R}^m \times \Omega \to \mathbb{R}$. We will say f is stationary if the distribution of the random variable $f(y, \cdot) : \Omega \to \mathbb{R}$ is independent of y, i.e., for all $a \in \mathbb{R}$, $\mathbb{P}(\{\omega : f(y, \omega) > a\})$ is independent of y. This is qualified by assuming the existence of a dynamical system $\tau_y : \Omega \to \Omega$ ($y \in \mathbb{R}^m$) and saying that $f : \mathbb{R}^m \times \Omega \to \mathbb{R}$ is stationary if*

$$f(y + y', \omega) = f(y, \tau_{y'}\omega) \quad \text{for all} \quad y, y' \in \mathbb{R}^m \quad \text{and} \quad \omega \in \Omega.$$

We say that a random variable $f : \mathbb{R}^m \times \Omega \to \mathbb{R}$ is stationary ergodic if it is stationary and the underlying dynamical system is ergodic.

Remark 1. *A function f is stationary ergodic if and only if there is some measurable function $\tilde{f} : \Omega \to \mathbb{R}$ such that*

$$f(x, \omega) = \tilde{f}(\tau_x \omega).$$

For a fixed $\omega \in \Omega$ the function $x \mapsto \tilde{f}(\tau_x \omega)$ of argument $x \in \mathbb{R}^m$ is said to be a realization of function $\tilde{f}$.

Let $L^p(\Omega)$ $(1 \leq p < \infty)$ denote the space formed by (the equivalence classes of) measurable functions that are $\mathbb{P}$-integrable with exponent p and $L^\infty(\Omega)$ be the space of measurable essentially bounded functions.

If $f \in L^p(\Omega)$, then $\mathbb{P}$-almost all realizations $f(\tau_x\omega)$ belong to $L^p_{\text{loc}}(\mathbb{R}^m)$.

Recalling:

$$L^2_{\mathrm{pot,loc}}(\mathbb{R}^m) := \{f \in L^2_{\mathrm{loc}}(\mathbb{R}^m;\mathbb{R}^m) \mid \forall \mathbf{U} \text{ bounded domain, } \exists\varphi \in H^1(\mathbf{U}) \;:\; f = \nabla\varphi\} \;,$$

$$L^2_{\mathrm{sol,loc}}(\mathbb{R}^m) := \left\{f \in L^2_{\mathrm{loc}}(\mathbb{R}^m;\mathbb{R}^m) \mid \int_{\mathbb{R}^m} f \cdot \nabla\varphi = 0 \;\forall\varphi \in C^1_c(\mathbb{R}^m)\right\}$$

we can then define corresponding spaces on Ω through

$$L^2_{\mathrm{pot}}(\Omega) := \{f \in L^2(\Omega;\mathbb{R}^m) \;:\; f_\omega \in L^2_{\mathrm{pot,loc}}(\mathbb{R}^m) \text{ for } \mathbb{P}-\text{a.e. } \omega \in \Omega\} \;,$$

$$L^2_{\mathrm{sol}}(\Omega) := \{f \in L^2(\Omega;\mathbb{R}^m) \;:\; f_\omega \in L^2_{\mathrm{sol,loc}}(\mathbb{R}^m) \text{ for } \mathbb{P}-\text{a.e. } \omega \in \Omega\} \;,$$

$$\mathcal{V}^2_{\mathrm{pot}}(\Omega) := \left\{f \in L^2_{\mathrm{pot}}(\Omega) \;:\; \int_\Omega f \, d\mathbb{P} = 0\right\} \;.$$

These spaces are closed and

$$L^2(\Omega;\mathbb{R}^m) = L^2_{\mathrm{sol}}(\Omega) \oplus \mathcal{V}^2_{\mathrm{pot}}(\Omega).$$

Random measures and random sets

By $\mathcal{M}(\mathbb{R}^m)$ we denote the space of finitely bounded Borel measures on $\mathbb{R}^m$ equipped with the vague topology, which makes $\mathcal{M}(\mathbb{R}^m)$ a separable metric space.

The σ-field defined by this topology is denoted by $\mathcal{B}(\mathcal{M})$ since it is a Borel σ-field on $\mathcal{M}$.

A random measure is a measurable mapping

$$\mu_\bullet : \ \Omega \to \mathcal{M}(\mathbb{R}^m) \, , \qquad \omega \mapsto \mu_\omega$$

which is equivalent to the measurability of all mappings $\omega \mapsto \mu_\omega(A)$, where $A \subset \mathbb{R}^m$ are arbitrary bounded Borel sets.

A random measure is stationary if the distribution of $\mu_\omega(A)$ is invariant under translations of A.

For stationary random measures we find the following important property.

Theorem 1 (Existence of Palm measure and Campbell's Formula). *Let $\mathcal{L}$ be the Lebesgue-measure on $\mathbb{R}^m$ with $dx := d\mathcal{L}(x)$.*

Then there exists a unique measure $\mu_{\mathcal{P}}$ on Ω such that

$$\int_{\Omega}\int_{\mathbb{R}^m} f(x,\tau_x\omega)\,\mathrm{d}\mu_\omega(x)\mathrm{d}\mathbb{P}(\omega) = \int_{\mathbb{R}^m}\int_{\Omega} f(x,\omega)\,\mathrm{d}\mu_{\mathcal{P}}(\omega)\mathrm{d}x$$

for all $\mathcal{B}(\mathbb{R}^m)\times\mathcal{B}(\Omega)$-measurable non negative functions and all $\mu_{\mathcal{P}}\times\mathcal{L}$- integrable functions.

Furthermore

$$\mu_{\mathcal{P}}(A) = \int_{\Omega}\int_{\mathbb{R}^m} g(s)\chi_A(\tau_s\omega)\mathrm{d}\mu_\omega(s)\mathrm{d}\mathbb{P}(\omega)\,, \tag{9}$$

$$\int_{\Omega} f(\omega)\mathrm{d}\mu_{\mathcal{P}} = \int_{\Omega}\int_{\mathbb{R}^m} g(s)f(\tau_s\omega)\mathrm{d}\mu_\omega(s)\mathrm{d}\mathbb{P}(\omega) \tag{10}$$

for an arbitrary $g\in L^1(\mathbb{R}^m,\mathcal{L})$ with $\int_{\mathbb{R}^m} g(x)\mathrm{d}x = 1$ and $\mu_{\mathcal{P}}$ is σ-finite.

The measure $\mu_{\mathcal{P}}$ is called Palm measure.

One important property of random measures is the following generalization of the Birkhoff ergodic theorem.

Lemma 1. *Let* $\boldsymbol{Q} \subset \mathbb{R}^m$ *be a bounded domain,* $\phi \in C(\overline{\boldsymbol{Q}})$ *and* $f \in L^1(\Omega; \mu_{\mathcal{P}})$*. Then, for almost every* $\omega \in \Omega$

$$\lim_{\varepsilon \to 0} \int_{\boldsymbol{Q}} \phi(x)\, f(\tau_{\frac{x}{\varepsilon}}\omega) \mathrm{d}\mu_\omega^\varepsilon(x) = \int_{\boldsymbol{Q}} \int_\Omega \phi(x) f(\tilde{\omega}) \mathrm{d}\mu_{\mathcal{P}}(\tilde{\omega})\, \mathrm{d}x\,. \tag{11}$$

A further useful result:

Lemma 2. *Let* $\boldsymbol{Q} \subset \mathbb{R}^m$ *be a bounded domain and let* $f \in L^\infty(\boldsymbol{Q} \times \Omega; \mathcal{L} \otimes \mu_{\mathcal{P}})$*. Then,* f *has a* $\mathcal{B}(\boldsymbol{Q}) \otimes \mathcal{F}$*-measurable representative which is an ergodic function in the sense that for almost every* $\omega \in \Omega$ *and for all* $\varphi \in C(\overline{\boldsymbol{Q}})$ *it holds*

$$\begin{aligned} \lim_{\varepsilon \to 0} \int_{\boldsymbol{Q}} f(x, \tau_{\frac{x}{\varepsilon}}\omega) \varphi(x)\, \mathrm{d}\mu_\omega^\varepsilon(x) &= \int_{\boldsymbol{Q}} \int_\Omega f(x, \tilde{\omega}) \varphi(x)\, \mathrm{d}\mu_{\mathcal{P}}(\tilde{\omega})\, \mathrm{d}x\,, \\ \lim_{\varepsilon \to 0} \int_{\boldsymbol{Q}} \left| f(x, \tau_{\frac{x}{\varepsilon}}\omega) \right|^p \varphi(x)\, \mathrm{d}\mu_\omega^\varepsilon(x) &= \int_{\boldsymbol{Q}} \int_\Omega |f(x, \tilde{\omega})|^p\, \varphi(x)\, \mathrm{d}\mu_{\mathcal{P}}(\tilde{\omega})\, \mathrm{d}x \end{aligned} \tag{12}$$

for every $1 \le p < \infty$*.*

We consider random sets of the following form.

For every $\omega \in \Omega$ the set $G(\omega)$ is an open subset of $\mathbb{R}^m$. The boundary $\Gamma(\omega) = \partial G(\omega)$ is a $(m-1)$-dimensional piece-wise Lipschitz manifold.

Furthermore, we assume that the measures

$$\mu_\omega(A) := \int_{A \cap G^{\complement}(\omega)} \mathrm{d}x\,, \qquad \mu_{\Gamma(\omega)}(A) := \mathcal{H}^{m-1}(A \cap \Gamma(\omega))$$

are stationary.

Hence, there exist corresponding Palm measures $\mu_{\mathcal{P}}$ for μ_ω and $\mu_{\Gamma,\mathcal{P}}$ for $\mu_{\Gamma(\omega)}$.

Remark 2. *If A is a bounded Borel set, then*

$$\mu_\omega^\varepsilon(A) := \varepsilon^m\, \mu_\omega(\varepsilon^{-1}\, A) \tag{13}$$

$$\mu_{\Gamma(\omega)}^\varepsilon(A) := \varepsilon^m\, \mu_{\Gamma(\omega)}(\varepsilon^{-1}\, A) = \varepsilon \mathcal{H}^{m-1}(A \cap \Gamma^\varepsilon(\omega)). \tag{14}$$

Concerning the random geometries, we make the assumptions listed below.

Definition 4. *An open set $G \subset \mathbb{R}^m$ is said to be minimally smooth with constants (δ, N, M) if we may cover $\Gamma = \partial G$ by a countable sequence of open sets $(U_i)_{i \in \mathbb{N}}$ such that*

1) *Each $x \in \mathbb{R}^m$ is contained in at most N of the open sets U_i.*

2) *For any $x \in \Gamma$, the ball $B_\delta(x)$ is contained in at least one U_i.*

3) *For any i, the portion of the boundary Γ inside U_i agrees (in some Cartesian system of coordinates) with the graph of a Lipschitz function whose Lipschitz semi-norm is at most M.*

Let $\boldsymbol{Q}$ be a bounded domain in $\mathbb{R}^m$. For given constants (δ, N, M), we consider $G(\omega)$ a random open set which is a.s. minimally smooth with constants (δ, N, M) (uniformly minimally smooth).

We furthermore assume that $G(\omega) := \bigcup_{i \in \mathbb{N}} G_i(\omega)$ is a countable union of disjoint open balls $G_i(\omega)$ with a maximal diameter d_0.

We consider $G^\varepsilon(\omega) := \varepsilon G(\omega)$ and

$$\boldsymbol{Q}^\varepsilon(\omega) := \boldsymbol{Q} \setminus \left(\bigcup_{i \in I_\varepsilon(\omega)} \varepsilon G_i(\omega) \right), \qquad \Gamma^\varepsilon_{\boldsymbol{Q}}(\omega) := \bigcup_{i \in I_\varepsilon(\omega)} \partial(\varepsilon G_i(\omega)), \tag{15}$$

where

$$I_\varepsilon(\omega) := \{ i \; : \; \varepsilon G_i(\omega) \subset \boldsymbol{Q} \text{ and } \varepsilon d_0 < \min \{ d(x,y) \; : \; x \in \partial(\varepsilon G_i(\omega)), \, y \in \partial \boldsymbol{Q} \} \} \, .$$

Lemma 3. *Suppose these assumptions are satisfied. Then, there exists a family of linear continuous extension operators* $\mathcal{E}_\varepsilon \; : \; W^{1,p}(\boldsymbol{Q}^\varepsilon) \to W^{1,p}(\boldsymbol{Q})$ *and a constant* $C > 0$ *independent of* ε *such that* $\mathcal{E}_\varepsilon \phi = \phi$ *in* $\boldsymbol{Q}^\varepsilon(\omega)$ *and*

$$\int_{\boldsymbol{Q}} |\mathcal{E}_\varepsilon \phi|^p \, dx \le C \int_{\boldsymbol{Q}^\varepsilon} |\phi|^p \, dx, \tag{16}$$

$$\int_{\boldsymbol{Q}} |\nabla(\mathcal{E}_\varepsilon \phi)|^p \, dx \le C \int_{\boldsymbol{Q}^\varepsilon} |\nabla \phi|^p \, dx, \tag{17}$$

$\mathbb{P}$*-a.s. for any* $\phi \in W^{1,p}(\boldsymbol{Q}^\varepsilon)$ *and for any* $p \in (1, +\infty)$.

Stochastic two-scale convergence

Definition 5. *Let* $\Psi := (\psi_i)_{i\in\mathbb{N}}$ *be the countable dense family of* $C_b(\Omega)$*-functions,* $\Lambda = (\varphi_i)_{i\in\mathbb{N}}$ *be a countable dense subset of* $C(\overline{\boldsymbol{Q}})$*,* $\omega \in \Omega_\Psi$ *(set of full measure) and* $u^\varepsilon \in L^2(0,T;L^2(\boldsymbol{Q}))$ *for all* $\varepsilon > 0$*.*

We say that u^ε *converges (weakly) in two scales to* $u \in L^2(0,T;L^2(\boldsymbol{Q};L^2(\Omega,\mathbb{P})))$*, and write* $u^\varepsilon \overset{2s}{\rightharpoonup} u$*, if for all continuous and piece-wise affine functions* $\phi : [0,T] \to \mathrm{span}\Psi \times \Lambda$ *there holds, with* $\phi_{\omega,\varepsilon}(t,x) := \phi(t,x,\tau_{\frac{x}{\varepsilon}}\omega)$*,*

$$\lim_{\varepsilon\to 0}\int_0^T\int_{\boldsymbol{Q}} u^\varepsilon(t,x)\phi_{\omega,\varepsilon}(t,x)dx\,dt = \int_0^T\int_{\boldsymbol{Q}}\int_\Omega u(t,x,\tilde\omega)\,\phi(t,x,\tilde\omega)\,d\mathbb{P}(\tilde\omega)\,dx\,dt\,. \tag{18}$$

We say that u^ε converges strongly in two scales to u, written $u^\varepsilon \overset{2s}{\to} u$, if for every weakly two-scale converging sequence $v^\varepsilon \in L^2(\boldsymbol{Q})$ with $v^\varepsilon \overset{2s}{\rightharpoonup} v \in L^2(\boldsymbol{Q};L^2(\Omega))$ as $\varepsilon \to 0$ there holds

$$\lim_{\varepsilon\to 0}\int_{\boldsymbol{Q}} u^\varepsilon v^\varepsilon\,\mathrm{d}x = \int_{\boldsymbol{Q}}\int_\Omega u\,v\,\mathrm{d}\mathbb{P}(\tilde\omega)\,\mathrm{d}x\,. \tag{19}$$

Lemma 4. *Let $T > 0$. Then, every sequence $(u^\varepsilon)_{\varepsilon>0}$ with $u^\varepsilon \in L^2(0,T;L^2(\boldsymbol{Q}))$ satisfying $\|u^\varepsilon\|_{L^2(0,T;L^2(\boldsymbol{Q}))} \leq C$ for some $C > 0$ independent from ε has a weakly two-scale convergent subsequence with limit function $u \in L^2(0,T;L^2(\boldsymbol{Q};L^2(\Omega,\mathbb{P})))$.*

Lemma 5. *There exists $\tilde{\Omega} \subset \Omega_\Psi$ of full measure such that for all $\omega \in \tilde{\Omega}$ the following holds: If $u^\varepsilon \in H^1(\boldsymbol{Q};\mathbb{R}^m)$ for all ε, with $\|\nabla u^\varepsilon\|_{L^2(\boldsymbol{Q})} < C$ for C independent from $\varepsilon > 0$, then there exists a subsequence denoted by u^ε, functions $u \in H^1(\boldsymbol{Q};\mathbb{R}^m)$ and $v \in L^2(\boldsymbol{Q};L^2_{pot}(\Omega))$ such that $u^\varepsilon \rightharpoonup u$ weakly in $H^1(\boldsymbol{Q})$ and*

$$\nabla u^\varepsilon \xrightarrow{2s} \nabla u + v \qquad \text{as } \varepsilon \to 0\,. \tag{20}$$

Lemma 6. *Let $T > 0$. Then, every sequence $(u^\varepsilon)_{\varepsilon>0}$ with $u^\varepsilon \in L^2(0,T;L^2(\boldsymbol{Q}))$ satisfying $\|u^\varepsilon\|_{L^2(0,T;L^2(\boldsymbol{Q}))} \leq C$ for some $C > 0$ independent from ε has a weakly two-scale convergent subsequence with limit function $u \in L^2(0,T;L^2(\boldsymbol{Q};L^2(\Omega,\mathbb{P})))$.*

Furthermore, if $\|\partial_t u^\varepsilon\|_{L^2(0,T;L^2(\boldsymbol{Q}))} \leq C$ uniformly in ε, then also $\partial_t u \in L^2(0,T;L^2(\boldsymbol{Q};L^2(\Omega,\mathbb{P})))$ and $\partial_t u^\varepsilon \xrightarrow{2s} \partial_t u$.

Domains with holes

Lemma 7. *Let* $u^\varepsilon \in L^2(\boldsymbol{Q})$ *be a sequence of functions such that* $\sup_{\varepsilon>0} \|u^\varepsilon\|_{L^2(\boldsymbol{Q})} < \infty$*. If* $(u^{\varepsilon'})_{\varepsilon'\to 0}$ *is a subsequence such that* $u^{\varepsilon'} \xrightarrow{2s} u$ *for some* $u \in L^2(\boldsymbol{Q}; L^2(\Omega))$*, then* $u^\varepsilon \chi_{\boldsymbol{Q}^\varepsilon} \xrightarrow{2s} u\, \chi_{G^\complement}$.

Lemma 8. *Let* $u^\varepsilon \in L^2(0,T; H^1(\boldsymbol{Q}^\varepsilon(\omega)))$ *be a sequence of functions such that*

$$\sup_{\varepsilon>0} \|u^\varepsilon\|_{L^2(0,T;H^1(\boldsymbol{Q}^\varepsilon(\omega)))} + \|\partial_t u^\varepsilon\|_{L^2(0,T;L^2(\boldsymbol{Q}^\varepsilon(\omega)))} < \infty\,.$$

Then there exist functions $u \in L^2(0,T;H^1(\boldsymbol{Q}))$ *with* $\partial_t u \in L^2(0,T;L^2(\boldsymbol{Q}))$ *and* $v \in L^2(0,T;L^2(\boldsymbol{Q};L^2_{\mathrm{pot}}(\Omega)))$ *such that* $\mathcal{E}_\varepsilon u^\varepsilon \rightharpoonup u$ *weakly in* $L^2(0,T;H^1(\boldsymbol{Q}))$ *and* $\mathcal{E}_\varepsilon u^\varepsilon \to u$ *strongly in* $L^2(0,T;L^2(\boldsymbol{Q}))$ *as well as*

$$u^\varepsilon \xrightarrow{2s} \chi_{G^\complement}\, u\,, \quad \partial_t u^\varepsilon \xrightarrow{2s} \chi_{G^\complement}\, \partial_t u\,, \quad \textit{and} \quad \nabla u^\varepsilon \xrightarrow{2s} \chi_{G^\complement} \nabla u + \chi_{G^\complement}\, v\,.$$

Homogenization

We obtain the following "deterministic" (i.e. for fixed $\omega \in \Omega$) existence and regularity result.

Theorem 2. *Suppose all the assumptions on our random domain hold.*

Then for $\mathbb{P}$-a.e. $\omega \in \Omega$ and for any $\varepsilon > 0$ the system (5)- (7) admits a unique maximal classical solution

$$u^\varepsilon_\omega = (u^\varepsilon_{\omega,1}, \dots, u^\varepsilon_{\omega,M})$$

such that

(i) there exists $\alpha \in (0,1)$, α depending only on $N, \lambda, \Lambda^\star, \varepsilon$ and ω, such that $u^\varepsilon \in C^{1+\alpha/2, 2+\alpha}([0,T] \times \boldsymbol{Q}^\varepsilon, \mathbb{R}^M)$ for $\mathbb{P}$-a.e. $\omega \in \Omega$ and

$$\|u^\varepsilon_\omega\|_{C^{1+\alpha/2,2+\alpha}([0,T]\times \boldsymbol{Q}^\varepsilon, \mathbb{R}^M)} \le C_0 = C_0(U_1, \|\eta\|_{L^\infty([0,T]\times\overline{\boldsymbol{Q}}\times\Omega)}, K, \varepsilon, \omega, \alpha); \qquad (21)$$

(ii) $u^\varepsilon_{\omega,j}(t,x) > 0$ for $(t,x) \in [0,T] \times \boldsymbol{Q}^\varepsilon$, $\mathbb{P}$-a.e. $\omega \in \Omega$ and $j = 1, \dots, M$.

In the sequel we shall rely on the fact that statements that hold $\mathbb{P}$-a.e. can be seen as deterministic assertions, since they hold whenever $\boldsymbol{Q}^\varepsilon$ is a set enjoying the regularity properties described previously.

Theorem 3. *Let $u^\varepsilon_\omega = (u^\varepsilon_{\omega,1}, \ldots, u^\varepsilon_{\omega,M})$ be a unique classical solution to the system (5)-(7), then*

$$\|u^\varepsilon_{\omega,1}\|_{L^\infty([0,T]\times\boldsymbol{Q}^\varepsilon)} \leq |U_1| + c\,\|\eta\|_{L^\infty([0,T]\times\overline{\boldsymbol{Q}}\times\Omega)}, \tag{22}$$

for $\mathbb{P}$-a.e. $\omega \in \Omega$, where c is independent of $\varepsilon > 0$.

In addition, there exists $K > 0$ such that

$$\|u^\varepsilon_{\omega,j}\|_{L^\infty([0,T]\times\boldsymbol{Q}^\varepsilon)} \leq K \qquad (1 < j \leq M) \tag{23}$$

for $\mathbb{P}$-a.e. $\omega \in \Omega$, uniformly with respect to $\varepsilon > 0$.

Theorem 4. *The sequence $(\nabla_x u^\varepsilon_{\omega,j})_{\varepsilon>0}$ ($1 \leq j \leq M$) is bounded in $L^2([0,T]\times\boldsymbol{Q}^\varepsilon)$ for $\mathbb{P}$-a.e. $\omega \in \Omega$, uniformly in ε.*

In addition, the sequence $(\partial_t u^\varepsilon_{\omega,j})_{\varepsilon>0}$ ($1 \leq j \leq M$) is bounded in $L^2([0,T]\times\boldsymbol{Q}^\varepsilon)$ for $\mathbb{P}$-a.e. $\omega \in \Omega$, uniformly in ε.

Main statement

Theorem 5. *Let* $u_s^\varepsilon(t,x)$ *(*$1 \le s \le M$*) be a family of nonnegative classical solutions to the system (5)-(7).*

Denote by a tilde the extension by zero outside $\boldsymbol{Q}^\varepsilon(\omega)$ *and let* $\chi_{G^{\complement}}$ *represent the characteristic function of the random set* $G^{\complement}(\omega)$ *(where* $G^{\complement}$ *is the complement of* G*, representing the set of random holes in* $\mathbb{R}^m$*).*

Then, the sequences $(\widetilde{u_s^\varepsilon})_{\varepsilon>0}$*,* $(\widetilde{\nabla_x u_s^\varepsilon})_{\varepsilon>0}$ *and* $(\widetilde{\partial_t u_s^\varepsilon})_{\varepsilon>0}$ *(*$1 \le s \le M$*) stochastically two-scale converge to:* $[\chi_{G^{\complement}}\, u_s(t,x)]$*,* $[\chi_{G^{\complement}}(\nabla_x u_s(t,x) + v_s(t,x,\omega))]$*,* $[\chi_{G^{\complement}}\, \partial_t\, u_s(t,x)]$ *(*$1 \le s \le M$*), respectively.*

The limiting functions $[(t,x) \mapsto u_s(t,x), (t,x,\omega) \mapsto v_s(t,x,\omega)]$ *(*$1 \le s \le M$*) are the unique solutions lying in* $L^2(0,T;H^1(\boldsymbol{Q})) \times L^2([0,T] \times \boldsymbol{Q}; L^2_{\mathrm{pot}}(\Omega))$ *of the following two-scale homogenized systems:*

If $s = 1$:

$$\begin{cases} \theta \, \dfrac{\partial u_1}{\partial t}(t,x) - div_x \left[D_1^\star(t,x)\, \nabla_x u_1(t,x) \right] & \\ +\theta\, u_1(t,x) \sum_{j=1}^{M} a_{1,j}\, u_j(t,x) = \displaystyle\int_\Omega \chi_{\Gamma_G \complement}\, \eta(t,x,\omega)\, d\mu_{\Gamma,\mathcal{P}}(\omega) & \text{in } [0,T] \times \boldsymbol{Q} \\ [D_1^\star(t,x)\, \nabla_x u_1(t,x)] \cdot n = 0 & \text{on } [0,T] \times \partial \boldsymbol{Q} \\ u_1(0,x) = U_1 & \text{in } \boldsymbol{Q} \end{cases} \tag{24}$$

If $1 < s < M$:

$$\begin{cases} \theta \, \dfrac{\partial u_s}{\partial t}(t,x) - div_x \left[D_s^\star(t,x)\, \nabla_x u_s(t,x) \right] & \\ +\theta\, u_s(t,x) \sum_{j=1}^{M} a_{s,j}\, u_j(t,x) & \\ = \dfrac{\theta}{2} \sum_{j=1}^{s-1} a_{j,s-j}\, u_j(t,x)\, u_{s-j}(t,x) & \text{in } [0,T] \times \boldsymbol{Q} \\ & \\ [D_s^\star(t,x)\, \nabla_x u_s(t,x)] \cdot n = 0 & \text{on } [0,T] \times \partial \boldsymbol{Q} \\ u_s(0,x) = 0 & \text{in } \boldsymbol{Q} \end{cases} \tag{25}$$

If $s = M$:

$$\begin{cases} \theta \dfrac{\partial u_M}{\partial t}(t,x) - div_x \left[D^\star_M(t,x) \, \nabla_x u_M(t,x) \right] \\ = \dfrac{\theta}{2} \sum_{\substack{j+k \geq M \\ k<M \, (\text{if } j=M) \\ j<M \, (\text{if } k=M)}} a_{j,k} \, u_j(t,x) \, u_k(t,x) & \text{in } [0,T] \times \boldsymbol{Q} \\ [D^\star_M(t,x) \, \nabla_x u_M(t,x)] \cdot n = 0 & \text{on } [0,T] \times \partial \boldsymbol{Q} \\ u_M(0,x) = 0 & \text{in } \boldsymbol{Q} \end{cases} \tag{26}$$

where $\theta = \int_\Omega \chi_{G^\complement} \, d\mu_{\mathcal{P}}(\omega) = \mathbb{P}(G^\complement)$.

$D^\star_s(t,x)$ is a deterministic matrix, called "effective diffusivity":

$$(D^\star_s)_{ij}(t,x) = \int_\Omega \chi_{G^\complement} \, D_s(t,x,\omega)(w_i(t,x,\omega) + \hat{e}_i) \cdot (w_j(t,x,\omega) + \hat{e}_j) \, d\mathbb{P}(\omega)$$

$(w_i)_{1 \leq i \leq m} \in L^2([0,T] \times \boldsymbol{Q}; L^2_{\text{pot}}(G^\complement))$ the family of solutions of the following microscopic problem:

$$\begin{cases} -div_\omega [D_s(t,x,\omega)(w_i(t,x,\omega) + \hat{e}_i)] = 0 & \text{in } G^\complement \\ D_s(t,x,\omega)[w_i(t,x,\omega) + \hat{e}_i] \cdot \nu_{\Gamma_{G^\complement}} = 0 & \text{on } \Gamma_{G^\complement}. \end{cases} \tag{27}$$

$$v_s(t,x,\omega) = \sum_{i=1}^m w_i(t,x,\omega) \, \frac{\partial u_s}{\partial x_i}(t,x) \quad (1 \leq s \leq M).$$

Proof of the main Theorem.

In view of the previous Theorems, the sequences

$\widetilde{(u_s^\varepsilon)}_{\varepsilon>0}$, $\widetilde{(\nabla_x u_s^\varepsilon)}_{\varepsilon>0}$ and $\widetilde{\left(\frac{\partial u_s^\varepsilon}{\partial t}\right)}_{\varepsilon>0}$ $(1 \leq s \leq M)$ are bounded in $L^2([0,T] \times \boldsymbol{Q})$.

Therefore, they two-scale converge, up to a subsequence, respectively, to:

$[\chi_{G^\complement}\, u_s(t,x)]$, $[\chi_{G^\complement}(\nabla_x u_s(t,x) + v_s(t,x,\omega))]$, $[\chi_{G^\complement}\partial_t u_s(t,x)]$, where
$u_s \in L^2(0,T;H^1(\boldsymbol{Q}))$ and $v_s \in L^2([0,T] \times \boldsymbol{Q}; L^2_{\text{pot}}(\Omega))$.

As test functions for homogenization, let us take

$$\phi^\varepsilon(t,x,\omega) := \phi_0(t,x) + \varepsilon\, \phi(t,x)\psi(\tau_{\frac{x}{\varepsilon}}\omega) \tag{28}$$

where $\phi_0, \phi \in C^1([0,T] \times \overline{\boldsymbol{Q}})$ and $\psi \in \Psi$, with Ψ being the set of bounded continuous functions.

In the case when $s = 1$, let us multiply the first equation of (5) by the test function ϕ^ε. Integrating, the divergence theorem yields

$$\int_0^T \int_{\boldsymbol{Q}^\varepsilon(\omega)} \frac{\partial u_1^\varepsilon}{\partial t} \phi^\varepsilon(t,x,\omega)\, dx\, dt + \int_0^T \int_{\boldsymbol{Q}^\varepsilon(\omega)} \Big\langle D_1(t,x,\tau_{\frac{x}{\varepsilon}}\omega)\nabla_x u_1^\varepsilon, \nabla\phi^\varepsilon \Big\rangle\, dx\, dt$$
$$+ \int_0^T \int_{\boldsymbol{Q}^\varepsilon(\omega)} u_1^\varepsilon \sum_{j=1}^M a_{1,j}\, u_j^\varepsilon\, \phi^\varepsilon(t,x,\omega)\, dx\, dt = \varepsilon \int_0^T \int_{\Gamma^\varepsilon_{\boldsymbol{Q}}(\omega)} \eta(t,x,\tau_{\frac{x}{\varepsilon}}\omega)\, \phi^\varepsilon(t,x,\omega)\, d\mathcal{H}^{m-1}\, dt.$$

Passing to the two-scale limit, as $\varepsilon \to 0$, we get

$$\begin{aligned}
&\int_0^T \int_{\boldsymbol{Q}} \int_\Omega \chi_{G^\complement} \frac{\partial u_1}{\partial t}(t,x)\, \phi_0(t,x)\, d\mathbb{P}(\omega)\, dx\, dt \\
&+ \int_0^T \int_{\boldsymbol{Q}} \int_\Omega \chi_{G^\complement} D_1(t,x,\omega)[\nabla_x u_1(t,x) + v_1(t,x,\omega)] \\
&\quad \cdot [\nabla_x \phi_0(t,x) + \phi(t,x)\nabla_\omega \psi(\omega)]\, d\mathbb{P}(\omega)\, dx\, dt \\
&+ \int_0^T \int_{\boldsymbol{Q}} \int_\Omega \chi_{G^\complement} u_1(t,x) \sum_{j=1}^M a_{1,j}\, u_j(t,x)\, \phi_0(t,x)\, d\mathbb{P}(\omega)\, dx\, dt \\
&= \int_0^T \int_{\boldsymbol{Q}} \int_\Omega \chi_{\Gamma_{G^\complement}}\, \eta(t,x,\omega)\, \phi_0(t,x)\, d\mu_{\Gamma,\mathcal{P}}(\omega)\, dx\, dt. \qquad (28)
\end{aligned}$$

The term on the right-hand side of (28) follows from the lemma

Lemma 9. *Let $(g_i)_{i\in\mathbb{N}}$ be a countable family in $L^\infty(\boldsymbol{Q}\times\Gamma;\mathcal{L}\times\mu_{\Gamma,\mathcal{P}})$. Then there exists a set of full measure $\Omega_\Psi\subset\Omega$ such that for almost every $\omega\in\Omega_\Psi$, every $i\in\mathbb{N}$, every $\psi\in\Psi$ and every $\varphi\in C_b(\overline{\boldsymbol{Q}})$ the following holds:*

$$\lim_{\varepsilon\to 0}\int_{\boldsymbol{Q}} g_i\left(x,\tau_{\frac{x}{\varepsilon}}\omega\right)\varphi(x)\psi(\tau_{\frac{x}{\varepsilon}}\omega)\mathrm{d}\mu^{\varepsilon}_{\Gamma(\omega)}(x)=\int_{\boldsymbol{Q}}\int_{\Omega} g_i(x,\tilde{\omega})\varphi(x)\psi(\tilde{\omega})\,\mathrm{d}\mu_{\Gamma,\mathcal{P}}(\tilde{\omega})\,\mathrm{d}x\,.$$

The last term on the left-hand side of (28) has been obtained by observing that

$$\mathcal{E}_\varepsilon u_j^\varepsilon\to u_j$$

strongly in $L^2(0,T;L^2(\boldsymbol{Q}))$ and that the two-scale convergence of

$$u_1^\varepsilon\xrightarrow{2s}\chi_{G^\complement}u_1$$

implies weak convergence of

$$u_1^\varepsilon\phi^\varepsilon(\cdot,\cdot,\omega)\rightharpoonup u_1\phi_0\int_\Omega\chi_{G^\complement}d\mathbb{P}(\omega)$$

in $L^2(0,T;L^2(\boldsymbol{Q}))$.

An integration by parts shows that (28) can be put in the strong form associated with the following homogenized system:

$$-div_\omega[D_1(t,x,\omega)(\nabla_x u_1(t,x) + v_1(t,x,\omega))] = 0 \qquad \text{in } [0,T] \times \boldsymbol{Q} \times G^{\complement} \tag{29}$$

$$[D_1(t,x,\omega)(\nabla_x u_1(t,x) + v_1(t,x,\omega))] \cdot \nu_{\Gamma_{G^{\complement}}} = 0 \qquad \text{on } [0,T] \times \boldsymbol{Q} \times \Gamma_{G^{\complement}} \tag{30}$$

$$\begin{aligned} &\theta \frac{\partial u_1}{\partial t}(t,x) - div_x\left[\int_\Omega \chi_{G^{\complement}} D_1(t,x,\omega)(\nabla_x u_1(t,x) + v_1(t,x,\omega)) d\mathbb{P}(\omega)\right] \\ &+ \theta\, u_1(t,x) \sum_{j=1}^{M} a_{1,j}\, u_j(t,x) - \int_\Omega \chi_{\Gamma_{G^{\complement}}} \eta(t,x,\omega)\, d\mu_{\Gamma,\mathcal{P}}(\omega) = 0 \qquad \text{in } [0,T] \times \boldsymbol{Q} \end{aligned} \tag{31}$$

$$\left[\int_\Omega \chi_{G^{\complement}} D_1(t,x,\omega)(\nabla_x u_1(t,x) + v_1(t,x,\omega))\, d\mathbb{P}(\omega)\right] \cdot n = 0 \qquad \text{on } [0,T] \times \partial\boldsymbol{Q}. \tag{32}$$

To conclude, by continuity, we have that

$$u_1(0,x) = U_1 \qquad \text{in } \boldsymbol{Q}.$$

The function $v_1(t,x,\omega)$, satisfying (29) and (30), can be expressed as follows

$$v_1(t,x,\omega) := \sum_{i=1}^{m} w_i(t,x,\omega)\,\frac{\partial u_1}{\partial x_i}(t,x) \tag{33}$$

where $(w_i)_{1\le i\le m} \in L^2([0,T]\times \boldsymbol{Q}; L^2_{\text{pot}}(G^{\complement}))$ is the family of solutions of the microscopic problem

$$\begin{cases} -div_\omega[D_1(t,x,\omega)(w_i(t,x,\omega)+\hat{e}_i)] = 0 & \text{in } G^{\complement} \\ D_1(t,x,\omega)[w_i(t,x,\omega)+\hat{e}_i]\cdot \nu_{\Gamma_{G^{\complement}}} = 0 & \text{on } \Gamma_{G^{\complement}} \end{cases} \tag{34}$$

and $\hat{e}_i$ is the i-th unit vector of the canonical basis of $\mathbb{R}^m$.

By using the relation (33) in Eqs.(31) and (32), we get

$$\theta \frac{\partial u_1}{\partial t}(t,x) - div_x\Big[D_1^\star(t,x)\,\nabla_x u_1(t,x)\Big] + \theta\, u_1(t,x)\sum_{j=1}^{M} a_{1,j}\, u_j(t,x)$$
$$- \int_\Omega \chi_{\Gamma_{G^\complement}}\, \eta(t,x,\omega)\, d\mu_{\Gamma,\mathcal{P}}(\omega) = 0 \qquad \text{in } [0,T]\times \boldsymbol{Q} \tag{35}$$

$$[D_1^\star \nabla_x u_1(t,x)]\cdot n = 0 \qquad\qquad \text{on } [0,T]\times \partial\boldsymbol{Q} \tag{36}$$

where the entries of the matrix $D_1^\star$ (called "effective diffusivity") are given by

$$(D_1^\star)_{ij}(t,x) = \int_\Omega \chi_{G^\complement}\, D_1(t,x,\omega)[w_i(t,x,\omega)+\hat{e}_i]\cdot[w_j(t,x,\omega)+\hat{e}_j]\,d\mathbb{P}(\omega). \tag{37}$$

The proof for the case $1 < s \leq M$ is achieved by applying exactly the same arguments.

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