From a microscopic to a macroscopic model for Alzheimer disease: Two-scale homogenization of the Smoluchowski equation in perforated domains.

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Abstract

In this paper, we study the homogenization of a set of Smoluchowski's discrete diffusion-coagulation equations modeling the aggregation and diffusion of β-amyloid peptide (Aβ), a process associated with the development of Alzheimer's disease. In particular, we define a periodically perforated domain Ω_ϵ, obtained by removing from the fixed domain Ω (the cerebral tissue) infinitely many small holes of size ϵ (the neurons), which support a non-homogeneous Neumann boundary condition describing the production of Aβ by the neuron membranes. Then, we prove that, when $\epsilon \to 0$, the solution of this micro-model two-scale converges to the solution of a macro-model asymptotically consistent with the original one. Indeed, the information given on the microscale by the non-homogeneous Neumann boundary condition is transferred into a source term appearing in the limiting (homogenized) equations. Furthermore, on the macroscale, the geometric structure of the perforated domain induces a correction in that the scalar diffusion coefficients defined at the microscale are replaced by tensorial quantities.

1 Introduction

The Smoluchowski equation [43] is a system of partial differential equations which describes the evolving densities of diffusing particles that are prone to coagulate in pairs [18, 19, 21, 22, 30, 32, 45]. In spite of the large literature concerning the use of the Smoluchowski equation in many branches of science (e.g. in aerosol science, polymer science, astrophysics, chemistry), this equation does not seem to have been considered extensively in the field of biomedical research. Applications of Smoluchowski equation to the description of the agglomeration of β-amyloid peptide (Aβ), a process associated with the development of Alzheimer's disease (AD), seem to appear for the first time in Murphy and Pallitto [33].

Nowadays, Alzheimer's disease is the most common form of senile dementia with enormous socio-economic implications. In recent years, besides *in vivo* and *in vitro* experimental models, there has been an increasing interest in mathematical modeling and computer simulations (the so-called *in silico* approach) [1, 6, 16, 20, 24, 41], in order to better understand the mechanisms for the onset and the evolution of AD. It is largely accepted that Aβ peptide (especially in soluble form) has a substantial role in the process of synaptic degeneration leading to neuronal death and eventually to dementia (the so-called *amyloid cascade hypothesis* [28]). Aβ, in monomeric form, is a normal product of cleavage of the amyloid precursor protein (APP), an integral membrane protein involved in signal transduction pathways. By unknown reasons (partially genetic), some neurons start to present an imbalance between production and clearance of Aβ amyloid during aging. Soluble Aβ (in the form of monomers) diffuses freely through neuronal tissue. At elevated levels, it produces pathological aggregates (that cannot be readily cleared): long insoluble amyloid fibrils, which accumulate in spherical deposits known as senile plaques. In addition, it has been recognised that Aβ is able to initiate an inflammatory response, which implicates the activation of microglia (the resident immune cells in the central nervous system) and therefore the release of neurotoxic produtcs that are involved in neuronal and synaptic damage.

In [33], the authors compare experimental data with numerical simulations based on the Smoluchowski equation without diffusion, in order to clarify the kinetics of conversion of monomeric β-amyloid peptide into macroscopic fibril aggregates. Very recently, the important role of Smoluchowski equation in modeling the evolution of AD at different scales has been investigated in [1, 23, 6]. In [1], the authors present a mathematical model for the aggregation and diffusion of β-amyloid in the brain affected by AD at a microscopic scale (the size of a single neuron) and at the early stage of the disease when small amyloid fibrils are free to move and to coalesce. In the model proposed in [1], a very small portion of the cerebral tissue is described by a bounded smooth region $\Omega \subset \mathbb{R}^3$, whereas the neurons are represented by a family of regular disjoint regions Ω_j (for $1 \leq j \leq \overline{M}$). Moreover, the production of Aβ in monomeric form at the level of neuron membranes is modeled by a non-homogeneous Neumann condition on the boundary of Ω_j, for $j = 1, \dots, \overline{M}$. On the other hand, in [6] 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 whole brain is represented by a region of the three-dimensional space, and the process of diffusion and aggregation of Aβ 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 a microscopic model to a macroscopic one has always been a common issue in mathematical modeling. As a matter of fact, one wants to start from differential equations that are assumed to hold on the micro-scale and to transform them into equations on the macro-scale, by performing a sort of 'averaging process'. To do that, in the seventies, mathematicians have developed a new method called homogenization [12, 13, 17]. This method allows to perform certain limits of the solutions of partial differential equations describing media with microstructures and to determine equations which the limits are solution of.

In the present work, the homogenization method has been applied to the model presented in [1], in order to describe the effects of the production and agglomeration of Aβ on the neuronal scale, at the macroscopic level. In particular, a periodically perforated domain Ω_ϵ, obtained by removing from the fixed domain Ω (the cerebral tissue) infinitely many small holes of size ϵ (the neurons) has been considered. Then, a system of Smoluchowski type equations has been defined, in order to describe the evolution of the β-amyloid peptide with respect to space and time. The production of Aβ in monomeric form from the neuron membranes has been modeled by coupling the diffusion-coagulation Smoluchowski equation for the concentration of monomers with a non-homogeneous Neumann boundary condition on the edge of the holes. These monomers, growing by binary coalescence, give rise to larger assemblies, which can diffuse in space with a constant diffusion coefficient, which depends on their size. It is assumed that, long fibrils, characterized by a very low diffusion, do not coagulate with each other. We prove that, when $\epsilon \to 0$, the solution of this micro-model two-scale converges to the solution of a macro-model, where the information given on the microscale by the non-homogeneous Neumann boundary condition is transferred into a global source term in the limiting (homogenized) evolution equation for the concentration of monomers. Moreover, on the macroscale, the geometric structure of the perforated domain induces a correction in the scalar diffusion coefficients, since they are replaced by a tensorial quantity with constant coefficients. The peculiarity of the two-scale convergence method, [3, 4, 5, 7, 14, 15, 25, 26, 27, 34, 36], used here to study the limiting behavior of the Smoluchowski type equations, is that, in a single process one can find the homogenized equations and prove the convergence of a sequence of solutions to the problem at hand. Moreover, while previous approaches were originally defined only for certain problem classes, two-scale convergence allows to pass to the limit in all sorts of problems featuring periodic microstructures.

It is noteworthy to outline that most of the models found in the scientific literature aim to describe AD pathology from a microscopic point of view, exploring events at the level of single cells or small groups of cells. Typically, the amyloid aggregation mechanism, the interactions of Aβ deposits, glial cell dynamics, inflammation and secretion of cytokines are some of the processes more intensively studied, as well as the stress, recovery and death of neuronal tissue [20]. Only a few models have been proposed at the macroscale to attempt a description of the evolution and progression of the disease over the entire lifetime of the patient [6]. The present paper suggests a possible bridge between these two approaches since, by using the homogenization theory, we derive a macroscopic model starting from a microscopic one. This issue is particularly relevant since it allows to model the onset and progression of the disease at the proper neuronal scale and then, through an asymptotic procedure, to obtain consistent macroscopic equations whose outcomes can be directly compared with the clinical data. In fact, despite the large number of experimental data that can be extracted from biomedical literature at the microscopic level, all the medical techniques for the evaluation of Alzheimer's disease operate normally at the macroscale. Among them, it is worth mentioning:

(i) PIB (Pittsburgh Compound-B)-PET (Positron Emission Tomography) technique which is used to image β-amyloid plaques in neuronal tissue;

(ii) FDG (Fluoro-Deoxy-D-Glucose)-PET technique which is used to measure cerebral metabolic rates of glucose (the decrease of cerebral glucose metabolism largely precedes the onset of AD symptoms);

(iii) MRI (Magnetic Resonance Imaging) technique which is used to measure structural tissue loss (i.e., atrophy).

The paper is organized as follows. Section 2 summarizes the main features of the discrete diffusive Smoluchowski equation, while in Section 3, a mathematical model describing the self-association and diffusion of β-amyloid peptide (which is the main trigger of Alzheimer's disease) is presented. Then, in Section 4, all necessary mathematical notations are defined and the general assumptions are stated. In Section 5, we prepare the ground for homogenization by obtaining some a priori estimates and then we prove our main results. The last section is devoted to some final remarks.

2 The Smoluchowski equation

The Smoluchowski coagulation equation models various kind of phenomena as for example: the evolution of a system of solid or liquid particles suspended in a gas (in aerosol science), polymerisation (in chemistry), aggregation of colloidal particles (in physics), formation of stars and planets (in astrophysics), red blood cell aggregation (in hematology), behaviour of fuel mixtures in engines (in engineering), etc. The original model proposed by Smoluchowski [43] was introduced to describe the binary coagulation of colloidal particles moving according to Brownian motions and several additional physical processes have been subsequently incorporated into the model (fragmentation, condensation, influence of external fields, see, e.g. [18, 30, 45]). In view of our subsequent applications, we present the appearance of the Smoluchowski equation in polymerisation [18, 30, 45]. 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.

In the model studied further on, 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). Other effects such as multiple coagulation or condensation, together with the influence of other external force fields are neglected. Under these assumptions, the discrete diffusive coagulation equations read [30, 45]

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

with appropriate initial and boundary conditions.

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

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

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

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

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

where $u = (u_i)_{i\geq 1}$. The coagulation rates $a_{i,j}$ are non negative constants such that $a_{i,j} = a_{j,i}$ and d_i denotes the diffusion coefficient of an i-cluster, $d_i > 0 \quad \forall i \geq 1$. The kinetic coefficient $a_{i,j}$ represents reaction in which an $(i+j)$-cluster is formed from an i-cluster and a j-cluster. Possible breakup of clusters is not taken into account. The term $Q_{g,i}$, given by (3), describes the creation of polymers of size i by coagulation of polymers of size j and $i-j$. The term $Q_{l,i}$, given by (4), corresponds to the depletion of polymers of size i after coalescence with other polymers. Since the size of clusters is not limited a priori, Eq. (1) describes a non-linear evolution equation of infinite dimension, for which even the existence of a local solution is not guaranteed by the general theory of reaction-diffusion equations. According to the form of the coalescence kernel $a_{i,j}$ we obtain or not solutions for the system of equations (1). In general, the coagulation rates are determined by the statistical probabilities of bond formation and depend upon the details of the physical process being considered. If there are no sources nor sinks of clusters in the reactions described by the initial-boundary value problem (1), the total mass of clusters is expected to be constant throughout the time evolution of the system, provided it is initially finite. It turns out however that this property may fail to be true in general for some physically relevant kinetic coefficients. The break-down of the mass conservation is then related to the so-called gelation phenomenon which corresponds to the appearance of an infinite cluster called gel, caused by the cascading growth of larger and larger clusters. We will however not consider this issue in the following.

3 A mathematical model for the aggregation and diffusion of β-amyloid peptide

In the present paper, we consider a mathematical model based on the discrete Smoluchowski equation in order to describe the aggregation and diffusion of β-amyloid peptide (Aβ) in the brain affected by Alzheimer's disease (AD) [1]. Aβ is naturally present in the brain and cerebrospinal fluid of humans throughout life, even if its role is currently unknown. By now, it is recognized that the mere presence of Aβ in the brain is not sufficient to support the diagnosis of AD. Neuronal injury is rather the result of ordered Aβ self-association [9, 20, 31, 35, 39, 46]. The amyloid plaques, which serve as a hallmark for AD, have been found to contain large amounts of Aβ organized into amyloid fibrils. There is no clear correlation, however, between the presence of the Aβ containing plaques in the brain and the severity of AD neurodegeneration. Therefore, in recent years, the research in this area has shifted its focus from senile plaques toward oligomeric conformations of Aβ. This oligomeric form of Aβ is highly toxic to the brain and is the trigger for loss of synapses and neuronal damage. However, the transient nature of small oligomeric aggregates makes it difficult to shed light on their formation process or structure. Most proposed pathways for the initial stages of Aβ amyloid fibril formation amount to a sequence of events that can be summarized as follows: unordered monomeric Aβ in solution converts into an 'activated' monomer that then recruits other Aβ molecules to form oligomers. The length-wise association of individual protofibrils produces the mature amyloid fibrils, whose structure has been studied in most detail due to their high stability under a wide range of physicochemical conditions. The mature fibrillar form and monomeric Aβ have both been confirmed on many occasions as the only non-toxic species.

In the present work, we discard fibril fragmentation, which can be considered as a secondary process in the mechanism of amyloid self-assembly (for a model with fragmentation, we refer to [23]). In the mathematical model proposed in [1] and reported below, the authors consider a portion of the hippocampus or of the cerebral cortex (the regions of the brain mainly affected by AD) whose size is comparable to a multiple of the size of a neuron, thus avoiding the description of intracellular phenomena. With this choice of scale, it is coherent to consider that the diffusion is uniform. Moreover, it is assumed that 'large' assemblies do not aggregate with each other. This assumption prevents blow-up phenomena for solutions at a finite time, but it is also consistent with experimental data [20, 33]. The portion of cerebral tissue considered in the following is represented by a bounded smooth region $\Omega_0 \subset \mathbb{R}^3$, whereas the neurons are represented by a family of regular regions Ω_j such that

(i) $\overline{\Omega}_j \subset \Omega_0$ if $j = 1, 2, \ldots, \overline{M}$;

(ii) $\overline{\Omega}_i \cap \overline{\Omega}_j = \varnothing$ if $i \neq j$.

Let us set

$$\Omega := \Omega_0 \setminus \bigcup_{j=1}^{\overline{M}} \overline{\Omega}_j$$

and consider a vector-valued function $u = (u_1, \ldots, u_M)$, where $M \in \mathbb{N}$ and $u_j = u_j(t,x)$, $t \in \mathbb{R}$, $t \geq 0$ (the time), and $x \in \Omega$. If $1 \leq j < M-1$, then $u_j(t,x)$ is the (molar) concentration at the point x and at the time t of an Aβ assembly of j monomers, while u_M takes into account aggregations of more than $M-1$ monomers. The production of Aβ in the monomeric form at the level of neuron membranes is modeled by a non-homogeneous Neumann condition on $\partial\Omega_j$, the boundary of Ω_j, for $j = 1, \ldots, \overline{M}$. Finally, an homogeneous Neumann condition on $\partial\Omega_0$ is meant to artificially isolate the portion of tissue considered from its environment. Thus, the following Cauchy-Neumann problem can be defined [1]:

$$\begin{cases} \dfrac{\partial u_1}{\partial t}(t,x) - d_1 \triangle_x u_1(t,x) + u_1(t,x) & \sum_{j=1}^{M} a_{1,j} u_j(t,x) = 0 \\[2em] \dfrac{\partial u_1}{\partial \nu} \equiv \nabla_x u_1 \cdot n = 0 & \text{on } \partial\Omega_0 \\[2em] \dfrac{\partial u_1}{\partial \nu} \equiv \nabla_x u_1 \cdot n = \psi_j & \text{on } \partial\Omega_j, \;\; j = 1, \ldots, \overline{M} \\[2em] u_1(0,x) = U_1 \geq 0 \end{cases} \tag{5}$$

where $0 \leq \psi_j \leq 1$ is a smooth function for $j = 1, \ldots, \overline{M}$ describing the production of the amyloid near the membrane of the neuron. Indeed, the experimental evidence shows that the production of Aβ is not uniformly distributed over the neuronal cells. This localization of the production is expressed by means of the choice of the functions ψ_j. Moreover, only the neurons affected by the disease are taken into account, i.e. it is assumed $\psi_j \neq 0$ for $j = 1, \ldots, \overline{M}$.

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

$$
\begin{cases}
\dfrac{\partial u_m}{\partial t}(t,x) - d_m \triangle_x u_m(t,x) + u_m(t,x) & \sum_{j=1}^{M} a_{m,j} u_j(t,x) = \\
 & \frac{1}{2}\sum_{j=1}^{m-1} a_{j,m-j} u_j u_{m-j} \\
\dfrac{\partial u_m}{\partial \nu} \equiv \nabla_x u_m \cdot n = 0 & \text{on } \partial\Omega_0 \\
\dfrac{\partial u_m}{\partial \nu} \equiv \nabla_x u_m \cdot n = 0 & \text{on } \partial\Omega_j, \;\; j = 1, \dots, \overline{M} \\
u_m(0,x) = 0 &
\end{cases}
\tag{6}
$$

and

$$
\begin{cases}
\dfrac{\partial u_M}{\partial t}(t,x) - d_M \triangle_x u_M(t,x) = \frac{1}{2}\sum_{\substack{j+k\geq M \\ k<M \\ j<M}} & a_{j,k}\, u_j\, u_k \\
\dfrac{\partial u_M}{\partial \nu} \equiv \nabla_x u_M \cdot n = 0 & \text{on } \partial\Omega_0 \\
\dfrac{\partial u_M}{\partial \nu} \equiv \nabla_x u_M \cdot n = 0 & \text{on } \partial\Omega_j, \;\; j = 1, \dots, \overline{M} \\
u_M(0,x) = 0 &
\end{cases}
\tag{7}
$$

For reasons related to the model, we can assume that the diffusion coefficients $d_j > 0$, $j = 1, \dots, M$, are small when j is large, since big assemblies do not move. The coagulation rates a_{ij} are symmetric $a_{ij} = a_{ji} > 0$, $i, j = 1, \dots, M$, but $a_{MM} = 0$. Let us remark that the meaning of u_M differs from that of u_m, $m < M$, since it describes the sum of the densities of all the ‘large’ assemblies. It is assumed that large assemblies exhibit all the same coagulation properties and do not coagulate with each other. Indeed, the present model only takes into account the evolution of the Aβ and ignores the role played by the microglia and astrocytes in neuronal death and in the formation of senile plaques.

4 Setting of the problem

Let Ω be a bounded open set in $\mathbb{R}^3$ with a smooth boundary $\partial\Omega$. Let Y be the unit periodicity cell $[0,1[^3$ having the paving property. We perforate Ω by removing from it a set T_ϵ of periodically distributed holes defined as follows. Let us denote by T an open subset of Y with a smooth boundary Γ, such that $\overline{T} \subset \operatorname{Int} Y$. Set $Y^* = Y \setminus T$ which is called in the literature the solid or material part. According to the model presented in Section 3, the set T represents a generic neuron, and Y^* the supporting cerebral tissue. We define $\tau(\epsilon\overline{T})$ to be the set of all translated images of $\epsilon\overline{T}$ of the form $\epsilon(k+\overline{T})$, $k \in \mathbb{Z}^3$. Then,

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

Introduce now the periodically perforated domain Ω_ϵ defined by

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

For the sake of simplicity, we make the following standard assumption on the holes [13, 17]: there exists a 'security' zone around $\partial\Omega$ without holes, i.e.

$$\exists\, \delta > 0 \text{ such that } \operatorname{dist}(\partial\Omega, T_\epsilon) \geq \delta. \tag{8}$$

Therefore, Ω_ϵ is a connected set ([13]). The boundary $\partial\Omega_\epsilon$ of Ω_ϵ is then composed of two parts. The first one is the union of the boundaries of the holes strictly contained in Ω. It is denoted by Γ_ϵ and is defined by

$$\Gamma_\epsilon := \cup \Big\{ \partial(\epsilon(k+\overline{T})) \mid \epsilon(k+\overline{T}) \subset \Omega \Big\}.$$

The second part of $\partial\Omega_\epsilon$ is its fixed exterior boundary denoted by $\partial\Omega$. It is easily seen that (see [4], Eq. (3))

$$\lim_{\epsilon\to 0} \epsilon \mid \Gamma_\epsilon|_{N-1} = \mid \Gamma|_{N-1} \frac{\mid \Omega \mid_N}{\mid Y \mid_N} \tag{9}$$

where $| \cdot |_N$ is the N-dimensional Hausdorff measure.

Throughout this paper, ϵ will denote the general term of a sequence of positive reals which converges to zero.

Let us rewrite the model problem presented in Section 3 as a family of equations in Ω_ϵ:

$$
\begin{cases}
\dfrac{\partial u_1^\epsilon}{\partial t} - \operatorname{div}(d_1 \nabla_x u_1^\epsilon) + u_1^\epsilon \sum_{j=1}^{M} a_{1,j} u_j^\epsilon = 0 & \text{in } [0,T] \times \Omega_\epsilon \\
\dfrac{\partial u_1^\epsilon}{\partial \nu} \equiv \nabla_x u_1^\epsilon \cdot n = 0 & \text{on } [0,T] \times \partial\Omega \\
\dfrac{\partial u_1^\epsilon}{\partial \nu} \equiv \nabla_x u_1^\epsilon \cdot n = \epsilon\, \psi(t, x, \frac{x}{\epsilon}) & \text{on } [0,T] \times \Gamma_\epsilon \\
u_1^\epsilon(0, x) = U_1 & \text{in } \Omega_\epsilon
\end{cases}
\tag{10}
$$

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

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

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

and U_1 is a positive constant such that

$$U_1 \leq \|\psi\|_{L^\infty(0,T;B)}. \tag{11}$$

Beyond the regularity properties mentioned above, ψ is a generic given function that should be specified in some way, if one has the ambition to make the model applicable. In general, if one wishes to emphasize simply a functional dependence of ψ which mimics the medical observations about the space-time distribution of Aβ produced by damaged neurons, a possible choice is the following: $\psi(t, x, \frac{x}{\epsilon}) = \psi_0(\frac{x}{\epsilon})\psi_1(t - g(x))$, where the function $\psi_1(s) \equiv 0$ for s near 0 and $\psi_1(s) \equiv 1$ for large $s > 0$. The function g takes into account that different cerebral regions are affected at different times. In the last section, it is suggested another more explicit formal expression for the function ψ, in an attempt to create a link between the model presented here and the one described in [6], for which numerical simulations have been carried out.

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

$$
\begin{cases}
\dfrac{\partial u_m^\epsilon}{\partial t} - \operatorname{div}(d_m \nabla_x u_m^\epsilon) + u_m^\epsilon \sum_{j=1}^M a_{m,j} u_j^\epsilon = f^\epsilon & \text{in } [0,T] \times \Omega_\epsilon \\[2em]
\dfrac{\partial u_m^\epsilon}{\partial \nu} \equiv \nabla_x u_m^\epsilon \cdot n = 0 & \text{on } [0,T] \times \partial\Omega \\[2em]
\dfrac{\partial u_m^\epsilon}{\partial \nu} \equiv \nabla_x u_m^\epsilon \cdot n = 0 & \text{on } [0,T] \times \Gamma_\epsilon \\[2em]
u_m^\epsilon(0,x) = 0 & \text{in } \Omega_\epsilon
\end{cases}
\tag{12}
$$

and

$$
\begin{cases}
\dfrac{\partial u_M^\epsilon}{\partial t} - \operatorname{div}(d_M \nabla_x u_M^\epsilon) = g^\epsilon & \text{in } [0,T] \times \Omega_\epsilon \\[2em]
\dfrac{\partial u_M^\epsilon}{\partial \nu} \equiv \nabla_x u_M^\epsilon \cdot n = 0 & \text{on } [0,T] \times \partial\Omega \\[2em]
\dfrac{\partial u_M^\epsilon}{\partial \nu} \equiv \nabla_x u_M^\epsilon \cdot n = 0 & \text{on } [0,T] \times \Gamma_\epsilon \\[2em]
u_M^\epsilon(0,x) = 0 & \text{in } \Omega_\epsilon
\end{cases}
\tag{13}
$$

where the gain terms f^ϵ and g^ϵ in (12) and (13) are given by

$$f^\epsilon = \frac{1}{2} \sum_{j=1}^{m-1} a_{j,m-j} \, u_j^\epsilon \, u_{m-j}^\epsilon \tag{14}$$

$$g^\epsilon = \frac{1}{2} \sum_{\substack{j+k \geq M \\ k<M \\ j<M}} a_{j,k} \, u_j^\epsilon \, u_k^\epsilon. \tag{15}$$

Theorem 4.1. *If* $\epsilon > 0$ *the system* (10) - (13) *has a unique solution*

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

such that

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

Proof. The proof can be carried out as in [1], using Theorem 1, p.111 of [42] for the function $(u_1^\epsilon - g^\epsilon, \ldots, u_M^\epsilon)$, where $g^\epsilon \in C^{1+\alpha/2,2+\alpha}([0,T] \times \Omega_\epsilon)$ solves the Cauchy-Neumann problem:

$$\begin{cases} \dfrac{\partial g^\epsilon}{\partial t} - \operatorname{div}(d_1 \nabla_x g^\epsilon) = 0 & \text{in } [0,T] \times \Omega_\epsilon \\ \\ \dfrac{\partial g^\epsilon}{\partial \nu} \equiv \nabla_x g^\epsilon \cdot n = 0 & \text{on } [0,T] \times \partial\Omega \\ \\ \dfrac{\partial g^\epsilon}{\partial \nu} \equiv \nabla_x g^\epsilon \cdot n = \epsilon\, \psi(t, x, \frac{x}{\epsilon}) & \text{on } [0,T] \times \Gamma_\epsilon \\ \\ g^\epsilon(0, x) = 0 & \text{in } \Omega_\epsilon. \end{cases}$$

Notice that the function g^ϵ is bounded in $[0,T] \times \Omega_\epsilon$, uniformly with respect to $\epsilon > 0$. This can be proven, for instance, following the arguments used in the proof of Lemmas 5.1 and 5.2.

□

Our aim is to study the homogenization of the set of equations (10)-(13) as $\epsilon \to 0$, i.e., to study the behaviour of $u_j^\epsilon (1 \le j \le M)$ as $\epsilon \to 0$ and obtain the equations satisfied by the limit. There is no clear notion of convergence for the sequence $u_j^\epsilon (1 \le j \le M)$ which is defined on a varying set Ω_ϵ. This difficulty is specific to the case of perforated domains. A natural way to get rid of this difficulty is given by Nguetseng-Allaire two-scale convergence [3, 36].

5 Homogenization of the Smoluchowski equation

5.1 Presentation of the main results

Theorem 5.1. *Let $u_m^\epsilon(t,x)$ $(1 \le m \le M)$ be a family of classical solutions to problems (10)-(13). The sequences $\widetilde{u_m^\epsilon}$ and $\widetilde{\nabla_x u_m^\epsilon}$ $(1 \le m \le M)$ two-scale converge to: $[\chi(y)\, u_m(t,x)]$ and $[\chi(y)(\nabla_x u_m(t,x) + \nabla_y u_m^1(t,x,y))]$ $(1 \le m \le M)$, respectively, where tilde denotes the extension by zero outside Ω_ϵ and $\chi(y)$ represents the characteristic function of Y^*. The limiting functions $(u_m(t,x), u_m^1(t,x,y))$ $(1 \le m \le M)$*

are the unique solutions in $L^2(0,T;H^1(\Omega))\times L^2([0,T]\times\Omega;H^1_{\#}(Y)/\mathbb{R})$ *of the following two-scale homogenized systems.*

If $m=1$ *we have:*

$$\begin{cases} \theta\,\dfrac{\partial u_1}{\partial t}(t,x) - div_x\Big[d_1\,A\,\nabla_x u_1(t,x)\Big] + \theta\,u_1(t,x)\sum_{j=1}^{M} a_{1,j}\,u_j(t,x) \\ = d_1 \displaystyle\int_\Gamma \psi(t,x,y)\,d\sigma(y) & in\ [0,T]\times\Omega \\ [A\,\nabla_x u_1(t,x)]\cdot n = 0 & on\ [0,T]\times\partial\Omega \\ u_1(0,x) = U_1 & in\ \Omega \end{cases} \tag{16}$$

if $1<m<M$ *we have:*

$$\begin{cases} \theta\,\dfrac{\partial u_m}{\partial t}(t,x) - div_x\Big[d_m\,A\,\nabla_x u_m(t,x)\Big] + \theta\,u_m(t,x)\sum_{j=1}^{M} a_{m,j}\,u_j(t,x) \\ = \dfrac{\theta}{2}\sum_{j=1}^{m-1} a_{j,m-j}u_j(t,x)\,u_{m-j}(t,x) & in\ [0,T]\times\Omega \\ [A\,\nabla_x u_m(t,x)]\cdot n = 0 & on\ [0,T]\times\partial\Omega \\ u_m(0,x) = 0 & in\ \Omega \end{cases} \tag{17}$$

if $m=M$ *we have:*

$$\begin{cases} \theta\,\dfrac{\partial u_M}{\partial t}(t,x) - div_x\Big[d_M\,A\,\nabla_x u_M(t,x)\Big] \\ = \dfrac{\theta}{2}\sum_{\substack{j+k\geq M\\ k<M\\ j<M}} a_{j,k}\,u_j(t,x)\,u_k(t,x) & in\ [0,T]\times\Omega \\ [A\,\nabla_x u_M(t,x)]\cdot n = 0 & on\ [0,T]\times\partial\Omega \\ u_M(0,x) = 0 & in\ \Omega \end{cases} \tag{18}$$

where

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

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

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 i-th unit vector in $\mathbb{R}^N$, and $(w_i)_{1\le i\le N}$ the family of solutions of the cell problem

$$\begin{cases} -div_y[\nabla_y w_i + \hat{e}_i] = 0 & in\ Y^* \\ (\nabla_y w_i + \hat{e}_i)\cdot n = 0 & on\ \Gamma \\ y \to w_i(y) \quad Y-periodic & \end{cases} \tag{19}$$

5.2 Preliminary a priori estimates

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

Since

$$\mathrm{div}(d_1\,\nabla_x u_1^\epsilon) - \frac{\partial u_1^\epsilon}{\partial t} \ge 0,$$

by the classical maximum principle [40] the following estimate holds.

Lemma 5.1. *Let $T>0$ be arbitrary and u_1^ϵ be a classical solution of (10). Then,*

$$\|u_1^\epsilon\|_{L^\infty(0,T;L^\infty(\Omega_\epsilon))} \le |U_1| + \|u_1^\epsilon\|_{L^\infty(0,T;L^\infty(\Gamma_\epsilon))}. \tag{20}$$

Thus, the boundedness of $u_1^\epsilon(t,x)$ in $L^\infty([0,T]\times\Gamma_\epsilon)$, uniformly in ϵ, can be immediately deduced from Lemma 5.2 below.

Lemma 5.2. *Let $T > 0$ be arbitrary and u_1^ϵ be a classical solution of (10). Then,*

$$\|u_1^\epsilon\|_{L^\infty(0,T;L^\infty(\Gamma_\epsilon))} \leq c\,\|\psi\|_{L^\infty(0,T;B)} \tag{21}$$

where c is independent of ϵ.

In order to establish Lemma 5.2, we will first need the following preliminary results [29, 37].

Lemma 5.3 ([29], Lemma 5.6)**.** *Let $(\tilde{z}_n)_{n\in\mathbb{N}_0}$ be a sequence of non-negative real numbers such that*

$$\tilde{z}_{n+1} \leq c\,b^n\,\tilde{z}_n^{r/2} \tag{22}$$

for all $n \in \mathbb{N}_0$, with fixed positive constants c, b, r, where $b > 1$ and

$$r = \frac{2(N+1)}{N} > 2.$$

If

$$\tilde{z}_0 \leq \theta := c^{-N}\,b^{-N^2} \tag{23}$$

then,

$$\tilde{z}_n \leq \theta\,b^{-nN} \tag{24}$$

for all $n \in \mathbb{N}_0$.

Theorem 5.2. *Assume that there exist positive constants T, $\hat{k} = \|\psi\|_{L^\infty(0,T;B)}$, γ, such that for all $k \geq \hat{k}$ we have*

$$\|u_\epsilon^{(k)}\|^2_{Q_\epsilon(T)} := \sup_{0\leq t\leq T} \int_{\Omega_\epsilon} |u_\epsilon^{(k)}|^2\,dx + \int_0^T dt \int_{\Omega_\epsilon} |\nabla u_\epsilon^{(k)}|^2\,dx \leq \epsilon\,\gamma\,k^2 \int_0^T dt\,|B_k^\epsilon(t)| \tag{25}$$

where $u_\epsilon^{(k)}(t) := (u_1^\epsilon(t) - k)_+$ and $B_k^\epsilon(t)$ is the set of points on Γ_ϵ at which $u_1^\epsilon(t,x) > k$.

Then

$$ess\ sup_{(t,x)\in[0,T]\times\Gamma_\epsilon} u_1^\epsilon(t,x) \leq 2\,m\,\hat{k} \tag{26}$$

where the positive constant m is independent of ϵ.

Proof. Let us choose

$$r = \frac{2(N+1)}{N} > 2$$

Then, it holds

$$\frac{1}{r} + \frac{(N-1)}{2r} = \frac{N}{4} \tag{27}$$

Let $\mathcal{M} \geq \hat{k}$ be arbitrary and define

$$k_n := (2 - 2^{-n})\,\mathcal{M} \geq \hat{k},$$

$$z_n := \epsilon^{2/r} \left[\int_0^T dt\, |B^{\epsilon}_{k_n}(t)| \right]^{2/r} \tag{28}$$

for all $n \in \mathbb{N}_0$. We prove that the sequence (z_n) satisfies the assumptions of Lemma 5.3. To this end, let $n \in \mathbb{N}_0$ be fixed. From the trivial estimate

$$|u^{(k_n)}_{\epsilon}(t)|^2 \geq (k_{n+1} - k_n)^2\, \mathbb{1}_{B^{\epsilon}_{k_{n+1}}}(t) \tag{29}$$

we get

$$\begin{aligned} z_{n+1} &\leq \epsilon^{2/r} \left[\int_0^T dt\, (k_{n+1} - k_n)^{-r} \int_{\Gamma_\epsilon} |u^{(k_n)}_{\epsilon}(t)|^r \, d\sigma_\epsilon(x) \right]^{2/r} \\ &= (k_{n+1} - k_n)^{-2}\, \epsilon^{2/r} \left[\int_0^T dt \int_{\Gamma_\epsilon} |u^{(k_n)}_{\epsilon}(t)|^r \, d\sigma_\epsilon(x) \right]^{2/r} \end{aligned} \tag{30}$$

Hence, since the condition (27) holds, by using (120) we obtain

$$\begin{aligned} &2^{-2(n+1)}\, \mathcal{M}^2\, z_{n+1} = (k_{n+1} - k_n)^2\, z_{n+1} \\ &\leq c\, \epsilon^{2/r}\, \epsilon^{-N - [\frac{2(1-N)}{r}]}\, \|u^{(k_n)}_{\epsilon}\|^2_{Q_\epsilon(T)} \end{aligned} \tag{31}$$

where c is a positive constant independent of ϵ. Therefore,

$$2^{-2(n+1)}\, \mathcal{M}^2\, z_{n+1} \leq c\, \epsilon^{-\frac{N}{(1+N)}}\, \|u^{(k_n)}_{\epsilon}\|^2_{Q_\epsilon(T)} \tag{32}$$

Moreover, from (25) and (28) we get

$$
\begin{aligned}
\|u_\epsilon^{(k_n)}\|^2_{Q_\epsilon(T)} &\le \gamma\, k_n^2\, z_n^{r/2} \le \gamma\,(2-2^{-n})^2\,\mathcal{M}^2\, z_n^{r/2} \\
&\le 4\,\gamma\,\mathcal{M}^2\, z_n^{r/2}
\end{aligned} \tag{33}
$$

Combining (32) and (33), we obtain

$$
z_{n+1} \le c_0\, \epsilon^{-\frac{N}{(1+N)}}\, 2^{2\,n}\, z_n^{r/2} \tag{34}
$$

where c_0 is a positive constant independent of ϵ.

Let us define

$$
d := \frac{(r-2)}{r}
$$

$$
\lambda := (c_0)^{-\frac{r}{(r-2)}}\, 2^{-\frac{4}{(r-2)d}}
$$

and choose

$$
\mathcal{M} := \hat{k} + \lambda^{-1/r}\,\sqrt{c'}\,\hat{k} \equiv m\,\hat{k} \tag{35}
$$

where c' is defined in (36) and $m > 1$. Now we want to estimate z_0 for the fixed value of $\mathcal{M}$ given by (35). From the definition (28) and (9), by following the same strategy which leads to (32) and (33), where we substitute $\hat{k}$ for k_n and $\mathcal{M}$ for k_{n+1}, we have

$$
\begin{aligned}
(\mathcal{M}-\hat{k})^2\, z_0 \le c\,\epsilon^{-\frac{N}{(1+N)}}\, \|u_\epsilon^{(\hat{k})}\|^2_{Q_\epsilon(T)} &\le c\,\epsilon^{-\frac{N}{(1+N)}} \left[\gamma\,\hat{k}^2\,T\,\frac{|\Gamma|_{N-1}\,|\Omega|_N}{|Y|_N}\right] \\
&:= c'\,\epsilon^{-\frac{N}{(1+N)}}\,\hat{k}^2
\end{aligned} \tag{36}
$$

so that

$$
z_0 \le \frac{c'\,\epsilon^{-\frac{N}{(1+N)}}\,\hat{k}^2}{(\mathcal{M}-\hat{k})^2} \tag{37}
$$

for all $\mathcal{M} \ge \hat{k}$. Therefore, from (37) and (35) we obtain that

$$
z_0 \le \epsilon^{-\frac{N}{(1+N)}}\,\lambda^{2/r}. \tag{38}
$$

For a fixed ϵ, we set

$$\tilde{z}_n = \epsilon^{\frac{N}{(1+N)}}\, z_n \tag{39}$$

for all $n \in \mathbb{N}_0$. Then, the recursion inequality (34) and the estimate (38) can be rewritten as follows:

$$\begin{cases} \tilde{z}_{n+1} \leq c_0\, 2^{2n}\, \epsilon^{-1}\, \tilde{z}_n^{r/2} \\ \tilde{z}_0 \leq \lambda^{2/r} = (c_0)^{-N}\, 2^{-2N^2} \end{cases} \tag{40}$$

Keeping in mind (40), it is easy to see that the sequence $(\tilde{z}_n)$ satisfies the assumptions of Lemma 5.3 with

$$c := \max\left\{c_0, \frac{c_0}{\epsilon}\right\} \text{ and } b := 4.$$

Therefore, in view of Lemma 5.3, one can conclude that $z_n \to 0$ as $n \to \infty$, which implies

$$u_1^\epsilon \leq \lim_{n\to\infty} k_n = 2\,\mathcal{M}$$

almost everywhere on Γ_ϵ for almost every $t \in [0,T]$ if we define $\mathcal{M}$ as in (35). This gives (26).

□

Proof of Lemma 5.2. Let $T > 0$ and $k \geq 0$ be fixed. Define: $u_\epsilon^{(k)}(t) := (u_1^\epsilon(t) - k)_+$ for $t \geq 0$, with derivatives:

$$\frac{\partial u_\epsilon^{(k)}}{\partial t} = \frac{\partial u_1^\epsilon}{\partial t}\, \mathbb{1}_{\{u_1^\epsilon > k\}} \tag{41}$$

$$\nabla_x u_\epsilon^{(k)} = \nabla_x u_1^\epsilon\, \mathbb{1}_{\{u_1^\epsilon > k\}}. \tag{42}$$

Moreover,

$$u_\epsilon^{(k)} \mid_{\partial\Omega} = (u_1^\epsilon \mid_{\partial\Omega} - k)_+ \tag{43}$$

$$u_\epsilon^{(k)} \mid_{\Gamma_\epsilon} = (u_1^\epsilon \mid_{\Gamma_\epsilon} - k)_+ \tag{44}$$

Let us assume $k \geq \hat{k}$, where $\hat{k} := \|\psi\|_{L^\infty(0,T;B)}$. Then, by (11),

$$u_1^\epsilon(0,x) = U_1 \leq \hat{k} \leq k. \tag{45}$$

For $t \in [0, T_1]$ with $T_1 \leq T$, we get

$$\begin{aligned} \frac{1}{2}\int_{\Omega_\epsilon} |u_\epsilon^{(k)}(t)|^2\, dx &= \int_0^t \frac{d}{ds}\left[\frac{1}{2}\int_{\Omega_\epsilon} |u_\epsilon^{(k)}(s)|^2\, dx\right] ds \\ &= \int_0^t ds \int_{\Omega_\epsilon} \frac{\partial u_\epsilon^{(k)}(s)}{\partial s}\, u_\epsilon^{(k)}(s)\, dx. \end{aligned} \tag{46}$$

Taking into account (41), (10) and Lemma A.1, we obtain that for all $s \in [0, T_1]$

$$\begin{aligned} &\int_{\Omega_\epsilon} \frac{\partial u_\epsilon^{(k)}(s)}{\partial s}\, u_\epsilon^{(k)}(s)\, dx = \int_{\Omega_\epsilon} \frac{\partial u_1^\epsilon(s)}{\partial s}\, u_\epsilon^{(k)}(s)\, dx \\ &= \int_{\Omega_\epsilon} \left[d_1\, \Delta_x u_1^\epsilon - u_1^\epsilon \sum_{j=1}^M a_{1,j} u_j^\epsilon\right] u_\epsilon^{(k)}(s)\, dx \\ &= -\int_{\Omega_\epsilon} u_1^\epsilon(s) \sum_{j=1}^M a_{1,j} u_j^\epsilon(s)\, u_\epsilon^{(k)}(s)\, dx + \epsilon\, d_1 \int_{\Gamma_\epsilon} \psi\left(s, x, \frac{x}{\epsilon}\right) u_\epsilon^{(k)}(s)\, d\sigma_\epsilon(x) \\ &- d_1 \int_{\Omega_\epsilon} \nabla_x u_1^\epsilon(s) \cdot \nabla_x u_\epsilon^{(k)}(s)\, dx \\ &\leq \epsilon\, d_1 \int_{\Gamma_\epsilon} \psi\left(s, x, \frac{x}{\epsilon}\right) u_\epsilon^{(k)}(s)\, d\sigma_\epsilon(x) - d_1 \int_{\Omega_\epsilon} \nabla_x u_1^\epsilon(s) \cdot \nabla_x u_\epsilon^{(k)}(s)\, dx \\ &\leq \frac{\epsilon\, d_1}{2} \int_{B_k^\epsilon(s)} \left|\psi\left(s, x, \frac{x}{\epsilon}\right)\right|^2 d\sigma_\epsilon(x) + \frac{\epsilon\, d_1}{2} \int_{\Gamma_\epsilon} |u_\epsilon^{(k)}(s)|^2\, d\sigma_\epsilon(x) \\ &- d_1 \int_{\Omega_\epsilon} \nabla_x u_1^\epsilon(s) \cdot \nabla_x u_\epsilon^{(k)}(s)\, dx \\ &\leq \frac{\epsilon\, d_1}{2} \int_{B_k^\epsilon(s)} \left|\psi\left(s, x, \frac{x}{\epsilon}\right)\right|^2 d\sigma_\epsilon(x) + \frac{C_1\, d_1}{2} \int_{A_k^\epsilon(s)} |u_\epsilon^{(k)}(s)|^2\, dx \\ &- d_1 \left(1 - \frac{C_1 \epsilon^2}{2}\right) \int_{\Omega_\epsilon} |\nabla_x u_\epsilon^{(k)}(s)|^2\, dx \end{aligned} \tag{47}$$

where we denote by $A_k^\epsilon(t)$ and $B_k^\epsilon(t)$ the set of points in Ω_ϵ and on Γ_ϵ, respectively, at which $u_1^\epsilon(t,x) > k$. It holds:

$$|A_k^\epsilon(t)| \leq |\Omega_\epsilon|$$

$$|B_k^\epsilon(t)| \leq |\Gamma_\epsilon|$$

with $|\cdot|$ being the natural Hausdorff measure.

Plugging (47) into (46) and varying over t, we arrive at the estimate:

$$\sup_{0\le t\le T_1}\left[\frac{1}{2}\int_{\Omega_\epsilon}|u_\epsilon^{(k)}(t)|^2\,dx\right]+d_1\left(1-\frac{C_1\,\epsilon^2}{2}\right)\int_0^{T_1}dt\int_{\Omega_\epsilon}|\nabla u_\epsilon^{(k)}(t)|^2\,dx$$
$$\le\frac{C_1\,d_1}{2}\int_0^{T_1}dt\int_{A_k^\epsilon(t)}|u_\epsilon^{(k)}(t)|^2\,dx+\frac{\epsilon\,d_1}{2}\int_0^{T_1}dt\int_{B_k^\epsilon(t)}\left|\psi\left(t,x,\frac{x}{\epsilon}\right)\right|^2 d\sigma_\epsilon(x) \tag{48}$$

Introducing the following norm

$$\|u\|^2_{Q_\epsilon(T)}:=\sup_{0\le t\le T}\int_{\Omega_\epsilon}|u(t)|^2\,dx+\int_0^T dt\int_{\Omega_\epsilon}|\nabla u(t)|^2\,dx \tag{49}$$

the inequality (48) can be rewritten as follows

$$\min\left\{\frac{1}{2},d_1\left(1-\frac{C_1\,\epsilon^2}{2}\right)\right\}\|u_\epsilon^{(k)}\|^2_{Q_\epsilon(T_1)}\le\frac{C_1\,d_1}{2}\int_0^{T_1}dt\int_{A_k^\epsilon(t)}|u_\epsilon^{(k)}(t)|^2\,dx$$
$$+\frac{\epsilon\,d_1}{2}\int_0^{T_1}dt\int_{B_k^\epsilon(t)}\left|\psi\left(t,x,\frac{x}{\epsilon}\right)\right|^2 d\sigma_\epsilon(x) \tag{50}$$

We estimate the right-hand side of (50). From Hölder's inequality we obtain

$$\int_0^{T_1}dt\int_{A_k^\epsilon(t)}|u_\epsilon^{(k)}(t)|^2\,dx\le\|u_\epsilon^{(k)}\|^2_{L^{\overline{r}_1}(0,T_1;L^{\overline{q}_1}(\Omega_\epsilon))}\,\|\mathbb{1}_{A_k^\epsilon}\|_{L^{r_1'}(0,T_1;L^{q_1'}(\Omega_\epsilon))} \tag{51}$$

with $r_1'=\dfrac{r_1}{r_1-1}$, $q_1'=\dfrac{q_1}{q_1-1}$, $\overline{r}_1=2\,r_1$, $\overline{q}_1=2\,q_1$, where, for $N>2$, $\overline{r}_1\in(2,\infty)$ and $\overline{q}_1\in(2,\frac{2\,N}{(N-2)})$ have been chosen such that

$$\frac{1}{\overline{r}_1}+\frac{N}{2\,\overline{q}_1}=\frac{N}{4}$$

In particular, $r_1',q_1'<\infty$, so that (51) yields

$$\int_0^{T_1}dt\int_{A_k^\epsilon(t)}|u_\epsilon^{(k)}(t)|^2\,dx\le\|u_\epsilon^{(k)}\|^2_{L^{\overline{r}_1}(0,T_1;L^{\overline{q}_1}(\Omega_\epsilon))}\,|\Omega|^{1/q_1'}\,T_1^{1/r_1'}. \tag{52}$$

If we choose

$$T_1^{1/r_1'}<\frac{\min\{1,d_1\}}{2C_1d_1}\,|\Omega|^{-1/q_1'}\le\frac{\min\left\{\frac{1}{2},d_1\left(1-\frac{C_1\,\epsilon^2}{2}\right)\right\}}{C_1d_1}\,|\Omega|^{-1/q_1'},$$

then from (117) it follows that

$$\frac{C_1\,d_1}{2}\int_0^{T_1}dt\int_{A_k^\epsilon(t)}|u_\epsilon^{(k)}(t)|^2\,dx\le\frac{1}{2}\min\left\{\frac{1}{2},d_1\left(1-\frac{C_1\,\epsilon^2}{2}\right)\right\}\|u_\epsilon^{(k)}\|^2_{Q_\epsilon(T_1)}. \tag{53}$$

Analogously, from Hölder's inequality we have, for $k \geq \hat{k}$

$$\frac{\epsilon\, d_1}{2} \int_0^{T_1} dt \int_{B_k^\epsilon(t)} \left| \psi\left(t, x, \frac{x}{\epsilon}\right) \right|^2 d\sigma_\epsilon(x) \leq \frac{\epsilon\, d_1\, k^2}{2} \left(\frac{\hat{k}^2}{k^2} \right) \| \mathbb{1}_{B_k^\epsilon} \|_{L^1(0,T_1;L^1(\Gamma_\epsilon))} \leq \frac{\epsilon\, d_1\, k^2}{2} \int_0^{T_1} dt\, |B_k^\epsilon(t)|. \tag{54}$$

Thus (50) yields

$$\| u_\epsilon^{(k)} \|^2_{Q_\epsilon(T_1)} \leq \epsilon\, \gamma\, k^2 \int_0^{T_1} dt\, |B_k^\epsilon(t)|. \tag{55}$$

Hence, by Theorem 5.2 we obtain

$$\| u_1^\epsilon \|_{L^\infty(0,T_1;L^\infty(\Gamma_\epsilon))} \leq 2\, m\, \hat{k}$$

where the positive constant m is independent of ϵ. Analogous arguments are valid for the cylinder $[T_s, T_{s+1}] \times \Omega_\epsilon$, $s = 1, 2, \ldots, p-1$ with

$$\left[T_{s+1} - T_s \right]^{1/r_1'} < \frac{\min\{1, d_1\}}{2 C_1 d_1} |\Omega|^{-1/q_1'}$$

and $T_p \equiv T$. Thus, after a finite number of steps, we obtain the estimate (21).

□

Lemma 5.4. *The sequence $\nabla_x u_1^\epsilon$ is bounded in $L^2([0,T] \times \Omega_\epsilon)$, uniformly in ϵ.*

Proof. Let us multiply the first equation in (10) by the function $u_1^\epsilon(t,x)$. Integrating, the divergence theorem yields

$$\frac{1}{2} \int_{\Omega_\epsilon} \frac{\partial}{\partial t} |u_1^\epsilon|^2\, dx + d_1 \int_{\Omega_\epsilon} |\nabla_x u_1^\epsilon|^2\, dx + \int_{\Omega_\epsilon} |u_1^\epsilon|^2 \sum_{j=1}^{M} a_{1,j}\, u_j^\epsilon\, dx = \epsilon\, d_1 \int_{\Gamma_\epsilon} \psi\left(t, x, \frac{x}{\epsilon}\right) u_1^\epsilon(t,x)\, d\sigma_\epsilon(x) \tag{56}$$

By Hölder's and Young's inequalities, the right-hand side of Eq. (56) can be rewritten as

$$\int_{\Gamma_\epsilon} \psi\left(t, x, \frac{x}{\epsilon}\right) u_1^\epsilon(t,x)\, d\sigma_\epsilon(x) \leq \frac{1}{2} \|\psi(t, \cdot, \frac{\cdot}{\epsilon})\|^2_{L^2(\Gamma_\epsilon)} + \frac{1}{2} \|u_1^\epsilon(t, \cdot)\|^2_{L^2(\Gamma_\epsilon)} \tag{57}$$

The following estimate holds [see Lemma B.1]

$$\epsilon \int_{\Gamma_\epsilon} |\psi(t, x, \frac{x}{\epsilon})|^2 \, d\sigma_\epsilon(x) \leq C_2 \, \|\psi(t)\|_B^2 \tag{58}$$

where C_2 is a positive constant independent of ϵ and $B = C^1[\overline{\Omega}; C^1_\#(Y)]$. Therefore, by combining Eqs. (56)-(58) and by using Lemma A.1, we deduce

$$\begin{aligned} &\int_{\Omega_\epsilon} \frac{\partial}{\partial t} |u_1^\epsilon|^2 \, dx + d_1 \, (2 - \epsilon^2 \, C_1) \int_{\Omega_\epsilon} |\nabla_x u_1^\epsilon|^2 \, dx \\ &\leq d_1 \, C_2 \, \|\psi(t)\|_B^2 + d_1 \, C_1 \int_{\Omega_\epsilon} |u_1^\epsilon|^2 \, dx \end{aligned} \tag{59}$$

since the third term on the left-hand side of (56) is non-negative. Integrating over $[0, t]$ with $t \in [0, T]$, we get

$$\|u_1^\epsilon(t)\|^2_{L^2(\Omega_\epsilon)} + d_1 \, (2 - \epsilon^2 \, C_1) \int_0^t ds \int_{\Omega_\epsilon} |\nabla_x u_1^\epsilon|^2 \, dx \leq C_3 + d_1 \, C_1 \, \|u_1^\epsilon\|^2_{L^2(0,T;L^2(\Omega_\epsilon))} \tag{60}$$

where C_1 and C_3 are positive constants independent of ϵ since, by (11),

$$u_1^\epsilon(0, x) = U_1 \leq \|\psi\|_{L^\infty(0,T;B)}.$$

Taking into account that the first term on the left-hand side of (60) is non-negative and the sequence u_1^ϵ is bounded in $L^\infty(0, T; L^\infty(\Omega_\epsilon))$, one has

$$d_1 \, (2 - \epsilon^2 \, C_1) \, \|\nabla_x u_1^\epsilon\|^2_{L^2(0,T;L^2(\Omega_\epsilon))} \leq C_4 \tag{61}$$

Thus the boundedness of $\nabla_x u_1^\epsilon(t, x)$ follows, provided that ϵ is close to zero.

□

Lemma 5.5. *Let $u_m^\epsilon(t, x)$ $(1 < m < M)$ be a classical solution of (12). Then*

$$\|u_m^\epsilon\|_{L^\infty(0,T;L^\infty(\Omega_\epsilon))} \leq K_m \tag{62}$$

uniformly with respect to ϵ, where

$$K_m = 1 + \frac{\left[\sum_{j=1}^{m-1} a_{j,m-j} K_j K_{m-j} \right]}{a_{m,m}} \tag{63}$$

Proof. The Lemma can be proved directly by induction following the same arguments presented in [45] (Lemma 2.2, p. 284). Since we have a zero initial condition for the system (12), we have chosen a function slightly different than what was done in [45] to test the mth equation of (12):

$$\phi_m \equiv p\,(u_m^\epsilon)^{(p-1)} \quad p \geq 2.$$

We stress that the functions ϕ_m are strictly positive and continuously differentiable in $[0,t] \times \overline{\Omega}$, for all $t > 0$. The rest of the proof carries over verbatim.

□

Lemma 5.6. *The sequence $\nabla_x u_m^\epsilon$ $(1 < m < M)$ is bounded in $L^2([0,T] \times \Omega_\epsilon)$, uniformly in ϵ.*

Proof. Let us multiply the first equation in (12) by the function $u_m^\epsilon(t,x)$. By the divergence theorem and Hölder's inequality, exploiting the boundedness of $u_j^\epsilon(t,x)$ $(1 \leq j \leq m-1)$ in $L^\infty(0,T;L^\infty(\Omega_\epsilon))$, we get

$$\frac{1}{2}\int_{\Omega_\epsilon} \frac{\partial}{\partial t}|u_m^\epsilon|^2\,dx + d_m \int_{\Omega_\epsilon} |\nabla_x u_m^\epsilon|^2\,dx \leq C_3\,\|u_m^\epsilon(t,\cdot)\|_{L^2(\Omega_\epsilon)} \tag{64}$$

where C_3 is a constant which does not depend on ϵ. Dividing by $\|u_m^\epsilon(t,\cdot)\|_{L^2(\Omega_\epsilon)}$ and integrating over $[0,t]$ with $t \in [0,T]$, we deduce

$$\int_0^t ds\,\frac{d}{ds}\|u_m^\epsilon(s,\cdot)\|_{L^2(\Omega_\epsilon)} + d_m\,C_4 \int_0^t ds \int_{\Omega_\epsilon} |\nabla_x u_m^\epsilon|^2\,dx \leq C_3\,T \tag{65}$$

exploiting the boundedness of $u_m^\epsilon(t,x)$ in $L^\infty(0,T;L^\infty(\Omega_\epsilon))$. Hence

$$\|u_m^\epsilon(t,\cdot)\|_{L^2(\Omega_\epsilon)} + d_m\,C_4 \int_0^t ds \int_{\Omega_\epsilon} |\nabla_x u_m^\epsilon|^2\,dx \leq C_5 \tag{66}$$

where C_4 and C_5 are positive constants independent of ϵ. Then, the boundedness of $\nabla_x u_m^\epsilon(t,x)$ in $L^2([0,T] \times \Omega_\epsilon)$, uniformly in ϵ, follows immediately from (66).

□

Lemma 5.7. *Let $u_M^\epsilon(t,x)$ be a classical solution of (13). Then*

$$\|u_M^\epsilon\|_{L^\infty(0,T;L^\infty(\Omega_\epsilon))} \leq K_M \tag{67}$$

uniformly with respect to ϵ, where

$$K_M = e^T \sum_{\substack{j+k\geq M\\ k<M\\ j<M}} a_{j,k}\, K_j\, K_k \tag{68}$$

with the constants K_j $(1 < j < M)$ given by (63).

Proof. Let us test the first equation of (13) with the function

$$\phi_M \equiv p\,(u_M^\epsilon)^{(p-1)} \qquad p \geq 2.$$

The function ϕ_M is strictly positive and continuously differentiable in $[0,t]\times\overline{\Omega}$, for all $t > 0$. Integrating, the divergence theorem yields

$$\begin{aligned}\int_0^t ds \int_{\Omega_\epsilon} \frac{\partial}{\partial s}(u_M^\epsilon)^p(s)\,dx = &- d_M\,p \int_0^t ds \int_{\Omega_\epsilon} \nabla_x u_M^\epsilon \cdot \nabla\Big[(u_M^\epsilon)^{(p-1)}\Big]\,dx\\ &+ \frac{p}{2}\int_0^t ds \int_{\Omega_\epsilon} \sum_{\substack{j+k\geq M\\ k<M\\ j<M}} a_{j,k}\, u_j^\epsilon u_k^\epsilon\,(u_M^\epsilon)^{(p-1)}\,dx\end{aligned} \tag{69}$$

Hence

$$\begin{aligned}\int_{\Omega_\epsilon} (u_M^\epsilon)^p(t)\,dx &+ d_M\,p\,(p-1)\int_0^t ds \int_{\Omega_\epsilon} |\nabla_x u_M^\epsilon|^2\,(u_M^\epsilon)^{(p-2)}\,dx\\ &= \frac{p}{2}\int_0^t ds \int_{\Omega_\epsilon} \sum_{\substack{j+k\geq M\\ k<M\\ j<M}} a_{j,k}\, u_j^\epsilon u_k^\epsilon\,(u_M^\epsilon)^{(p-1)}\,dx\end{aligned} \tag{70}$$

Taking into account the boundedness of u_j^ϵ $(1 \leq j < M)$ in $L^\infty(0,T;L^\infty(\Omega_\epsilon))$ we get

$$\begin{aligned}\int_{\Omega_\epsilon} (u_M^\epsilon)^p(t)\,dx &+ d_M\,p\,(p-1)\int_0^t ds \int_{\Omega_\epsilon} |\nabla_x u_M^\epsilon|^2\,(u_M^\epsilon)^{(p-2)}\,dx\\ &\leq p\int_0^t ds \int_{\Omega_\epsilon} \Big[\sum_{\substack{j+k\geq M\\ k<M\\ j<M}} a_{j,k}\, K_j\, K_k\Big](u_M^\epsilon)^{(p-1)}\,dx =: I_3\end{aligned} \tag{71}$$

In order to estimate I_3, it is now convenient to use Young's inequality in the following form [8]:

$$a\, b \le \eta\, a^{p'} + \eta^{1-p}\, b^p \quad \forall a \ge 0,\ b \ge 0 \tag{72}$$

with $p' = \frac{p}{p-1}$. We find

$$\begin{aligned} I_3 &\le \int_0^t ds \int_{\Omega_\epsilon} p^p \Bigg[\sum_{\substack{j+k\ge M\\ k<M\\ j<M}} a_{j,k}\, K_j\, K_k \Bigg]^p \eta^{1-p}\, dx + \int_0^t ds \int_{\Omega_\epsilon} \eta\, (u_M^\epsilon)^p\, dx \\ &\le p^{p-1} \left(\frac{p}{p-1} \right)^{1-p} \Bigg[\sum_{\substack{j+k\ge M\\ k<M\\ j<M}} a_{j,k}\, K_j\, K_k \Bigg]^p \eta^{1-p}\, |\Omega_\epsilon|\, t + \eta \int_0^t ds \int_{\Omega_\epsilon} (u_M^\epsilon)^p\, dx \end{aligned} \tag{73}$$

Taking $\eta = p$ yields

$$I_3 \le \Bigg[\sum_{\substack{j+k\ge M\\ k<M\\ j<M}} a_{j,k}\, K_j\, K_k \Bigg]^p |\Omega_\epsilon|\, t + p \int_0^t ds \int_{\Omega_\epsilon} (u_M^\epsilon)^p\, dx \tag{74}$$

Finally from (71) and (74) it follows that

$$\|u_M^\epsilon(t)\|^p_{L^p(\Omega_\epsilon)} \le \Bigg[\sum_{\substack{j+k\ge M\\ k<M\\ j<M}} a_{j,k}\, K_j\, K_k \Bigg]^p |\Omega_\epsilon|\, T + \int_0^t ds\, p\, \|u_M^\epsilon(s)\|^p_{L^p(\Omega_\epsilon)} \tag{75}$$

The Gronwall Lemma applied to (75) leads to the estimate

$$\|u_M^\epsilon(t)\|^p_{L^p(\Omega_\epsilon)} \le \Bigg[\sum_{\substack{j+k\ge M\\ k<M\\ j<M}} a_{j,k}\, K_j\, K_k \Bigg]^p |\Omega_\epsilon|\, T\, e^{p\, t} \tag{76}$$

Hence

$$\sup_{t\in[0,T]} \lim_{p\to\infty} \left[\int_{\Omega_\epsilon} (u_M^\epsilon(t,x))^p\, dx \right]^{1/p} \le \sum_{\substack{j+k\ge M\\ k<M\\ j<M}} a_{j,k}\, K_j\, K_k\, e^T \tag{77}$$

□

Lemma 5.8. *The sequence $\nabla_x u_M^\epsilon$ is bounded in $L^2([0,T]\times\Omega_\epsilon)$, uniformly in ϵ.*

The proof of Lemma 5.8 is achieved by applying exactly the same arguments considered in the proof of Lemma 5.6.

Lemma 5.9. *The sequence $\partial_t u_j^\epsilon$ $(1 \le j \le M)$ is bounded in $L^2([0,T] \times \Omega_\epsilon)$, uniformly in ϵ.*

Proof. Case $j = 1$: let us multiply the first equation in (10) by the function $\partial_t u_1^\epsilon(t,x)$. By the divergence theorem, by Hölder's and Young's inequalities, exploiting the boundedness of $u_j^\epsilon(t,x)$ $(1 \le j \le M)$ in $L^\infty(0,T; L^\infty(\Omega_\epsilon))$, one get

$$\int_{\Omega_\epsilon} \left| \frac{\partial u_1^\epsilon}{\partial t} \right|^2 dx + d_1 \frac{\partial}{\partial t} \int_{\Omega_\epsilon} |\nabla_x u_1^\epsilon|^2 \, dx \le C_1 + 2\,\epsilon\, d_1 \int_{\Gamma_\epsilon} \psi\left(t, x, \frac{x}{\epsilon}\right) \frac{\partial u_1^\epsilon}{\partial t} \, d\sigma_\epsilon(x) \quad (78)$$

Integrating over $[0,t]$ with $t \in [0,T]$, we obtain

$$\begin{aligned} \int_0^t ds \int_{\Omega_\epsilon} \left| \frac{\partial u_1^\epsilon}{\partial s} \right|^2 dx + d_1 \int_{\Omega_\epsilon} |\nabla_x u_1^\epsilon(t,x)|^2 \, dx &\le C_1\, T \\ &+ 2\,\epsilon\, d_1 \int_{\Gamma_\epsilon} \psi\left(t, x, \frac{x}{\epsilon}\right) u_1^\epsilon(t,x) \, d\sigma_\epsilon(x) \\ &- 2\,\epsilon\, d_1 \int_0^t ds \int_{\Gamma_\epsilon} \frac{\partial}{\partial s} \psi\left(s, x, \frac{x}{\epsilon}\right) u_1^\epsilon(s,x) \, d\sigma_\epsilon(x) \end{aligned} \quad (79)$$

since $\psi\left(t = 0, x, \frac{x}{\epsilon}\right) \equiv 0$. Taking into account the inequalities (57)-(58) and Lemma A.1, Eq. (79) can be rewritten as follows

$$\int_0^t ds \int_{\Omega_\epsilon} \left| \frac{\partial u_1^\epsilon}{\partial s} \right|^2 dx + d_1(1 - \epsilon^2 C_3) \int_{\Omega_\epsilon} |\nabla_x u_1^\epsilon|^2 \, dx \le C_1\, T + C_4 + C_7 \quad (80)$$

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 $L^\infty(0,T; L^\infty(\Omega_\epsilon))$, $\nabla_x u_1^\epsilon$ is bounded in $L^2(0,T; L^2(\Omega_\epsilon))$ and the following inequality holds

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

with $\tilde{C}$ and C_5 independent of ϵ. For a sequence ϵ of positive numbers going to zero: $(1 - \epsilon^2 C_3) \ge 0$. Then, the second term on the left-hand side of (80) is non-negative, and one has

$$\|\partial_t u_1^\epsilon\|^2_{L^2(0,T;L^2(\Omega_\epsilon))} \le C \quad (81)$$

where $C \ge 0$ is a constant independent of ϵ.

Case $1 < j < M$: let us multiply the first equation in (12) by the function $\partial_t u_m^\epsilon(t,x)$. By the divergence theorem, by Hölder's and Young's inequalities, exploiting the boundedness of $u_j^\epsilon(t,x)$ $(1 \leq j \leq M)$ in $L^\infty(0,T;L^\infty(\Omega_\epsilon))$, one get

$$\int_{\Omega_\epsilon} \left| \frac{\partial u_m^\epsilon}{\partial t} \right|^2 dx + 2\, d_m \frac{\partial}{\partial t} \int_{\Omega_\epsilon} |\nabla_x u_m^\epsilon|^2 \, dx \leq 2\, C_1 + C_2 \tag{82}$$

Integrating over $[0,t]$ with $t \in [0,T]$, we obtain

$$\int_0^t ds \int_{\Omega_\epsilon} \left| \frac{\partial u_m^\epsilon}{\partial s} \right|^2 dx + 2\, d_m \int_{\Omega_\epsilon} |\nabla_x u_m^\epsilon(t,x)|^2 \, dx \leq C_3\, T \tag{83}$$

Since the second term on the left-hand side of (83) is non-negative, we conclude that

$$\|\partial_t u_m^\epsilon\|^2_{L^2(0,T;L^2(\Omega_\epsilon))} \leq C \tag{84}$$

where $C \geq 0$ is a constant independent of ϵ.

By applying exactly the same arguments considered in proving the boundedness of $\partial_t u_j^\epsilon(t,x)$ $(1 < j < M)$ in $L^2(0,T;L^2(\Omega_\epsilon))$, one can derive also the following estimate

$$\|\partial_t u_M^\epsilon\|^2_{L^2(0,T;L^2(\Omega_\epsilon))} \leq C \tag{85}$$

where $C \geq 0$ is a constant independent of ϵ.

□

5.3 Proof of the main theorem

Let us now come back to the proof of the main results stated in Theorem 5.1. In view of Lemmas 5.1-5.2 and 5.4-5.8 the sequences $\widetilde{u_m^\epsilon}$ and $\widetilde{\nabla_x u_m^\epsilon}$ $(1 \leq m \leq M)$ are bounded in $L^2([0,T]\times\Omega)$, and by application of Theorem B.1 and Theorem B.3 they two-scale converge, up to a subsequence, to: $[\chi(y)\, u_m(t,x)]$ and $[\chi(y)(\nabla_x u_m(t,x) + \nabla_y u_m^1(t,x,y))]$ $(1 \leq m \leq M)$. Similarly, in view of Lemma 5.9, it is possible to prove that the sequence $\left(\widetilde{\frac{\partial u_m^\epsilon}{\partial t}}\right)$ $(1 \leq m \leq M)$ two-scale converges to: $\left[\chi(y)\, \frac{\partial u_m}{\partial t}(t,x)\right]$ $(1 \leq m \leq M)$.

We can now find the homogenized equations satisfied by $u_m(t,x)$ and $u_m^1(t,x,y)$ $(1 \leq m \leq M)$.

In the case $m = 1$, let us multiply the first equation of (10) by the test function

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

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

$$\begin{aligned}&\int_0^T\int_{\Omega_\epsilon}\frac{\partial u_1^\epsilon}{\partial t}\,\phi_\epsilon(t,x,\frac{x}{\epsilon})\,dt\,dx + d_1\int_0^T\int_{\Omega_\epsilon}\nabla_x u_1^\epsilon\cdot\nabla\phi_\epsilon\,dt\,dx\\ &+\int_0^T\int_{\Omega_\epsilon}u_1^\epsilon\sum_{j=1}^M a_{1,j}\,u_j^\epsilon\,\phi_\epsilon\,dt\,dx = \epsilon\,d_1\int_0^T\int_{\Gamma_\epsilon}\psi\left(t,x,\frac{x}{\epsilon}\right)\phi_\epsilon\,dt\,d\sigma_\epsilon(x)\end{aligned} \tag{86}$$

Passing to the two-scale limit we get

$$\begin{aligned}&\int_0^T\int_\Omega\int_{Y^*}\frac{\partial u_1}{\partial t}(t,x)\,\phi(t,x)\,dt\,dx\,dy\\ &+d_1\int_0^T\int_\Omega\int_{Y^*}[\nabla_x u_1(t,x)+\nabla_y u_1^1(t,x,y)]\cdot[\nabla_x\phi(t,x)+\nabla_y\phi_1(t,x,y)]\,dt\,dx\,dy\\ &+\int_0^T\int_\Omega\int_{Y^*}u_1(t,x)\sum_{j=1}^M a_{1,j}\,u_j(t,x)\,\phi(t,x)\,dt\,dx\,dy\\ &= d_1\int_0^T\int_\Omega\int_\Gamma\psi(t,x,y)\,\phi(t,x)\,dt\,dx\,d\sigma(y).\end{aligned} \tag{87}$$

The last term on the left-hand side of (87) has been obtained by using Theorem B.2, while the term on the right-hand side has been attained by application of Theorem B.5. An integration by parts shows that (87) is a variational formulation associated to the following homogenized system:

$$-\text{div}_y[d_1(\nabla_x u_1(t,x)+\nabla_y u_1^1(t,x,y))] = 0 \qquad \text{in } [0,T]\times\Omega\times Y^* \tag{88}$$

$$[\nabla_x u_1(t,x)+\nabla_y u_1^1(t,x,y)]\cdot n = 0 \qquad \text{on } [0,T]\times\Omega\times\Gamma \tag{89}$$

$$\begin{aligned}&\theta\,\frac{\partial u_1}{\partial t}(t,x) - \text{div}_x\left[d_1\int_{Y^*}(\nabla_x u_1(t,x)+\nabla_y u_1^1(t,x,y))dy\right]\\ &+\theta\,u_1(t,x)\sum_{j=1}^M a_{1,j}\,u_j(t,x) - d_1\int_\Gamma\psi(t,x,y)\,d\sigma(y) = 0 \qquad \text{in } [0,T]\times\Omega\end{aligned} \tag{90}$$

$$\left[\int_{Y^*} (\nabla_x u_1(t,x) + \nabla_y u_1^1(t,x,y))\, dy\right] \cdot n = 0 \qquad \text{on } [0,T] \times \partial\Omega \tag{91}$$

where

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

is the volume fraction of material. To conclude, by continuity, we have that

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

Taking advantage of the constancy of the diffusion coefficient d_1, Eqs. (88) and (89) can be reexpressed as follows

$$\triangle_y u_1^1(t,x,y) = 0 \qquad \text{in } [0,T] \times \Omega \times Y^* \tag{92}$$

$$\nabla_y u_1^1(t,x,y) \cdot n = -\nabla_x u_1(t,x) \cdot n \qquad \text{on } [0,T] \times \Omega \times \Gamma \tag{93}$$

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

$$u_1^1(t,x,y) = \sum_{i=1}^{N} w_i(y)\, \frac{\partial u_1}{\partial x_i}(t,x) \tag{94}$$

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

$$\begin{cases} -\mathrm{div}_y[\nabla_y w_i + \hat{e}_i] = 0 & \text{in } Y^* \\ (\nabla_y w_i + \hat{e}_i) \cdot n = 0 & \text{on } \Gamma \\ y \to w_i(y) \quad Y-\text{periodic} \end{cases} \tag{95}$$

By using the relation (94) in Eqs. (90) and (91) we get

$$\begin{aligned} \theta \frac{\partial u_1}{\partial t}(t,x) - \mathrm{div}_x\left[d_1\, A\, \nabla_x u_1(t,x)\right] + \theta\, u_1(t,x) \sum_{j=1}^{M} a_{1,j}\, u_j(t,x) \\ - d_1 \int_\Gamma \psi(t,x,y)\, d\sigma(y) = 0 \qquad \text{in } [0,T] \times \Omega \end{aligned} \tag{96}$$

$$[A\,\nabla_x u_1(t,x)]\cdot n = 0 \qquad \text{on } [0,T]\times\partial\Omega \tag{97}$$

where A is a matrix with constant coefficients defined by

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

In the case $1 < m < M$, let us multiply the first equation of (12) by the test function

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

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

$$\begin{aligned}
&\int_0^T \int_{\Omega_\epsilon} \frac{\partial u_m^\epsilon}{\partial t}\,\phi_\epsilon(t,x,\frac{x}{\epsilon})\,dt\,dx + d_m \int_0^T \int_{\Omega_\epsilon} \nabla_x u_m^\epsilon \cdot \nabla\phi_\epsilon\,dt\,dx \\
&+ \int_0^T \int_{\Omega_\epsilon} u_m^\epsilon \sum_{j=1}^{M} a_{m,j}\,u_j^\epsilon\,\phi_\epsilon\,dt\,dx = \frac{1}{2}\int_0^T \int_{\Omega_\epsilon} \sum_{j=1}^{m-1} a_{j,m-j}\,u_j^\epsilon\,u_{m-j}^\epsilon\,\phi_\epsilon\,dt\,dx
\end{aligned} \tag{98}$$

Passing to the two-scale limit we get

$$\begin{aligned}
&\int_0^T \int_\Omega \int_{Y^*} \frac{\partial u_m}{\partial t}(t,x)\,\phi(t,x)\,dt\,dx\,dy \\
&+ d_m \int_0^T \int_\Omega \int_{Y^*} [\nabla_x u_m(t,x) + \nabla_y u_m^1(t,x,y)]\cdot[\nabla_x \phi(t,x) + \nabla_y \phi_1(t,x,y)]\,dt\,dx\,dy \\
&+ \int_0^T \int_\Omega \int_{Y^*} u_m(t,x) \sum_{j=1}^{M} a_{m,j}\,u_j(t,x)\,\phi(t,x)\,dt\,dx\,dy \\
&= \frac{1}{2}\int_0^T \int_\Omega \int_{Y^*} \sum_{j=1}^{m-1} a_{j,m-j}\,u_j(t,x)\,u_{m-j}(t,x)\,\phi(t,x)\,dt\,dx\,dy.
\end{aligned} \tag{99}$$

The last term on the left-hand side of (99) and the term on the right-hand side have been obtained by using Theorem B.2. An integration by parts shows that (99) is a variational formulation associated to the following homogenized system:

$$-\mathrm{div}_y[d_m(\nabla_x u_m(t,x) + \nabla_y u_m^1(t,x,y))] = 0 \qquad \text{in } [0,T]\times\Omega\times Y^* \tag{100}$$

$$[\nabla_x u_m(t,x) + \nabla_y u_m^1(t,x,y)] \cdot n = 0 \qquad \text{on } [0,T]\times\Omega\times\Gamma \tag{101}$$

$$\theta \frac{\partial u_m}{\partial t}(t,x) - \mathrm{div}_x \left[d_m \int_{Y^*} (\nabla_x u_m(t,x) + \nabla_y u_m^1(t,x,y)) dy \right]$$
$$+ \theta\, u_m(t,x) \sum_{j=1}^{M} a_{m,j}\, u_j(t,x) - \frac{\theta}{2} \sum_{j=1}^{m-1} a_{j,m-j} u_j(t,x)\, u_{m-j}(t,x) = 0 \ \text{ in } [0,T]\times\Omega \tag{102}$$

$$\left[\int_{Y^*} (\nabla_x u_m(t,x) + \nabla_y u_m^1(t,x,y))\, dy \right] \cdot n = 0 \qquad \text{on } [0,T]\times\partial\Omega \tag{103}$$

where

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

is the volume fraction of material. Moreover, by continuity

$$u_m(0,x) = 0 \qquad \text{in } \Omega.$$

Taking advantage of the constancy of the diffusion coefficient d_m, Eqs. (100) and (101) can be reexpressed as follows

$$\triangle_y u_m^1(t,x,y) = 0 \qquad \text{in } [0,T]\times\Omega\times Y^* \tag{104}$$

$$\nabla_y u_m^1(t,x,y)\cdot n = -\nabla_x u_m(t,x)\cdot n \qquad \text{on } [0,T]\times\Omega\times\Gamma \tag{105}$$

Then, $u_m^1(t,x,y)$ satisfying (104)-(105) can be written as

$$u_m^1(t,x,y) = \sum_{i=1}^{N} w_i(y)\, \frac{\partial u_m}{\partial x_i}(t,x) \tag{106}$$

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

$$\begin{cases} -\mathrm{div}_y[\nabla_y w_i + \hat{e}_i] = 0 & \text{in } Y^* \\ (\nabla_y w_i + \hat{e}_i)\cdot n = 0 & \text{on } \Gamma \\ y \to w_i(y) \quad Y-\text{periodic} & \end{cases} \tag{107}$$

By using the relation (106) in Eqs. (102) and (103) we get

$$\begin{aligned}
&\theta \frac{\partial u_m}{\partial t}(t,x) - \mathrm{div}_x \Big[d_m \, A \, \nabla_x u_m(t,x) \Big] + \theta \, u_m(t,x) \sum_{j=1}^{M} a_{m,j} \, u_j(t,x) \\
&- \frac{\theta}{2} \sum_{j=1}^{m-1} a_{j,m-j} \, u_j(t,x) \, u_{m-j}(t,x) = 0 \qquad \text{in } [0,T] \times \Omega
\end{aligned} \tag{108}$$

$$[A \, \nabla_x u_m(t,x)] \cdot n = 0 \qquad\qquad \text{on } [0,T] \times \partial\Omega \tag{109}$$

where A is a matrix with constant coefficients defined by

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

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

Theorem 5.1 shows that the macroscale (homogenized) model, obtained from Eqs. (10)-(13) as $\epsilon \to 0$, is asymptotically consistent with the original model and resolves both the coarse and the small scale. The information given on the micro-scale, by the non-homogeneous Neumann boundary condition in (10), is transferred into the source term in the first equation of (16), describing the limit model. Furthermore, on the macro-scale, the geometric structure of the perforated domain induces a correction in that the scalar diffusion coefficients d_i $(1 \leq i \leq M)$, defined at the microscale, are replaced by a tensorial quantity with constant coefficients.

6 Final remarks

Alzheimer disease is characterized pathologically by the formation of senile plaques composed of the amyloid-β (Aβ) peptide. In the present paper, we analyze a set of Smoluchowski's discrete diffusion-coagulation equations modeling the aggregation and diffusion of Aβ. In particular, the information given on the micro-scale, by the non-homogeneous Neumann boundary condition in (10), describing the production of Aβ in monomeric form by the damaged neurons, is transferred, using the homogenization theory, into the global source term which appears in the limit equation (16). This model can be related to the one introduced in [6], where the process of diffusion and agglomeration of Aβ is described on the macro-scale by a Smoluchowski system with a source term, coupled with a kinetic-type transport equation for the distribution function of the degree of malfunctioning of neurons that keeps into account the spreading of the disease through a neuron-to-neuron prion-like transmission. In particular, the mathematical analysis carried out in this paper can be regarded as a formal derivation (that is, neglecting regularity issues), starting from the micro-scale, of the source term $\mathcal{F}$, introduced ad hoc in the second equation of (2.16) in [6], in order to describe the production of Aβ in monomeric form by neurons. A comparison between the model equation (16) and the second equation of (2.16) in [6] allows us to make the following choice of the function $\psi(t, x, y)$ appearing in (16):

$$\psi(t, x, y) = C_{\mathcal{F}} \int_0^1 (\mu_0 + a)\,(1 - a)\, f(x, a, t)\, da\, g(y) \tag{110}$$

with

$$\int_\Gamma g(y)\, d\sigma(y) = const.$$

In Eq. (110), the parameter $a \in [0, 1]$ describes the degree of malfunctioning of a neuron: a close to 0 stands for 'the neuron is healthy' whereas a close to 1 for 'the neuron is dead'. Given $x \in \Omega$, $t \geq 0$ and $a \in [0, 1]$,

$$f(x, a, t)\, da$$

indicates the fraction of neurons close to x with degree of malfunctioning at time t between a and $a + da$. Furthermore, the small constant $\mu_0 > 0$ in (110) accounts for Aβ production by healthy neurons. In [6], an evolution equation for the distribution function f has been proposed:

$$\partial_t f + \partial_a (f\, v[f]) = J[f] \tag{111}$$

where $v = v(x, a, t)$ indicates the deterioration rate of the health state of the neurons. We assume that

$$v[f] = \iint_{\Omega \times [0,\, 1]} \mathcal{K}(x,\, a,\, y,\, b) f(y,\, b,\, t)\, dy\, db. \tag{112}$$

The integral term describes the possible prion-like propagation of AD through the neural pathway. Malfunctioning neighbours are harmful for a neuron's health state, while healthy ones are not:

$$\mathcal{K}(x,\, a,\, y,\, b) \geq 0 \qquad\qquad \forall\, x,\, y \in \Omega,\ a,\, b \in [0,\, 1],$$
$$\mathcal{K}(x,\, a,\, y,\, b) = 0 \qquad\qquad \text{if } a > b.$$

The term $J[f]$ in (111) accounts for the onset of AD, since it is written in terms of the probability that, in randomly chosen parts of the cerebral tissue, the degree of malfunctioning of neurons randomly jumps to higher values due to external agents or genetic factors. What prevents our homogenization results from being considered a fully rigorous derivation of the source term $\mathcal{F}$, appearing in the second equation of (2.16) in [6], is the fact that the solutions of Eq. (111) do not satisfy, in general, all the regularity properties assumed on ψ. However, Eq. (110) allows us to establish a link, at least formally, between the limit model derived here and the one presented in [6], suggesting a possible choice for ψ, considered, in the present paper, as a generic given function.

It is worth noting that the plots of f, at different times, can be directly compared with medical Fluorodeoxyglucose PET images [6]. The numerical simulations reported in [6] are in good qualitative agreement with clinical images of the disease distribution in the brain which vary from early to advanced stages.

A Appendix A

Lemma A.1. *The following estimate holds: if $v \in \mathrm{Lip}(\Omega_\epsilon)$, then*

$$\|v\|^2_{L^2(\Gamma_\epsilon)} \leq C_1 \left[\epsilon^{-1} \int_{\Omega_\epsilon} |v|^2\, dx + \epsilon \int_{\Omega_\epsilon} |\nabla_x v|^2\, dx\right] \tag{113}$$

where C_1 is a constant which does not depend on ϵ.

The inequality (113) can be easily obtained from the standard trace theorem by means of a scaling argument [4, 10, 11].

Lemma A.2. *Suppose that the domain Ω_ϵ is such that assumption (8) is satisfied. Then there exists a family of linear continuous extension operators*

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

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

$$P_\epsilon v = v \quad in\ \Omega_\epsilon$$

and

$$\int_\Omega |P_\epsilon v|^p dx \le C \int_{\Omega_\epsilon} |v|^p dx \ , \tag{114}$$

$$\int_\Omega |\nabla (P_\epsilon v)|^p dx \le C \int_{\Omega_\epsilon} |\nabla v|^p dx \tag{115}$$

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

For the proof of this Lemma see for instance [10].

As a consequence of the existence of extension operators one can derive the Sobolev inequalities in $W^{1,p}(\Omega_\epsilon)$ with a constant independent of ϵ.

Lemma A.3 (Anisotropic Sobolev inequalities in perforated domains)**.**
(i) For arbitrary $v \in H^1(0,T; L^2(\Omega_\epsilon)) \cap L^2(0,T; H^1(\Omega_\epsilon))$ and q_1 and r_1 satisfying the conditions

$$\begin{cases} \dfrac{1}{r_1} + \dfrac{N}{2q_1} = \dfrac{N}{4} \\ r_1 \in [2, \infty],\ q_1 \in [2, \frac{2N}{N-2}] \quad for\ N > 2 \end{cases} \tag{116}$$

the following estimate holds

$$\|v\|_{L^{r_1}(0,T;L^{q_1}(\Omega_\epsilon))} \le c\, \|v\|_{Q_\epsilon(T)} \tag{117}$$

where c is a positive constant independent of ϵ and

$$\|v\|^2_{Q_\epsilon(T)} := \sup_{0 \le t \le T} \int_{\Omega_\epsilon} |v(t)|^2\, dx + \int_0^T dt \int_{\Omega_\epsilon} |\nabla v(t)|^2\, dx \tag{118}$$

(ii) For arbitrary $v \in H^1(0,T; L^2(\Omega_\epsilon)) \cap L^2(0,T; H^1(\Omega_\epsilon))$ and q_2 and r_2 satisfying the conditions

$$\begin{cases} \dfrac{1}{r_2} + \dfrac{(N-1)}{2q_2} = \dfrac{N}{4} \\ r_2 \in [2, \infty],\ q_2 \in [2, \frac{2(N-1)}{(N-2)}] \quad \textit{for } N \geq 3 \end{cases} \tag{119}$$

the following estimate holds

$$\|v\|_{L^{r_2}(0,T;L^{q_2}(\Gamma_\epsilon))} \leq c\,\epsilon^{-\frac{N}{2}-\frac{(1-N)}{q_2}}\,\|v\|_{Q_\epsilon(T)} \tag{120}$$

where c is a positive constant independent of ϵ and the norm $\|v\|_{Q_\epsilon(T)}$ is defined as in (118).

Proof.

(i) The extension Lemma A.2 ensures the well-definiteness of a linear continuous extension operator P_ϵ which satisfies (114) and (115). By the classical multiplicative Sobolev inequalities valid in Ω (see [29] and [37]), we have that

$$\|P_\epsilon v\|_{L^{r_1}(0,T;L^{q_1}(\Omega))} \leq c_1\,\|P_\epsilon v\|_{Q(T)} \tag{121}$$

where $c_1 \geq 0$ depends only on Ω, r_1, q_1, with r_1 and q_1 satisfying the conditions (116) and

$$\|P_\epsilon v\|^2_{Q(T)} := \sup_{0\leq t\leq T} \int_\Omega |P_\epsilon v(t)|^2\,dx + \int_0^T dt \int_\Omega |\nabla(P_\epsilon v(t))|^2\,dx \tag{122}$$

By using (114), (115) and (121), we conclude that

$$\begin{aligned} \|v\|_{L^{r_1}(0,T;L^{q_1}(\Omega_\epsilon))} &\leq C'\,\|P_\epsilon v\|_{L^{r_1}(0,T;L^{q_1}(\Omega))} \\ &\leq C'\,c_1\,\|P_\epsilon v\|_{Q(T)} \leq C'\,c_1\,C\,\|v\|_{Q_\epsilon(T)} \end{aligned} \tag{123}$$

where $c := C'\,c_1\,C$ is independent of ϵ.

(ii) Let us rewrite the anisotropic Sobolev inequality valid on $\partial\Omega$ (see [29] and [37]):

$$\begin{aligned} &\left[\int_0^T dt \left[\int_{\partial\Omega} |v(t)|^{q_2}\,d\mathcal{H}^{N-1}\right]^{\frac{r_2}{q_2}}\right]^{\frac{1}{r_2}} \\ &\leq c_1 \left[\sup_{0\leq t\leq T} \int_\Omega |v(t)|^2\,dy + \int_0^T dt \int_\Omega |\nabla v(t)|^2\,dy\right]^{1/2} \end{aligned} \tag{124}$$

where $c_1 \geq 0$ depends only on r_2, q_2 and on local properties of the surface $\partial\Omega$ (which is assumed to be piecewise smooth) with r_2 and q_2 satisfying the conditions (119). By performing the change of variable $y = \frac{x}{\epsilon}$, it is easy to obtain the corresponding re-scaled estimates:

$$\begin{aligned} &\epsilon^{\frac{(1-N)}{q_2}} \left[\int_0^T dt \left[\int_{\Gamma_\epsilon} |v(t)|^{q_2} \, d\mathcal{H}^{N-1} \right]^{\frac{r_2}{q_2}} \right]^{\frac{1}{r_2}} \\ &\leq c_1 \, \epsilon^{-\frac{N}{2}} \left[\sup_{0 \leq t \leq T} \int_{\Omega_\epsilon} |v(t)|^2 \, dx + \epsilon^2 \int_0^T dt \int_{\Omega_\epsilon} |\nabla v(t)|^2 \, dx \right]^{1/2} \end{aligned} \tag{125}$$

$$\begin{aligned} &\left[\int_0^T dt \left[\int_{\Gamma_\epsilon} |v(t)|^{q_2} \, d\mathcal{H}^{N-1} \right]^{\frac{r_2}{q_2}} \right]^{\frac{1}{r_2}} \\ &\leq c \, \epsilon^{-\frac{N}{2} - \frac{(1-N)}{q_2}} \left[\sup_{0 \leq t \leq T} \int_{\Omega_\epsilon} |v(t)|^2 \, dx + \int_0^T dt \int_{\Omega_\epsilon} |\nabla v(t)|^2 \, dx \right]^{1/2} \end{aligned} \tag{126}$$

where c is a positive constant independent of ϵ.

□

B Appendix B

Let us introduce some definitions and results on two-scale convergence from [3, 4, 36], slightly modified to allow for homogenization with a parameter (the time t) [14, 27, 34].

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

$$\lim_{\epsilon \to 0} \int_0^T \int_\Omega v^\epsilon(t,x) \, \phi\Big(t, x, \frac{x}{\epsilon}\Big) \, dt \, dx = \int_0^T \int_\Omega \int_Y v_0(t,x,y) \, \phi(t,x,y) \, dt \, dx \, dy \tag{127}$$

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

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

Theorem B.1. *If v^ϵ is a bounded sequence in $L^2([0,T] \times \Omega)$, then there exists a function $v_0(t,x,y)$ in $L^2([0,T] \times \Omega \times Y)$ such that, up to a subsequence, v^ϵ two-scale converges to v_0.*

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

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

$$\lim_{\epsilon\to 0}\int_0^T\int_\Omega |v^\epsilon(t,x)|^2\,dt\,dx = \int_0^T\int_\Omega\int_Y |v_0(t,x,y)|^2\,dt\,dx\,dy \tag{128}$$

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

$$\begin{aligned}\lim_{\epsilon\to 0}\int_0^T\int_\Omega & v^\epsilon(t,x)\,w^\epsilon(t,x)\,\phi\Big(t,x,\frac{x}{\epsilon}\Big)\,dt\,dx\\ &= \int_0^T\int_\Omega\int_Y v_0(t,x,y)\,w_0(t,x,y)\,\phi(t,x,y)\,dt\,dx\,dy\end{aligned} \tag{129}$$

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

The next theorems yield a characterization of the two-scale limit of the gradients of bounded sequences v^ϵ. This result is crucial for applications to homogenization problems.

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

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

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

Theorem B.3. *Let v^ϵ be a bounded sequence in $L^2(0,T;H^1(\Omega))$ that converges weakly to a limit $v(t,x)$ in $L^2(0,T;H^1(\Omega))$. Then, v^ϵ two-scale converges to $v(t,x)$, and there exists a function $v_1(t,x,y)$ in $L^2([0,T]\times\Omega;H^1_\#(Y)/\mathbb{R})$ such that, up to a subsequence, ∇v^ϵ two-scale converges to $\nabla_x v(t,x)+\nabla_y v_1(t,x,y)$.*

Theorem B.4. *Let v^ϵ and $\epsilon\nabla v^\epsilon$ be two bounded sequences in $L^2([0,T]\times\Omega)$. Then, there exists a function $v_1(t,x,y)$ in $L^2([0,T]\times\Omega;H^1_\#(Y)/\mathbb{R})$ such that, up to a subsequence, v^ϵ and $\epsilon\nabla v^\epsilon$ 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 in $L^2([0,T]\times\Gamma_\epsilon)$.

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

$$\epsilon\int_0^T\int_{\Gamma_\epsilon}|v^\epsilon(t,x)|^2\,dt\,d\sigma_\epsilon(x)\le C \tag{130}$$

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

$$\lim_{\epsilon\to0}\epsilon\int_0^T\int_{\Gamma_\epsilon}v^\epsilon(t,x)\,\phi\Big(t,x,\frac{x}{\epsilon}\Big)\,dt\,d\sigma_\epsilon(x)=\int_0^T\int_\Omega\int_\Gamma v_0(t,x,y)\,\phi(t,x,y)\,dt\,dx\,d\sigma(y) \tag{131}$$

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

The proof of Theorem B.5 is very similar to the usual two-scale convergence theorem [3]. It relies on the following lemma [4]:

Lemma B.1. *Let $B=C[\overline{\Omega};C_\#(Y)]$ be the space of continuous functions $\phi(x,y)$ on $\overline{\Omega}\times Y$ which are Y-periodic in y. Then, B is a separable Banach space which is dense in $L^2(\Omega;L^2(\Gamma))$, and such that any function $\phi(x,y)\in B$ satisfies*

$$\epsilon\int_{\Gamma_\epsilon}\Big|\phi(x,\frac{x}{\epsilon})\Big|^2\,d\sigma_\epsilon(x)\le C\,\|\phi\|_B^2, \tag{132}$$

and

$$\lim_{\epsilon\to0}\epsilon\int_{\Gamma_\epsilon}\Big|\phi\Big(x,\frac{x}{\epsilon}\Big)\Big|^2\,d\sigma_\epsilon(x)=\int_\Omega\int_\Gamma|\phi(x,y)|^2\,dx\,d\sigma(y). \tag{133}$$

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