



HAL
open science

A second order asymptotic model for diffusion MRI in permeable media

Marwa Kchaou, Jing-Rebecca Li

► **To cite this version:**

Marwa Kchaou, Jing-Rebecca Li. A second order asymptotic model for diffusion MRI in permeable media. ESAIM: Mathematical Modelling and Numerical Analysis, 2023, 57 (4), pp.1953-1980. <10.1051/m2an/2023043>. <hal-04149697>

HAL Id: hal-04149697

<https://hal.science/hal-04149697v1>

Submitted on 3 Jul 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

A SECOND ORDER ASYMPTOTIC MODEL FOR DIFFUSION MRI IN PERMEABLE MEDIA

MARWA KCHAOU^{1,2}  AND JING-REBECCA LI^{3,*} 

Abstract. Starting from a reference partial differential equation model of the complex transverse water proton magnetization in a voxel due to diffusion-encoding magnetic field gradient pulses, one can use periodic homogenization theory to establish macroscopic models. A previous work introduced an asymptotic model that accounted for permeable interfaces in the imaging medium. In this paper we formulate a higher order asymptotic model to treat higher values of permeability. We explicitly solved this new asymptotic model to obtain a system of ordinary differential equations that can model the diffusion MRI signal and we present numerical results showing the improved accuracy of the new model in the regime of higher permeability.

Mathematics Subject Classification. 35K10.

Received July 27, 2022. Accepted May 15, 2023.

1. INTRODUCTION

Diffusion Magnetic Resonance Imaging (dMRI) is a non-invasive imaging technique to investigate structural and transport properties of porous media as well as to study anatomical, physical, and functional properties of biological tissues and organs such as brain, muscles and bones [7, 10, 18, 22, 27, 30]. The results contained in this paper came out of the process of providing mathematical justifications, through homogenization theory [4], for the use of higher order diffusion tensors in the modeling of diffusion MRI. For example, the imaging community has proposed the so-called diffusion kurtosis imaging (DKI) (see, for instance, [3, 15, 16, 20, 25]). DKI is used to directly measure the non-Gaussian property of water diffusion characterized by a fourth-order tensor referred to as the diffusion kurtosis tensor. In three-dimensional space, the kurtosis tensor has 81 components, but, owing to the full symmetry with respect to an interchange of indices, only 15 elements are independent. Higher-order homogenization expansions have been employed in many other contexts in the literature and we refer the reader to [1, 2, 9, 23, 28] and the references therein for an account of the vast literature on the subject.

The classical dMRI experiment consists in applying two pulsed gradient magnetic fields with a 180 degree spin reversal between the two pulses in order to encode the displacement of water molecules between them [5, 6, 21, 26]. Following the approach proposed in [8, 12], we consider the Bloch–Torrey partial differential equation as a

Keywords and phrases. Bloch–Torrey equation, diffusion MRI, homogenization, higher-order diffusion tensor.

¹ ESPRIT-School of Engineering, 1, 2 rue André Ampère – 2083 – Pôle Technologique – El Ghazala, Tunis, Tunisia.

² ENIT-LAMSIN, Université de Tunis El Manar, B.P. 37, Belvedere, 1002 Tunis, Tunisia.

³ Inria Saclay, IDEFIX Team, Institut Polytechnique de Paris, UMA, ENSTA Paris, Palaiseau, France.

*Corresponding author: jingrebecca.li@inria.fr

reference fine scale model for the complex-valued transverse water proton magnetization due to diffusion-encoding magnetic field gradient pulses. The goal of this paper is to determine higher-order asymptotic expansions of the solution in terms of the ratio of the cell-size to the voxel-size. This ratio is assumed to be small in the dMRI application. The new model of this paper can be seen as a higher order extension of the lower ordered model derived in [8, 19]. Similarly to [8, 11], we then rely on the interpretation of the macroscopic model in the Fourier domain to derive a system of ordinary differential equations (ODEs) whose solution directly gives the dMRI signal. We then validated the accuracy of the new higher ordered model through some two-dimensional numerical simulations. We show in particular that the new model is more accurate in the regime of higher interface permeability.

The paper is organized as follows. We present the reference fine-scale Bloch–Torrey PDE model and periodic homogenization in Section 2. In Section 3 we provide the key steps to compute the different terms of the two-scale asymptotic expansions and give explicit expressions up to order 2. We present in Section 4 the system of ODEs that results from the order 2 asymptotic model. We give in Section 5 numerical validation using two dimension geometries and in Section 6 we show improvement for higher permeability. For the readers’ convenience, we complement our paper with an Appendix A containing some technical details associated with Section 3.

2. MATHEMATICAL CONTEXT

Let Ω be a domain (open set) containing biological tissue, excluding the boundaries of the biological cells, and let Γ be the union of the cell boundaries. The open set Ω is the union of the extra-cellular domain Ω^e and the intra-cellular domain Ω^c :

$$\Omega = \Omega^e \cup \Omega^c.$$

Suppose \mathcal{D} is the intrinsic diffusion coefficient:

$$\mathcal{D} = \begin{cases} \mathcal{D}^e, & \text{in } \Omega^e, \\ \mathcal{D}^c, & \text{in } \Omega^c. \end{cases}$$

The effective time profile, $f(t)$, represents the sequence of applied diffusion-encoding gradient pulses, and obeys the following property:

$$\int_0^{T_E} f(t) dt = 0, \tag{2.1}$$

where T_E is the time at which the signal is measured called the echo time.

A reference model for the complex-valued transverse water proton magnetization $\mathbf{M} = M_x + \iota M_y$ subject to diffusion-encoding is the following Bloch–Torrey equation [29]:

$$\begin{cases} \frac{\partial \mathbf{M}}{\partial t}(\mathbf{x}, t) + \iota f(t) \mathbf{q} \cdot \mathbf{x} \mathbf{M}(\mathbf{x}, t) - \operatorname{div}(\mathcal{D}(\mathbf{x}) \nabla \mathbf{M}(\mathbf{x}, t)) = 0, & \text{in } \Omega \times]0, T_E[, \\ [\mathcal{D}(\mathbf{x}) \nabla \mathbf{M}(\mathbf{x}, t) \cdot \boldsymbol{\nu}] = 0, & \text{on } \Gamma \times]0, T_E[, \\ \mathcal{D}(\mathbf{x}) \nabla \mathbf{M}(\mathbf{x}, t) \cdot \boldsymbol{\nu} = \kappa [\mathbf{M}(\mathbf{x}, t)], & \text{on } \Gamma \times]0, T_E[, \\ \mathbf{M}(\cdot, 0) = \mathbf{M}_{\text{init}}, & \text{in } \Omega, \end{cases} \tag{2.2}$$

where $\boldsymbol{\nu}$ is the unit normal vector pointing exterior to the intra-cellular domain, the brackets $[\cdot]$ denote the jump across the interfaces Γ , κ is the membrane permeability, ι in the imaginary unit, $T_E > 0$ is the echo time, \mathbf{M}_{init} is the initial spin density. The constant vector in \mathbb{R}^d , $\mathbf{q} = q\mathbf{n}$, contains the amplitude q , which is the product of the diffusion-encoding gradient amplitude multiplied by the gyro-magnetic ratio of the water proton, the unit vector \mathbf{n} points in the direction of the applied diffusion-encoding magnetic field gradient.

The dMRI signal at echo time T_E is the integral of magnetization $\mathbf{M}(\mathbf{x}, T_E)$, normalized by the mass:

$$S := \frac{1}{|\Omega|} \int_{\Omega} \mathbf{M}(\mathbf{x}, T_E) d\mathbf{x}. \tag{2.3}$$

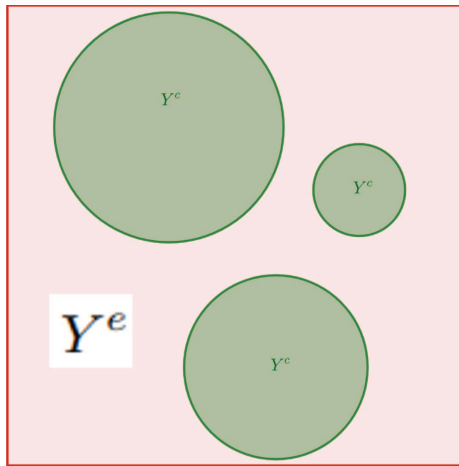


FIGURE 1. Periodicity box Y containing 3 biological cells. It is composed of Y^e , the extra-cellular domain (red), Y^c the intra-cellular domain (green), Γ^m the boundary of Y^c (dark green), and the sides of the box (dark red).

Numerically, the signal is usually plotted against a quantity called the b -value

$$b(|\mathbf{q}|) := |\mathbf{q}|^2 \int_0^{T_E} (F(t))^2 dt, \tag{2.4}$$

where

$$F(t) = \int_0^t f(s) ds. \tag{2.5}$$

2.1. Periodic homogenization

In this work, we will apply periodic homogenization to derive asymptotic solutions of the Bloch–Torrey equation, assuming that the size of the period, ε , is small. We define the unit periodicity box

$$Y =]0, 1[^d, Y = Y^e \cup Y^c, \Gamma^m = \partial Y^c = \partial Y^e \setminus \partial \bar{Y}, \tag{2.6}$$

with the analogous intra-cellular and extra-cellular subsets. See illustration in Figure 1.

The geometric assumption of periodic homogenization is that the domain Ω contains the union of periodic copies of Y . If the domain Ω is finite, the notation is more complicated than if $\Omega = \mathbb{R}^{\dim}$. See illustration in Figure 2.

First, we give the notation when Ω is finite. The intra-cellular and extra-cellular domains are defined as periodic extensions of Y^e and Y^c :

$$\Omega_\varepsilon^c = \bigcup_{\xi \in \mathbb{Z}^d} \{\varepsilon(\xi + Y^c) \cap \Omega\}, \quad \Omega_\varepsilon^e = \bigcup_{\xi \in \mathbb{Z}^d} \{\varepsilon(\xi + Y^e) \cap \Omega\}, \quad \Omega_\varepsilon = \Omega_\varepsilon^c \cup \Omega_\varepsilon^e.$$

The interior boundaries are defined as the periodic extension of Γ^m :

$$\Gamma_\varepsilon^m = \bigcup_{\xi \in \mathbb{Z}^d} \{\varepsilon(\xi + \Gamma^m) \cap \Omega\}.$$

However, to simplify the presentation in this paper by avoiding complications coming from imposing external boundary conditions on $\partial\Omega$, we will choose to take $\Omega = \mathbb{R}^d$, d is the space dimension. This assumption is reasonable if the diffusion distance is small compared to the size of the imaging voxel.

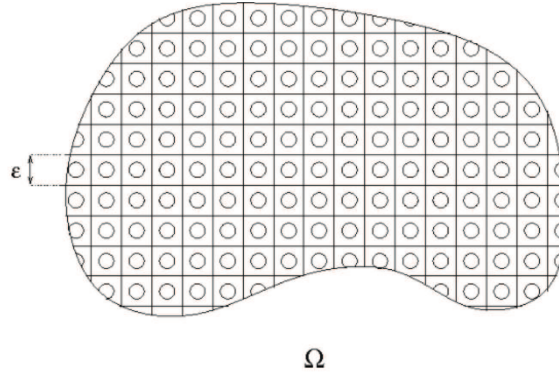


FIGURE 2. Periodic extension of the periodicity box, contained inside a finite Ω .

Finally, on Ω_ε defined as the union of infinite periodic extensions, the PDE becomes:

$$\begin{cases} \frac{\partial M_\varepsilon}{\partial t}(\mathbf{x}, t) + \iota f(t) \mathbf{q} \cdot \mathbf{x} M_\varepsilon(\mathbf{x}, t) - \operatorname{div}(\mathcal{D}_\varepsilon(\mathbf{x}) \nabla M_\varepsilon(\mathbf{x}, t)) = 0, & \text{in } \Omega_\varepsilon \times]0, T[, \\ \mathcal{D}_\varepsilon(\mathbf{x}) \nabla M_\varepsilon(\mathbf{x}, t) \cdot \boldsymbol{\nu} = \kappa_\varepsilon [M_\varepsilon(\mathbf{x}, t)], & \text{on } \Gamma_\varepsilon^m \times]0, T[, \\ [\mathcal{D}_\varepsilon(\mathbf{x}) \nabla M_\varepsilon(\mathbf{x}, t) \cdot \boldsymbol{\nu}] = 0, & \text{on } \Gamma_\varepsilon^m \times]0, T[, \\ M_\varepsilon(\cdot, 0) = M_{\text{init}}, & \text{in } \Omega_\varepsilon, \end{cases} \tag{2.7}$$

where $\mathcal{D}_\varepsilon(\mathbf{x}) := \mathcal{D}(\frac{\mathbf{x}}{\varepsilon})$. We assume that the initial data M_{init} defined on Ω are independent of ε and belong to $L^2(\Omega) \cap L^1(\Omega)$.

3. DERIVATION OF ASYMPTOTIC MODEL

Following the classical periodic homogenization technique [4, 17, 28], we use the two-scale asymptotic expansions for the solution M_ε in Ω_ε^e and Ω_ε^c :

$$M_\varepsilon(\mathbf{x}, t) = \begin{cases} M_\varepsilon^e(\mathbf{x}, t) = \sum_{n=0}^{+\infty} \varepsilon^n M_n^e\left(\mathbf{x}, \frac{\mathbf{x}}{\varepsilon}, t\right), & \text{in } \Omega_\varepsilon^e, \\ M_\varepsilon^c(\mathbf{x}, t) = \sum_{n=0}^{+\infty} \varepsilon^n M_n^c\left(\mathbf{x}, \frac{\mathbf{x}}{\varepsilon}, t\right), & \text{in } \Omega_\varepsilon^c, \end{cases} \tag{3.1}$$

where the component functions $M_n^\alpha(\mathbf{x}, \mathbf{y}, t)$ are defined on $\Omega \times Y^\alpha \times]0, T[$, $\alpha \in \{e, c\}$ and are Y -periodic in \mathbf{y} . The aim is to separate the macroscopic variations and the microscopic ones to obtain a new problem involving only macroscopic quantities.

3.1. Preliminaries

We substitute the asymptotic expansions (3.1) into the periodic model (2.7), and multiply the first equation in (2.7) by ε^2 to obtain

$$\begin{cases} \sum_{n=0}^{+\infty} \varepsilon^{n+2} \frac{\partial}{\partial t} M_n^\alpha + \iota \mathbf{q} \cdot \mathbf{x} f(t) \sum_{n=0}^{+\infty} \varepsilon^{n+2} M_n^\alpha - \sum_{n=0}^{+\infty} \varepsilon^{n+2} \operatorname{div}_\mathbf{x}(\mathcal{D}^\alpha \nabla_\mathbf{x} M_n^\alpha) \\ - \sum_{n=0}^{+\infty} \varepsilon^{n+1} (\operatorname{div}_\mathbf{x}(\mathcal{D}^\alpha \nabla_\mathbf{y} M_n^\alpha) + \operatorname{div}_\mathbf{y}(\mathcal{D}^\alpha \nabla_\mathbf{x} M_n^\alpha)) - \sum_{n=0}^{+\infty} \varepsilon^n \operatorname{div}_\mathbf{y}(\mathcal{D}^\alpha \nabla_\mathbf{y} M_n^\alpha) = 0 \end{cases} \tag{3.2}$$

for (\mathbf{x}, \mathbf{y}) in $\Omega \times Y_\alpha$. In order to obtain the condition for the traces on the interface Γ_ε^m , we observe that

$$[\mathbf{M}_\varepsilon(\mathbf{x}, t)]_{\Gamma_\varepsilon^m} = \sum_{n=0}^{+\infty} \varepsilon^n \left(\mathbf{M}_n^e \left(\mathbf{x}, \frac{\mathbf{x}}{\varepsilon}, t \right) - \mathbf{M}_n^c \left(\mathbf{x}, \frac{\mathbf{x}}{\varepsilon}, t \right) \right), \tag{3.3}$$

and

$$\left[\hat{\mathcal{D}}_\varepsilon(\mathbf{x}) \nabla \mathbf{M}_\varepsilon(\mathbf{x}, t) \cdot \boldsymbol{\nu} \right]_{\Gamma_\varepsilon^m} = \sum_{n=0}^{+\infty} \varepsilon^n \left(\mathcal{D}^e \nabla \mathbf{M}_n^e \left(\mathbf{x}, \frac{\mathbf{x}}{\varepsilon}, t \right) \cdot \boldsymbol{\nu} - \mathcal{D}^c \nabla \mathbf{M}_n^c \left(\mathbf{x}, \frac{\mathbf{x}}{\varepsilon}, t \right) \cdot \boldsymbol{\nu} \right). \tag{3.4}$$

By identifying each power of ε , the no-jump relation for the flux becomes

$$\begin{cases} \mathcal{D}^e \nabla_{\mathbf{y}} \mathbf{M}_0^e \cdot \boldsymbol{\nu} = \mathcal{D}^c \nabla_{\mathbf{y}} \mathbf{M}_0^c \cdot \boldsymbol{\nu}, \\ \mathcal{D}^e \nabla_{\mathbf{y}} \mathbf{M}_n^e \cdot \boldsymbol{\nu} + \mathcal{D}^e \nabla_{\mathbf{x}} \mathbf{M}_{n-1}^e \cdot \boldsymbol{\nu} = \mathcal{D}^c \nabla_{\mathbf{y}} \mathbf{M}_n^c \cdot \boldsymbol{\nu} + \mathcal{D}^c \nabla_{\mathbf{x}} \mathbf{M}_{n-1}^c \cdot \boldsymbol{\nu}, \quad \text{for } n \geq 1. \end{cases} \tag{3.5}$$

Using (3.3), the jump relation for the fields becomes

$$\begin{cases} \varepsilon^0 \mathcal{D}^\alpha \nabla_{\mathbf{y}} \mathbf{M}_0^\alpha \cdot \boldsymbol{\nu} + \varepsilon^1 \mathcal{D}^\alpha (\nabla_{\mathbf{y}} \mathbf{M}_1^\alpha \cdot \boldsymbol{\nu} + \nabla_{\mathbf{x}} \mathbf{M}_0^\alpha \cdot \boldsymbol{\nu}) + \varepsilon^2 \mathcal{D}^\alpha (\nabla_{\mathbf{y}} \mathbf{M}_2^\alpha \cdot \boldsymbol{\nu} + \nabla_{\mathbf{x}} \mathbf{M}_1^\alpha \cdot \boldsymbol{\nu}) \\ + \sum_{n=2}^{+\infty} \varepsilon^{n+1} \mathcal{D}^\alpha (\nabla_{\mathbf{y}} \mathbf{M}_{n+1}^\alpha \cdot \boldsymbol{\nu} + \nabla_{\mathbf{x}} \mathbf{M}_n^\alpha \cdot \boldsymbol{\nu}) = \sum_{n=0}^{+\infty} \varepsilon^{n+1} \kappa^\varepsilon (\mathbf{M}_n^e - \mathbf{M}_n^c), \end{cases} \tag{3.6}$$

for (\mathbf{x}, \mathbf{y}) in $\Omega \times \Gamma^m$. The initial conditions are,

$$\mathbf{M}_0^\alpha(\mathbf{x}, \mathbf{y}, 0) = \mathbf{M}_{\text{init}}(\mathbf{x}) \quad \text{and} \quad \mathbf{M}_n^\alpha(\mathbf{x}, \mathbf{y}, 0) = 0 \quad \text{for } n > 0, \quad \alpha \in \{e, c\}. \tag{3.7}$$

We define the following volume fractions and surface to volume ratios:

$$\eta^\alpha := \frac{|Y^\alpha|}{|Y|}, \tag{3.8}$$

$$\theta^\alpha := \frac{|\Gamma^m|}{|Y^\alpha|}, \tag{3.9}$$

$$\theta := \frac{|\Gamma^m|}{|Y|}. \tag{3.10}$$

Notation

In order to shorten the formulas, we respectively denote by $:$, \cdot and $::$ the contraction products with respect to the last 2, 3 and 4 indices of the given two tensors. For instance, for any fourth-order tensors \mathcal{C} and \mathcal{P} ,

$$(\mathcal{C} : \mathcal{P})_{i,l} = \sum_{j,k} \mathcal{C}_{iljk} \mathcal{P}_{iljk}, \quad (\mathcal{C} \cdot \mathcal{P})_i = \sum_{l,j,k} \mathcal{C}_{iljk} \mathcal{P}_{iljk}, \quad (\mathcal{C} :: \mathcal{P}) = \sum_{i,l,j,k} \mathcal{C}_{iljk} \mathcal{P}_{iljk}.$$

The tensor product of two vectors \mathbf{u} and \mathbf{v} is defined by

$$(\mathbf{u} \otimes \mathbf{v})_{ij} = u_i v_j.$$

3.2. Second order asymptotic model under scaling $\kappa_\varepsilon = \sigma_0 \varepsilon$

From homogenization theory, we know that the choice of a scaling for the permeability coefficient κ_ε has an influence on the nature of the asymptotic model. We take a special form of the scaling of the permeability coefficient corresponding to

$$\kappa_\varepsilon = \sigma_0 \varepsilon, \tag{3.11}$$

that was used previously in [8]. This case corresponds to moderately permeable membranes and leads to a two-compartment macroscopic model [8]. In this paper, we derive higher order asymptotic for this choice of κ .

First we need to define averages and jumps of functions that are solutions of PDEs that will appear later.

Definition 3.1. These are the average and jump quantities in the domain and on the interfaces.

$$\widehat{\mathbf{M}}_n^\alpha(\mathbf{x}, t) := \langle \mathbf{M}_n^\alpha(\mathbf{x}, \cdot, t) \rangle_{Y^\alpha} := \frac{1}{|Y^\alpha|} \int_{Y^\alpha} \mathbf{M}_n^\alpha(\mathbf{x}, \mathbf{y}, t) \, d\mathbf{y}, \quad \alpha \in \{e, c\}, \tag{3.12}$$

$$[\widehat{\mathbf{M}}_n(\mathbf{x}, t)] := \widehat{\mathbf{M}}_n^e(\mathbf{x}, t) - \widehat{\mathbf{M}}_n^c(\mathbf{x}, t). \tag{3.13}$$

$$\langle \omega \rangle_{\Gamma^m} := \frac{1}{|\Gamma^m|} \int_{\Gamma^m} \omega \, ds(\mathbf{y}), \tag{3.14}$$

$$[\omega] := \omega^e - \omega^c. \tag{3.15}$$

Now we summarize the equations satisfied by $\widehat{\mathbf{M}}_0^\alpha$, $\widehat{\mathbf{M}}_1^\alpha$ and $\widehat{\mathbf{M}}_2^\alpha$ which are obtained after substituting (3.1) into (2.7) and equating the same powers of ε . The formal procedure is detailed in Appendix A.

We obtain the homogenized equations for $\widehat{\mathbf{M}}_0^\alpha$:

$$\begin{cases} \frac{\partial}{\partial t} \widehat{\mathbf{M}}_0^e - \operatorname{div}_{\mathbf{x}} \left(\mathbb{D}^e \nabla_{\mathbf{x}} \widehat{\mathbf{M}}_0^e \right) + \theta^e \sigma_0 [\widehat{\mathbf{M}}_0] = 0, & \text{in } \Omega \times]0, T[, \\ \widehat{\mathbf{M}}_0^e(\cdot, 0) = \mathbf{M}_{\text{init}}, & \text{in } \Omega, \\ \frac{\partial}{\partial t} \widehat{\mathbf{M}}_0^c - \operatorname{div}_{\mathbf{x}} \left(\mathbb{D}^c \nabla_{\mathbf{x}} \widehat{\mathbf{M}}_0^c \right) - \theta^c \sigma_0 [\widehat{\mathbf{M}}_0] = 0, & \text{in } \Omega \times]0, T[, \\ \widehat{\mathbf{M}}_0^c(\cdot, 0) = \mathbf{M}_{\text{init}}, & \text{in } \Omega. \end{cases} \tag{3.16}$$

with the homogenized second-order tensor \mathbb{D}^α defined by

$$\mathbb{D}_{ij}^\alpha := \langle \mathcal{D}^\alpha \nabla \omega_j^\alpha \cdot \mathbf{e}_i + \mathcal{D}^\alpha \mathbf{e}_i \cdot \mathbf{e}_j \rangle_{Y^\alpha} = \langle \mathcal{D}^\alpha (\nabla \omega_j^\alpha + \mathbf{e}_j) \cdot (\nabla \omega_i^\alpha + \mathbf{e}_i) \rangle_{Y^\alpha}, \quad i, j = 1, \dots, d, \quad \alpha \in \{c, e\}, \tag{3.17}$$

where to obtain \mathbb{D}^α we need to compute solutions of d time-independent problems posed on the unit box Y :

$$\begin{cases} -\operatorname{div}_{\mathbf{y}} (\mathcal{D}^\alpha \nabla_{\mathbf{y}} \omega_i^\alpha + \mathcal{D}^\alpha \mathbf{e}_i) = 0, & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha \nabla_{\mathbf{y}} \omega_i^\alpha \cdot \boldsymbol{\nu} + \mathcal{D}^\alpha \mathbf{e}_i \cdot \boldsymbol{\nu} = 0, & \text{on } \Gamma^m, \\ \omega_i^\alpha \text{ is } Y\text{-periodic, } \langle \omega_i^\alpha \rangle_{Y^\alpha} = 0, & \end{cases} \tag{3.18}$$

with $\mathbf{e}_i, i = 1, \dots, d$ are the vectors of the canonical basis of \mathbb{R}^d .

Likewise, the equations for $\widehat{\mathbf{M}}_1^\alpha$ can be written as

$$\begin{cases} \frac{\partial}{\partial t} \widehat{\mathbf{M}}_1^e - \operatorname{div}_{\mathbf{x}} \left(\mathbb{D}^e \nabla_{\mathbf{x}} \widehat{\mathbf{M}}_1^e \right) + \theta^e \sigma_0 [\widehat{\mathbf{M}}_1] + \theta^e \sigma_0 \langle [\omega] \rangle_{\Gamma^m} \cdot \nabla_{\mathbf{x}} \widehat{\mathbf{M}}_0^c = 0, & \text{in } \Omega \times]0, T[, \\ \widehat{\mathbf{M}}_1^e(\cdot, 0) = 0, & \text{in } \Omega, \\ \frac{\partial}{\partial t} \widehat{\mathbf{M}}_1^c - \operatorname{div}_{\mathbf{x}} \left(\mathbb{D}^c \nabla_{\mathbf{x}} \widehat{\mathbf{M}}_1^c \right) - \theta^c \sigma_0 [\widehat{\mathbf{M}}_1] - \theta^c \sigma_0 \langle [\omega] \rangle_{\Gamma^m} \cdot \nabla_{\mathbf{x}} \widehat{\mathbf{M}}_0^e = 0, & \text{in } \Omega \times]0, T[, \\ \widehat{\mathbf{M}}_1^c(\cdot, 0) = 0, & \text{in } \Omega. \end{cases} \tag{3.19}$$

No new homogenized tensors are needed.

Finally, the equations for $\widehat{\mathbf{M}}_2^\alpha$ involve new homogenized tensors and can be written as

$$\left\{ \begin{array}{l} \frac{\partial}{\partial t} \widehat{\mathbf{M}}_2^e - \operatorname{div}_{\mathbf{x}} \left(\mathbb{D}^e \nabla_{\mathbf{x}} \widehat{\mathbf{M}}_2^e \right) + \theta^e \sigma_0 \left[\widehat{\mathbf{M}}_2 \right] + \theta^e \sigma_0 \langle [\omega] \rangle_{\Gamma^m} \cdot \nabla_{\mathbf{x}} \widehat{\mathbf{M}}_1^e \\ \quad = - \operatorname{div}_{\mathbf{x}} \left(\mathbb{B}^e \cdot \nabla_{\mathbf{x}}^3 \widehat{\mathbf{M}}_0^e \right) + \iota f(t) \mathbb{S}^e : \mathbf{q} \otimes \nabla_{\mathbf{x}} \widehat{\mathbf{M}}_0^e + \sigma_0 \operatorname{div}_{\mathbf{x}} \left(\mathbb{I}^e \nabla_{\mathbf{x}} \left[\widehat{\mathbf{M}}_0 \right] \right) \\ \quad + \sigma_0 \operatorname{div}_{\mathbf{x}} \left(\mathbb{Z}^{e,e} \nabla_{\mathbf{x}} \widehat{\mathbf{M}}_0^e \right) - \sigma_0 \operatorname{div}_{\mathbf{x}} \left(\mathbb{Z}^{e,c} \nabla_{\mathbf{x}} \widehat{\mathbf{M}}_0^c \right) - \theta^e \sigma_0^2 \langle [\psi] \rangle_{\Gamma^m} \left[\widehat{\mathbf{M}}_0 \right], \quad \text{in } \Omega \times]0, T[, \\ \widehat{\mathbf{M}}_2^e(\cdot, 0) = 0, \quad \text{in } \Omega, \\ \frac{\partial}{\partial t} \widehat{\mathbf{M}}_2^c - \operatorname{div}_{\mathbf{x}} \left(\mathbb{D}^c \nabla_{\mathbf{x}} \widehat{\mathbf{M}}_2^c \right) - \theta^c \sigma_0 \left[\widehat{\mathbf{M}}_2 \right] - \theta^c \sigma_0 \langle [\omega] \rangle_{\Gamma^m} \cdot \nabla_{\mathbf{x}} \widehat{\mathbf{M}}_1^e \\ \quad = - \operatorname{div}_{\mathbf{x}} \left(\mathbb{B}^c \cdot \nabla_{\mathbf{x}}^3 \widehat{\mathbf{M}}_0^c \right) + \iota f(t) \mathbb{S}^c : \mathbf{q} \otimes \nabla_{\mathbf{x}} \widehat{\mathbf{M}}_0^c + \sigma_0 \operatorname{div}_{\mathbf{x}} \left(\mathbb{I}^c \nabla_{\mathbf{x}} \left[\widehat{\mathbf{M}}_0 \right] \right) \\ \quad + \sigma_0 \operatorname{div}_{\mathbf{x}} \left(\mathbb{Z}^{c,e} \nabla_{\mathbf{x}} \widehat{\mathbf{M}}_0^e \right) - \sigma_0 \operatorname{div}_{\mathbf{x}} \left(\mathbb{Z}^{c,c} \nabla_{\mathbf{x}} \widehat{\mathbf{M}}_0^c \right) + \theta^c \sigma_0^2 \langle [\psi] \rangle_{\Gamma^m} \left[\widehat{\mathbf{M}}_0 \right], \quad \text{in } \Omega \times]0, T[, \\ \widehat{\mathbf{M}}_2^c(\cdot, 0) = 0, \quad \text{in } \Omega. \end{array} \right. \quad (3.20)$$

The needed tensors are \mathbb{B}^α , \mathbb{S}^α , $\mathbb{Z}^{\alpha,\beta}$, \mathbb{I}^α and they require the solutions ω_i^α , χ_{ij}^α , φ_{ij}^α and ψ^α for $i, j, k = 1, \dots, d$. The functions ω_i^α are defined as solutions to the problem (3.18) and the rest of the required functions are solutions to the following box problems:

$$\left\{ \begin{array}{l} - \operatorname{div}_{\mathbf{y}} \left(\mathcal{D}^\alpha \nabla_{\mathbf{y}} \chi_{ij}^\alpha \right) = \frac{\partial}{\partial y_i} \left(\mathcal{D}^\alpha \omega_j^\alpha \right), \quad \text{in } Y^\alpha, \\ \mathcal{D}^\alpha \nabla_{\mathbf{y}} \chi_{ij}^\alpha \cdot \boldsymbol{\nu} + \mathcal{D}^\alpha \omega_j^\alpha \nu_i = 0, \quad \text{on } \Gamma^m, \\ \chi_{ij}^\alpha \text{ is } Y\text{-periodic}, \quad \langle \chi_{ij}^\alpha \rangle_{Y^\alpha} = 0, \end{array} \right. \quad (3.21)$$

$$\left\{ \begin{array}{l} - \operatorname{div}_{\mathbf{y}} \left(\mathcal{D}^\alpha \nabla_{\mathbf{y}} \varphi_{ij}^\alpha \right) = \mathcal{D}^\alpha \frac{\partial}{\partial y_i} \omega_j^\alpha + \mathcal{D}^\alpha \delta_{ij} - \mathbb{D}_{ij}^\alpha, \quad \text{in } Y^\alpha, \\ \mathcal{D}^\alpha \nabla_{\mathbf{y}} \varphi_{ij}^\alpha \cdot \boldsymbol{\nu} = 0, \quad \text{on } \Gamma^m, \\ \varphi_{ij}^\alpha \text{ is } Y\text{-periodic}, \quad \langle \varphi_{ij}^\alpha \rangle_{Y^\alpha} = 0, \end{array} \right. \quad (3.22)$$

$$\left\{ \begin{array}{l} - \operatorname{div}_{\mathbf{y}} \left(\mathcal{D}^\alpha \nabla_{\mathbf{y}} \psi^\alpha \right) = \mp \theta^\alpha, \quad \text{in } Y^\alpha, \\ \mathcal{D}^\alpha \nabla_{\mathbf{y}} \psi^\alpha \cdot \boldsymbol{\nu} = 1, \quad \text{on } \Gamma^m, \\ \psi^\alpha \text{ is } Y\text{-periodic}, \quad \langle \psi^\alpha \rangle_{Y^\alpha} = 0. \end{array} \right. \quad (3.23)$$

The symmetric second-order tensor \mathbb{S}^α is defined by

$$\mathbb{S}_{ij}^\alpha = - \langle \omega_i^\alpha \cdot \omega_j^\alpha \rangle_{Y^\alpha}. \quad (3.24)$$

The symmetric fourth-order tensor \mathbb{B}^α is the Burnett tensor that is defined by Allaire *et al.* [1, 2]

$$\mathbb{B}^\alpha = - \mathbb{T}^\alpha + \mathbb{D}^\alpha \otimes \mathbb{S}^\alpha, \quad (3.25)$$

where the fourth-order tensor \mathbb{T}^α is defined by

$$\mathbb{T}_{ijkl}^\alpha = \left\langle - \mathcal{D}^\alpha \frac{\partial}{\partial y_i} \left(\chi_{jk}^\alpha + \varphi_{jk}^\alpha \right) \omega_l^\alpha + \mathcal{D}^\alpha \left(\chi_{jk}^\alpha + \varphi_{jk}^\alpha \right) \frac{\partial}{\partial y_i} \omega_l^\alpha \right\rangle_{Y^\alpha} - \langle \mathcal{D}^\alpha \omega_k^\alpha \omega_l^\alpha \delta_{ij} \rangle_{Y^\alpha}. \quad (3.26)$$

The coefficients of the second-order tensor $\mathbb{Z}^{\alpha,\beta}$ and \mathbb{I}^α are defined by

$$\mathbb{Z}_{ij}^{\alpha,\beta} = \pm \theta^\alpha \left\langle \omega_i^\beta \omega_j^\alpha \right\rangle_{\Gamma^m} - \pm \theta^\alpha \left\langle \chi_{ij}^\beta + \varphi_{ij}^\beta \right\rangle_{\Gamma^m}, \quad (3.27)$$

and

$$\mathbb{I}_{ij}^\alpha = \left\langle - \mathcal{D}^\alpha \frac{\partial}{\partial y_j} \psi^\alpha \omega_i^\alpha + \mathcal{D}^\alpha \psi^\alpha \frac{\partial}{\partial y_j} \omega_i^\alpha \right\rangle_{Y^\alpha} \pm \theta^\alpha \mathbb{S}_{ij}^\alpha, \quad (3.28)$$

respectively. We will use \pm sign where $+$ corresponds to $\alpha = e$ and $-$ corresponds to $\alpha = c$ and \mp inversely. These simplified expressions (3.26), (3.24), (3.27) and (3.28) are justified in the Appendix A.

By combining the equations for $\widehat{\mathbf{M}}_0^\alpha$, $\widehat{\mathbf{M}}_1^\alpha$ and $\widehat{\mathbf{M}}_2^\alpha$ given in (3.16), (3.19) and (3.20), we get the following equations for the second order approximation of (2.7), $\mathbf{M}_\varepsilon \approx \mathbf{M}_{\varepsilon,2}^e + \mathbf{M}_{\varepsilon,2}^c$,

$$\mathbf{M}_{\varepsilon,2}^e \equiv \eta_e \left(\widehat{\mathbf{M}}_0^e + \varepsilon \widehat{\mathbf{M}}_1^e + \varepsilon^2 \widehat{\mathbf{M}}_2^e \right) \quad \text{and} \quad \mathbf{M}_{\varepsilon,2}^c \equiv \eta_c \left(\widehat{\mathbf{M}}_0^c + \varepsilon \widehat{\mathbf{M}}_1^c + \varepsilon^2 \widehat{\mathbf{M}}_2^c \right), \quad (3.29)$$

namely,

$$\left\{ \begin{array}{l} \frac{\partial}{\partial t} \mathbf{M}_{\varepsilon,2}^e - \operatorname{div}_{\mathbf{x}} (\mathbb{D}^e \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^e) + (\sigma_0 \theta^e + \varepsilon^2 \sigma_0^2 \theta^e \langle [\psi] \rangle_{\Gamma^m}) \mathbf{M}_{\varepsilon,2}^e - (\sigma_0 \theta^c + \varepsilon^2 \sigma_0^2 \theta^c \langle [\psi] \rangle_{\Gamma^m}) \mathbf{M}_{\varepsilon,2}^e \\ \quad + \varepsilon \sigma_0 \theta^c \langle [\omega] \rangle_{\Gamma^m} \cdot \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^c = -\varepsilon^2 \operatorname{div}_{\mathbf{x}} (\mathbb{B}^e \cdot \nabla_{\mathbf{x}}^3 \mathbf{M}_{\varepsilon,2}^e) + \varepsilon^2 \iota f(t) \mathbb{S}^e : \mathbf{q} \otimes \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^e \\ \quad + \varepsilon^2 \sigma_0 \operatorname{div}_{\mathbf{x}} ((\mathbb{I}^e + \mathbb{Z}^{e,e}) \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^e) - \frac{\eta_e}{\eta_c} \varepsilon^2 \sigma_0 \operatorname{div}_{\mathbf{x}} ((\mathbb{I}^e + \mathbb{Z}^{e,c}) \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^e), & \text{in } \Omega \times]0, T[, \\ \mathbf{M}_{\varepsilon,2}^e(\cdot, 0) = \eta_e \mathbf{M}_{\text{init}}, & \text{in } \Omega, \\ \frac{\partial}{\partial t} \mathbf{M}_{\varepsilon,2}^c - \operatorname{div}_{\mathbf{x}} (\mathbb{D}^c \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^c) - (\sigma_0 \theta^e + \varepsilon^2 \sigma_0^2 \theta^e \langle [\psi] \rangle_{\Gamma^m}) \mathbf{M}_{\varepsilon,2}^e + (\sigma_0 \theta^c + \varepsilon^2 \sigma_0^2 \theta^c \langle [\psi] \rangle_{\Gamma^m}) \mathbf{M}_{\varepsilon,2}^c \\ \quad - \varepsilon \sigma_0 \theta^e \langle [\omega] \rangle_{\Gamma^m} \cdot \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^e = -\varepsilon^2 \operatorname{div}_{\mathbf{x}} (\mathbb{B}^c \cdot \nabla_{\mathbf{x}}^3 \mathbf{M}_{\varepsilon,2}^c) + \varepsilon^2 \iota f(t) \mathbb{S}^c : \mathbf{q} \otimes \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^c \\ \quad + \frac{\eta_c}{\eta_e} \varepsilon^2 \sigma_0 \operatorname{div}_{\mathbf{x}} ((\mathbb{I}^c + \mathbb{Z}^{c,e}) \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^e) - \varepsilon^2 \sigma_0 \operatorname{div}_{\mathbf{x}} ((\mathbb{I}^c + \mathbb{Z}^{c,c}) \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^c), & \text{in } \Omega \times]0, T[, \\ \mathbf{M}_{\varepsilon,2}^c(\cdot, 0) = \eta_c \mathbf{M}_{\text{init}}, & \text{in } \Omega. \end{array} \right. \quad (3.30)$$

We note in the case that the intra-cellular domain is finite, then the tensor \mathbb{D}^c defined by (3.17) is identically zero [8], hence $\mathbb{B}^c = -\mathbb{T}^c$.

4. COUPLED ODE MODEL FOR DMRI SIGNAL

In this section, we derive a system of ODEs whose solution gives the dMRI signal of the new asymptotic model. The reference normalized signal is measured at the echo time T_E and it is given by

$$S_\varepsilon^{BT}(\mathbf{q}) := \frac{\int_{\mathbb{R}^d} \mathbf{M}_\varepsilon(\mathbf{x}, T_E) \, d\mathbf{x}}{\int_{\mathbb{R}^d} \mathbf{M}_{\text{init}} \, d\mathbf{x}},$$

where M_ε is the solution of the reference Bloch–Torrey equation (2.7). For the new second order asymptotic model, we have

$$\widetilde{S}_\varepsilon^2(\mathbf{q}) := \frac{\int_{\mathbb{R}^d} \mathbf{M}_{\varepsilon,2}^e(\mathbf{x}, T_E) \, d\mathbf{x} + \int_{\mathbb{R}^d} \mathbf{M}_{\varepsilon,2}^c(\mathbf{x}, T_E) \, d\mathbf{x}}{\int_{\mathbb{R}^d} \mathbf{M}_{\text{init}} \, d\mathbf{x}}, \quad (4.1)$$

where $\mathbf{M}_{\varepsilon,2}^e$ and $\mathbf{M}_{\varepsilon,2}^c$ are the solutions of (3.30).

We now prove that the second order signal obtained from solving (3.30) can be equivalently obtained by solving a simpler system of coupled ODEs.

Theorem 4.1. *If we assume that f satisfies (2.1), the signal $\widetilde{S}_\varepsilon^2$ is well defined and can be computed as*

$$\widetilde{S}_\varepsilon^2(\mathbf{q}) = m_\varepsilon^e(T_E) + m_\varepsilon^c(T_E), \quad (4.2)$$

where $(m_\varepsilon^e, m_\varepsilon^c)$ is the solution of the second-order ODE model

$$\left\{ \begin{array}{l} \frac{d}{dt} m_\varepsilon^e(t) + ((\mathbf{D}_0^e(\mathbf{q}, t) + \sigma_0 \theta^e) + \varepsilon^2 \mathbf{E}_2^e(\mathbf{q}, t)) m_\varepsilon^e(t) - (\sigma_0 \theta^c + \varepsilon \mathbf{G}_1^c(\mathbf{q}, t) + \varepsilon^2 \mathbf{G}_2^c(\mathbf{q}, t)) m_\varepsilon^c(t) = 0, \\ \frac{d}{dt} m_\varepsilon^c(t) + (\sigma_0 \theta^c) + \varepsilon^2 \mathbf{E}_2^c(\mathbf{q}, t) m_\varepsilon^c(t) - (\sigma_0 \theta^e + \varepsilon \mathbf{G}_1^e(\mathbf{q}, t) + \varepsilon^2 \mathbf{G}_2^e(\mathbf{q}, t)) m_\varepsilon^e(t) = 0, \\ m_\varepsilon^e(0) = \eta_e \quad \text{and} \quad m_\varepsilon^c(0) = \eta_c, \end{array} \right. \quad (4.3)$$

where

$$\mathbf{D}_0^e(\mathbf{q}, t) := F(t)^2 q^2 \mathbb{D}^e : (\mathbf{n} \otimes \mathbf{n}) \tag{4.4}$$

$$\mathbf{G}_1^e(\mathbf{q}, t) := -\iota \sigma_0 \theta^e F(t) q \langle [\omega] \rangle_{\Gamma^m} \cdot \mathbf{n} \tag{4.5}$$

$$\mathbf{G}_1^c(\mathbf{q}, t) := \iota \sigma_0 \theta^c F(t) q \langle [\omega] \rangle_{\Gamma^m} \cdot \mathbf{n} \tag{4.6}$$

$$\begin{aligned} \mathbf{E}_2^e(\mathbf{q}, t) := & \sigma_0^2 \theta^e \langle [\psi] \rangle_{\Gamma^m} + F(t)^4 q^4 \mathbb{B}^e :: (\mathbf{n} \otimes \mathbf{n} \otimes \mathbf{n} \otimes \mathbf{n}) - f(t) F(t) q^2 \mathbb{S}^e : (\mathbf{n} \otimes \mathbf{n}) \\ & + \sigma_0 F^2(t) q^2 (\mathbb{I}^e + \mathbb{Z}^{e,e}) : (\mathbf{n} \otimes \mathbf{n}), \end{aligned} \tag{4.7}$$

$$\begin{aligned} \mathbf{E}_2^c(\mathbf{q}, t) := & \sigma_0^2 \theta^c \langle [\psi] \rangle_{\Gamma^m} + F(t)^4 q^4 \mathbb{B}^c :: (\mathbf{n} \otimes \mathbf{n} \otimes \mathbf{n} \otimes \mathbf{n}) - f(t) F(t) q^2 \mathbb{S}^c : (\mathbf{n} \otimes \mathbf{n}) \\ & - \sigma_0 F^2(t) q^2 (\mathbb{I}^c + \mathbb{Z}^{c,c}) : (\mathbf{n} \otimes \mathbf{n}), \end{aligned} \tag{4.8}$$

$$\mathbf{G}_2^e(\mathbf{q}, t) := \sigma_0^2 \theta^e \langle [\psi] \rangle_{\Gamma^m} - \sigma_0 \frac{\eta^c}{\eta^e} F^2(t) q^2 (\mathbb{I}^c + \mathbb{Z}^{c,e}) : (\mathbf{n} \otimes \mathbf{n}), \tag{4.9}$$

$$\mathbf{G}_2^c(\mathbf{q}, t) := \sigma_0^2 \theta^c \langle [\psi] \rangle_{\Gamma^m} + \sigma_0 \frac{\eta^e}{\eta^c} F^2(t) q^2 (\mathbb{I}^e + \mathbb{Z}^{e,c}) : (\mathbf{n} \otimes \mathbf{n}). \tag{4.10}$$

To give an idea of the proof, we first transform the macroscopic model (3.30) by introducing new unknown variables $\widetilde{M}_{\varepsilon,2}^e$ and $\widetilde{M}_{\varepsilon,2}^c$ defined almost everywhere on $\mathbb{R}^d \times]0, T[$ as

$$\widetilde{M}_{\varepsilon,2}^e(\mathbf{x}, t) = \mathbf{M}_{\varepsilon,2}^e(\mathbf{x}, t) e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} \quad \text{and} \quad \widetilde{M}_{\varepsilon,2}^c(\mathbf{x}, t) = \mathbf{M}_{\varepsilon,2}^c(\mathbf{x}, t) e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)}.$$

After the calculations detailed in Section A.4 of the appendix, we obtain the system of equations for $\widetilde{M}_{\varepsilon,2}^e$ and $\widetilde{M}_{\varepsilon,2}^c$. After that, we denote by $\mathcal{M}_{\varepsilon,2}^e$ and $\mathcal{M}_{\varepsilon,2}^c$ the Fourier transform with respect to the space variable of respectively $\widetilde{M}_{\varepsilon,2}^e$ and $\widetilde{M}_{\varepsilon,2}^c$, and denote the dual variable by ξ :

$$\mathcal{M}_{\varepsilon,2}^\alpha(\xi, t) = \int_{\mathbb{R}^d} \widetilde{M}_{\varepsilon,2}^\alpha(\mathbf{x}, t) e^{-\iota \xi \mathbf{x}} \, d\mathbf{x} \Leftrightarrow \widetilde{M}_{\varepsilon,2}^\alpha(\mathbf{x}, t) = \frac{1}{2\pi} \int_{\mathbb{R}^d} \mathcal{M}_{\varepsilon,2}^\alpha(\xi, t) e^{\iota \xi \mathbf{x}} \, d\xi.$$

We apply the Fourier transform to the system of equations satisfied by $\widetilde{M}_{\varepsilon,2}^e$ and $\widetilde{M}_{\varepsilon,2}^c$, and set

$$m_\varepsilon^e(t) := \mathcal{M}_{\varepsilon,2}^e(0, t) \quad \text{and} \quad m_\varepsilon^c(t) := \mathcal{M}_{\varepsilon,2}^c(0, t),$$

which can be formally written as

$$\begin{aligned} m_\varepsilon^e(t) &= \int_{\mathbb{R}^d} \widetilde{M}_{\varepsilon,2}^e(\mathbf{x}, t) \, d\mathbf{x} \quad \text{and} \quad m_\varepsilon^c(t) = \int_{\mathbb{R}^d} \widetilde{M}_{\varepsilon,2}^c(\mathbf{x}, t) \, d\mathbf{x}, \\ m_\varepsilon^e(0) &= \eta_e \int_{\mathbb{R}^d} \mathbf{M}_{\text{init}} \, d\mathbf{x} \quad \text{and} \quad m_\varepsilon^c(0) = \eta_c \int_{\mathbb{R}^d} \mathbf{M}_{\text{init}} \, d\mathbf{x}. \end{aligned}$$

We observe that for $\xi = 0$, the system of equations for $\mathcal{M}_{\varepsilon,2}^e$ and $\mathcal{M}_{\varepsilon,2}^c$ directly implies the ODE model (4.3). Finally, for the signal, we have the result that for $\alpha = e, c$, using $F(T_E) = 0$,

$$\int_{\mathbb{R}^d} \mathbf{M}_{\varepsilon,2}^\alpha(\mathbf{x}, T_E) \, d\mathbf{x} = \int_{\mathbb{R}^d} \widetilde{M}_{\varepsilon,2}^\alpha(\mathbf{x}, T_E) e^{-\iota q \mathbf{x} \cdot \mathbf{n} F(T_E)} \, d\mathbf{x} = \int_{\mathbb{R}^d} \widetilde{M}_{\varepsilon,2}^\alpha(\mathbf{x}, T_E) \, d\mathbf{x} = m_\varepsilon^\alpha(T_E).$$

We refer to Section A.4 in the appendix for more details on the proof of Theorem 4.1.

Remark 4.2. We recall that the Bloch–Torrey signal S is in theory complex-valued. The real part of \mathbf{M} represents the solution due to diffusion, the imaginary part is not relevant to diffusion. We note that the function \mathbf{G}_1^α , $\alpha \in \{e, c\}$ is imaginary.

For this reason, the second-order ODE model (4.3) can be simplified by removing \mathbf{G}_1^c and \mathbf{G}_1^e to get the ODE system

$$\begin{cases} \frac{d}{dt}m_\varepsilon^e(t) + ((\mathbf{D}_0^e(\mathbf{q}, t) + \sigma_0\theta^e) + \varepsilon^2\mathbf{E}_2^e(\mathbf{q}, t))m_\varepsilon^e(t) - (\sigma_0\theta^c + \varepsilon^2\mathbf{G}_2^c(\mathbf{q}, t))m_\varepsilon^c(t) = 0, \\ \frac{d}{dt}m_\varepsilon^c(t) + ((\sigma_0\theta^c) + \varepsilon^2\mathbf{E}_2^c(\mathbf{q}, t))m_\varepsilon^c(t) - (\sigma_0\theta^e + \varepsilon^2\mathbf{G}_2^e(\mathbf{q}, t))m_\varepsilon^e(t) = 0, \\ m_\varepsilon^e(0) = \eta_e \quad \text{and} \quad m_\varepsilon^c(0) = \eta_c. \end{cases} \tag{4.11}$$

Suppose one only wants the first order approximation, the signal \tilde{S}_ε^1 can be computed as

$$\tilde{S}_\varepsilon^1(\mathbf{q}) = m_\varepsilon^e(T_E) + m_\varepsilon^c(T_E) \tag{4.12}$$

where $(m_\varepsilon^e, m_\varepsilon^c)$ is the solution of the first-order ODE model.

$$\begin{cases} \frac{d}{dt}m_\varepsilon^e(t) + (\mathbf{D}_0^e(\mathbf{q}, t) + \sigma_0\theta^e)m_\varepsilon^e(t) - (\sigma_0\theta^c + \varepsilon\mathbf{G}_1^c(\mathbf{q}, t))m_\varepsilon^c(t) = 0, \\ \frac{d}{dt}m_\varepsilon^c(t) + (\sigma_0\theta^c)m_\varepsilon^c(t) - (\sigma_0\theta^e + \varepsilon\mathbf{G}_1^e(\mathbf{q}, t))m_\varepsilon^e(t) = 0, \\ m_\varepsilon^e(0) = \eta_e \quad \text{and} \quad m_\varepsilon^c(0) = \eta_c. \end{cases} \tag{4.13}$$

Suppose one wants the zeroth order approximation, the signal \tilde{S}_ε^0 that can be computed as

$$\tilde{S}_\varepsilon^0(\mathbf{q}) = m_0^e(T_E) + m_0^c(T_E). \tag{4.14}$$

where (m_0^e, m_0^c) is the solution of the zeroth-order ODE model

$$\begin{cases} \frac{d}{dt}m_0^e(t) + (\mathbf{D}_0^e(\mathbf{q}, t) + \sigma_0\theta^e)m_0^e(t) - \sigma_0\theta^cm_0^c(t) = 0, \\ \frac{d}{dt}m_0^c(t) + (\sigma_0\theta^c)m_0^c(t) - \sigma_0\theta^em_0^e(t) = 0, \\ m_0^e(0) = \eta_e \quad \text{and} \quad m_0^c(0) = \eta_c. \end{cases} \tag{4.15}$$

The above is precisely the asymptotic model derived previously in [8].

Remark 4.3. We recall that the Bloch–Torrey signal S is in theory complex-valued. The real part of \mathbf{M} represents the solution due to diffusion, the imaginary part is not relevant to diffusion. For this reason, the real part of the dMRI signal can be obtained just by solving the zeroth-order ODE model (4.15), there is no need to compute the first-order ODE model (4.13).

Remark 4.4. The new second order model we derived is not unconditionally stable. Its stability depends on the choice of the model parameters. For a given choice of parameters one can show stability numerically by computing the eigenvalues of the time-dependent matrix in the ODE system.

5. NUMERICAL RESULTS

Our objective is to validate the accuracy of the new second-order asymptotic model and measure its improvement over the previously derived zeroth-order asymptotic model of [8]. Our reference solution will be provided by the numerical solution of the reference Bloch–Torrey model (2.7). The three models we compare will be denoted by:

- (1) “Ref”: the reference solution from solving the Bloch–Torrey PDE.
- (2) “R0”: the zeroth-order asymptotic model given in (4.15).
- (3) “R2”: the newly derived second-order asymptotic model given in (4.11).

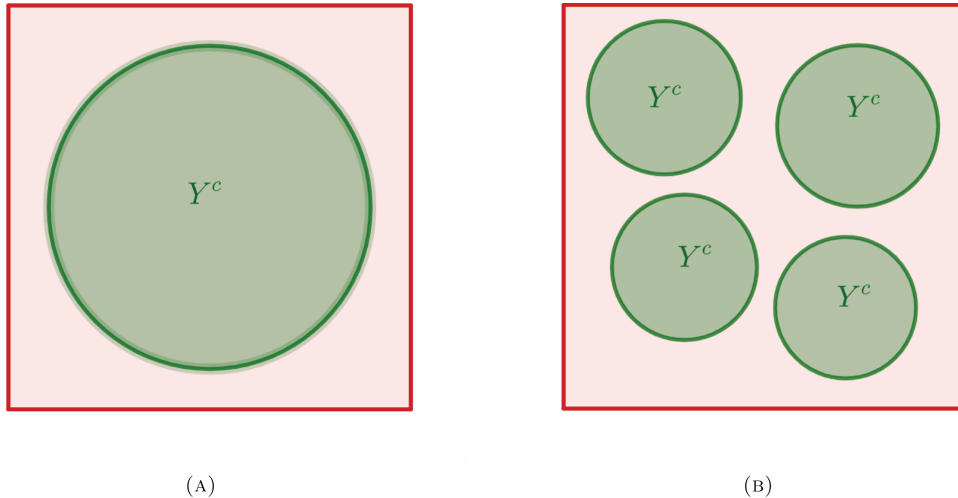


FIGURE 3. Periodicity box $Y = [0, 1]^2$ with two different configurations.

We use the classical Pulsed Gradient Spin Echo (PGSE) sequence, with two rectangular pulses of duration δ , separated by a time interval $\Delta - \delta$:

$$f(t) = \begin{cases} 1, & \text{if } 0 < t \leq \delta, \\ -1, & \text{if } \Delta < t \leq \Delta + \delta, \\ 0, & \text{elsewhere.} \end{cases}$$

We take the echo time $T_E = \delta + \Delta$. We remind that for this time profile the b -value is written as

$$b(q) = q^2 \int_0^{T_E} \left(\int_0^t f(s) \, ds \right)^2 dt = q^2 \delta^2 \left(\Delta - \frac{\delta}{3} \right).$$

We choose the gradient direction to be $\mathbf{n} = e_y$. We fix σ_0 , Δ , δ and b and vary the non-dimensional parameter ε in order to stay within physically reasonable parameters. The values of the intrinsic diffusivities $\mathcal{D}_e = 3 \times 10^{-3} \text{ mm}^2/\text{s}$, $\mathcal{D}_c = 1.7 \times 10^{-3} \text{ mm}^2/\text{s}$, are chosen close to the values often used in the literature [13, 31].

We validate the convergence in simple two-dimensional geometries, see Figure 3.

5.1. Finite element solution

To compute numerical solutions, we used the finite element method (P_1 elements on triangular elements in two dimensions), implemented in the open software FreeFem++ [14]. For example for the geometry on the left in Figure 3 we use 15 380 triangles in Y_e and 15664 triangles in Y_c .

5.1.1. Reference signal

In order to solve the Bloch–Torrey problem (2.7), we will consider the case of constant \mathbf{M}_{init} and recall that we take $\Omega = \mathbb{R}^d$. Following the approach of [24], we transform the Bloch–Torrey equation by defining a new unknown $\widetilde{\mathbf{M}}_\varepsilon^{BT}$ almost everywhere on $\mathbb{R}^d \times]0, T[$ by

$$\widetilde{\mathbf{M}}_\varepsilon^{BT}(\mathbf{x}, t) = \mathbf{M}_\varepsilon(\mathbf{x}, t) e^{i q \mathbf{x} \cdot \mathbf{n} F(t)}.$$

Multiplying the equation of the system (2.7) by $e^{\iota \mathbf{q} \cdot \mathbf{n} F(t)}$ and using the definition of $\widetilde{\mathbf{M}}_\varepsilon^{BT}(\mathbf{x}, t)$, we obtain the following transformed PDE on the box:

$$\begin{cases} \frac{\partial}{\partial t} \widetilde{\mathbf{M}}_\varepsilon^{BT}(\mathbf{x}, t) - \operatorname{div} \left(\mathcal{D}_\varepsilon(\mathbf{x}) \nabla \widetilde{\mathbf{M}}_\varepsilon^{BT}(\mathbf{x}, t) - \iota \mathbf{q} \mathbf{n} F(t) \mathcal{D}_\varepsilon(\mathbf{x}) \widetilde{\mathbf{M}}_\varepsilon^{BT}(\mathbf{x}, t) \right) \\ \quad + \iota \mathbf{q} \mathbf{n} F(t) \mathcal{D}_\varepsilon(\mathbf{x}) \nabla \widetilde{\mathbf{M}}_\varepsilon^{BT}(\mathbf{x}, t) + q^2 F(t)^2 \mathcal{D}_\varepsilon(\mathbf{x}) \widetilde{\mathbf{M}}_\varepsilon^{BT}(\mathbf{x}, t) = 0, & \text{in } Y_\varepsilon \times]0, T[, \\ \left[\mathcal{D}_\varepsilon(\mathbf{x}) \nabla \widetilde{\mathbf{M}}_\varepsilon^{BT}(\mathbf{x}, t) \cdot \boldsymbol{\nu} - \iota \mathbf{q} \mathbf{n} F(t) \mathcal{D}_\varepsilon(\mathbf{x}) \widetilde{\mathbf{M}}_\varepsilon^{BT} \cdot \boldsymbol{\nu} \right] |_{\Gamma_\varepsilon^m} = 0, & \text{on } \Gamma_\varepsilon^m \times]0, T[, \\ \mathcal{D}_\varepsilon(\mathbf{x}) \nabla \widetilde{\mathbf{M}}_\varepsilon^{BT}(\mathbf{x}, t) \cdot \boldsymbol{\nu} - \iota \mathbf{q} \mathbf{n} F(t) \mathcal{D}_\varepsilon(\mathbf{x}) \widetilde{\mathbf{M}}_\varepsilon^{BT} \cdot \boldsymbol{\nu} |_{\Gamma_\varepsilon^m} = \kappa_\varepsilon \left[\widetilde{\mathbf{M}}_\varepsilon^{BT}(\mathbf{x}, t) \right], & \text{on } \Gamma_\varepsilon^m \times]0, T[, \\ \widetilde{\mathbf{M}}_\varepsilon^{BT}(\cdot, 0) = \mathbf{M}_{\text{init}}, & \text{in } Y_\varepsilon, \\ \widetilde{\mathbf{M}}_\varepsilon^{BT} \text{ is } Y_\varepsilon\text{-periodic,} & \end{cases} \quad (5.1)$$

where $Y_\varepsilon = \varepsilon Y$. The normalized signal is

$$S_\varepsilon^{\text{Ref}} = \frac{1}{\mathbf{M}_{\text{init}}|Y_\varepsilon|} \int_{Y_\varepsilon} \mathbf{M}_\varepsilon(\mathbf{x}, T_E) \, d\mathbf{x}.$$

5.1.2. Second-order reduced model

To obtain the second order reduced model, we observe that the ODE model (4.11) is

$$\frac{d}{dt} m(t) + A(\mathbf{q}, t) m(t) = 0,$$

where $m(t) = \begin{pmatrix} m_\varepsilon^e(t) \\ m_\varepsilon^c(t) \end{pmatrix}$ and

$$A(\mathbf{q}, t) = \begin{pmatrix} ((\mathbf{D}_0^e(\mathbf{q}, t) + \sigma_0 \theta^e) + \varepsilon^2 \mathbf{E}_2^e(\mathbf{q}, t)) & -(\sigma_0 \theta^c + \varepsilon^2 \mathbf{G}_2^c(\mathbf{q}, t)) \\ -(\sigma_0 \theta^e + \varepsilon^2 \mathbf{G}_2^e(\mathbf{q}, t)) & ((\sigma_0 \theta^c) + \varepsilon^2 \mathbf{E}_2^c(\mathbf{q}, t)) \end{pmatrix}. \quad (5.2)$$

The above quantities are written as functions of 11 tensors $\mathbb{D}^e, \mathbb{B}^e, \mathbb{B}^c, \mathbb{S}^e, \mathbb{S}^c, \mathbb{I}^e, \mathbb{I}^c, \mathbb{Z}^{e,e}, \mathbb{Z}^{e,c}, \mathbb{Z}^{c,c}, \mathbb{Z}^{c,e}$ (3.17), (3.26), (3.24), (3.25), (3.27) and (3.28). In order to obtain these tensors, we need to solve four periodic box problems (3.18), (3.21), (3.22) and (3.23) on Y . Numerically, we solve these four box problems by using the finite element method (P_1 on triangular elements in two dimensions). We solved the variational problems and obtained the tensors. To solve the ODE model we used the θ -method.

5.1.3. Zeroth-order Reduced model

To obtain the zeroth order reduced model, the ODE model (4.15) only requires

$$A(\mathbf{q}, t) = \begin{pmatrix} ((\mathbf{D}_0^e(\mathbf{q}, t) + \sigma_0 \theta^e)) & -(\sigma_0 \theta^c) \\ -(\sigma_0 \theta^e) & ((\mathbf{D}_0^c(\mathbf{q}, t) + \sigma_0 \theta^c)) \end{pmatrix}.$$

5.2. Convergence

In Figure 4 we display the logarithm of the computed signals as a function of ε for the reference signal Ref, the order zero approximation $R0$ and the order two approximation $R2$. The zeroth-order signal is a horizontal line because the model (4.15) does not depend on ε . One clearly observes the improvement of the second-order approximation over the zeroth-order approximation.

In Figure 5 we show the convergence of the approximation errors $|S_{\text{Ref}} - S_{R0}|$ and $|S_{\text{Ref}} - S_{R2}|$ as functions of ε for three different choices of (Δ, b) . The convergence order is numerically computed to be 1.8 for the zeroth-order model and it is numerically computed to be around 3.5 for the new second-order asymptotic model. The convergence orders are consistent in that $R2$ converges 2 orders faster than $R0$. The appearance of the half order is typical for diffusion problems.

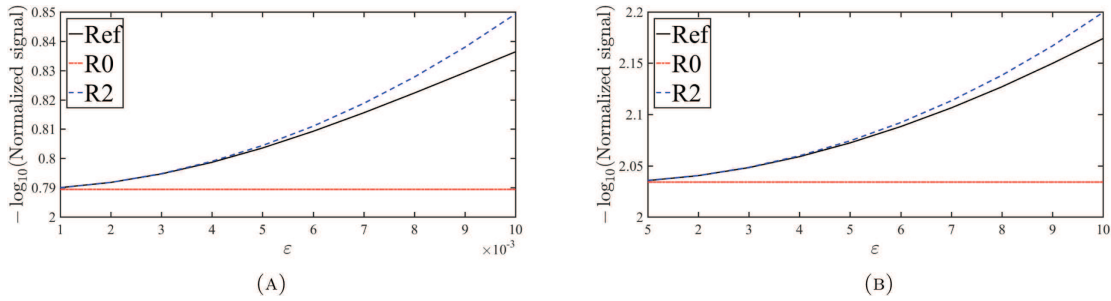


FIGURE 4. Logarithm of the normalized signals *versus* ε , which is varied between 1×10^{-3} and 1×10^{-2} . The geometry is a single disk of radius $R = 0.2$ mm. The experiment parameters are $\mathcal{D}_e = 3 \times 10^{-3}$ mm²/s, $\mathcal{D}_c = 1.7 \times 10^{-3}$ mm²/s, $\sigma_0 = 2 \times 10^{-2}$ m/s, $\mathbf{n} = e_y$ and $\delta = 5$ ms. (a) $\Delta = 15$ ms, $b = 850$ s/mm². (b) $\Delta = 30$ ms, $b = 2500$ s/mm².

6. IMPROVEMENT FOR HIGHER PERMEABILITY

For application to dMRI, we observe that the ODE models (4.15) and (4.11) are independent from the choice of the measuring unit of the unit box Y . For instance, if one replaces Y by $Y' = \rho Y$ where ρ is a scaling factor and y by $y' = \rho y$, then one should change ε by ε/ρ . If we denote by ω_ρ^α , χ_ρ^α , φ_ρ^α , ψ_ρ^α and λ_ρ^α the solution of the box problems computed by replacing Y with Y' , one can easily check that

$$\begin{aligned} \theta_\rho^\alpha &= \frac{1}{\rho} \theta^\alpha, & \theta_\rho &= \frac{1}{\rho} \theta, & \eta_\rho^\alpha &= \eta^\alpha, \\ \omega_\rho^\alpha(y') &= \rho \omega^\alpha(y), & (\chi_\rho^\alpha + \varphi_\rho^\alpha)(y') &= \rho^2 (\chi^\alpha + \varphi^\alpha)(y), \\ \psi_\rho^\alpha(y') &= \rho \psi^\alpha(y), & \text{and } \lambda_\rho^\alpha(y') &= \lambda^\alpha(y), \end{aligned}$$

where ω^α , χ^α , φ^α and ψ^α are the solutions of the box problems (3.18), (3.21), (3.22) and (3.23), respectively. These equalities confirm the independence of the ODE models from the box size.

We will choose a value of $\varepsilon = 1 \times 10^{-2}$ which allows us to use the periodicity box $Y_\varepsilon = \varepsilon Y$ of $10 \mu\text{m}^2$. This means that we assume that the periodicity is on the order of the sizes of brain cells ($O(\mu\text{m})$). Let us emphasize that we did not check that this periodicity length assumption is valid with experimental data. Our comparison will be done with the solution to the Bloch–Torrey equation. Physically, diffusion time in the brain in the range of 1 ms–100 ms can be measured which correspond to average diffusion distance of $2.5 \mu\text{m}$ – $25 \mu\text{m}$. In addition, the permeability coefficient κ varies among the different tissues from sub 10^{-6} m/s to more than 10^{-3} m/s. For instance, for values of κ between 10^{-6} m/s and 10^{-4} m/s, the membranes are semi-permeable while bigger values of κ correspond to very permeable membranes. If κ is below 10^{-6} m/s, the membranes can be considered as impermeable.

In our numerical tests, we will vary the diffusion time Δ and the cell permeability κ . We see clearly in Figures 6a and 6b that the signal of $R2$ is closer to the reference signal when we use a long diffusion time Δ . In Figures 6c and 6d, we consider the effect of the membrane permeability. We can see with varying κ that at higher permeability, $R2$ is closer to Ref.

Two interesting quantities in dMRI are the ADC (the apparent diffusion coefficient) and the AK (the apparent kurtosis). According to [16], the ADC and the AK can be fitted from the signal using

$$S \approx S_0 e^{-\text{ADC}b + \frac{1}{6} \text{AK}(\text{ADC}b)^2}.$$

In Figure 7, we see that the ADC and AK of the $R2$ model are closer to the reference values than the $R0$ model.

We show in Figure 8 that in a configuration of 4 biological cells, the $R2$ model is more accurate than the $R0$ model for a wide range of b -values and especially at higher permeability.

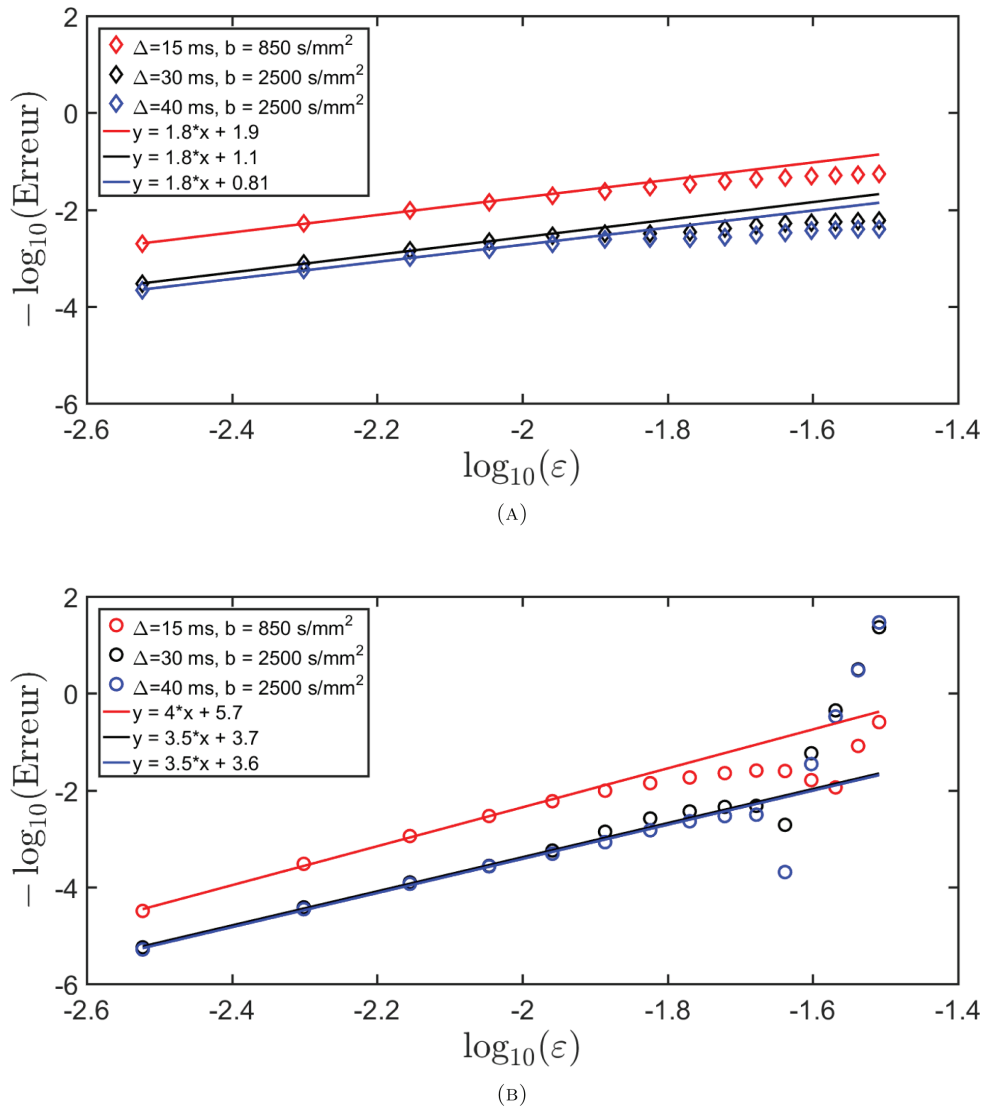


FIGURE 5. Signal convergence for a single disk of radius $R = 0.2$ mm in the periodicity unit box. The experiment other parameters are $\mathcal{D}_e = 3 \times 10^{-3} \text{ mm}^2/\text{s}$, $\mathcal{D}_c = 1.7 \times 10^{-3} \text{ mm}^2/\text{s}$, $\sigma_0 = 2 \times 10^{-2} \text{ m/s}$, $\mathbf{n} = e_y$ and $\delta = 5 \text{ ms}$. (a) $R0$. (b) $R2$.

The new second order model is not unconditionally stable. Its numerical stability depends on the choice of the model parameters. For the choice of parameters in the previous simulations, we show the stability numerically, by computing the eigenvalues of the matrix $A(\mathbf{q}, t)$ in (5.2). Recall that the new second order model can be written as the ODE system

$$\frac{d}{dt}m(t) + A(\mathbf{q}, t)m(t) = 0.$$

Therefore, to have stability, both eigenvalues of $A(\mathbf{q}, t)$ must be non-negative. In Figure 9, we plot the two eigenvalues as a function of time for two values of κ and different values of b and Δ . According to Figure 9, we can see that both eigenvalues are always non-negative which shows numerical stability.

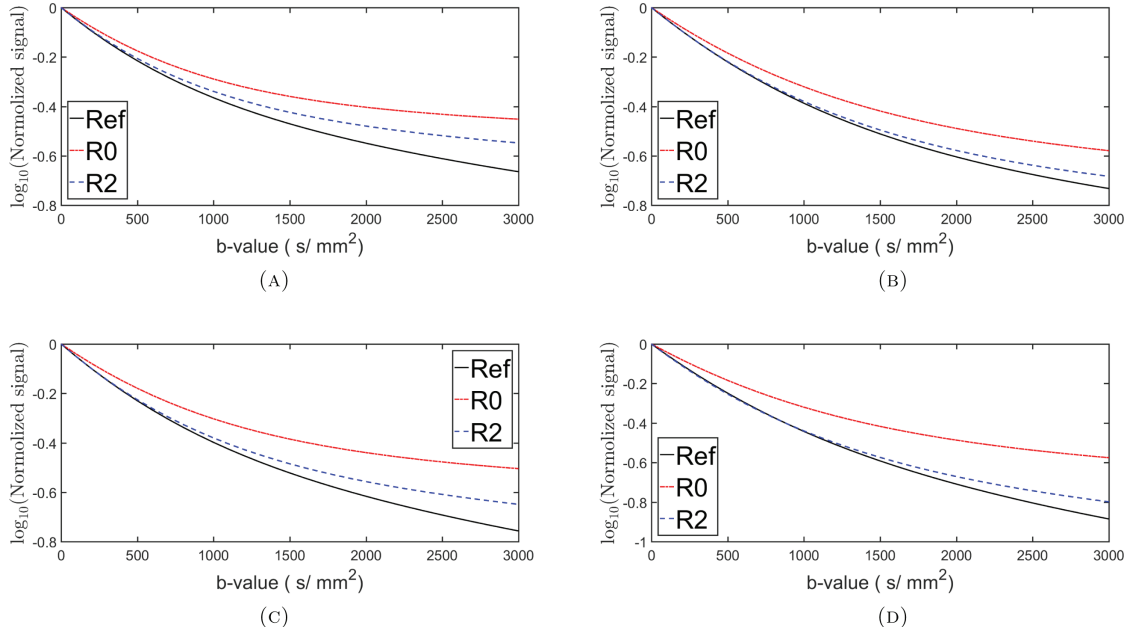


FIGURE 6. \log_{10} Normalized signals *versus* the b -value for a single circular biological cell of radius $R = 4 \mu\text{m}$ in a periodicity box Y_ε of $10 \mu\text{m}^2$, with $\mathcal{D}_e = 3 \times 10^{-3} \text{mm}^2/\text{s}$, $\mathcal{D}_c = 1.7 \times 10^{-3} \text{mm}^2/\text{s}$, $\mathbf{n} = e_y$ and $\delta = 5 \text{ms}$. (a) $\Delta = 25 \text{ms}$, $\kappa = 5 \times 10^{-5} \text{m/s}$. (b) $\Delta = 50 \text{ms}$, $\kappa = 5 \times 10^{-5} \text{m/s}$. (c) $\Delta = 25 \text{ms}$, $\kappa = 7 \times 10^{-5} \text{m/s}$. (d) $\Delta = 25 \text{ms}$, $\kappa = 1 \times 10^{-4} \text{m/s}$.

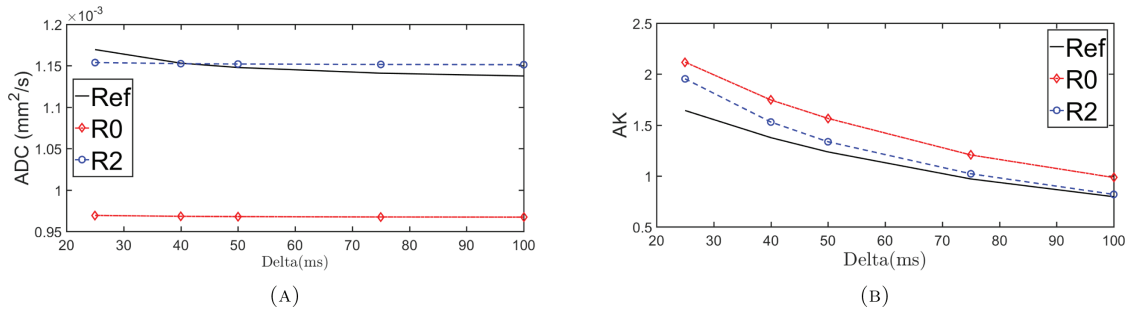


FIGURE 7. ADC and AK of homogenized models and the reference model for one circular biological cell of radius $R = 4 \mu\text{m}$ in a periodicity box Y_ε of $10 \mu\text{m}^2$, with $\mathcal{D}_e = 3 \times 10^{-3} \text{mm}^2/\text{s}$, $\mathcal{D}_c = 1.7 \times 10^{-3} \text{mm}^2/\text{s}$, $\mathbf{n} = e_y$, $\delta = 5 \text{ms}$ and $\kappa = 5 \times 10^{-5} \text{m/s}$.

Remark 6.1. Finally, we say a few words about the practical utility of the derived model for diffusion MRI applications. This question depends very much on whether the regime of validity of this model coincides with the achievable experimental settings, given the physical sizes and membrane permeability of the biological cells. We have shown in the numerical results that at least for the sizes of cells in the micron range and membrane permeability in the larger range of what is found in the literature, the second order model offers an improvement over the zeroth order model. However, since brain cells have many different scales depending on whether one is examining the somas of neurons or the axons and dendrite trees, the validity of the new model may be

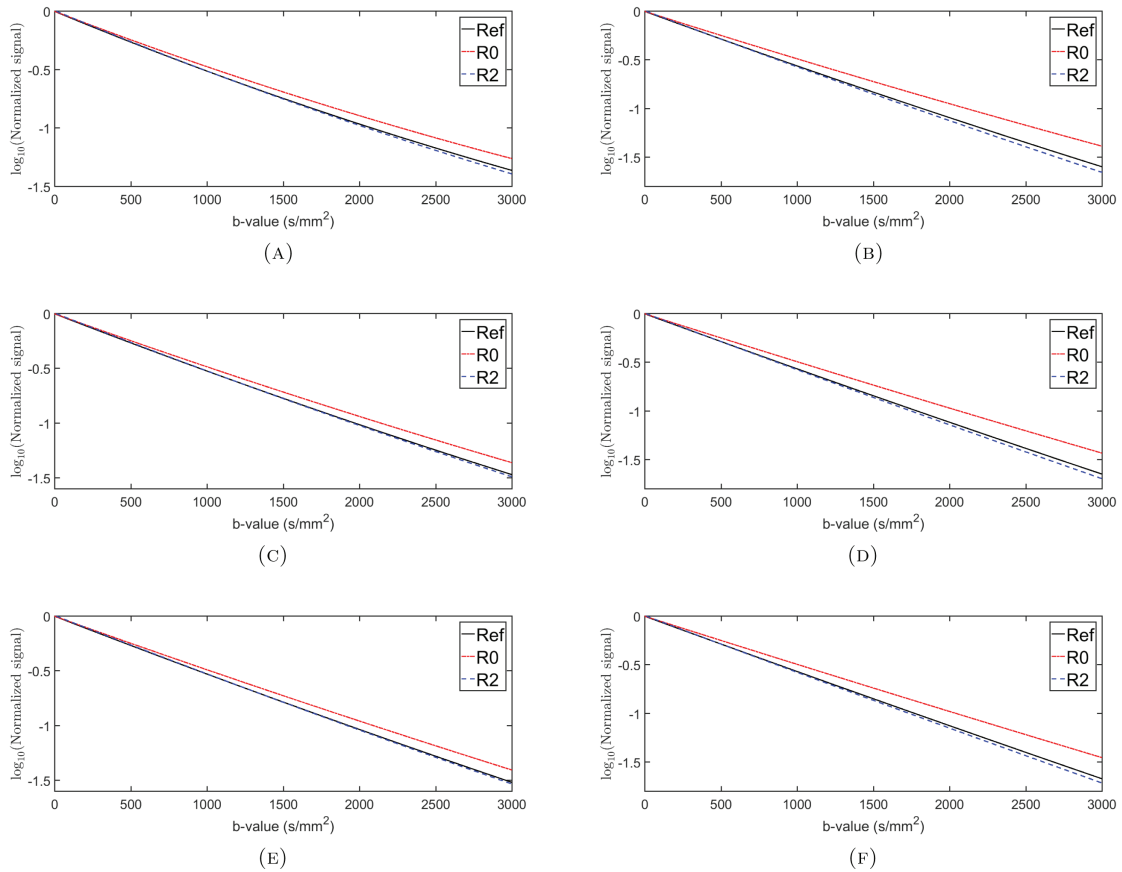


FIGURE 8. \log_{10} Normalized signals *versus* the b -value for 4 circular biological cells in a periodicity box Y_ε of $2\mu\text{m}^2$, with $\mathcal{D}_e = 3 \times 10^{-3} \text{mm}^2/\text{s}$, $\mathcal{D}_c = 1.7 \times 10^{-3} \text{mm}^2/\text{s}$, $\mathbf{n} = e_y$ and $\delta = 5 \text{ms}$. (a) $\Delta = 5 \text{ms}$, $\kappa = 3 \times 10^{-4} \text{m/s}$. (b) $\Delta = 5 \text{ms}$, $\kappa = 6 \times 10^{-4} \text{m/s}$. (c) $\Delta = 10 \text{ms}$, $\kappa = 3 \times 10^{-4} \text{m/s}$. (d) $\Delta = 10 \text{ms}$, $\kappa = 6 \times 10^{-4} \text{m/s}$. (e) $\Delta = 15 \text{ms}$, $\kappa = 3 \times 10^{-4} \text{m/s}$. (f) $\Delta = 15 \text{ms}$, $\kappa = 6 \times 10^{-4} \text{m/s}$.

questionable or it may not offer improved accuracy over the zeroth order model when the cells or cell components in questions are much larger or much smaller than what we have simulated in this paper.

7. CONCLUSIONS

In this paper, we formulated a second order asymptotic model to treat higher values of permeability. We explicitly solved this new asymptotic model to obtain a system of ordinary differential equations that can model the diffusion MRI signal and we present numerical results showing the improved accuracy of the new model in the regime of higher permeability.

Higher-order homogenization expansions have been employed in many other contexts in the literature and we made ample use of higher dimensional tensors in the development of our asymptotic model. We hope our work will offer insight into the role higher dimensional tensors play in multiple scale diffusion phenomena.

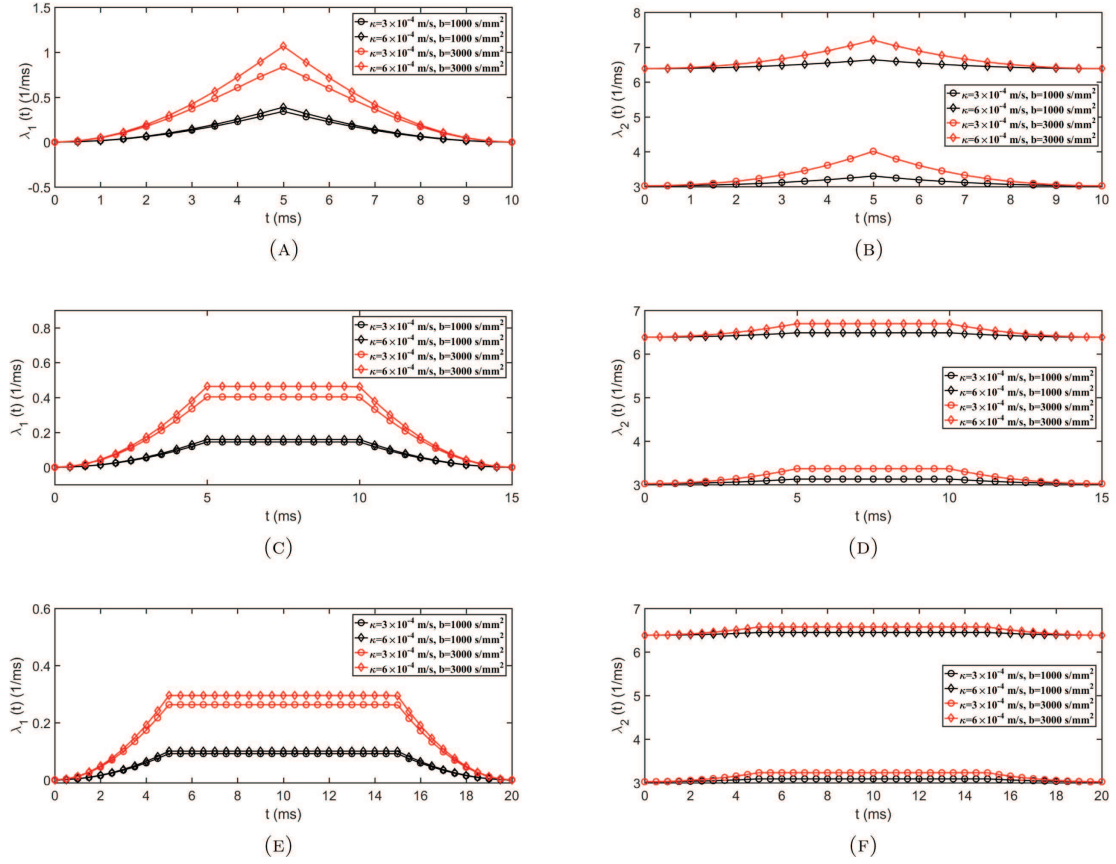


FIGURE 9. The two matrix eigenvalues (the smaller one on the left, the larger one on the right) of the second order model as a function of time for the geometry of 4 circular biological cells in a periodicity box Y_ε of $2\mu\text{m}^2$, for different values of Δ , with $\mathcal{D}_e = 3 \times 10^{-3} \text{mm}^2/\text{s}$, $\mathcal{D}_c = 1.7 \times 10^{-3} \text{mm}^2/\text{s}$, $\mathbf{n} = \mathbf{e}_y$, $\delta = 5 \text{ms}$. (a) $\Delta = 5 \text{ms}$. (b) $\Delta = 5 \text{ms}$. (c) $\Delta = 10 \text{ms}$. (d) $\Delta = 10 \text{ms}$. (e) $\Delta = 15 \text{ms}$. (f) $\Delta = 15 \text{ms}$.

APPENDIX A.

We here give some details of the calculations that lead to the macroscopic equations for \widehat{M}_0^α , \widehat{M}_1^α and \widehat{M}_2^α as well as some symmetry properties for the homogenized tensors. The convention of summation on repeated indices is adopted in the following expressions. Using the differentiation rules we observe that

$$\nabla M_n^\alpha \left(\mathbf{x}, \frac{\mathbf{x}}{\varepsilon}, t \right) = \nabla_{\mathbf{x}} M_n^\alpha \left(\mathbf{x}, \frac{\mathbf{x}}{\varepsilon}, t \right) + \varepsilon^{-1} \nabla_{\mathbf{y}} M_n^\alpha \left(\mathbf{x}, \frac{\mathbf{x}}{\varepsilon}, t \right), \quad \alpha \in \{c, e\},$$

and therefore

$$\begin{aligned} \operatorname{div}(\mathcal{D}^\alpha \nabla M_n^\alpha) &= \operatorname{div}_{\mathbf{x}}(\mathcal{D}^\alpha \nabla_{\mathbf{x}} M_n^\alpha + \mathcal{D}^\alpha \varepsilon^{-1} \nabla_{\mathbf{y}} M_n^\alpha) + \varepsilon^{-1} \operatorname{div}_{\mathbf{y}}(\mathcal{D}^\alpha \nabla_{\mathbf{x}} M_n^\alpha + \mathcal{D}^\alpha \varepsilon^{-1} \nabla_{\mathbf{y}} M_n^\alpha) \\ &= \operatorname{div}_{\mathbf{x}}(\mathcal{D}^\alpha \nabla_{\mathbf{x}} M_n^\alpha) + \varepsilon^{-1} \operatorname{div}_{\mathbf{x}}(\mathcal{D}^\alpha \nabla_{\mathbf{y}} M_n^\alpha) + \varepsilon^{-1} \operatorname{div}_{\mathbf{y}}(\mathcal{D}^\alpha \nabla_{\mathbf{x}} M_n^\alpha) \\ &\quad + \varepsilon^{-2} \operatorname{div}_{\mathbf{y}}(\mathcal{D}^\alpha \nabla_{\mathbf{y}} M_n^\alpha). \end{aligned}$$

Substituting M_ε by the asymptotic expansion (3.1) in problem (2.7) and multiplying the first two equations by ε^2 , we then obtain (3.5)–(3.7).

To derive the averaged equations, we need the following theorem, which can be proved using the Green’s identities.

Theorem A.1. *For problem of the form*

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}(\mathcal{D}^\alpha(\mathbf{y})\nabla_{\mathbf{y}}u^\alpha(\mathbf{y})) = g^\alpha(\mathbf{y}), & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha(\mathbf{y})\nabla_{\mathbf{y}}u^\alpha(\mathbf{y}) \cdot \boldsymbol{\nu} = h^\alpha(\mathbf{y}), & \text{on } \Gamma^m, \\ u^\alpha(\mathbf{y}) \text{ is } Y\text{-periodic,} \end{cases}$$

for some regular data g^α and h^α , there is a unique solution, up to an additive constant, if and only if the compatibility condition holds

$$\int_{Y^\alpha} g^\alpha(\mathbf{y}) \, d\mathbf{y} + \int_{\Gamma^m} h^\alpha(\mathbf{y}) \, ds(\mathbf{y}) = 0. \tag{A.1}$$

A.1. Macroscopic model for \widehat{M}_0

By equating the zeroth-order terms in ε we get

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}(\mathcal{D}^\alpha\nabla_{\mathbf{y}}M_0^\alpha) = 0, & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha\nabla_{\mathbf{y}}M_0^\alpha \cdot \boldsymbol{\nu} = 0, & \text{on } \Gamma^m, \\ M_0^\alpha \text{ is } Y\text{-periodic.} \end{cases} \tag{A.2}$$

It is clear that M_0^α does not depend on \mathbf{y} and therefore $\langle [M_0] \rangle_{\Gamma^m} = [M_0] = [\widehat{M}_0]$.

By equating the first-order terms in ε we get

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}(\mathcal{D}^\alpha\nabla_{\mathbf{y}}M_1^\alpha + \mathcal{D}^\alpha\nabla_{\mathbf{x}}\widehat{M}_0^\alpha) = 0, & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha(\nabla_{\mathbf{y}}M_1^\alpha + \nabla_{\mathbf{x}}\widehat{M}_0^\alpha) \cdot \boldsymbol{\nu} = 0, & \text{on } \Gamma^m, \\ M_1^\alpha \text{ is } Y\text{-periodic.} \end{cases} \tag{A.3}$$

The compatibility condition (A.1) is automatically verified which guarantees a unique (up to an additive constant) solution M_1^α that depends on $\nabla_{\mathbf{x}}\widehat{M}_0^\alpha$. Then, by linearity we obtain

$$M_1^\alpha = \omega^\alpha \cdot \nabla_{\mathbf{x}}\widehat{M}_0^\alpha + \widehat{M}_1^\alpha, \quad \text{in } Y^\alpha \tag{A.4}$$

where $\widehat{M}_1^\alpha = \langle M_1^\alpha \rangle_{Y^\alpha}$ and for $i = 1, \dots, d$ ω_i^α are solutions of box problems (3.18).

Next, by equating the second-order terms in ε we get

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}(\mathcal{D}^\alpha\nabla_{\mathbf{y}}M_2^\alpha + \mathcal{D}^\alpha\nabla_{\mathbf{x}}M_1^\alpha) = W^\alpha, & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha\nabla_{\mathbf{y}}M_2^\alpha \cdot \boldsymbol{\nu} + \mathcal{D}^\alpha\nabla_{\mathbf{x}}M_1^\alpha \cdot \boldsymbol{\nu} = \sigma_0[M_0], & \text{on } \Gamma^m, \\ M_2^\alpha \text{ is } Y\text{-periodic} \end{cases} \tag{A.5}$$

where

$$W^\alpha := \operatorname{div}_{\mathbf{x}}(\mathcal{D}^\alpha\nabla_{\mathbf{y}}M_1^\alpha + \mathcal{D}^\alpha\nabla_{\mathbf{x}}\widehat{M}_0^\alpha) - \frac{\partial}{\partial t}\widehat{M}_0^\alpha. \tag{A.6}$$

We use the notation

$$\frac{\partial}{\partial t}\widehat{M}_0^\alpha = \frac{\partial}{\partial t}\widehat{M}_0^\alpha + \iota Q(\mathbf{x})f(t)\widehat{M}_0^\alpha.$$

It is easy to see that the compatibility condition (A.1) for problem (A.5) implies

$$\begin{cases} \langle W^e \rangle_{Y^e} + \sigma_0\theta^e \langle [M_0] \rangle_{\Gamma^m} = 0, \\ \langle W^c \rangle_{Y^c} - \sigma_0\theta^c \langle [M_0] \rangle_{\Gamma^m} = 0. \end{cases} \tag{A.7}$$

Replacing M_1^α by its expression (A.4) we obtain the macroscopic model (3.16) satisfied by \widehat{M}_0^α .

A.2. Macroscopic model for \widehat{M}_1^α

We here would like to determine the correction given by first-order terms. To derive the macroscopic model for \widehat{M}_1^α , we need to get the expression of M_2^α . By inserting the expression of M_1^α (A.4) into (A.5), we can look for a solution M_2^α such that

$$M_2^\alpha = M_2^{\alpha,1} + M_2^{\alpha,2} + M_2^{\alpha,3} + M_2^{\alpha,4} + \widehat{M}_2^\alpha,$$

where $\widehat{M}_2^\alpha = \langle M_2^\alpha \rangle_{Y^\alpha}$

– $M_2^{\alpha,1}$ is the solution of

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}(\mathcal{D}^\alpha \nabla_{\mathbf{y}} M_2^{\alpha,1}) = \operatorname{div}_{\mathbf{y}}(\mathcal{D}^\alpha \nabla_{\mathbf{x}} \widehat{M}_1^\alpha), & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha \nabla_{\mathbf{y}} M_2^{\alpha,1} \cdot \boldsymbol{\nu} + \mathcal{D}^\alpha \nabla_{\mathbf{x}} \widehat{M}_1^\alpha \cdot \boldsymbol{\nu} = 0, & \text{on } \Gamma^m, \\ M_2^{\alpha,1} \text{ is } Y\text{-periodic.} \end{cases} \quad (\text{A.8})$$

Thus, using for $i = 1, \dots, d$ the cell problems (3.18), which are well posed according to (A.1), one can express the solution as

$$M_2^{\alpha,1} = \omega^\alpha \cdot \nabla_{\mathbf{x}} \widehat{M}_1^\alpha + \widehat{M}_2^{\alpha,1}, \quad \text{in } Y^\alpha, \quad (\text{A.9})$$

where $\widehat{M}_2^{\alpha,1} = \langle M_2^{\alpha,1} \rangle_{Y^\alpha}$.

– $M_2^{\alpha,2}$ is the solution of

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}(\mathcal{D}^\alpha \nabla_{\mathbf{y}} M_2^{\alpha,2}) = \operatorname{div}_{\mathbf{y}}(\mathcal{D}^\alpha \nabla_{\mathbf{x}} (\omega^\alpha \cdot \nabla_{\mathbf{x}} \widehat{M}_0^\alpha)), & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha \nabla_{\mathbf{y}} M_2^{\alpha,2} \cdot \boldsymbol{\nu} + \mathcal{D}^\alpha \nabla_{\mathbf{x}} (\omega^\alpha \cdot \nabla_{\mathbf{x}} \widehat{M}_0^\alpha) \cdot \boldsymbol{\nu} = 0, & \text{on } \Gamma^m, \\ M_2^{\alpha,2} \text{ is } Y\text{-periodic.} \end{cases} \quad (\text{A.10})$$

For $i, j = 1, \dots, d$ the cell problems (3.21) are well posed, one can express the solution as

$$M_2^{\alpha,2} = \chi^\alpha : \nabla_{\mathbf{x}}^2 \widehat{M}_0^\alpha + \widehat{M}_2^{\alpha,2}, \quad \text{in } Y^\alpha, \quad (\text{A.11})$$

where $\widehat{M}_2^{\alpha,2} = \langle M_2^{\alpha,2} \rangle_{Y^\alpha}$.

According to (A.7), we can write

$$\begin{cases} W^e = W^e - \langle W^e \rangle_{Y^e} - \theta^e \sigma_0 [M_0], \\ W^c = W^c - \langle W^c \rangle_{Y^c} + \theta^c \sigma_0 [M_0]. \end{cases} \quad (\text{A.12})$$

– $M_2^{\alpha,3}$ is the solution of

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}(\mathcal{D}^\alpha \nabla_{\mathbf{y}} M_2^{\alpha,3}) = W^\alpha - \langle W^\alpha \rangle_{Y^\alpha}, & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha \nabla_{\mathbf{y}} M_2^{\alpha,3} \cdot \boldsymbol{\nu} = 0, & \text{on } \Gamma^m, \\ M_2^{\alpha,3} \text{ is } Y\text{-periodic.} \end{cases} \quad (\text{A.13})$$

We have

$$W^\alpha - \langle W^\alpha \rangle_{Y^\alpha} = \left(\nabla_{\mathbf{x}}^2 \widehat{M}_0^\alpha \right)_{ij} \left(\mathcal{D}^\alpha \frac{\partial}{\partial y_i} \omega_j^\alpha + \mathcal{D}^\alpha \delta_{ij} - \mathbb{D}_{ij}^\alpha \right).$$

So, we can express the solution of (A.13) as

$$M_2^{\alpha,3} = \varphi^\alpha : \nabla_{\mathbf{x}}^2 \widehat{M}_0^\alpha + \widehat{M}_2^{\alpha,3} \quad \text{in } Y^\alpha, \quad (\text{A.14})$$

where $\widehat{M}_2^{\alpha,3} = \langle M_2^{\alpha,3} \rangle_{Y^\alpha}$ and for $i, j = 1, \dots, d$ φ_{ij}^α are solutions of box problems (3.22).

– $M_2^{\alpha,4}$ is the solution of

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}(\mathcal{D}^\alpha \nabla_{\mathbf{y}} M_2^{\alpha,4}) = \mp \theta^\alpha \sigma_0 [\widehat{M}_0], & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha \nabla_{\mathbf{y}} M_2^{\alpha,4} \cdot \boldsymbol{\nu} = \sigma_0 [\widehat{M}_0], & \text{on } \Gamma^m, \\ M_2^{\alpha,4} \text{ is } Y\text{-periodic,} \end{cases} \tag{A.15}$$

which can be expressed as

$$M_2^{\alpha,4} = \sigma_0 \psi^\alpha [\widehat{M}_0] + \widehat{M}_2^{\alpha,4}, \tag{A.16}$$

where $\widehat{M}_2^{\alpha,4} = \langle M_2^{\alpha,4} \rangle_{Y^\alpha}$ and ψ^α is solution of box problem (3.23).

Finally, we regroup all the solutions obtained $M_2^{\alpha,i}$ for $i \in \{1, 2, 3, 4\}$

$$M_2^\alpha = \omega^\alpha \cdot \nabla_{\mathbf{x}} \widehat{M}_1^\alpha + (\chi^\alpha + \varphi^\alpha) : (\nabla_{\mathbf{x}}^2 \widehat{M}_0^\alpha) + \sigma_0 \psi^\alpha [\widehat{M}_0] + \widehat{M}_2^\alpha \quad \text{in } Y^\alpha, \tag{A.17}$$

where $\omega^\alpha, \chi^\alpha, \varphi^\alpha$ and ψ^α are the solutions of cell problems which are defined in (3.18), (3.21), (3.22) and (3.23), respectively.

By equating the third-order terms in ε we get

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}(\mathcal{D}^\alpha \nabla_{\mathbf{y}} M_3^\alpha + \mathcal{D}^\alpha \nabla_{\mathbf{x}} M_2^\alpha) = G^\alpha, & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha \nabla_{\mathbf{y}} M_3^\alpha \cdot \boldsymbol{\nu} + \mathcal{D}^\alpha \nabla_{\mathbf{x}} M_2^\alpha \cdot \boldsymbol{\nu} = \sigma_0 [M_1], & \text{on } \Gamma^m, \\ M_3^\alpha \text{ is } Y\text{-periodic.} \end{cases} \tag{A.18}$$

Let us define

$$G^\alpha := \operatorname{div}_{\mathbf{x}}(\mathcal{D}^\alpha \nabla_{\mathbf{y}} M_2^\alpha + \mathcal{D}^\alpha \nabla_{\mathbf{x}} M_1^\alpha) - \frac{\partial}{\partial t} M_1^\alpha. \tag{A.19}$$

Then, the compatibility condition for (A.18) implies

$$\begin{cases} \langle G^e \rangle_{Y_e} - \sigma_0 \theta^e \langle [M_1] \rangle_{\Gamma^m} = 0, \\ \langle G^c \rangle_{Y_c} + \sigma_0 \theta^c \langle [M_1] \rangle_{\Gamma^m} = 0. \end{cases} \tag{A.20}$$

By replacing M_1^α and M_2^α by their expressions (A.4) and (A.17) and after recollection we obtain

$$\langle [M_1] \rangle_{\Gamma^m} = [\widehat{M}_1] + \langle \omega_e \rangle_{\Gamma^m} \cdot \nabla_{\mathbf{x}} \widehat{M}_0^e - \langle \omega_c \rangle_{\Gamma^m} \cdot \nabla_{\mathbf{x}} \widehat{M}_0^c. \tag{A.21}$$

Then,

$$\begin{aligned} \frac{\partial}{\partial t} \widehat{M}_1^\alpha - \operatorname{div}_{\mathbf{x}}(\mathbb{D}^\alpha \nabla_{\mathbf{x}} \widehat{M}_1^\alpha) \pm \theta^\alpha \sigma_0 [\widehat{M}_1] &= \operatorname{div}_{\mathbf{x}}(\mathbb{H}^\alpha : \nabla_{\mathbf{x}}^2 \widehat{M}_0^\alpha) + \sigma_0 \mathbf{p}^\alpha \cdot \nabla_{\mathbf{x}} [M_0] \\ &\quad - \pm \sigma_0 \theta^\alpha (\langle \omega_e \rangle_{\Gamma^m} \cdot \nabla_{\mathbf{x}} \widehat{M}_0^e - \langle \omega_c \rangle_{\Gamma^m} \cdot \nabla_{\mathbf{x}} \widehat{M}_0^c). \end{aligned}$$

Since \mathbb{H}^α is antisymmetric in its last two indices, it follows that $\operatorname{div}_{\mathbf{x}}(\mathbb{H}^\alpha : \nabla_{\mathbf{x}}^2 \widehat{M}_0^\alpha) = 0$.

We introduce the vector \mathbf{p}^α through

$$\mathbf{p}_i^\alpha = \left\langle \mathcal{D}^\alpha \frac{\partial}{\partial y_i} \psi^\alpha \right\rangle_{Y^\alpha}, \quad i = 1, \dots, d, \tag{A.22}$$

which can also be expressed in the simplified form

$$\mathbf{p}_i^\alpha = \pm \theta^\alpha \langle \omega_i^\alpha \rangle_{\Gamma^m}. \tag{A.23}$$

Then, we obtain the macroscopic model (3.19) satisfied by \widehat{M}_1^α .

A.3. Macroscopic model for \widehat{M}_2^α

To derive the macroscopic model for \widehat{M}_2^α in this case of scaling, we need to have an expression for M_3^α in terms of \widehat{M}_0^α , \widehat{M}_1^α and \widehat{M}_2^α . So we consider the problem (A.18) and replace M_1^α and M_2^α by their expressions (A.4) and (A.17). We look for a solution M_3^α such that

$$M_3^\alpha = M_3^{\alpha,1} + M_3^{\alpha,2} + M_3^{\alpha,3} + M_3^{\alpha,4} + M_3^{\alpha,5} + M_3^{\alpha,6} + \widehat{M}_3^\alpha$$

where $\widehat{M}_3^\alpha = \langle M_3^\alpha \rangle_{Y^\alpha}$.

– $M_3^{\alpha,1}$ is the solution of

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}\left(\mathcal{D}^\alpha \nabla_{\mathbf{y}} M_3^{\alpha,1}\right) = \operatorname{div}_{\mathbf{y}}\left(\mathcal{D}^\alpha \nabla_{\mathbf{x}} \widehat{M}_2^\alpha\right), & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha \nabla_{\mathbf{y}} M_3^{\alpha,1} \cdot \boldsymbol{\nu} + \mathcal{D}^\alpha \nabla_{\mathbf{x}} \widehat{M}_2^\alpha \cdot \boldsymbol{\nu} = 0, & \text{on } \Gamma^m, \\ M_3^{\alpha,1} \text{ is } Y\text{-periodic,} \end{cases} \quad (\text{A.24})$$

which can be expressed as

$$M_3^{\alpha,1} = \omega^\alpha \cdot \nabla_{\mathbf{x}} \widehat{M}_2^\alpha + \widehat{M}_3^{\alpha,1}, \quad \text{in } Y^\alpha, \quad (\text{A.25})$$

where ω_i^α is the solution of the cell problem (3.18). Since we have $\langle \omega^\alpha \rangle_{Y^\alpha} = 0$, $\widehat{M}_3^{\alpha,1} = \langle M_3^{\alpha,1} \rangle_{Y^\alpha}$.

– $M_3^{\alpha,2}$ is the solution of

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}\left(\mathcal{D}^\alpha \nabla_{\mathbf{y}} M_3^{\alpha,2}\right) = \operatorname{div}_{\mathbf{y}}\left(\mathcal{D}^\alpha \nabla_{\mathbf{x}} M_2^{\alpha,1}\right), & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha \nabla_{\mathbf{y}} M_3^{\alpha,2} \cdot \boldsymbol{\nu} + \mathcal{D}^\alpha \nabla_{\mathbf{x}} M_2^{\alpha,1} \cdot \boldsymbol{\nu} = 0, & \text{on } \Gamma^m, \\ M_3^{\alpha,2} \text{ is } Y\text{-periodic.} \end{cases} \quad (\text{A.26})$$

By linearity, we obtain

$$M_3^{\alpha,2} = \left(\nabla_{\mathbf{x}}^2 \widehat{M}_1^\alpha\right) : \chi^\alpha + \widehat{M}_3^{\alpha,2}, \quad \text{in } Y^\alpha, \quad (\text{A.27})$$

where χ^α is the solution of the cell problem (3.21) and $\widehat{M}_3^{\alpha,2} = \langle M_3^{\alpha,2} \rangle_{Y^\alpha}$.

– $M_3^{\alpha,3}$ is the solution of

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}\left(\mathcal{D}^\alpha \nabla_{\mathbf{y}} M_3^{\alpha,3}\right) = \operatorname{div}_{\mathbf{y}}\left(\mathcal{D}^\alpha \nabla_{\mathbf{x}}\left(M_2^{\alpha,2} + M_2^{\alpha,3}\right)\right), & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha \nabla_{\mathbf{y}} M_3^{\alpha,3} \cdot \boldsymbol{\nu} + \mathcal{D}^\alpha \nabla_{\mathbf{x}}\left(M_2^{\alpha,2} + M_2^{\alpha,3}\right) \cdot \boldsymbol{\nu} = 0, & \text{on } \Gamma^m, \\ M_3^{\alpha,3} \text{ is } Y\text{-periodic,} \end{cases} \quad (\text{A.28})$$

which can be expressed as

$$M_3^{\alpha,3} = \left(\nabla_{\mathbf{x}}^3 \widehat{M}_0\right) \cdot \mathcal{R}_\alpha + \widehat{M}_3^{\alpha,3}, \quad \text{in } Y^\alpha. \quad (\text{A.29})$$

The third-order tensor \mathcal{R}^α is defined as the solution to:

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}\left(\mathcal{D}^\alpha \nabla_{\mathbf{y}} \mathcal{R}_{ijk}^\alpha\right) = \frac{\partial}{\partial y_i}\left(\mathcal{D}^\alpha\left(\chi_{jk}^\alpha + \varphi_{jk}^\alpha\right)\right), & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha \nabla_{\mathbf{y}} \mathcal{R}_{ijk}^\alpha \cdot \boldsymbol{\nu} + \mathcal{D}^\alpha\left(\chi_{jk}^\alpha + \varphi_{jk}^\alpha\right) \nu_i = 0, & \text{on } \Gamma^m, \\ \mathcal{R}_{ijk}^\alpha \text{ is } Y\text{-periodic,} \quad \left\langle \mathcal{R}_{ijk}^\alpha \right\rangle_{Y^\alpha} = 0, \end{cases} \quad (\text{A.30})$$

where χ_{jk}^α and φ_{jk}^α are solutions to (3.21) and (3.22), respectively.

We have assumed $\langle \mathcal{R}_{ijk}^\alpha \rangle_{Y^\alpha} = 0$ and so $\widehat{M}_3^{\alpha,3} = \langle M_3^{\alpha,3} \rangle_{Y^\alpha}$.

– $M_3^{\alpha,4}$ is the solution of

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}\left(\mathcal{D}^\alpha\nabla_{\mathbf{y}}M_3^{\alpha,4}\right) = \sigma_0\operatorname{div}_{\mathbf{y}}\left(\mathcal{D}^\alpha\nabla_{\mathbf{x}}\left(\psi^\alpha[\mathbf{M}_0]\right)\right), & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha\nabla_{\mathbf{y}}M_3^{\alpha,4}\cdot\nu + \sigma_0\mathcal{D}^\alpha\nabla_{\mathbf{x}}\left(\psi^\alpha[\mathbf{M}_0]\right)\cdot\nu = 0, & \text{on } \Gamma^m, \\ M_3^{\alpha,4} \text{ is } Y\text{-periodic.} \end{cases} \tag{A.31}$$

Then, $M_3^{\alpha,4}$ can be expressed as

$$M_3^{\alpha,4} = \sigma_0\nabla_{\mathbf{x}}\left[\widehat{M}_0\right]\cdot\xi^\alpha + \widehat{M}_3^{\alpha,4}, \quad \text{in } Y^\alpha, \tag{A.32}$$

where $\widehat{M}_3^{\alpha,4} = \langle M_3^{\alpha,4} \rangle_{Y^\alpha}$ and for $i = 1, \dots, d$ ξ_i^α are solutions of box problems:

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}\left(\mathcal{D}^\alpha\nabla_{\mathbf{y}}\xi_i^\alpha\right) = \frac{\partial}{\partial y_i}\left(\mathcal{D}^\alpha\psi^\alpha\right), & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha\nabla_{\mathbf{y}}\xi_i^\alpha\cdot\nu + \mathcal{D}^\alpha\psi^\alpha\nu_i = 0, & \text{on } \Gamma^m, \\ \xi_i^\alpha \text{ is } Y\text{-periodic, } \langle \xi_i^\alpha \rangle_{Y^\alpha} = 0. \end{cases} \tag{A.33}$$

According to (A.20), we note that

$$\begin{cases} G^e = G^e - \langle G^e \rangle_{Y^e} + \sigma_0\theta^e\langle [\mathbf{M}_1] \rangle_{\Gamma^m} = 0, \\ G^c = G^c - \langle G^c \rangle_{Y^c} - \sigma_0\theta^c\langle [\mathbf{M}_1] \rangle_{\Gamma^m} = 0. \end{cases}$$

– $M_3^{\alpha,5}$ is the solution of

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}\left(\mathcal{D}^\alpha\nabla_{\mathbf{y}}M_3^{\alpha,5}\right) = G^\alpha - \langle G^\alpha \rangle_{Y^\alpha}, & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha\nabla_{\mathbf{y}}M_3^{\alpha,5}\cdot\nu = 0, & \text{on } \Gamma^m, \\ M_3^{\alpha,5} \text{ is } Y\text{-periodic.} \end{cases} \tag{A.34}$$

Then, we have that

$$\begin{aligned} G^\alpha - \langle G^\alpha \rangle_{Y^\alpha} &= \left(\nabla_{\mathbf{x}}^2\widehat{M}_1^\alpha\right)_{ij}\left(\mathcal{D}^\alpha\frac{\partial}{\partial y_i}\omega_j^\alpha + \mathcal{D}^\alpha\delta_{ij} - \mathbb{D}_{ij}^\alpha\right) \\ &+ \left(\nabla_{\mathbf{x}}^3\widehat{M}_0^\alpha\right)_{ijk}\left(\mathcal{D}^\alpha\frac{\partial}{\partial y_i}\left(\chi_{jk}^\alpha + \varphi_{jk}^\alpha\right) + \mathcal{D}^\alpha\omega_k^\alpha\delta_{ij} - \mathbb{H}_{ijk}^\alpha\right) \\ &- \omega^\alpha\cdot\nabla_{\mathbf{x}}\operatorname{div}_{\mathbf{x}}\left(\mathbb{D}^\alpha\nabla_{\mathbf{x}}\widehat{M}_0^\alpha\right) + \iota\omega^\alpha\cdot\mathbf{q}f(t)\widehat{M}_0^\alpha \\ &+ \sigma_0\left(\nabla_{\mathbf{x}}\left[\widehat{M}_0\right]\right)_i\left(\mathcal{D}^\alpha\frac{\partial}{\partial y_i}\psi^\alpha - \mathbf{p}_i^\alpha\right) \\ &\pm \sigma_0\theta^\alpha\omega^\alpha\cdot\nabla_{\mathbf{x}}\left[\widehat{M}_0\right]. \end{aligned}$$

One can express the solution of (A.34) as

$$\begin{aligned} M_3^{\alpha,5} &= \nabla_{\mathbf{x}}^2\widehat{M}_1^\alpha\cdot\varphi^\alpha + \nabla_{\mathbf{x}}^3\widehat{M}_0^\alpha\cdot\mathcal{Q}^\alpha - \mathcal{L}^\alpha\cdot\nabla_{\mathbf{x}}\operatorname{div}_{\mathbf{x}}\left(\mathbb{D}^\alpha\nabla_{\mathbf{x}}\widehat{M}_0^\alpha\right) + \iota f(t)\mathcal{L}^\alpha\cdot\mathbf{q}\widehat{M}_0^\alpha \\ &+ \sigma_0\nabla_{\mathbf{x}}\left[\widehat{M}_0\right]\left(\mathcal{E}^\alpha \pm \theta^\alpha\mathcal{L}^\alpha\right) + \widehat{M}_3^{\alpha,5}, \quad \text{in } Y^\alpha, \end{aligned} \tag{A.35}$$

where $\widehat{M}_3^{\alpha,5} = \langle M_3^{\alpha,5} \rangle_{Y^\alpha}$. The tensor \mathcal{Q}^α is the solution of

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}(\mathcal{D}^\alpha \nabla_{\mathbf{y}} \mathcal{Q}_{ijk}^\alpha) = \frac{\partial}{\partial y_k}(\mathcal{D}^\alpha(\chi_{ij}^\alpha + \varphi_{ij}^\alpha)) + \mathcal{D}^\alpha \omega_i^\alpha \delta_{jk} - \mathbb{H}_{ijk}^\alpha, & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha \nabla_{\mathbf{y}} \mathcal{Q}_{ijk}^\alpha \cdot \boldsymbol{\nu} = 0, & \text{on } \Gamma^m, \\ \mathcal{Q}_{ijk}^\alpha \text{ is } Y\text{-periodic, } \langle \mathcal{Q}_{ijk}^\alpha \rangle_{Y^\alpha} = 0. \end{cases} \tag{A.36}$$

For $i = 1, \dots, d$, we also obtain the cell problems

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}(\mathcal{D}^\alpha \nabla_{\mathbf{y}} \mathcal{L}_i^\alpha) = \omega_i^\alpha, & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha \nabla_{\mathbf{y}} \mathcal{L}_i^\alpha \cdot \boldsymbol{\nu} = 0, & \text{on } \Gamma^m, \\ \mathcal{L}_i^\alpha \text{ is } Y\text{-periodic, } \langle \mathcal{L}_i^\alpha \rangle_{Y^\alpha} = 0, \end{cases} \tag{A.37}$$

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}(\mathcal{D}^\alpha \nabla_{\mathbf{y}} \mathcal{E}_i^\alpha) = \frac{\partial}{\partial y_j}(\mathcal{D}^\alpha \psi^\alpha) - \left\langle \frac{\partial}{\partial y_j}(\mathcal{D}^\alpha \psi^\alpha) \right\rangle_{Y^\alpha}, & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha \nabla_{\mathbf{y}} \mathcal{E}_i^\alpha \cdot \boldsymbol{\nu} = 0, & \text{on } \Gamma^m, \\ \mathcal{E}_i^\alpha \text{ is } Y\text{-periodic, } \langle \mathcal{E}_i^\alpha \rangle_{Y^\alpha} = 0. \end{cases} \tag{A.38}$$

– $M_3^{\alpha,6}$ is the solution of

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}(\mathcal{D}^\alpha \nabla_{\mathbf{y}} M_3^{\alpha,6}) = \pm \theta^\alpha \sigma_0 \langle [M_1] \rangle_{\Gamma^m}, & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha \nabla_{\mathbf{y}} M_3^{\alpha,6} \cdot \boldsymbol{\nu} = \sigma_0 [M_1], & \text{on } \Gamma^m, \\ M_3^{\alpha,6} \text{ is } Y\text{-periodic.} \end{cases} \tag{A.39}$$

According to (A.21), one can express the solution of (A.39) as

$$M_3^{\alpha,6} = \sigma_0 \psi^\alpha [\widehat{M}_1] + \sigma_0 \mathcal{N}^{\alpha,e} \cdot \nabla_{\mathbf{x}} \widehat{M}_0^e - \sigma_0 \mathcal{N}^{\alpha,c} \cdot \nabla_{\mathbf{x}} \widehat{M}_0^c + \widehat{M}_3^{\alpha,6}, \quad \text{in } Y^\alpha, \tag{A.40}$$

where $\widehat{M}_3^{\alpha,6} = \langle M_3^{\alpha,6} \rangle_{Y^\alpha}$. For $\alpha, \beta \in \{e, c\}$, we take

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}(\mathcal{D}^\alpha \nabla_{\mathbf{y}} \mathcal{N}_i^{\alpha,\beta}) = \pm \theta^\alpha \langle \omega_i^\beta \rangle_{\Gamma^m}, & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha \nabla_{\mathbf{y}} \mathcal{N}_i^{\alpha,\beta} \cdot \boldsymbol{\nu} = \omega_i^\beta, & \text{on } \Gamma^m, \\ \mathcal{N}_i^{\alpha,\beta} \text{ is } Y\text{-periodic, } \langle \mathcal{N}_i^{\alpha,\beta} \rangle_{Y^\alpha} = 0. \end{cases} \tag{A.41}$$

We will use \pm sign where $+$ corresponds to $\alpha = e$ and $-$ corresponds to $\alpha = c$.

Therefore, the expression of M_3^α is written as (A.42). To derive the macroscopic model for \widehat{M}_2^α , we will look for the expression of M_3^α . Therefore, we can express the solution to (A.18) as

$$\begin{aligned} M_3^\alpha &= \omega^\alpha \cdot \nabla_{\mathbf{x}} \widehat{M}_2^\alpha + \nabla_{\mathbf{x}}^2 \widehat{M}_1^\alpha : (\chi^\alpha + \varphi^\alpha) + \nabla_{\mathbf{x}}^3 \widehat{M}_0^\alpha : (\mathcal{R}^\alpha + \mathcal{Q}^\alpha) \\ &\quad + \sigma_0 \nabla_{\mathbf{x}} [\widehat{M}_0] (\xi^\alpha + \mathcal{E}^\alpha \pm \theta^\alpha \mathcal{L}^\alpha) + \sigma_0 \nabla_{\mathbf{x}} \widehat{M}_0^e \cdot \mathcal{N}^{\alpha,e} - \sigma_0 \nabla_{\mathbf{x}} \widehat{M}_0^c \cdot \mathcal{N}^{\alpha,c} \\ &\quad - \mathcal{L}^\alpha \cdot \nabla_{\mathbf{x}} \operatorname{div}_{\mathbf{x}} (\mathbb{D}^\alpha \nabla_{\mathbf{x}} \widehat{M}_0^\alpha) + \iota f(t) \mathcal{L}^\alpha \cdot \mathbf{q} \widehat{M}_0^\alpha + \sigma_0 \psi^\alpha [\widehat{M}_1] + \widehat{M}_3^\alpha, \quad \text{in } Y^\alpha. \end{aligned} \tag{A.42}$$

By equating the fourth-order terms in ε we get

$$\begin{cases} -\operatorname{div}_{\mathbf{y}}(\mathcal{D}^\alpha \nabla_{\mathbf{y}} M_4^\alpha + \mathcal{D}^\alpha \nabla_{\mathbf{x}} M_3^\alpha) = V^\alpha, & \text{in } Y^\alpha, \\ \mathcal{D}^\alpha \nabla_{\mathbf{y}} M_4^\alpha \cdot \boldsymbol{\nu} + \mathcal{D}^\alpha \nabla_{\mathbf{x}} M_3^\alpha \cdot \boldsymbol{\nu} = \sigma_0 [M_2], & \text{on } \Gamma^m, \\ M_4^\alpha \text{ is } Y\text{-periodic.} \end{cases} \tag{A.43}$$

where

$$V^\alpha := \operatorname{div}_{\mathbf{x}}(\mathcal{D}^\alpha \nabla_{\mathbf{y}} \mathbf{M}_3^\alpha + \mathcal{D}^\alpha \nabla_{\mathbf{x}} \mathbf{M}_2^\alpha) - \frac{\tilde{\partial}}{\partial t} \mathbf{M}_2^\alpha. \tag{A.44}$$

The compatibility condition for this problem implies

$$\begin{cases} \langle V^e \rangle_{Y^e} - \sigma_0 \theta^e \langle [\mathbf{M}_2] \rangle_{\Gamma^m} = 0, \\ \langle V^c \rangle_{Y^c} + \sigma_0 \theta^c \langle [\mathbf{M}_2] \rangle_{\Gamma^m} = 0. \end{cases} \tag{A.45}$$

Substituting the expressions (A.17) and (A.42) for \mathbf{M}_2^α and \mathbf{M}_3^α in (A.45), and after some simplification, we obtain the macroscopic model (3.20) for $\widehat{\mathbf{M}}_2^\alpha$.

\mathbb{T} is the homogenized fourth-order tensor $\mathbb{T} = \eta_e \mathbb{T}^e + \eta_c \mathbb{T}^c$. The coefficients of the homogenized fourth-order tensor \mathbb{T}^α are given by

$$\mathbb{T}_{ijkl}^\alpha = \left\langle \mathcal{D}^\alpha \frac{\partial}{\partial y_l} (\mathcal{R}_{ijk}^\alpha + \mathcal{Q}_{ijk}^\alpha) \right\rangle_{Y^\alpha}, \quad i, j, k, l = 1, \dots, d,$$

which can be simplified as (3.26) and \mathbb{S} is the symmetric homogenized second-order tensor $\mathbb{S} = \eta_e \mathbb{S}^e + \eta_c \mathbb{S}^c$. The components of the symmetric second-order tensor \mathbb{S}^α are

$$\mathbb{S}_{ij}^\alpha = \left\langle \mathcal{D}^\alpha \frac{\partial}{\partial y_j} \mathcal{L}_i^\alpha \right\rangle_{Y^\alpha},$$

which can be simplified as (3.24).

For $\{\alpha, \beta\} \in \{e, c\}$, $\mathbb{Z}_{ij}^{\alpha, \beta}$ and \mathbb{I}_{ij}^α are defined by

$$\mathbb{Z}_{ij}^{\alpha, \beta} = \left\langle \mathcal{D}^\alpha \frac{\partial}{\partial y_j} \mathcal{N}_i^{\alpha, \beta} \right\rangle_{Y^\alpha} - \pm \theta^\alpha \langle \chi_{ij}^\beta + \varphi_{ij}^\beta \rangle_{\Gamma^m}, \tag{A.46}$$

and

$$\mathbb{I}_{ij}^\alpha = \left\langle \mathcal{D}^\alpha \frac{\partial}{\partial y_j} (\xi_i^\alpha + \mathcal{E}_i^\alpha) \right\rangle_{Y^\alpha} \pm \theta^\alpha \mathbb{S}_{ij}^\alpha, \tag{A.47}$$

Using again the divergence theorem, we get

$$\left\langle \mathcal{D}^\alpha \frac{\partial}{\partial y_j} \mathcal{N}_i^{\alpha, \beta} \right\rangle_{Y^\alpha} = \pm \theta^\alpha \langle \omega_i^\beta \omega_j^\alpha \rangle_{\Gamma^m}, \tag{A.48}$$

and

$$\left\langle \mathcal{D}^\alpha \frac{\partial}{\partial y_j} (\xi_i^\alpha + \mathcal{E}_i^\alpha) \right\rangle_{Y^\alpha} = \left\langle -\mathcal{D}^\alpha \frac{\partial}{\partial y_j} \psi^\alpha \omega_i^\alpha + \mathcal{D}^\alpha \psi^\alpha \frac{\partial}{\partial y_j} \omega_i^\alpha \right\rangle_{Y^\alpha}. \tag{A.49}$$

Then, we obtain (3.27) and (3.28).

A.4. The proof of Theorem 4.1

Our object is to show the first equation of the ODE model (4.3). We start by transforming the macroscopic model (3.30) by introducing new unknown variables $\widetilde{M}_{\varepsilon, 2}^e$ and $\widetilde{M}_{\varepsilon, 2}^c$ defined almost everywhere on $\mathbb{R}^d \times]0, T[$ by

$$\widetilde{M}_{\varepsilon, 2}^e(\mathbf{x}, t) = \mathbf{M}_{\varepsilon, 2}^e(\mathbf{x}, t) e^{\iota \mathbf{q} \mathbf{x} \cdot \mathbf{n} F(t)} \quad \text{and} \quad \widetilde{M}_{\varepsilon, 2}^c(\mathbf{x}, t) = \mathbf{M}_{\varepsilon, 2}^c(\mathbf{x}, t) e^{\iota \mathbf{q} \mathbf{x} \cdot \mathbf{n} F(t)}. \tag{A.50}$$

To simplify the exposition, we shall use the following notation.

$$\frac{\tilde{\partial}}{\partial t} \mathbf{M}_n^\alpha = \frac{\partial}{\partial t} \mathbf{M}_n^\alpha + \iota \mathbf{q} \cdot \mathbf{x} f(t) \mathbf{M}_n^\alpha. \tag{A.51}$$

Using definition (2.5) and (A.51), we obtain

$$\frac{\partial}{\partial t} \widetilde{M}_{\varepsilon,2}^\alpha = \left(\frac{\partial}{\partial t} \mathbf{M}_{\varepsilon,2}^\alpha + \iota q f(t) \mathbf{x} \cdot \mathbf{n} \mathbf{M}_{\varepsilon,2}^\alpha \right) e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} := \frac{\widetilde{\partial}}{\partial t} \mathbf{M}_{\varepsilon,2}^\alpha e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} \quad (\text{A.52})$$

and

$$\nabla_{\mathbf{x}} \widetilde{M}_{\varepsilon,2}^\alpha = (\nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^\alpha + \iota F(t) q \mathbf{n} \mathbf{M}_{\varepsilon,2}^\alpha) e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)}. \quad (\text{A.53})$$

So, we have

$$\operatorname{div}_{\mathbf{x}} \left(\mathbb{D}^\alpha \nabla_{\mathbf{x}} \widetilde{M}_{\varepsilon,2}^\alpha \right) = (\operatorname{div}_{\mathbf{x}} (\mathbb{D}^\alpha \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^\alpha) + \iota q F(t) \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^\alpha \cdot \mathbf{n}) e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} + \iota q F(t) \mathbb{D}^\alpha : (\nabla_{\mathbf{x}} \widetilde{M}_{\varepsilon,2}^\alpha \otimes \mathbf{n}). \quad (\text{A.54})$$

According to the equation (A.53),

$$\nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^\alpha e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} = \nabla_{\mathbf{x}} \widetilde{M}_{\varepsilon,2}^\alpha - \iota F(t) q \mathbf{n} \widetilde{M}_{\varepsilon,2}^\alpha. \quad (\text{A.55})$$

Taking the expression of $\nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^\alpha e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)}$ and replacing it in (A.54), we obtain

$$\begin{aligned} \operatorname{div}_{\mathbf{x}} (\mathbb{D}^\alpha \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^\alpha) e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} &= \operatorname{div}_{\mathbf{x}} \left(\mathbb{D}^\alpha \nabla_{\mathbf{x}} \widetilde{M}_{\varepsilon,2}^\alpha \right) - q^2 F^2(t) \mathbb{D}^\alpha : (\mathbf{n} \otimes \mathbf{n}) \widetilde{M}_{\varepsilon,2}^\alpha \\ &\quad - 2 \iota q F(t) \mathbb{D}^\alpha : (\nabla_{\mathbf{x}} \widetilde{M}_{\varepsilon,2}^\alpha \otimes \mathbf{n}) \end{aligned} \quad (\text{A.56})$$

and the same for

$$\begin{aligned} \operatorname{div}_{\mathbf{x}} \left((\mathbb{I}^\alpha + \mathbb{Z}^{\alpha,\beta}) \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^\beta \right) e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} &= \operatorname{div}_{\mathbf{x}} \left((\mathbb{I}^\alpha + \mathbb{Z}^{\alpha,\beta}) \nabla_{\mathbf{x}} \widetilde{M}_{\varepsilon,2}^\beta \right) \\ &\quad - q^2 F^2(t) (\mathbb{I}^\alpha + \mathbb{Z}^{\alpha,\beta}) : (\mathbf{n} \otimes \mathbf{n}) \widetilde{M}_{\varepsilon,2}^\beta - 2 \iota q F(t) (\mathbb{I}^\alpha + \mathbb{Z}^{\alpha,\beta}) : (\nabla_{\mathbf{x}} \widetilde{M}_{\varepsilon,2}^\beta \otimes \mathbf{n}), \quad \alpha, \beta \in \{e, c\}. \end{aligned} \quad (\text{A.57})$$

Our objective now is to write $\operatorname{div}_{\mathbf{x}} (\mathbb{B}^\alpha : \nabla_{\mathbf{x}}^3 \widetilde{M}_{\varepsilon,2}^\alpha) e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)}$ in terms of $\widetilde{M}_{\varepsilon,2}^\alpha$, we have

$$\nabla_{\mathbf{x}}^2 \widetilde{M}_{\varepsilon,2}^\alpha = (\nabla_{\mathbf{x}}^2 \mathbf{M}_{\varepsilon,2}^\alpha + 2 \iota F(t) q (\nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^\alpha \otimes \mathbf{n})) e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} - q^2 F^2(t) (\mathbf{n} \otimes \mathbf{n}) \widetilde{M}_{\varepsilon,2}^\alpha \quad (\text{A.58})$$

and

$$\begin{aligned} \nabla_{\mathbf{x}}^3 \widetilde{M}_{\varepsilon,2}^\alpha &= (\nabla_{\mathbf{x}}^3 \mathbf{M}_{\varepsilon,2}^\alpha + 3 \iota F(t) q \nabla_{\mathbf{x}}^2 \mathbf{M}_{\varepsilon,2}^\alpha \otimes \mathbf{n} - 3 q^2 F^2(t) (\mathbf{n} \otimes \mathbf{n} \otimes \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^\alpha)) e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} \\ &\quad - \iota q^3 F^3(t) \mathbf{n} \otimes \mathbf{n} \otimes \mathbf{n} \widetilde{M}_{\varepsilon,2}^\alpha. \end{aligned} \quad (\text{A.59})$$

So, we obtain

$$\begin{aligned} \operatorname{div}_{\mathbf{x}} \left(\mathbb{B}^\alpha : \nabla_{\mathbf{x}}^3 \widetilde{M}_{\varepsilon,2}^\alpha \right) &= \operatorname{div}_{\mathbf{x}} \left(\mathbb{B}^\alpha : \nabla_{\mathbf{x}}^3 \mathbf{M}_{\varepsilon,2}^\alpha e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} \right) + \operatorname{div}_{\mathbf{x}} \left(3 \iota F(t) q \mathbf{n} \otimes \nabla_{\mathbf{x}}^2 \mathbf{M}_{\varepsilon,2}^\alpha e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} \right) \\ &\quad - \operatorname{div}_{\mathbf{x}} \left(3 q^2 F^2(t) \mathbf{n} \otimes \mathbf{n} \otimes \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^\alpha e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} \right) - \operatorname{div}_{\mathbf{x}} \left(\iota q^3 F^3(t) \mathbf{n} \otimes \mathbf{n} \otimes \mathbf{n} \widetilde{M}_{\varepsilon,2}^\alpha \right). \end{aligned} \quad (\text{A.60})$$

After some simplifications, we find

$$\begin{aligned} \operatorname{div}_{\mathbf{x}} \left(\mathbb{B}^\alpha : \nabla_{\mathbf{x}}^3 \mathbf{M}_{\varepsilon,2}^\alpha \right) e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} &= \operatorname{div}_{\mathbf{x}} \left(\mathbb{B}^\alpha : \nabla_{\mathbf{x}}^3 \widetilde{M}_{\varepsilon,2}^\alpha \right) - 4 \iota F(t) q \mathbb{B}^\alpha : \mathbf{n} \otimes \nabla_{\mathbf{x}}^3 \mathbf{M}_{\varepsilon,2}^\alpha e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} \\ &\quad + 6 q^2 F^2(t) \mathbb{B}^\alpha : \mathbf{n} \otimes \mathbf{n} \otimes \nabla_{\mathbf{x}}^2 \mathbf{M}_{\varepsilon,2}^\alpha e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} + 4 \iota q^3 F^3(t) \mathbb{B}^\alpha : \mathbf{n} \otimes \mathbf{n} \otimes \mathbf{n} \otimes \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^\alpha e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} \\ &\quad - q^4 F^4(t) \mathbb{B}^\alpha : \mathbf{n} \otimes \mathbf{n} \otimes \mathbf{n} \otimes \mathbf{n} \widetilde{M}_{\varepsilon,2}^\alpha. \end{aligned} \quad (\text{A.61})$$

Using (A.55), (A.58) and (A.59), we find

$$\nabla_{\mathbf{x}}^2 \mathbf{M}_{\varepsilon,2}^\alpha e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} = \nabla_{\mathbf{x}}^2 \widetilde{M}_{\varepsilon,2}^\alpha - 2 \iota F(t) q (\nabla_{\mathbf{x}} \widetilde{M}_{\varepsilon,2}^\alpha \otimes \mathbf{n}) - q^2 F^2(t) (\mathbf{n} \otimes \mathbf{n}) \widetilde{M}_{\varepsilon,2}^\alpha \quad (\text{A.62})$$

and

$$\nabla_{\mathbf{x}}^3 \mathbf{M}_{\varepsilon,2}^\alpha e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} = \nabla_{\mathbf{x}}^3 \widetilde{\mathbf{M}}_{\varepsilon,2}^\alpha - 3\iota F(t) q \mathbf{n} \otimes \nabla_{\mathbf{x}}^2 \widetilde{\mathbf{M}}_{\varepsilon,2}^\alpha - 3q^2 F^2(t) \mathbf{n} \otimes \mathbf{n} \otimes \nabla_{\mathbf{x}} \widetilde{\mathbf{M}}_{\varepsilon,2}^\alpha + \iota q^3 F^3(t) \mathbf{n} \otimes \mathbf{n} \otimes \mathbf{n} \widetilde{\mathbf{M}}_{\varepsilon,2}^\alpha. \quad (\text{A.63})$$

Finally, we replace (A.55), (A.62) and (A.63) in (A.61), we obtain

$$\begin{aligned} \operatorname{div}_{\mathbf{x}} (\mathbb{B}^\alpha \cdot \nabla_{\mathbf{x}}^3 \mathbf{M}_{\varepsilon,2}^\alpha) e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} &= \operatorname{div}_{\mathbf{x}} (\mathbb{B}^\alpha \cdot \nabla_{\mathbf{x}}^3 \widetilde{\mathbf{M}}_{\varepsilon,2}^\alpha) - 4\iota F(t) q \mathbb{B}^\alpha \cdot \mathbf{n} \otimes \nabla_{\mathbf{x}}^3 \widetilde{\mathbf{M}}_{\varepsilon,2}^\alpha \\ &\quad - 6q^2 F^2(t) \mathbb{B}^\alpha \cdot \mathbf{n} \otimes \mathbf{n} \otimes \nabla_{\mathbf{x}}^2 \widetilde{\mathbf{M}}_{\varepsilon,2}^\alpha + 4\iota q^3 F^3(t) \mathbb{B}^\alpha \cdot \mathbf{n} \otimes \mathbf{n} \otimes \mathbf{n} \otimes \nabla_{\mathbf{x}} \widetilde{\mathbf{M}}_{\varepsilon,2}^\alpha \\ &\quad + q^4 F^4(t) \mathbb{B}^\alpha \cdot \mathbf{n} \cdot \mathbf{n} \otimes \mathbf{n} \otimes \mathbf{n} \widetilde{\mathbf{M}}_{\varepsilon,2}^\alpha. \end{aligned} \quad (\text{A.64})$$

By multiplying the first equation of the model (3.30) by $e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)}$, we obtain

$$\begin{aligned} \frac{\partial}{\partial t} \mathbf{M}_{\varepsilon,2}^e e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} - \operatorname{div}_{\mathbf{x}} (\mathbb{D}^e \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^e) e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} + (\sigma_0 \theta^e + \varepsilon^2 \sigma_0^2 \theta^e \langle [\psi] \rangle_{\Gamma_m}) \mathbf{M}_{\varepsilon,2}^e e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} \\ - (\sigma_0 \theta^c + \varepsilon^2 \sigma_0^2 \theta^c \langle [\psi] \rangle_{\Gamma_m}) \mathbf{M}_{\varepsilon,2}^c e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} + \varepsilon \sigma_0 \theta^c \langle [\omega] \rangle_{\Gamma_m} \cdot \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^c e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} \\ = -\varepsilon^2 \operatorname{div}_{\mathbf{x}} (\mathbb{B}^e \cdot \nabla_{\mathbf{x}}^3 \mathbf{M}_{\varepsilon,2}^e) e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} + \varepsilon^2 \iota f(t) \mathbb{S}^e : \mathbf{q} \otimes \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^e e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} \\ + \varepsilon^2 \sigma_0 \operatorname{div}_{\mathbf{x}} ((\mathbb{I}^e + \mathbb{Z}^{e,e}) \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^e) e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)} - \frac{\eta^e}{\eta^c} \varepsilon^2 \sigma_0 \operatorname{div}_{\mathbf{x}} ((\mathbb{I}^e + \mathbb{Z}^{e,c}) \nabla_{\mathbf{x}} \mathbf{M}_{\varepsilon,2}^c) e^{\iota q \mathbf{x} \cdot \mathbf{n} F(t)}. \end{aligned} \quad (\text{A.65})$$

We take (A.55)–(A.57) and (A.64) and replace them in (A.65), we obtain

$$\begin{aligned} \frac{\partial}{\partial t} \widetilde{\mathbf{M}}_{\varepsilon,2}^e - \operatorname{div}_{\mathbf{x}} (\mathbb{D}^e \nabla_{\mathbf{x}} \widetilde{\mathbf{M}}_{\varepsilon,2}^e) + q^2 F^2(t) \mathbb{D}^e (\mathbf{n} \otimes \mathbf{n}) \widetilde{\mathbf{M}}_{\varepsilon,2}^e + 2\iota q F(t) \mathbb{D}^2 \nabla_{\mathbf{x}} \widetilde{\mathbf{M}}_{\varepsilon,2}^e \otimes \mathbf{n} \\ + (\sigma_0 \theta^e + \varepsilon^2 \sigma_0^2 \theta^e \langle [\psi] \rangle_{\Gamma_m}) \widetilde{\mathbf{M}}_{\varepsilon,2}^e - (\sigma_0 \theta^c + \varepsilon^2 \sigma_0^2 \theta^c \langle [\psi] \rangle_{\Gamma_m}) \widetilde{\mathbf{M}}_{\varepsilon,2}^c + \varepsilon \sigma_0 \theta^c \langle [\omega] \rangle_{\Gamma_m} \cdot (\nabla_{\mathbf{x}} \widetilde{\mathbf{M}}_{\varepsilon,2}^c - \iota F(t) q \mathbf{n} \widetilde{\mathbf{M}}_{\varepsilon,2}^c) \\ = -\varepsilon^2 \operatorname{div}_{\mathbf{x}} (\mathbb{B}^e \cdot \nabla_{\mathbf{x}}^3 \widetilde{\mathbf{M}}_{\varepsilon,2}^e) + \varepsilon^2 4\iota F(t) q \mathbb{B}^e \cdot (\mathbf{n} \otimes \nabla_{\mathbf{x}}^3 \widetilde{\mathbf{M}}_{\varepsilon,2}^e) + \varepsilon^2 6q^2 F^2(t) \mathbb{B}^e \cdot (\mathbf{n} \otimes \mathbf{n} \otimes \nabla_{\mathbf{x}}^2 \widetilde{\mathbf{M}}_{\varepsilon,2}^e) \\ - \varepsilon^2 4\iota q^3 F^3(t) \mathbb{B}^e \cdot (\mathbf{n} \otimes \mathbf{n} \otimes \mathbf{n} \otimes \nabla_{\mathbf{x}} \widetilde{\mathbf{M}}_{\varepsilon,2}^e) - \varepsilon^2 q^4 F^4(t) \mathbb{B}^e \cdot (\mathbf{n} \otimes \mathbf{n} \otimes \mathbf{n} \otimes \mathbf{n}) \widetilde{\mathbf{M}}_{\varepsilon,2}^e \\ + \varepsilon^2 \iota f(t) \mathbb{S}^e : \mathbf{q} \otimes (\nabla_{\mathbf{x}} \widetilde{\mathbf{M}}_{\varepsilon,2}^e - \iota F(t) q \mathbf{n} \widetilde{\mathbf{M}}_{\varepsilon,2}^e) + \varepsilon^2 \sigma_0 (\operatorname{div}_{\mathbf{x}} ((\mathbb{I}^e + \mathbb{Z}^{e,e}) \nabla_{\mathbf{x}} \widetilde{\mathbf{M}}_{\varepsilon,2}^e) - q^2 F^2(t) (\mathbb{I}^e + \mathbb{Z}^{e,e}) \\ : (\mathbf{n} \otimes \mathbf{n}) \widetilde{\mathbf{M}}_{\varepsilon,2}^e - 2\iota q F(t) (\mathbb{I}^e + \mathbb{Z}^{e,e}) : (\nabla_{\mathbf{x}} \widetilde{\mathbf{M}}_{\varepsilon,2}^e \otimes \mathbf{n})) - \frac{\eta^e}{\eta^c} \varepsilon^2 \sigma_0 (\operatorname{div}_{\mathbf{x}} ((\mathbb{I}^e + \mathbb{Z}^{e,c}) \nabla_{\mathbf{x}} \widetilde{\mathbf{M}}_{\varepsilon,2}^c) \\ - q^2 F^2(t) (\mathbb{I}^e + \mathbb{Z}^{e,c}) : (\mathbf{n} \otimes \mathbf{n}) \widetilde{\mathbf{M}}_{\varepsilon,2}^c - 2\iota q F(t) (\mathbb{I}^e + \mathbb{Z}^{e,c}) : (\nabla_{\mathbf{x}} \widetilde{\mathbf{M}}_{\varepsilon,2}^c \otimes \mathbf{n})). \end{aligned} \quad (\text{A.66})$$

By using the same approach on the second equation of the model (3.30), we obtain the system of equation for $\widetilde{\mathbf{M}}_{\varepsilon,2}^e$ and $\widetilde{\mathbf{M}}_{\varepsilon,2}^c$.

We denote by $\mathcal{M}_{\varepsilon,2}^e$ and $\mathcal{M}_{\varepsilon,2}^c$ the Fourier transform with respect to the space variable of respectively $\widetilde{\mathbf{M}}_{\varepsilon,2}^e$ and $\widetilde{\mathbf{M}}_{\varepsilon,2}^c$ and denote the dual variable by ξ .

$$\mathcal{M}_{\varepsilon,2}^\alpha(\xi, t) = \int_{\mathbb{R}^d} \widetilde{\mathbf{M}}_{\varepsilon,2}^\alpha(\mathbf{x}, t) e^{-\iota \xi \mathbf{x}} d\mathbf{x} \Leftrightarrow \widetilde{\mathbf{M}}_{\varepsilon,2}^\alpha(\mathbf{x}, t) = \frac{1}{2\pi} \int_{\mathbb{R}^d} \mathcal{M}_{\varepsilon,2}^\alpha(\xi, t) e^{\iota \xi \mathbf{x}} d\xi. \quad (\text{A.67})$$

We now apply the Fourier transform to the system of equations satisfied by $\widetilde{\mathbf{M}}_{\varepsilon,2}^e$ and $\widetilde{\mathbf{M}}_{\varepsilon,2}^c$. For example $-\operatorname{div}_{\mathbf{x}} (\mathbb{D}^e \nabla_{\mathbf{x}} \widetilde{\mathbf{M}}_{\varepsilon,2}^e)$ will become $\mathbb{D}^e \xi \cdot \xi \mathcal{M}_{\varepsilon,2}^e$.

We set

$$m_\varepsilon^e(t) := \mathcal{M}_{\varepsilon,2}^e(0, t) \quad \text{and} \quad m_\varepsilon^c(t) := \mathcal{M}_{\varepsilon,2}^c(0, t)$$

which can be formally written as

$$\begin{aligned} m_\varepsilon^e(t) &= \int_{\mathbb{R}^d} \widetilde{M}_{\varepsilon,2}^e(\mathbf{x}, t) \, d\mathbf{x} \quad \text{and} \quad m_\varepsilon^c(t) = \int_{\mathbb{R}^d} \widetilde{M}_{\varepsilon,2}^c(\mathbf{x}, t) \, d\mathbf{x}, \\ m_\varepsilon^e(0) &= \eta_e \int_{\mathbb{R}^d} \mathbf{M}_{\text{init}} \, d\mathbf{x} \quad \text{and} \quad m_\varepsilon^c(0) = \eta_c \int_{\mathbb{R}^d} \mathbf{M}_{\text{init}} \, d\mathbf{x}. \end{aligned}$$

We observe that for $\xi = 0$, the system of equations for $\mathcal{M}_{\varepsilon,2}^e$ and $\mathcal{M}_{\varepsilon,2}^c$ directly implies the ODE model (4.3).

Finally, for the signal we have for $\alpha = e, c$, using $F(T_E) = 0$,

$$\int_{\mathbb{R}^d} \mathbf{M}_{\varepsilon,2}^\alpha(\mathbf{x}, T_E) \, d\mathbf{x} = \int_{\mathbb{R}^d} \widetilde{M}_{\varepsilon,2}^\alpha(\mathbf{x}, T_E) e^{-i\mathbf{q}\mathbf{x} \cdot \mathbf{n}F(T_E)} \, d\mathbf{x} = \int_{\mathbb{R}^d} \widetilde{M}_{\varepsilon,2}^\alpha(\mathbf{x}, T_E) \, d\mathbf{x} = m_\varepsilon^\alpha(T_E)$$

which concludes the proof. □

REFERENCES

- [1] G. Allaire and T. Yamada, Optimization of dispersive coefficients in the homogenization of the wave equation in periodic structures. *Numer. Math.* **140** (2018) 265–326.
- [2] G. Allaire, M. Briane and M. Vanninathan, A comparison between two-scale asymptotic expansions and Bloch wave expansions for the homogenization of periodic structures. *SeMA* **73** (2016) 237–259.
- [3] I.V. Andrianov, V.I. Bolshakov, V.V. Danishevskyy and D. Weichert, Higher order asymptotic homogenization and wave propagation in periodic composite materials. *Proc. Roy. Soc. A* **464** (2008) 1181–1201.
- [4] A. Bensoussan, J.L. Lions and G. Papanicolaou, *Asymptotic Analysis for Periodic Structures*. AMS Chelsea Publishing, Providence, RI (2011).
- [5] P.T. Callaghan and J. Stepienik, Frequency-domain analysis of spin motion using modulated-gradient NMR. *J. Magn. Reson. Ser. A* **117** (1995) 118–122.
- [6] P.T. Callaghan, A. Coy, D. MacGowan, K.J. Packer and F.O. Zelaya, Diffraction-like effects in NMR diffusion studies of fluids in porous solids. *Nature* **351** (1991) 467–469.
- [7] J. Chen, W. Liu, H. Zhang, L. Lacy, X. Yang, S.-K. Song, S.A. Wickline and X. Yu, Regional ventricular wall thickening reflects changes in cardiac fiber and sheet structure during contraction: quantification with diffusion tensor MRI. *Am. J. Physiol. – Heart Circulatory Physiol.* **289** (2005) H1898–H1907.
- [8] J. Coatléven, H. Haddar and J.-R. Li, A new macroscopic model including membrane exchange for diffusion MRI. *SIAM J. Appl. Math.* **74** (2014) 516–546.
- [9] C. Conca, R. Orive and M. Vanninathan, On Burnett coefficients in periodic media. *J. Math. Phys.* **3** (2006) 11.
- [10] D.S. Grebenkov, From the microstructure to diffusion MRI, and back, in *Diffusion NMR of Confined Systems: Fluid Transport in Porous Solids and Heterogeneous Materials. New Developments in NMR*, edited by R. Valiullin. The Royal Society of Chemistry, Cambridge (2017) 52–110.
- [11] H. Haddar, J.-R. Li and S. Schiavi, Adapting the Kärger model to account for finite diffusion-encoding pulses in diffusion MRI. *IMA J. Appl. Math.* **81** (2016) 779–794.
- [12] H. Haddar, J.-R. Li and S. Schiavi, A macroscopic model for the diffusion MRI signal accounting for time-dependent diffusivity. *SIAM J. Appl. Math.* **76** (2016) 930–949.
- [13] K.D. Harkins, J.-P. Galons, T.W. Secomb and T.P. Trouard, Assessment of the effects of cellular tissue properties on ADC measurements by numerical simulation of water diffusion. *Magn. Reson. Med.* **62** (2009) 1414–1422.
- [14] F. Hecht, O. Pironneau and J. Morice, Freefem. www.freefem.org.
- [15] T. Hui and C. Oskay, A high order homogenization model for transient dynamics of heterogeneous media including micro-inertia effects. *Comput. Methods Appl. Mech. Eng.* **273** (2014) 181–203.
- [16] J.H. Jensen, J.A. Helpert, A. Ramani, H. Lu and K. Kaczynski, Diffusional kurtosis imaging: the quantification of non-gaussian water diffusion by means of magnetic resonance imaging. *Magn. Reson. Med.* **53** (2005) 1432–1440.
- [17] M. Kchaou, H. Haddar and M. Moakher, The derivation of homogenized diffusion kurtosis models for diffusion MRI. *J. Magn. Reson.* **298** (2019) 48–57.
- [18] D. Le Bihan and H. Johansen-Berg, Diffusion MRI at 25: exploring brain tissue structure and function. *NeuroImage* **61** (2012) 324–341.
- [19] J.-R. Li, H.T. Nguyen, D. Van Nguyen, H. Haddar, J. Coatléven and D. Le Bihan, Numerical study of a macroscopic finite pulse model of the diffusion MRI signal. *J. Magn. Reson.* **248** (2014) 54–65.
- [20] H. Lu, J.H. Jensen, A. Ramani and J.A. Helpert, Three dimensional characterization of non Gaussian water diffusion in humans using diffusion kurtosis imaging. *NMR Biomed.* **19** (2006) 236–247.
- [21] S. Mori, *Introduction to Diffusion Tensor Imaging*. Elsevier, Amsterdam (2007).

- [22] M.E. Moseley, J. Kucharczyk, J. Mintorovitch, Y. Cohen, J. Kurhanewicz, N. Derugin, H. Asgari and D. Norman, Diffusion-weighted MR imaging of acute stroke: correlation with T2-weighted and magnetic susceptibility-enhanced MR imaging in cats. *Am. J. Neuroradiol.* **11** (1990) 423–429.
- [23] S. Moskow and M. Vogelius, First-order corrections to the homogenized eigenvalues of a periodic composite medium. A convergence proof. *Proc. Roy. Soc. Edin.* **127** (1997) 1263–1278.
- [24] D.V. Nguyen, *A finite elements method to solve the Bloch–Torrey equation applied to diffusion magnetic resonance imaging of biological tissues*. Ph.D. thesis, CMAP, Ecole Polytechnique (2014).
- [25] M. Peerlings M. Ameen and R.H.J. Geers, Higher-order asymptotic homogenization of periodic linear elastic composite materials at low scale separation. *Contrib. Found. Multi. Res. Mech.* **3** (2016) 2544–2545.
- [26] W.S. Price, Pulsed-field gradient nuclear magnetic resonance as a tool for studying translational diffusion: Part 1. Basic theory. *Concepts Magn. Reson.* **9** (1997) 299–336.
- [27] D. Rohmer, A. Sitek and G.T. Gullberg, *Reconstruction and visualization of fiber and sheet structure with regularized tensor diffusion MRI in the human heart*. Lawrence Berkeley National Laboratory Publication. LBNL-60277 (2006).
- [28] F. Santosa and W. Synes, A dispersive effective medium for wave propagation in periodic composites. *SIAM J. Appl. Math* **51** (1991) 984–1005.
- [29] H.C. Torrey, Bloch equations with diffusion terms. *Phys. Rev. Online Arch. (Prola)* **104** (1956) 563–565.
- [30] S. Warach, D. Chien, W. Li, M. Ronthal and R.R. Edelman, Fast magnetic resonance diffusion-weighted imaging of acute human stroke. *Neurology* **42** (1992) 1717–1723.
- [31] J. Xu, M.D. Does and J.C. Gore, Numerical study of water diffusion in biological tissues using an improved finite difference method. *Phys. Med. Biol.* **52** (2007) N111.



Please help to maintain this journal in open access!

This journal is currently published in open access under the Subscribe to Open model (S2O). We are thankful to our subscribers and supporters for making it possible to publish this journal in open access in the current year, free of charge for authors and readers.

Check with your library that it subscribes to the journal, or consider making a personal donation to the S2O programme by contacting subscribers@edpsciences.org.

More information, including a list of supporters and financial transparency reports, is available at <https://edpsciences.org/en/subscribe-to-open-s2o>.