Atti Accademia Nazionale Lincei Classe Scienze Fisiche Matematiche Naturali

Rendiconti Lincei
Matematica e Applicazioni

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Oxygen exchange between multiple capillaries and living tissues: An homogenisation study

Atti della Accademia Nazionale dei Lincei. Classe di Scienze Fisiche, Matematiche e Naturali. Rendiconti Lincei. Matematica e Applicazioni, Serie 9, Vol. **13** (2002), n.2, p. 149–164.

Accademia Nazionale dei Lincei

<http://www.bdim.eu/item?id=RLIN_2002_9_13_2_149_0>

Atti della Accademia Nazionale dei Lincei. Classe di Scienze Fisiche, Matematiche e Naturali. Rendiconti Lincei. Matematica e Applicazioni, Accademia Nazionale dei Lincei, 2002.

Rend. Mat. Acc. Lincei
s. 9, v. 13:149-164 (2002)

Fisica matematica. — *Oxygen exchange between multiple capillaries and living tissues: An homogenisation study.* Nota di ANDRO MIKELIĆ e MARIO PRIMICERIO, presentata (*) dal Socio M. Primicerio.

ABSTRACT. — A mathematical model for a problem of blood perfusion in a living tissue through a system of parallel capillaries is studied. Oxygen is assumed to be transported in two forms: freely diffusing and bounded (to erytrocytes in blood, to myoglobin in tissue). Existence of a weak solution is proved and a homogensation procedure is carried out in the case of randomly distribuited capillaries.

KEY WORDS: Oxygen diffusion; Hemodynamics; Homogenisation.

RIASSUNTO. — *Scambio di ossigeno tra un tessuto e un sistema di capillari. Uno studio di omogeneizzazione.* Si studia un modello matematico per un problema di perfusione sanguigna in un tessuto vivente da parte di un sistema di capillari paralleli. Si suppone che l'ossigeno sia trasportato in due forme: libero di diffondere e legato (agli eritrociti nel sangue, alla mioglobina nel tessuto). Si dimostra l'esistenza di una soluzione debole e si utilizza un procedimento di omogeneizzazione per il caso di capillari distribuiti aleatoriamente.

1. INTRODUCTION

This paper deals with the analysis of a mathematical model for a problem of advection/diffusion/consumption of oxygen in a living tissue which is perfused by a network of capillaries. The problem has been widely studied also in its mathematical aspects starting from the pioneering paper of Krogh [8] in 1919. Substantial information on classical literature can be found in [13, 5], while review of more recent papers is provided *e.g.* in [16, 9, 4].

There are two main ingredients that make the peculiarity of the problem: (*i*) the presence of a large number of capillaries, and (*ii*) the dynamics of transport of oxygen in blood and in tissues.

Concerning (*i*), a self-suggesting technique is homogenisation. In this paper we consider a rather simplified geometry, *i.e.* a bundle of parallel and non interconnected capillaries, but this is, in our knowledge, the first attempt to use these techniques in the area of microcirculation (see [15, 16], for the other approaches used to deal with multicapillary system). Question under (*ii*) requires some explanation: oxygen is carried by blood essentially in two forms: (*a*) *dissolved* in blood plasma (the substrate) and (*b*) *bound* to erytrocytes (*i.e.* red cells) in form of hemoglobin. The same is true for oxygen in the tissue that can be *freely diffusing* or *bound* to myoglobin.

Let us refer *e.g.* to blood. In the framework of continuum physics, in any REV (representative elementary volume) of the blood it is possible to define three quantities: the concentration c of oxygen in plasma (mass O_2 per unit volume of plasma), the

(*) Nella seduta dell'8 febbraio 2002.

concentration l of oxygen in erythrocytes (mass O_2 per unit volume of red cells) and the volume fraction $\alpha \in [0\,,1]$ occupied by plasma. Thus the time derivative of

$$M = \alpha c + (1-\alpha) l \tag{1.1}$$

will be set equal, in the mass balance, to the proper flux and/or volumetric sources or sinks.

Note that in convective flux both c and l will appear (assume α is a given constant, for sake of simplicity), but only ∇c will be present in the diffusive flux.

Thus, the problem has to be completed by prescribing a relationship between c and l.

The dynamics of the exchange between bound and free oxygen can be modeled in different ways. Some authors postulate that

$$\tau \frac{dl}{dt} = \varphi(c - l)\,, \tag{1.2}$$

where φ is a non-decreasing function $\varphi(0) = 0$, or more generally

$$\tau \frac{dl}{dt} = \varphi(\gamma(c) - l) \tag{1.3}$$

where $\gamma(c)$ is a monotone function ($\gamma(0) = 0$) representing the equilibrium concentration of the bound oxygen corresponding to concentration c of the substrate and τ is the relaxation time. But in most cases the time scale of the phenomena under consideration is large enough, so that one can take $\tau = 0$ and assume that equilibrium is realized at any time (see [2] as well as the papers quoted above):

$$l = \gamma(c). \tag{1.4}$$

A typical equilibrium profile is given by the so-called Michaelis-Menten law

$$l = \beta \frac{c^s}{c^s + B^s} \tag{1.5}$$

where β and B are given constants and s (the Michaelis-Menten exponent) is a given number which for blood is approximately 2.5 (see *e.g.* [9], an alternative law for equilibrium profile is quoted in [14]).

Having in mind this approach we can pass to the description of a model problem (one capillary surrounded by living tissue) to introduce the problem which will be considered in the sequel.

Let the capillary be the cylinder $r \le R, \quad z \in [0\,, B]$ and let R be small enough so that radial variations of the relevant quantities within the capillary as well as axial diffusion can be neglected w.r.t. convection.

The latter assumption is justified by noting that $D_1/uB << 1$ where D_1 is the diffusivity of oxygen in blood (which is of the order of 10^{-5} cm^2/sec) and u is the speed of blood in the capillary, assumed to be constant. Mass balance for oxygen in the capillary reads

$$\left(\frac{\partial}{\partial t} + u \frac{\partial}{\partial z}\right)(\alpha c + (1-\alpha) l) = F \tag{1.6}$$

where F is the flux of O_2 through the walls of capillary. Using assumption (1.4) we can write with obvious notation

$$\frac{\partial}{\partial t}\Phi(c) + u\frac{\partial}{\partial z}\Phi(c) = F. \tag{1.7}$$

Equation (1.7) (in which term F will be specified) has to be supplemented with condition on $t = 0$ and on $z = 0$.

In the tissue we will have, with obvious analogous meaning of C and L,

$$\frac{\partial}{\partial t}(\overline{\alpha}C + (1-\overline{\alpha})L) = D\Delta C + Q \tag{1.8}$$

where Q represents the power of volumetric sources/sinks and D is the oxygen diffusion coefficient assumed constant. Again an assumption as (1.4) transforms the l.h.s. of (1.8) in the derivative $\frac{\partial}{\partial t}M(C)$, where $M(C)$ is an increasing function of C.

The mathematical scheme is completed once conditions on the «outer» boundary and for $t = 0$ are given and once the situation on the boundary $r = R$ is better described.

Concerning the latter, a reasonable assumption is that c and C are proportional, through the solubility constant ν (Henry law):

$$C = \nu c, \quad at \quad r = R. \tag{1.9}$$

Alternatively, one could assume, as in [12] a Robin's law of linear relationship berween flux and jump of concentrations. On the other hand , now we are in position of giving the flux term in (1.7).

$$F = \frac{D}{\pi R^2}\int_0^{2\pi} \left.\frac{\partial C}{\partial \underline{e}_r}\right|_{r=R} R d\theta. \tag{1.10}$$

Having in mind the model problem discussed above, we can pass to the statement and the analysis of the problem we will study in Sections 2-5 and that will be homogenized in Section 6. According to the example of the Michaelis-Menten law we will assume:

- (H1) $\Phi(c)$ is a strictly monotone Lipschitz continuous function on $\mathbb{R}$ with subquadratic growth.
- (H2) $M(C)$ is a strictly monotone Lipschitz continuous function on $\mathbb{R}$ with subquadratic growth.

2. Statement of the problem

Let $\underline{x} = (x, y, z) \in \mathbb{R}^3$ and consider the cylinders

$$C_i \equiv \left\{\underline{x} : (x - x_i)^2 + (y - y_i)^2 < R_i, \quad 0 < z < B\right\}, \quad i = 1, 2, \ldots, n \tag{2.1}$$

In our model the set

$$\Omega_c = \bigcup_{i=1}^{n} C_i \tag{2.2}$$

will represent the space occupied by an array of parallel cylindrical capillaries. Assume that Ω_c is strictly contained in the box

$$\Omega \equiv \{\underline{x} \in \mathbb{R}^3 : \quad 0 < x < L, \quad 0 < y < L, \quad 0 < z < B\} , \tag{2.3}$$

and that

$$\Omega_T = \Omega \backslash \Omega_c \tag{2.4}$$

is occupied by the living tissue. According to the model discussed in Section 1, we assume that the oxygen concentration C in the tissue satisfies

$$\frac{\partial}{\partial t} M(C) - D \Delta C = Q, \quad \text{in} \quad \Omega_T \times (0 , T) , \tag{2.5}$$

and that the oxygen concentration of the blood in the i_th capillary satisfies

$$\frac{\partial}{\partial t} \Phi(c) + u \frac{\partial}{\partial z} \Phi(c) = \frac{D}{\pi R_i} \int_0^{2\pi} \frac{\partial C}{\partial \underline{e}_r} (R_i , \theta , z , t) d\theta \quad \text{in } \Omega_c \times (0 , T) \tag{2.6}$$

where u is the speed of the blood assumed to be a given positive number. On the boundary S_i between the i_th capillary and the tissue we have $C(R_i , \theta , z , t) = \nu c(z , t)$, where we wrote $C(R_i , \theta , z , t)$ to denote $C(x_i + R_i \cos\theta , y_i + R_i \sin\theta , z , t)$, $\theta \in \in (0 , 2\pi)$ and ν denote the (positive) solubility ratio. Upon rescaling ($\nu c \to c$), we can write

$$C(R_i , \theta , z , t) = c(z , t) , \quad \text{on} \quad S_i \times (0 , T) , \quad i = 1 , 2 , \dots , n. \tag{2.7}$$

Let $\Gamma_0 \equiv (\underline{x} \in \partial\Omega : z = 0)$ and $\Gamma_B \equiv (\underline{x} \in \partial\Omega : z = B)$ denote the «bottom» and «top» faces of Ω and set

$$\Gamma_{0C} = \Gamma_0 \cap \overline{\Omega}_C , \quad \Gamma_{BC} = \Gamma_B \cap \overline{\Omega}_C .$$

Let $C^0(\underline{x})$ be a function such that $C^0 \in H^1(\Omega) \cap L^\infty(\Omega)$, and that $C^0 = C^{0i}(z)$, for $\underline{x} \in C_i$.

We give the following boundary conditions

$$C = \text{tr}\, C^0 F(t) , \quad \underline{x} \in \Gamma_0 \backslash \Gamma_{0C} , \quad t \in (0 , T) , \tag{2.8}$$

$$c = \text{tr}\, C^0 F(t) , \quad \underline{x} \in \Gamma_{0C} , \quad t \in (0 , T) , \tag{2.9}$$

$$D \cdot \nabla C \cdot \underline{n} = 0 , \quad \underline{x} \in \partial\Omega \backslash (\Gamma_0 \cup \Gamma_{BC}) , \quad t \in (0 , T). \tag{2.10}$$

Finally, we assume that for $t = 0$ c and C coincide with C^0 in their respective domain of definition

$$C(\underline{x} , 0) = C^0(\underline{x}) , \quad \underline{x} \in \Omega_T , \tag{2.11}$$

$$c(\underline{x} , 0) = C^0(\underline{x}) , \quad \underline{x} \in \Omega_C . \tag{2.12}$$

We will give problem (2.5)-(2.12) a suitable variational formulation in Section 3. In Section 4 we will summarize the proof of existence of a weak solution; then we will derive in Section 5 basic estimates, independent on the number n of the capillary tubes. Finally, Section 6 will be devoted to the homogenisation of the problem.

3. Variational formulation

We denote by $g_i(z)$ $(i = 1, \dots, n)$ any set of unknown functions in $H^1(0, B)$, each defined on the boundary of the i-th capillary and not dependent on the angular variable θ on it. Let

(3.1) $$V = \left\{ \varphi \in H^1(\Omega) : \varphi = g_i(z) \quad on \quad \partial C_i \cap \Omega, \quad \varphi(x, y, 0) = 0 \right\}.$$

Then, $\forall \varphi \in V$, (2.6) implies

$$\int_{\partial\Omega_C \cap \Omega} D \frac{\partial C}{\partial \underline{e}_r} \varphi d\Sigma = \sum_{i=1}^{n} D \int_0^B \int_0^{2\pi} \frac{\partial C}{\partial \underline{e}_r}(R_i, \theta, z, t) \varphi(R_i, \theta, z) R_i d\theta dz =$$
$$= \sum_{i=1}^{n} \pi R_i^2 \int_0^B g_i(z) \left[\frac{\partial}{\partial t}\Phi(c) + u \frac{\partial}{\partial z}\Phi(c) \right] dz.$$

Using the notation $C|_i \equiv \dfrac{1}{2\pi}\displaystyle\int_0^{2\pi} C(R_i, \theta, z, t) d\theta$ and setting $\widehat{C}^0(\underline{x}, t) = C^0(\underline{x}) F(t)$, assuming $F(0) = 1$ we state the following

Problem (P). Find $C(\underline{x}, t)$, s.t.

(a) $C - \widehat{C}^0 \in L^2(0, T; V)$

(b) $M(C) \in L^\infty(0, T; L^1(\Omega))$

(c) $\Phi(C|_i) \in L^\infty(0, T; L^1(0, B))$

(d) $M_t(C) \in L^2(0, T; V')$

(e) $\Phi_t(C|_i) \in L^2(0, T; H^{-1}(0, B))$

(f) initial conditions (2.11), (2.12) are satisfied in the sense that

$$\forall \xi \in L^2(0, T; V) \cap W^{1,1}(0, T; L^\infty(\Omega)), \quad \xi(T) = 0$$

it is

(3.2) $$\int_0^T < M_t(C), \xi >_{V', V} dt + \int_0^T \int_{\Omega_T} \left[M(C) - M(C^0) \right] \xi_t dx dt = 0$$

(3.2′) $$\int_0^T < \Phi_t(C|_i), \xi|_i >_{H^{-1}(0,B), H^1(0,B)} dt +$$
$$+ \int_0^T \int_0^B \left[\Phi(C|_i) - \Phi(C^0|_i) \right] \frac{\partial}{\partial t} \xi|_i dz dt = 0 \quad i = 1, \dots, n.$$

(g) The following integral relationship is satisfied for any $\xi \in L^2(0, T; V)$

$$\int_0^T < M_t(C), \xi >_{V', V} dt + \sum_{i=1}^{n} \pi R_i^2 \int_0^T < \Phi_t(C|_i), \xi|_i >_{H^{-1}(0,B), H^1(0,B)} dt +$$
$$+ \sum_{i=1}^{n} \pi R_i^2 u \int_0^T \int_0^B \xi|_i \Phi_z(C|_i) dz dt + D \int_0^T \int_{\Omega_T} \nabla C \nabla \xi d\underline{x} dt = \int_0^T \int_{\Omega_T} Q \xi dz dt.$$

The variational formulation (a)-(g) is in the same line as in [1] with the modifications needed to incorporate condition (2.6). These modifications will be reflected in the proof of the existence theorem and will require the Lipschitz conditions (H1), (H2) on the non-linearities $M(C)$ and $\Phi(C)$.

Incidentally, we note that if $u < 0$ everything can be repeated provided that- as it is obvious- conditions (2.8),(2.9) are prescribed on $\Gamma_B \backslash \Gamma_{BC}$ and on Γ_{BC} respectively and condition (2.10) is imposed on $\partial\Omega \backslash (\Gamma_B \cup \Gamma_{0C})$. Hence definition of V is changed accordingly.

4. Existence

The following existence theorem holds true.

Theorem 1. *Let M and Φ satisfy assumptions* (H1) *and* (H2) *of Section* 1. *Let $C^0 \in$ $\in H^1(\Omega) \cap L^\infty(\Omega)$, $\frac{\partial C^0}{\partial z} \in L^\infty(\Omega_c)$, $C^0(\underline{x}) = C^{0i}(z)$ for $\underline{x} \in C_i$; finally let $F(t)$ in* (2.8), (2.9) *be such that*

$$\left| \frac{dF}{dt} \right|_{L^1(0\,,\,T)} \leq K, \tag{4.1}$$

$$F(0) = 1\,. \tag{4.2}$$

Then problem (2.5)-(2.12) *has a weak solution,* i.e. *problem* (P) *has a solution.*

Proof. The proof is rather technical and its arguments follow the strategy of [1]. Therefore, we confine ourselves to sketch the main steps of the proof, assuming in addition that the source/sink term Q is a smooth function of x and t and does not depend on C.

Actually, introducing this additional nonlinearity introduces just formal complications in the existence proof. On the other hand dependence of Q on C has crucial role in the estimate of the norm of the solution which is considered in detail in Section 5 below where we will assume $Q = Q(C, x, t)$.

Step 1. We choose a base $v_j \in V \cap L^\infty(\Omega)$ and we select $V_m = \operatorname{span}(v_1\,, \ldots\,, v_m)$ and define C_m^0 by projection. Then, we discretize time interval $(0\,, T)$ in N steps of width $h = \frac{T}{N}$ and define

$$F_h(t) = 1\,, \quad -h < t < 0\,, \tag{4.3}$$

$$F_h(t) = \frac{1}{h} \int_{(k-1)h}^{kh} F(\tau)\,d\tau\,, \quad t \in ((k-1)h\,, kh)\,, \quad k = 1\,, \ldots\,, N, \tag{4.4}$$

thus defining $\widehat{C}_{hm}(t\,, \underline{x}) = C_m^0(\underline{x}) F_h(t)$. At this point, we can look for a function

$$C_{hm}(t\,, \underline{x}) = \widehat{C}_{hm}^0(t\,, \underline{x}) + \sum_{j=1}^{m} \mu_j^{hm}(t) v_j(\underline{x}) \tag{4.5}$$

where $\mu_j^{hm} \in L^\infty(0\,,\,T)$ are to be found solving the system of equations obtained by writing (3.3) in each time step once the time derivatives have been replaced by backward difference quotients and $\xi \in V_m$.

This system can be written as a system $\Psi_{hm}(v_\mu) = 0$ of m nonlinear algebraic equations in $v_\mu = \sum_{j=1}^m \mu_j v_j$ for every value of t. We define

$$\beta(C) = M(C)C - \int_0^C M(s)ds\,, \tag{4.6}$$

$$\Xi(C) = \Phi(C)C - \int_0^C \Phi(s)ds\,, \tag{4.7}$$

Then, using (H1), (H2) and therefore the non-negativity of Legendre transforms of potentials of M and Φ, we conclude $\Psi_{hm}(v_\mu)\mu \to +\infty$ when $|\mu| \to +\infty$.

Hence μ_j^{hm} can be actually be found.

STEP 2. We prove the energy estimate

$$\begin{aligned}\sup_{t\in(0\,,\,T)}&\left\{\int_{\Omega_T}\beta(C_{hm})d\underline{x} + \sum_i \pi R_i^2\int_0^B \Xi(C_{hm}|_i)dz\right\} + \int_0^T\int_{\Omega_T}|\nabla C_{hm}|^2 d\underline{x}dt \le\\ &\le K\left[\sup_{(0\le\sigma\le\overline{C})}\{M(\sigma)+\Phi(\sigma)\}[\overline{C}+\overline{C}^3 + \|Q\|^2_{L^2(\Omega_T\times x(0\,,\,T))} + \|\widehat{C}^0_{hm}\|^2_{L^2(\Omega_T\times x(0\,,\,T))}]\right],\end{aligned} \tag{4.8}$$

with K depending on $\overline{C}$, where

$$\overline{C} = \|\widehat{C}^0_{hm}\|_{C([0\,,\,T];L^\infty((0\,,\,L)^2);W^{1\,,\,\infty}(0\,,\,B)))}. \tag{4.9}$$

To obtain (4.8), we use as test function in the discretized version of (3.3) $\xi = C_{hm} - \widehat{C}^0_{hm}$, we make use of the monotonicity of M and Φ and of the obvious inequality

$$|M(\sigma)| \le \delta\beta(\sigma) + \sup_{\sigma\in(0\,,\,\delta^{-1})}|M(\sigma)|\,, \quad \forall\delta > 0. \tag{4.10}$$

STEP 3. Take any $\tau \in (0\,,\,T)$ and k such that $\tau + kh \le T$. Define $\tau_j = \tau + jh$, $j = 1\,,\,\dots\,,\,k$.

From the discretized version of (3.3) one obtains

$$\begin{aligned}&\int_{\Omega_T}\{M(C_{hm}(\tau + kh\,,\,\underline{x})) - M(C_{hm}(\tau\,,\,\underline{x}))\}\xi d\underline{x} +\\ &\quad + \sum_{i=1}^n \pi R_i^2\int_0^B\{\Phi(C_{hm}(\tau + kh\,,\,z)|_i) - \Phi(C_{hm}(\tau\,,\,z)|_i)\}\xi|_i dz +\\ &\quad + h\sum_{i=1}^n \pi R_i^2\sum_{j=0}^{k-1}\int_0^B u\frac{\partial}{\partial z}\Phi(C_{hm}(\tau_{j+1}\,,\,z)|_i)\xi|_i dz +\\ &\qquad + Dh\sum_{j=0}^{k-1}\int_{\Omega_T}\nabla C_{hm}(\tau_{j+1}\,,\,\underline{x})\nabla\xi d\underline{x} = h\sum_{j=0}^{k-1}\int_\Omega Q\xi d\underline{x}.\end{aligned} \tag{4.11}$$

Now we choose the test functions in the following way

$$\xi(\tau, \underline{x}) = C_{hm}(\tau + kh, \underline{x}) - C_{hm}(\tau, \underline{x}) \equiv \omega_{hm}^{k}(\tau, \underline{x}) \tag{4.12}$$

and integrate with respect to τ.

$$\int_0^{T-kh} \int_{\Omega_T} h\partial_t^{-h} M\omega_{hm}^k d\underline{x} d\tau + \sum_{i=1}^{n} \pi R_i^2 \int_0^{T-kh} \int_0^B h\partial_t^{-h} \Phi|_i \omega_{hm}^k|_i dz d\tau = J_1 + J_2 + J_3, \tag{4.13}$$

where J_1 is the integral containing $u\dfrac{\partial \Phi}{\partial z}$ and J_2 and J_3, containing $\nabla C \nabla \omega$ and $Q\omega$ are readily estimated as

$$|J_2| + |J_3| \le Khk \tag{4.14}$$

for some constant K.

STEP 4. Estimating $|J_1|$ is the most delicate point of the proof, where the assumption u =constant is crucial.

By rather standard steps we obtain

$$|J_1| \le Khk \int_0^T \sum_{i=1}^{n} \pi R_i^2 \| c_{hm}(\tau, z)|_i \|^2_{H^{\frac{1}{2}}(0, B)} d\tau. \tag{4.15}$$

Next, one estimates $\|v\|_{H^{\frac{1}{2}}(0,B)}$ by $\|v\|_{H^1(\Omega_T)}$ using Fourier transform; passing through lenghty calculations the following estimate is obtained

$$|J_1| \le C \left(\sum_{i=1}^{n} \frac{R_i^{p+1}}{d_i^{p-1}} \right)^{2/p} \| C_{hm} \|^2_{L^2(0, T; H^1(\Omega_T))} \tag{4.16}$$

for any $p > 1$, where d_i is the distance from the i_th capillary to the nearest one.

In addition, we suppose that

$$g(p) = \left(\sum_{i=1}^{n} \frac{R_i^{p+1}}{d_i^{p-1}} \right)^{1/p}$$

will remain uniformly bounded (when we will let n increase in the homogenisation procedure) for some p and we note that for a periodic system of capillaries $g(p)$ is uniformly bounded with respect to n for any $p > 1$.

Finally, recalling (4.13) and (4.14) and using the estimate (4.8) of Step 2 above, we obtain

$$\begin{aligned} &\int_0^{T-kh} \int_{\Omega_T} h^2 \partial_t^{-kh} M(C_{hm}(\tau + kh, \underline{x})) \partial_t^{-kh} C_{hm}(\tau + kh, \underline{x}) d\underline{x} d\tau + \\ &+ \sum_{i=1}^{n} \pi h^2 R_i^2 \int_0^{T-kh} \int_0^B \partial_t^{-kh} \Phi(C_{hm}(\tau + kh, \underline{x})|_i \partial_t^{-kh} (C_{hm}(\tau + kh, \underline{x})|_i dz d\tau \le Kkh. \end{aligned} \tag{4.17}$$

STEP 5. Since C_{hm} is piecewise constant in time, we can replace kh by any instant $\eta \in$ $\in (0, T)$.Now, estimates (4.16), with $kh = \eta$ and (4.8) allow us to choose a subsequence

$\{C_{hm}\}$ with the following properties (see [1, 6] for more details):

(4.18) $\quad C_{hm} \longrightarrow C \quad$ strongly in $\quad L^2(0\,,\,T;L^2(\Omega_T))\,,$

(4.19) $\quad C_{hm}|_i \longrightarrow C|_i \quad$ strongly in $\quad L^2(0\,,\,T;L^2(0\,,\,B))\,, \quad i=1\,,2\,,\ldots\,,n$

(4.20) $\quad C_{hm} \rightharpoonup C \quad$ weakly in $\quad L^2(0\,,\,T;V).$

Convergences (4.18)-(4.20) allow to pass to the limit in (4.11) and thus to conclude the proof of Theorem 4.1. □

5. Additional estimates

First, we prove

Proposition 5.1. *Let Q be a smooth bounded function of C, $\underline{x}$ and t such that*

$$Q(C\,,\underline{x}\,,t) \geq 0 \quad \textit{for} \quad C \leq 0. \tag{5.1}$$

Moreover assume

$$C^0(\underline{x}) \geq 0\,, \quad F(t) \geq 0. \tag{5.2}$$

Then

$$C(\underline{x}\,,t) \geq 0 \quad \text{a.e.} \quad \textit{in} \quad \Omega_T \times (0\,,T). \tag{5.3}$$

Proof. We follow the idea of [6] and consider the problem discretized in time after passing to the limit for $m \to \infty$. We have a family of functions $\{C_h^k\}_{1\leq k\leq N}$ satisfying the following elliptic system

$$\begin{aligned}
&\sum_{i=1}^{n} \pi R_i^2 \int_0^B \Phi(C_h^k|_i)\xi|_i dz + \int_{\Omega_T} M(C_h^k)\xi d\underline{x} + \\
&\quad + h\sum_{i=1}^{n} \pi R_i^2 \int_0^B \xi|_i u \Phi_z(C_h^k|_i) dz + Dh\int_{\Omega_T} \nabla C_h^k \nabla \xi d\underline{x} = \\
&= h\int_{\Omega_t} Q(C_h^k\,,\underline{x}\,,t)\xi d\underline{x} + \int_{\Omega_T} M(C_h^{k-1})\xi d\underline{x} + \\
&\quad + \sum_{i=1}^{n} \pi R_i^2 \int_0^B \Phi(C_h^{k-1}|_i)\xi|_i dz, \quad \forall \xi \in V, \quad i=1\,,\ldots\,,n.
\end{aligned} \tag{5.4}$$

It is sufficient to prove that $C_h^{k-1} \geq 0$ a.e. implies $C_h^k \geq 0$ a.e. $\forall k$.

We use as test functions

$$(C_h^k)_- = -\min(C_h^k\,,0)\,, \quad (C_h^k)_- \in V \quad \textit{a.e.} \quad \text{in} \quad (0\,,T).$$

The r.h.s of (5.4) with this choice of ξ is non-negative because of our assumptions.

Moreover, writing C instead of C_h^k to save notation and setting $C_+ = \max(C, 0)$, so that $C = C_+ - C_-$, we have for the second term in the l.h.s. of (5.4)

$$\int_{\Omega_T} M(C)C_- d\underline{x} = \int_{\Omega_T} \{M(C) - M(C_+)\}(C_+ - C)d\underline{x} \leq 0. \tag{5.5}$$

For the first term, noting that for $C \in V$ it is $C_-|_i = (C|_i)_-$ so that we simply write $C_{i\_}$.

$$\Phi(C_i)(C_{i\_}) = \Phi(-C_{i\_})C_{i\_} \leq 0. \tag{5.6}$$

In the third term of the l.h.s. we find

$$\begin{aligned}\int_0^B \Phi'(C_i)\left(\frac{\partial}{\partial z}C_i\right)C_{i\_}dz &= -\int_0^B \Phi'(-C_{i\_})\left(\frac{\partial}{\partial z}C_{i\_}\right)C_{i\_}dz = \\ &= -u\left\{\Xi(-C_{i\_}(B,t) - \Xi(-C_{i\_}(0,t))\right\} \leq 0,\end{aligned} \tag{5.7}$$

because the first term is non-negative and the second is zero by our assumptions.

Summing up, we have that the last term on the l.h.s. is non-negative, *i.e.*

$$-Dh\int_{\Omega_T} |\nabla C_-|^2 dx \geq 0. \tag{5.8}$$

Thus yielding $(C_h^k)_- = 0$ a.e. in Ω_T and the conclusion of the proof. □

Next we have

PROPOSITION 5.2. *Let assumptions of Proposition 5.1 be satisfied. Assume in addition*

$$C^0(\underline{x}) \leq E, \tag{5.9}$$

$$Q(C, \underline{x}, t) \leq 0, \quad \textit{for} \quad C \geq E. \tag{5.10}$$

Then

$$C(\underline{x}, t) \leq E, \quad \text{a.e.} \quad \textit{in} \quad \Omega_T \times (0, T). \tag{5.11}$$

PROOF. It is analogous to the proof of Proposition 5.1, but now we choose the test function ξ in (5.4) as $(C_h^k - E)_+$. The conclusion is

$$(C_h^k - E)_+ = 0 \quad \textit{a.e.} \tag{5.12}$$

and thus the proof of Proposition 5.2. □

6. Homogenisation of a random network of parallel capillaries

In this section we consider the model with many capillaries obtained as a realization of randomly placed circular sections.

Following [7] we choose the appropriate setting to describe the random circular structure.

Let $(G, \mathcal{O}, \mu)$ be a probability space and let $\mathcal{T}$ be a dynamical system with 2-dimensional time given on $\mathcal{O}$. With this measurable dynamics we associate a

2-parameter group of strongly continuous unitary operators on $L^2(G) = L^2(G, \mathcal{O}, \mu)$ by $(U(x, y)f)(\omega) = f(\mathcal{T}(x, y)\omega)$, $\quad f \in L^2(G)$.

We suppose that the dynamical system $\{\mathcal{T}(x, y)\}$ is ergodic and we fix a measurable set $\mathcal{F} \in \mathcal{O}$, such that $\mu(\mathcal{F}) > 0$ and the porosity $\vartheta = \mu(G \setminus \mathcal{F}) > 0$. Then we consider a random stationary set $F \subset \mathbb{R}^2$, obtained from $\mathcal{F}$ by

$$F = F(\omega) = \{(x, y) \in \mathbb{R}^2, \quad \mathcal{T}(x, y)\omega \in \mathcal{F}\}. \tag{6.1}$$

The set $F = F(\omega)$ is said to be a *random circular structure* if, for almost all $\omega \in G$, F consists of closed circles having no interior points in common; the radii of the balls belong to a fixed interval $[R_1, R_2]$, $0 < R_1 < R_2 < +\infty$, R_1, R_2 being independent of ω.

We suppose F to be a random circular structure and introduce F_ε by $F_\varepsilon = \{(x, y) \in \in \mathbb{R}^2 : \varepsilon^{-1}(x, y) \in F\}$ (homothetic dilation by ε^{-1} times) and define the set of capillary tubes T_ε by

$$T_\varepsilon = \bigcup_i \{\text{all circles from } F_\varepsilon \text{ strictly contained in } (0, L)^2\}. \tag{6.2}$$

The tissue part is

$$\Omega^\varepsilon_{\text{tis}} = \left((0, L)^2 \setminus \overline{T_\varepsilon}\right) \times (0, B). \tag{6.3}$$

As already noted for similar problems in [7, 11], the main difficulty in homogenizing PDEs in such geometries and with our particular boundary conditions is with extending the fluxes to $(0, L)^2 \times (0, B)$, $\forall t$.

The extension problem was considered in [7, 11] for 3D structures. The approach from [7] leads, after lengthy calculations, to the following precise results

LEMMA 6.1 (Extension lemma). *Let $Z = \{x \in \mathbb{R}^2 : |x_i| < 1, \ i = 1, 2\}$, $B_h = \{x \in \in \mathbb{R}^2 : |x| < h < 1\}$ and let $p \in L^2(Z \setminus B_h)^2$ satisfy the conditions*

$$-\text{div}\, p = f \quad \text{in} \quad Z \setminus B_h \tag{6.4}$$

$$\int_{\partial B_h} p \cdot \vec{n}\, d\sigma = \int_{B_h} f\, dxdy \tag{6.5}$$

where $f \in L^2(Z)$ and $\vec{n}$ is the outward unit normal at ∂B_h.

Then there exists a vector field $\tilde{p} \in L^\alpha(Z)^2$ such that $\forall \alpha < 2$

$$\tilde{p} = p \quad \text{in} \quad Z \setminus B_h; \qquad -\text{div}\, \tilde{p} = f \quad \text{in} \quad Z \tag{6.6}$$

and

$$\|\tilde{p}\|^2_{L^\alpha(B_h)2} \le \frac{c_0(\alpha)}{1 - h}\left(\|p\|_{L^2(Z \setminus B_h)2} + \|f\|^2_{L^2(Z)}\right). \tag{6.7}$$

Now it is clear that the extension of solenoidal vector fields requires some additional conditions to be imposed on the arrangement of balls: For each circular component of the set F we introduce the parameter $\nu = \min\{\frac{d}{\varrho}, \frac{1}{2}\}$, where d is the distance from the component to the nearest one and ϱ its radius. For (a.e) $\omega \in G$ we set

$$\limsup_{r\to+\infty} r^{-2}\sum_i \nu_i^{-k} = \ell_k <+\infty \tag{6.8}$$

where the summation is performed over all circles from $F = F(\omega)$, which intersect the circle $\sqrt{x^2+y^2} \le r$ and $k > 1$.

Using Lemma 6.1 and after lengthy calculations we obtain

LEMMA 6.2. *Let* (6.8) *hold true for some* $k > 1$ *and let* $\psi \in L^2(0\,,L)^2$. *Let* $p_\varepsilon \in L^2((0\,,L)^2 \setminus T_\varepsilon)^2$ *satisfy for every* $\xi \in C^\infty([0\,,L]^2)$, $\nabla\xi = 0$ *on* T_ε,

$$\int_{(0\,,L)^2\setminus T_\varepsilon} p_\varepsilon \nabla\xi\; dxdy = \int_{(0\,,L)^2\setminus T_\varepsilon} \psi\xi\; dxdy\,, \tag{6.9}$$

$$\langle \rho_\varepsilon \cdot \overrightarrow{n}\,, 1\rangle_{-\frac12\,,\frac12} = \int_{C_i^\varepsilon} \psi\; dxdy\,, \qquad \textit{for every ball } C_i \subset T_i. \tag{6.10}$$

Then there is an extension $\widetilde{p}_\varepsilon \in L^2(0\,,L)^2$ *such that*

$$\int_{(0\,,L)^2} \widetilde{p}_\varepsilon \nabla\xi\; dxdy = \int_{(0\,,L)^2} \psi\xi\; dxdy\,, \quad \forall\xi \in C^\infty([0\,,L]^2) \tag{6.11}$$

$$\widetilde{p}_\varepsilon = p_\varepsilon \quad \textit{on} \quad T_\varepsilon \quad \textit{and, for} \quad \alpha = \frac{2k}{k+1}\,, \tag{6.12}$$

$$\|\widetilde{p}_\varepsilon\|_{L^\alpha((0\,,L)^2)^2} \le \overline{c_0}\left\{\|p_\varepsilon\|_{L^2((0\,,L)^2\setminus T_\varepsilon)^2} + \|\psi\|_{L^2((0\,,L)^2)^2}\right\}. \tag{6.13}$$

COROLLARY 1. *Let* (6.8) *hold true. Then there exists an extension operator* $E_\varepsilon^\alpha \in \mathcal{L}(L^2((0\,,L)^2 \setminus T_\varepsilon)^2\,, L^\alpha((0\,,L)^2)^2)$, $E_\varepsilon^\alpha p_\varepsilon = \widetilde{p}_\varepsilon$ *for almost every* ω.

Next, we define the stochastic auxiliary problem.

Let X be the closure in $L^2(G)^2$ of all potential vector fields with zero expectation, attaining the zero value on $\mathcal{F}$. Then for a given $\lambda \in \mathbb{R}^2$, $\eta_\lambda^s \in X$ is a unique solution for

$$\inf_{h\in X;\mathbb{E}\{h\}=0} \int_{G\setminus\mathcal{F}} |\lambda + h|^2\; d\mu\,, \tag{6.14}$$

if η^s is a random matrix with columns $\eta_{e_j}^\varepsilon$, then we set

$$A_s = \int_{G\setminus\mathcal{F}} (I+\eta^s)\; d\mu\,. \tag{6.15}$$

It is easy to see that A_s is symmetric and positive definite matrix. Furthermore, the Birkhoff ergodic theorem implies

$$\begin{cases} E_\varepsilon^\alpha\; \eta_\lambda^s\left(\mathcal{T}\left(\dfrac{x}{\varepsilon}\,,\dfrac{y}{\varepsilon}\right)\omega\right) \rightharpoonup A_s\lambda & \text{weakly in } \; L^\alpha_{\text{loc}}(\mathbb{R}^2)\,, \\ & \text{(a.e.) on } \; G \\ \chi_{(0\,,L)^2\setminus T_\varepsilon} \rightharpoonup \vartheta = \mu(G\setminus\mathcal{F}) & \text{weakly in } \; L^\beta_{\text{loc}}(\mathbb{R}^2)\,, \\ & \forall\beta\in[1\,,+\infty)\,, \quad \text{(a.e.) on } \; G. \end{cases} \tag{6.16}$$

Before passing to the limit in the solution C^ε, we extend it to $(0\,,\,L)^2\times(0\,,\,B)\times(0\,,\,T)=$ $=Q_T$.

For a random circular structure F, let $\widetilde{P}z$ be the extension of z inside the i-th circle by its boundary value. Let

$$V^\varepsilon=\{\varphi\in H^1(\Omega^\varepsilon_{\text{tis}})|\ \varphi \ \text{ is cte(z) on } \ \partial T_\varepsilon\subset(0\,,\,L)^2 \ \text{ and } \ \varphi|_{z=0}=0\} \tag{6.17}$$

and

$$\widetilde{V}^\varepsilon=\{\varphi\in H^1((0\,,\,L)^2\times(0\,,\,B))|\ \nabla_{x,y}\varphi=0 \ \text{ on } \ T_\varepsilon\times(0\,,\,B) \ \text{ and } \ \varphi|_{z=0}=0\} \tag{6.18}$$

Theorem 2. *Let us suppose* (6.8) *with* $k>1$ *and let* $\mathcal{M}$ *and* Φ *be strictly monotone continuously differentiable functions. Let* C^ε *be a weak solution for the problem* (2.5)-(2.12), *let* $Q=Q(C,x,t)$ *and let the hypothesis of Theorem* 4.1 *and Propositions* 5.1-5.2 *hold true. Then* $\widetilde{C}^\varepsilon=\widetilde{P}_\varepsilon C^\varepsilon$ *satisfies the following a priori estimates*

$$\|\widetilde{C}^\varepsilon\|_{L^\infty(Q_T)}\le E;\quad \widetilde{C}^\varepsilon\ge 0 \ \textit{on} \ Q_T;\quad \widetilde{C}^\varepsilon\in\widetilde{P}_\varepsilon C^{0,\varepsilon}+L^2(0\,,\,T;\widetilde{V}^\varepsilon) \tag{6.19}$$

$$\sup_{0\le t\le T}\int_0^B\left\{\int_{(0\,,\,L)^2}\mathcal{B}(\widetilde{C}^\varepsilon(t))\,dxdy+\int_{(0\,,\,L)^2\setminus T_\varepsilon}\Xi(\widetilde{C}^\varepsilon(t))\,dxdy\right\}dz+ \tag{6.20}$$

$$+D\int_0^T\int_{(0\,,\,L)^2\times(0\,,\,B)}|\nabla\widetilde{C}|^2\,dxdydzdt\le\overline{C}$$

$$\int_0^{T-\eta}\int_{(0\,,\,L)^2\times(0\,,\,B)}|M(\widetilde{C}^\varepsilon(\tau+\eta))-M(\widetilde{C}^\varepsilon(\tau))|\,dxdydzd\tau\le\overline{C}\eta^\beta\,, \tag{6.21}$$

for some $\beta>0$. *Furthermore,*

$$\widetilde{C}^\varepsilon\rightarrow C\in L^2(0\,,\,T;H^1(\Omega))\cap L^\infty(Q_T)\,,\quad C\ge 0 \tag{6.22}$$

weakly in $L^2(0\,,\,T;H^1(\Omega))$ *and weak** *in* $L^\infty(Q_T)$ *and*

$$\widetilde{C}^\varepsilon\rightarrow C \ \textit{ strongly in } \ L^1(Q_T) \ \textit{ and (a.e.) on } \ Q_T \ \textit{ as } \ \varepsilon\rightarrow 0. \tag{6.23}$$

Proof. We note that (6.8) implies the bound for J_2 in the 4^{th} step of Theorem 4.1, with $p=k+1$. Other calculations are straightforward. □

Remark 6.1 The result of Theorem 6.1 is valid for almost every $\omega\in G$ and C depends on the realization ω. We denote $D\left(\dfrac{\partial C^\varepsilon}{\partial x}\,,\,\dfrac{\partial C^\varepsilon}{\partial y}\right)$ by Υ_ε.

Let $\widetilde{\text{div}}$ and $\widetilde{\nabla}$ be the operators div and ∇, but only with respect to x and y.

Let $\varphi \in H^1(0\,,B)\,,\varphi(0)=0$ and $\xi \in H^1(0\,,T)\,,\xi(T)=0$. Then we write our differential equation in the form

$$(6.24)\qquad -\widetilde{\operatorname{div}}\{D\widetilde{\nabla}\int_0^T\int_0^B C^\varepsilon\varphi(z)\xi(t)\ dzdt\} = \varphi^\varepsilon(x\,,y)$$

(a.e.) in $(0\,,L)^2\setminus T_\varepsilon$, where

$$(6.25)\qquad \varphi^\varepsilon(x\,,y) = \int_0^T\int_0^B Q(C^\varepsilon\,,x\,,t)\varphi\xi\ dzdt + \int_0^T\int_0^B M(C^\varepsilon)\varphi\partial_t\xi\ dzdt + \\ + \int_0^B M(C^{0\,,\varepsilon})\varphi(z)\xi(0)\ dz - D\int_0^T\int_0^B \frac{\partial C^\varepsilon}{\partial z}\frac{\partial\varphi}{\partial z}\xi\ dzdt$$

$$(6.26)\qquad \hat{\Upsilon}_\varepsilon = D\widetilde{\nabla}\int_0^T\int_0^B C^\varepsilon\varphi(z)\xi(t)\ dzdt = \int_0^T\int_0^B \Upsilon_\varepsilon\varphi(z)\xi(t)\ dzdt$$

$$(6.27)\qquad \widetilde{\varphi}^\varepsilon(x\,,y) = \begin{cases} \varphi^\varepsilon(x\,,y) \text{ if } (x\,,y)\in(0\,,L)^2\setminus T_\varepsilon \\ \int_0^B \Phi\left(-\int_{\partial T_i^\varepsilon} C^{0\,,\varepsilon}\right)\varphi\xi(0)\ dz + \\ \qquad + \int_0^T\int_0^B \Phi\left(-\int_{\partial T_i^\varepsilon} C^\varepsilon\right)(\varphi\partial_t\xi + u\xi\partial_z\varphi)\ dzdt \\ -\int_0^T \Psi(F(t)) - \int_{\partial T_i^\varepsilon} C^{0\,,\varepsilon}|_{z=B})\varphi(B)\xi\ dt \quad \text{in} \quad T_\varepsilon \end{cases}$$

Proposition 6.1. *Under the assumptions of Theorem 6.1, we have for* $\alpha = (2k)/(k+1) > 1$

$$(6.28)\qquad -\widetilde{\operatorname{div}}E_\varepsilon^\alpha\hat{\Upsilon}_\varepsilon = \widetilde{\varphi}^\varepsilon \quad \text{in} \quad (0\,,L)^2$$

(a.e.) *and*

$$(6.29)\qquad \|E_\varepsilon^\alpha\hat{\Upsilon}\|_{L^\alpha((0\,,L)^2)} \le \overline{C}.$$

Furthermore, there is $\Upsilon \in L^\alpha(Q_T)^2$ *such that*

$$(6.30)\qquad E_\varepsilon^\alpha\Upsilon_\varepsilon \to \Upsilon \quad \text{weakly in} \quad L^\alpha(Q_T)^2.$$

Υ *satisfies the following PDE*

$$(6.31)\qquad -\widetilde{\operatorname{div}}\Upsilon - \frac{\partial^2 C}{\partial z^2} + \frac{\partial}{\partial t}\{\vartheta M(C) + (1-\vartheta)\Phi(C)\} + (1-\vartheta)u\frac{\partial}{\partial z}\Phi(C) = \\ = \vartheta Q(C, x, t) \quad \text{in} \quad \mathcal{D}'(Q_T)$$

Proof. For proving (6.28)-(6.29) we use Lemma 6.2 and (6.27). (6.31) is a consequence of Theorem 6.1. □

THEOREM 3. *We suppose the assumptions of Theorem* 6.1. *Then for almost every realization* ω, *there is a subsequence of* $\widetilde{C}^{\varepsilon}$, *denoted by the same symbol, converging weakly in* $L^2(0\,, T; H^1(\Omega))$, *weak* in* $L^{\infty}(Q_T)$ *and strongly in* $L^1(Q_T)$ *to a limit* $C \in L^2(0\,,\, T; H^1(\Omega)) \cap L^{\infty}(Q_T)$, $C \geq 0$, *satisfying the variational equation*

$$-\int_{Q_T} \{\vartheta M(C) + (1-\vartheta)\Phi(C)\}\partial_t \xi \; dVdt -$$
$$-\int_{(0\,,L)^2\times(0\,,B)} \left\{\int_{G\setminus\mathcal{F}} M(C^0(\mathcal{T}(x,y)\omega,z))\,d\mu + \int_{\mathcal{F}} \Phi(C^0(\mathcal{T}(x,y)\omega,z))\,d\mu\right\} \xi|_{t=0} dV +$$
$$(6.32)\qquad + \int_{Q_T} D\left[\begin{array}{c|c} A_s & 0 \\ \hline 0 & 1 \end{array}\right]\nabla C \nabla \xi \; dVdt + (1-\varphi)u \int_{Q_T} \frac{\partial}{\partial z}\Phi(C)\xi \; dVdt =$$
$$= \int_{Q_T} \varphi Q(C, \underline{x}\,, t)\; dVdt,$$
$$\forall\, \xi \in L^2(0\,,\, T; H^1((0\,,\, L)^2 \times (0\,,\, B))) \cap W^{1\,,\,1}(0\,,\, T; L^{\infty}((0\,,\, L)^2 \times (0\,,\, B)))\,,$$
$$\xi(T) = 0 \quad \textit{and} \quad \xi|_{z=0} = 0$$

$$(6.33)\qquad C|_{z=0} = \mathbb{E}\{C^0\}|_{z=0}$$

$$(6.34)\qquad \partial_t\{\vartheta M(C) + (1-\vartheta)\Phi(C)\} \in L^2(0\,,\, T; H^{-1}((0\,,\, L)^2 \times (0\,,\, B)))\,,$$

where $C^{0\,,\,\varepsilon} = C^0(\mathcal{T}(\frac{x}{\varepsilon}\,, \frac{y}{\varepsilon})\omega\,,\, z)$ *is a given Lipschitz function in z and continuous in x and y.*

PROOF. We know after [7, 11] that $\Upsilon = DA_s\widetilde{\nabla} C$ The rest follows. □

THEOREM 4. *For almost every realization* ω, *every bounded weak solution for* (6.32)-(6.34) *is an entropy solution. Furthermore, for every realization* ω, C *is unique.*

PROOF. We refer to the theory of entropy solutions for degenerate parabolic equation from [3]. □

COROLLARY 2. *Under assumptions of Theorem* 6.1, *the whole sequence* $\{\widetilde{C}^{\varepsilon}\}$ *converge to the unique limit C which is deterministic.*

PROOF. For every realization ω, $C(\omega)$ is unique. Since the limit problem does not depend on realizations, C is deterministic. □

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Pervenuta il 21 dicembre 2001,
in forma definitiva il 18 febbraio 2002.

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