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ON THE MICHAELIS-MENTEN ENZYME MECHANISM

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Abstract. The aim of this paper is to study the asymptotic behavior of the solution of a nonlinear problem arising in the modeling of enzymatic reactions through porous media. The domain is considered to be a fixed bounded open subset $\Omega\subset\mathbf{R}^n$, in which identical and periodically distributed perforations of size ε are made. The asymptotic behavior of the solution of such a problem is governed by a new elliptic boundary-value problem with an extra zero-order term that captures the effect of the enzymatic reactions.

Key words: homogenization, enzymes, Michaelis-Menten model.

1. INTRODUCTION

The aim of this paper is to study the homogenization of some nonlinear reactive flows through periodically perforated media. Such problems are very natural in the study of enzymatic reactions through porous media and, more precisely, in the study of the so-called Michaelis-Menten model (for a nice presentation of the chemical aspects involved in such a model and for some historical backgrounds, see [8]-[9] and the references therein).

Enzymes are proteins that speed up the rate of a chemical reaction without being used up. Enzymes are usually specific to particular substrates. The substrates in the reaction bind to active sites on the surface of the enzyme. The enzyme-substrate complex then undergoes a reaction to form a product along with the original enzyme. The rate of chemical reactions increases with the substrate concentration. However, enzymes become saturated when the substrate concentration is high. Additionally, the reaction rate depends on the properties of the enzyme and the enzyme concentration. We can describe the reaction rate with a simple equation to understand how enzymes affect chemical reactions. Michaelis-Menten equation remains the most generally applicable equation for describing enzymatic reactions.

Let Ω be an open bounded set in $\mathbf{R}^n$ and let us perforate it by holes. As a result, we obtain an open set Ω^ε, which will be referred to as being the *perforated domain*; ε represents a small parameter related to the characteristic size of the perforations. We shall deal with the case in which the perforations are identical and periodically distributed and their size is of the order of ε.

The nonlinear problem studied in this paper concerns the stationary flow of a fluid confined in Ω^ε, of concentration u^ε, reacting inside Ω^ε and on the boundary of the perforations:

$$\begin{cases} -D_f \Delta u^\varepsilon + \beta(u^\varepsilon) = f \quad \text{in } \Omega^\varepsilon, \\ -D_f \dfrac{\partial u^\varepsilon}{\partial \nu} = a\varepsilon\, g(u^\varepsilon) \quad \text{on } S^\varepsilon, \\ u^\varepsilon = 0 \quad \text{on } \partial\Omega, \end{cases} \tag{1}$$

where ν is the exterior unit normal to Ω^ε, $a > 0$, $f \in L^2(\Omega)$, S^ε is the boundary of the perforations and $\partial\Omega$ is the external boundary of Ω, D_f is a constant diffusion coefficient, characterizing the homogeneous and isotropic fluid.

We shall consider that the function β in (1) is a continuously differentiable function, monotonously non-decreasing and such that $\beta(0) = 0$. Also, in the semilinear boundary condition on the surface of the perforations in (1) the function g is assumed to be given and we shall address here the case in which *g* is a single-valued maximal monotone graph with $g(0) = 0$, i.e. the case in which g is the subdifferential of a convex lower semicontinuous function *G*.

This general situation is well illustrated by the following important practical example, arising in the diffusion of enzymes and, more precisely, in the so-called *Michaelis-Menten model*:

$$g(v) = \begin{cases} \dfrac{\delta v}{v+\gamma}, & v \geq 0 \\ 0, & v < 0 \end{cases}, \quad \delta, \gamma > 0.$$

The existence and uniqueness of a weak solution of (1) can be settled by using the theory of semilinear monotone problems (see [1] and [7]). As a result, we know that there exists a unique weak solution $u^\varepsilon \in V^\varepsilon \bigcap H^2(\Omega^\varepsilon)$, where

$$V^\varepsilon = \left\{ v \in H^1(\Omega^\varepsilon) \mid v = 0 \text{ on } \partial\Omega \right\}.$$

If with Ω^ε we associate the nonempty, convex subset of V^ε

$$K^\varepsilon = \left\{ v \in V^\varepsilon \mid G(v)\big|_{S^\varepsilon} \in L^1(S^\varepsilon) \right\},$$

then u^ε is also the unique solution of the variational problem

$$
\begin{cases}
\text{Find } u^{\varepsilon} \in K^{\varepsilon} \text{ such that} \\
D_f \int_{\Omega^{\varepsilon}} Du^{\varepsilon} D(v^{\varepsilon} - u^{\varepsilon})\, dx + \int_{\Omega^{\varepsilon}} \beta(u^{\varepsilon})(v^{\varepsilon} - u^{\varepsilon}) dx - \\
- \int_{\Omega^{\varepsilon}} f(v^{\varepsilon} - u^{\varepsilon}) dx + a \left\langle \mu^{\varepsilon}, G(v^{\varepsilon}) - G(u^{\varepsilon}) \right\rangle \geq 0, \quad \forall v^{\varepsilon} \in K^{\varepsilon},
\end{cases} \tag{2}
$$

where μ^{ε} is the linear form on $W_0^{1,1}(\Omega)$ defined by

$$\left\langle \mu^{\varepsilon}, \varphi \right\rangle = \varepsilon \int_{S^{\varepsilon}} \varphi \, d\sigma, \quad \forall \varphi \in W_0^{1,1}(\Omega).$$

We shall prove that the solution u^{ε}, extended to the whole of Ω, converges weakly in $H_0^1(\Omega)$ to the unique solution of the following variational inequality:

$$
\begin{cases}
u \in H_0^1(\Omega) \\
\int_{\Omega} QDuD\,(v - u)\, dx + \int_{\Omega} \beta(u)(v - u) dx - \\
- \int_{\Omega} f(v - u) dx + a \dfrac{|\partial T|}{|Y^*|} \int_{\Omega} (G(v) - G(u)) dx \geq 0, \quad \forall v \in H_0^1(\Omega
\end{cases} \tag{3}
$$

Here, $Q = ((q_{ij}))$ is the homogenized matrix, whose entries are defined by:

$$q_{ij} = D_f \, (\delta_{ij} + \frac{1}{|Y^*|} \int_{Y^*} \frac{\partial \chi_j}{\partial y_i} dy), \tag{4}$$

in terms of the functions χ_j, solutions of the so-called cell problems

$$
\begin{cases}
-\Delta \chi_i = 0 \quad \text{in} \quad Y^*, \\
\dfrac{\partial(\chi_i + y_i)}{\partial \nu} = 0 \quad \text{on} \quad \partial T, \\
\chi_i \quad Y - \text{periodic.}
\end{cases} \tag{5}
$$

The approach we used is the so-called energy method introduced by L. Tartar [10] for studying homogenization problems. It consists of constructing suitable test functions that are used in our variational problems.

The structure of our paper is as follows: first, let us mention that we shall just focus on the case $n \geq 3$, which will be treated explicitly. The case $n = 2$ is much simpler and we shall omit to treat it here. In Chapter 2 we introduce some useful notations and assumptions and we give the main result. In Chapter 3 we give the proof of the main convergence result of this paper.

2. SETTING OF THE PROBLEM AND THE MAIN RESULT

2.1. Notation and assumptions

Let Ω be a bounded connected open set in $\mathbf{R}^n$, with boundary $\partial\Omega$ of class C^2. Let $Y = [0, l_1[\times[0, l_2[\times\ldots\times[0, l_n[$ be the representative cell in $\mathbf{R}^n$ and T an open subset of Y with boundary ∂T of class C^2, such that $\overline{T} \subset Y$. We shall refer to T as being *the elementary hole*. We shall denote by $T^{\varepsilon,k}$ the translated image of εT by εkl, $k \in \mathbf{Z}^n$. Also, we shall denote by T^{ε} the set of all the holes contained in Ω and by $\Omega^{\varepsilon} = \Omega \setminus \overline{T^{\varepsilon}}$. Hence, Ω^{ε} is a periodically perforated domain with holes of the same size as the period.

We shall use the following notations:

$$Y^* = Y \setminus \overline{T}, \quad S^{\varepsilon} = \partial T^{\varepsilon}, \quad \theta = \frac{|Y^*|}{|Y|}.$$

Also, we shall denote by χ^{ε} the characteristic function of the domain Ω^{ε}.

2.2. Setting of the problem

As already mentioned, we are interested in studying the behavior of the solution, in such a perforated domain, of the following problem:

$$\begin{cases} -D_f \Delta u^{\varepsilon} + \beta(u^{\varepsilon}) = f \quad \text{in } \Omega^{\varepsilon}, \\ -D_f \dfrac{\partial u^{\varepsilon}}{\partial \nu} = a\varepsilon g(u^{\varepsilon}) \quad \text{on } S^{\varepsilon}, \\ u^{\varepsilon} = 0 \quad \text{on } \partial\Omega, \end{cases} \tag{6}$$

Here, ν is the exterior unit normal to Ω^{ε}, $a > 0$, S^{ε} is the boundary of the holes and $\partial\Omega$ is the external boundary of Ω, D_f is a constant diffusion coefficient, characterizing the homogeneous and isotropic fluid.

We shall consider that the function β in (6) is a continuously differentiable function, monotonously non-decreasing and such that $\beta(0) = 0$.

Also, in the semilinear boundary condition on the surface of the perforations in

(6), the function g is assumed to be given and we shall address here the case in which g is a single-valued maximal monotone graph in $\mathbf{R}\times\mathbf{R}$ with $g(0)=0$, i.e. the case in which g is the subdifferential of a proper convex lower semicontinuous function G. Moreover, we shall suppose that the domain $D(g)=\mathbf{R}$, g is continuous and there exist a positive constant C and an exponent q, with $0\le q<n/(n-2)$, such that

$$\left|\frac{\partial\beta}{\partial v}\right|\le C(1+|v|^q),$$
$$|g(v)|\le C(1+|v|^q). \tag{7}$$

Let $G(v)=\int_0^v g(s)ds.$

This general situation is well illustrated by the above mentioned important practical example (Michaelis-Menten model).

The existence and uniqueness of a weak solution of (1) can be settled by using the classical theory of semilinear monotone problems (see [1] and [7]). As a result, we know that there exists a unique weak solution $u^\varepsilon \in V^\varepsilon \bigcap H^2(\Omega^\varepsilon),$ where

$$V^\varepsilon=\left\{v\in H^1(\Omega^\varepsilon)\;\middle|\; v=0 \text{ on } \partial\Omega\right\}.$$

If with Ω^ε we associate the nonempty, convex subset of V^ε

$$K^\varepsilon=\left\{v\in V^\varepsilon \;\middle|\; G(v)\big|_{S^\varepsilon}\in L^1(S^\varepsilon)\right\},$$

then u^ε is also the unique solution of the variational problem

$$\begin{cases} \text{Find } u^\varepsilon\in K^\varepsilon \text{ such that} \\ D_f\int_{\Omega^\varepsilon} Du^\varepsilon D(v^\varepsilon-u^\varepsilon)\,dx+\int_{\Omega^\varepsilon}\beta(u^\varepsilon)(v^\varepsilon-u^\varepsilon)dx- \\ -\int_{\Omega^\varepsilon} f(v^\varepsilon-u^\varepsilon)dx+a\left\langle\mu^\varepsilon, G(v^\varepsilon)-G(u^\varepsilon)\right\rangle\ge 0,\ \ \forall v^\varepsilon\in K^\varepsilon, \end{cases} \tag{8}$$

where μ^ε is the linear form on $W_0^{1,1}(\Omega)$ defined by

$$\left\langle\mu^\varepsilon,\varphi\right\rangle=\varepsilon\int_{S^\varepsilon}\varphi\, d\sigma,\quad \forall\varphi\in W_0^{1,1}(\Omega). \tag{9}$$

In order to describe the asymptotic behavior of the solution of problem (8), let us recall the following well-known extension results (see [2]-[3]):

Lemma 2.1. There exists a linear continuous extension operator $P^{\varepsilon} \in L(L^2(\Omega^{\varepsilon}); L^2(\Omega)) \cap L(V^{\varepsilon}; H_0^1(\Omega))$ and a positive constant C, independent of ε, such that, for any $v \in V^{\varepsilon}$,

$$\left\| P^{\varepsilon} v \right\|_{L^2(\Omega)} \leq C \left\| v \right\|_{L^2(\Omega^{\varepsilon})}$$

and

$$\left\| \nabla P^{\varepsilon} v \right\|_{L^2(\Omega)} \leq C \left\| \nabla v \right\|_{L^2(\Omega^{\varepsilon})}.$$

As a consequence, the following Poincaré's inequality holds true in V^{ε}:

Lemma 2.2. There exists a positive constant C, independent of ε, such that

$$\left\| v \right\|_{L^2(\Omega^{\varepsilon})} \leq C \left\| \nabla v \right\|_{L^2(\Omega^{\varepsilon})},$$

for any $v \in V^{\varepsilon}$.

2.3. The main result

The main result of this paper is the following one:

Theorem 2.3. Let u^{ε} be the unique solution of the problem (8). Then, there exists an extension $P^{\varepsilon} u^{\varepsilon}$ of u^{ε} into all Ω such that $P^{\varepsilon} u^{\varepsilon} \xrightarrow{w} u$ weakly in $H_0^1(\Omega)$ and u is the unique solution of the following problem:

$$\begin{cases} u \in H_0^1(\Omega) \\ \int_{\Omega} QDuD(v-u)\,dx + \int_{\Omega} \beta(u)(v-u)dx - \\ - \int_{\Omega} f(v-u)dx + a\dfrac{|\partial T|}{|Y^*|}\int_{\Omega}(G(v)-G(u))dx \geq 0, \quad \forall v \in H_0^1(\Omega). \end{cases} \tag{10}$$

Here, $Q = ((q_{ij}))$ is the homogenized matrix, whose entries are defined by (4)-(5).

3. PROOF OF THE MAIN RESULT

Proof of Theorem 2.3. Let u^ε be the solution of the variational problem (8) and let $P^\varepsilon u^\varepsilon$ be the extension given by Lemma 2.1. Taking $\varphi = u^\varepsilon$ as a test function in (8), it is not difficult to see that $P^\varepsilon u^\varepsilon$ is bounded in $H_0^1(\Omega)$. So, by extracting a subsequence, one can assume that there exists $u \in H_0^1(\Omega)$ such that

$$P^\varepsilon u^\varepsilon \xrightarrow{w} u \quad \text{weakly in } H_0^1(\Omega). \tag{11}$$

It remains to identify the limit equation satisfied by u. Let $\varphi \in C_0^\infty(\Omega)$. By classical regularity results, $\chi_i \in L^\infty$. Using the boundedness of φ and χ_i, there exists $M \geq 0$ such that

$$\left\| \frac{\partial \varphi}{\partial x_i} \right\|_{L^\infty} \|\chi_i\|_{L^\infty} < M.$$

Let

$$v^\varepsilon = \varphi + \sum_i \varepsilon \frac{\partial \varphi}{\partial x_i}(x) \chi_i(\frac{x}{\varepsilon}). \tag{12}$$

Then, $v^\varepsilon \in K^\varepsilon$. Moreover, $v^\varepsilon \to \varphi$ strongly in $L^2(\Omega)$. Let us compute Dv^ε :

$$Dv^\varepsilon = \sum_i \frac{\partial \varphi}{\partial x_i}(x)(e_i + D\chi_i(\frac{x}{\varepsilon})) + \varepsilon \sum_i D\frac{\partial \varphi}{\partial x_i}(x)\chi_i(\frac{x}{\varepsilon}).$$

Using v^ε as a test function in (8), we have

$$D_f \int_\Omega DP^\varepsilon u^\varepsilon (Dv^\varepsilon \tilde{)} dx + \int_{\Omega^\varepsilon} \beta(u^\varepsilon)(v^\varepsilon - u^\varepsilon) dx \geq .$$

$$\geq D_f \int_{\Omega^\varepsilon} Du^\varepsilon Du^\varepsilon dx + \int_{\Omega^\varepsilon} f(v^\varepsilon - u^\varepsilon) dx - a\langle \mu^\varepsilon, G(v^\varepsilon) - G(u^\varepsilon)\rangle \tag{13}$$

Denote

$$\rho Q e_j = \frac{1}{|Y^*|} D_f \int_{Y^*} (D\chi_j + e_j) dy. \tag{14}$$

Neglecting the term $\varepsilon \sum_i D\frac{\partial \varphi}{\partial x_i}(x)\chi_i(\frac{x}{\varepsilon})$, which tends strongly to zero, we can pass to the limit in the left-hand side of (13). Hence

$$D_f \int_\Omega DP^\varepsilon u^\varepsilon (Dv^\varepsilon \tilde{)} dx \to \int_\Omega \rho Q D u D\varphi \, dx. \tag{15}$$

For the second term in the left-hand side of (13), let us notice that, exactly like in [6], one can easily prove that for any $\varphi \in C_0^\infty(\Omega)$ and for any $z^\varepsilon \xrightarrow{w} z$ weakly in $H_0^1(\Omega)$, we get

$$\varphi\beta(z^\varepsilon) \to \varphi\beta(z) \quad \text{strongly in } L^{\bar{q}}(\Omega),$$

where

$$\bar{q} = \frac{2n}{q(n-2)+n}.$$

Therefore, we have

$$\int_{\Omega^\varepsilon} \beta(u^\varepsilon)(v^\varepsilon - u^\varepsilon)dx \to \int_\Omega \beta(u)\rho(\varphi - u)dx. \tag{16}$$

It is not difficult to pass to the limit in the second term of the right-hand side of (13). We get

$$\int_{\Omega^\varepsilon} f(v^\varepsilon - u^\varepsilon)dx = \int_\Omega f\chi_{\Omega^\varepsilon}(v^\varepsilon - P^\varepsilon u^\varepsilon)dx \to \int_\Omega f\rho(\varphi - u)dx.. \tag{17}$$

In order to pass to the limit in the last term of (13), following [3] and [6], let us introduce the linear form μ^ε on $W_0^{1,1}(\Omega)$ defined by

$$\langle \mu^\varepsilon, \varphi \rangle = \varepsilon \int_{S^\varepsilon} \varphi \, d\sigma, \quad \forall \varphi \in W_0^{1,1}(\Omega).$$

From [3], we know that

$$\mu^\varepsilon \to \mu \quad \text{strongly in } W_0^{-1,\infty}(\Omega), \tag{18}$$

where

$$\langle \mu \ , \varphi \rangle = \frac{|\partial T|}{|Y|} \int_\Omega \varphi \, dx.$$

On the other hand, if F is a continuously differentiable function, monotonously non-decreasing, with $F(0) = 0$ and such that there exist a positive constant and an exponent q, with $0 \le q < n/(n-2)$ such that

$$\left| \frac{\partial F}{\partial v} \right| \le C(1 + |v|^q),$$

it is not difficult to prove (see [6]) that for any $\varphi \in C_0^\infty(\Omega)$ and for any $z^\varepsilon \xrightarrow{w} z$ weakly in $H_0^1(\Omega)$, one has

$$\varphi F(z^\varepsilon) \xrightarrow{w} \varphi F(z) \quad \text{weakly in } W_0^{1,\bar{q}}(\Omega), \tag{19}$$

where

$$\bar{q} = \frac{2n}{q(n-2)+n}.$$

Now, for the last term in the right-hand side of (13), assuming (7) for the monotone graph g and using (19) written for G and for $z^\varepsilon = P^\varepsilon u^\varepsilon$, we have

$$G(P^\varepsilon u^\varepsilon) \to G(u) \quad \text{weakly in } W_0^{1,\bar{q}}(\Omega).$$

Combining this with the convergence (18), we obtain

$$\left\langle \mu^\varepsilon, G(P^\varepsilon u^\varepsilon)\right\rangle \to \frac{|\partial T|}{|Y|}\int_\Omega G(u)dx.$$

Hence, we get

$$\left\langle \mu^\varepsilon, G(v^\varepsilon) - G(P^\varepsilon u^\varepsilon)\right\rangle \to \frac{|\partial T|}{|Y|}\int_\Omega (G(\varphi) - G(u))dx. \tag{20}$$

It remains to pass to the limit only in the last term of (13). For doing this, we can write the subdifferential inequality

$$D_f \int_{\Omega^\varepsilon} Du^\varepsilon Du^\varepsilon dx \geq D_f \int_{\Omega^\varepsilon} Dw^\varepsilon Dw^\varepsilon dx + 2D_f \int_{\Omega^\varepsilon} Dw^\varepsilon (Du^\varepsilon - Dw \tag{21}$$

for any $w^\varepsilon \in H_0^1(\Omega)$. Reasoning as before and choosing

$$w^\varepsilon = \bar{\varphi} + \sum_i \varepsilon \frac{\partial \bar{\varphi}}{\partial x_i}(x)\chi_i(\frac{x}{\varepsilon}),$$

where $\bar{\varphi}$ and $\bar{M}$ enjoy similar properties as the corresponding φ and M, the right-hand side of the inequality (21) passes to the limit and one has

$$\liminf_{\varepsilon\to 0} D_f \int_{\Omega^\varepsilon} Du^\varepsilon Du^\varepsilon dx \geq \int_\Omega \rho\, QD\bar{\varphi}D\bar{\varphi}dx + 2\int_\Omega \rho\, QD\bar{\varphi}(Du - D\bar{\varphi})dx,$$

for any $\bar{\varphi} \in C_0^\infty(\Omega)$ and, by density, for any $\bar{\varphi} \in H_0^1(\Omega)$. Hence, for $u \in H_0^1(\Omega)$, we conclude

$$\liminf_{\varepsilon\to 0}\int_{\Omega^\varepsilon} A^\varepsilon Du^\varepsilon Du^\varepsilon dx \geq \int_\Omega \rho\, QDuDudx. \tag{22}$$

Putting together (15)-(22), we get

$$\int_\Omega \rho\, QDuD\varphi\, dx + \int_\Omega \beta(u)\rho(\varphi - u) \geq$$

$$\geq \int_\Omega \rho\, QDuDudx + \int_\Omega f\rho(\varphi - u)dx - a\frac{|\partial T|}{|Y|}\int_\Omega (G(\varphi) - G(u))dx,$$

for any $\varphi \in C_0^\infty(\Omega)$ and hence, by density, for any $v \in H_0^1(\Omega)$. So, finally, we obtain

$$\int_\Omega QDuD(v-u)dx + \int_\Omega \beta(u)(v-u)dx \geq \int_\Omega f(v-u)dx -$$

$$- a\frac{|\partial T|}{|Y^*|}\int_\Omega (G(v) - G(u))dx,$$

which is just the limit problem (10). Since $u \in H_0^1(\Omega)$ (i.e. $u = 0$ on $\partial\Omega$) and u is uniquely determined, the whole sequence $P^\varepsilon u^\varepsilon$ converges and Theorem 2.3. is proved.

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