Romanian Reports in Physics, Vol. 61, No. 2, P. 269–279, 2009

MULTISCALE ANALYSIS IN DYNAMICAL HEAT TRANSFER PROBLEMS IN BIOLOGICAL TISSUES*

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(Received July 2, 2008)

Abstract. The asymptotic behavior of the solution of a nonlinear problem describing the bio-heat transfer in biological tissues is analyzed. Our model, based on Pennes' bio-heat transfer equation, with a temperature-dependent blood perfusion term, allows us to predict the effective temperature of such a complicated structure.

Key words: homogenization, bio-heat equation, temperature-dependent blood perfusion.

1. INTRODUCTION AND SETTING OF THE PROBLEM

The purpose of this paper is to rigorously justify, using the homogenization theory, a nonlinear heat transfer model in living tissues. The model, based on Pennes' bio-heat equation, with a temperature-dependent blood perfusion term, can be applied to predict the temperature in such a complicated structure.

The heat transport in living tissues is a complex process involving multiple mechanisms, such as heat conduction in tissues, heat transfer due to perfusion of the arterial-venous blood through the pores of the tissue (blood convection), metabolic heat generation and external interactions, such as electromagnetic radiation emitted from cell phones, etc. Bio-heat transfer models have significant applications in many clinical and environmental sciences. In particular, the heat transfer mechanism in biological tissues is important for therapeutic practices, such as cancer hyperthermia, burn injury, brain hypothermia resuscitation, disease diagnostics, cryosurgery, etc.

During the last two decades, the mathematical modeling of temperature distribution in such tissues have attracted the attention of many researchers and a number of significant steps towards developing a bioheat transfer theory have been made.

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* Paper presented at the Annual Scientific Conference, June 6, 2008, Faculty of Physics, Bucharest University, Romania.

It is a very difficult task to establish an appropriate physical model for the heat transport in the human body. In 1948, based on experimental observation, H. H. Pennes (see [18]) proposed a simple linear mathematical model for describing the thermal interaction between human tissues and perfused blood, taking also into account the effects of the metabolism. Later on, alternative models for describing the heat exchange between tissues and blood have been developed (see [5], [12], [20] and the references therein). The general form of Pennes original equation is the following one:

$$\rho c = \frac{\partial u}{\partial t} - K\Delta u + Wc_b\left(u - u_b\right) = Q_e + Q_m,$$

where ρ is the density, c and c_b are specific heat of tissue and blood, K is the thermal conductivity, u_b is the blood temperature, W is the mass flow rate of blood per unit volume of tissue, Q_e is the power deposition term and Q_m is the metabolic heat generation term. Here, we need to know the arterial blood temperature u_b. Pennes compressed all of the perfusion information into the term $Wc_b(u - u_b)$. He checked the validity of this approximation by comparing the temperatures predicted by his equation with the experimentally measured temperatures in the human forearm. In his approach, the blood perfusion term W was adjusted until the predicted temperatures agreed well with the measured temperatures.

Most of the papers dealing with the problem of modeling the temperature in biological tissues assume a constant rate blood perfusion within each type of tissue. However, several experiments and numerical simulations have shown that the physiological responses (blood perfusion and metabolism) in living tissues are temperature dependent (see [15]). Therefore, by considering variable metabolic heat generation and variable blood perfusion in Pennes' equation, we get a more accurate description of the heat transfer process in living tissues.

To obtain the temperature distribution given by such a complicated heat transfer model we need to find the solution of a time-dependent partial differential equation in a complex geometry, involving a special nonlinearity due to the perfusion term and different material properties of the tissues. The temperature is highly nonuniformly distributed in space and time. Of course, some approximation is clearly needed in the bioheat transfer calculations. In such a situation, an asymptotic analysis becomes necessary.

The homogenization method provides a general framework for obtaining the global behavior of such a complicated structure and for getting its macroscale properties, eliminating the dificulties related to the explicit determination of a solution of the problem at the microscale and offering a less detailed description, but one which is applicable to much more complex systems.

Let Ω be an open bounded set in $\mathbb{R}^n\left(n \geq 2\right)$. For the model we intent to analyze, i.e. the problem of bio-heat transfer in microvascular tissues, we can consider that Ω is an ε-periodic structure, consisting of two parts: a solid tissue part

Ω^ε of temperature u^ε and small regions of blood $\Omega/\bar{\Omega}^\varepsilon$ of a certain temperature. ε represents a small parameter related to the characteristic size of the blood regions.

The nonlinear problem studied in this paper concerns the nonstationary heat transfer in the solid tissue part, in contact with the blood regions. We shall assume that we have some external thermal sources f inside Ω^ε and some nonlinear sink term describing heat loss (cell-destruction energy, generated, possible, by special chemical reactions), given by a nonlinear function β. Also, we shall suppose that this complicated microstructure is dynamically evolving and the blood perfusion is temperature dependent and we shall take this into account by imposing a nonlinear dynamic boundary condition on the boundaries of the blood zones.

If we denote by (0, T) the time interval of interest, we shall analyze the asymptotic behaviour, as $\varepsilon \to 0$, of the solution of the following problem:

$$\rho c = \frac{\partial u^\varepsilon}{\partial t} - K\Delta u^\varepsilon + \beta\left(u^\varepsilon\right) = f\left(t,x\right), \quad \text{in} \quad \Omega^\varepsilon \times \left(0,T\right), \tag{1.1}$$

$$K\frac{\partial u^\varepsilon}{\partial v} + \alpha\varepsilon\frac{\partial u^\varepsilon}{\partial t} = \varepsilon c_b W\left(u^\varepsilon\right)\left(u_b^\varepsilon - u^\varepsilon\right), \quad \text{on} \quad S^\varepsilon \times \left(0,T\right), \tag{1.2}$$

$$u^\varepsilon\left(0,x\right) = u^0\left(x\right), \quad \text{in} \quad \Omega^\varepsilon \tag{1.3}$$

$$u^\varepsilon = 0, \quad \text{on} \quad \partial\Omega \times \left(0,T\right). \tag{1.4}$$

Here, v is the exterior unit normal to Ω^ε, $f \in L^2\left(0,T;L^2\left(\Omega\right)\right), u^0 \in H_0^1\left(\Omega\right)$, $c > 0, K > 0, \alpha > 0, c_b > 0, \rho > 0, u_b^\varepsilon \in H^1\left(\Omega\right)$ and S^ε is the boundary of the blood regions. We shall assume that the nonlinear functions β and W are given (see Section 2). For important examples of such functions, see [16].

The existence and uniqueness of a weak solution of problem (1.1)-(1.4) can be settled by using the theory of nonlinear monotone problems (see Section 2). We shall be interested in getting the asymptotic behavior, when $\varepsilon \to 0$, of the solution of problem (1.1)-(1.4). Using Tartar's method of oscillating test functions, coupled with monotonicity methods and results from the theory of semilinear problems, we can prove that the solution of problem (1.1)-(1.4), properly extended to the whole of Ω, converges to the unique solution of a new nonlinear problem, defined all over the domain Ω, given by a new operator and containing extra terms, capturing the effect of the blood perfusion and of the dynamic part of the condition imposed on the boundary of the blood regions (see Section 2).

The results of this paper constitute a generalization of some of the results obtained in [12], by considering nonstationary processes, dynamical conditions on the boundaries of the blood regions and a nonlinear sink term acting inside the solid tissue, modeling cell-destruction energy, which can be of huge importance,

for instance, in destroying malignant cells by hyperthermia (see [20]). Also, we generalize the results in [24], by considering temperature-dependent blood perfusion processes.

From a mathematical point of view, problems similar to this one have been considered by D. Cioranescu and P. Donato [6], D. Cioranescu, P. Donato and H.I. Ene [8], C. Conca and P. Donato [11], C. Conca, J.I. Díaz and C. Timofte [10], H. Ene and D. Polisevski [14], C. Timofte [21], [22], [23], [24], A. Bourgeat and L. Pankratov [3], L. Pankratov, A. Piatnitskii and V. Rybalko [17].

The plan of the paper is as follows: in the second section we introduce some useful notations and assumptions and we give the main convergence result of this paper. For obtaining it, we need some preliminary results, which are given in Section 3. Also, this last section is devoted to the proof of the convergence result.

2. ASSUMPTIONS AND THE MAIN RESULT

Let Ω be a bounded connected open subset of $\mathbb{R}^n \left(n \geq 2\right)$, with $\partial\Omega$ of class C^2 and let $[0, T]$ be the time interval of interest. Let $Y = [0, l_1[\times\ldots[0, l_n[$ be the representative cell in $\mathbb{R}^n$ and F an open subset of Y with boundary ∂F of class C^2, such that $\overline{F} \subset Y$.

We shall denote by $F\left(\varepsilon, \mathbf{k}\right)$ the translated image of εF by the vector $\varepsilon\mathbf{kl}$, $\mathbf{k} \in \mathbb{Z}^n$, $\mathbf{k}1 = \left(k_1 l_1, ..., k_n l_n\right)$.

$$F\left(\varepsilon, \mathbf{k}\right) = \varepsilon\left(\mathbf{k}\mathrm{l} + F\right).$$

Also, we shall denote by F^ε the set of all the blood regions contained in Ω. So

$$F^\varepsilon = \bigcup_{\mathbf{k}\in\mathbb{Z}^n} \left\{F\left(\varepsilon, \mathbf{k}\right) \middle| \overline{F}\left(\varepsilon, \mathbf{k}\right) \subset \Omega\right\}.$$

Let $\Omega^\varepsilon = \Omega \setminus \overline{F}^\varepsilon$. Hence, Ω^ε is a periodic structure with blood regions of the same size as the period.

We shall use the following notations:

$$Y^* = Y \setminus \overline{F}, \tag{2.1}$$

$$\theta = \frac{\left|Y^*\right|}{\left|Y\right|}. \tag{2.2}$$

Also, we shall denote by χ^{ε} the characteristic function of the domain Ω^{ε} and throughout the paper, by C we shall denote a generic fixed strictly positive constant, whose value can change from line to line.

As already mentioned, we are interested in studying the asymptotic behavior, as $\varepsilon \to 0$, of the solution of the parabolic problem (1.1)-(1.4).

We shall consider that the function β in (1.1) is continuously differentiable, monotonously non-decreasing and such that $\beta(0) = 0$. Moreover, we shall assume that there exist $C \geq 0$ and an exponent q such that

$$\left|\beta(v)\right| \leq C\left(1+\left|v\right|^{q}\right), \tag{2.3}$$

with $0 \leq q < n/(n-2)$ if $n \geq 3$ and $0 \leq q < +\infty$ if $n = 2$.

For the blood temperature u_b^{ε} we shall assume that $u_b^{\varepsilon} \in H^1(\Omega)$ and $\left\|u_b^{\varepsilon}\right\|_{H^1(\Omega)} \leq C$. Moreover, if we denote by $g(v) = W(v)(v - v_b)$, where v_b is a given constant, we assume that g is continuously differentiable, monotonously non-decreasing and satisfies suitable growth conditions (see (2.3)). Indeed, for some ranges of temperatures which are of interest for therapeutical practices (see [16]) and some special type of tissues, like muscle, for instance, we may assume that the term modeling the blood perfusion contribution is, from a mathematical point of view, given by such a nonlinear function g.

Remark 1. The results of this paper will be obtained for the case $n \geq 3$. All of them are still valid, under our assumptions, in the case in which $n = 2$. Of course, for this case, $n/(n-2)$ has to be replaced by $+\infty$.

Also, let us notice that due to the compactness injection theorems in Sobolev spaces, it would be enough, with the same reasoning as in the paper, to assume that β satisfies, for $n \geq 3$, the growth condition (2.3) for some $0 \leq q < (n+2)/(n-2)$ For $n = 2$, $(n+2)/(n-2)$ have to be replaced by $+\infty$.

The existence and uniqueness of a weak solution of (1.1)-(1.4) can be settled by using the classical theory of semilinear monotone problems (see [1, 4, 3, 21 24]). As a result, we know that there exists a unique weak solution

$$u^{\varepsilon} \in C\left([0,T]; H^1_{\partial\Omega}\left(\Omega^{\varepsilon}\right)\right) \bigcap L^2\left(0,T; Y_1\left(\Omega^{\varepsilon}\right)\right),$$

with

$$\frac{\partial u^{\varepsilon}}{\partial t} \in L^2\left(0,T; L^2\left(\Omega^{\varepsilon}\right)\right)$$

and

$$\frac{\partial\gamma\left(u^{\varepsilon}\right)}{\partial t}\in L^{2}\left(0,T;L^{2}\left(S^{\varepsilon}\right)\right).$$

Here, $H^{1}_{\partial\Omega}\left(\Omega^{\varepsilon}\right)$ is the space of elements of $H^{1}\left(\Omega^{\varepsilon}\right)$ which vanish (in the sense of traces) on $\partial\Omega$, $Y_{1}\left(\Omega^{\varepsilon}\right)=\left\{v\in H^{1}_{\partial\Omega}\left(\Omega^{\varepsilon}\right)\middle|-\Delta v\in L^{2}\left(\Omega^{\varepsilon}\right),\quad R\frac{\partial v}{\partial n}\in L^{2}_{\partial\Omega}\left(\partial\Omega^{\varepsilon}\right)\right.$ and $\gamma: H^{1}\left(\Omega^{\varepsilon}\right)\to L^{2}\left(S^{\varepsilon}\right)$ is the trace operator with respect to S^{ε}, which is continuous. Moreover, for a function φ defined on $\partial\Omega^{\varepsilon}$, $R\varphi$ denotes its restriction to S^{ε}.

The main convergence result of this paper is given by the following theorem:

Theorem 1. *One can construct an extension* $P^{\varepsilon}u^{\varepsilon}$ *of the solution* u^{ε} *of the problem* (1.1)-(1.4) *such that* $P^{\varepsilon}u^{\varepsilon}$, u *weakly in* $L^{2}\left(0,T;H^{1}_{0}\left(\Omega\right)\right)$, *where u is the unique solution of the following nonlinear problem*:

$$\begin{cases}\rho c\left(1+\delta\right)\dfrac{\partial u}{\partial t}-\displaystyle\sum_{i,j=1}^{n}q_{ij}\,\frac{\partial^{2}u}{\partial x_{i}\partial x_{j}}+\beta\left(u\right)+\\ +c_{b}\,\dfrac{\left|\partial F\right|}{\left|Y^{*}\right|}W\left(u\right)\left(u-u_{b}\right)=f,\ x\in\Omega,\quad t\in\left(0,T\right),\\ u=0,\quad x\in\partial\Omega,\quad t\in\left(0,T\right),\\ u\left(0,x\right)=u_{0}\left(x\right),\quad x\in\Omega.\end{cases}\tag{2.4}$$

Here,

$$\delta=\frac{\alpha}{\rho c}\frac{\left|\partial F\right|}{\left|Y^{*}\right|}$$

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

$$q_{ij}=K\left(\delta_{ij}+\frac{1}{\left|Y^{*}\right|}\int_{Y^{*}}\frac{\partial\chi_{j}}{\partial y_{i}}\mathrm{d}y\right)\tag{2.5}$$

in terms of the functions χ_{i}, $i=1,...,n$, solutions of the cell problems

$$\begin{cases} -\Delta\chi_i = 0 \quad \text{in} \quad Y^*, \\ \dfrac{\partial(\chi_i + y_i)}{\partial\nu} = 0 \quad \text{on} \quad \partial F, \\ \chi_i \quad Y-\text{periodic}. \end{cases} \tag{2.6}$$

Thus, in the limit, when $\varepsilon \to 0$, we get a constant coefficient heat equation, with a Dirichlet boundary condition and with extra-terms, coming from the well-balanced contribution of the blood perfusion term and of the dynamic part of the condition imposed on the boundary of the blood regions.

Remark 2. There exists a unique solution of the macromodel problem (2.4).

3. PROOF OF THE MAIN RESULT

As already mentioned, there exists a unique solution for the nonlinear problem (1.1)-(1.4),

$$u^\varepsilon \in C\left([0,T]; H^1_{\partial\Omega}\left(\Omega^\varepsilon\right)\right) \bigcap L^2\left(0,T; L^2\left(\Omega^\varepsilon\right)\right),$$

with

$$\frac{\partial u^\varepsilon}{\partial t} \in L^2\left(0,T; L^2\left(\Omega^\varepsilon\right)\right)$$

and

$$\frac{\partial \gamma\left(u^\varepsilon\right)}{\partial t} \in L^2\left(0,T; L^2\left(S^\varepsilon\right)\right)$$

For getting the effective behavior of our solution u^ε, we have to pass to the limit in the variational formulation of problem (1.1)-(1.4). To this end, let us introduce, for any $h \in L^{s'}(\partial F)$, $1 \le s' \le \infty$, the linear form μ_h^ε on $W_0^{1,s}(\Omega)$ defined by

$$\left\langle \mu_h^\varepsilon, \varphi \right\rangle = \varepsilon \int_{S^\varepsilon} h\left(\frac{x}{\varepsilon}\right)\varphi \, d\sigma \quad \forall \varphi \in W_o^{1,s}(\Omega),$$

with $1/s + 1/s' = 1$. It is proven in [6] that

$$\mu_h^\varepsilon \to \mu_h \quad \text{strongly in} \quad \left(W_0^{1,s}(\Omega)\right)', \tag{3.1}$$

where

$$\left\langle \mu_h, \varphi \right\rangle = \mu_h \int_{\Omega} \varphi \mathrm{d}x,$$

with

$$\mu_h = \frac{1}{|Y|} \int_{\partial F} h(y) \mathrm{d}\sigma.$$

If $h \in L^{\infty}(\partial F)$ or even if h is constant, we have (see [8])

$$\mu_h^{\varepsilon} \to \mu_h \quad \text{strongly in} \quad W^{-1,\infty}(\Omega).$$

We denote by μ^{ε} the above introduced measure in the case in which $h = 1$. Also, for obtaining the limit behavior of our homogenization problem, let us recall another result from [10].

Let H be a continuously differentiable function, monotonously non-decreasing. We shall suppose that there exist a positive constant C and an exponent q, with $0 \le q < n/(n-2)$, such that $|H| \le C\left(1 + |v|^q\right)$. If we denote by

$$\overline{q} = \frac{2n}{q(n-2)+n},$$

one can prove (see [10]) that for any z^{ε} , z weakly in $H_0^1(\Omega)$, we get

$$H\left(z^{\varepsilon}\right) \text{ , } H(z) \quad \text{weakly in} \quad W_0^{1,\overline{q}}(\Omega). \tag{3.3}$$

Let us consider the variational formulation of problem (1.1)-(1.4):

$$\begin{aligned} &\rho c \int_0^T \int_{\Omega^{\varepsilon}} \dot{u}^{\varepsilon} \varphi \, \mathrm{d}x\mathrm{d}t + K \int_0^T \int_{\Omega^{\varepsilon}} \nabla u^{\varepsilon} \cdot \nabla \varphi \, \mathrm{d}x\mathrm{d}t + \\ &+ \int_0^T \int_{\Omega^{\varepsilon}} \beta \varphi \, \mathrm{d}x\mathrm{d}t + c_b \varepsilon \int_0^T \int_{S^{\varepsilon}} W\left(u^{\varepsilon}\right)\left(u^{\varepsilon} - u_b^{\varepsilon}\right) \varphi \, \mathrm{d}x\mathrm{d}t + \\ &+ \alpha \varepsilon \int_0^T \int_{S^{\varepsilon}} \dot{u}^{\varepsilon} \varphi \, \mathrm{d}x\mathrm{d}t = \int_0^T \int_{\Omega^{\varepsilon}} f \varphi \, \mathrm{d}x\mathrm{d}t, \end{aligned} \tag{3.4}$$

for any $\varphi \in C_0^{\infty}\left([0,T] \times \Omega^{\varepsilon}\right)$. Here, we have denoted by the partial derivative with respect to the time.

As already mentioned, by classical existence and uniqueness results, we know that there exists a unique weak solution of (3.4). Taking it as a test function in the variational formulation of our problem and using our assumptions on the

data and Cauchy-Schwartz, Poincaré's and Young's inequalities, we can obtain suitable energy estimates, independent of ε, for our solution (see [2, 3, 10, 19, 21]).

In order to prove our main result, we need to extend the above solution to the whole of Ω. Using classical extension results (see [9]) and denoting by $P^\varepsilon u^\varepsilon$ such an extension of u^ε, one can see that $P^\varepsilon u^\varepsilon$ is bounded in $L^2\left(0,T;H_0^1(\Omega)\right)$ and $\dfrac{\partial P^\varepsilon u^\varepsilon}{\partial t}$ is bounded in $L^2\left(0,T;L^2(\Omega)\right)$ (see, for details, [10, 21 24]). So, by passing to a subsequence, we have

$$P^\varepsilon u^\varepsilon \text{ , } u$$

weakly in $L^2\left(0,T;H_0^1(\Omega)\right)$ and strongly in $L^2\left(0,T;L^2(\Omega)\right)$ and

$$\frac{\partial P^\varepsilon u^\varepsilon}{\partial t} \text{ , } \frac{\partial u}{\partial t}$$

weakly in $L^2\left(0,T;L^2(\Omega)\right)$.

It is well-known by now how to pass to the limit, with $\varepsilon \to 0$, in the linear terms of (3.4) defined on Ω^ε (see, for instance [10] and [21]). Also, recall that θ is the weak-* limit in $L^\infty(\Omega)$ of χ^ε. Thus, we get:

$$\int_0^T \int_{\Omega^\varepsilon} \dot{u}^\varepsilon \varphi \, dx dt \to \int_0^T \int_\Omega \dot{u} \theta \varphi \, dx dt, \tag{3.5}$$

$$K \int_0^T \int_{\Omega^\varepsilon} \nabla u^\varepsilon \cdot \nabla \varphi \, dx dt \to + \int_0^T \int_\Omega \theta Q \nabla u \cdot \nabla \varphi \, dx dt, \tag{3.6}$$

$$\int_0^T \int_{\Omega^\varepsilon} f \varphi \, dx dt \to \int_0^T \int_\Omega \theta f \varphi \, dx dt. \tag{3.7}$$

Let us see now how we can pass to the limit in the nonlinear terms in (3.4). For the third term in the left-hand side of (3.4), let us notice that, exactly like in [10] (see (3.3)), one can prove that for any z^ε , z weakly in $H_0^1(\Omega)$, we see that $\beta\left(z^\varepsilon\right) \to \beta(z)$ strongly in $L^{\bar{q}}(\Omega)$, where $\bar{q} = \dfrac{2n}{q(n-2)+n}$. Therefore, we have

$$\int_0^T \int_{\Omega^\varepsilon} \beta\left(u^\varepsilon\right) \varphi \, dx dt \to \int_0^T \int_\Omega \beta(u) \theta \varphi \, dx dt. \tag{3.8}$$

For the other terms in (3.4), using the convergence (3.2) written for $h = 1$, and the fact that

$$u_b^\varepsilon \ , \ u_b ,$$

weakly in $H^1(\Omega)$, we obtain that

$$\varepsilon \int_{S^\varepsilon} W\left(u^\varepsilon\right)\left(u^\varepsilon - u_b^\varepsilon\right)\varphi \, \mathrm{d}x \to \frac{|\partial F|}{|Y|}\int_\Omega W\left(u\right)\left(u - u_b\right)\varphi \, \mathrm{d}x ,$$

and

$$\varepsilon \int_{S^\varepsilon} \dot{u}^\varepsilon \varphi \, \mathrm{d}x \to \frac{|\partial F|}{|Y|}\int_\Omega \dot{u}\varphi \, \mathrm{d}x.$$

Hence, integrating in time and using Lebesgue's convergence theorem, it is not difficult to see that

$$c_b \varepsilon \int_0^T \int_{S^\varepsilon} W\left(u^\varepsilon\right)\left(u_b^\varepsilon - u^\varepsilon\right)\varphi \, \mathrm{d}x\mathrm{d}t \to c_b \frac{|\partial F|}{|Y|}\int_0^T \int_\Omega W\left(u\right)\left(u_b - u\right)\varphi \, \mathrm{d}x\mathrm{d}t , \quad (3.9)$$

and

$$\alpha\varepsilon \int_0^T \int_{S^\varepsilon} \dot{u}^\varepsilon \varphi \, \mathrm{d}x\mathrm{d}t \to \alpha \frac{|\partial F|}{|Y|}\int_0^T \int_\Omega \dot{u}\varphi \, \mathrm{d}x\mathrm{d}t. \quad (3.10)$$

Putting together (3.5)-(3.10), we can pass to the limit in all the terms in (3.4) and we obtain exactly the variational formulation of the limit problem (2.4). As u is uniquely determined, the whole sequence $P^\varepsilon u^\varepsilon$ converges to u and this completes the proof of Theorem 1.

Acknowledgments. This work was supported by the CNCSIS Grant Ideas 992, under contract 31/2007.

REFERENCES

1. V. Barbu, *Boundary value problems for partial differential equations*, Editura Academiei Române, Bucharest, 1993.
2. I. Bejenaru, J. I. Díaz and I. I. Vrabie, *An abstract approximate controllability result and applications to elliptic and parabolic systems with dynamic boundary conditions*, Electronic Journal of Differential Equation, **48**, 1–19 (2001).
3. A. Bourgeat and L. Pankratov, *Homogenization of semilinear parabolic equations in domains with spherical traps*, Appl. Anal., **64**, 303–317 (1997).
4. H. Brézis, *Analyse Fonctionnelle. Theorie et Applications*, Masson, 1983.
5. C. K. Charney, *Mathematical models of bioheat transfer*, Adv. Heat Trans., **22**, 19–155 (1992).

6. D. Cioranescu and P. Donato, *Homogénéisation du problµeme de Neumann non homogµene dans des ouverts perforès*, Asymptotic Anal., **1**, 115–138 (1988).
7. D. Cioranescu and P. Donato, *An Introduction to Homogenization*, Oxford Lecture Series in Mathematics and its Applications, **17**, The Clarendon Press, Oxford University Press, New York, 1999.
8. D. Cioranescu, P. Donato and H. Ene, *Homogenization of the Stokes problem with non homogeneous slip boundary conditions*, Mathematical Methods in Applied Sciences, **19**, 857–881 (1996).
9. D. Cioranescu and J. Saint Jean Paulin, *Homogenization in open sets with holes*, J. Math. Anal. Appl., **71**, 590–607 (1979).
10. C. Conca, J.I. Díaz and C. Timofte, *Effective Chemical Processes in Porous Media*, Math. Models Methods Appl. Sci. (M3AS), **13**, *10*, 1437–1462 (2003).
11. C. Conca and P. Donato, Non homogeneous *Neumann problems in domains with small holes*, RAIRO Modél. Math. Anal., **22**, 561–607 (1988).
12. P. Deuflhard and R. Hochmuth, *Multiscale analysis of thermoregulation in the human microvascular system*, Math. Meth. Appl. Sci., **27**, *8*, 971–989 (2004).
13. J. I. Díaz, *Nonlinear Partial Differential Equations and Free Boundaries*, Pitman, London, 1985.
14. H. Ene and D. Polisevski, *Thermal Flow in Porous Media*, Reidel, Dordrecht, 1987.
15. T.R. Gowrishankar, D.A. Stewart, G. T. Martin and J. C. Weaver, *Transport lattice models of heat transport in skin with spatially heterogeneous, temperature-dependent perfusion*, BioMedical Engineering OnLine, **3**, *42* (2004).
16. J. Lang, B. Erdmann, M. Seebass, *Impact of Nonlnear Heat Transfer on Temperature Control in Regional Hyperthermia*, IEEE Transactions on Biomedical Engineering, **46**, *9*, 1129–1138 (1999).
17. L. Pankratov, A. Piatnitskii and V. Rybalko, *Homogenized model of reaction-di®usion in a porous medium*, C.R. Mecanique, **331**, 253–258 (2003).
18. H.H. Pennes, *Analysis of tissue and arterial blood temperatures in the resting forearm*, J. Appl. Physiol., **1**, 93–122 (1948).
19. L. Popescu and A. Rodriguez-Bernal, *On a singularly perturbed wave equation with dynamic boundary conditions*, Proc. Royal Soc. Edinburgh Section A-Mathematics, **134**, *2*, 389–413 (2004).
20. A. Szasz and G. Vincze, *Dose concept of oncological hyperthermia: Heat-equation considering the cell destruction*, J. Can. Res. Ther., **2**, 171–181 (2006).
21. C. Timofte, *Homogenization results for parabolic problems with dynamical boundary conditions*, Romanian Rep. Phys., **56**, 131–140 (2004).
22. C. Timofte, *Upscaling of variational inequalities arising in nonlinear problems with unilateral constraints*, Z. Angew. Math. Mech., **87**, *6*, 406–411 (2007).
23. C. Timofte, *Upscaling in Diffusion Problems in Domains with Semipermeable Boundaries*, Acta Physica Polonica B, **38**, *8*, 2433–2443 (2007).
24. C. Timofte, *Upscaling in dynamical heat transfer problems in biological tissues*, Acta Physica Polonica B, **39**, *11*, 2811–2822 (2008).