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Diffusion of calcium in biological tissues and accompanying mechano-chemical effects

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In this paper we consider the coupling between chemical and mechanical effects accompanying the diffusion of calcium, either in biological tissues or in a single long cell. The tissue is treated either as a 3-D, or as a quasi-2-D thin layer, of visco-elastic medium, whereas the cell is represented as a thin long cylinder. In particular, the influence of viscosity on the properties of calcium travelling waves is studied. In principle, we explore here the simplest model of calcium diffusion which is based on an effective diffusion coefficient, thus neglecting the details of the role played by buffers. The mechano-chemical coupling in the model is realized by the presence of a traction tensor, in addition to the viscoelastic stress tensor in the mechanical equations, and the strain tensor in the source term of the calcium diffusion equation, as proposed in [1–4]. Our aim is to provide a simple and effective theory, which can be useful in studying various effects influencing propagation of calcium waves. Since in the absence of viscosity the whole mechano-chemical system for calcium and buffers is easily reduced to the "chemical one", i.e. it consists only of reaction diffusion equations, therefore we decided to perform expansion with respect to the viscosity. Treating, thus, viscous forces as a perturbation, we reduce the problem in each case to a single reaction diffusion equation for the calcium concentration. In this way we avoid the question of the existence of travelling wave solutions as for the so obtained models, their existence follows simply from already known theorems [5–9].

Key words: calcium waves, reaction-diffusion systems, mechano-chemical coupling.

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1. Introduction

The diffusion of calcium seems to play an important role in the living cells. It is mainly manifested in the existence of waves of calcium concentration. These waves have been extensively studied during the last twenty years, as it is believed that their propagation through a cell (intracellular waves) or across

the tissue (intercellular waves) is responsible for the coordination of the response to the local changes of the conditions [1, 2]. In supporting calcium waves, the nonlinear, autocatalytic mechanism, represented by a bi-stable source term in the respective diffusion equation [1, 2, 10–12]

$$c_t = D\Delta c + f(c), \tag{1.1}$$

plays an important role. At low concentrations, but higher than the equilibrium calcium concentration, the calcium is absorbed by internal stores (mitochondria, cellular reticulum etc.). However, after reaching some concentration threshold, the calcium ions by a positive feedback stimulate their own release. Thus the source term should have two stable equilibriums and one unstable in between. The following third-order polynomial in c $f = A(c - c_1)(c - c_2)(c - c_3)$ with $A < 0$ and $0 \leq c_1 < c_2 < c_3$, can serve as an example of such a source term function. Here c_1, c_3 are stable equilibriums, whereas c_2 is an unstable one. In this approach the calcium wave represents a travelling front joining the two stable equilibriums. The lowest equilibrium represents the ground state to which the highest state eventually relaxes after a long time, as the result of some complex processes which are not taken into account in the simple model considered here. Therefore the heteroclinic travelling front solution of a bi-stable reaction diffusion equation is only an approximation, valid in certain vicinity of the front of the real wave. The real calcium wave takes in fact a form of a homoclinic pulse with a sharp front and a long tail [13]. It should be noticed that the proposed here simple quasilinear reaction diffusion equation for calcium concentration with constant diffusion coefficient is a rough approximation. The whole process is much more complicated ; there are other complex particles, called buffers (e.g. some proteins), which can bind and then release calcium ions. These buffers may diffuse as well. As a result, the effective calcium diffusion is about ten times slower as compared to the one predicted by a single reaction diffusion equation, with diffusion coefficient for calcium. To describe this process, a system of reaction diffusion equations for calcium and buffers concentrations should be used [2, 4, 6, 7]. In the simplest case of a single buffer one has:

$$\begin{aligned} c_t &= D\Delta c + f(c) + k_1 b - k_2 c(b_* - b), \\ b_t &= D_b \Delta b - k_1 b + k_2 c(b_* - b). \end{aligned} \tag{1.2}$$

Here b represents the concentration of buffer proteins with Ca^{++} bound, D_b is their diffusion coefficient, k_1, k_2 represent the rates of binding and unbinding of calcium and the constant b_* is the total buffering molecules concentrations. D, c, $f(c)$ have the same meaning as before.

In many cases, the system can be replaced by a single effective (or asymptotic, as in the case of fast buffers [2, 14, 15]) equation. For this reason we confine

ourselves to this possibility. There is no problem however to apply the procedure of this paper to the whole system of equations for calcium and buffers as Eqs. (1.2). One should also mention that the propagating intercellular wave must pass somehow the cell membranes. This again is rather a complex process which completely slows down and modifies the overall diffusion [2, 16].

Finally, it appears that there is another complication accompanying the calcium diffusion. The well known experimental fact that calcium waves can be generated by local mechanical stimulation [13, 18] strongly suggests that there is some coupling between the chemical (change of calcium concentration) and mechanical processes (deformation). Simple model of such a coupling is proposed in [1–3] and it consists of a reaction diffusion equation for calcium concentration c, coupled with mechanical equations of a visco-elastic material. The "chemical effects" in mechanical equations are represented by the presence of traction forces depending on calcium concentration [16, 17], whereas the nonlinear source term in calcium diffusion equation depends also on the deformation tensor. The deformation induced by the variation of calcium concentration can serve as a mechanism of movement of cells (e.g. crawling motility of keratocytes) [18]. The existence of travelling waves in purely chemical case (i.e. calcium and buffers without mechanical interactions) has been already established [5, 6]. The existence of mechanochemical waves in the simple case when the transversal deformation of the cell is not taken into account and where the mechanical coupling coefficient was treated as a small parameter was studied via the implicit function theorem in Banach spaces in [19]. In [15] we considered a similar case, taking into account not only longitudinal but also possible transversal motion of the cell, by using however viscosity as a small parameter. This approach seems to be more adequate in case when Winkler forces are not present, since in the case of vanishing viscosity, the mechanical effects due to elastic and traction forces are still incorporated in the model. In this case the system reduces to a purely "chemical system" consisting of reaction diffusion equations for calcium and buffers concentrations with a modified source term in the equation for calcium concentration.

2. Equations of the model

2.1. Reaction diffusion equation with mechanical coupling

Experiments show that stretching the cell results in the increase of the cytosolic calcium concentration. Therefore the calcium diffusion equation with incorporated mechanical effects [1–3] can be postulated in the following form:

$$c_t = D\Delta c + f(c, \theta) \tag{2.1}$$

where θ denotes the dilation (the trace of a deformation tensor).

The experimental determination of the source function $f(c,\theta)$ seems to be rather difficult, especially because the proposed mathematical model should be treated as an approximation of a much more complex reality. The source term $f(c,\theta)$ should satisfy some physical restrictions, e.g. it should be nonnegative when concentration c approaches zero. In [1, 2] f is proposed as a sum:

$$f(c,\theta) = f(c) + \gamma\theta, \tag{2.2}$$

which can be thought of as the first term in the power series expansion of $f(c,\theta)$ with respect to the dilation θ. To explain how the calcium wave can be mechanically generated within the presented model, let us imagine that a certain part of a cell undergoes sufficiently strong stretching. As a result θ becomes positive, therefore if initially the system was in the lower stable state c_1 (ground state), then when θ increases during the gradual stretching, the ground state $c_1(\theta)$ increases till the moment when the minimum of the function $f(c) + \gamma\theta$ with respect to c becomes equal to zero. At this moment the stable and unstable states merge and c_1 becomes unstable for positive perturbations of c. When θ is still increasing, the state c_1 (as well as c_2) cease to exist and the system jumps to the upper stable state c_3. In this way the local concentration becomes high enough in the stretched region to start the propagation of a travelling wave, supported in its further evolution by the autocatalytic mechanism encoded in the model by bi-stability of the function $f(c)$. Let us note however, that this simplified form proposed by Eq. (2.2), can however sometimes lead to unphysical behavior. For negative values of θ of sufficiently large magnitude, the source term (2.2) can become negative for $c = 0$, what may lead to unphysical negative values of calcium concentrations. Still Eq. (2.2) can be useful in explaining some interesting features of the mechano-chemical coupling.

In a number of experiments calcium waves are generated by squeezing locally the tissue or part of a cell (see [6]). This may seem to suggest that the coupling constant should be negative. One must be however aware that local squeezing evokes some stretching in adjacent regions.

2.2. Mechanical part

Since the deformations induced by traction are rather small, we assume that the tissue can be treated as a visco-elastic material, whose stress tensor has the following form [20–23]:

$$\sigma_{ij} = \lambda\theta\delta_{ij} + 2\mu\epsilon_{ij} + \nu_1\dot{\theta}\delta_{ij} + \nu_2\dot{\epsilon}_{ij} + \tau_{ij}, \tag{2.3}$$

where λ and μ are the Lamé coefficients, $\hat{\epsilon} = (\epsilon_{ij})$ is the infinitesimal strain tensor, $\theta = \operatorname{Tr}\hat{\epsilon}$ is the dilation, ν_1 and ν_2 are the viscosities and $\hat{\tau} = \hat{\tau}(c)$ is the

symmetric traction tensor representing traction forces, generated by the sol-gel transition of the cytoplasm. This transition is caused by the change of calcium concentration [1–3]. In the above equation, the "dot" over the symbol denotes the time derivative.

Small deformations induced by the traction justifies the assumption made in this paper that the characteristics of the material (i.e. λ, μ, ν_1, ν_2) are constant (it is enough to assume that μ, ν_2 are constant). The diffusion of calcium is rather slow (e.g. the speed of calcium wave is of the order of ten microns per second), therefore the inertial forces can be neglected and the equation of motion of the medium reduces to the quasi-static balance of forces:

$$\frac{\partial}{\partial x^j}\sigma_{ij} + F_i = 0. \tag{2.4}$$

In the last equation and in the following, the Einstein summation convention over repeated indices is assumed. The term $\mathbf{F}$ represents possible volume forces. Such forces can appear also within the well-known Winkler model. In the case of tissue $\mathbf{F}$ can represent forces exerted on the cytogel by extracellular matrix consisting of a net of actin fibers [1–3]. The simplest approximation in such a case is to assume that $\mathbf{F}$ is a restoring force, proportional to the displacement vector field $u(x)$

$$\mathbf{F} = -k\mathbf{u}. \tag{2.5}$$

In the subsequent sections we consider the diffusion of calcium and accompanying mechanical effects in three basic structures: in the bulk tissue – mathematically in a 3-dimensional space, in a thin tissue layer (basically 2-dimensional space) and in an infinitely thin cylindrical volume (basically a 1-dimensional space). These three cases correspond respectively to calcium diffusion in a bulk tissue, diffusion in a biological membrane or in a long cell. As mentioned above, in the two last cases we will assume that the stress vanishes on the free surface of the material. Another simple possibility that there is no transversal deformation, brings the two last cases to the first one. Although, it is possible to do the analysis for other boundary conditions as well, we confine ourselves to these relatively simple, but representative ones.

3. Diffusion in the whole $\mathbb{R}^3$

In this section we assume that the traction tensor is isotropic, $\tau_{ij} = \tau\delta_{ij}$. Expressing the strain tensor in terms of the displacement vector field $\mathbf{u}(x)$,

$$\epsilon_{ij} = \frac{1}{2}(u_{i,j} + u_{j,i}), \tag{3.1}$$

we can write Eq. (2.3) as

$$\nabla\left\{(\mu+\lambda)\theta+\nu_1\dot{\theta}+\frac{1}{2}\nu_2\operatorname{div}\dot{\mathbf{u}}+\tau\right\}+\mu\Delta\mathbf{u}+\frac{1}{2}\nu_2\Delta\dot{\mathbf{u}}=k\mathbf{u}.$$

Thus to solve this equation we can introduce the potential for the displacement vector-field $\mathbf{u}$, i.e. $\mathbf{u}(x)=\operatorname{grad}\psi$. Then, denoting

$$\nu=\nu_1+\nu_2 \tag{3.2}$$

and noticing that $\theta=\Delta\psi$, we obtain:

$$\nabla\{(2\mu+\lambda)\theta+\nu\dot{\theta}+\tau-k\psi\}=0.$$

Assuming that the stresses are vanishing at infinity we have

$$(2\mu+\lambda)\theta+\nu\dot{\theta}+\tau=k\psi. \tag{3.3}$$

By the definition of θ we obtain the following linear evolutionary equation:

$$\nu\frac{\partial}{\partial t}\Delta\psi+(2\mu+\lambda)\Delta\psi-k\psi+\tau=0 \tag{3.4}$$

for the displacement potential ψ, if τ is treated as a given function of (t,x,y,z). However, τ is a given function of calcium concentration c, which satisfies appropriate reaction diffusion equation, Eq. (2.1).

In general, the viscous forces are much smaller than the elastic ones, so they can be treated as a perturbation. Therefore in the following, the viscosities ν_1, ν_2 will be treated as small parameters of the same order. In the case just considered, we have to deal with the sum (3.2), thus we write

$$\epsilon_{ij}=\epsilon_{ij}^{(0)}+\nu\epsilon_{ij}^{(1)}+\ldots, \tag{3.5}$$

and consequently

$$\theta=\theta^{(0)}+\nu\theta^{(1)}+\ldots \qquad \text{and} \qquad \psi=\psi^{(0)}+\nu\psi^{(1)}+\ldots. \tag{3.6}$$

For the zero order approximation we obtain

$$(2\mu+\lambda)\theta^{(0)}+\tau=k\psi^{(0)}, \tag{3.7}$$

whereas for the first correction terms we obtain

$$(2\mu+\lambda)\theta^{(1)}-k\psi^{(1)}+\dot{\theta}^{(0)}=0,$$

so

$$\theta^{(1)}-\frac{k}{2\mu+\lambda}\psi^{(1)}=\frac{1}{(2\mu+\lambda)^2}\left(\dot{\tau}-k\dot{\psi}^{(0)}\right). \tag{3.8}$$

Since $\theta = \Delta\psi$, therefore Eq. (3.7) and Eq. (3.8) are equivalent to the pair of coupled Helmholtz equations for zero order and first order corrections $\psi^{(0)}$, $\psi^{(1)}$

$$\Delta\psi^{(0)} - \frac{k}{2\mu+\lambda}\psi^{(0)} = -\frac{1}{2\mu+\lambda}\tau, \tag{3.9}$$

$$\Delta\psi^{(1)} - \frac{k}{2\mu+\lambda}\psi^{(1)} = \frac{1}{(2\mu+\lambda)^2}\left(\dot{\tau} - k\dot{\psi}^{(0)}\right). \tag{3.10}$$

Having $\tilde{\psi} = \psi^{(0)} + \nu\psi^{(1)}$ we can compute the approximate displacement field $u = \nabla\tilde{\psi}$. The asymptotic analysis of Eqs. (3.3) and (3.5) for large and small k is possible. Here we consider mainly the case of $k = 0$.

The case of $k = 0$. In this case we have

$$\theta^{(0)} = -\frac{\tau}{2\mu+\lambda} \qquad \text{and} \qquad \theta^{(1)} = \frac{1}{(2\mu+\lambda)^2}\dot{\tau}. \tag{3.11}$$

In our approximation: $\theta = \theta^{(0)} + \nu\theta^{(1)}$. Assuming that $\theta^{(0)}(c) = -\tau(c)/(2\mu+\lambda)$ is already encoded in the form of the source term f, that is assuming that

$$f(c,\theta) = f(c) + \gamma\theta^{(0)}(c) + \gamma\theta^{(1)} = g(c) + \gamma\nu\theta^{(1)}, \tag{3.12}$$

we obtain for g

$$g(c) = f(c) - \gamma\frac{\tau(c)}{2\mu+\lambda} \tag{3.13}$$

and for the calcium diffusion in the first approximation:

$$c_t = D\Delta c + g(c) + \gamma\nu\theta^{(1)}$$

or

$$c_t = D\Delta c + g(c) + \gamma\frac{\nu}{(2\mu+\lambda)^2}\dot{\tau}. \tag{3.14}$$

Noticing that $\dot{\tau} = \tau_{,c}c_t$, we arrive finally at a single reaction diffusion equation

$$\beta(c)c_t = D\Delta c + g(c), \tag{3.15}$$

where the coefficient $\beta(c)$ is given by

$$\beta = \left(1 - \gamma\frac{\nu}{(2\mu+\lambda)^2}\tau_{,c}\right). \tag{3.16}$$

Equation (3.15) describes the diffusion of calcium influenced by accompanying mechanical effects. Having concentration $c(t,x,y,z)$, we can solve Eq. (3.4) (with

$k = 0$) for the displacement potential to determine the deformation of the material. One can use also the following approximate equation for $\tilde{\psi} = \psi^{(0)} + \nu\psi^{(1)}$:

$$\Delta\tilde{\psi} = -\frac{1}{2\mu+\lambda}\left(\tau - \frac{\nu}{2\mu+\lambda}\dot{\tau}\right),$$

which follows from the approximation $\theta = \theta^{(0)} + \nu\theta^{(1)}$, in agreement with (3.11).

The existence of travelling waves for Eq. (3.15) (if only $\beta > 0$) follows immediately from the appropriate theorem for a single reaction diffusion equation, provided that $g(c)$ is of a bi-stable type. In the case when β is a non-vanishing constant or does not change much, the viscosity influences only the speed of the wave, leaving the wave profile unchanged. This can be shown by rescaling the time variable.

The case of large k. For very large k, when other terms except of ψ and τ can be neglected, we have $\psi = -k^{-1}\tau$ and then the reaction diffusion equation for calcium concentration becomes

$$c_t = (D - \gamma k^{-1}\tau_{,c})\Delta c - \gamma k^{-1}\tau_{,cc}(\nabla c)^2 + f(c),$$

or in a conservative form

$$c_t = \operatorname{div}\{(D - \gamma k^{-1}\tau_{,c})\nabla c\} + f(c).$$

Thus in this case the source term remains unchanged whereas the diffusion coefficient is modified. Clearly the modified diffusion coefficient must be positive, hence $k > \gamma\tau_{,c}/D$, otherwise the last equation does not make sens.

4. Diffusion in a thin layer of a visco-elastic material

Now we consider a thin layer of visco-elastic material: $(x^1, x^2, x^3) \in \mathbb{R}^2 \times [-d, d]$ with free, unloaded upper and lower surfaces. Under the influence of internal stresses, such a layer can in principle undergo buckling. This possibility, however, will not be analyzed here. In this Section we assume that the traction tensor $\hat{\tau}$ can be somewhat anisotropic, i.e. it can be of the following form:

$$\hat{\tau} = \begin{bmatrix} \tau & 0 & 0 \\ 0 & \tau & 0 \\ 0 & 0 & \tau_{33} \end{bmatrix}, \tag{4.1}$$

Together with notation x^1, x^2, x^3 we use here x, y, z and $\bar{x} = (x^1, x^2)$ for convenience.

Since the layer is thin, we can expand the displacement vector-field in powers of z $(= x^3)$ up to the second order terms (the dependence on t is suppressed for convenience)

$$u_i = a_i^{(0)}(\bar{x}) + a_i^{(1)}(\bar{x})z + a_i^{(2)}(\bar{x})z^2. \tag{4.2}$$

The plane $(x^1, x^2, 0)$ is assumed to be a symmetry plane, so we have

$$\begin{cases} u_\alpha(\bar{x}, z) = u_\alpha(\bar{x}, z), \quad \alpha = 1, 2, \\ u_3(\bar{x}, -z) = -u_3(\bar{x}, z). \end{cases} \tag{4.3}$$

This implies: $u_3 = a_3^{(1)} z$ and $u_\alpha^1 \equiv 0$, so finally

$$\begin{cases} u_\alpha = a_\alpha^{(0)}(\bar{x}) + a^{(2)}(\bar{x})z^2, \\ u_3 = a_3^{(1)}(\bar{x})z. \end{cases} \tag{4.4}$$

Consequently, the strain tensor is given by:

$$\begin{aligned} \epsilon_{\alpha\beta} &= \frac{1}{2}\left\{a_{\alpha,\beta}^{(0)} + a_{\alpha,\beta}^{(2)} z^2 + a_{\beta,\alpha}^{(0)} + a_{\beta,\alpha}^{(2)} z^2\right\}, \\ \epsilon_{\alpha 3} &= \frac{1}{2}\left\{2a_\alpha^{(2)} + a_{3,\alpha}^{(1)}\right\} z, \\ \epsilon_{33} &= a_3^{(1)}. \end{aligned} \tag{4.5}$$

Let us note that if we do the averaging of Eqs. (4.5) over the layer thickness 2d, we obtain the strain tensor, whose coefficients are not depending on variable z. Indeed, we have

$$\epsilon_{\alpha\beta} = \frac{1}{2}(a_{\alpha,\beta} + a_{\beta,\alpha}) + \frac{1}{2}\left(a_{\alpha,\beta}^{(2)} + a_{\beta,\alpha}^{(2)}\right)\frac{d^2}{3}, \qquad \epsilon_{\alpha 3} = 0, \qquad \epsilon_{33} = a_3^{(1)}. \tag{4.6}$$

Let us note also that:

1. If the calculations are made up to the main, i.e. zero order terms in d, then the coefficients of the strain tensor are depending only on x and y. Indeed, we have

$$\epsilon_{\alpha\beta} = \frac{1}{2}(a_{\alpha,\beta} + a_{\beta,\alpha}), \qquad \epsilon_{\alpha 3} = 0, \qquad \epsilon_{33} = a_3^{(1)}.$$

2. If second order terms in d are preserved, then as it can be easily verified, the averaging of the mechanical equilibrium equations over the layer thickness, denoted here by $\langle\,\rangle$, commutes with differentiation along other directions

$$\left\langle \frac{\partial}{\partial x^j}\sigma_{ij} \right\rangle = \frac{\partial}{\partial x^j}\langle \sigma_{ij} \rangle. \tag{4.7}$$

Therefore, mechanical equilibrium equations

$$\sigma_{ij,j} = \hat{k}u, \qquad \text{where } \hat{k} = \begin{bmatrix} k & 0 & 0 \\ 0 & k & 0 \\ 0 & 0 & 0 \end{bmatrix}, \tag{4.8}$$

in both types of approximations are reduced to $\sigma_{\alpha\beta,\beta} = ku_\alpha$, with $\alpha, \beta = 1, 2$; or in more explicit form

$$(\lambda\theta\delta_{\alpha\beta} + 2\mu\epsilon_{\alpha\beta} + \nu_1\dot{\theta}\delta_{\alpha\beta} + \nu_2\dot{\epsilon}_{\alpha\beta} + \tau_{\alpha\beta})_{,\beta} = ku_\alpha. \tag{4.9}$$

Since $\tau_{\alpha\beta} = \tau\delta_{\alpha\beta}$ for $\alpha, \beta = 1, 2, ,$ then the traction forces are of gradient type, therefore we can introduce potential function $\phi(t, x^1, x^2)$ for the two-dimensional displacement vector field u_α

$$u_\alpha = \frac{\partial}{\partial x^\alpha}\phi, \qquad \alpha, \beta = 1, 2. \tag{4.10}$$

Then we have

$$\theta = \Delta\phi + 2\epsilon_{33}. \tag{4.11}$$

Expressing Eq. (4.4) the in terms of we obtain the following equation:

$$[(\lambda + 2\mu)\theta - 2\mu\epsilon_{33} + \nu\dot{\theta} - \nu_2\dot{\epsilon}_{33} + \tau]_{,\alpha} = ku_\alpha, \tag{4.12}$$

which after integration is reduced to a single scalar equation

$$(\lambda + 2\mu)\theta - 2\mu\epsilon_{33} + \nu\dot{\theta} - \nu_2\dot{\epsilon}_{33} + \tau - k\phi = 0. \tag{4.13}$$

Boundary conditions. Since the top and bottom surfaces are free, unloaded surfaces, the following relations must be satisfied for $z = \pm d$:

$$1.\ \sigma_{\alpha 3} = 0, \qquad \text{which implies } 2\mu\epsilon_{\alpha 3} + \nu_2\dot{\epsilon}_{\alpha 3} = 0, \tag{4.14}$$

$$2.\ \sigma_{33} = 0, \qquad \text{which implies } \lambda\theta + 2\mu\epsilon_{33} + \nu_1\dot{\theta} + \nu_2\dot{\epsilon}_{33} + \tau_{33} = 0. \tag{4.15}$$

The first of the above equations tells us that if initially $\epsilon_{\alpha 3}$ is not zero, then after ashort time of the order of $\nu_2/2\mu$ it relaxes to zero. Let us note that Eq. (4.8) and Eq. (4.10) form a system of equations for θ and ϵ_{33}:

$$(\lambda + 2\mu)\theta - 2\mu\epsilon_{33} + \nu\dot{\theta} - \nu_2\dot{\epsilon}_{33} + \tau - k\phi = 0, \tag{4.16}$$

$$\lambda\theta + 2\mu\epsilon_{33} + \nu_1\dot{\theta} + \nu_2\dot{\epsilon}_{33} + \tau_{33} = 0. \tag{4.17}$$

Here as before $\nu = \nu_1 + \nu_2$. From these two equations we have

$$2(\lambda + \mu)\theta + \tilde{\nu}\dot{\theta} + \tau + \tau_{33} - k\phi = 0, \tag{4.18}$$

where $\tilde{\nu} = 2\nu_1 + \nu_2$. Similarly as before, we can look for approximate solutions of this system by expanding the solution in powers of $\tilde{\nu}$

$$\begin{aligned}\theta &= \theta^{(0)} + \tilde{\nu}\theta^{(1)} + \dots,\\ \phi &= \phi^{(0)} + \tilde{\nu}\phi^{(1)} + \dots,\\ \epsilon_{33} &= \epsilon_{33}^{(0)} + \tilde{\nu}\epsilon_{33}^{(1)} + \dots.\end{aligned}$$

For a zero order approximation we obtain from (4.18)

$$\begin{aligned}\theta^{(0)} &= \frac{-1}{2(\mu+\lambda)}\left(\tau_{33} + \tau - k\phi^{(0)}\right),\\ \epsilon_{33}^{(0)} &= \frac{-1}{4\mu(\mu+\lambda)}\left[(2\mu+\lambda)\tau_{33} - \lambda(\tau - k\phi^{(0)})\right].\end{aligned} \tag{4.19}$$

Thus in view of Eq. (4.11) we obtain the following equation for the zero order approximation of the displacement potential $\phi(t, x, y)$

$$\Delta\phi^{(0)} - k\frac{2\mu+\lambda}{2\mu}\phi^{(0)} = \frac{1}{4\mu(\mu+\lambda)}\{\lambda\tau_{33} - (2\mu+\lambda)\tau\} = 0. \tag{4.20}$$

Similarly, the first order approximation can be computed:

$$\begin{aligned}\theta^{(1)} &= \frac{-1}{2(\mu+\lambda)}\left[\dot{\theta}^{(0)} - k\phi^{(1)}\right],\\ \tilde{\nu}\epsilon_{33}^{(1)} &= \frac{-1}{4\mu(\mu+\lambda)}\left[(2\mu\nu_1 - \lambda\nu)\dot{\theta}^{(0)} + (2\mu+\lambda)\nu_2\dot{\epsilon}_{33}^{(0)} - \nu k\phi^{(1)}\right].\end{aligned} \tag{4.21}$$

Equations (4.21) can be used to obtain an equation for the first order correction $\phi^{(1)}$ to the displacement potential. However, let us pass now to the case $k = 0$, since in this case θ can be effectively determined in zero order as well as in the first order approximation.

Case of $k = 0$. In this case Eq. $(4.19)_1$ gives us explicit expression for $\theta^{(0)}(c)$, therefore according to formula (3.12) we have:

$$g(c, \theta) = f(c) + \gamma\theta^{(0)}(c) = f(c) - \frac{\gamma}{2(\mu+\lambda)}[\tau_{33}(c) + \tau(c)], \tag{4.22}$$

and the equation for c with the first order corrections, $c_t = D\Delta c + g(c) + \gamma\tilde{\nu}\theta^{(1)}$, takes the form

$$c_t = D\Delta c + g(c) + \frac{\gamma(2\nu_1+\nu_2)}{4(\mu+\lambda)^2}\left[\dot{\tau}_{33}(c) + \dot{\tau}(c)\right].$$

Executing the time differentiation on RHS, we finally come to a similar equation as Eq. (3.15)

$$\beta(c)c_t = D\Delta c + g(c); \tag{4.23$_1$}$$

but in this case

$$\beta(c) = 1 - \frac{\gamma(2\nu_1 + \nu_2)}{4(\mu+\lambda)^2}\left[\tau_{33}(c) + \tau(c)\right]_{,c}. \tag{4.23$_2$}$$

Equation $(4.23)_1$ shows how the diffusion of calcium in a thin layer of a tissue is influenced by the accompanying mechanical effects. According to Eq. (4.22), the zero order term is already included in the definition of $g(c)$.

5. Diffusion in a long thin fiber

In this case we assume that traction tensor $\hat{\tau}(c)$ is symmetric with respect to x $(= x^1)$ axis and it is of the following form:

$$\hat{\tau} = \begin{bmatrix} \tau_{11} & 0 & 0 \\ 0 & \tau & 0 \\ 0 & 0 & \tau \end{bmatrix}. \tag{5.1}$$

Concerning the elastic bulk forces we assume that only $k_{11} \neq 0$; hence these forces may only act along the x-axis. Since the problem is axially symmetric, the cylindrical coordinates could be used, but it is not necessary. The symmetry says that in the Cartesian system of coordinates

$$\epsilon_{22} = \epsilon_{33}, \quad \sigma_{12} = \sigma_{13}, \quad \sigma_{23} = 0 \qquad \text{and hence we have} \qquad \theta = \epsilon_{11} + 2\epsilon_{33}.$$

Taking into account the symmetries of the problem, the form of approximate displacement vector-field can be postulated in this case as

$$\begin{cases} u_1 = a(x) + a_2(x)\varrho^2, \\ u_\alpha = b(x)\varrho_\alpha, \end{cases} \quad \text{where } \bar{\varrho} = (y,z),\ \varrho^2 = y^2 + z^2 \text{ and } \alpha = 2,3, \tag{5.2}$$

for $x \in \mathbb{R}^1$ and $\varrho^2 < d^2$.

Having in mind the above relations, it is enough to take the boundary conditions at the cross-section of the fiber with one of the planes passing through the symmetry axis, e.g. plane (x,z). Then similarly as before, $\sigma_{i3} = 0$ at $z = \pm d$:

$$\begin{aligned} &1.\ \sigma_{\alpha 3} = 0, \quad \text{which implies} \quad 2\mu\epsilon_{\alpha 3} + \nu_2\dot{\epsilon}_{\alpha 3} = 0, \\ &2.\ \sigma_{33} = 0, \quad \text{which implies} \quad \lambda\theta + 2\mu\epsilon_{33} + \nu_1\dot{\theta} + \nu_2\dot{\epsilon}_{33} + \tau = 0. \end{aligned} \tag{5.3}$$

Again, since all quantities appearing in these equations are depending only on x^1, the mechanical equilibrium equations are reduced to

$$\frac{\partial}{\partial x}(\lambda\theta + 2\mu\epsilon_{11} + \nu_1\dot{\theta} + \nu_2\dot{\epsilon}_{11} + \tau_{11}) = ku_1. \tag{5.4}$$

Introducing potential $\varphi(x)$, $u_1 = \varphi_{,x}$, we can integrate Eq. (5.4). Then Eq. (5.3) together with integrated Eq. (5.4), form the system allowing for determination of strain tensor components

$$\begin{cases} (2\mu + \lambda)\theta - 4\mu\epsilon_{33} + (\nu_1 + \nu_2)\dot{\theta} - 2\nu_2\dot{\epsilon}_{33} + \tau_{11} = k\varphi, \\ \lambda\theta + 2\mu\epsilon_{33} + \nu_1\dot{\theta} + \nu_2\dot{\epsilon}_{33} + \tau = 0. \end{cases} \tag{5.5}$$

Appropriate combination of these equations gives us an equation for θ

$$(2\mu + 3\lambda)\theta + (3\nu_1 + \nu_2)\dot{\theta} + 2\tau + \tau_{11} = k\varphi.$$

Making the perturbation analysis similarly as before, but this time with respect to

$$\tilde{\tilde{\nu}} = 3\nu_1 + \nu_2,$$

we obtain for zero order approximation

$$\begin{aligned} \theta^{(0)} &= \frac{1}{2\mu + 3\lambda}\left(k\varphi^{(0)} - \tau_{11} - 2\tau\right), \\ \epsilon_{33}^{(0)} &= \frac{1}{2\mu(2\mu + 3\lambda)}\left[\lambda(\tau_{11} - k\varphi^{(0)}) - (2\mu + \lambda)\tau\right], \end{aligned} \tag{5.6}$$

whereas for the first order correction for θ we have

$$\theta^{(1)} = \frac{1}{2\mu + 3\lambda}\left[k\varphi^{(1)} - \dot{\theta}^{(0)}\right]. \tag{5.7$_1$}$$

From the second of Equations (5.5) we have then

$$2\mu\tilde{\tilde{\nu}}\epsilon_{33}^{(1)} + \tilde{\tilde{\nu}}\lambda\theta^{(1)} + \nu_1\dot{\theta}^{(0)} + \nu_2\dot{\epsilon}_{33}^{(0)} = 0, \tag{5.7$_2$}$$

which permits us to compute $\epsilon_{33}^{(1)}$. Having in mind that $\theta = \epsilon_{11} + 2\epsilon_{33}$, one can obtain the equations for the potential $\varphi^{(0)}(t,x)$, $\varphi^{(1)}(t,x)$ (note that $\epsilon_{11} = \varphi_{,x}$). In the following we restrict ourselves to the case of $k = 0$. Expressing Eq. $(5.7)_1$ with $k = 0$ in terms of traction tensor components, we arrive at

$$\theta^{(1)} = -\frac{1}{(2\mu + 3\lambda)^2}\left[\dot{\tau}_{11}(c) + 2\dot{\tau}(c)\right].$$

This again leads to the reaction diffusion equation of the form

$$\beta(c)c_t = Dc_{xx} + g(c), \tag{5.8}$$

where this time

$$\beta(c) = 1 - \gamma\frac{3\nu_1 + \nu_2}{(2\mu + 3\lambda)^2}[\tau_{11}(c) + 2\tau(c)]_{,c},$$

whereas for $g(c) = f(c) + \gamma\theta^{(0)}$ we have

$$g(c) = f(c) - \frac{\gamma}{2\mu + 3\lambda}(\tau_{11}(c) + 2\tau(c)). \tag{5.9}$$

As it can be noticed, the "dimensionality" of the problem has a strong influence on the calcium wave velocity. Indeed, when looking for the travelling wave we put $c = \vartheta(x - \nu t)$. Thus we obtain $-\nu\beta\vartheta' = D\vartheta'' + g(c)$. If ν_0 denotes velocity for $\beta = 1$, then $\nu \cong \nu_0/\beta$ (we have equality for constant β), which demonstrates the influence of viscosity. The dimensionality also influences strongly the form of the effective source term $g(c)$. To make it more transparent we summarize in Conclusions the influence of dimensionality on the form of $g(c)$ and $\beta(c)$.

6. Conclusions

Starting from the coupled system of equations, consisting of the reaction diffusion equation for calcium concentration $c_t = D\Delta c + f(c) + \gamma\theta$ and equations of mechanical equilibrium with vanishing volume forces ($k = 0$), i.e.

$$\frac{\partial}{\partial x^j}(\lambda\theta\delta_{ij} + 2\mu\epsilon_{ij} + \nu_1\dot{\theta}\delta_{ij} + \nu_2\dot{\epsilon}_{ij} + \tau_{ij}) = 0,$$

under the assumption of vanishing surface forces on the free surface of the material, we derived by the perturbation technique, the single reaction diffusion equation

$$\beta(c)c_t = D\Delta c + g(c)$$

for three cases, which can be of some importance in biological applications. The appropriate formulas are expressed in terms of bulk and shear viscosities, ν_1, ν_2. The expressions for $\beta(c)$ and $g(c)$ in these specific cases are as follows:

1. Diffusion of calcium with accompanying mechanical effects in bulk tissue (formally 3-D case). In this case, assuming that the traction tensor is isotropic, $\hat{\tau} = (\tau(c)\delta_{ij})$, we have

$$g(c) = f(c) - \gamma\frac{1}{2\mu + \lambda}\tau(c), \qquad \beta = \left(1 - \gamma\frac{\nu_1 + \nu_2}{(2\mu + \lambda)^2}\tau_{,c}\right).$$

2. Diffusion of calcium in thin biological membranes with free unloaded top and bottom surfaces (formally 2-D case). We allow here the traction tensor to be not totally isotropic. It can have different values in the directions parallel (x_1, x_2) and perpendicular (x_3) to the membrane, $\hat{\tau} = \mathrm{diag}(\tau, \tau, \tau_{33})$. In this case

$$g(c,\theta) = f(c) - \frac{\gamma}{2(\mu+\lambda)}\left[\tau_{33}(c) + \tau(c)\right],$$
$$\beta(c) = 1 - \gamma\frac{2\nu_1+\nu_2}{4(\mu+\lambda)^2}\left[\tau_{33}(c) + \tau(c)\right]_{,c}.$$

In particular, for isotropic traction we have

$$g(c,\theta) = f(c) - \gamma\frac{1}{\mu+\lambda}\tau(c),$$
$$\beta(c) = 1 - \gamma\frac{2\nu_1+\nu_2}{2(\mu+\lambda)^2}[\tau(c)]_{,c}.$$

3. Diffusion of calcium in long cylindrical fibers e.g. long cells, like myocytes, which can be almost 1 cm long. Here also we assume that the cell surface is free of stresses, x_1 is the axis of symmetry, whereas $\hat{\tau} = \mathrm{diag}(\tau_{11}, \tau, \tau)$. In this case we obtain

$$g(c) = f(c) - \frac{\gamma}{2\mu+3\lambda}\left[\tau_{11}(c) + 2\tau(c)\right],$$
$$\beta(c) = 1 - \gamma\frac{3\nu_1+\nu_2}{(2\mu+3\lambda)^2}\left[\tau_{11}(c) + 2\tau(c)\right]_{,c}.$$

For isotropic traction tensor we have

$$g(c) = f(c) - 3\frac{\gamma}{2\mu+3\lambda}\tau(c),$$
$$\beta(c) = \left\{1 - 3\gamma\frac{3\nu_1+\nu_2}{(2\mu+3\lambda)^2}[\tau(c)]_{,c}\right\}.$$

One may hope that the obtained formulae can be useful in experimental determination of some features of the mathematical model, for example, the source function $f(c)$. Although our considerations are based on the simplest possible model of calcium diffusion, there is no problem to generalize these results to the buffered systems or to a fully nonlinear reaction diffusion equation.

REMARK. If d denotes the dimensionality of the problem ($d = 3$ for waves in bulk tissue, $d = 2$ for waves in thin membranes and $d = 1$ for waves in thin

fibers), then the coefficient $\beta(c)$ appearing in the corrected form (up to the first-order terms in viscosity) by the mechanical effect reaction diffusion equation for calcium, has the general form

$$\beta(c) = \left\{1 - \gamma \frac{(4-d)\nu_1 + \nu_2}{[2\mu + (4-d)\lambda]^2} \left[\tau^{\parallel}(c) + (3-d)\tau^{\perp}(c)\right]_{,c}\right\}, \tag{6.1}$$

where $\tau^{\parallel}(c)$, $\tau^{\perp}(c)$ are respectively components of the diagonal traction tensor respectively in the directions parallel and perpendicular to the tissue. This form shows that β may vanish or can even be negative for higher values of viscosity if τ is an increasing function of calcium concentration. Negative β leads to a wrong (unstable in the sense of Hadamard), reaction diffusion equation. To avoid such an unexpected problem, it is reasonable to replace formula (6.1) by the following one:

$$\beta(c) = \left\{1 + \gamma \frac{(4-d)\nu_1 + \nu_2}{[2\mu + (4-d)\lambda]^2} \left[\tau^{\parallel}(c) + (3-d)\tau^{\perp}(c)\right]_{,c}\right\}^{-1},$$

which, up to the leading order in viscosity, is equivalent to Eq. (6.1). It should be noticed here that to obtain the corrected source functions $g(c)$, which can be written as

$$g(c) = f(c) - \frac{\gamma}{2\mu + (4-d)\lambda} \left[\tau^{\parallel}(c) + (3-d)\tau^{\perp}(c)\right],$$

the perturbation procedure was not used, so in the case of vanishing viscosity we have exact formulas for $g(c)$.

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