

Reaction-diffusion equation modelling calcium waves with fast buffering in visco-elastic environment

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THE MODEL WE CONSIDER TREATS a cell or a group of cells as a viscoelastic medium whose stress tensor has a term - the traction- representing the stresses generated in the medium by the actomyosin molecules. We consider three kinds of domains (“shapes” of cells): the thin circular cylinder mimicking a long cell, the thin slab being a caricature of a tissue, and the unbounded space. We assume that the viscous effects are much weaker than the elastic ones and consider two extreme cases: either the body force is negligible or it is strong. This leads to three pairs, one pair for each domain, of approximations for the dilatation. We interpolate between the approximated expressions forming one pair and as the result we obtain a single calcium conservation equation and a system of buffer equations. Using the rapid buffering approximation we reduce the problem to a single reaction-diffusion equation. We study the travelling wave solutions to these equations. We show that not only the high affinity buffers but also the mechanical effects alone can prevent the formation and propagation of the waves if the supply of calcium is not sufficiently substantial.

Key words: bistable reaction-diffusion equations, mechano-chemical coupling, Robin boundary condition, calcium waves.

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1. Introduction

IRRITATION OF A CELL OR A GROUP OF CELLS generates some aggregation of calcium ions Ca^{2+} . The nature of such an irritation can be very diverse. For instance, it can be a sperm penetrating an egg or a mechanical or electric agent. In some types of cells the density of such an aggregation becomes so large that the aggregation starts to propagate as a wave. The role of the calcium waves is not totally clear; however, the common opinion is that they enable many physiological processes; in particular, they enable the transmission of information within a single cell or a group of cells. That is why it is so important to understand the leading mechanisms governing the calcium motion.

Despite the fact that the complexity of the problem is huge, it turned out that even relatively simple models can be very useful. The simplest model [1, 2]

is based on the reaction-diffusion equation

$$(1.1) \quad \frac{\partial c}{\partial t} = D\Delta c + f(c),$$

where t is the time, Δ is the Laplacian with respect to $\mathbf{x} = (x_1, x_2, x_3)$ – the position, c is the calcium concentration normalised to the interval $[0, 1]$, $D > 0$ is the coefficient of diffusion, and the source term $f(c)$ describes the kinetics of calcium transportation into and out of the cytosol. As it is known, the concentration of calcium ions in a cell is low in normal conditions, since pure calcium is toxic. Therefore, it is stored in special compartments which open when the concentration of the local aggregation reaches a threshold value. Then some amount of calcium is secreted what raises the local value of its concentration and stimulates further secretion. Thus, the calcium waves are maintained by an autocatalytic mechanism. So, the function $f(c)$ must be bistable; that is, it must have two stable equilibria and one unstable between them [1, 2]. More precisely, we assume that $f(c)$ is continuously differentiable with respect to $c \in [0, 1]$ and such that

$$(1.2) \quad \begin{aligned} f(0) = f(c_T) = f(1) = 0, \quad \text{for only one } c_T \in (0, 1), \\ f'_c(0) < 0, \quad f'_c(c_T) > 0 \quad \text{and} \quad f'_c(1) < 0. \end{aligned}$$

The simplest candidate is

$$(1.3) \quad f(c) = Ac(1 - c)(c - c_T),$$

where $A > 0$ is a constant. The bistable reaction-diffusion equations of the form (1.1) occur in many other problems of applied sciences. The analysis of the existence and uniqueness of travelling calcium waves in equations like (1.1) can be found for instance in [3].

A model more refined than the one formulated by Eq. (1.1) accounts for calcium buffering. Buffers are large proteins of various chemical structures able to bind and release Ca^{2+} . In fact, about 99% of calcium is bound to the buffers. The simplest model accounting for free calcium and bounds to buffers is as follows (see [2, 4, 5]):

$$(1.4) \quad \frac{\partial c}{\partial t} = D\Delta c + f(c) + \sum_{i=1}^n [k_-^i b_i - k_+^i c(b_0^i - b_i)]$$

and

$$(1.5) \quad \frac{\partial b_i}{\partial t} = D_i \Delta b_i - [k_-^i b_i - k_+^i c(b_0^i - b_i)], \quad i = 1, 2, \dots, n,$$

where b_i denotes the concentration of the i -th buffer that has bound the calcium ions, b_0^i is the total concentration of the i -th buffer, assumed to be constant, the positive constants k_+^i and k_-^i represent the rates of binding and releasing calcium, respectively. $D > 0$ and $D_i \geq 0$ are the diffusion coefficients of free calcium and buffered calcium, respectively.

The models like (1.1) or (1.4) and (1.5) do not take into account the fact that calcium and buffers move through the physiological medium. The variations in the calcium concentration generate some tension in the surrounding medium which, in response, modifies the propagation of calcium waves. Essentially, the tissue or the cell cytoplasm is modelled as a viscoelastic medium. Its stress tensor with components σ_{ij} , $i, j = 1, 2, 3$, is assumed to be of the following form [1, 2, 13, 14]:

$$(1.6) \quad \sigma_{ij} = \left(\frac{E}{1+\nu} + \mu_1 \frac{\partial}{\partial t} \right) \varepsilon_{ij} + \delta_{ij} \left(\frac{E}{1+\nu} \frac{\nu}{1-2\nu} + \mu_2 \frac{\partial}{\partial t} \right) \theta + \tau \delta_{ij},$$

where δ_{ij} , $i, j = 1, 2, 3$ is the Kronecker symbol, E is the constant Young modulus, ν is the constant Poisson ratio, μ_1 , μ_2 are the constant shear and bulk viscosities, ε_{ij} , $i, j = 1, 2, 3$, are the components of the strain tensor, defined by

$$(1.7) \quad \varepsilon_{ij} = \frac{1}{2} \left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right),$$

where $u_i = u_i(\mathbf{x}, t)$, $i = 1, 2, 3$ are components of the displacement vector. In Eq. (1.6) θ represents dilatation which is responsible for volumetric changes in the medium; it is defined by $\theta = \text{div } \mathbf{u}$. The last quantity on the right-hand side of Eq. (1.6) $\tau = \tau(c)$ represents the contribution to the stresses resulting from the fact that the interior of a cell should not be treated as a totally amorphous viscoelastic material. Namely, there are molecules called actins and myosins which form a sort of network and react to the changes of the calcium concentration: when the calcium concentration starts to grow the network exerts a contraction stress on the cytoplasm; however, if the calcium concentration reaches a sufficiently large value the network starts to break down, consequently the traction disappears [13, 14]. Due to that, we assume that τ are completely determined by calcium concentration c and is such that

$$(1.8) \quad \tau(c) \geq 0, \quad 0 \leq c \leq 1, \quad \tau(0) = \tau(1) = 0.$$

Ignoring the very small inertial terms we reduce the equations of motion to equations expressing quasi-static balance of forces

$$(1.9) \quad \frac{\partial}{\partial x_j} \sigma_{ij} + F_i = 0, \quad i = 1, 2, 3,$$

where F_i , $i = 1, 2, 3$, are the components of the vector of the body force which comes from a permanent resistance to deformations of the cell material. The simplest approximation to this sort of resistance consists in the assumption that it is an elastic force

$$(1.10) \quad F_i = -\rho u_i, \quad i = 1, 2, 3,$$

where ρ is a given positive constant.

The final problem is the calcium conservation equation. Since the stretching of the cell elevates the cytosolic calcium concentration (this phenomenon is known as the “stretch activation”), Eq. (1.1) is replaced by the following one [1, 2, 13, 14]:

$$(1.11) \quad \frac{\partial c}{\partial t} = D\Delta c + f(c) + \gamma\theta.$$

The first attempt of finding the travelling wave solutions of the system (1.6)–(1.11) is contained in the quoted paper by MURRAY and OSTER [13], but the real progress was made by LANE *et al.* [14], who used these equations to explain the phenomenon of calcium waves on the surface of a fertilized egg. The first mathematically rigorous paper on calcium waves in the mechanochemical model (1.6)–(1.11) was published by FLORES *et al.* [15]. They proved the existence and uniqueness of travelling wave solutions under the (among others) assumption that the coupling between mechanical and chemical effects is weak by treating the parameter γ in Eq. (1.11) as small. The stability of such waves, under the same working assumption that γ is small, was proved later by FLORES and PLAZA [16]. The existence of calcium wave solutions for the considered system under different auxiliary assumptions was shown also by PERADZYŃSKI and KAŻMIERCZAK [17]. They considered two cases: either the body force is totally negligible ($\rho = 0$ in Eq. (1.10)) and the viscous effects are sufficiently small or these effects are absent ($\mu_1 = \mu_2 = 0$) and ρ is large. Recently, PERADZYŃSKI [18] (see also [21]) considered the mechanochemical model (1.6)–(1.11) in domains with boundaries, and showed how to reduce this system to a single equation of the reaction-diffusion type whose details depended on the specific set of the adopted simplifying assumptions. For so simplified equations, KAŻMIERCZAK and DYZMA [19] succeeded in finding some exact solutions.

In the mechanochemical model (1.6)–(1.11), the existence of buffers was ignored. But, as it is known, 99% of calcium is bound to buffers; therefore, it is necessary to incorporate buffers into the mechanochemical model. The simplest way to construct such a model is to add the term $\gamma\theta$ to Eq. (1.4), thus receiving the following equation:

$$(1.12) \quad \frac{\partial c}{\partial t} = D\Delta c + f(c) + \sum_{i=1}^n [k_-^i b_i - k_+^i c(b_0^i - b_i)] + \gamma\theta.$$

Now, the system of equations aimed to model the buffered calcium waves with accompanying mechanical effects consists of the buffer conservation equation (1.5), the mechanical equations (1.6)–(1.11), and the calcium conservation equation (1.12). The existence and uniqueness of calcium wave solutions to such a really complex model was considered by KAŻMIERCZAK and VOLPERT [20] under simplifying assumptions that buffers were immobile and with the body force $\rho\mathbf{u}$ neglected. Very recently, this analysis was pursued by KAŻMIERCZAK and PERADZYŃSKI [21], who considered the case of diffusing buffers and the case of rapid buffers in the sense of WAGNER and KEIZER [4], and showed the convergence of the speeds and pure calcium concentration profile to the profile of the travelling wave of the reduced equation of rapid buffers.

A model very similar to that formed by Eqs. (1.5)–(1.12) was proposed by GOODWIN and TAINOR in [22]. This model was studied in a few papers (see [23, 24] and references therein).

If the cell or tissue is contained in a volume Ω , at least partially limited by the boundary $\partial\Omega$, then some boundary conditions are necessary. Let $\mathbf{n} = \mathbf{n}(\mathbf{x}, t)$ be the outward vector normal to the boundary $\partial\Omega$ at the point $\mathbf{x} \in \partial\Omega$ and time t . Following PERADZYŃSKI [18] and KAŻMIERCZAK and DYZMA [19] we assume that the boundary $\partial\Omega$ is unloaded, that is we assume:

$$(1.13) \quad \sigma_{ij}n_j|_{\partial\Omega} = 0, \quad i = 1, 2, 3.$$

We need also boundary conditions for the free calcium concentration c and the buffers b_i . The internal concentration of calcium in the cell is low, whereas in the extracellular matrix is much higher. Usually, the supply of calcium from the internal stores, represented in the considered model by the function $f(c)$, is insufficient and the cell pumps in the calcium from the outside through special calcium channels. The large difference in concentrations does not play any role, since the influx of calcium is strictly controlled by the cell. It takes place only if the cell needs more calcium when stimulated, and it is stopped if the concentration of calcium reaches the point of saturation. More information on calcium dynamics can be found in the monograph by KEENER and SNEYD [2]. In the present paper we mimic this process by imposing the boundary condition of the Robin type. This condition relates, on the boundary, the value of the calcium flux in the direction of the outward normal to the boundary and the value of the calcium concentration on the interior side of the cell boundary. This condition can be formulated as follows:

$$(1.14) \quad D \frac{\partial c}{\partial \mathbf{n}} = R(c, \mathbf{x}, t), \quad \mathbf{x} \in \partial\Omega,$$

where R is a given function representing this admitted amount of calcium which the cell takes from its surrounding or removes from its interior. If $R(c, \mathbf{x}, t) \geq 0$

at a point of the boundary, then calcium flows in the interior of the cell, if $R(c, \mathbf{x}, t) \leq 0$ then some amount of calcium is removed from the cell. We will precise the form of R later as now we do not need its details. The boundary conditions for the buffers are assumed to be of the form:

$$(1.15) \quad D_i \frac{\partial b_i}{\partial \mathbf{n}} = 0, \quad \mathbf{x} \in \partial\Omega, \quad i = 1, 2, \dots, n,$$

since there is no flux of buffers through the boundary of the cell.

Finally, we take the following initial conditions:

$$(1.16) \quad \begin{aligned} c(\mathbf{x}, 0) &= \bar{c}(\mathbf{x}), & b_i(\mathbf{x}, 0) &= \bar{b}_i(\mathbf{x}), & \mathbf{x} &\in \Omega, \\ \mathbf{u}(\mathbf{x}, 0) &= \mathbf{0}, & \mathbf{x} &\in \Omega. \end{aligned}$$

The last condition follows from the definition of the displacement

2. Nondimensionalisation

According to the standard procedure we rewrite all equations introduced in the preceding section in a nondimensional form (see [14]). Let L_0 and T_0 be the typical length and time scales, respectively. The dimensionless time, position, and the displacement are defined by

$$(2.1) \quad t^* = \frac{t}{T_0}, \quad \mathbf{x}^* = \frac{\mathbf{x}}{L_0}, \quad \mathbf{u}^* = \frac{\mathbf{u}}{L_0}.$$

Using these quantities, we define

$$(2.2) \quad \begin{aligned} \mu_1^* &= \frac{1-2\nu}{1-\nu} \frac{\mu_1(1+\nu)}{ET_0}, & \mu_2^* &= \frac{1-2\nu}{1-\nu} \frac{\mu_2(1+\nu)}{ET_0}, \\ \rho^* &= \frac{1-2\nu}{1-\nu} \frac{\rho L_0^2(1+\nu)}{E}, & \tau^* &= \frac{1-2\nu}{1-\nu} \frac{(1+\nu)}{E} \tau, \\ D^* &= \frac{DT_0}{L_0^2}, & D_i^* &= \frac{D_i T_0}{L_0^2}, & k_-^{i*} &= T_0 k_-^i, & k_+^{i*} &= T_0 k_+^i, \\ & & f^* &= T_0 f, & \gamma^* &= T_0 \gamma, \end{aligned}$$

The nondimensionalized form of the system (1.12), (1.5), (1.9) along with (1.6), (1.7), (1.10), is

$$(2.3) \quad \frac{\partial c}{\partial t} = D\Delta c + f(c) + \sum_{i=1}^n [k_-^i b_i - k_+^i c(b_0^i - b_i)] + \gamma\theta,$$

$$(2.4) \quad \frac{\partial b_i}{\partial t} = D_i \Delta b_i - [k_-^i b_i - k_+^i c(b_0^i - b_i)], \quad i = 1, 2, \dots, n,$$

and

$$(2.5) \quad \frac{\partial \cdot}{\partial x_j} \left[\left(\frac{1-2\nu}{1-\nu} + \mu_1 \frac{\partial}{\partial t} \right) \varepsilon_{ij} + \left(\frac{\nu}{1-\nu} + \mu_2 \frac{\partial}{\partial t} \right) \theta \delta_{ij} + \tau \delta_{ij} \right] = \rho u_i, \quad i = 1, 2, 3,$$

where we have suppressed the asterisks for notational convenience; and, naturally, from now on all the quantities will be nondimensional.

3. Geometry motivated approximations

In this section, we present procedures generated by the geometry of the considered domains, which lead to some simplification of the boundary value problems posed in Section 1. We limit ourselves to thin domains only.

3.1. Thin circular fibre

In this subsection, we consider the transportation of calcium in a long thin fibre of a circular cross section of the radius a . We limit our considerations to the case when the problem possesses the cylindrical symmetry. It means that every function q defined on the fibre is of the form

$$(3.1) \quad q(x_1, x_2, x_3, t) = q(x_1, \varsigma, t), \quad \varsigma = \frac{x_2^2 + x_3^2}{a^2},$$

where the coordinate system we use is as follows: the x_1 -axis coincides with the central axis of the cylinder and the x_2 - and x_3 -axes are perpendicular to it.

We assume that the displacements are of the form

$$(3.2) \quad u_1 = \frac{\partial \varphi}{\partial x_1}, \quad u_2 = w x_2, \quad u_3 = w x_3.$$

Under assumptions (3.1)–(3.2) the force balance equations (2.5) reduce to two following ones

$$(3.3) \quad 2 \left(\varsigma \frac{\partial}{\partial \varsigma} + 1 \right) \frac{\partial}{\partial \varsigma} \left(\frac{1-2\nu}{1-\nu} + \mu_1 \frac{\partial}{\partial t} \right) \varphi = a^2 \left[\rho \varphi - \tau - \left(1 + (\mu_1 + \mu_2) \frac{\partial}{\partial t} \right) \Delta_1 \varphi - \left(\frac{1}{1-\nu} + (\mu_1 + 2\mu_2) \frac{\partial}{\partial t} \right) \left(\varsigma \frac{\partial}{\partial \varsigma} + 1 \right) w \right],$$

$$(3.4) \quad \frac{\partial}{\partial \varsigma} \left[\left(\frac{1}{1-\nu} + (\mu_1 + 2\mu_2) \frac{\partial}{\partial t} \right) \Delta_1 \varphi + 4 \left(1 + (\mu_1 + \mu_2) \frac{\partial}{\partial t} \right) \left(\varsigma \frac{\partial}{\partial \varsigma} + 1 \right) w + 2\tau \right] = a^2 \left[\rho w - \frac{1}{2} \left(\frac{1-2\nu}{1-\nu} + \mu_1 \frac{\partial}{\partial t} \right) \Delta_1 w \right],$$

where we introduced the symbol $\Delta_1 = \partial^2/\partial x_1^2$ of one-dimensional ‘‘Laplacian’’ for sake of consistency of notation, which will be used in the future.

The calcium equation (2.3) becomes

$$(3.5) \quad D\left(\varsigma \frac{\partial}{\partial \varsigma} + 1\right) \frac{\partial c}{\partial \varsigma} = \frac{a^2}{4} \left[\frac{\partial c}{\partial t} - D\Delta_1 c - \sum_{i=1}^n [k_-^i b_i - k_+^i c(b_0^i - b_i)] - f - \gamma\theta \right],$$

where

$$(3.6) \quad \theta = \Delta_1 \varphi + 2\left(\varsigma \frac{\partial}{\partial \varsigma} + 1\right)w,$$

and the buffer equations (2.4) take the form

$$(3.7) \quad D_i\left(\varsigma \frac{\partial}{\partial \varsigma} + 1\right) \frac{\partial b_i}{\partial \varsigma} = \frac{a^2}{4} \left[\frac{\partial b_i}{\partial t} - D_i \Delta_1 b_i + (k_-^i b_i - k_+^i c(b_0^i - b_i)) \right].$$

Now, let us consider the boundary conditions (1.13)–(1.15). The normal vector for the boundary is

$$\mathbf{n} = \left(0, \frac{x_2}{a}, \frac{x_3}{a} \right).$$

Hence, owing to (3.1) and (3.2) the boundary conditions (1.13) reduce to two equations of the form

$$(3.8) \quad \left[2\left(\frac{1-2\nu}{1-\nu} + \mu_1 \frac{\partial}{\partial t}\right) \frac{\partial \varphi}{\partial \varsigma} + a^2 \left(\frac{1-2\nu}{1-\nu} + \mu_1 \frac{\partial}{\partial t}\right) w \right]_{\varsigma=1} = 0,$$

$$(3.9) \quad \left[\left(\frac{\nu}{1-\nu} + \mu_2 \frac{\partial}{\partial t}\right) (\Delta_1 \varphi + w) + \left(2\varsigma \frac{\partial}{\partial \varsigma} + 1\right) \left(1 + (\mu_1 + \mu_2) \frac{\partial}{\partial t}\right) w + \tau \right]_{\varsigma=1} = 0.$$

Finally, let us consider the conditions (1.14) and (1.15). We assume that

$$(3.10) \quad R = a\psi(\mathbf{b}),$$

where $\mathbf{b} = (c, b_1, \dots, b_n)$. Hence, the boundary conditions (1.14) and (1.15) reduce to:

$$(3.11) \quad \left[D \frac{\partial c}{\partial \varsigma} - \frac{a^2}{4} \psi \right]_{\varsigma=1} = 0, \quad \left[D_i \frac{\partial b_i}{\partial \varsigma} \right]_{\varsigma=1} = 0, \quad i = 1, 2, \dots, n.$$

We proceed to solving the boundary value problem (3.4)–(3.11). We seek solutions in the form of the asymptotic expansion with respect to powers of a^2 . This means that every quantity represented by q is assumed to admit an expansion of the form

$$(3.12) \quad q(x_1, \varsigma, t) = \sum_{k=0}^{\infty} q_k(x_1, \varsigma, t)a^{2k},$$

where a^2 is treated as the small parameter.

Next, we admit, that every quantity P like τ , ψ , etc. depends on $\mathbf{b} = (c, b_1, \dots, b_n)$ and on x_1, t only, but does not depend on a . However, as \mathbf{b} depends on a , so does P , and that is why it must be developed in powers of a^2 . This expansion is of the form

$$(3.13) \quad P = \sum_{k=0}^{\infty} P_k(\mathbf{b}_0, \mathbf{b}_1, \dots, \mathbf{b}_k, x_1, t)a^{2k},$$

where the first coefficients are

$$(3.14) \quad P_0 = P(\mathbf{b}_0), \quad P_1(\mathbf{b}_0, \mathbf{b}_1) = P'_b(\mathbf{b}_0)\mathbf{b}_1, \quad \text{etc,}$$

where $\mathbf{b}_0, \mathbf{b}_1, \dots, \mathbf{b}_k$ are coefficients in the expansion of the type (3.12).

Setting formally $a = 0$ in (3.3), (3.4) and (3.5), (3.7) we obtain the equations of the lowest order of approximation

$$(3.15) \quad \left(\varsigma \frac{\partial}{\partial \varsigma} + 1 \right) \frac{\partial}{\partial \varsigma} \left(\frac{1 - 2\nu}{1 - \nu} + \mu_1 \frac{\partial}{\partial t} \right) \varphi_0 = 0,$$

$$(3.16) \quad \frac{\partial}{\partial \varsigma} \left[\left(\frac{1}{1 - \nu} + (\mu_1 + 2\mu_2) \frac{\partial}{\partial t} \right) \Delta_1 \varphi_0 + 4 \left(1 + (\mu_1 + \mu_2) \frac{\partial}{\partial t} \right) \left(\varsigma \frac{\partial}{\partial \varsigma} + 1 \right) w_0 + 2\tau_0 \right] = 0,$$

$$(3.17) \quad \left(\varsigma \frac{\partial}{\partial \varsigma} + 1 \right) \frac{\partial c_0}{\partial \varsigma} = 0, \quad \left(\varsigma \frac{\partial}{\partial \varsigma} + 1 \right) \frac{\partial b_{i0}}{\partial \varsigma} = 0,$$

subject to the conditions

$$(3.18) \quad \left[\left(\frac{1 - 2\nu}{1 - \nu} + \mu_1 \frac{\partial}{\partial t} \right) \frac{\partial \varphi_0}{\partial \varsigma} \right]_{\varsigma=1} = 0,$$

$$(3.19) \quad \left[\left(\frac{\nu}{1 - \nu} + \mu_2 \frac{\partial}{\partial t} \right) (\Delta_1 \varphi_0 + w_0) + \left(2\varsigma \frac{\partial}{\partial \varsigma} + 1 \right) \left(1 + (\mu_1 + \mu_2) \frac{\partial}{\partial t} \right) w_0 + \tau_0 \right]_{\varsigma=1} = 0,$$

$$(3.20) \quad \left[\frac{\partial c_0}{\partial \varsigma} \right]_{\varsigma=1} = 0, \quad \left[\frac{\partial b_{i0}}{\partial \varsigma} \right]_{\varsigma=1} = 0,$$

where w_{00} is an arbitrary function which can depend on x_1, t . We take

ASSUMPTION 1. For any $k = 0, 1, 2, \dots$, and $\varsigma \in [0, 1]$, the functions $q_k(x_1, x_2, t, \varsigma)$ together with their derivatives with respect to ς are bounded.

Integrating Eq. (3.15) with respect to ς and using the condition of Assumption 2 we obtain

$$(3.21) \quad \left(\frac{1-2\nu}{1-\nu} + \mu_1 \frac{\partial}{\partial t} \right) \varphi_0 = \varphi_{00},$$

where φ_{00} is an arbitrary function of x_1, t . The general solution of Eq. (3.21) is

$$(3.22) \quad \varphi_0 = \left(\bar{\varphi}_{00}(x_1, \varsigma) + \frac{1}{\mu_1} \int_0^t \varphi_{00}(x_1, \xi) \exp \left[\frac{1-2\nu}{1-\nu} \frac{\xi}{\mu_1} \right] d\xi \right) \exp \left[-\frac{1-2\nu}{1-\nu} \frac{t}{\mu_1} \right],$$

where $\bar{\varphi}_{00}(x_1, \varsigma)$ is another arbitrary function, which, in general, may depend on ς . To determine this function we use the following initial condition: $\varphi_0(x_1, \varsigma, 0) = 0$ which results from the initial condition (1.16) for the displacement \mathbf{u} and the definition (3.2) of φ . The solution (3.22) satisfies the adopted initial condition if and only if $\bar{\varphi}_{00}(x_1, \varsigma) \equiv 0$. Owing to this we conclude that φ_0 is an arbitrary function of x_1 and t that is $\varphi_0 = \varphi_0(x_1, t)$. With such φ_0 , the boundary condition (3.18) is trivially satisfied. Next, it follows immediately from Eqs. (3.17) that c_0 and b_{i0} , $i = 1, 2, \dots, n$ are functions of x_1 and t only, and they do not depend on ς . Of course, such functions satisfy the boundary conditions (3.20) identically. The equations for φ_0, c_0, b_{i0} will be found by considering suitable equations of the next order approximations. It remains to consider Eq. (3.16) subject to the boundary condition (3.19). Since c_0, \mathbf{b}_0 do not depend on ς , so does the function $\tau_0 = \tau(c_0)$. Due to that and due to the fact that φ_0 does not depend on ς either, Eq. (3.16) reduces to

$$\frac{\partial}{\partial \varsigma} \left[\left(1 + (\mu_1 + \mu_2) \frac{\partial}{\partial t} \right) \left(\varsigma \frac{\partial}{\partial \varsigma} + 1 \right) w_0 \right] = 0.$$

One can easily write down its general bounded solution. It reads:

$$(3.23) \quad \left(1 + (\mu_1 + \mu_2) \frac{\partial}{\partial t} \right) w_0 = w_{00},$$

where $w_{00} = w_{00}(x_1, t)$ is an arbitrary function of x_1, t only. The above equation is a linear ordinary differential equation, whose general solution is

$$w_0 = \left(\bar{w}_{00}(x_1, \varsigma) + \frac{1}{\mu_1} \int_0^t w_{00}(x_1, \xi) \exp \left[\frac{1-2\nu}{1-\nu} \frac{\xi}{\mu_1 + \mu_2} \right] d\xi \right) \times \exp \left[-\frac{1-2\nu}{1-\nu} \frac{t}{\mu_1 + \mu_2} \right],$$

where $\bar{w}_{00}(x_1, \varsigma)$ is an arbitrary function, which, in general, may depend on ς . However, w_0 has to satisfy the initial condition $w_0(t=0) = 0$, formulated in (1.16). Therefore, $\bar{w}_{00}(x_1, \varsigma)$ must be equal to zero. Hence, w_0 does not depend on ς . Using this fact in the boundary condition (3.19) we obtain the equation:

$$(3.24) \quad \left(\frac{\nu}{1-\nu} + \mu_2 \frac{\partial}{\partial t} \right) \Delta_1 \varphi_0 + \left(\frac{1}{1-\nu} + (\mu_1 + 2\mu_2) \frac{\partial}{\partial t} \right) w_0 + \tau_0 = 0.$$

To determine φ_0 and \mathbf{b}_0 we consider the next order approximation to Eqs. (3.3), (3.5) and (3.7). These equations read

$$(3.25) \quad 2 \left(\varsigma \frac{\partial}{\partial \varsigma} + 1 \right) \frac{\partial}{\partial \varsigma} \left(\frac{1-2\nu}{1-\nu} + \mu_1 \frac{\partial}{\partial t} \right) \varphi_1 \\ = \rho \varphi_0 - \tau_0 - \left(1 + (\mu_1 + \mu_2) \frac{\partial}{\partial t} \right) \Delta_1 \varphi_0 - \left(\frac{1}{1-\nu} + (\mu_1 + 2\mu_2) \frac{\partial}{\partial t} \right) w_0,$$

$$(3.26) \quad D \left(\varsigma \frac{\partial}{\partial \varsigma} + 1 \right) \frac{\partial c_1}{\partial \varsigma} = \frac{1}{4} \left[\frac{\partial c_0}{\partial t} - D \Delta_1 c_0 - f_0 - \gamma \theta_0 \right],$$

$$(3.27) \quad D_i \left(\varsigma \frac{\partial}{\partial \varsigma} + 1 \right) \frac{\partial b_{i1}}{\partial \varsigma} = \frac{1}{4} \left[\frac{\partial b_{i0}}{\partial t} - D_i \Delta_1 b_{i0} + (k_-^i b_i - k_+^i c_0 (b_0^i - b_{i0})) \right].$$

The boundary conditions (3.8) and (3.11) yield

$$(3.28) \quad \left[2 \left(\frac{1-2\nu}{1-\nu} + \mu_1 \frac{\partial}{\partial t} \right) \frac{\partial \varphi_1}{\partial \varsigma} + \left(\frac{1-2\nu}{1-\nu} + \mu_1 \frac{\partial}{\partial t} \right) w_0 \right]_{\varsigma=1} = 0,$$

$$(3.29) \quad \left[D \frac{\partial c_1}{\partial \varsigma} - \frac{1}{4} \psi^{(0)} \right]_{\varsigma=1} = 0, \quad \left[D_i \frac{\partial b_{i1}}{\partial \varsigma} \right]_{\varsigma=1} = 0, \quad i = 1, 2, \dots, n.$$

Some terms on the right-hand side of Eqs. (3.25)–(3.27) are omitted due to that φ_0 , w_0 , c_0 do not depend on ς .

Equation (3.25) and Assumption 1 result in

$$(3.30) \quad 2 \frac{\partial}{\partial \varsigma} \left(\frac{1-2\nu}{1-\nu} + \mu_1 \frac{\partial}{\partial t} \right) \varphi_1 \\ = \rho \varphi_0 - \tau_0 - \left(1 + (\mu_1 + \mu_2) \frac{\partial}{\partial t} \right) \Delta_1 \varphi_0 - \left(\frac{1}{1-\nu} + (\mu_1 + 2\mu_2) \frac{\partial}{\partial t} \right) w_0.$$

Similarly, Eqs. (3.26) and (3.27) along with Assumption 1 yield

$$(3.31) \quad D \frac{\partial c_1}{\partial \varsigma} = \frac{1}{4} \left[\frac{\partial c_0}{\partial t} - D \Delta_1 c_0 - \sum_{i=1}^n [k_-^j b_{j0} - k_+^j c_0 (b_0^j - b_{j0})] - f_0 - \gamma \theta_0 \right],$$

$$(3.32) \quad D_i \frac{\partial b_{i1}}{\partial \varsigma} = \frac{1}{4} \left[\frac{\partial b_{i0}}{\partial t} - D_i \Delta_1 b_{i0} + (k_-^i b_i - k_+^i c_0 (b_0^i - b_{i0})) \right].$$

Inserting (3.30) into the boundary condition (3.28) we conclude that this condition is fulfilled provided that φ_0 is such that

$$(3.33) \quad \left(1 + (\mu_1 + \mu_2) \frac{\partial}{\partial t}\right) \Delta_1 \varphi_0 + 2 \left(\frac{\nu}{1 - \nu} + \mu_2 \frac{\partial}{\partial t}\right) w_0 + \tau_0 = \rho \varphi_0.$$

Similarly, inserting (3.31) into the first of the boundary condition (3.29) and inserting (3.32) into the boundary conditions (3.29) for b_{i1} we find that these conditions are fulfilled if c_0 is a solution of the following equation:

$$(3.34) \quad \frac{\partial c_0}{\partial t} = D \Delta_1 c_0 + \sum_{i=1}^n [k_-^j b_{j0} - k_+^j c_0 (b_0^j - b_{j0})] + f_0 + \psi_0 + \gamma \theta_0,$$

and b_{i1} satisfy

$$(3.35) \quad \frac{\partial b_{i0}}{\partial t} = D_i \Delta_1 b_{i0} + (k_-^i b_i - k_+^i c_0 (b_0^i - b_{i0})), \quad i = 1, 2, \dots, n,$$

where

$$(3.36) \quad \theta_0 = \Delta_1 \varphi_0 + 2w_0.$$

Equations (3.24) and (3.33)–(3.35) form a closed system of $n + 3$ equations for $n + 3$ unknown functions $\varphi_0, w_0, c_0, b_{10}, \dots, b_{n0}$.

3.2. Thin slab

Now we consider the motion of calcium in visco-elastic material filling a thin slab with plane parallel walls, i.e., $(x_1, x_2, x_3) \in \mathbb{R}^2 \times [-a, a]$, with the plane $(x_1, x_2, 0)$ being the plane of symmetry. We limit ourselves to a simpler case when the displacements within any plane parallel to the walls of the slab are potential. We assume also that the phenomenon under investigation is symmetric with respect to the x_3 . Under these assumptions we can write

$$(3.37) \quad \begin{aligned} u_\alpha(x_1, x_2, x_3) &= \frac{\partial \varphi(x_1, x_2, \varsigma, t)}{\partial x_\alpha}, \quad \alpha = 1, 2, \quad u_3 = w(x_1, x_2, \varsigma, t) x_3, \\ c &= c(x_1, x_2, \varsigma, t), \quad b_i = b_i(x_1, x_2, \varsigma, t), \quad i = 1, 2, \dots, n, \quad \varsigma = \left(\frac{x_3}{a}\right)^2. \end{aligned}$$

Thanks to these assumptions the force balance equations (2.5) reduce to two equations

$$(3.38) \quad \begin{aligned} &\left(2\varsigma \frac{\partial}{\partial \varsigma} + 1\right) \frac{\partial}{\partial \varsigma} \left(\frac{1 - 2\nu}{1 - \nu} + \mu_1 \frac{\partial}{\partial t}\right) \varphi \\ &= a^2 \left[\rho \varphi - \tau - \left(1 + (\mu_1 + \mu_2) \frac{\partial}{\partial t}\right) \Delta_2 \varphi \right. \\ &\quad \left. - \frac{1}{2} \left(\frac{1}{1 - \nu} + (\mu_1 + 2\mu_2) \frac{\partial}{\partial t}\right) \left(2\varsigma \frac{\partial}{\partial \varsigma} + 1\right) w \right], \end{aligned}$$

and

$$(3.39) \quad \frac{\partial}{\partial \varsigma} \left[\left(\frac{1}{1-\nu} + (\mu_1 + 2\mu_2) \frac{\partial}{\partial t} \right) \Delta_2 \varphi + 2 \left(2\varsigma \frac{\partial}{\partial \varsigma} + 1 \right) \left(1 + (\mu_1 + \mu_2) \frac{\partial}{\partial t} \right) w + 2\tau \right] \\ = a^2 \left[\rho w - \frac{1}{2} \left(\frac{1-2\nu}{1-\nu} + \mu_1 \frac{\partial}{\partial t} \right) \Delta_2 w \right],$$

for two unknown functions φ and w , where $\Delta_2 = \frac{\partial}{\partial x_1^2} + \frac{\partial}{\partial x_2^2}$ is the two-dimensional Laplacian. The calcium equation (2.3) can be written as

$$(3.40) \quad D \left(2\varsigma \frac{\partial}{\partial \varsigma} + 1 \right) \frac{\partial c}{\partial \varsigma} = \frac{a^2}{2} \left(\frac{\partial c}{\partial t} - \Delta_2 c - \sum_{i=1}^n [k_-^i b_j - k_+^i c(b_0^i - b_j)] - f - \gamma \theta \right),$$

where

$$(3.41) \quad \theta = \Delta_2 \varphi + \left(2\varsigma \frac{\partial}{\partial \varsigma} + 1 \right) w,$$

and buffer equations (2.4) take the form

$$(3.42) \quad D_i \left(\varsigma \frac{\partial}{\partial \varsigma} + 1 \right) \frac{\partial b_i}{\partial \varsigma} = \frac{a^2}{2} \left[\frac{\partial b_i}{\partial t} - D_i \Delta_1 b_i + (k_-^i b_i - k_+^i c(b_0^i - b_i)) \right].$$

The vector normal to the upper boundary is $\mathbf{n}_+ = (0, 0, 1)$, whereas the normal to the lower boundary is $\mathbf{n}_- = (0, 0, -1)$. Therefore, owing to (3.37), the boundary conditions (1.13) reduce to two equations of the form

$$(3.43) \quad \left[2 \left(\frac{1-2\nu}{1-\nu} + \mu_1 \frac{\partial}{\partial t} \right) \frac{\partial \varphi}{\partial \varsigma} + a^2 \left(\frac{1-2\nu}{1-\nu} + \mu_1 \frac{\partial}{\partial t} \right) w \right]_{\varsigma=1} = 0,$$

and

$$(3.44) \quad \left[\left(\frac{\nu}{1-\nu} + \mu_2 \frac{\partial}{\partial t} \right) \Delta_2 \varphi + \left(2\varsigma \frac{\partial}{\partial \varsigma} + 1 \right) \left(1 + (\mu_1 + \mu_2) \frac{\partial}{\partial t} \right) w + \tau \right]_{\varsigma=1} = 0.$$

Finally, we consider the boundary conditions (1.14) and (1.15). We assume that

$$(3.45) \quad R = x_3 \psi(\mathbf{b}, x_1, x_2, t).$$

Hence, the boundary conditions (1.14) and (1.15) reduce to:

$$(3.46) \quad \left[D \frac{\partial c}{\partial \varsigma} - \frac{a^2}{2} \psi \right]_{\varsigma=1} = 0, \quad \left[D_i \frac{\partial b_i}{\partial \varsigma} \right]_{\varsigma=1} = 0, \quad i = 1, 2, \dots, n.$$

We proceed to solving the equations (3.38)–(3.44) subject to the boundary conditions (3.43), (3.44), and (3.46). We seek solutions in the form of the asymptotic expansion with respect to powers of a^2 . This means that every quantity represented by P is assumed to admit an expansion of the form

$$(3.47) \quad q(x_1, x_2, \varsigma, t) = \sum_{k=0}^{\infty} q_k(x_1, x_2, \varsigma, t) a^{2k},$$

where a^2 is treated as the small parameter.

Next, we assume that each quantity P like τ , ψ , etc. can depend on \mathbf{b} and on x_1, x_2, t only, but does not depend on a . However, as \mathbf{b} depends on a , so does P , and that is why P must be developed in powers of a^2 . This expansion is of the form

$$(3.48) \quad P = \sum_{k=0}^{\infty} P_k(\mathbf{b}_0, \mathbf{b}_1, \dots, \mathbf{b}_k, x_1, x_2, t) a^{2k},$$

where the coefficients P_k are defined in (3.14). The procedure, which we exploit now is so similar to that used in the preceding subsection that we omit presenting the details and give only the final approximating equations being a sort of counterpart of equations (3.24), (3.33)–(3.36). The present equations read:

$$(3.49) \quad \left(\frac{\nu}{1-\nu} + \mu_2 \frac{\partial}{\partial t} \right) \Delta_2 \varphi_0 + \left(1 + (\mu_1 + \mu_2) \frac{\partial}{\partial t} \right) w_0 + \tau_0 = 0,$$

$$(3.50) \quad \left(1 + (\mu_1 + \mu_2) \frac{\partial}{\partial t} \right) \Delta_2 \varphi_0 + \left(\frac{\nu}{1-\nu} + \mu_2 \frac{\partial}{\partial t} \right) w_0 + \tau_0 = \rho \varphi_0,$$

$$(3.51) \quad \frac{\partial c_0}{\partial t} = D \Delta_2 c_0 + \sum_{i=1}^n \left[k_-^i b_{j_0} - k_+^i c_0 (b_0^i - b_{j_0}) \right] + f(c_0) + \psi_0 + \gamma \theta_0,$$

$$(3.52) \quad \frac{\partial b_{i0}}{\partial t} = D_i \Delta_2 b_{i0} + (k_-^i b_i - k_+^i c_0 (b_0^i - b_{i0})), \quad i = 1, 2, \dots, n,$$

where

$$(3.53) \quad \theta_0 = \Delta_2 \varphi_0 + w_0.$$

4. Mechanics motivated approximations

The systems (3.24), (3.33)–(3.36) and/or (3.49)–(3.53), although being much simpler than the original ones formulated in Section 1 are still so complicated that it is impossible to draw any detailed conclusions of the problem under

consideration. Because of that we are forced to pursue the procedure of simplification. To this end, let us notice that the calcium conservation equations (3.34) and (3.51) are coupled with the mechanical effects only through the term containing the dilatation θ . Hence, it is enough to find a formula relating the dilatation to the traction (assumed to be known) in order to obtain closed systems (3.34), (3.35) or (3.51), (3.52) describing the chemical part of the phenomenon of calcium waves. Receiving such formulae is the goal of the present section.

4.1. Thin fibre

The system composed of equations (3.24) and (3.35) relates three quantities φ_0 , w_0 , and θ_0 , with the latter given by (3.38). We use Eq. (3.38) to eliminate w_0 from equations (3.26) and (3.35) and obtain the following system:

$$(4.1) \quad \left(\frac{1-2\nu}{1-\nu} + \mu_1 \frac{\partial}{\partial t} \right) \Delta_1 \varphi - \left(\frac{1}{1-\nu} + (\mu_1 + 2\mu_2) \frac{\partial}{\partial t} \right) \theta - 2\tau = 0,$$

$$(4.2) \quad \left(\frac{1+\nu}{1-\nu} + (\mu_1 + 3\mu_2) \frac{\partial}{\partial t} \right) \theta + 3\tau = \rho\varphi.$$

For sake of brevity of notation we omitted the subscript ‘0’ by τ , φ and θ . Following PERADZYŃSKI [18] we consider two extreme cases

CASE 1. *Weak restoring force.* We assume that

$$\mu_1 + \mu_2 \rightarrow 0 \quad \text{and} \quad \rho = O((\mu_1 + \mu_2)^2).$$

Under such assumptions we get from Eq. (4.2) the following expansion:

$$(4.3) \quad \theta_{\text{weak}} = -3 \frac{1-\nu}{1+\nu} \tau + 3(\mu_1 + 3\mu_2) \left(\frac{1-\nu}{1+\nu} \right)^2 \frac{\partial}{\partial t} \tau.$$

Using this in Eq. (4.1) we can obtain an approximating formula for $\Delta_1 \varphi$, but this quantity will be not used in our future considerations and due to that we gave up presenting it. Equations (3.35) for the buffers dynamics are left intact.

CASE 2. *Strong restoring force.* We consider the case when

$$\rho \rightarrow \infty, \quad \mu_1 + \mu_2 = O\left(\frac{1}{\rho}\right).$$

We present some details of the construction of the asymptotics, because the present case is more difficult than the previous one. We define

$$(4.4) \quad \varphi = \frac{\tilde{\varphi}}{\rho},$$

and treat $\mu_1\rho$ and $\mu_2\rho$ as quantities of order of magnitude 1 as $\rho \rightarrow \infty$. Introducing the small parameter ε by

$$\varepsilon = \frac{1}{\rho},$$

we give the equations (4.1) and (4.2) the following form:

$$\begin{aligned} \varepsilon \left(\frac{1-2\nu}{1-\nu} + \varepsilon\mu_1\rho \frac{\partial}{\partial t} \right) \Delta_1 \tilde{\varphi} - \left(\frac{1}{1-\nu} + \varepsilon(\mu_1 + 2\mu_2)\rho \frac{\partial}{\partial t} \right) \theta - 2\tau &= 0, \\ \left(\frac{1+\nu}{1-\nu} + \varepsilon(\mu_1 + 3\mu_2)\rho \frac{\partial}{\partial t} \right) \theta + \tau &= \tilde{\varphi}. \end{aligned}$$

Now, the asymptotic expansions of the solutions of this system can be easily constructed. They are

$$(4.5) \quad \theta_{\text{strong}} = -2(1-\nu)\tau + \frac{(1-2\nu)^2}{\rho} \Delta_1 \tau + 2(1-\nu)^2(\mu_1 + 2\mu_2) \frac{\partial}{\partial t} \tau,$$

and the asymptotic expansion for φ is not given, because it does not interest us.

4.2. Thin slab

Similarly as we did in the previous case we eliminate w_0 from equations (3.49) and (3.50) and obtain

$$(4.6) \quad \left(\frac{1-2\nu}{1-\nu} + \mu_1 \frac{\partial}{\partial t} \right) \Delta_2 \varphi - \left(1 + (\mu_1 + \mu_2) \frac{\partial}{\partial t} \right) \theta - \tau = 0,$$

$$(4.7) \quad \left(\frac{1}{1-\nu} + (\mu_1 + 2\mu_2) \frac{\partial}{\partial t} \right) \theta + 2\tau = \rho\varphi.$$

The application of the same procedure as in the case of fibre yields:

CASE 1. *Weak restoring force, when $\mu_1 + \mu_2 \rightarrow 0$ and $\rho = O((\mu_1 + \mu_2)^2)$.*

$$(4.8) \quad \theta_{\text{weak}} = -2(1-\nu)\tau + 2(\mu_1 + 2\mu_2)(1-\nu)^2 \frac{\partial}{\partial t} \tau.$$

The expansion of $\Delta_2\varphi$ is not included since we will not need it in the future.

CASE 2. *Strong restoring force, when $\rho \rightarrow \infty$, $\mu_1 + \mu_2 = O(1/\rho)$.* Now we get

$$(4.9) \quad \theta_{\text{strong}} = -\tau + \frac{1}{\rho} \left(\frac{1-2\nu}{1-\nu} \right)^2 \Delta_1 \tau + (\mu_1 + \mu_2) \frac{\partial}{\partial t} \tau,$$

and the expansion for φ , which we do not present.

4.3. Unbounded space

For sake of references and completeness of our studies we include some remarks concerning the influence of mechanical effects on the calcium motion in the unbounded space \mathbb{R}^3 .

We apply the divergence operator to both sides of Eq. (1.9) with the stress tensor given by (1.6) and arrive at

$$(4.10) \quad \Delta_3 \left(\left(1 + (\mu_1 + \mu_2) \frac{\partial}{\partial t} \right) \theta + \tau \right) = \rho \theta,$$

where $\Delta_3 \equiv \Delta$ is the three-dimensional Laplacian. Now, we follow the reasoning presented in [18] and consider two extreme cases.

CASE 1. *Weak restoring force:* $\mu_1 + \mu_2 \rightarrow 0$, $\rho = O((\mu_1 + \mu_2)^2)$. In this case we obtain from Eq. (4.10) the following approximate formula (under the assumption that θ is bounded and vanishes at infinity):

$$(4.11) \quad \theta_{\text{weak}} = -\tau + (\mu_1 + \mu_2) \frac{\partial \tau}{\partial t}.$$

The buffer equations (2.4) remain unaffected.

CASE 2. *Strong restoring force:* $(\mu_1 + \mu_2) = O(1)$, $\rho \rightarrow \infty$. In this case it can be deduced from Eq. (4.10) that

$$(4.12) \quad \theta_{\text{strong}} = \frac{1}{\rho} \Delta \tau.$$

4.4. Interpolated equations

In the preceding three subsections we received three pairs of formulae supposed to approximate the expression for the dilatation θ . We considered two extreme situations: the cell very susceptible to deformations ($\rho \rightarrow 0$: Eqs. (4.3), (4.8) and (4.11), respectively) or very resistant to them ($\rho \rightarrow \infty$: Eqs. (4.5), (4.9) and (4.12)). The question of a simple approximating formula for θ in the case of intermediate values of ρ was not discussed. Based on the pre-assumption of the Murray–Oster theory [13], [14] that all the mechanical effects are weak, we propose to resolve this question by means of interpolation between θ_{weak} and θ_{strong} , the two elements of the considered pair. To construct such a “bridge” we multiply θ_{weak} by $1/(1 + \rho^2)$, whereas θ_{strong} is multiplied by $\rho^2/(1 + \rho^2)$ and get in this way the following expression supposed to approximate θ :

$$(4.13) \quad \theta = \frac{1}{1 + \rho^2} \theta_{\text{weak}} + \frac{\rho^2}{1 + \rho^2} \theta_{\text{strong}}.$$

Explicitly, if the pairs $(\theta_{\text{weak}}, \theta_{\text{strong}})$ are given by (4.3) and (4.5), or (4.8) and (4.9), or else (4.11) and (4.12), the proposal (4.13) takes the form

$$(4.14) \quad \theta = -\frac{\eta}{\gamma} \tau + \frac{\alpha}{\gamma} \frac{\partial \tau}{\partial t} + \frac{\delta}{\gamma} \Delta_d \tau, \quad d = 1, 2, 3,$$

where d denotes the “dimension” of the domain, $d = 1$ refers to the thin fibre, $d = 2$ is used for the thin slab, and $d = 3$ is the dimension of the unbounded space. The coefficients α, δ, η depend on the case considered and are given explicitly in Table 1.

Table 1. The coefficients α, δ and η in Eq. (4.14).

	α	δ	η
Thin fibre $d = 1$	$\gamma \frac{3(\mu_1 + 3\mu_2) \left(\frac{1-\nu}{1+\nu}\right)^2 + 2\rho^2(\mu_1 + 2\mu_2)(1-\nu)^2}{1+\rho^2}$	$\gamma \frac{\rho(1-2\nu)^2}{1+\rho^2}$	$\gamma \frac{3\frac{1-\nu}{1+\nu} + 2(1-\nu)\rho^2}{1+\rho^2}$
Thin slab $d = 2$	$\gamma \frac{(1-\nu)^2 2(\mu_1 + 2\mu_2) + \rho^2(\mu_1 + \mu_2)}{1+\rho^2}$	$\frac{\gamma\rho}{1+\rho^2} \left(\frac{1-2\nu}{1-\nu}\right)^2$	$\gamma \frac{2(1-\nu) + \rho^2}{1+\rho^2}$
All space \mathbb{R}^3 $d = 3$	$\gamma \frac{\mu_1 + \mu_2}{1+\rho^2}$	$\frac{\gamma\rho}{1+\rho^2}$	$\frac{\gamma}{1+\rho^2}$

Equation (4.14) has a clear interpretation, namely it says that local changes in the volume of the cell are caused by the contractive forces of the traction, as well as the viscous effects: the coefficient $\alpha = 0$ only if both coefficients of viscosity: the shear viscosity $\mu_1 = 0$ and the bulk viscosity $\mu_2 = 0$. The last term, $\delta\Delta_d\tau$, in Eq. (4.14) represents the contribution to volumetric changes generated by the passive forces of resistance of the cell to deformations: vanishing of the coefficient δ means that these forces are ignored (see Table 1). Hence, an equation like (4.14) can be written down based on a purely heuristic sort of argument without evoking many details of a mechanical model of the interior of a cell except for the active traction forces. Our idea consists in using Eq. (4.14) in calcium conservation equations (3.34) or (3.52) or else (1.4), in accordance with the “dimension” d of the domain. The resulting equations are all of the form:

$$(4.15) \quad \frac{\partial}{\partial t}(c - \alpha\tau) = \Delta_d(Dc + \delta\tau) + \sum_{i=1}^n [k_-^i b_j - k_+^i c(b_0^i - b_j)] + f + \psi_d - \eta\tau.$$

For $d = 1, 2$ the functions ψ_d are equal to these functions ψ , which were considered in Sections 3.1 and 3.2, whereas $\psi_3 \equiv 0$, i.e., in the case of the unbounded space. The calcium equations (4.15) are supplemented by the suitable buffer

equation (3.37), (3.52) or (2.4). These equations can be written jointly as

$$(4.16) \quad \frac{\partial b_i}{\partial t} = D_i \Delta_d b_i + (k_-^i b_i - k_+^i c(b_0^i - b_i)), \quad i = 1, 2, \dots, n, \quad d = 1, 2, 3.$$

For biological reasons, it is obvious that the inequality

$$(4.17) \quad c - \alpha \tau \geq 0$$

should be satisfied, since it says simply that the amount of calcium engaged in generating the traction cannot exceed the amount of free calcium available in the cell. The condition (4.17) is equivalent to the following one:

$$(4.18) \quad \alpha \sup_{0 \leq c \leq 1} \frac{\tau(c)}{c} < 1.$$

and this is a limitation imposed on the range of the parameter α : it simply cannot be too large; that is, the coupling between mechanical and chemical effects cannot be too strong.

5. Fast buffering approximation

Equations (4.15) and (4.16) are still too complicated as for the needs of the qualitative analysis of the calcium waves. In this paper we will use the so-called rapid buffering approximation introduced by WAGNER and KEIZER in [4]. It has turned out to be very accurate in many cases. That is why it is so popular and used by many authors [2, 6, 7, 8]. Here, by the way it is worth to mention another sort of simplification consisting in assuming that the buffers are immobile, i.e., $D_i = 0$, $i = 1, 2, \dots, n$. Such models were studied in [7–12, 20]. The problems considered in these papers concern the existence, uniqueness and stability of the calcium waves. In papers [7, 8] many additional facts and comments concerning the relations between rapid buffering approximation, immobile buffer approximation and the full models (1.4) and (1.5) can be found. In the model with rapidly buffered calcium, it is assumed that the buffer kinetics is fast [2, 4–7]. It means that the buffering time scales given by the inverse of every association parameters k_+^i and those of dissociation k_-^i are much shorter than the time of diffusion [4]. Hence, the fast buffering process is a singular perturbation. We eliminate the fast buffering time scale from Eq. (4.15) by adding to it the sum of all equations (4.16). This leads to the equation of the form:

$$(5.1) \quad g_1(c) \frac{\partial c}{\partial t} = \sum_{i=1}^d \frac{\partial}{\partial x_i} \left(g_2(c) \frac{\partial c}{\partial x_i} \right) + g_0(c), \quad d = 1, 2, 3,$$

where

$$(5.2) \quad g_0(c) = f(c) + \psi_d(c) - \eta \tau(c),$$

$$(5.3) \quad g_1(c) = \sum_{i=0}^n \frac{db_i(c)}{dc} - \alpha \tau \frac{d\tau(c)}{dc},$$

$$(5.4) \quad g_2(c) = \sum_{i=0}^n D_i \frac{db_i(c)}{dc} + \delta \frac{d\tau}{dc},$$

where $b_0(c) \equiv c$, $D_0 = D$ and Eqs. (4.16) in the considered type of approximation lead to algebraic equations of form:

$$(5.5) \quad k_-^i b_i - k_+^i c(b_0^i - b_i) = 0, \quad i = 1, 2, \dots, n,$$

whose solutions are

$$(5.6) \quad b_i = b_i(c) = \frac{b_0^i c}{c + K_i}, \quad K_i = \frac{k_-^i}{k_+^i}, \quad i = 1, 2, \dots, n.$$

As we can see the approximate expressions for the buffered calcium concentration do not, in general, satisfy the initial conditions imposed on buffers formulated in (1.16). Hence, this approximation is not applicable during some initial period. Such an effect is typical and is prescribed to the singular character of the procedure leading to Eqs. (5.5).

The rapid buffering approximation provides us with a motivation of treating the b_i 's as given functions of the calcium concentration c . Mostly, we will not use the explicit forms of the functions $b_i(c)$ given by (5.6), with the exception of using them for examples, but we will need their analytic properties. Therefore, we take the following assumption concerning this function:

ASSUMPTION 2. *The functions $b_i : [0, 1] \rightarrow \mathbb{R}^1$, $i = 1, 2, \dots, n$, are continuous together with their second derivative, and such that*

$$(5.7) \quad b_i(c) \geq 0 \text{ with } b_i(0) = 0, \quad \frac{db_i(c)}{dc} \geq 0, \quad \frac{d^2b_i(c)}{dc^2} \leq 0, \\ i = 1, 2, \dots, n, \quad \forall c \in [0, 1].$$

The rapid buffer approximation was obtained both in [4] and [6] in a purely formal way. A rigorous mathematical proof of the asymptotic convergence is given by KAŹMIERCZAK and PERADZYŃSKI [21], but for travelling wave solutions only.

We take the following:

ASSUMPTION 3. *The functions $g_i : [0, 1] \rightarrow \mathbb{R}^1$, $i = 1, 2$ are continuous and strictly positive on their domain.*

COMMENT. Under Assumption 2, Eq. (5.1) admits a very intuitive interpretation. To this end, let us consider the quantity

$$(5.8) \quad z = z(c) = \frac{\int_0^c g_1(y)dy}{\int_0^1 g_1(y)dy} = \frac{\sum_{i=0}^n b_i(c) - \alpha \tau(c)}{\sum_{i=0}^n b_i(1)}.$$

The denominator is just a normalizing factor; hence, as such it has no influence on the sense of z . The numerator in (5.8) is the difference between the sum $\sum_{i=0}^n b_i(c)$ being the total amount of calcium – free calcium ions and the buffered ones – and the amount of it which has been used in developing the active stresses within the cell – the traction – represented in (5.1) by the term $\alpha\tau$. Hence, z is the concentration of this calcium which can be used in the physiological processes other than mechanical stresses. Example of such physiological process are calcium waves. Next, the term on the right-hand side of Eq. (5.1), which contains g_2 , says that all constituents diffuse, including the calcium engaged in developing the traction. The form of the last g_0 , in Eq. (5.1), represents the “stretch activation” effect consisting, in the present case, in lowering the level of calcium in the cell due to the contraction force exerted by the actomyosin molecules, the traction [13, 14].

The dependence of Eq. (5.1) on the geometry of the domain is noticeable. It is visible not only in the form of the constants α, δ, η (cf. Table 1), but also in the number of t space variables $x_i, 1 \leq i \leq d$.

Equation (5.8) defines a one-to-one transformation of the interval $[0, 1]$ onto itself. Let $c = \Psi(z)$ be the transformation inverse to this one. The new variable z satisfies, as it follows from Eqs. (5.1), a reaction-diffusion equation of the form

$$(5.9) \quad \frac{\partial z}{\partial t} = \sum_{i=1}^d \frac{\partial}{\partial x_i} \left(\mathcal{D}(\Psi(z)) \frac{\partial z}{\partial x_i} \right) + G(z), \quad d = 1, 2, 3,$$

where

$$(5.10) \quad G(z) = \frac{g_0(\Psi(z))}{\int_0^1 g_1(y)dy}$$

and

$$(5.11) \quad \mathcal{D}(c) = \frac{g_2(c)}{g_1(c)}.$$

6. Calcium waves

If we set formally $\tau(c) \equiv 0$ in Eqs. (5.2)–(5.4); then, Eq. (5.9) (or strictly speaking its one-dimensional version) coincides with Eq. (10) of reference [7] or

Eq. (2.5) of reference [8]. Since, the proofs of theorems concerning solutions of Eq. (5.9) for the case of $\tau(c) \equiv 0$ given in [7, 8] are based on the fact that the functions g_1 and g_2 are positive, they can be applied to the case when $\tau(c) \geq 0$, provided that Assumption 3 holds. In particular, this is true for the solutions in the form of travelling waves. These are solutions of the form

$$(6.1) \quad z(x, t) = z(\xi), \quad \xi = x - Ut,$$

where $U \in \mathbb{R}^1$ is interpreted as the speed of the wave. We take also the following conditions:

$$(6.2) \quad \lim_{\xi \rightarrow -\infty} z(\xi) = 0, \quad \lim_{\xi \rightarrow +\infty} z(\xi) = 1, \quad \lim_{\xi \rightarrow \mp\infty} \frac{dz(\xi)}{d\xi} = 0.$$

Inserting (6.1) into (5.9) we obtain for $z(\xi)$ the following ordinary differential equation:

$$(6.3) \quad \frac{d}{d\xi} \left(\mathcal{D}(\Psi(z)) \frac{dz}{d\xi} \right) + U \frac{dz}{d\xi} + G(z) = 0.$$

We assume that the function $G(z)$ is bistable. Because of physiological reasons, only these travelling waves are accepted as calcium waves which are waves of excitation. Due to what was said above we have

THEOREM 1 ([8]). *Let $\mathcal{D}(c)$ be a given positive function, and let $G(z)$ be bistable on $[0, 1]$. Then, there exists a unique travelling wave solution of Eq. (4.3) with negative wave speed $U < 0$ if and only if the following inequality holds:*

$$(6.4) \quad \int_0^1 G(z) dz > 0.$$

Moreover, this solution is asymptotically stable and satisfies $dz/d\xi > 0$.

By (5.10) and (5.11) condition (6.4) is equivalent to

$$(6.5) \quad \int_0^1 g_0(c)g_2(c)dc > 0.$$

The disclosed form of the above condition reads:

$$(6.6) \quad \sum_{i=0}^n D_i \int_0^1 g(c) \frac{db_i}{dc} dc + \delta \int_0^1 g(c) \frac{d\tau}{dc} dc > \eta \sum_{i=0}^n D_i \int_0^1 \tau(c) \frac{db_i}{dc} dc,$$

where we denoted

$$(6.7) \quad g(c) = f(c) + \psi_d(c).$$

With the use of (5.11), the inequality (6.6) takes the following form:

$$(6.8) \quad \sum_{i=0}^n \int_0^1 (\alpha D_i + \delta) f(c) \mathcal{F}(c) \frac{db_i}{dc} dc > \alpha \eta \sum_{i=0}^n D_i \int_0^1 \tau(c) \frac{db_i}{dc} dc,$$

where

$$(6.9) \quad 0 < \mathcal{F}(c) = \frac{\alpha D(c)}{\alpha D(c) + \delta} = \alpha \frac{\sum_{i=0}^n D_i \frac{db_i}{dc} + \delta \frac{d\tau}{dc}}{\sum_{i=0}^n (\alpha D_i + \delta) \frac{db_i}{dc}} < 1.$$

To proceed any further it is necessary to have a formula for the function $g(c)$. We assume that it is a bistable function on $[0, 1]$. Then it can be represented in the form

$$(6.10) \quad g(c) = V(c)[V'_c(c_T) - V'_c(c)],$$

where the function V is such that:

$$\begin{aligned} V &\in C^3([0, 1]), & V(0) = V(1) = 0, & V(c) > 0 \quad \text{for } c \in (0, 1), \\ V'_c(0) &> 0, & V'_c(1) < 0, & \exists! c_0 \in (0, 1) \quad \text{such that } V'_c(c_0) = 0, \\ V''_c(c) &\leq 0 & \text{for } c \in [0, 1]. \end{aligned}$$

It is obvious that if such a function V is given and g is of the form (6.10), then g is bistable. Inversely, let the bistable function g be given, then Eq. (6.10) is an equation for V . It can be proved (see [3]) that this equation has a unique solution satisfying all of the conditions (6.10). In what follows we will use an approximate and simpler expression for the function g . By the Lagrange mean value theorem we have

$$V'_c(c) - V'_c(c_T) = (c - c_T)V''_c(\tilde{c}),$$

where \tilde{c} is an intermediate point between c and c_T . Our simplification consists in replacing $V''_c(\tilde{c})$ by $V''_c(c)$. Then (6.10) becomes

$$(6.11) \quad g(c) = F(c)(c - c_T), \quad c \in [0, 1], \quad c_T \in (0, 1),$$

where $F(c) = -V(c)V_c''(c)$. We assume that F does not depend on c_T , and that it satisfies the following conditions:

$$(6.12) \quad \begin{aligned} F \in C^2([0, 1]), \quad F(0) = F(1) = 0, \quad F(c) > 0 \quad \text{for } c \in (0, 1) \\ F_c'(0) > 0, \quad F_c'(1) < 0. \end{aligned}$$

From now on we will consider only this case when f is of the form (6.11). By inserting (6.11) into (6.6) and solving for c_T , we obtain

$$(6.13) \quad c_T < \frac{\sum_{i=0}^n \int_0^1 (\alpha D_i + \delta) c F(c) \mathcal{F}(c) \frac{db_i}{dc} dc}{\sum_{i=0}^n \int_0^1 (\alpha D_i + \delta) \mathcal{F}(c) F(c) \frac{db_i}{dc} dc} - \alpha \eta \frac{\sum_{i=0}^n D_i \int_0^1 \tau(c) \frac{db_i}{dc} dc}{\sum_{i=0}^n \int_0^1 (\alpha D_i + \delta) \mathcal{F}(c) F(c) \frac{db_i}{dc} dc}.$$

The first term on the right-hand side is positive and bounded from above by unity, whereas the second one is negative. Hence, it is possible that the right-hand side of (6.13) is negative. In such a case no calcium wave is admitted. This is an essential difference between the present model with mechanical effects incorporated and the counterpart model with mechanical effects ignored. Namely, in the absence of the mechanical effects, the criterion of the admissibility of calcium waves does not contain any negative term like the second one in (6.13). Hence, the immobile buffers, i.e., such ones that $D_i = 0$, $i = 1, 2, \dots, n$, cannot eliminate the calcium wave (see [7–12]). However, this ceases to be true if the mechanical effects are included. The right-hand side in (6.13) can be negative even if there is no buffering, particularly if

$$\frac{\eta \int_0^1 \tau(c) dc}{\int_0^1 F(c) dc} \gg 1.$$

A more precise condition is given in the following:

THEOREM 2. *If*

$$(6.14) \quad \frac{\eta \int_0^1 \tau(c) dc}{\int_0^1 F(c) dc} > \frac{B_0}{\alpha B_1},$$

where

$$B_0 = \sum_{i=0}^n (\alpha D_i + \delta) \frac{db_i(c)}{dc} \Big|_{c=0}, \quad B_1 = \sum_{i=0}^n D_i \frac{db_i(c)}{dc} \Big|_{c=1},$$

then $c_T < 0$; hence, no calcium wave can exist.

P r o o f. Using in (6.14) the following two estimates:

$$\frac{\sum_{i=0}^n \int_0^1 (\alpha D_i + \delta) c F(c) \mathcal{F}(c) \frac{db_i}{dc} dc}{\sum_{i=0}^n \int_0^1 (\alpha D_i + \delta) F(c) \mathcal{F}(c) \frac{db_i}{dc} dc} < 1,$$

and

$$\sum_{i=0}^n \int_0^1 (\alpha D_i + \delta) \mathcal{F}(c) F(c) \frac{db_i}{dc} dc < \sum_{i=0}^n (\alpha D_i + \delta) \int_0^1 F(c) \frac{db_i}{dc} dc$$

we get

$$(6.15) \quad c_T < 1 - \alpha \eta \frac{\sum_{i=0}^n D_i \int_0^1 \tau(c) \frac{db_i}{dc} dc}{\sum_{i=0}^n (\alpha D_i + \delta) \int_0^1 F(c) \frac{db_i}{dc} dc}.$$

Now, by (5.7) the derivatives db_i/dc are decreasing; therefore, the following estimates hold true

$$\sum_{i=0}^n D_i \int_0^1 \tau(c) \frac{db_i}{dc} dc > B_1 \int_0^1 \tau(c) dc,$$

and

$$\sum_{i=0}^n (\alpha D_i + \delta) \int_0^1 F(c) \frac{db_i}{dc} dc \leq \sum_{i=0}^n \int_0^1 F(c) \frac{db_i}{dc} dc \leq B_0 (\alpha D + \delta) \int_0^1 F(c) dc.$$

Thus, we can replace the right-hand side of (6.15) by

$$c_T < 1 - \frac{DB_1 \alpha \eta}{B_0 (\alpha D + \delta)} \frac{\int_0^1 \tau(c) dc}{\int_0^1 F(c) dc}.$$

Under the assumption (6.14), the quantity c_T is negative. The proof is complete. \square

To illustrate the condition (6.14) let us consider a much simpler case when there is only one buffer with $b_1(c)$ given by (5.6). In such a case, (6.15) takes the form

$$(6.16) \quad \frac{\beta \int_0^1 \tau(c) dc}{\int_0^1 F(c) dc} > \left(\frac{1 + K_1}{K_1} \right)^2 \frac{K_1^2(\alpha D + \delta) + (\alpha D_1 + \delta)b_0^1 K_1}{\alpha D(1 + K_1)^2 + \alpha D_1 b_0^1 K_1}.$$

The following conclusions follow from this inequality:

1. We see clearly that the mechanical resistance can eliminate the calcium wave even if the buffer is stationary, i.e., if $D_1 = 0$. In this case, (6.16) reduces to

$$\frac{\eta \int_0^1 \tau(c) dc}{\int_0^1 F(c) dc} > 1 + \frac{\delta}{\alpha D},$$

what seems to be a realistic condition. This contradicts the predictions of the counterpart mechanics-free theory by SNEYD, DALE and DUFFY [7].

2. If the buffer is of low affinity, i.e., if the rate of binding calcium ions k_+ is much smaller than that of the reverse process k_- , $K_1 \gg 1$, then satisfaction of the relation

$$\frac{\eta \int_0^1 \tau(c) dc}{\int_0^1 F(c) dc} \sim 1$$

is sufficient to eliminate the wave.

3. If the buffer is of high affinity, i.e., if $K_1 \ll 1$, then (6.16) implies that

$$\frac{\eta \int_0^1 \tau(c) dc}{\int_0^1 F(c) dc} \sim \frac{1}{K_1^2} \gg 1,$$

what is rather unrealistic from physiological point of view since the ratio on the left-hand side has to be too large. Such a quite unrealistic result must be prescribed to the fact that, when deducing (6.14), we have estimated the first term on the right-hand side in (6.13) by its upper bound equal to one, but in reality this term may be quite small as in the case of high affinity buffers.

It is worth to put much attention to high affinity buffers as in some situations they can eliminate the calcium wave, what was observed experimentally [25], and

such buffers are used in experiments for visualisation reasons. Some caution is necessary when for a buffer, say i -th, the parameter $K_i \rightarrow 0$ because then the expression given by (5.6) loses its sense for $c = 0, K_i = 0$.

For sake of simplicity of the presentation we consider the case when there is only one buffer with b_1 given by (5.6). The range of the function $\mathcal{F}(c, K_1)$, for every fixed $K_1 > 0$ is a closed interval $[\mathcal{F}_m, 1]$, where

$$(6.17) \quad 0 \leq \mathcal{F}_m = \mathcal{F}_m(K_1) = \inf_{0 \leq c \leq 1} F(c, K_1) \leq 1.$$

We begin with two lemmas.

LEMMA 1. *Let the function $F \in C^1([0, 1])$ be such that $F(0) = 0$. Then the following estimate takes place:*

$$(6.18) \quad \int_0^1 \frac{cF(c)}{(c+K)^2} dc = \int_0^1 \frac{F(c)}{c} dc + O(K \log K) \quad \text{as } K \downarrow 0.$$

Proof. We have

$$\begin{aligned} \left| \int_0^1 \frac{cF(c)}{(c+K)^2} dc - \int_0^1 \frac{F(c)}{c} dc \right| &\leq K \left[2 \int_0^1 \frac{dc}{c+K} + K \int_0^1 \frac{dc}{(c+K)^2} \right] \sup_{c \in [0,1]} \frac{F(c)}{c} \\ &= O(K \log K). \end{aligned}$$

The proof is complete. □

LEMMA 2. *Let the function $F \in C^2([0, 1])$ be such that $F(0) = 0$. Then the following equality takes place:*

$$(6.19) \quad \int_0^1 \frac{F(c)}{(c+K)^2} dc = -F'_c(0) \log K + O(1) \quad \text{as } K \downarrow 0.$$

Proof. By the Taylor formula we have

$$\left| \int_0^1 \frac{F(c)}{(c+K)^2} dc - \int_0^1 \frac{cF'_c(0)}{(c+K)^2} dc \right| \leq \frac{1}{2} \sup_{c \in [0,1]} |F''_c(c)| \int_0^1 \frac{c^2}{(c+K)^2} dc.$$

It remains to evaluate the integral

$$\int_0^1 \frac{c}{(c+K)^2} dc$$

to obtain the thesis. The proof is complete. □

THEOREM 3. *If*

- (i) *the positive constants D, α, δ are independent of K_1 ,*
- (ii) *the function F is independent of $K_1 > 0$ and satisfies conditions (6.12),*
- (iii) *there are constants $K_0 > 0$ and $\mathcal{F}_0 > 0$ such that $\mathcal{F}_m(K_1) > \mathcal{F}_0 > 0$ for $K_1 \in (0, K_0)$,*
- (iv) *there is a constant $\omega > 0$ such that $(\alpha D_1 + \delta)b_0^1 K_1 > \omega > 0$ for $K_1 \in (0, K_0)$.*

Then

$$(6.20) \quad c_T < c_+ = \frac{(\alpha D + \delta) \int_0^1 cF(c)\mathcal{F}(c)dc + (\alpha D_i + \delta)b_0^1 K_1 \int_0^1 \frac{cF(c)\mathcal{F}(c)}{(c + K_1)^2} dc}{(\alpha D + \delta) \int_0^1 F(c)\mathcal{F}(c)dc + (\alpha D_i + \delta)b_0^1 K_1 \int_0^1 \frac{F(c)\mathcal{F}(c)}{(c + K_1)^2} dc} \\ = O\left(\frac{1}{\mathcal{F}_0 \omega \log K_1}\right)$$

for $K_1 \in (0, K_0)$.

P r o o f. Ignoring the first term in the denominator of c_+ we obtain

$$c_+ < \frac{\alpha D + \delta}{(\alpha D_1 + \delta)b_0^1 K} \frac{\int_0^1 cF(c)\mathcal{F}(c)d}{\int_0^1 \frac{F(c)\mathcal{F}(c)}{(c + K_1)^2} dc} + \frac{\int_0^1 \frac{cF(c)\mathcal{F}(c)}{(c + K_1)^2} dc}{\int_0^1 \frac{F(c)\mathcal{F}(c)}{(c + K_1)^2} dc}.$$

By Assumption (iii) we get for $K_1 \in (0, K_0)$

$$c_+ < \frac{1}{\mathcal{F}_0} \frac{\alpha D + \delta}{(\alpha D_1 + \delta)b_0^1 K} \frac{\int_0^1 cF(c)d}{\int_0^1 \frac{F(c)}{(c + K_1)^2} dc} + \frac{1}{\mathcal{F}_0} \frac{\int_0^1 \frac{cF(c)}{(c + K_1)^2} dc}{\int_0^1 \frac{F(c)}{(c + K_1)^2} dc}.$$

At last, using Lemmas 1 and 2 we obtain

$$(6.21) \quad c_+ < \frac{1}{\mathcal{F}_0 F'_c(0)} \frac{\alpha D + \delta}{(\alpha D_i + \delta)b_0^1 K_1 - \log K_1 + O(1)} \frac{\int_0^1 cF(c)d}{\int_0^1 \frac{F(c)}{c} dc + O(K_1 \log K_1)} \\ + \frac{1}{\mathcal{F}_0 F'_c(0)} \frac{\int_0^1 \frac{F(c)}{c} dc + O(K_1 \log K_1)}{-\log K_1 + O(1)}.$$

These estimates and assumptions (iii) and (iv) mean that (6.20) holds. The proof is complete. \square

COMMENT. Since the positive term in the condition (6.13) is very small for high affinity buffers, the right-hand side of this inequality can very easily be negative, hence ruling out the existence of any calcium waves. The prediction of elimination of calcium waves by high affinity buffers agrees with experimental results [26].

REMARK 1. If we take a stronger assumption then Assumption (iii), that is if

$$(6.22) \quad F(c, K_1) \equiv L(K_1) = \text{const.} \quad \text{in } c,$$

then we will get an estimate of the form

$$c_T = O\left(\frac{1}{\omega \log K_1}\right),$$

which is more precise than that of (6.20). This estimate results from the fact that the constant \mathcal{F}_0 , which may be quite small, drops out under assumption (6.22), because the quantity c_+ does not depend on $L(K_1)$.

From the definition (6.9) of \mathcal{F} and from (6.22) we obtain the equation for the diffusivity \mathcal{D} :

$$(6.23) \quad (1 - L)\alpha\mathcal{D} = \delta L.$$

Two cases are interesting:

CASE 1. $L = 1$ and $\delta = 0$. Then \mathcal{D} can be arbitrary positive. But, as it follows from Table 1, $\delta = 0$ implies $\rho = 0$ what means that the natural passive resistance of the cell to deformations is ignored. In such a model, the high affinity buffer can block the formation and propagation of calcium wave if its coefficient of diffusion is high enough and if it is in a sufficiently large amount. The present result is an extension of the suggestions of SNEYD, DALE and DUFFY [7] who gave a numerical evidence of such a phenomenon.

CASE 2. $0 < L < 1$. Now, Eq. (6.23) implies that the diffusivity \mathcal{D} is constant in c , what changes Eq. (5.11) to a very simple ordinary differential equation of the first order for the traction τ . Such an equation has a solution satisfying the two-point boundary conditions (1.8) only if

$$(6.24) \quad \mathcal{D} = \bar{D} = \frac{\sum_{i=0}^n D_i b_i(1)}{\sum_{i=0}^n b_i(1)}.$$

Then, the traction is given the following explicit formula:

$$(6.25) \quad \tau(c) = \frac{1}{\alpha\bar{D} + \delta} \sum_{i=1}^n (\bar{D} - D_i)(b_i(c) - cb_i(1)).$$

Hence, according to (6.20), in a cell of moderate stiffness (i.e., moderate value of δ) an immobile high affinity buffer, if in large amount, can prevent the formation and propagation of calcium wave. This is a new prediction compared to those of [7], where mechanical effects were omitted.

Problem of bistability

In the above discussion we have assumed tacitly that $g(c)$ and $\eta\tau(c)$ are such that $g_0(c)$ defined by (5.2) is bistable. One can doubt, however, whether the conditions (1.2) and (1.8) alone guarantee the bistability of $g_0(c)$. In general, without imposing some additional conditions for $g(c)$ and $\eta\tau(c)$ one can expect that the answer to this question must be negative, what we see below. To simplify the discussion we assume that $g(c)$ is of the form (6.11), i.e.,

$$(6.26) \quad g_0(c) = F(c)(c - c_T) - \eta\tau(c), \quad 0 < c_T < 1.$$

It follows from (6.26) and the assumed properties of the functions $F(c)$ and $\tau(c)$ that

$$(6.27) \quad g_0(0) = 0, \quad g_0(1) = 0, \quad g'_{0,c}(0) = -F'_c(0) - \eta\tau'_c(0) < 0.$$

Hence, $g_0(c)$ has two equilibria $c = 0$ and $c = 1$. The first point of equilibrium is stable, but at the second state we have $g'_{0,c}(1) = F'_c(1)(1 - c_T) - \eta\tau'_c(1)$. In order to have $g_0(c)$ bistable we have to impose an additional assumption that $g'_{0,c}(1) < 0$. We formulate this important result in the form of

PROPOSITION 1. The necessary condition of bistability of the function $g_0(c)$ is

$$(6.28) \quad 0 < c_T < 1 - \eta \frac{\tau'_c(1)}{F'_c(1)}.$$

COMMENT. It follows from the above considerations that the condition of bistability imposes an additional, apart from (6.13), condition which has to be satisfied by the threshold value c_T . Each of the conditions (6.13) and (6.28), on their own, can eliminate calcium waves. Let us note that, in general, the fulfilment of (6.13) and (6.28) does not guarantee the existence of the calcium waves, because (6.28) does not imply the bistability of the function g_0 . By the assumption that (6.28) is satisfied, we conclude that $g_0(c)$ has at least one zero in the open interval $(0, 1)$. However, a bistable function has to have only one zero in this interval. The class of functions satisfying (6.27) and (6.28) and having a single zero in the open interval $(0, 1)$ is very abundant and difficult to be described briefly. On the other hand, it is usually very difficult to solve the equation $g_0(c) = 0$ and show that it has a solution in the interval $(0, 1)$ and that this solution is unique. Hence, a sufficient criterion would be desirable. The simplest example is the following:

PROPOSITION 2. *The function $g_0(c)$ defined by (6.26) is bistable on $[0, 1]$ if the condition (6.28) holds and if*

$$(6.29) \quad \eta \frac{d}{dc} \left(\frac{\tau(c)}{F(c)} \right) < 1$$

for $c \in [0, 1]$.

P r o o f. The function g_0 can be represented in the form:

$$(6.30) \quad g_0(c) = F(c)X(c), \quad c \in [0, 1],$$

where

$$(6.31) \quad \begin{aligned} X(c) &= c - c_T - \eta \frac{\tau(c)}{F(c)}, & c \in (0, 1), \\ X(0) &= -c_T - \eta \frac{\tau'_c(0)}{F'_c(0)}, \\ X(1) &= 1 - c_T - \eta \frac{\tau'_c(1)}{F'_c(1)}. \end{aligned}$$

We have $X(0) < 0$, and due to (6.28) we have $X(1) > 0$. Hence, $X(c)$ has at least one zero within the interval $(0, 1)$. This zero is unique if, for example, $X(c)$ is monotonically increasing, what is expressed by (6.29). The proof is complete. \square

We see from the above discussion that the demand of the bistability of Eq. (5.1), equivalently Eq. (5.9), imposes additional serious constrains for the existence of calcium waves: the threshold parameter c_T has to satisfy two restrictions (6.13) and (6.28) instead of only one as it is in the models which neglect mechanical effects [7]. We have shown that not only the high affinity buffers but also the mechanical effects alone can prevent the formation and propagation of calcium wave. We have concluded that the remedy is a sufficiently strong supply of calcium to the cell.

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