MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **10**, Number **3**, June **2013**

doi:10.3934/mbe.2013.10.743

pp. **743–759**

CALCIUM WAVES WITH MECHANO-CHEMICAL COUPLINGS

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Abstract. As follows from experiments, waves of calcium concentration in biological tissues can be easily excited by a local mechanical stimulation. Therefore the complete theory of calcium waves should also take into account coupling between mechanical and chemical processes. In this paper we consider the existence of travelling waves for buffered systems, as in [22], completed, however, by an equation for mechanical equilibrium and respective mechanochemical coupling terms. Thus the considered, coupled system consists of reaction-diffusion equations (for the calcium and buffers concentrations) and equations for the balance of mechanical forces.

1. **Introduction.** One of the most important mechanisms by which cells control their activity and coordinate it with their neighbours are calcium oscillations and waves. According to their speed, they can be divided into the following classes: *ultraslow* (speed range from 0.1 to 1 nm/s), *slow* (speed range from 0.1 to 1 $\mu m/s$), *fast* (speed range from 1 to 50 $\mu m/s$), *ultrafast* (speed range from 10 to 100 cm/s) (see [8] and the webpage of Jaffe & Creton). The ultraslow waves are rather hypothetical, whereas the ultrafast calcium waves are electrically supported. In this paper we will be interested in the analysis of slow and fast waves. From experimental observation, we know that mechanical forces can influence or even generate the calcium waves propagation (see, e.g. [7], [10],[15],[25]). It is agreed that the mechanical stimulation of a sufficiently large amplitude evokes the release of calcium from internal stores, and initiates a wave propagation by the autocatalytic mechanism (calcium induced calcium release abreviated as CICR). In [9], the experimental evidence and a physical explanation concerning the possibility of another mechanism *calcium induced calcium influx* - CICI) supporting a new class of fast waves, by stretch-activated calcium channnels on the surface of the cell membrane, is reported. The speed of these waves ranges from 100 to 1000$\mu m/s$. In conclusion, we assert that the mechanics influences calcium concentration. In fact, the cytosolic calcium concentration influences also the deformation field of the medium.

2010 *Mathematics Subject Classification.* Primary: 35K57, 35C07; Secondary: 35Q92.

Key words and phrases. Calcium waves, reaction-diffusion systems, mechanochemical coupling.

The paper was supported by MNiSW grant N N201548738. B. K. was also partially supported by FNP project TEAM/2009-3/6.

Treating tissue as a visco-elastic medium and having in mind that the deformation accompanying the calcium waves is relatively small, we can describe the balance of the mechanical forces by the equation $\nabla \cdot \sigma = k\mathbf{u}$, i.e.

$$\nabla \cdot \left\{ \frac{E}{1+\nu} \left[\boldsymbol{\epsilon} + \frac{\nu}{1-2\nu} \theta \mathbf{I} \right] + \mu_1 \frac{\partial \boldsymbol{\epsilon}}{\partial t} + \mu_2 \frac{\partial \theta}{\partial t} \mathbf{I} + \boldsymbol{\tau}(c) \right\} = k\mathbf{u}. \tag{1}$$

(see [16] p.591). In the above equation inertial forces are absent, because, taking into account the low speed of calcium waves, it can be shown that they are by ten orders smaller than the elastic forces. The quantities in Eq.(1) have the following meaning: $\mathbf{u} = \mathbf{u}(\mathbf{x}, t)$ - displacement, $\boldsymbol{\epsilon}$ - strain tensor, i.e. $\boldsymbol{\epsilon} = 1/2(\nabla \mathbf{u} + \nabla \mathbf{u}^T)$, $\theta = \nabla \cdot \mathbf{u}$ - dilation, E - Young modulus, ν - Poisson ratio, μ_1, μ_2 - shear and bulk viscosities, $\mathbf{I}$ - unit matrix, c - calcium concentration, $\boldsymbol{\tau}(c)$-active concentration stress tensor resulting from the actomyosin traction. The external forces $k\mathbf{u}$ measure the strength of the attachment of cells to the surrounding medium. They appear within the Winkler model approximation, where the considered layer of material or a cell is fastened to some sort of immobile foundation. In the paper, however, we will confine our attention to the case when these forces are negligible, i.e. $k = 0$.

As the coefficients of the mechanical equation (including $\boldsymbol{\tau}$) depend on c, the variation in calcium concentration across the wave profile will in general cause the mechanical response of the tissue.

The aim of the present paper is to analyze the existence and properties of mechano-chemical calcium travelling waves propagating in either of the following specific geometrical structures:

- : a. plane waves in a 3-dimensional bulk tissue, which can be considered as a limit of spherical waves far from the centre of propagation. In this case we assume that the displacements of the medium can have only x_1-direction. Consequently, $\varepsilon_{ij} = 0$, except for ε_{11} and thus $\theta = \varepsilon_{11}$.
- : b. 'plane' waves in a thin quasi two dimensional layer of tissue perpedicular to x_3-axis ($\epsilon_{22} = 0$).
- : c. waves in thin biological fibers (e.g. long cells as myocytes) oriented in agreement with x_1.

In cases b. and c. we assume that the lateral boundaries are free, mechanically unloaded surfaces, i.e. if n is the unit vector perpendicular to the surface, then $\sum_{j=1,2,3} \sigma_{ij} n_j \equiv 0$

In the derivation of simplified equations governing the propagation of mechano-chemical calcium waves in thin 2-d layers or in thin fibers, we use the asymptotic approach to the equation for mechanical deformation, using power expansion of the displacement field in the direction perpendicular to the lateral boundary. By a suitable truncation [18],[11] we can make the stress tensor independent of the variable perpendicular to the lateral boundary, although, in general, we have the motion of the material in this direction. This motion influences the solution contributing to the dissipation of energy and, as will be seen later, through the coupling of chemical (diffusion and release of calcium) and mechanical processes influences also the speed of propagation of the calcium wave. The advantage of this asymptotic approach consists in the fact that it retains the mechanical effects, although the components of the travelling wave solution (such as calcium concentration and the entries of the stress) depend only on the wave variable $x_1 - qt$, where q is the speed of the travelling wave. For example, in the case of thin fibers we have to do also

	K	μ	τ	$\boldsymbol{\tau}$	$\boldsymbol{\epsilon}$
BULK MEDIUM	$\frac{E(1-\nu)}{(1+\nu)(1-2\nu)}$	$\mu_1+\mu_2$	τ_{11}	$\mathrm{diag}(\tau_{11},\tau_{11},\tau_{11})$	$\mathrm{diag}(\epsilon_{11},0,0)$
THIN LAYER	$\frac{E}{(1+\nu)(1-2\nu)}$	$2\mu_1+\mu_2$	$\tau_{11}+\tau_{33}$	$\mathrm{diag}(\tau_{11},\tau_{11},\tau_{33})$	$\mathrm{diag}(\epsilon_{11},0,\epsilon_{33})$
THIN FIBER	$\frac{E}{1-2\nu}$	$3\mu_1+\mu_2$	$\tau_{11}+2\tau_{33}$	$\mathrm{diag}(\tau_{11},\tau_{33},\tau_{33})$	$\mathrm{diag}(\epsilon_{11},\epsilon_{33},\epsilon_{33})$

TABLE 1. The coefficients K, μ and τ in Eq.(2)

with the radial motion of the material, despite of the fact that the stress tensor depends only on the variable $x_1 - qt$. In this approximation the strain tensor ϵ in the Cartesian system of coordinates is diagonal [11],[18], [20] as given in Table 1. Thus, in the bulk case only $\epsilon_{11} \neq 0$, in the case of thin layers we have two nonvanishing components ϵ_{11}, ϵ_{33}, whereas in the case of thin fibers we have three nonvanishing components ϵ_{11}, ϵ_{22}, ϵ_{33} with $\epsilon_{22} = \epsilon_{33}$ because of the axial symmetry. Therefore, when looking for travelling wave solutions, the mechanical equation can be reduced to two equations for $\theta = \sum_{i=1,2,3} \epsilon_{ii}$ and for ϵ_{33}.

In all of the above cases the dilation θ satisfies the equation

$$K\theta + \mu\frac{\partial\theta}{\partial t} + \tau = \sigma_0, \tag{2}$$

The constant of integration σ_0 represents the external stress that can be applied to the medium along the direction of propagation. Such a stress can influence the speed of the wave, what, in principle, can be experimentally verified. In the following we will assume that $\sigma_0 = 0$. The effective elasticity and viscosity coefficients K and μ, the effective traction τ, as well as the the form of the traction matrix in each of the considered cases are given in Table 1 (see [18]).

For the bulk medium we have $\epsilon_{22} = \epsilon_{33} = 0$. For thin layers $\epsilon_{22} = 0$, whereas for thin fibers $\epsilon_{22} = \epsilon_{33}$ are not identically zero. By means of the results of [18] we conclude that, in the case of thin layers and fibers, the equation for $\epsilon_{33} := \eta$, reads:

$$\mu_2\frac{\partial\eta}{\partial t} + K_1\eta + \theta[K_2 - \beta K] - \beta\tau + \tau_{33} = 0, \tag{3}$$

where $\beta = \mu_1\mu^{-1}$, $K_1 = \frac{E}{1+\nu}$, $K_2 = \frac{\nu E}{(1-2\nu)(1+\nu)}$, and where K, μ and τ are given in Table 1. The derivations of Eq.(2) and Eq.(3) are given in the papers [11], [18].

If viscosity effects are negligible, then the above equations for θ and η can be immediately solved. It seems, however, that for some tissues viscosity may play a significant role. As follows from Eq.(1) the ratio of viscous to elastic forces is equal to

$$R_{vis} = \frac{F_{viscous}}{F_{elastic}} = \frac{\mu|\boldsymbol{\epsilon}_{,t}|}{K|\boldsymbol{\epsilon}|}, \tag{4}$$

where μ denotes the effective viscosity and K the effective elasticity coefficient.

The strain tensor $\boldsymbol{\epsilon}$ is a dimensionless quantity. Let T be the characteristic time. The dimension of $\frac{|\boldsymbol{\epsilon}_{,t}|}{|\boldsymbol{\epsilon}|}$ is T^{-1}. Hence formula (4) takes the form $R_{vis} = \mu/KT$. In the paper we are interested in travelling waves, therefore the characteristic time scale is equal to $T = W/q$, where W denotes the width W of the calcium wave. Thus we obtain

$$R_{vis} \cong \frac{\mu q}{KW}. \tag{5}$$

Specific values of R_{vis} depend essentially on the kind of considered tissues, but typically its value is of the order of 10^{-1} as in the case of aortic endothelial cells ([3],[21]) or smooth muscles of pulmonary arteries ([1],[3]).

We can also estimate the ratio of the characteristic value of τ and the coefficient K. From paper [4] concerning the movement of fish keratocytes, one can find $K \cong 2 \cdot 10^3\ Pa$ and $\tau \cong 10^3 Pa$, thus $\frac{\tau}{K} \cong 10^{-1}$, which, by means of Eq.(2), leads to $|\theta| \cong 0.1$ (in the limit of vanishing μ).

The simplest mathematical model describing the dynamics of calcium concentration is provided by a single "bistable" reaction-diffusion equation, having two stable equilibria: the ground state (low calcium concentration) and the excited state (with a high calcium concentration). It is known that such an equation has a solution in the form of a heteroclinic travelling wave joining the above mentioned equilibria. On the other hand, experimental observations seem to show that the excited state relaxes slowly to the ground state. Due to this fact, in some papers (see, e.g. [22]) more realistic models are considered, where the scalar reaction-diffusion equation for calcium concentration is supplemented by an ordinary differential equation for the evolution of an additional, so called, *recovery variable* to form a FitzHugh-Nagumo (FHN) like model. Thus the travelling waves of the calcium concentration should be in the form of homoclinic pulses rather than heteroclinic fronts. The recovery variable does not yet have a clear physical interpretation. Moreover, the time during which the release sites in the cell stay in their activated state is much larger than the time necesssary for their activation. For example, in experiments described in [25] calcium waves were mechanically stimulated in long myocyte cells. The time of sharp increase in calcium concentration (which includes the time of mechanichal stimulation and inactivation time) is of the order of $1\,s$, whereas the time of slow decrease is of the order of hundreds of seconds (see Fig.1 in [25]). Thus in the description of the calcium wave in the neighbourhood of the leading front we may confine ourselves to the heteroclinic approximation.

The dynamics of Ca^{++} in cells is significantly influenced by the presence of buffers [5],[15], i.e. chemicals, mostly proteins of molecular masses about tens of kDa (e.g. parvalbumin and EGTA), able to bind the calcium ions. Up to 99% of Ca^{++} can be bound to different kind of buffer molecules.

We will consider here the system of reaction-diffusion equations for the calcium and buffer concentrations (see [15], [22]) taking into account the mechanochemical interaction. The mechanochemical source term $S(c, \boldsymbol{\epsilon})$ will depend on the calcium concentration c and on the strain tensor ϵ, more precisely on its invariants. The system has the following form:

$$\begin{aligned} \frac{\partial c}{\partial t} &= D_0 \Delta c + \sum_{i=1}^{n} [k_-^i v_i - k_+^i c(b_0^i - v_i)] + S(c, \boldsymbol{\epsilon}), \\ \frac{\partial v_i}{\partial t} &= D_i \Delta v_i - [k_-^i v_i - k_+^i c(b_0^i - v_i)], \quad i = 1, \ldots, n, \end{aligned} \tag{6}$$

where c denotes the calcium concentration and D_0 its diffusion coefficient and D_i - buffers diffusion coefficients. Here $v_i = [Ca^{++}\, B_i]$ denotes the concentration of buffers which form a complex with the calcium ions, whereas b_0^i denotes the total concentration of the i-th buffer ($b_0^i = [B_i] + [Ca^{++}\, B_i]$). $k_-^i > 0, k_+^i > 0$ are appropriate kinetic constants.

Remark 1. The mechanochemical term suggested in [16] and used, e.g. in [19],[18], [11],[6] is simply of the form $g(c) + \gamma\theta$, where g is of bistable type, thus takes into account only the compression of the medium. However, S may depend on all of the eigenvalues of the strain tensor ϵ, not only on their sum θ. Experiments show that also shear mechanical stresses can generate chemical calcium waves (see [7]). Let us give some arguments supporting this idea. It seems reasonable to assume that the flux of the calcium released from an organelle under the action of the strain, should be rather related to the variation of the area than the volume. In such a case the deformation, which is preserving the volume may also lead to the release of calcium. As an example let us take the organelle in an ellipsoidal shape. Let a_1, a_2, a_3, be the radii of the ellipsoid and for simplicity we assume that the deformation tensor is diagonal in the coordinate system with axes parallel to the main axes of the ellipsoid. We apply here the approximate formula for the area of the surface of the ellipsoid, which turns out to be quite accurate (up to 1.5%): $S = 2\pi[(a_1a_2)^p + (a_1a_3)^p + (a_2a_3)^p]^{1/p}$, where $p = ln3/ln2$. Evaluating the variation of the area with respect to the variation of the radii we obtain:

$$dS = 2\pi \left[\frac{1}{2}\sum_{i,j;i\neq j}(a_ia_j)^p\right]^{\frac{1-p}{p}} \sum_{i,j;i\neq j}(a_ia_j)^p\frac{da_j}{a_j}$$

Constant diagonal strain tensor implies the displacement field in the form $u_i = \epsilon_{ii}x_i$. Thus, the axis of the ellipsoid will stretch by $da_j = \epsilon_{jj}a_j$, $i = 1, 2, 3$, hence $da_j/a_j = \epsilon_{jj}$. Thus in general the variation of the area surface of the organelle under the infinitesimal deformation is a linear function of all the eigenvalues of the deformation tensor, not only the function of its trace, although in the case of of fully symmetrical body (cube, ball) this variation, indeed becomes proportional to the trace of the deformation tensor.

In the cases analyzed in the paper the tensor $\boldsymbol{\epsilon}$ is diagonal and is entirely determined by the quantities θ and $\eta = \epsilon_{33}$. It is convenient to write $S = S(c, \theta, \eta)$ and decompose the function S in the following form:

$$S(c, \theta, \eta) = g(c) + R(c, \theta, \eta), \tag{7}$$

where $R(c, \theta, \eta) = S(c, \theta, \eta) - S(c, 0, 0)$ and $g(c) = S(c, 0, 0)$.

Assumption 1. *Suppose that the function $g(\cdot) \in C^2(\mathbb{R}^1)$ is of a bistable type, that is to say the equation $g(c) = 0$ has exactly three solutions: $c_1 > 0$, $c_3 > c_1$ and $c_2 \in (c_1, c_3)$, where the zeros c_1 and c_3 are stable, i.e. $g'(c_1) < 0$, $g'(c_3) < 0$, and c_2 is unstable, i.e. $g'(c_2) > 0$. Suppose that the function R is of C^1 class of its arguments.*

A simple example of a function satisfying the above assumptions is a cubic polynomial $g(c) = A(c - c_1)(c_3 - c)(c - c_2)$ with $c_2 \in (c_1, c_3)$.

From the physical point of view it is important that the values of calcium and buffer particles concentrations cannot become negative within the considered model. To guarantee this we will impose an additional, physically justified assumption concerning the source term S, i.e. $S \geq 0$ for $c = 0$. As the stable ground state of the calcium concentration is positive, i.e. $c_1 > 0$, therefore the cell homeostasis requires even positive S for $c = 0$.

Assumption 2. *Let $S(0, \theta, \eta) > 0$ for all $\theta, \eta \in \mathbb{R}^1$.*

In Section 4 by means of Assumption 2, we will show the non-negativity of calcium and buffers concentration for the profiles of travelling wave solutions. Let us note that $S = g(c) + \gamma\theta$ (as taken in [16]) does not guarantee the positivity of calcium concentration.

Our aim is to analyze travelling wave solutions propagating along x_1-direction to system composed (2),(3),(6), under the assumption of relative smallness of the viscosity coefficient. Please note that in the bulk case $\eta \equiv 0$ thus Eq.(3) is absent. Thus in our considerations we will concentrate on the cases of thin layer and thin fibers, where η is non zero. To obtain formally a small parameter describing the ratio of viscous and inertial forces, we have to carry out appropriate scaling procedure. This can be done as in [11],[18], [20].

To avoid technical complications and for clarity of exposition we have assumed here that the elasicity coefficients K, K_1, K_2 and viscosity coefficients μ_1, μ_2 do not depend on the entries of the mechanical stress tensor $\boldsymbol{\epsilon}$

Assumption 3. *Suppose that $\mu_1 = \mu_1(c)$, $\mu_2 = \mu_2(c)$, $K = K(c)$, $K_1 = K_1(c)$, $K_2 = K_2(c)$ are functions of $C^2(R^1)$ class, whereas the entries of $\boldsymbol{\tau} = \boldsymbol{\tau}(c)$ are of $C^3(R^1)$ class.*

Remark. To avoid technical difficulties, we have assumed in Assumption 3 that all the functions considered in the paper have been extented for all $c \in \mathbb{R}^1$. However, by means of Assumption 2, we show in Section 4 that travelling wave solutions to the considered system satisfy the non-negativity condition $c \geq 0$.

In the rescaled variables (for simplicity we use the same symbols), the system takes the following form:

$$\varepsilon^2\mu(c)\frac{\partial\theta}{\partial t} + K(c)\theta + \tau(c) = 0, \tag{8}$$

$$\varepsilon^2\mu_2\beta\frac{\partial\eta}{\partial t} + K_1\eta + \theta[K_2 - \beta K] - \beta\tau + \tau_{33} = 0. \tag{9}$$

$$\begin{aligned} \frac{\partial c}{\partial t} &= D_0\frac{\partial^2}{\partial x_1^2}c + g(c) + \sum_{i=1}^{n} G_i(c, v_i) \ + R(c, \theta, \eta) \\ \frac{\partial v_i}{\partial t} &= D_i\frac{\partial^2}{\partial x_1^2}v_i - G_i(c, v_i), \quad i = 1, \ldots, n, \end{aligned} \tag{10}$$

where

$$\varepsilon^2 = \frac{\mu_0 q_s}{K_0 W_s}, \quad \text{and} \quad G_i(c, v_i) = k_-^i v_i - k_+^i c(b_0^i - v_i).$$

Here $\mu_0 = \mu(c_3)$, $K_0 = K(c_3)$, whereas q_s and W_s are the characteristic speed and width of the calcium chemical waves. Below, ε^2 will be supposed to be sufficiently small. All the variables in the above system and functions are in their rescaled non-dimensional form. In particular the quantity $\mu(c) = \mu(c)(\mu(c_3))^{-1}$, and $K = K(c)(K(c_3))^{-1}$, thus they are of order 1.

Remark. The rescaled space and time variables are given as $x_1^* = x_1 W_s^{-1}$, $t^* = q_s W_s^{-1} t$, The rescaled calcium and buffer concentrations are equal to: $c^* = cc_3^{-1}$, $v_i^* = v_i c_3^{-1}$, the rescaled source function $g^*(c^*) = [W_s/(q_s c_3)]g(c^* c_3)$. Other quantities are rescaled in the similar way. In the derivation of system (8)-(10) we have also used the fact that in the new spatial variable $x_1^* = x_1/W_s$ the new displacement u^* satisfies the relation $u = W_s u^*$. Morever, $u_{,x_1} = u_{x_1^*}^*$, hence $\theta^* = \theta$ and $\eta^* = \eta$.

2. **Chemical calcium waves.** For $R = 0$ the mechano-chemical coupling in Eqs (10) is formally switched off. In this case we can consider strictly chemical travelling waves connecting two stable constant steady states of system (10). For $R = 0$, there are exactly three constant steady states of system (10): $\tilde{P}_1$, $\tilde{P}_2$ and $\tilde{P}_3$, corresponding to the three solutions $\tilde{c}_1, \tilde{c}_2, \tilde{c}_3$ of the equation $g(c) = 0$, which are defined in Assumption 1. We have:

$$\tilde{P}_k = (\tilde{c}_k, w_1^k, \dots, w_n^k), \quad k = 1, 2, 3, \tag{11}$$

where

$$w_j^k = \tilde{c}_k \frac{k_+^j b_0^j}{(k_-^j + k_+^j \tilde{c}_k)}. \tag{12}$$

As, by Assumption 1, $\tilde{c}_1 < \tilde{c}_2 < \tilde{c}_3$, then

$$w_j^1 < w_j^2 < w_j^3, \quad j = 1, \dots, n, \tag{13}$$

thus component wise we may write

$$\tilde{P}_1 < \tilde{P}_2 < \tilde{P}_3. \tag{14}$$

We are interested in the travelling wave solutions to system (6) joining the constant steady states $\tilde{P}_1$ and $\tilde{P}_3$. We are seeking solutions to system (6) in the form

$$c(x_1, t) = c(\xi), \quad v_i(x_1, t) = v_i(\xi), \quad i = 1, \dots, n, \tag{15}$$

where $\xi = x_1 - qt$, satisfying the following conditions:

$$\begin{gathered} \lim_{\xi \to -\infty}(c(\xi), v_1(\xi), \dots, v_n(\xi)) = (\tilde{c}_1, w_1^1, \dots, w_n^1) = \tilde{P}_1, \\ \lim_{\xi \to \infty}(c(\xi), v_1(\xi), \dots, v_n(\xi)) = (\tilde{c}_3, w_1^3, \dots, w_n^3) = \tilde{P}_3, \\ \lim_{|\xi| \to \infty}(c'(\xi), v_1'(\xi), \dots, v_n'(\xi)) = (0, 0, \dots, 0). \end{gathered} \tag{16}$$

Thus, this travelling wave connects the state of low concentration of calcium (both free and bound to buffers) with a state of a large concentration of calcium (both free and bound to the buffers).

The functions $c(\xi), v_i(\xi), i = 1, \dots, n$, satisfy the following system of ordinary differential equations:

$$D_0 c'' + q c' + g(c) + \sum_{i=1}^{n} G_i(c, v_i) = 0, \tag{17}$$

$$D_i v_i'' + q v_i' - G_i(c, v_i) = 0, \quad i = 1, \dots, n, \tag{18}$$

where $'$ denotes differentiation with respect to the variable ξ.

Remark. $c(x_1 - qt)$ and $v_i(x_1 - qt), i = 1, \dots, n$, are travelling wave solution to system (10) with $R(c, \theta, \eta) \equiv 0$. Let $U = (U_0, \dots, U_n) := (c, v_1, \dots, v_n)$. System (10) can be written in the form

$$\frac{\partial U}{\partial t} = A \frac{\partial^2}{\partial x_1^2} U + F(U), \tag{19}$$

where $A = \operatorname{diag}(D_0, \dots, D_n)$ is a diagonal matrix with positive entries and $C^1 \ni F(\cdot) : \mathbb{R}^{n+1} \to \mathbb{R}^{n+1}$. We say that system (19) is monotone, if

$$\frac{\partial F_i}{\partial U_j} \geq 0, \qquad i, j = 0, ..., n, i \neq j.$$

It easy to note that system (10) satisfies the above monotonicity conditions.

The following theorem holds.

Theorem 2.1. *The constant states $\tilde{P}_1$ and $\tilde{P}_3$ are stable. The state $\tilde{P}_2$ is unstable. There exists a heteroclinic pair $(q_0, c_0(\cdot), v_{10}(\cdot), \dots, v_{n0}(\cdot))$ satisfying system (17)-(18) and conditions (15). This pair is unique (modulo shifts in the ξ-space) in the class of solutions such that $c'(\xi), v_1'(\xi), \dots, v_n'(\xi) > 0$ for all $\xi \in \mathbb{R}^1$.*

This theorem is a straightforward conclusion from Theorem 2.1, p.15 in [24] (see also [12],[13]).

As mentioned in the Introduction, heteroclinic wave is an approximation of the leading front of the real calcium wave under the condition that the heteroclinic front is representing an advancing wave, i.e. it is moving from large to low concentration. *Within the boundary conditions assumed above, it means that the speed of the wave is negative* ($q < 0$).

3. **Mechanochemical calcium waves.** In this section we will take into account the mechanical term R in the equation describing the evolution of the free calcium.

As we suggested in the Introduction we may suppose that

$$\frac{q_s \mu_0}{W_s K_0} := \varepsilon^2 << 1.$$

This parameter describes the ratio between the viscous forces and the elastic forces. Below, we will consider the existence of mechano-chemical travelling wave solutions under the condition that ε^2 is sufficiently small.

For non-vanishing viscosity, i.e. for $\varepsilon^2 > 0$, θ and η are governed by Eqs.(8) and (9). In the absence of viscosity ($\varepsilon^2 = 0$), θ and η can be explicitly calculated from (8),(9), to obtain:

$$\theta_0(c) = -K(c)^{-1}\tau(c), \tag{20}$$

$$\eta_0(c) = -K_1(c)^{-1}\left(\theta_0(c)K_2(c) + \tau_{33}(c)\right). \tag{21}$$

In this way, the case $\varepsilon = 0$ is reduced to the case of purely chemical waves. Indeed, in system (8),(9),(10), $\theta = \theta_0(c)$ and $\eta = \eta_0(c)$, hence we obtain system (17)-(18) with a new source function:

$$f(c) = g(c) + R(c, \theta_0(c), \eta_0(c)). \tag{22}$$

instead of g. This fact will be the starting point of our considerations.

Therefore for nonvanishing viscosity ($\varepsilon^2 > 0$), it is convenient to introduce the variables, measuring the deviation from the non-viscous case

$$h := \theta - \theta_0(c), \quad b := \eta - \eta_0(c), \tag{23}$$

$$r(c, h, b) := R\left(c, \theta_0(c) + h, \eta_0(c) + b\right) - R(c, \theta_0(c), \eta_0(c)).$$

and rewrite the system (8),(9),(10) in terms of h and b. We will thus consider the following system of equations:

$$\frac{\partial h}{\partial t} + (\varepsilon^2\mu)^{-1}Kh - \left[\frac{\tau(c)}{K(c)}\right]_{,c}\frac{\partial c}{\partial t} = 0, \tag{24}$$

$$\frac{\partial b}{\partial t} + (\varepsilon^2\mu_2\beta)^{-1}\left(K_1 b + h[K_2 - \beta K]\right) + \eta_{0,c}(c)\frac{\partial h}{\partial t} = 0. \tag{25}$$

$$\frac{\partial c}{\partial t} = D_0\frac{\partial^2 c}{\partial x^2} + f(c) + r(c, h, b) + \sum_{i=1}^{n} G_i(c, v_i), \tag{26}$$

$$\frac{\partial v_i}{\partial t} = D_i\frac{\partial^2 v_i}{\partial x^2} - G_i(c, v_i), \quad i = 1, \dots, n. \tag{27}$$

Assumption 4. *Suppose that:*

- : *1. The function $f(\cdot) \in C^2(\mathbb{R}^1)$ is of the bistable type i.e. the equation $f(c) = 0$ has exactly three solutions: $c_1 > 0$, $c_3 > c_2$ and $c_2 \in (c_2, c_3)$. The zeros c_1 and c_3 are stable, i.e. $f'(c_1) < 0$, $f'(c_3) < 0$, whereas c_2 is unstable, i.e. $f'(c_2) > 0$.*
- : *2. The purely chemical wave associated with f instead of g in system (17),(18) (see Theorem 2.1) has negative speed $q_0 < 0$.*

Consequently, there are exactly three constant steady states to system (24)-(27):

$$(h, b, c, v_1, \dots, v_n) = P_k, \quad k = 1, 2, 3, \quad \text{where} \quad P_k = (0, 0, c_k, v_1^k, \dots, v_n^k)$$

and, as in the case of strictly chemical waves,

$$v_j^k = c_k \frac{k_+^j b_0^j}{(k_-^j + k_+^j c_k)}, \quad j = 1, \dots, n. \tag{28}$$

Obviously, $P_1 < P_2 < P_3$ component-wise.

We are seeking solutions in the form

$$h(x,t) = h(\xi), \;\; b(x,t) = b(\xi), \;\; c(x,t) = c(\xi), \;\; v_i(x,t) = v_i(\xi), \quad i = 1, \dots, n, \tag{29}$$

where

$$\xi = x_1 - qt.$$

Inserting this into system (24),(26),(27) we arrive at the following system of ordinary differential equations

$$h' - (\varepsilon^2 q\mu)^{-1} K h - \left[\frac{\tau(c)}{K(c)}\right]_{,c} c' = 0, \tag{30}$$

$$b' - (\varepsilon^2 q\mu_2\beta)^{-1} \left(K_1 b + h[K_2 - \beta K]\right) + \eta_{0,c}(c)c' = 0. \tag{31}$$

$$D_0 c'' + qc' + f(c) + \sum_{i=1}^{n} G_i(c, v_i) + r(c, h, b) = 0, \tag{32}$$

$$D_i v_i'' + q v_i' - G_i(c, v_i) = 0, \quad i = 1, \dots, n, \tag{33}$$

where, as before, $'$ denotes the differentiation with respect to $\xi = x_1 - qt$. We are interested in solutions to system (30)-(33) satisfying the conditions:

$$\begin{gathered}
\lim_{\xi \to -\infty} (h(\xi), b(\xi), c(\xi), v_1(\xi), \dots, v_n(\xi)) = P_1, \\
\lim_{\xi \to \infty} (h(\xi), b(\xi), c(\xi), v_1(\xi), \dots, v_n(\xi)) = P_3, \\
\lim_{|\xi| \to \infty} (h'(\xi), b'(\xi), c'(\xi), v_1'(\xi), \dots, v_n'(\xi)) = (0, 0, 0, 0, \dots, 0).
\end{gathered} \tag{34}$$

Please note that the parameter q is also an unknown, and its value must be found appropriately to satisfy conditions (34).

Let us shortly discuss the strategy of our existence proof. In Eqs (30),(31) we have to do with singular perturbations. Nevertheless, by formal integration (using the boundary conditions), Eqs (30) and (31) can be written in the form

$$\begin{aligned}
h(\xi) &= H(c, q, \varepsilon)(\xi), \\
b(\xi) &= L(c, q, \varepsilon)(\xi)
\end{aligned}$$

where H and L are nonlinear integral operators, which will be defined below. As it will be shown for $\varepsilon \to 0$ the functions H and L together with their Frechet derivatives DH and DL with respect to (c, q) tend to 0 for $\varepsilon \to 0$:

$$H(c, q, \varepsilon),\; L(c, q, \varepsilon),\; DH(c, q, \varepsilon),\; DL(c, q, \varepsilon) \to 0 \quad \text{as } \varepsilon \to 0.$$

Having shown this property, and noticing that in the limit $\varepsilon \to 0$ the above system tends formally to the purely chemical system (32),(33) with $h \equiv 0$, $b \equiv 0$, we will apply the implicit function theorem, and show the existence of functions $h_\varepsilon, b_\varepsilon, c_\varepsilon, v_{1\varepsilon}, \ldots, v_{n\varepsilon}$ and the speed parameter q_ε satisfying system (30)-(33) for sufficiently small $|\varepsilon|$. These functions can be determined only up to a translation $\xi \to \xi + a$. To get rid of this nonuniqueness we will impose an additional condition $c_\varepsilon(0) = \frac{1}{2}[c_\varepsilon(-\infty) + c_\varepsilon(\infty)]$ (see (35)).

Remark. As mentioned before, for physical reasons, we will confine ourselves to the case $q < 0$ corresponding to advancing travelling waves, i.e. the waves which propagate in the direction opposite to the gradient of calcium concentration.

Definition 3.1. For $i = 0, 1, 2$, let B_i denote the space of functions $u(\xi)$ of $C^i(\mathbb{R})$ class tending to finite limits as $\xi \to \pm\infty$ together with their derivatives (which tend to zero). Let B_i^* denote the subspace of B_i consisting of functions vanishing for $\xi = \pm\infty$ and B_{i0} the subspace of functions u satisfying the condition:

$$u(0) = \frac{1}{2}[u(-\infty) + u(\infty)]. \tag{35}$$

The norms in the spaces B_j are taken to be $\|u\|_{B_j} = \sum_{k=0}^{j} \sup_{\xi \in \mathbb{R}^1} \left| \frac{d^k}{d\xi^k} u(\xi) \right|$. Let

$$B_2^n := \underbrace{B_2 \times B_2 \times \ldots \times B_2}_{n \text{ times}}.$$

As we mentioned above, given the function c, the solution to Eq.(30) can be formally written as $h(\xi) = H(c, q, \varepsilon)(\xi)$, where:

$$H(c,q,\varepsilon)(\xi) = \int_0^\xi \exp\left[\int_s^\xi \frac{1}{\varepsilon^2}\frac{K(c(\zeta))}{q\mu(c(\zeta))}d\zeta\right]\frac{1}{K}\tau_{,c}(c(s))c'(s)ds + \widetilde{C}\exp\left[\int_0^\xi \frac{1}{\varepsilon^2}\frac{K(c(s))}{q\mu(c(s))}ds\right],$$

The constant $\widetilde{C}$ should be chosen in such a way that $H(c, q, \varepsilon)(\xi) \to 0$ as $\xi \to \pm\infty$. It is easy to note that for $q < 0$ one should take

$$\widetilde{C} = -\int_0^{-\infty} \exp\left[-\int_0^s \frac{1}{\varepsilon^2}\frac{K(c(\zeta))}{q\mu(c(\zeta))}d\zeta\right]\frac{1}{K}\tau_{,c}(c(s))c'(s)\,ds.$$

Hence

$$H(c,q,\varepsilon)(\xi) = \int_{-\infty}^\xi \exp\left[\int_s^\xi \frac{1}{\varepsilon^2}\frac{K(c(\zeta))}{q\mu(c(\zeta))}d\zeta\right]\frac{1}{K}\tau_{,c}(c(s))c'(s)\,ds. \tag{36}$$

In the similar way, given the function c, the solution to Eq.(31) can be formally written as $b(\xi) = L(c, q, \varepsilon)(\xi)$, where

$$L(c,q,\varepsilon)(\xi) = \int_{-\infty}^\xi \exp\left[\int_s^\xi \frac{1}{\varepsilon^2}\frac{K_1(c(\zeta))}{\mu_2(c(\zeta))\beta(c(\zeta))}\frac{1}{q}d\zeta\right]\widetilde{\kappa}(s)\,ds \tag{37}$$

and

$$\widetilde{\kappa}(s) = \varepsilon^{-2}\left(q\mu_2(c(s))\beta(c(s))\right)^{-1}[K_2(c(s)) - \beta(c(s))K(c(s))]H(c,q,\varepsilon)(s) + \eta_{0,c}(c(s))c'(s).$$

Here β, K_1 and K_1 are defined after Eq.(3) and η_0 in (21).

The following lemma holds.

Lemma 3.2. *H can be extended (by $H = 0$ for $\varepsilon = 0$) to a well defined continuous operator acting from of $B_{20} \times (-\infty, 0) \times \mathbb{R}^1$ to B_1^* and for fixed c and q*

$$\|H(c, q, \varepsilon)(\cdot)\|_{B_1^*} = O(\varepsilon^2) \quad \text{for} \quad \varepsilon \to 0. \tag{38}$$

The Frechet derivative $DH(c, q, \varepsilon)$ of the operator H with respect to (c, q) at a point (c, q, ε) acting on the vector $[\delta c, \delta q]$ is well defined and

$$\|DH(c, q, \varepsilon)[\delta c, \delta q]\|_{B_1^*} = O(\varepsilon^2)\ (\|\delta c\|_{B_2} + |\delta q|) \quad \text{for} \quad \varepsilon \to 0. \tag{39}$$

The proof of Lemma 3.2 will be given in Appendix 1. Likewise, it can be proved that:

Lemma 3.3. *The thesis of Lemma 3.2 holds also for the operator L.*

Now, let us note that Eqs (30),(31) can be written as:

$$\Phi_1(h, b, c, v_1, \dots, v_n, q, \varepsilon) := h - H(c, q, \varepsilon) = 0, \quad \Phi_2(h, b, c, v_1, \dots, v_n, q, \varepsilon) := h - L(c, q, \varepsilon) = 0.$$

Likewise, system (32),(33) can be written as

$$\Phi_3(h, b, c, v_1, \dots, v_n, q, \varepsilon) = 0,$$

where Φ_3 has $n + 1$ components determined respectively by the left hand sides of equations in system (32),(33).

First of all, let us notice that the purely chemical wave $(c_0, v_{10}, \dots, v_{n0})(\xi)$ with negative velocity $q_0 < 0$, associated with the function f (point 2. Assumption 4), satisfies the system $\Phi_i = 0$, $i = 1, 2, 3$, with $\varepsilon = 0$, $h = 0$, $b = 0$. It is obvious that we can assume that c_0 satisfies condition (35) by choosing a proper shift, so $c_0 \in B_{20}$.

By Lemmas 3.2, 3.3 and the assumptions concerning the functions $f(c)$ and $r(c, h, b)$, the mappings Φ_1, Φ_2, Φ_3 are well determined mappings of some open neighbourhood of $(0, 0, c_0, v_{10}, \dots, v_{n0}, q_0, 0) \in B_1^* \times B_1^* \times B_{20} \times B_2^n \times \mathbb{R}^1 \times \mathbb{R}^1$ to the space B_1^*, B_1^* and $B_0 \times B_0^n$ respectively. They are also continuously Frechet differentiable with respect to $(h, b, c, v_1, \dots, v_n, q)$.

According to the implicit function theorem, to prove the existence of solutions for $\varepsilon \neq 0$, it suffices to show that the linear operator

$$D\Phi(h, b, c, v_1, \dots, v_n, q, \varepsilon)|_{(0,0,c_0,v_{10},\dots,v_{n0},q_0,0)} = (D\Phi_1, D\Phi_2, D\Phi_3)\,(0, 0, c_0, v_{10}, \dots, v_{n0}, q_0, 0)$$

(acting from the space $B_1^* \times B_1^* \times B_{20} \times B_2^n \times \mathbb{R}^1$ to the space $B_1^* \times B_1^* \times B_0 \times B_0^n$) is boundedly invertible. By means of Theorem 4.2-H p.180 in [23]), it is sufficient to prove that the system:

$$D\Phi_i(0, 0, c_0, v_{10}, \dots, v_{n0}, q_0, 0)[\delta h, \delta b, \delta c, \delta v_1, \dots, \delta v_n, \delta q] = f_i, \quad i = 1, 2, 3,$$

has for all $f_1 \in B_1^*, f_2 \in B_1^*, f_3 \in B_0 \times B_0^n$ a uniquely determined solution

$$(\delta h, \delta b, \delta c, \delta v_1, \dots, \delta v_n, \delta q) \in B_1^* \times B_1^* \times B_{20} \times B_2^n \times \mathbb{R}^1.$$

Let us note that, by Lemmas 3.2 and 3.3, that for $i = 1, 2$ the equations

$$D\Phi_i(0, 0, c_0, v_{10}, \dots, v_{n0}, q_0, 0)[\delta h, \delta b, \delta c, \delta v_1, \dots, \delta v_n, \delta q] = f_i$$

have simply the form:

$$\delta h = f_1, \quad \delta b = f_2$$

so they are uniquely solvable. In this way the problem is led to the solvability of the system

$$D\Phi_3(0,0,c_0,v_{10},\dots,v_{n0},q_0,0)[f_1,f_2,\delta c,\delta v_1,\dots,\delta v_n,\delta q] = f_3, \tag{40}$$

for δc, $\delta v_1,\dots,\delta v_n$ and δq, where f_1 and f_2 are given.

This will be proven in Appendix 2.

We have thus proved the following existence theorem.

Theorem 3.4. *Let Assumptions 1-4 hold. Then for ε^2 sufficiently small there exists a unique value of the parameter q_ε and a corresponding heteroclinic solution $(h_\varepsilon(\cdot), b_\varepsilon(\cdot), c_\varepsilon(\cdot), v_{\varepsilon 1}(\cdot),\dots,v_{\varepsilon n}(\cdot))$ of system (30),(31), (32),(33) satisfying conditions (34), belonging to the space $B_1\times B_1\times B_{20}\times B_2^n$ such that as $\varepsilon\to 0$*

$$q_\varepsilon \to q_0, \quad \|h_\varepsilon\|_{B_1}\to 0, \quad \|b_\varepsilon\|_{B_1}\to 0,$$
$$\|c_\varepsilon - c_0\|_{B_{20}}\to 0, \quad \|v_{\varepsilon i}-v_{0i}\|_{B_2}\to 0, \quad i=1,\dots,n.$$

4. **Positivity of calcium and buffers concentrations.** In this section we prove that Assumption 2 implies non-negativity of concentration of calcium and buffers in the case travelling wave solutions.

Theorem 4.1. *Let $(h_\varepsilon(\cdot), b_\varepsilon(\cdot), c_\varepsilon(\cdot), v_{\varepsilon 1}(\cdot),\dots,v_{\varepsilon n}(\cdot))$ denote the unique heteroclinic solution of system (30),(31), (32),(33) given in Theorem 3.4 corresponding to a unique speed parameter q_ε. Suppose that $k_-^i>0$, $k_+^i>0$ and that Assumption 2 holds. Then $c_\varepsilon(\xi)>0$ and $0<v_{\varepsilon i}(\xi)<b_0^i$ for all $\xi\in\mathbb{R}^1$, $i=1,\dots,n$.*

Proof. Let

$$\theta_\varepsilon = h_\varepsilon + \theta_0(c_\varepsilon), \quad \eta_\varepsilon = b_\varepsilon + \eta_0(c_\varepsilon).$$

Obviously, $(c_\varepsilon(\cdot), v_{\varepsilon 1}(\cdot),\dots,v_{\varepsilon n}(\cdot))$ satisfy the system

$$D_0 c'' + qc' + S(c,\theta_\varepsilon,\eta_\varepsilon) + \sum_{i=1}^n [k_-^i v_i - k_+^i c(b_0^i - v_i)] = 0 \tag{41}$$

$$D_i v_i'' + qv_i' - [k_-^i v_i - k_+^i c(b_0^i - v_i)] = 0 \tag{42}$$

where we have suppressed the dependence of $c(\cdot)$ and $v_i(\cdot)$ on the parameter ε for simplicity of notation (but we retained it as an index in θ_ε and η_ε). Though the function $S(c,\theta,\eta)$ has no physical sense for negative concentrations of calcium, yet, for the need of the monotonicity proof, it is necessary to extend it also for $c<0$. By means of Assumption 2, we can conclude that for every C^1-extension of S, there exists $c_m<0$ such that

$$S(c,\theta,\eta)>0 \quad \text{for} \quad c\in[c_m,0] \tag{43}$$

independently of $\theta,\eta\in\mathbb{R}^1$. Moreover, by decreasing c_m, if necessary, we can guarantee that

$$k_-^j + k_+^j c_m > 0. \tag{44}$$

The idea of the proof is to take advantage of the continuous dependence of the solutions on the parameter ε. For $\varepsilon=0$, according to Theorem 2.1, the functions $c(\xi)$ and $v_i(\xi)$ are monotone, so non-negative (because they satisfy conditions (34)).

Suppose to the contrary that there exists $\varepsilon > 0$ such that at a point $\xi = y$ we have $c(y) \in (c_m, 0]$ and that this is a global minimum of the function $c(\cdot)$. According to (43) we have from (41):

$$\sum_{i=1}^{n} [k_-^i v_i(y) - k_+^i(c(y))c(y)(b_0^i - v_i(y))] < 0 \tag{45}$$

thus at least for one i, say for $i = j$, we have

$$[k_-^j v_j(y) - k_+^j(c(y))c(y)(b_0^j - v_j(y))] < 0. \tag{46}$$

Moreover, as $v_j \in B_2$, then it must attain a global minimum at some point y_j, which y_j may be finite or infinite. In both of the cases we have

$$[k_-^j v_j(y_j) - k_+^j(c(y_j))c(y_j)(b_0^j - v_j(y_j))] \geq 0. \tag{47}$$

Using (43),(44) and solving (46) and (47) we get

$$v_j(y) < b_0^j k_+^j(c(y))c(y)/(k_-^j + k_+^j(c(y))c(y)) \tag{48}$$

and

$$v_j(y_j) \geq b_0^j k_+^j(c(y_j))c(y_j)/(k_-^j + k_+^j(c(y_j))c(y_j)), \tag{49}$$

with

$$c(y) \leq c(y_j), \quad v_j(y_j) \leq v_j(y). \tag{50}$$

Note that the function $p/(k_-^j + p)$ is strictly increasing with p for all $p > -k_-^j$. Hence as, according to (44) the left hand side of (48) is not larger than the right hand side of (49). Hence

$$v_j(y) < v_j(y_j).$$

Thus we have arrived at contradiction as v_j has been assumed to achieve its global minimum for $\xi = y_j$. Thus $c(\xi) > 0$ for all ξ. Having proved the positivity of the function c we can easily prove that $v_j(\xi) > 0$ for all ξ. (By supposing that v_j attains a non-positive minimum at some point y_j we arrive at contradiction by using the maximum principle.) Likewise, we can easily prove that $v_j(\xi) < b_0^j$. □

5. **Conclusions.** Applying the power series expansion in the variables orthogonal to the lateral boundary of the tissue (thin layer, or thin cylinder), it is possible to obtain approximate equations for mechanical equilibrium of the viscoelastic material, such that the entries of the strain tensor are dependent only on the wave variable $x_1 - qt$, yet the motion of the material in the other directions is possible. In the frame of this approximation we prove the existence of travelling wave solutions to reaction-diffusion equations for calcium and buffers coupled with equations for mechanical equilibrium. Under the physically justified Assumption 2, we prove also positivity of the calcium and buffer concentrations. The existence of mechano-chemical travelling waves was discussed also in [11], under the condition od infinitely fast reaction terms for buffers. In such a case the chemical part of the system is reduced to a single reaction-diffusion equation with additional quadratic gradient term. In [18] the perturbation technique is applied to obtain a single approximate reaction-diffusion equation describing the propagation of mechanochemical waves; this again is possible to do for very fast buffers.

Appendix 1. Proof of Lemma 3.2

Below, for the sake of clarity, we will confine ourselves to the case of constant μ_1, μ_2, E and ν. This implies that the quantities μ, K and β are constant.

Lemma 5.1. *Let $\varepsilon^2 > 0$, $F \in B_1(\mathbb{R}^1), G > 0$. Then*

$$I(\xi) := \int_{-\infty}^{\xi} \exp[-(\xi - s)/(\varepsilon^2 G)]F(s)ds = \varepsilon^2 GF(\xi) + O(\varepsilon^4) \tag{51}$$

and

$$I'(\xi) = \varepsilon^2 GF'(\xi) + o(\varepsilon^2) \tag{52}$$

as $\varepsilon \to 0$. Moreover, $I(\xi)$ and $I'(\xi)$ are continuous functions of ε^2.

Proof. In the proof we will make use of the following indefinite integral identity:

$$\int x^m \exp(ax)dx = \exp(ax)\{a^{-1}x^m + \sum_{k=1}^{m}(-1)^k a^{-k-1}x^{m-k} \\ m(m-1)\dots(m-k+1)\}.$$

To prove the first equality of the lemma, let us divide the region of integration $(-\infty, \xi)$ into two parts $(-\infty, \xi - \omega]$ and $(\xi - \omega, \xi)$, where $\omega = |\varepsilon|^{5/4}$. In the first interval we have

$$|\int_{-\infty}^{\xi-\omega} \exp[-(\xi - s)/(\varepsilon^2 G)]F(s)ds| \le \|F\|_{B_0}\varepsilon^2 G \exp[-1/(|\varepsilon|^{3/4}G))] = \\ O(\exp[-1/(|\varepsilon|^{3/4}G)]), \tag{53}$$

as $\varepsilon^2 \to 0$. As F is continuously differentiable, then for $s \in (\xi - \omega, \xi)$, $F(s) = F(\xi) + q(s, \xi)(s - \xi)$. So, in the second interval we have

$$\int_{\xi-\omega}^{\xi} \exp[-(\xi - s)/(\varepsilon^2 G)]F(s)ds = \\ \int_{\xi-\omega}^{\xi} \exp[-(\xi - s)/(\varepsilon^2 G)][F(\xi) + q(s, \xi)(s - \xi)]ds = \varepsilon^2 GF(\xi) + O(\varepsilon^4). \tag{54}$$

Hence we obtain (51). Consequently

$$I'(\xi) = F(\xi) - 1/(\varepsilon^2 G)\int_{-\infty}^{\xi} \exp[-(\xi - s)/(\varepsilon^2 G)]F(s)ds =$$

$$1/(\varepsilon^2 G)\int_{-\infty}^{\xi-\omega}[-(\xi - s)/(\varepsilon^2 G)](F'(\xi + \theta(s, \xi)(s - \xi))(s - \xi)ds$$

$$+1/(\varepsilon^2 G)\int_{\xi-\omega}^{\xi}[-(\xi - s)/(\varepsilon^2 G)](F'(\xi + \theta(s, \xi)(s - \xi))(s - \xi)ds) =$$

$$O(\exp[-1/(|\varepsilon|^{3/4}G)]) + \varepsilon^2 F'(\xi)G + o(\varepsilon^2)$$

proving the second equality of the lemma. □

Taking $1/G = -K(\mu q)^{-1}$ we conclude that

$$H(c, q, \varepsilon)(\xi) = -\varepsilon^2 K^{-1}\mu q\, \kappa(c(\xi))\ c'(\xi) + O(\varepsilon^4), \tag{55}$$

so we have $\|H(c, q, \varepsilon)(\cdot)\|_{B_0} \to 0$ as $\varepsilon \to 0$. By Eq.(30) and Lemma 5.1 we conclude that for all $\xi \in \mathbb{R}^1$

$$(H(c, q, \varepsilon)(\xi))' = O(\varepsilon^2). \tag{56}$$

Hence,

$$\|H(c, q, \varepsilon)(\cdot)\|_{B_1^*} \to 0 \quad \text{for} \quad \varepsilon \to 0. \tag{57}$$

Thus the definition of the operator can be extended to the segment $(-\varepsilon_0, \varepsilon_0)$ by taking

$$H(c, q, 0) = 0.$$

For simplicity, the extended operator will be denoted also by H. Now, let us note that for any $(c, q) \in B_{20} \times \mathbb{R}^1$, the Frechet derivative $DH(c, q, \varepsilon)$ of the operator H with respect to (c, q) at a point (c, q, ε) with acting on the vector $[\delta c, \delta q]$ has the following form:

$$DH(c,q,\varepsilon)[\delta c,\delta q](\xi) = \int_{-\infty}^{\xi} \exp\left[-(\xi - s)\frac{K}{\varepsilon^2 \mu q}\right] \times$$
$$\frac{1}{K}\left\{\tau_{,cc}(c(s))c'(s)\delta c(s) + \tau_{,c}(c(s))(\delta c)'(s) + (\xi - s)\frac{K}{\varepsilon^2 \mu q^2}\tau_{,c}(c(s))c'(s)\delta q\right\} ds \tag{58}$$

Now, using Assumption 3, we may proceed similarly as in the proof of Lemma 5.1, dividing the region of integration into two parts and carrying out appropriate estimations. Thus

$$DH(c,q,\varepsilon)[\delta c,\delta q](\xi) =$$

$$\varepsilon^2 \tfrac{\mu}{K^2} q \left\{\tau_{,cc}(c(\xi))c'(\xi)\delta c(\xi) + (\tau_{,c}(c(\xi))(\delta c)'(\xi) + (\tau_{,c}(c(\xi))q^{-1}\delta q\right\} + O(\varepsilon^4).$$

Differentiating (58) and continuing as in the proof of Lemma 5.1, one can show that

$$\|DH(c,q,\varepsilon)[\delta c,\delta q]\|_{B_1^*} = O(\varepsilon^2)\ (\|\delta c\|_{B_2} + |\delta q|) \quad \text{for} \quad \varepsilon \to 0. \tag{59}$$

Thus for $\varepsilon \in (-\varepsilon_0, 0) \cup (0, \varepsilon_0)$ the Frechet derivative $DH(c, q, \varepsilon)$ is well defined and $DH : B_{20} \times \mathbb{R}^1 \to B_1^*$. Moreover, similarly as in the case of H, we can extend the definition of DH also for $\varepsilon = 0$, by means of (39). Namely, we set

$$DH(c, q, 0) = 0. \tag{60}$$

Hence DH is continuous with respect to ε and $DH \to 0$ in the operator norm as $\varepsilon \to 0$.

Appendix 2. Solvability of system (40)

System (40) (for δc, $\delta v_1, \ldots, \delta v_n$ and δq) can be written explicitly as

$$A\delta U'' + q_0 \delta U' + \delta q\, U' + \partial_U F(U(\xi))\delta U = l, \tag{61}$$

Above we have denoted

$$U(\xi) = (U_0(\xi), U_1(\xi), \ldots, U_n(\xi)) := (c_0(\xi), v_{10}(\xi), \ldots, v_{n0}(\xi)),$$
$$\delta U = (\delta c, \delta v_1, \ldots, \delta v_n)^T,$$
$$A = \operatorname{diag}(D_0, D_1, \ldots, D_n),$$
$$F_0(U) = f(U_0) + \textstyle\sum_{i=1}^n G_i(U_0, U_i), \quad F_i(U) = -G_i(U_0, U_i), \quad i = 1, \ldots, n,$$

and

$$l = \left(f_{30} - (r_{,h}(c_0, 0, 0)f_1 + r_{,b}(c_0, 0, 0)f_2), f_{32}, \ldots, f_{3n}\right).$$

Let us consider the homogeneous part of system (61), assuming for a while that δq is known:

$$A\delta U'' + q_0 \delta U' + \partial_U F(U(\xi))\delta U = 0. \tag{62}$$

It is easy to check, by using Assumption 4 and the form of the functions G_i, $i = 1, \ldots, n$, that we can use Theorem 4.5.1 in [24] to conclude that system (62) has no other bounded solution, but $\delta U(\xi) = U'(\xi)$. This solution, does not, however, belong to the space B_{20}, because $U_0'(0) = c_0'(0) \neq 0$, (according to Theorem 2.1),

so condition (35) is not satisfied. Similarly, by Theorem 4.5.1 in [24], there exists exactly one bounded solution V of the adjoint system:

$$AV'' - q_0 V' + (\partial_U F(U(\xi)))^T V = 0. \tag{63}$$

All components V_i of V are positive.

Now, we can write system (62) as a system of first order equations:

$$\begin{pmatrix} \delta U \\ \delta Z \end{pmatrix}' + \mathbf{B} \begin{pmatrix} \delta U \\ \delta Z \end{pmatrix} = 0, \tag{64}$$

where

$$\mathbf{B} = \begin{pmatrix} 0_{(n+1)\times(n+1)} & -I_{(n+1)\times(n+1)} \\ A^{-1}\partial F(U(\xi)) & A^{-1} I_{(n+1)\times(n+1)} q_0 \end{pmatrix} \tag{65}$$

where δZ is a vector variable standing for $\delta U' = ((\delta c)', (\delta v_1)', \ldots, (\delta v_n)')^T$. Let us note that, for any $q_0 \in \mathbb{R}^1$, the eigenvalues of the matrices $\mathbf{B}(-\infty)$ and $\mathbf{B}(\infty)$ have nonzero real part. To be more precise, exactly $n+1$ of their eigenvalues have negative real part and $n+1$ eigenvalues have positive real part (Theorems 3.2 and 3.3 in [2]). By what we have said above, there is only one bounded solution of system (64) and one bounded solution to the system adjoint to (64). Hence, by using Lemma 4.2 in [17], we infer that the linear operator J given by the left hand side of (64) (as acting from the space of vector functions $(\delta U, \delta Z) \in (B_1(\mathbb{R}^1))^{n+1} \times (B_1(\mathbb{R}^1))^{n+1}$ to $(B_0(\mathbb{R}^1))^{n+1} \times (B_0(\mathbb{R}^1))^{n+1}$) is Fredholm with index 0. Thus, the equation $J(\delta U, \delta Z)^T = f$ has a unique bounded solution provided f is orthogonal to the mentioned above solution of the adjoint system. Applying these results to system (61), we conclude that it has a unique solution $(c, v_1, \ldots, v_n) \in B_{20} \times (B_2)^n$, iff

$$\int_{\mathbb{R}^1} \sum_{k=0}^{n} [l_k(\xi) - \delta q U_k'(\xi)] V_k(\xi) d\xi = 0, \tag{66}$$

This condition determines uniquely δq. Thus the unique solvability of system (40) is proven. Similar approach to the problem of solvability of system (40) is given in [14].

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Received June 13, 2012; Accepted November 05, 2012.

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