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Calcium waves with fast buffers and mechanical effects

Bogdan Kaźmierczak · Zbigniew Peradzyński

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Abstract In the paper we consider the existence of calcium travelling waves for systems with fast buffers. We prove the convergence of the travelling waves to an asymptotic limit as the kinetic coefficients characterizing the interaction between calcium and buffers tend to infinity. To be more precise, we prove the convergence of the speeds as well as the calcium component concentration profile to the profile of the travelling wave of the reduced equation. Additionally, we take into account the effect of coupling between the mechanical and chemical processes and show the existence as well the monotonicity of the profiles of concentrations. This property guarantees their positivity.

Keywords Calcium waves · Reaction–diffusion systems · Mechanochemical coupling

1 Introduction

Calcium waves have been extensively studied in the last decade as it is believed that their propagation through an individual cell or across a group of cells is responsible for the coordination of the response to the local changes of the conditions. It seems that the crucial role in supporting calcium waves is played by an autocatalytic mechanism; after reaching some concentration threshold, the calcium ions by a positive

B. Kaźmierczak (✉) · Z. Peradzyński
Institute of Fundamental Technological Research,
Polish Academy of Sciences, Warsaw, Poland
e-mail: bkazmier@ippt.gov.pl

Z. Peradzyński
Institute of Applied Mathematics and Mechanics,
Warsaw University, Warsaw, Poland

feedback stimulate their own release. The simplest mathematical model is provided by a single "bistable" reaction–diffusion equation for the calcium concentration. The reaction term of this equation has two stable equilibria: the ground state (low calcium concentration) and the excited state (of high calcium concentration). It is known (Fife 1979; Diekmann and Temme 1976) that such an equation has a solution in the form of a heteroclinic travelling wave joining the above mentioned equilibria. One encounters the same situation in the case of buffered systems (see Sneyd et al. 1998; Tsai and Sneyd 2005; Shenq Guo and Tsai 2006) presenting more realistic description of calcium dynamics. On the other hand experimental observations suggest that the excited state relaxes slowly to the ground state (Young et al. 1999). Due to this fact, in the paper Sneyd et al. (1998) the scalar Reaction–diffusion equation for calcium concentration is supplemented by an ordinary differential equation for the evolution of a new, so called *recovery variable*, to form a FitzHugh–Nagumo (FHN) like model. Since the recovery process is slow, travelling waves of calcium concentration, as seen in experiments (Young et al. 1999), have the form of homoclinic pulses with a sharp leading edge and a long tail. The movement of the leading edge can be well approximated by an *advancing* heteroclinic travelling front, i.e. moving in the direction opposite to the concentration gradient (see Fig. 5 in Sneyd et al. 1998). Such an approximation will be adopted in this work.

The dynamics of Ca^{++} in cells is significantly influenced by the presence of buffers (see Sneyd 2002; Sneyd et al. 1998; Falcke 2004). These are proteins of molecular masses about tens of kDa (e.g. parvalbumin and EGTA) being able to bind the calcium ions. The percentage of Ca^{++} which can be bound to different kind of buffers can achieve the value of 99. For simplicity, we confine here our considerations to the case of one representative buffer. However the same considerations can be applied to systems with many buffers. The evolution of the free calcium and the buffer concentrations are described by the following system of Reaction–diffusion equations:

$$\frac{\partial c}{\partial t} = D_c \nabla^2 c + f(c) + \beta^{-2}[k_- b - k_+ c(b_* - b)], \tag{1}$$

$$\frac{\partial b}{\partial t} = D_b \nabla^2 b - \beta^{-2}[k_- b - k_+ c(b_* - b)], \tag{2}$$

where c denotes the free cytosolic calcium concentration, b denotes the concentration of proteins with Ca^{++} bound, D_c and D_b are respective diffusion coefficients, $b_* = const$ is the total buffering molecules concentration ($0 \le b \le b_*$), k_+ and k_- are the rates of binding and unbinding of calcium by the buffer respectively, $f(c)$ is the function describing calcium transport into and out of the cytosol. $\beta^{-2} > 0$ is a formal parameter which will be used in our asymptotic analysis. Thus large β^{-2} means that the buffer kinetics is much faster than the diffusion of the buffer. The assumption of very fast buffer kinetics makes it possible to analyze the influence of the buffer on the calcium dynamics. Indeed, in the limit $\beta^{-2} \to \infty$, one can expect that

$$[k_- b - k_+ c(b_* - b)] = 0, \tag{3}$$

yet the expression $\beta^{-2}(k_-b - k_+c(b_* - b))$ may not tend to zero, thus contributing to the equation for c. Differentiating the relation (3), we can express $\partial b/\partial t - D_b\nabla^2 b$, hence also $\beta^{-2}(k_-b - k_+c(b_* - b))$, by means of the partial derivatives of c. Putting this into Eq. 1 we arrive at a single Reaction–diffusion equation for the free calcium concentration:

$$\frac{\partial c}{\partial t} = \frac{D_c + D_b S(c)}{1 + S(c)}\nabla^2 c - \frac{2D_b S(c)}{(c + \mathcal{L})(1 + S(c))}|\nabla c|^2 + \frac{f(c)}{1 + S(c)}, \tag{4}$$

where $S(c) = b_*\mathcal{L}/(\mathcal{L} + c)^2$ and $\mathcal{L} = k_-/k_+$ (see Keener and Sneyd 1998). This equation can in turn be used to analyze the existence and properties of travelling wave solutions for system (1–2) as it is done in Sneyd et al. (1998), and Keener and Sneyd (1998). Thus a system of many equations (there may be many kinds of buffer particles) is, in a way, replaced by a single Reaction–diffusion equation, which is much easier to analyze. The aim of this paper is to justify this heuristic reasoning. We will be interested in a strict mathematical proof that the calcium component of the travelling wave solutions tends to the travelling wave solution of the scalar equation (4). This is the main result of the paper.

An additional aim of this work is to study the mechano-chemical effects, which accompany travelling waves of calcium concentration. Local variations of calcium concentration induce local variations of mechanical properties of the cytogel, and in consequence the appearance of mechanical stresses which can cause the cytogel deformation (Murray 1993).

On the other hand, mechanical deformations of the medium can evoke local changes of calcium concentration. The local cytogel deformations can lead to the change of calcium concentration, by releasing the calcium from internal stores situated in endoplasmic reticulum. Thus a mechanical stimulus (e.g. poking an end of a cell with a micropipette) can induce a wave of calcium concentration (see Fig. 12.8 in [14]).

To incorporate these mechano-chemical effects into our considerations we will use the simplified model presented in Murray (1993), where cells are treated as a visco-elastic medium. According to this model Eq. 1 should be completed by the mechanical term $\gamma\theta$ to obtain

$$\frac{\partial c}{\partial t} = D_c\nabla^2 c + f(c) + \beta^{-2}[k_-b - k_+c(b_* - b)] + \gamma\theta,$$

where $\theta = \nabla \cdot \mathbf{u}$ is the mechanical dilation ($\mathbf{u}$ is the mechanical displacement). In this case the system is supplemented by the equation describing the balance of mechanical forces:

$$\nabla \cdot \left\{ \frac{E(c)}{1 + \nu(c)}\left[\epsilon + \frac{\nu(c)}{1 - 2\nu(c)}\theta\mathbf{I}\right] + \mu_1(\theta, c)\frac{\partial \epsilon}{\partial t} + \mu_2(\theta, c)\frac{\partial \theta}{\partial t}\mathbf{I} + \hat{\tau}(c)\right\} = 0. \tag{5}$$

The first term under the divergence symbol is the elastic part of the stress tensor, the second and the third term are the viscous part of the stress tensor and the fourth term is so called traction tensor. It represents the forces which are caused by the changes of the calcium concentration in the cytosol. The inertial terms in Eq. 5 have been neglected.

This is justified as the motions of the medium induced by changes of the calcium concentration is very slow. [The speed of calcium waves is of order of $10 \div 30$ microns per second (Jaffe 1991)]. Sometimes, one can also take into consideration volume forces of the form $k\mathbf{u}$ measuring the strength of attachment of cells to the surrounding medium (Winkler model). These forces are also neglected.

The quantities in Eq. 5 have the following meaning: $\mathbf{u} = \mathbf{u}(\mathbf{x}, t)$, displacement; ϵ, strain tensor i.e. $\epsilon = 1/2(\nabla\mathbf{u} + \nabla\mathbf{u}^T)$; $\theta = \nabla \cdot \mathbf{u}$, dilation; E, Young modulus; ν, Poisson ratio; μ_1, μ_2, shear and bulk viscosities; $\mathbf{I}$, unit matrix; c, calcium concentration; $\hat{\tau}(c)$-active concentration stress tensor resulting from the actomyosin traction. In Murray (1993) it is assumed that $\hat{\tau}(c)$ is isotropic: $\tau(c)\mathbf{I}$, but this assumption will be relaxed in the paper. As the concentration influences the mechanical properties of the medium, then we assume that the coefficients E, ν, μ_1 and μ_2 are the functions of c. Additionally we assume that μ_1 and μ_2 depend on dilation θ.

Viscosity coefficients μ_1, μ_2 of any physical medium are nonnegative and the Poisson ratio for usual materials satisfies the inequality $0 \le \nu < 1/2$ (Fung 1965). Also, the Young modulus of any real physical medium is positive and finite. From the physical point of view the values of the calcium concentration c are non-negative. However, due to the possibility of appropriate extensions of the coefficient functions for the negative values of c, we take the following assumption:

Assumption 1 Let us assume that, for all $c \in \mathbb{R}^1$ and $\theta \in \mathbb{R}^1$, $\nu(c)$, $E(c)$, $\tau(c)$, $\mu_1(\theta, c)$ and $\mu_2(\theta, c)$ are C^3-functions of their arguments, such that $\nu(c) \in (0, 1/2)$, $\mu_1(\theta, c) > 0$, $\mu_2(\theta, c) > 0$ and $0 < E_1 \le E(c) < \infty$, where E_1 is a constant.

Remark As one will notice later, c will take values from the vicinity of a bounded interval $[c_1, c_3]$ (see Assumption 2). Similarly, θ will take only values from some bounded interval containing 0.

In this paper we are interested in travelling plane waves propagating in long cylindrical cells in the x-direction. We assume also that in the Cartesian coordinates where x-axis is the axis of the cylinder, the traction tensor is diagonal and $\hat{\tau} = \text{diag}(\tau_x, \tau_r, \tau_r)$ – thus assuming that the problem is axially symmetric.

We will confine ourselves to two extreme cases:

1. Waves in cells whose lateral boundaries cannot move in the directions perpendicular to the axis of the cylinder
2. Waves in cells with free lateral surface (when the forces acting at each point of the lateral surface are negligible)

In both of these cases Eq. 5 takes the form

$$\mu(\theta, c)\frac{\partial\theta}{\partial t} + K(c)\theta + \tau(c) = \sigma_0. \tag{6}$$

Here σ_0 is the integration constant, which has the meaning of an asymptotic (external) stress.

In case 1. $\mathbf{u} = (u_x, 0, 0)$, $\epsilon_{xx} = u_{x,x}(x)$, whereas the other components of the tensor ϵ are equal to zero. Thus $\theta = u_{x,x}(x)$ and by integration with respect to x we obtain Eq. 6 with

$$K(c) = E(c)(1-\nu(c))/[(1+\nu(c))(1-2\nu(c))],$$
$$\mu(\theta,c) = \mu_1(\theta,c) + \mu_2(\theta,c), \quad \tau(c) = \tau_x(c),$$

whereas in case 2. we have

$$K(c) = \frac{E(c)}{1-2\nu(c)}, \quad \mu(\theta,c) = \mu_1(\theta,c) + 3\mu_2(\theta,c), \quad \tau(c) = 2\tau_r(c) + \tau_x(c). \tag{7}$$

To derive relations (7), let us consider a long cell of radius r_0, whose lateral boundary is free (unloaded). For convenience we express here the strain–stress relations using the Lame coefficients G, λ instead of E and ν and do not denote their explicit dependence on c (as well as the dependence of μ_1 and μ_2 on c and θ). We thus have the relations:

$$\sigma = 2G\epsilon + \lambda I\theta + \mu_1\epsilon_{,t} + \mu_2 I\theta_{,t} + \hat{\tau}, \tag{8}$$

where

$$\lambda = \frac{E\nu}{(1+\nu)(1-2\nu)}, \quad G = \frac{E}{2(1+\nu)} \tag{9}$$

and $\hat{\tau}$ represents the traction tensor (in general not isotropic). In the cylindrical system of coordinates (r, ϕ, x) the cell will be represented as an infinite cylinder $\{(r,\phi,x) : r \le r_0, \phi \in [0, 2\pi), x \in \mathbb{R}^1\}$, whereas relations (8) take the form:

$$\begin{aligned}
\sigma_{rr} &= 2G\epsilon_{rr} + \lambda\theta + \mu_1\epsilon_{rr,t} + \mu_2\theta_{,t} + \tau_r, \quad \sigma_{\phi\phi} = 2G\epsilon_{\phi\phi} + \lambda\theta + \mu_1\epsilon_{\phi\phi,t} + \mu_2\theta_{,t} + \tau_\phi,\\
\sigma_{xx} &= 2G\epsilon_{xx} + \lambda\theta + \mu_1\epsilon_{xx,t} + \mu_2\theta_{,t} + \tau_x, \quad \sigma_{r\phi} = 2G\epsilon_{r\phi} + \mu_1\epsilon_{r\phi,t},\\
\sigma_{\phi x} &= 2G\epsilon_{\phi x} + \mu_1\epsilon_{\phi x,t}, \quad \sigma_{rx} = 2G\epsilon_{rx} + \mu_1\epsilon_{rx,t},
\end{aligned} \tag{10}$$

where $\theta = \epsilon_{rr} + \epsilon_{\phi\phi} + \epsilon_{xx}$. We assume here that our problem is axially symmetric, thus $\hat{\tau} = \mathrm{diag}(\tau_r, \tau_r, \tau_x)$. (Note that $\hat{\tau}$ may behave differently along the axial and perpendicular directions.) We assume that $\mathbf{u} = (u_r, u_\phi, u_x)$ with $u_\phi = 0$. By assumption r_0 is small, so we take the first order approximation in r:

$$u_x = a(x,t) + a_1(x,t)r + O(r^2), \quad u_r = b_0(t,x) + b(t,x)r + O(r^2). \tag{11}$$

The strain tensor components have thus the following form:

$$\epsilon_{rr} = u_{r,r}, \quad \epsilon_{\phi\phi} = r^{-1}u_r, \quad \epsilon_{xx} = u_{x,x}$$
$$\epsilon_{r\phi} = 0, \quad \epsilon_{\phi x} = 0, \quad \epsilon_{xr} = \frac{1}{2}\left(u_{x,r} + u_{r,x}\right).$$

To avoid singularity in $\epsilon_{\phi\phi}$ at $r = 0$, we have to assume that $b_0(x, t) \equiv 0$. Since the displacement vector is expressed up to linear terms in r, therefore it is reasonable to compute strain tensor up to zero order terms in r (differentiation lowers the order of approximation by 1). In such an approach $\epsilon_{rr} = \epsilon_{\phi\phi}$ and the tensor ϵ and consequently stress tensor σ does not depend on r. It depends only on x. This is important, since in this way we obtain ordinary differential equation for the wave profile. Otherwise, the wave profile would depend also on r. The equations of mechanical equilibrium read (see Fung 1965, Section 4.12):

$$\sigma_{rr,r} + \sigma_{xr,x} + r^{-1}(\sigma_{rr} - \sigma_{\phi\phi}) = 0$$
$$\sigma_{rx,r} + \sigma_{xx,x} + r^{-1}\sigma_{rx} = 0$$

whereas the boundary conditions on the unloaded lateral surface of the cylinder read

$$\sigma_{rr} = 0, \quad \sigma_{rx} = 0 \quad \text{for} \quad r = r_0.$$

The second condition for $\sigma_{rx} = 0$ implies that $a_1(x, t) = 0$, hence $\sigma_{rx} \equiv 0$. As $\sigma_{rr} = \sigma_{\phi\phi}$, then finally the full set of equations is reduced to:

$$\sigma_{rr} = 0 \tag{12}$$
$$\sigma_{xx,x} = 0. \tag{13}$$

Since in our case $\epsilon_{rr} = \epsilon_{\phi\phi}$ then

$$\theta = 2\epsilon_{rr} + \epsilon_{xx}.$$

Integrating equation (13) with respect to x and putting the integration constant equal to σ_0, we obtain

$$2\sigma_{rr} + \sigma_{xx} = \sigma_0$$

which gives us an equation for θ

$$(2G + 3\lambda)\theta + (\mu_1 + 3\mu_2)\theta_{,t} + (2\tau_r + \tau_x) = \sigma_0.$$

By means of (9) we rewrite the last equation as

$$K\theta + \mu\theta_{,t} + \tau = \sigma_0$$

where

$$K = 2G + 3\lambda = \frac{E}{1 - 2\nu}, \quad \mu = \mu_1 + 3\mu_2, \quad \tau = (2\tau_r + \tau_x).$$

We thus obtain (7).

For $\mu = 0$ Eq. 6 can be solved for θ to obtain

$$\theta_0(c, \sigma_0) = (K(c))^{-1}(\sigma_0 - \tau(c)). \tag{14}$$

Since σ_0 is constant, the explicit dependence of θ_0 on σ_0 will be further suppressed for simplicity.

For solutions depending only on x and t, Eqs. 1, and 2 can be written as:

$$\frac{\partial c}{\partial t} = D_c \frac{\partial^2 c}{\partial x^2} + g(c) + \gamma(\theta - \theta_0(c)) + (\beta^{-2})[k_- b - k_+ c(b_* - b)] = 0. \tag{15}$$

$$\frac{\partial b}{\partial t} = D_b \frac{\partial^2 b}{\partial x^2} - \beta^{-2}[k_- b - k_+ c(b_* - b)], \tag{16}$$

where

$$g(c) = f(c) + \gamma\theta_0(c). \tag{17}$$

System (6–16) describes the process of diffusion and reactions of calcium and buffer particles together with the accompanying mechanical effects. As we are interested in travelling wave solutions we impose the following assumption.

Assumption 2 The function $g(c)$ is of C^2 class. It is bistable with $c_1,\ c_3 > c_1$ the stable zeros and $c_2 \in (c_1, c_3)$ the unstable zero.

Remark Let us note that experimentally the function $g(\cdot)$ is determined rather than the function $f(\cdot)$.

For $\mu = 0$, we have $\theta \equiv \theta_0$ and the equation corresponding to (4) has the following form

$$\frac{\partial c}{\partial t} = \frac{D_c + D_b S(c)}{1 + S(c)} \nabla^2 c - \frac{2 D_b S(c)}{(c + \mathcal{L})(1 + S(c))} |\nabla c|^2 + \frac{g(c)}{1 + S(c)}, \tag{18}$$

2 Existence and properties of travelling wave solutions

Looking for travelling wave solutions we assume that

$$\theta(x,t) = \theta(x - vt), \quad c(x,t) = c(x - vt), \quad b(x,t) = b(x - vt).$$

Inserting this into system (6), (15–16) we arrive at the following system of equations

$$-\mu(\theta, c)v\theta' + K\theta + \tau(c) = \sigma_0 \tag{19}$$

$$D_c c'' + vc' + g(c) + \gamma(\theta - \theta_0(c)) + (\beta^{-2})[k_- b - k_+ c(b_* - b)] = 0 \tag{20}$$

$$D_b b'' + vb' - (\beta^{-2})[k_- b - k_+ c(b_* - b)] = 0, \tag{21}$$

where $'$ denotes differentiation with respect to $z = x - vt$. As we are interested in heteroclinic solutions to system (19–21) we assume that the first and second derivatives of the functions $\theta(\cdot)$, $c(\cdot)$ $b(\cdot)$ tend to zero at infinities and that

$$\lim_{z\to-\infty} c(s) = c_1, \quad \lim_{z\to\infty} c(z) = c_3,$$
$$\lim_{z\to-\infty} \theta(z) = \theta_0(c_1), \quad \lim_{z\to\infty} \theta(s) = \theta_0(c_3), \tag{22}$$
$$\lim_{z\to-\infty} b(z) = b_1 := b_* k_+ \frac{c_1}{k_+ c_1 + k_-}, \quad \lim_{z\to\infty} b(z) = b_3 := b_* k_+ \frac{c_3}{k_+ c_3 + k_-}.$$

The quantities at the right hand side are the components of the constant steady state solutions of the considered system.

2.1 Existence of waves

Using the implicit function theorem in the appropriate Banach spaces, we will show the existence of travelling wave solutions of the system (6), (15), (16). First, we will write the considered system in a non-dimensional form to exhibit the small parameter related to the influence of viscosity.

Let l denote the typical width of the calcium wave profile in the considered medium, that is to say the effective length of the interval in which the free calcium concentration changes substantially, e.g. $(c_3 - c_1)/\max_z c'(z)$. Let P denote the typical speed of the calcium waves in the considered medium. The values of l are of order of $10 \div 20$ microns and the value of P is of order of $10 \div 30$ microns per second (see Jaffe 1991; Kupferman et al. 1997). We will introduce the dimensionless wave variable:

$$z^* = z/l \tag{23}$$

and the following dimensionless dependent variables

$$c^* = c/c_3, \quad b^* = b/c_3. \tag{24}$$

In these variables, system (19–21) can be written in the following way:

$$-\varepsilon^2 v^* \mu^*(\theta^*, c^*)\theta^{*'} + K^*(c^*)\theta^* + \tau^*(c^*) = \sigma_0^*, \tag{25}$$
$$D^* c^{*''} + v^* c^{*'} + g^*(c^*) + \gamma^*(\theta^* - \theta_0^*(c^*)) + \beta^{-2} G^*(c^*, b^*) = 0 \tag{26}$$
$$D^* b^{*''} + v^* b^{*'} - \beta^{-2} G^*(c^*, b^*) = 0, \tag{27}$$

where $'$ denotes the differentiation with respect to $z^* = z/l$,

$$\varepsilon^2 = \frac{\mu_0 P}{K_0 l} \tag{28}$$

and

$$D_c^* = D_c/(lP), \quad D_b^* = D_b/(lP), \quad g^*(c^*) = [l/(Pc_3)] g(c^* c_3), \quad \gamma^* = [l/(Pc_3)]\gamma$$
$$v^* = v/P, \quad G_i^*(c^*, b^*) = k_-^* b^* - k_+^* c^*(b_*^* - b^*), \quad k_-^* = lk_-/P, k_+^* = lk_+ c_3/P,$$

$$b_*^* = b_*/c_3, \quad \mu^*(\theta^*, c^*) = (\mu_0)^{-1}\mu(\theta^*, c^* c_3), \quad K^*(c^*) = (K_0)^{-1}K(c^* c_3),$$
$$\tau^*(c^*) = (K_0)^{-1}\tau(c^* c_3), \quad \sigma_0^* = \frac{\sigma_0}{K_0}, \quad \mu_0 = \mu(0, c_3), \quad K_0 = K(c_3). \tag{29}$$

Remark The reason for choosing the small parameter in the form ε^2 comes from the fact that we want to use the implicit function theorem in the open neighbourhood of $\varepsilon = 0$, which corresponds to zero viscosity.

Remark In the derivation of system (25–27) we used the fact that in the new spatial variable $x^* = x/l$ the new displacement u^* satisfies the relation $u = lu^*$. Moreover, $\partial u/\partial x = \partial u^*/\partial x^*$, thus $\theta = \theta^*$. According to relations (22) the asymptotic states for the new system (25–27) are now $\theta^*(-\infty) = \theta_0(c_1)$, $c^*(-\infty) = c_1^* = c_1/c_3$, $b^*(-\infty) = b_1^* = b_1/c_3$, $\theta^*(\infty) = \theta_0(c_3)$, $c^*(\infty) = c_3^* = c_3/c_3 = 1$, $b^*(\infty) = b_3^* = b_3/c_3$.

Below, we will assume that ε^2 is sufficiently small. For example in smooth muscles of pulmonary arteries ε^2 is less then 0.1 (see Bia et al. 2004). From now on, for simplicity, the stars by the variables will be omitted. Hence we obtain the following system of equations with two small parameters ε and β:

$$-\varepsilon^2 v\mu(\theta, c)\theta' + K(c)\theta + \tau(c) = \sigma_0, \tag{30}$$
$$D_c c'' + vc' + g(c) + \gamma[\theta - \theta_0(c)] + \beta^{-2}[k_- b - k_+ c(b_* - b)] = 0 \tag{31}$$
$$D_b b'' + vb' - \beta^{-2}[k_- b - k_+ c(b_* - b)] = 0, \tag{32}$$

Instead of the variables θ, c and b, let us introduce the new dependent variables h, c and η, where

$$h = \theta - \theta_0(c), \quad \eta = k_- b - k_+ c(b_* - b). \tag{33}$$

The quantities h and η measure the deviation from the zeroth order approximations ($\varepsilon = 0$, $\beta = 0$) of θ and b. Therefore it is convenient to rewrite the system (30–32) in variables h, c and η. By Eqs. 32 and 33 we have

$$\beta^{-2}\eta = vb' + D_b b''. \tag{34}$$

Solving the second equality in (33) we obtain

$$(\eta + k_+ c b_*)(k_- + k_+ c)^{-1} = b.$$

By differentiation of the last relation we have

$$b' = m(c)^{-1}\eta' + b_*\mathcal{L}/(\mathcal{L} + c)^2 c' - \eta k_+ m(c)^{-2} c'$$

and

$$b'' = m(c)^{-1}\eta'' + b_*\mathcal{L}/(\mathcal{L}+c)^2 c'' + \left[-2b_*\mathcal{L}/(\mathcal{L}+c)^3 + 2\eta k_+^2\, m(c)^{-3}\right] c'^2$$
$$-\eta' c' k_+\, m(c)^{-2} - \eta k_+\, m(c)^{-2} c'',$$

where

$$\mathcal{L} = \frac{k_-}{k_+}, \quad m(c) = (k_- + k_+ c).$$

Putting these relations into Eq. 34, we can express the term $\beta^{-2}[k_- b - k_+ c(b_* - b)]$ by means of $c, c', c'', \eta, \eta' \eta''$ and eliminate it from Eq. 31. Hence one may arrive at the system for h, c and η of the form:

$$h' - (\varepsilon^2 v\mu)^{-1} K h - \left[\frac{\tau(c) - \sigma_0}{K(c)}\right]_{,c} c' = 0 \tag{35}$$

$$D_1(c,\eta)c'' - D_2(c)c'^2 + vc' + (1+S(c))^{-1}\left[g(c) + \gamma h\right]$$
$$+\Phi_1(c, c', \eta, \eta', \eta'', v) = 0 \tag{36}$$

$$D_b \frac{1}{m(c)}\eta'' - \beta^{-2}\eta + \Phi_2(c, c', c'', \eta, \eta', v) = 0 \tag{37}$$

with

$$S(c) = \frac{b_*\mathcal{L}}{(\mathcal{L}+c)^2}\,, \quad D_1(c,\eta) = \frac{D_c + D_b S(c) - D_b k_+ m(c)^{-2}\eta}{1+S(c)},$$
$$D_2(c) = \frac{2D_b S(c)}{(\mathcal{L}+c)(1+S(c))},$$

$$\Phi_1(c, c', \eta, \eta', \eta'', v)$$
$$= (1+S(c))^{-1}\left\{\frac{2D_b k_+^2 \eta c'^2}{m(c)^3} + \frac{v\eta'}{m(c)} - \frac{k_+ c'(v\eta + D_b\eta')}{m(c)^2} + \frac{D_b\eta''}{m(c)}\right\}, \tag{38}$$

$$\Phi_2(c, c', c'', \eta, \eta', v) = \left\{\frac{2D_b k_+^2 \eta c'^2}{m(c)^3} + \frac{v\eta'}{m(c)} - \frac{k_+ c'(v\eta + D_b\eta')}{m(c)^2} + S(c)vc'\right.$$
$$\left. + D_b b_* \left[\frac{c}{\mathcal{L}+c}\right]'' - D_b \eta k_+\, m(c)^{-2} c''\right\}. \tag{39}$$

Let us note that

$$\Phi_1(c, c', \eta, \eta', \eta'', v) \equiv 0 \qquad \text{for} \quad \eta \equiv 0 \tag{40}$$

and Φ_2 does not contain η''. The coefficient by c'' in Φ_2 is equal to $D_b S(c) - D_b \eta k_+\, m(c)^{-2}$, so if we calculate c'' from Eq. 36 and put it into Eq. 37 we obtain an equation of the form:

$$W^{-1}\eta'' - \beta^{-2}\eta + W^{-1}F(h, c, c', \eta, \eta', v) = 0. \tag{41}$$

where

$$(W(c, \eta))^{-1} = \frac{D_b}{m(c)}\left[\frac{D_c}{D_c + D_b S(c) - D_b k_+ \eta (m(c))^{-2}}\right]. \tag{42}$$

The function F is rather complicated, so, due to the fact that its precise form is not essential, we do not write it explicitly here. One notes that $(W(c, 0))^{-1} > 0$, so $(W(c, \eta))^{-1}$ is positive for η sufficiently small. Equation 41 can be written as

$$\eta'' - W(c, \eta)\beta^{-2}\eta + F(h, c, c', \eta, \eta', v) = 0. \tag{43}$$

Remark It may be verified that the functions Φ_1 and F are of C^2 class of their arguments for c from some neighbourhood of the interval $[0, 1]$, η from some nighbourhood of 0 and all $h, c', \eta', \eta'' \in \mathbb{R}^1$. In Eq. 35 the function μ should be treated as a function of the variables h and c due to the definition (33).

For $\beta = 0$ and $\varepsilon = 0$ Eqs. 35 and 37 are satisfied for $h = 0$ and $\eta = 0$. (This can be seen by multiplying these equations by ε^2 and β^2, respectively.) Thus, due to 40, Eq. 36 changes to:

$$D_1(c, 0)c'' - D_2(c)c'^2 + vc' + (1 + S(c))^{-1}g(c) = 0 \tag{44}$$

with S, D_1 and D_2 defined after system (35–37). According to Keener and Sneyd (1998) (pp. 342–344), under suitable assumption on the term $(1 + S(c))$, there exists a unique heteroclinic pair $(c(\cdot), v) = (C(\cdot), V) \in C^2(\mathbb{R}^1) \times \mathbb{R}^1$ satisfying Eq. 44 such that $C(-\infty) = c_1$, $C(\infty) = c_3$ and $C(0) = \frac{1}{2}[C(-\infty) + C(\infty)]$ and $C'(z) > 0$ for all $z \in \mathbb{R}^1$. As we mentioned in the Introduction, we consider here only the advancing waves. As $c_3 > c_1$, this condition is equivalent to the demand that the wave velocity for $\varepsilon = 0$ satisfies the inequality

$$V < 0. \tag{45}$$

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

$$u(0) = \frac{1}{2}[u(-\infty) + u(\infty)]. \tag{46}$$

The norms in the spaces B_j are taken to be

$$\|u\|_{B_j} = \sum_{k=0}^{j} \sup_{z\in\mathbb{R}^1} \left| \frac{d^k}{dz^k} u(z) \right|.$$

For, $v \neq 0$ and some $\varepsilon_0 > 0$, let us consider the operator: $H : B_1^* \times B_{20} \times \mathbb{R}^1 \times (-\varepsilon_0, 0) \cup (0, \varepsilon_0) \to B_1^*$:

$$H(h, c, v, \varepsilon)(z) = \int_0^z \exp\left[\int_s^z \frac{1}{\varepsilon^2} \frac{1}{\chi(h(\zeta), c(\zeta))} \frac{1}{v} d\zeta \right] \kappa(c(s))c'(s)ds + \widetilde{C} \exp\left[\int_0^z \frac{1}{\varepsilon^2} \frac{1}{\chi(h(\zeta), c(\zeta))} \frac{1}{v} ds \right],$$

where

$$\kappa(c(s)) := \left[\frac{\tau(c) - \sigma_0}{K(c)} \right]_{,c} \Big|_{c=c(s)} \tag{47}$$

and

$$\chi(h(\zeta), c(\zeta)) := \frac{\mu(h(\zeta), c(\zeta))}{K(c(\zeta))}.$$

In fact $H(z)$ is the solution to Eq. 35 with $h(\cdot)$ and $c(\cdot)$ in the coefficients μ and K treated as the given functions. The constant $\widetilde{C}$ should be chosen in such a way that $H(h, c, v, \varepsilon) \in B_1^*$. It is easy to note that accordingly to the sign of the parameter v one should take

$$\widetilde{C} = \begin{cases} -\int_0^\infty \exp\left[-\int_0^s \frac{1}{\varepsilon^2} \frac{1}{\chi(h(\zeta),c(\zeta))} \frac{1}{v} d\zeta \right] \kappa(c(s))c'(s)\, ds & \text{for} \quad v > 0 \\ -\int_0^{-\infty} \exp\left[-\int_0^s \frac{1}{\varepsilon^2} \frac{1}{\chi(h(\zeta),c(\zeta))} \frac{1}{v} d\zeta \right] \kappa(c(s))c'(s)\, ds & \text{for} \quad v < 0 \end{cases}$$

Hence

$$H(h, c, v, \varepsilon)(z) = \begin{cases} -\int_z^\infty \exp\left[\int_s^z \frac{1}{\varepsilon^2 \chi(h(\zeta),c(\zeta))} \frac{1}{v} d\zeta \right] \kappa(c(s))c'(s)\, ds & \text{for} \quad v > 0 \\ \int_{-\infty}^z \exp\left[\int_s^z \frac{1}{\varepsilon^2} \frac{1}{\chi(h(\zeta),c(\zeta))} \frac{1}{v} d\zeta \right] \kappa(c(s))c'(s)\, ds & \text{for} \quad v < 0 \end{cases} \tag{48}$$

Our considerations will be carried out for $v < 0$, i.e. for the advancing waves.

Lemma 1 *Let* $\varepsilon^2 > 0$, $G, F \in B_1(\mathbb{R}^1)$, $G > G_0 > 0$. *Then*

$$I(z) := \int_{-\infty}^{z} \exp\left[-\int_{s}^{z} 1/(\varepsilon^2 G(\zeta))d\zeta\right] F(s)ds = \varepsilon^2 G(z)F(z) + O(\varepsilon^4)$$

and

$$I'(z) = \varepsilon^2 G(z)F'(z) + \varepsilon^2 G'(z)F(z) + o(\varepsilon^2)$$

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

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

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

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

$$\left|\int_{-\infty}^{z-\omega} \exp\left[-\int_{s}^{z} 1/(\varepsilon^2 G(\zeta))d\zeta\right] F(s)ds\right| \le \|F\|_{B_0} \int_{-\infty}^{z-\omega} \exp\left[-\int_{s}^{z} 1/(\varepsilon^2 \|G\|_{B_0})d\zeta\right]ds$$
$$\le \|F\|_{B_0}\varepsilon^2\|G\|_{B_0} \exp\left[-1/(|\varepsilon|^{3/4}\|G\|_{B_0})\right] = O(\exp[-1/(|\varepsilon|^{3/4}\|G\|_{B_0})]), \quad (49)$$

as $\varepsilon^2 \to 0$. As F and G are continuously differentiable, then for $\zeta \in (s, z)$, $s \in (z-\omega, z)$, $1/G(\zeta) = 1/G(z) + p(\zeta, z)(\zeta - z)$, $F(s) = F(z) + q(s, z)(s - z)$. By the mean value theorem $\int_s^z p(\zeta, z)(\zeta - z)d\zeta = p(\zeta^*, z)(\zeta^* - z)(z - s)$ for some $\zeta^* \in (s, z)$. Let $k(y) := (\exp(y) - 1)/y$. We can write

$$\exp[-\varepsilon^{-2}p(\zeta^*, z)(\zeta^* - z)(z - s)] = 1 + \varepsilon^{-2}k(s, z)p(\zeta^*, z)(\zeta^* - z)(s - z).$$

Since $\zeta^* \in (s, z)$ and $s \in (z - |\varepsilon|^{5/4}, z)$, then $\varepsilon^{-2}(\zeta^* - z)(s - z) \le |\varepsilon|^{1/2}$ and $k(s, z) \to 1$ as $|\varepsilon| \to 0$. Hence in the second interval we have

$$\begin{aligned}
&\int\limits_{z-\omega}^{z} \exp\left[-\int\limits_{s}^{z} 1/(\varepsilon^2 G(\zeta))d\zeta\right] F(s)ds \\
&= \int\limits_{z-\omega}^{z} \exp\left[-\int\limits_{s}^{z} \{1/(\varepsilon^2 G(z))\right] \exp\left[-\int\limits_{s}^{z} \varepsilon^{-2} p(\zeta, z)(\zeta - z)d\zeta\right] \\
&\quad \times [F(z) + q(s,z)(s-z)]ds \\
&= \int\limits_{z-\omega}^{z} \exp[-(z-s)/(\varepsilon^2 G(z))]\left[1 + \varepsilon^{-2} k(s,z) p(\zeta^*, z)(\zeta^* - z)(s-z)\right] \\
&\quad \times [F(z) + q(s,z)(s-z)]ds \\
&=: \varepsilon^2 G(z) F(z)[1 - \exp[-1/(|\varepsilon|^{3/4} G(z)]] + U(z).
\end{aligned} \tag{50}$$

We thus have

$$\begin{aligned}
U(z) = &\int\limits_{z-|\varepsilon|^{5/4}}^{z} \exp[-(z-s)/\varepsilon^2 G(z)] \\
&\times \left\{\left[1 + \varepsilon^{-2} k(s,z) p(\zeta^*, z)(\zeta^* - z)(s-z)\right] q(s,z)(s-z)\right. \\
&\left. + \varepsilon^{-2} k(s;z) p(\zeta^* z)(\zeta^* - z)(s-z) F(z)\right\} ds.
\end{aligned}$$

Consequently

$$\begin{aligned}
|U(z)| \le &\int\limits_{z-|\varepsilon|^{5/4}}^{z} \exp[-(z-s)/\varepsilon^2 G(z)] \\
&\times \left\{\left[1 + \varepsilon^{-2} |k(s,z)||p(\zeta^*, z)|(s-z)^2\right] |q(s,z)||(s-z)| + \varepsilon^{-2} |k(s;z)|\right. \\
&\left. \times |p(\zeta^* z)|(s-z)^2 |F(z)|\right\} ds \le c_U \varepsilon^4 \left(1 + \exp[-1/(|\varepsilon|^{3/4} G(z))]\right)
\end{aligned}$$

with the constant c_U independent of z and ε^2. Combining the above inequalities, we obtain the first equality of the lemma. Using this equality, inequality (49) and the definition of $U(z)$, we have

$$\begin{aligned}
I'(z) &= F(z) - 1/(\varepsilon^2 G(z)) \int\limits_{-\infty}^{z} \exp\left[-\int\limits_{s}^{z} 1/\varepsilon^2 G(\zeta)d\zeta\right] F(s)ds \\
&= [-U(z) + O(\exp(-1/(|\varepsilon|^{3/4} \|G\|_{B_0}))]/(\varepsilon^2 G(z)) \\
&= -U(z)/(\varepsilon^2 G(z)) + O\left(\exp(-1/(|\varepsilon|^{3/5} \|G\|_{B_0}))\right).
\end{aligned}$$

Moreover, as we mentioned above $k(s,z) \to 1$ as $\varepsilon^2 \to 0$ for all $s \in (z - |\varepsilon|^{5/4}, z)$, whereas $(\zeta^* - z)(s-z) \to (s-z)^2/2, q(s,z) \to F'(z)$ and $p(s,z) \to -G'(z)/G^2(z)$. Hence

$$\begin{aligned}
-U(z)/(\varepsilon^2 G(z)) &= -1/(\varepsilon^2 G(z)) \int_{z-|\varepsilon|^{5/4}}^{z} \exp[-(z-s)/(\varepsilon^2 G(z))] \\
&\quad \times \left\{ F'(z)(s-z) - (2\varepsilon^2)^{-1} G'(z)/G^2(z)(s-z)^2 F(z) \right\} ds + h.o.t \\
&= \varepsilon^2 G'(z)F(z)) + \varepsilon^2 G(z)F'(z) + o(\varepsilon^2)
\end{aligned} \tag{51}$$

proving the second equality of the lemma. □

Using Lemma 1 we conclude that

$$H(h,c,v,\varepsilon)(z) = -\varepsilon^2 \chi(h(z),c(z)) v \kappa(c(z))\ c'(z) + O(\varepsilon^4), \tag{52}$$

so we have $\|H(h,c,v,\varepsilon)(\cdot)\|_{B_0} \to 0$ as $\varepsilon \to 0$. By Eq. 35 and Lemma 1 that for all $z \in \mathbb{R}^1$

$$(H(h,c,v,\varepsilon)(z))' = O(\varepsilon^2). \tag{53}$$

Hence, for $v \neq 0$,

$$\|H(h,c,v,\varepsilon)(\cdot)\|_{B_1^*} \to 0 \quad \text{for} \quad \varepsilon \to 0. \tag{54}$$

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

$$H(h,c,v,0) = 0.$$

For simplicity, the extended operator will be denoted also by H. Now, let us note that for any $(h,c,v) \in B_1^* \times B_{20} \times \mathbb{R}^1$, $v \neq 0$, the Frechet derivative $DH(h,c,v,\varepsilon)$ of the operator H with respect to (h,c,v) at a point (h,c,v,ε) with $v < 0$ acting on the vector $[\delta h, \delta c, \delta v]$ has the following form:

$$\begin{aligned}
DH(h,c,v,\varepsilon)[\delta h,\delta c,\delta v](z) &= \int_{-\infty}^{z} \exp\left[\int_s^z \frac{1}{\varepsilon^2}\frac{1}{\chi(\zeta)}\frac{1}{v} d\zeta\right] \\
\times &\left\{ \kappa_{,c}(c(s))c'(s)\delta c(s) + \kappa(c(s))(\delta c)'(s) - \varepsilon^{-2}\kappa(c(s))c'(s) \right. \\
\times &\left. \int_s^z \frac{1}{\chi^2}\frac{1}{v}[\chi_{,h}\delta h + \chi_{,c}\delta c + \chi v^{-1}\delta v] d\zeta \right\} ds.
\end{aligned} \tag{55}$$

Now, using Assumption 1, we may proceed similarly as in the proof of Lemma 1, dividing the region of integration into two parts and carrying out appropriate estimations. Thus, using the Taylor expansion, we infer that for $s \in (z - |\varepsilon|^{5/4}, z)$ the integral in the integrand is equal to $(z-s)\kappa(c(z))c'(z)[\chi_{,h}(z)\delta h(z) + \chi_{,c}(z)\delta c(z) + \chi(z)v^{-1}\delta v]/(\chi^2(z)v) + O(|\varepsilon|^{5/2})$, so

$$
\begin{aligned}
DH(h,c,v,\varepsilon)[\delta h, \delta c, \delta v](z) = \varepsilon^2\{&\chi(z)v\,\kappa_{,c}(c(z))c'(z)\delta c(z) + \kappa(c(z))(\delta c)'(z) \\
&-\kappa(c(z))c'(z)[v\chi_{,h}(z)\delta h(z) + v\chi_{,c}(z)\delta c \\
&+\chi(z)\delta v]\} + O(\varepsilon^4).
\end{aligned}
$$

(For simplicity, we denoted $\chi(h(z), c(z))$ by $\chi(z)$. Similar remark concerns the derivatives of the function χ.) Differentiating (55) and continuing as in the proof of Lemma 1, one can show that

$$
\|DH(h,c,v,\varepsilon)[\delta h, \delta c, \delta v]\|_{B_1^*} = O(\varepsilon^2)\left(\|\delta h\|_{B_1^*} + \|\delta c\|_{B_2} + |\delta v|\right) \quad \text{for} \quad \varepsilon \to 0. \tag{56}
$$

Thus for $\varepsilon \in (-\varepsilon_0, 0) \cup (0, \varepsilon_0)$ the Frechet derivative $DH(h,c,v,\varepsilon)$ is well defined and $DH: \ B_1^* \times B_{20} \times \mathbb{R}^1 \to B_1^*$. Moreover, similarly as in the case of H, we can extend the definition of DH also for $\varepsilon = 0$, by means of (56). Namely, for $v \neq 0$, we set

$$
DH(h,c,v,0) = 0. \tag{57}
$$

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

Now, let us note that Eq. 35 can be written in the form

$$
Q_1(h,c,\eta,v,\varepsilon,\beta) = 0,
$$

where

$$
Q_1(h,c,\eta,v,\varepsilon,\beta) = h - H(h,c,v,\varepsilon). \tag{58}
$$

According to the above considerations the following lemma holds.

Lemma 2 *Let Q_1 be defined by (58). Then for all η, β and all (h,c,v,ε) from some neighbourhood of $(0, C, V, 0)$:*

1. *Q_1 is a continuous mapping from $B_1^* \times B_{20} \times B_2 \times \mathbb{R}^1 \times \mathbb{R}^1 \times \mathbb{R}^1$ to B_1^* and*

$$
\|Q_1(h,c,\eta,v,\varepsilon,\beta) - h\|_{B_1^*} = O(\varepsilon^2)
$$

as $\varepsilon \to 0$

2. *Q_1 is continuously Frechet differentiable with respect to (h, c, η, v) and*

$$\|DQ_1(h, c, \eta, v, \varepsilon, \beta)[\delta h, \delta c, \delta \eta, \delta v] - \delta h\|_{B_1^*} = \varepsilon^2\, O\left(\|\delta h\|_{B_1^*} + \|\delta c\|_{B_2} + |\delta v|\right)$$

as $\varepsilon \to 0$. Consequently for $h = 0$, $c = C$, $\eta = 0$, $v = V$, $\varepsilon = 0$, $\beta = 0$ we have

$$DQ_1(0, C, 0, V, 0, 0)[\delta h, \delta c, \delta v] = \delta h. \tag{59}$$

Now, for $y \in B_2$ and fixed $(c, \eta, \beta) \in B_{20} \times B_2 \times \mathbb{R}^1$, let $A : B_2 \to B_0$ be defined by the equality

$$[A(c, \eta, \beta)y](z) := y''(z) - W(c(z), \eta(z))\beta^{-2} y(z), \tag{60}$$

where W is defined by (42). For c such that $c(z) > -k_-/(2k_+)$ for all $z \in \mathbb{R}^1$, $\|\eta\|_{B_0} \leq l_\eta \|c\|_{B_0}$ with l_η sufficiently small and $\beta^2 > 0$, A has a bounded inverse $A^{-1} : B_0 \to B_2$ and Eq. 43 can be written as

$$Q_3(h, c, \eta, v, \varepsilon, \beta) := \eta - A^{-1}(c, \eta, \beta) F(h, c, c', \eta, \eta', v) = 0. \tag{61}$$

The following lemma holds.

Lemma 3 *Let Q_3 be defined by (61). Then for all $(h, c, \eta, v, \varepsilon, \beta)$ from some neighbourhood of $(0, C, 0, V, 0, 0)$:*

1. *Q_3 is a continuous mapping from $B_1^* \times B_{20} \times B_2 \times \mathbb{R}^1 \times \mathbb{R}^1 \times \mathbb{R}^1$ to B_2 and*

$$\|Q_3(h, c, \eta, v, \varepsilon, \beta) - \eta\|_{B_2} = O(|\beta|) \quad \text{as} \quad \beta \to 0$$

2. *Q_3 is continuously Frechet differentiable with respect to (h, c, η, v) and*

$$\begin{aligned} &\|DQ_3(h, c, \eta, v, \varepsilon, \beta)[\delta h, \delta c, \delta \eta, \delta v] - \delta \eta\|_{B_2} \\ &\quad = |\beta| O(\|\delta h\|_{B_1^*} + \|\delta c\|_{B_2} + \|\delta \eta\|_{B_2} + |\delta v|) \end{aligned}$$

as $\beta \to 0$.

Thus definition of the operator Q_3 and its derivative DQ_3 can be extended to $\beta = 0$ by taking

$$Q_3(h, c, \eta, v, \varepsilon, 0) = \eta, \quad DQ_3(h, c, \eta, v, \varepsilon, 0)[\delta h, \delta c, \delta \eta, \delta v] = \delta \eta.$$

For simplicity, the extended operators will be denoted in the same way.

Lemma 3 is analogous to Lemma 1 in Kazmierczak and Peradzyński (1996). However, for the reader's convenience we give its proof in the Appendix 1. Lemmas 2 and 3 allow us to use the implicit function theorem and reduce effectively the problem of travelling wave existence to the analysis of one second order equation for the concentration of calcium. Let us note that due to the above considerations system (19–21) can be written in the form:

$$Q_1(h, c, \eta, v, \varepsilon, \beta) = 0, \quad Q_2(h, c, \eta, v, \varepsilon, \beta) = 0, \quad Q_3(h, c, \eta, v, \varepsilon, \beta) = 0, \tag{62}$$

where Q_2 is the left hand side of Eq. 36, or more concisely in the form

$$Q(h, c, \eta, v, \varepsilon, \beta) = (Q_1(h, c, \eta, v, \varepsilon, \beta), Q_2(h, c, \eta, v, \varepsilon, \beta), Q_3(h, c, \eta, v, \varepsilon, \beta))$$

with $Q : B_1^* \times B_{20} \times B_2 \times \mathbb{R}^1 \times \mathbb{R}^1 \times \mathbb{R}^1 \to B_1^* \times B_0 \times B_2$. Obviously, for $\varepsilon = 0$ and $\beta = 0$ this system is satisfied by the quadruple $(h(\cdot), c(\cdot), \eta(\cdot), v) = (0, C(\cdot), 0, V)$. We will show that for $|\varepsilon|, |\beta|$ sufficiently small there exists a unique heteroclinic quadruple

$$(h(\cdot, \varepsilon, \beta), c(\cdot, \varepsilon, \beta), \eta(\cdot, \varepsilon, \beta), v(\varepsilon, \beta))$$

to system (62) such that $(h(\cdot, \varepsilon, \beta), c(\cdot, \varepsilon, \beta), \eta(\cdot, \varepsilon, \beta), v(\varepsilon, \beta)) \to (0, C, 0, V)$ as $(\varepsilon, \beta) \to 0$. According to the implicit function theorem, it suffices to show that the operator $DQ(0, C, 0, V, 0, 0)$ has a bounded inverse.

Lemma 4 *The system*

$$DQ_i(0, C, 0, V, 0, 0)[\delta h, \delta c, \delta \eta, \delta v] = f_i, \quad i = 1, 2, 3,$$

has for all $f_1 \in B_1^*$, $f_2 \in B_0$, $f_3 \in B_2$ uniquely determined solution

$$(\delta h, \delta c, \delta \eta, \delta v) \in B_1^* \times B_{20} \times B_2 \times \mathbb{R}^1.$$

Proof According to Lemmas 2 and 3

$$DQ_1(0, C, 0, V, 0, 0)[\delta h, \delta c, \delta \eta, \delta v] = \delta h,$$
$$DQ_3(0, C, 0, V, 0, 0)[\delta h, \delta c, \delta \eta, \delta v] = \delta \eta.$$

Hence the equations

$$DQ_1(0, C, 0, V, 0, 0)[\delta h, \delta c, \delta \eta, \delta v] = f_1,$$
$$DQ_3(0, C, 0, V, 0, 0)[\delta h, \delta c, \delta \eta, \delta v] = f_3$$

have obviously uniquely determined solutions $B_1^* \ni \delta h = f_1$ and $B_2 \ni \delta \eta = f_3$, respectively. Having δh and $\delta \eta$ we can solve the equation

$$DQ_2(0, C, 0, V, 0, 0)[\delta h, \delta c, \delta \eta, \delta v] = f_2$$

with respect to $\delta c \in B_{20}$ and $\delta v \in \mathbb{R}^1$. One can check that

$$DQ_2[\delta h, \delta c, \delta\eta, \delta v] = L_0\delta c + C'\delta v + (1 + S(C))^{-1}\gamma\delta h + D_{1,\eta}(C, 0)C''\delta\eta + \mathcal{F} \tag{63}$$

where

$$L_0\delta c = D_1(C, 0)\delta c'' - (2D_2(C)C' - V)\delta c' + \frac{\partial}{\partial c}\left\{(1 + S(c))^{-1}g(c) + D_1(c, 0)C'' - D_2(c)C'^2\right\}\Big|_{c=C} \delta c. \tag{64}$$

and

$$\mathcal{F} = \sum_{j=0,1,2} \Phi_{1,\eta^{(j)}}(C, C', 0, 0, 0, V)(\delta\eta^{(j)}).$$

($\Phi_{1,c^{(j)}}(0, 0, 0, C, C', V) = 0$, $j = 0, 1$, and $\Phi_{1,v}(0, 0, 0, C, C', V) = 0$ according to 40). Let us note that the function C' satisfies the equation $L_0\delta c = 0$. This function however does not belong to the space B_{20}. Using these facts one can prove that for any $\widetilde{f_2} \in B_2$ there exists a unique pair $(\delta c, \delta v) \in B_{20} \times \mathbb{R}^1$ and that the operator $L_0\delta c + C'\delta v$ defines an isomorphism between the spaces $B_{20} \times \mathbb{R}^1$ and B_2 (Kazmierczak and Peradzyński 1996; Kazmierczak and Volpert 2003, see also Crooks and Toland 1998; Kazmierczak 2001). Thus noting that $\mathcal{F} \in B_0$ we can uniquely solve the equation

$$L_0\delta c + C'\delta v = -(1 + S(C))^{-1}\gamma\delta h - D_{1,\eta}(C, 0)C''\delta\eta - \mathcal{F} + f_2 := \widetilde{f_2},$$

with respect to δc and δv. For instance, the value of δv is determined from the following condition

$$\int_{-\infty}^{\infty} C'(z) \exp\left(\int_0^z a(s)ds\right)\left\{C'(z)\delta v - \widetilde{f_2}(z)\right\} dz = 0, \tag{65}$$

where $a(z) = -[2D_2(C(z))C'(z) - V]$. Using the implicit function theorem we obtain the thesis of the lemma. □

Theorem 1 *Assume that all the functions in system* (6), (15), (16) *are of* C^1 *class of their arguments and that Assumption* (2) *and condition* (45) *are satisfied. Suppose that Eq.* 44 *has a unique* (*up to translations*) *heteroclinic solution pair* $(C(\cdot), V)$ *satisfying the conditions* $\lim_{z\to-\infty} C(z) = c_1$, $\lim_{z\to\infty} C(z) = c_3$. *Then for* $|\varepsilon|, |\beta|$ *sufficiently small there exists a heteroclinic quadruple*

$$(h(\cdot, \varepsilon, \beta), c(\cdot, \varepsilon, \beta), \eta(\cdot, \varepsilon, \beta), v(\varepsilon, \beta)) \tag{66}$$

solving system (62) *such that*

$$(h(\cdot,\varepsilon,\beta), c(\cdot,\varepsilon,\beta), \eta(\cdot,\varepsilon,\beta), v(\varepsilon,\beta)) \to (0, C(\cdot), 0, V)$$

in the norm of the space $B_1^* \times B_2 \times B_2 \times \mathbb{R}^1$ *as* $(\varepsilon,\beta) \to 0$*. Consequently for sufficiently small* $|\varepsilon|$ *and* $|\beta|$ *there exists a travelling wave solution* $(\mathcal{T}, \mathcal{C}, \mathcal{B})$ *of the system* (6)*,* (15)*,* (16)*:* $\mathcal{T}(x,t;\varepsilon,\beta) = \theta(x - v(\varepsilon,\beta)t;\varepsilon,\beta)$*,* $\mathcal{C}(x,t;\varepsilon,\beta) = c(x - v(\varepsilon,\beta)t;\varepsilon,\beta)$*,* $\mathcal{B}(x,t;\varepsilon,\beta) = b(x - v(\varepsilon,\beta)t;\varepsilon,\beta)$*, such that*

$$c(z;\varepsilon,\beta) \to c_1, \quad \theta(z;\varepsilon,\beta) \to \theta_0(c_1), \quad b(z;\varepsilon,\beta) \to b_* k_+ \frac{c_1}{k_+ c_1 + k_-}$$

as $z \to -\infty$ *whereas*

$$c(z;\varepsilon,\beta) \to c_3, \quad \theta(z;\varepsilon,\beta) \to \theta_0(c_3), \quad b(z;\varepsilon,\beta) \to b_* k_+ \frac{c_3}{k_+ c_3 + k_-}$$

as $z \to \infty$*. This solution is unique up to translation in the variable* $z = x - v(\varepsilon,\beta)t$ *and for* $(\varepsilon,\beta) \to (0,0)$

$$\theta(\cdot;\varepsilon,\beta) \to \theta_0(c(\cdot;\varepsilon,\beta)), \quad c(\cdot;\varepsilon,\beta) \to C(\cdot), \quad b(\cdot;\varepsilon,\beta) \to b_* k_+ \frac{c(\cdot;\varepsilon,\beta)}{c(\cdot;\varepsilon,\beta)k_+ + k_-}$$

whereas $v(\varepsilon,\beta) \to V$ *in the norms of the spaces* B_1*,* B_{20}*,* B_2 *and* $\mathbb{R}^1$*, respectively.*

2.2 First order approximations for h, v and η

In this section, we derive approximate expressions for the functions h and η corresponding to small values of β^2 and ε^2 in the considered system. We will consider the two cases: the case of nonzero viscosity with infinitely fast buffers and the case of zero viscosity and finitely fast buffers. In the first case we assume for simplicity that $\mu = const$, $K = const$. We thus have $\eta \equiv 0$ and system (35–36) changes to the system

$$\varepsilon^2 \mu v h' - K h - K^{-1} \varepsilon^2 \mu v \tau(c(z))' = 0. \tag{67}$$

$$D_1(c,0)c'' - D_2(c)c'^2 + vc' + (1 + S(c))^{-1}[g(c) + \gamma h] = 0 \tag{68}$$

In the zeroth approximation $h \equiv 0$, whereas the first order correction to h is equal to

$$h_1(z) = -K^{-2} \varepsilon^2 \mu V (\tau(C(z))'. \tag{69}$$

Taking $\widetilde{f_2} = -(1 + S(C))^{-1}\gamma\delta h$ in Eq. 65 we obtain

$$\delta v = B_v^{-1} K^{-2} \varepsilon^2 \mu\gamma V \int\limits_{-\infty}^{\infty} (1 + S(C(z)))^{-1} C'(z)[\tau(C(z))]' \exp\left[\int\limits_0^z a(s)ds\right] dz \tag{70}$$

where $B_v = \int_{-\infty}^{\infty}(C'(z))^2 \exp[\int_0^z a(s)ds]dz$. It follows that, for $\gamma > 0$, $\delta v < 0$ ($\delta v > 0$) and the absolute value of the speed increases (decreases), if for all $c \in [c_1, c_3]$ we have $\tau_{,c}(c) > 0$ ($\tau_{,c}(c) < 0$).

To obtain the approximate expression for the function η in the second case ($\beta^2 \neq 0$, $\mu = 0$), we will use Eqs. 37, 39. Thus in the first approximation

$$\eta(z) \cong \beta^2 \Phi_2(0, 0, C, C', C'', V)(z) \cong \beta^2 \left\{ S(C)VC' + D_b b_* \left[\frac{C}{\mathcal{L} + C}\right]'' \right\}(z) \tag{71}$$

It follows that $\eta(z) < 0$ for all $z \in \mathbb{R}^1$ if only D_b is sufficiently small. Let us note that according to (33)

$$b(z) = \frac{b_* k_+ c(z) + \eta(z)}{k_- + k_+ c(z)}.$$

In consequence also

$$b(z) - b_a(z) := b(z) - \frac{b_* k_+ c(z)}{k_- + k_+ c(z)} = \frac{\eta(z)}{k_- + k_+ c(z)} < 0. \tag{72}$$

3 Numerical simulations

To analyze how the travelling wave solutions are approaching the appropriate solutions of the asymptotic equation (18) when $\varepsilon \to 0$ and $\beta \to 0$ we made two series of numerical simulations. In the first one, the viscosity effects were suppressed by assuming that $\varepsilon = 0$ and consequently that $\theta = \theta_0$ in system (15–16). For the values of diffusion coefficients we took: $D_c = 300\,\mu\text{m}^2/\text{s}$, $D_b = 20\,\mu\text{m}^2/\text{s}$ (see Keener and Sneyd 1998; Tsai and Sneyd 2005), whereas for the kinetic coefficients and the total buffering molecules concentration appearing in Eq. 16 we assumed: $k_- = 100/\text{s}$, $k_+ = 10\,\mu\text{M/s}$ and $b_* = 150\,\mu\text{M}$. Let us note that for $\beta^{-2} = 5$ the quantities k_-, k_+ attain the values corresponding to typical endogeneous buffers (see, e.g. [12]). The function $g(c)$ in both cases was modeled by $g(c) = A(c - c_1)(c - c_2)(c_3 - c)$, where, inspired by Keener and Sneyd (1998), we took $c_3 = 1\,\mu\text{M}$, whereas for c_1 we took $c_1 = 0$ for simplicity as in most cases $c_1 = 0.01 \div 0.1\,\mu\text{M}$. In any case the values $c_1 = 0$ and $c_3 = 1$ can be achieved by a linear transformation of the variable c. For this model of $g(c)$ we have advancing waves for Eq. 18 only if $\int_{c_1}^{c_3} g(c)[1 + D_b S(c)/D_c]dc > 0$,

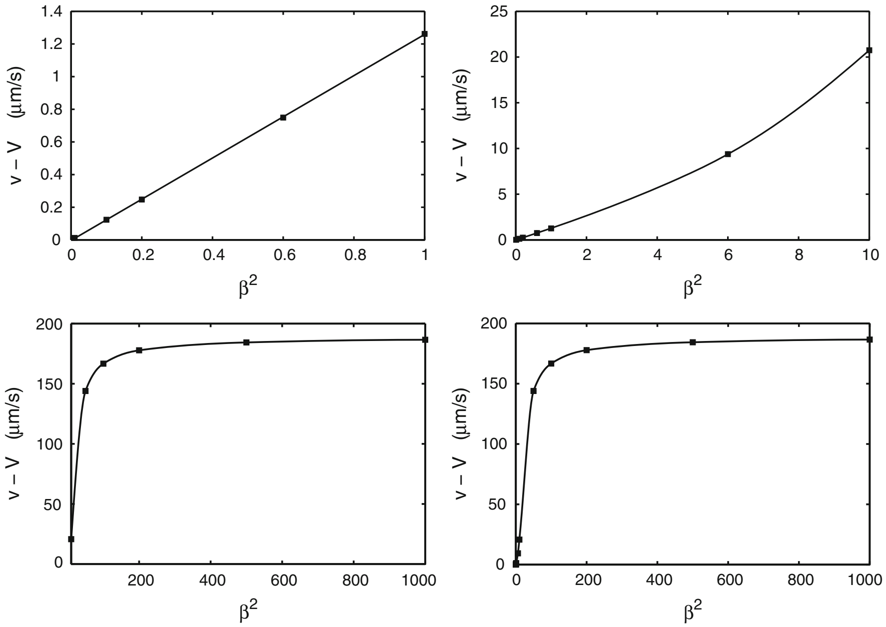

Fig. 1 The dependence of the speed of the travelling wave solutions for system (15–16) on the parameter β^2 for $\varepsilon = 0$ for different ranges of β^2: [0,1], [0,10], [10,1,000] and [0,1,000]. For small values of β^2 the difference $v - V$ changes linearly with β^2. As $\beta \to \infty$ the speed tends to speed of the travelling wave for Eq. 73

where $S(c)$ is defined after (Eq. 4) [see inequality (12.40) in Keener and Sneyd (1998)], so for waves with monotone profiles only if $0 < c_2 < 1/2\,\mu$M. Since the real form of the function $g(\cdot)$ seems to be not well known and our considerations have rather qualitative character we assumed the intermediate value $c_2 = 0.25\,\mu$M. In order to obtain realistic travelling wave velocities, the constant A was chosen to be equal to $1{,}150$. For this choice, the absolute value of the speed of the travelling wave for the asymptotic equation (18) is equal to $V = 18.9635\,\mu\text{m/s}$, so lies in the interval of characteristic speeds for calcium waves (Keener and Sneyd 1998; Jaffe 1991). Waves obtained in numerical simulations were moving from the right to the left, so with negative speed. In figures representing numerical results *the sign of the speed was reversed* for the reader convenience. By solving numerically system (15–16) we found travelling wave solutions propagating along the x-axis with the absolute value of the speed equal to v. Figure 1 shows the dependence of the difference $v - V$ on β^2 for four different ranges of β^2: [0, 1], [0, 10], [10, 1,000] and [0, 1,000]. It can be noticed that v tends to the speed for the reduced equation (18) linearly with β^2 as can be seen form the upper left panel of Fig. 1. On the other hand, for $\beta^2 \to \infty$, the influence of the buffer term vanishes and the speed of the wave tends, as can be expected, to the speed of the scalar equation

$$\frac{\partial c}{\partial t} = D_c \nabla^2 c + g(c). \tag{73}$$

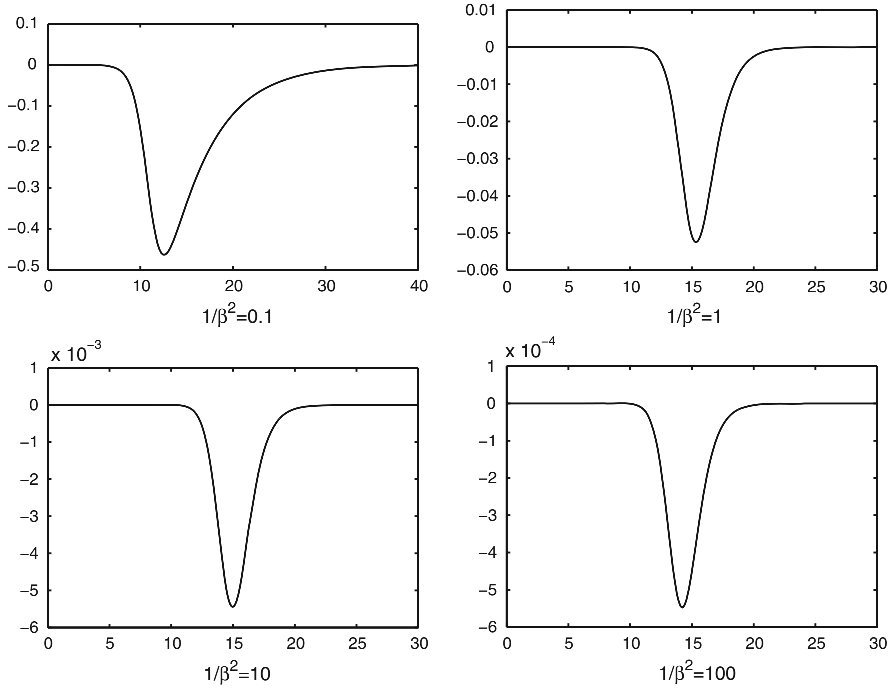

Fig. 2 The relative difference between the concentration of buffers $b(z)$ and the approximate concentration of buffers obtained from Eq. 3 for different values of the parameter β^2 and $\varepsilon^2 = 0$. The difference is scaled by the upper buffer state b_3 given by (22)

The travelling wave solution for this equation can be found explicitly and its speed is equal to $(1 - 2 \cdot 1/4) \cdot \sqrt{AD_c/2} = 207.666$. This can be seen in the lower right panel of Fig. 1; for $\beta^2 = 1{,}000$, v is equal to 205.5291.

Figure 2 shows the dependence of the relative difference between the concentration $b(z)$ of the buffer particles with bound calcium and the asymptotic concentration $b_a(z)$ obtained by solving the equation $k_- b(z) - k_+ c(z)(b_* - b(z)) = 0$ implied by Eq. 3. This difference is normalized by b_3—the higher asymptotic state defined by (22). It is seen that for the considered values of β^2 this function is very small—for example for the case of typical endogeneous buffers ($\beta^{-2} = 5$) its amplitude is of order 10^{-2}. Moreover, it is negative for all $z \in \mathbb{R}^1$, as it has been foreseen by inequality (72).

Figure 3 shows the graph of the difference $C(z) - c(z)$ for $\beta^2 = 0.1$, $\beta = 1$, $\beta^2 = 5$ and $\beta^2 = 10$, where C denotes the profile of the travelling wave solution for the asymptotic equation (18) and c denotes the profile of the calcium concentration of the travelling wave solution for system (15–16). To calculate this difference the profiles are shifted along the z-axis, so that for $z = 0$ they both attain the same value equal to $1/2$ in agreement with condition (46). It is seen that for β^2 sufficiently small, this difference has almost the same shape and its amplitude is proportional to β^2. For $\beta^{-2} = 5$ (typical endogeneous buffers) the amplitude of the difference is of order $2 \cdot 10^{-3}$ μM.

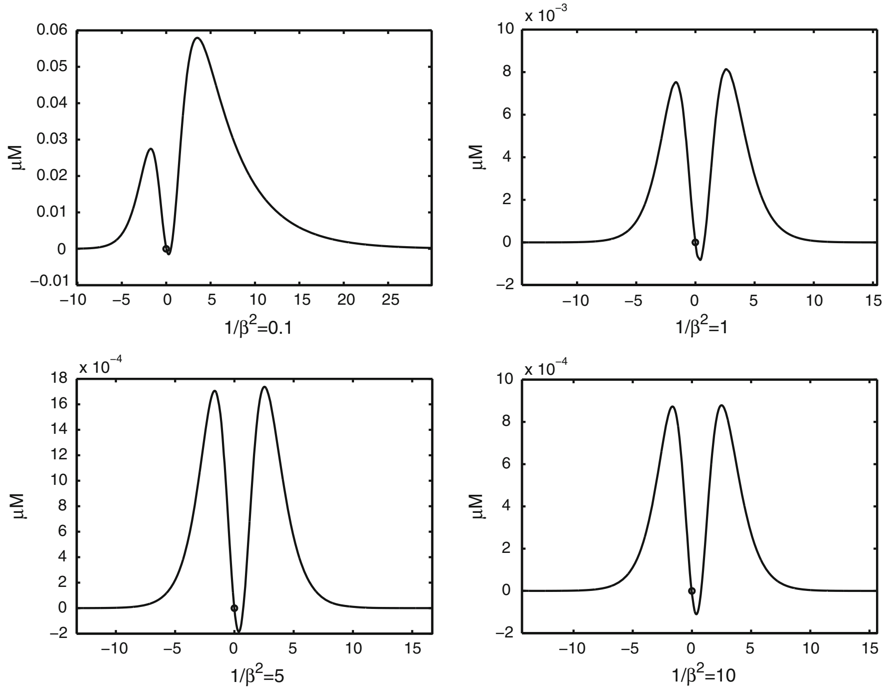

Fig. 3 The difference $C(z) - c(z)$ between the profile of the travelling wave of the reduced equation (18) and the profile of the travelling wave for system (15–16) for vanishing viscosity. To determine the profiles uniquely, we assume that $C(0) = 1/2$ and $c(0) = 1/2$

In the second series of simulations we assumed that the buffer kinetics is infinitely fast ($\beta = 0$) and solved numerically the equation

$$\frac{\partial c}{\partial t} = \frac{D_c + D_b S(c)}{1 + S(c)} \nabla^2 c - \frac{2 D_b S(c)}{(c + \mathcal{L})(1 + S(c))} |\nabla c|^2 + \frac{g(c) + \gamma h}{1 + S(c)}, \tag{74}$$

that is to say Eq. 18 with the additional mechanical term. We took $\gamma = \pm 100\ \mu\mathrm{M/s}$. This choice of the absolute value of γ can be justified by a rough analysis of experiments with generation of calcium waves by mechanical deformations of cells (Young et al. 1999). h is defined by (33). If we assume, for simplicity, that μ and K are constants, then h satisfies the equation

$$\frac{\partial h}{\partial t} + (\varepsilon^*)^{-1} h - (K^{-1}\tau)_{,c} \frac{\partial c}{\partial t} = 0, \tag{75}$$

with $\varepsilon^* = \mu/K$, which can be obtained from Eq. 6. Let us note that, that according to (28), the relation between the non-dimensional parameter ε^2 and ε^* has the form

$$\varepsilon^2 = \varepsilon^* P/l,$$

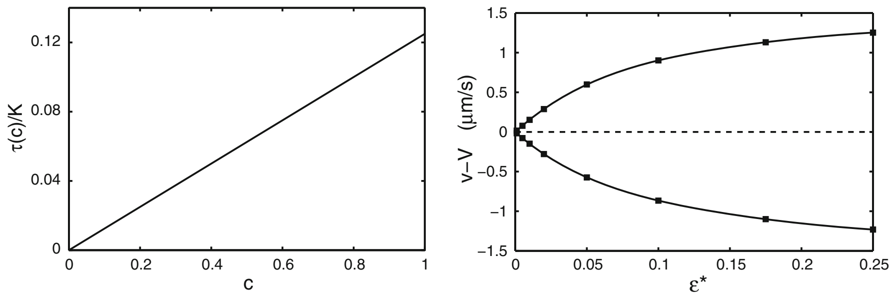

Fig. 4 The influence of nonzero viscosity on the speed of the travelling wave solutions for τ/K as on the *left panel*. The *upper curve* on the *right panel* corresponds to $\gamma = 100\,\mu\text{M/s}$, the *lower one* to $\gamma = -100\,\mu\text{M/s}$

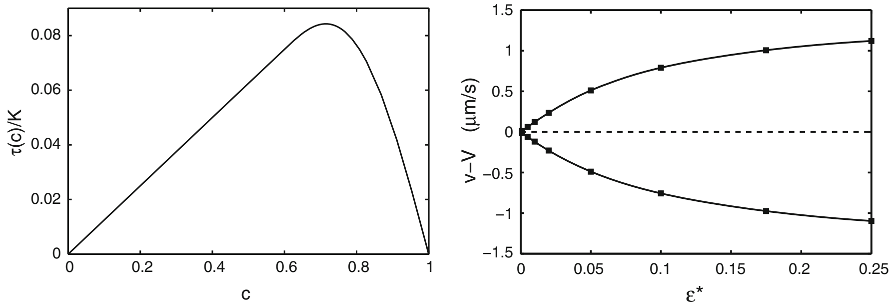

Fig. 5 The influence of nonzero viscosity on the speed of the travelling wave solutions for τ/K as on the *left panel*. The *upper curve* on the *right panel* corresponds to $\gamma = 100\,\mu\text{M/s}$, the *lower one* to $\gamma = -100\,\mu\text{M/s}$

where P is the characteristic speed and l the characteristic length. In our case $P \cong 20\,\mu\text{m/s}$ and $l \cong 20 \div 30\,\mu\text{m}$. They are thus of the same order, so the smallness of ε^* implies the smallness of ε^2. We also assume that the ratio between the maximal value of the traction force τ to the effective Young modulus K is of order of 1/10 (see, e.g. Murray 1993). In the case of monotone calcium travelling waves only this part of the shape of the function $\tau(c)$ is important, which is contained between c_1 and c_3.

The calculations have been made for two hypothetical shapes of the function τ. To some extent, these are two extreme cases, as in the first case τ is linearly increasing on $(c_1, c_3) \equiv (0, 1)$ and in the second case τ is of a single bump type function on this interval. The results are shown in Figs. 4 and 5.

4 Conclusions

In the paper we proved the existence of mechano-chemical travelling wave solutions

$$(\theta(z), c(z), b(z)), \quad z = x - vt$$

for system (6–16), if the parameters ε^2 and β^2 are sufficiently small. Here ε^2 defined in (28) is the parameter describing the relative magnitude of the viscous effects and

β^{-2} determines the rate of the reactions of binding or unbinding calcium ions by the buffer molecules. (Let us recall that $\varepsilon^2 = \mu_0 P/K_0 l$, where K_0 and μ_0 are the typical values of viscosity and elastic modulus, whereas P and l the typical speed and length of the calcium wave in the given medium.) These waves are unique up to a translation in z. For $\varepsilon^2 \to 0$ and $\beta^2 \to 0$, the speed v of these waves tends to the speed V of the travelling wave of the reduced equation, whereas

$$\theta(z) \to \theta_0(C(z)), \quad c(z) \to C(z), \quad b(z) \to b_0(C(z))$$

uniformly for $z \in \mathbb{R}^1$, together with their derivatives. Here $(C(\cdot), V)$ is the heteroclinic pair for the reduced equation (Eq. 18) obtained by assuming infinitely fast buffer-calcium reactions ($\beta = 0$) and zero viscosity, $\theta_0(c, \sigma_0) = (K(c))^{-1}(\sigma_0 - \tau(c))$ denotes the solution to the mechanical equation (Eq. 6) obtained by neglecting the viscosity terms and

$$b_0(c(z)) = b_* k_+ \frac{c(z)}{c(z)k_+ + k_-}$$

denotes the asymptotic concentration of the buffer molecules obtained by assuming infinitely fast buffer-calcium reactions. These theoretical statements have been confirmed by numerical simulations described in Sect. 3. In particular, the calculations confirmed the fact, that for buffers with sufficiently fast kinetics system (15–16) is very well approximated by Eqs. 3 and 18. For $\mu = 0$, we found the speeds of the waves for relatively large span of the parameter β^2. As $\beta \to \infty$ the speed of the wave tends to the speed of the scalar Reaction–diffusion obtained from the equation for the calcium concentration by neglecting the influence of the buffers, i.e. putting formally $\beta = \infty$ (Eq. 73).

The profile $C(\cdot)$ of the travelling wave for the asymptotic equation (44) satisfies the condition $C'(\xi) > 0$ for all $\xi \in \mathbb{R}^1$. In Appendix 2 we show that for large reaction rates ($|\beta| << 1$) and $|\varepsilon|$ sufficiently small the obtained solution satisfies the inequalities $c'(\xi) > 0$, $b'(\xi) > 0$ for all $\xi \in \mathbb{R}^1$. In Appendix 3 we show the similar property for $\beta = 0$.

A question arises, if the mechanomechanical coupling can destroy the existence of advancing travelling waves for the buffer system. Though the existence proof has been done only for small values of viscosities (represented by the parameter ε^2), numerical calculations suggest that the travelling wave solutions of advancing type exists also for larger values of viscosity. Thus, it seems that the viscosity cannot prevent the existence of traveling waves unless the bistability condition is violated. To explain it, let us notice that for larger viscosity the cell deformation are smaller, thus in the limit of infinite viscosity mechanical effects cease to be visible—the system behaves as purely chemical (i.e. we have equations for calcium and buffers only) with a bistable source function $f(c)$ (see Eqs. 1 and 2). It is interesting that the system formally is reduced to the purely chemical system also in the case of vanishing viscosity. However the source function $g(c)$ in this case is related to $f(c)$ (see Eqs. 15, 16 and 17) by

$$g(c) = f(c) + \gamma\theta_0(c, \sigma_0).$$

Here we can assume, that $\theta_0(c_1, \sigma_0) = 0$. Therefore, if both functions f and g are bistable, then viscosity cannot prevent the existence of traveling waves, otherwise the existence may depend on the value of viscosity. Also by applying additional stress on the lateral boundaries of the cell or just by stretching the cell we may destroy the bistability of the source function and thus the waves may cease to exist.

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Appendix 1: Proof of Lemma 3

The substitution $y'/y = w$ changes the equation

$$y''(z) - \beta^{-2} Q(z) y(z) = 0 \tag{76}$$

into the Riccati-type equation $w' + w^2 - \beta^{-2} Q(z) = 0$. Let $w = \widetilde{w} + \phi$, where $\widetilde{w}(z) = |\beta|^{-1}\sqrt{Q(z)}$. Then ϕ satisfies the equation

$$\phi'(z) + \frac{2}{\beta}\sqrt{Q(z)}\phi + \phi^2 + \frac{Q'(z)}{2|\beta|\sqrt{Q(z)}} = 0. \tag{77}$$

Let

$$K_\beta : C^1(\mathbb{R}^1) \to C^0(\mathbb{R}^1), \quad C^1(\mathbb{R}^1) \ni \phi \overset{K_\beta}{\to} \phi' + \frac{2}{|\beta|}\sqrt{Q}\phi,$$

where $Q \in C^2(\mathbb{R}^1)$, $Q(z) > \widetilde{Q} > 0$. For $f \in C^1(\mathbb{R}^1)$ we have

$$(K_\beta^{-1} f)(z) = \int_{-\infty}^{z} \exp\left[-\int_s^z \frac{2\sqrt{Q(\zeta)}}{|\beta|} d\zeta\right] f(s) ds \to \frac{|\beta|}{2\sqrt{Q(z)}} f(z) \quad \text{as} \quad |\beta| \to 0 \tag{78}$$

in the norm of the space $C^1(\mathbb{R}^1)$ (see Lemma 1 and Remark after it). In particular for $f = -Q'/(2|\beta|\sqrt{Q})$ the last expression is equal to $-Q'/4Q$. Eq. 77 can be written as

$$\mathcal{K}(\phi, \beta) := \phi + K_\beta^{-1}\left(\phi^2 + \frac{Q'}{2|\beta|\sqrt{Q}}\right) = 0.$$

$\mathcal{K}$ may be treated as a mapping from the space $C^1(\mathbb{R}^1) \times \mathbb{R}^1$ to $C^1(\mathbb{R}^1)$. One notes that as $\beta \to 0$

$$\mathcal{K}(\phi, \beta) \to \phi - S,$$

where $S = -\frac{Q'}{4Q}$. It follows that the mapping can be defined also for $\beta = 0$ by taking $\mathcal{K}(\phi, 0 = \phi - S$. Moreover, by means of the methods used in the proofs of Lemmas 1 and 2 we can prove that $\mathcal{K}(\phi, \beta)$ has a well determined Frechet derivative $D\mathcal{K}(\phi, \beta)$ with respect to ϕ, which is continuous in a neighbourhood of the point $(\phi, \beta) = (S, 0)$, and $D\mathcal{K}(S, 0)\delta\phi = \delta\phi$. Consequently, we can apply the implicit function theorem to prove that for $|\beta|$ sufficiently small there exists a unique solution in $BC^1(\mathbb{R}^1)$ to Eq. 77 close to $\phi_1 = S$ being the limit of the sequence of successive approximations $\phi_1, \phi_2, \ldots$ Thus in the second approximation we have (see Crandall 1977)

$$\phi_2 - \phi_1 = -[D\mathcal{K}(S, 0)]^{-1}\mathcal{K}(\phi_1, \beta) = -\mathcal{K}(\phi_1, \beta),$$

that is to say

$$\phi_2(z) - S(z) = -S(z) - K_\beta^{-1}\left(S^2 + \frac{Q'}{2|\beta|\sqrt{Q}}\right)(z). \tag{79}$$

Now, identifying ε^2 with $|\beta|$, G with $(2\sqrt{Q})^{-1}$, F with $S^2 + \frac{Q'}{2|\beta|\sqrt{Q}}$ and using Lemma 2 together with its proof [especially relations (50) and (51)], we obtain

$$\phi_2(z) = S(z) + |\beta|\left[\frac{Q''}{8Q^{3/2}} - \frac{5Q'^2}{32Q^{5/2}}\right](z),$$

and $\phi(z) = \phi_2(z) + o(|\beta|)$. Using the fact that $w = \widetilde{w} + \phi$ and $y'/y = w$ we obtain by simple integration the form of a solution Y_+ to Eq. 76 behaving as $\exp(\int_0^z \sqrt{Q(s)}ds)$ for $|z| \to \infty$. Namely, we have

$$(\ln|y(z)|)_{,z} = |\beta|^{-1}\sqrt{Q(z)} + \phi_2(z) + o(|\beta|).$$

As $-\frac{Q'(z)}{4Q(z)} = (\ln|Q^{-\frac{1}{4}}|)_{,z}$, we obtain

$$Y_+(z) = Q^{-\frac{1}{4}}(z)\exp\left[|\beta|^{-1}\int_0^z\left\{\sqrt{Q(s)} + |\beta|^2\left(\frac{Q''}{8Q^{3/2}} - \frac{5Q'^2}{32Q^{5/2}}\right)(s) + o(|\beta|^2)\right\}ds\right]. \tag{80}$$

In the similar way, taking $\widetilde{w}(z) = |\beta|^{-1}\sqrt{Q(z)}$, we can obtain a solution behaving as $\exp(-\int_0^z \sqrt{Q(s)}ds)$. It can be written as

$$Y_-(z) = Q^{-\frac{1}{4}}(z)\exp\left[|\beta|^{-1}\int_0^z\left\{-\sqrt{Q(s)} - |\beta|^2\left(\frac{Q''}{8Q^{3/2}} - \frac{5Q'^2}{32Q^{5/2}}\right)(s) + o(|\beta|^2)\right\}ds\right]. \tag{81}$$

The Wronskian of this pair of solutions, independent of z, is equal to

$$2|\beta|^{-1} + O(1) + O(|\beta|) = \frac{2}{|\beta|}[1 + s(\beta)\beta],$$

where $\lim_{\beta\to 0} |s(\beta)| = s_0$. Thus for $f \in B_0$ the unique B_2 solution of the equation

$$y''(z) - \beta^{-2}Q(z)y(z) = f(z) \tag{82}$$

can be written in the form

$$y(z,\beta) = 2^{-1}|\beta|[1 + s(\beta)\beta]^{-1}\left\{Y_-(z)\int_{-\infty}^{z} Y_+(s)f(s)ds + Y_+\int_{z}^{\infty} Y_-(s)f(s)ds\right\}. \tag{83}$$

Below for simplicity we will use the symbols $\|\cdot\|_j$ instead of $\|\cdot\|_{B_j}$. For $f \in B_1$ (see Definition 1), according to Lemma 2, $y(z,\beta) = \beta^2 f(z)Q(z)^{-1} + O(|\beta|^3\|f\|_1)$. Differentiating we obtain the equation $Z''(z) - \beta^{-2}Q(z)Z(z) = f'(z) + \beta^{-2}Q'(z)Z(z)$, $Z := y'$. This yields $\|y\|_1 = O(\beta^2)\|f\|_1$. Combining the above estimations we obtain

$$\|y\|_1 = O(\beta^2)\|f\|_1 \qquad \|y\|_2 = O(|\beta|)\|f\|_1. \tag{84}$$

Now, we are in a position to prove Lemma 3. Part 1. follows straightforwardly from the estimations (84). To prove the second part, let us note that W defined implicitly by (42) can be treated as a mapping acting from the space $B_{20} \times B_2$ to the space B_0. Let us also introduce the operator $\hat{F}$ acting from $B_1^* \times B_{20} \times B_2 \times \mathbb{R}^1$ to B_0:

$$\hat{F}(h, c, \eta, v)(z) := -F(h(z), c(z), c'(z), \eta(z), \eta'(z), v),$$

where F is the function appearing in Eq. 41. Let $(\underline{c}, \underline{\eta})$ and (c, η) satisfy the conditions guaranteeing the existence and boundedeness of the operator A^{-1} formulated after the definition (60). Let y and $\underline{y}$ be the solutions of the equations

$$y'' - \beta^{-2}W(c,\eta)y = \hat{F}(h, c, \eta, v)$$
$$\underline{y}'' - \beta^{-2}W(\underline{c},\underline{\eta})\underline{y} = \hat{F}(\underline{h},\underline{c},\underline{\eta},\underline{v}).$$

The difference $Y := y - \underline{y}$ satisfies the equation

$$Y'' - \beta^{-2}W(\underline{c},\underline{\eta})(z)Y = [\hat{F}(h,c,\eta,v) - \hat{F}(\underline{h},\underline{c},\underline{\eta},\underline{v}) + \beta^{-2}y(W(c,\eta) - W(\underline{c},\underline{\eta}))](z)$$

W and $\hat{F}$ are Frechet differentiable as mappings from $B_1^* \times B_{20} \times B_2 \times \mathbb{R}^1$ to B_0 (see the remark after [43)], thus according to the definition of the operator A, we obtain from the last equation:

$$Y = A^{-1}(\underline{c}, \underline{\eta}, \beta)\left(D\hat{F}(\underline{h}, \underline{c}, \underline{\eta}, \underline{v}) + \beta^{-2} y DW(\underline{c}, \underline{\eta})\right)[\delta h, \delta c, \delta\eta, \delta v]$$
$$+A^{-1}(\underline{c}, \underline{\eta}, \beta)(R_F(\delta h, \delta c, \delta\eta, \delta v) + R_W(\delta h, \delta c, \delta\eta, \delta v)), \quad (85)$$

where $\delta h = h - \underline{h},\ \delta c = c - \underline{c},\ \delta\eta = \eta - \underline{\eta},\ \delta v = v - \underline{v}$, $D\hat{F}$ and DW denote the Frechet derivatives of the mappings $\hat{F}$ and W with respect to (h, c, η, v) at $(\underline{h}, \underline{c}, \underline{\eta}, \underline{v})$. Here $\|R_F(\delta h, \delta c, \delta\eta, \delta v)\|_1$, $\|R_W(\delta h, \delta c, \delta\eta, \delta v)\|_1$ are of order of $o(\|\delta h\|_1, \|\delta c\|_2 + \|\delta\eta\|_2 + |\delta v|)$ as $\|\delta h\| + \|\delta c\|_2 + \|\eta\|_2 + |\delta v| \to 0$.

Now taking into account that the functions on which A^{-1} acts have their B_1 norms bounded (according to the definition of the mappings $\hat{F}$ and W) we infer that the Frechet derivative of the operator A^{-1} acting on the vector $[\delta h, \delta c, \delta\eta, \delta v]$ is equal to

$$A^{-1}(\underline{c}, \underline{\eta}, \beta)\left((D\hat{F} + \beta^{-2} y DW)[\delta h, \delta c, \delta\eta, \delta v]\right).$$

According to the part 1. of Lemma 3 we obtain the validity of the part 2, thus the whole lemma is proved.

Appendix 2: Monotonicity of solutions

According to Theorem 1 there exist $\beta_0 > 0$ and $\varepsilon_0 > 0$ such that for all (β, ε) satisfying $|\beta| < \beta_0$, $|\varepsilon| < \varepsilon_0$ there exists a unique solution $(c(\beta, \varepsilon, \cdot), b(\beta, \varepsilon, \cdot), h(\beta, \varepsilon, (\cdot))$ to system (30), (31), (32) with h defined in (35) together with the speed $v(\beta, \varepsilon)$. If β_0 and ε_0 is sufficiently small then $v(\beta, \varepsilon) < 0$ (as the initial speed $V < 0$ by assumption (43)). For $\varepsilon = 0$ the solution is monotone, i.e. $c'(\beta, 0, \xi) > 0$, $b'(\beta, 0, \xi) > 0$ for all $\xi \in \mathbb{R}^1$ according to Theorem 2.1, p. 15 in Volpert et al. (1994). We will show that for $|\varepsilon|$ sufficiently small (*in general depending on* $|\beta|$) the inequalities $c'(\beta, \varepsilon, \xi) > 0$ and $b'(\beta, \varepsilon, \xi) > 0$ hold also for all $\xi \in \mathbb{R}^1$. For simplicity, we will denote the functions $c(\beta, \varepsilon, \xi), b(\beta, \varepsilon, \xi), h(\beta, \varepsilon, \xi)$ simply by $c(\xi), b(\xi), h(\xi)$. Because the position of the front profile is fixed by the condition $c(0) = (c_1 + c_3)/2$, therefore for any finite interval $(\mathcal{A}_-, \mathcal{A}_+) \ni 0$, the functions c and b have positive derivatives for all sufficiently small $|\varepsilon|$, what follows from their continuous dependence on the parameter ε. We will divide our considerations into two parts: for negative and positive values of ξ. We will start from the interval $(-\infty, 0]$. As we mentioned, for a fixed $\mathcal{A}_- < 0$ there exists $\varepsilon_- \in (0, \varepsilon_0]$, such that for all $|\varepsilon| < \varepsilon_-$ we have the inequalities $c'(\xi) > 0$, $b'(\xi) > 0$ for $\xi \in (\mathcal{A}_-, 0]$. Our task will be thus to show that the monotonicity property remains valid also for $\xi \in (-\infty, \mathcal{A}_-)$. By defining: $u = (u_1, u_2) := (c, b)$, $d_1 = D_c$ and $d_2 = D_b$, $D = \text{diag}(d_1, d_2)$, $H = (H_1, H_2)$, $H_1 = g + M$, $H_2 = g - H_1$, $M := \beta^{-2}[k_- b - k_+ c(b_* - b)]$, system (31–32) can be written in the form:

$$Du'' + vu' + H(u) + \gamma \begin{pmatrix} 1 \\ 0 \end{pmatrix} h(\xi) = 0. \quad (86)$$

Let us note that $H(u)$ has two stable steady states (c_1, b_1) and (c_3, b_3) and has its diagonal entries negative and off-diagonal entries positive in some neighbourhoods of these states.

Theorem 2 *Let* $0 < |\beta| < \beta_0$. *Then there exists* $\varepsilon_- \in (0, \varepsilon_0]$ *such that for all* $|\varepsilon| < \varepsilon_-$, $c'(\xi) > 0$ *and* $b'(\xi) > 0$ *for all* $\xi \in (-\infty, 0]$.

Proof The proof of the theorem will be based on Lemmas 5,6 and 7 which will be proved later. By differentiation of system (86) we obtain:

$$DU''(\xi) + vU'(\xi) + \sum_{j=1,2} \mathcal{H}(u(\xi))U(\xi) + \gamma \begin{pmatrix} 1 \\ 0 \end{pmatrix} h'(\xi) = 0, \quad (87)$$

where $U = (U_1, U_2) := (u_1', u_2')$ and $\mathcal{H}$ is the Jacobian matrix of H, i.e. $\mathcal{H}_{ij}(u) = H_{i,u_j}(u)$. In the proof we will use the fact that, if c' attains a global extremum for some $\xi = \xi^*$, then it is possible to estimate $h'(\xi^*)$ only by the values of $c'(\xi^*)$. Thus, we will be able to apply the method based on the notion of the Perron–Frobenius eigenvector of $\mathcal{H}(u)$ (Volpert et al. 1994). Let $P = (P_1, P_2)$, denote the Perron–Frobenius eigenvector (with positive components) assigned to the negative eigenvalue of the matrix $\mathcal{H}(c_1, b_1)$ (Kazmierczak and Volpert 2008). As $(c(\xi, b(\xi)) \to (c_1, b_1)$ for $\xi \to -\infty$, then, if $|\mathcal{A}_-|$ is taken sufficiently large, $(c(\xi), b(\xi))$ will lie sufficiently close to (c_1, b_1) and the inequality $\mathcal{H}(c(\xi), b(\xi))P < 0$ will hold for all $\xi \in (-\infty, \mathcal{A}_-)$.

Let $\underline{\rho} = \sup_{\xi \in (-\infty, \mathcal{A}_-)} (|c(\xi) - c_1| + |b(\xi) - b_1|)$. Note that by decreasing $\mathcal{A}_-$ we decrease both ε_- and $\underline{\rho}$. For a given $\mathcal{A}_-$ and $|\varepsilon| < \varepsilon_-$, let us also denote

$$\rho = \max\{\underline{\rho}, \varepsilon^2\}.$$

Our basic lemma gives the estimation of $h'(\xi)$ at a point of an extremum of $c'(\cdot)$. □

Lemma 5 *Let* $c''(z) = 0$ *for some* $z \in (-\infty, \mathcal{A}_-)$. *Then there exist bounded constants* J *and* B (*independent of* z) *such that*

$$|h'(z)| \le \rho J \sup_{\xi \in (-\infty, z)} |c'(\xi)| + \varepsilon^2 B \sup_{\xi \in (-\infty, z)} |b'(\xi)|. \quad (88)$$

Suppose that $b'(\xi)$ attains a non-positive minimum for $\xi = \tilde{z}$. By differentiating the equation for b (Eq. 32) and using the maximum principle we note that it is possible only if $c'(\tilde{z}) \le 0$. Hence, we may confine ourselves to the proof that the function $c'(\cdot)$ is positive. Suppose that there exists ξ_2 such that the function c' attains a global non-positive minimum at $\xi = \xi_2$ on the set $(-\infty, \mathcal{A}_-)$. Two cases are possible: i. there exists a point $\xi_1 < \xi_2$ such that c' attains a global positive maximum at ξ_1 on the interval $(-\infty, \xi_2)$ and $\sup_{\xi \in (-\infty, \xi_2)} |c'(\xi)| = c'(\xi_1)$, ii. $|c'(\xi)| < |c'(\xi_2)|$ for all $\xi \in (-\infty, \xi_2)$.

Let us consider case i. The following lemma holds.

Lemma 6 *Suppose that there exists a point* $\xi_1 < \xi_2$ *such that the function* $c'(\xi)$ *attains a global positive maximum for* $\xi = \xi_1$ *on the interval* $(-\infty, \xi_2)$ *and* $\sup_{\xi\in(-\infty,\xi_2)} |c'(\xi)| = c'(\xi_1)$. *Then the function* b' *must have a global positive maximum for some* $\xi_b \in (-\infty, \xi_2)$. *Moreover,* $|b'(\xi_b)| \le C|c'(\xi_1)|$, *where* C *independent of* ε.

If, instead of c and b, we consider the functions $(-c)$ and $(-b)$, then these functions will have negative minima at points ξ_1 and ξ_b. The vector function $(V_1, V_2) = (-c_1', -b_2')$ satisfies the system

$$d_i V_i''(\xi) + v V_i'(\xi) + \sum_{j=1,2} \mathcal{H}_{ij}(u(\xi))V_j(\xi) - \gamma\delta_{i1}h'(\xi) = 0, \quad i = 1, 2. \tag{89}$$

Let $s = \max\{s_c, s_b\}$, where s_c and s_b are constants satisfying $s_c P_1 - c'(\xi_1) = 0$ and $s_b P_2 - b'(\xi_b) = 0$. For the above choice of $s > 0$, the vector function $\mathcal{V}_s(\xi) := (V_1(\xi), V_2(\xi)) + s(P_1, P_2) \ge 0$ componentwise for all $\xi \in (-\infty, \xi_2)$. Moreover, there exists $\xi^* \in (-\infty, \xi_2)$ such that $\mathcal{V}_s(\xi^*) = 0$ or there exists an index $l \in \{1, 2\}$ such that $V_l(\xi^*) + sP_l > 0$, while $V_k(\xi^*) + sP_k = 0$, where k is an index complementary to l and $V_k(\cdot)$ attains its global minimum at $\xi = \xi^*$. Thus $V_k(\xi^*) = -sP_k$, $V_k'(\xi^*) = 0$ and $V_k''(\xi^*) \ge 0$. Let us consider the first situation, that is to say, let us assume that $(V_1(\xi^*), V_2(\xi^*)) = -s(P_1, P_2)$ for some $\xi^* \in (-\infty, \xi_2)$. Thus the functions c' and b' attain their maximal values (global maxima) on the interval $(-\infty, \xi_2)$ at $\xi = \xi^* = \xi_1 = \xi_b$. By Lemmas 5 and 6, $|h'(\xi^*)| \le \rho J|c'(\xi^*)| + \varepsilon^2 B|b'(\xi^*)| \le (\rho J + \varepsilon^2 BC)|c'(\xi^*)|$, so we can write the system (89) for $\xi = \xi^*$ in the following form:

$$d_i V_i''(\xi^*) + \sum_{j=1,2} \mathcal{H}^*_{ij}(u(\xi^*))V_j(\xi^*) = 0, \tag{90}$$

where $\mathcal{H}^*_{ij}(u(\xi^*)) = \mathcal{H}_{ij}(u(\xi^*)) - C^*\rho\delta_{i1}\delta_{j1}$ for some bounded constant C^*. (Recall the definition of ρ.) The matrix $\mathcal{H}^*(u(\xi^*))$ is thus an $O(\rho)$ perturbation of the matrix $\mathcal{H}(c_1, b_1)$. Hence, for $i = 1, 2$, $\sum_{j=1,2} \mathcal{H}^*_{ij}[-sP_j] > 0$, if only ρ is sufficiently small, i.e. if $\mathcal{A}_-$ is taken sufficiently small. As $V_i''(\xi^*) \ge 0$, then we arrive at contradiction with (90).

Now, suppose that $(V_1(\xi^*), V_2(\xi^*)) + s(P_1, P_2) \ne 0$, but $V_k(\xi^*) + sP_k = 0$ and $V_k(\cdot)$ attains its global minimum at $\xi = \xi^*$. Then $V_l(\xi^*) + sP_l > 0$, where l is the index complementary to k. We will show that in this case

$$\sum_{j=1,2} \mathcal{H}^*_{kj}(u(\xi^*))\; V_j(\xi^*) > 0. \tag{91}$$

First, note that if $\xi^* = \xi_1$, then Lemma 5 holds. If $\xi = \xi_b$, then the estimation given by this lemma is not necessary, as in (91) we have no non-local terms. Let us consider the function $\phi_k(y) = \sum_{j=1,2} \mathcal{H}^*_{kj}(u(\xi^*))[V_j(\xi^*)(1-y) - sP_j y]$. We have $\phi_k(1) = \sum \mathcal{H}^*_{kj}(u(\xi^*))[-sP_j] > 0$ and $\phi_k'(y) < 0$ due to the fact that

$\phi'_k(y) = \mathcal{H}^*_{kl}(u(\xi^*))[-V_l - sP_l] = -\mathcal{H}^*_{kl}[V_l + sP_l] < 0$, as for $l \neq k$, we have $V_l(\xi^*) + sP_l > 0$ and $\mathcal{H}^*_{kl}(u(\xi^*)) > 0$. Hence $\phi_J(0) = \phi_k(1) - \phi'_k(y) \cdot 1 > 0$. Thus inequality (91) is proved. But this leads to contradiction as $V''_k(\xi^*) \geq 0$. Thus, the monotonicity property is proved in this case.

Let us consider case ii. Analogously to Lemma 6 the following lemma holds.

Lemma 7 *Suppose that* $|c'(\xi)| < |c'(\xi_2)|$ *for all* $\xi \in (-\infty, \xi_2)$*. Then the function* b' *must have a global negative minimum for some* $\xi_b \in (-\infty, \xi_2)$*. Moreover,* $|b'(\xi_b)| \leq C|c'(\xi_1)|$*, where* C *is a constant independent of* ρ*.*

We may thus repeat the considerations of the previous case, by taking advantage of the fact that $\sup_{\xi\in(-\infty,\xi_2)} |c'(\xi)| = |c'(\xi_2)|$. This time we can apply the above reasoning to functions c and b on the interval $(-\infty, \mathcal{A}_-)$ and use system (87). The theorem is proved.

Proof of Lemma 5 According to Eq. 48 the function $h \in C^1$ satisfies the equality

$$\begin{aligned} h(z) &= \int_{-\infty}^{z} \exp\left[-\int_{s}^{z} (\varepsilon^2 G(\zeta))^{-1} d\zeta\right] \kappa(c(s))c'(s)ds \\ &= \int_{-\infty}^{z} \exp\left[-\int_{s}^{z} (\varepsilon^2 G(\zeta))^{-1} d\zeta\right] \kappa(c(z))c'(z)ds \\ &\quad + \int_{-\infty}^{z} \exp\left[-\int_{s}^{z} (\varepsilon^2 G(\zeta))^{-1} d\zeta\right] (\kappa(c(s))c'(s) - \kappa(c(z))c'(z))ds \\ &=: I_1(z) + I_2(z). \end{aligned} \tag{92}$$

Here we denoted $G(\zeta) := |v|\chi(h(\zeta), c(\zeta))$ and κ is given by (47). Obviously, $I_1(z) = \varepsilon^2\kappa(c(z))c'(z)G(z)(1 + O(\varepsilon^2))$ as $\varepsilon^2 \to 0$. Using the equation for h, which can be written as $h'(z) + \varepsilon^{-2}(G(z))^{-1}h(z) - \kappa(c(z))c'(z) = 0$, we conclude that $h'(z) = \kappa(c(z))c'(z)O(\varepsilon^2) - \varepsilon^{-2}(G(z))^{-1}I_2(z)$. We have $\kappa(c(s))c'(s) - \kappa(c(z))c'(z) = \kappa(c(s))(c'(s) - c'(z)) + c'(z)(\kappa(c(s)) - \kappa(c(z)))$. The second term is proportional to $c'(z)$. Thus, as $(\kappa(c(s)) - \kappa(c(z))) \leq C\rho$, we conclude that for a bounded function ϕ_0:

$$\begin{aligned} I_2(z) &= \phi_0(z)\rho\varepsilon^2 c'(z) + I_3, \\ I_3(z) &= \int_{-\infty}^{z} \exp\left[-\int_{s}^{z} (\varepsilon^2 G(\zeta))^{-1} d\zeta\right] \kappa(c(s))(c'(s) - c'(z))ds. \end{aligned} \tag{93}$$

By choosing $|\mathcal{A}_-|$ sufficiently large (implying that ρ is sufficiently small), we can guarantee that $\kappa(c(s))$ is of constant sign for $s \in (-\infty, \mathcal{A}_-)$. Hence for some bounded functions $\widetilde{\theta}(z, s)$ and $\psi(z)$, the integral I_3 can be written as

$$c''(z+\widetilde{\theta}(z,s)(s-z))\int\limits_{-\infty}^{z}\exp\left[-\int\limits_{s}^{z}(\varepsilon^2 G(\zeta))^{-1}d\zeta\right](s-z)\kappa(c(s))ds$$
$$=\varepsilon^4\psi(z)\ c''(z+\widetilde{\theta}(z,s)(s-z)).$$

We thus conclude that for some bounded functions ϕ_1 and ϕ_2,

$$h'(z)=\rho\phi_1(z)c'(z)+\varepsilon^2\phi_2(z)c''(z^*(z)) \tag{94}$$

where $z^*(z)\in(-\infty,z)$. To finish the proof one must estimate $c''(\xi)$ for $\xi\in(-\infty,z)$. This can be done by differentiating the equation for c. If $c''(z)=0$ and $c''(-\infty)=0$, then there must exist a point of an extremum on the interval $(-\infty,z)$ of the function c''. For ε^2 sufficiently small, this allows us, by means of inequality (94), to find the estimation for $|c''(\xi)|$ and obtain estimation (88). □

Proof of Lemma 6 Assume that $b'(\xi_2)>0$ and that $b'(\xi)$ does not attain a positive maximum in $(-\infty,\xi_2)$. Suppose that there exists $\xi_b<\xi_2$ such that $|b'(\xi_b)|$ is a global maximum of $|b'|$ on the interval $(-\infty,\xi_2)$, in particular that $|b'(\xi_b)|\geq|b'(\xi_1)|$. By means of the maximum principle at $\xi=\xi_b$ we have the estimation

$$|b'(\xi_b)|\leq B_{bb}|c'(\xi_b)|\leq B_{bb}|c'(\xi_1)|, \tag{95}$$

where $B_{bb}=-H_{2,c}(c(\xi_b),b(\xi_b))[H_{2,b}(c(\xi_b),b(\xi_b))]^{-1}$. Hence the condition $c'''(\xi_1)\leq 0$, according to Lemma 5 and (95), gives

$$b'(\xi_1)\geq B_{b1}c'(\xi_1), \tag{96}$$

where $B_{b1}=-A_c/A_b$, $A_c=H_{1,c}(c(\xi_1),b(\xi_1))(1+O(\rho))<0$, $A_b=H_{1,b}(c(\xi_1),b(\xi_1))(1+O(\rho))>0$. In particular, it means $b'(\xi_1)>0$. Similarly, using the fact that $c'''(\xi_2)\geq 0$, we arrive at the condition $-[\widetilde{A}_c c'(\xi_2)+\widetilde{A}_b b'(\xi_2)+O(\rho)c'(\xi_1)]\geq 0$, where $\widetilde{A}_c=H_{1,c}(c(\xi_2),b_1(\xi_2))<0$, $\widetilde{A}_b=H_{1,b}(c(\xi_2),b(\xi_2))>0$. Hence we obtain $b'(\xi_2)\leq B_{b2}\rho c'(\xi_1)$, and $|c'(\xi_2)|\leq\rho B_{c2}c'(\xi_1)$, where B_{b2} and B_{c2} have the obvious meaning. Combining these estimations with (96), we obtain $\rho B_{b2}c'(\xi_1)\geq b'(\xi_2)\geq b'(\xi_1)\geq B_{b1}c'(\xi_1)>0$, as B_{b2} and B_{b1} stay can be estimated by constants independent of ρ. We would thus arrive at contradiction with our assumption according to which $b'(\xi_2)\geq b'(\xi_1)$. If we assume that ξ_b satisfying the above assumption does not exist (meaning that $|b'(\xi)|\leq b'(\xi_1)$ on the interval $(-\infty,\xi_1)$), then we can arrive at contradiction in the same way.

Now, assume that $b'(\xi_2)\leq 0$. Suppose that $b'(\xi_1)<0$. If $\sup_{\xi\in(-\infty,\xi_1]}|b'(\xi)|=|b'(\xi_1)|$, then we arrive at a contradiction at ξ_1 with the condition $c'''(\xi_1)\leq 0$. If there exists $\xi_b<\xi_1$ such that $\sup_{\xi\in(-\infty,\xi_1]}|b'(\xi)|=|b'(\xi_b)|$, the relation $|b'(\xi_b)|\leq C_1|c'(\xi_b)|\leq C_2|c'(\xi_1)|$ leads to the same contradiction at $\xi=\xi_1$. □

The proof of Lemma 7 can be carried out similarly to the proof of Lemma 6.

Now, let us consider the monotonicity property on the interval $(0,\infty)$. This time we will assume that the function $\kappa(c)$ appearing in the integral I_3 (see Eq. 93), satisfies the inequality $\kappa(c)<0$ close to $c=c_3$. This is equivalent to the demand that

$$\tau_{,c}(c)K(c) + K_{,c}(c)(\sigma_0 - \tau(c)) < 0 \tag{97}$$

for $|c - c_3| \leq r$, $r > 0$. It is seen that for $\sigma_0 = 0$ and $K = const$ it is implied by the inequality $\tau_{,c}(c_3) < 0$. For all $\mathcal{A}_+ > 0$ we can find $\varepsilon_+ \in (0, \varepsilon_0]$, such that, for all $|\varepsilon| < \varepsilon_+$ and all $\xi \in (0, \mathcal{A}_+)$, $c'(\xi) > 0$, $b'(\xi) > 0$. Let us assume that $\mathcal{A}_+$ is so large and $\varepsilon_+ > 0$ so small that for all $|\varepsilon| < \varepsilon_+$ and $\xi > (\mathcal{A}_+, \infty)$ the inequality $\mathcal{H}(c(\xi), b(\xi))Q < 0$ holds, where Q is the Perron-Frobenius eigenvector of the matrix $\mathcal{H}(c_3, b_3)$.

Similarly as before let us define $\overline{\rho} = \sup_{\xi \in (\mathcal{A}_+, \infty)} |c(\xi) - c_3|$. The following auxiliary lemma holds. □

Lemma 8 *Assume that $c'(z) \leq 0$ for $z \in (\mathcal{A}_+, \infty)$ and $c'(\xi) - c'(z) > 0$ for $\xi \in (0, z)$. Suppose that (97) holds. Then, for some constant L independent of ε and $\overline{\rho}$, we have $h'(z) \geq (\overline{\rho} + \varepsilon^2)Lc'(z)$.*

Proof From the proof of Theorem 2, it follows that it suffices to show that the integral I_3 is non-positive. Let us take $\varepsilon_+ > 0$ so small and $\mathcal{A}_+ > 0$ so large that $c(\xi) > c_3 - r/4$ for $\xi > \mathcal{A}_+$. As $c'(\xi) > 0$ for $\xi \in (0, \mathcal{A}_+)$, then we can define ξ_j, $j = 1, 2, 3, 4$, by the equalities $c(\xi_j) = c_3 - jr/4$. Let also ε_+ be so small that $\sup_{\xi \in (\xi_4, \xi_2)} |c'(\xi) - c'(\beta, 0, \xi)| \leq \inf_{\xi \in (\xi_4, \xi_2)} c'(\beta, 0, \xi)/2 =: \underline{\eta}$. Consequently, $\inf_{\xi \in (\xi_4, \xi_2)} c'(\xi) \geq \underline{\eta}$ and $\sup_{\xi \in (\xi_4, \xi_2)} c'(\xi) \leq 3\overline{\eta}$, where $\overline{\eta} = \sup_{\xi \in (\xi_4, \xi_2)} c'(\beta, 0, \xi)/2$. Note that the ratio $\overline{\eta}/\underline{\eta}$ depends only on the solution $c(\beta, 0, \cdot)$, hence is independent of ε. As $c'(z) \leq 0$ and $\kappa(c(\xi)) < 0$ for $\xi \in (\xi_4, \infty)$, then using the denotations of Lemma 5, we have:

$$\begin{aligned}
I_3 \leq& \int_{-\infty}^{\xi_4} \exp\left\{-\int_s^z [\varepsilon^2 G(\zeta)]^{-1} d\zeta\right\} \kappa(c(s))c'(s)ds \\
&+ \int_{\xi_3}^{\xi_2} \exp\left\{-\int_s^z [\varepsilon^2 G(\zeta)]^{-1} d\zeta\right\} \kappa(c(s))c'(s)ds \\
\leq& \exp\left\{-\int_{\xi_4}^z [\varepsilon^2 G(\zeta)]^{-1} d\zeta\right\} \int_{-\infty}^{\xi_4} \exp\left\{-\int_s^{\xi_4} [\varepsilon^2 G(\zeta)]^{-1} d\zeta\right\} \kappa(c(s))c'(s)ds \\
&+ \exp\left\{-\int_{\xi_2}^z [\varepsilon^2 G(\zeta)]^{-1} d\zeta\right\} \int_{\xi_3}^{\xi_2} \exp\left\{-\int_s^{\xi_2} [\varepsilon^2 G(\zeta)]^{-1} d\zeta\right\} \kappa(c(s))c'(s)ds \\
\leq& \exp\left\{-\int_{\xi_2}^z [\varepsilon^2 G(\zeta)]^{-1} d\zeta\right\} \varepsilon^2 \left[\max\{\overline{k}, 0\}\, \overline{G} \exp\left\{-\int_{\xi_4}^{\xi_2} [\varepsilon^2 G(\zeta)]^{-1} d\zeta\right\}\right. \\
&\left. + \underline{k}\underline{\eta}\underline{G}\left(1 - O(\exp\{(\xi_2 - \xi_3)/(\varepsilon^2 \underline{G})\})\right)\right],
\end{aligned}$$

where $\underline{k} = \sup_{c \in (c_3 - r/2, c_3 - 3r/4)} \kappa(c) < 0$, $\underline{G} = \inf_{\xi \in (\xi_3, \xi_2)} G(\xi)$, $\overline{k} = \sup_{\xi \in (-\infty, \xi_4)} \kappa(c(\xi))c'(\xi)$ and $\overline{G} = \sup_{\xi \in (-\infty, \xi_4)} G(\xi)$. As $\xi_2 - \xi_4 \geq r/(6\overline{\eta})$, $\xi_2 - \xi_3 \geq r/(12\overline{\eta})$ and $\underline{G} > G_* > 0$ with G_* not depending on ε, it is seen that for $|\varepsilon|$ sufficiently small, $I_3 \leq 0$. The lemma is proved. □

Theorem 3 *Let inequality* (97) *hold. Let* $0 < |\beta| < \beta_0$. *Then there exists* $\varepsilon_+ \in (0, \varepsilon_0]$, *such that for all* $|\varepsilon| < \varepsilon_+$, $c'(z) > 0$ *and* $b'(z) > 0$ *for all* $z \in (0, \infty)$.

Suppose to the contrary that it is not true. Let a point z_c, where the global non-positive minimum for the function c' in the interval takes place. Due to the last lemma and the maximum principle, $b'(z_c)$ must be non-positive. Let us note that $c'(z_c) = 0$ implies $b'(z_c) = 0$. If $b'(z) < 0$ for some $z \in (0, \infty)$, then $c'(z) < 0$ also, which a contradiction with the assumption that $c'(z_c) = 0$ is a global minimum. If $b'(\xi) \geq 0$ for all ξ, then $b''(z_c) = 0$ and from the uniqueness of the solutions to system (86) it follows that $c(z_c) = c_3$ and $b(z_c) = b_3$ implying that $z_c = \infty$ and the theorem is proved. Thus there exists $z_b > \mathcal{A}_+$ such that the function b' attains its negative global minimum. This implies that $c'(z_c) \leq c'(z_b) < 0$. The rest of the proof can be done similarly to the case ii. in the proof of Theorem 2.

Remark As we mentioned above, the maximal value of ε^2 in Theorems 2 and 3 depends in general on the value of β^2.

Appendix 3: Monotonicity of the asymptotic solution

Letting $\beta = 0$ we arrive at the asymptotic equation which is obtained by putting $\eta = 0$ in Eq. 36. It reads

$$D_1(c, 0)c'' - D_2(c)c'^2 + vc' + (1 + S(c))^{-1} \left[g(c) + \gamma h\right] = 0. \tag{98}$$

For $\varepsilon = 0$, $h \equiv 0$, thus according to Keener and Sneyd (1998); Sneyd et al. (1998), the heteroclinic solution $C(\cdot)$ to this equation is monotone, i.e. $C'(\xi) > 0$ for all $\xi \in \mathbb{R}^1$. From Theorem 1 it follows that there exist $\varepsilon_0 > 0$ such that for all ε such that $|\varepsilon| < \varepsilon_0$ there exists a unique solution $(c(\varepsilon, \cdot), h(\varepsilon, (\cdot))$ to Eqs (98),(30) together with the speed $v(\varepsilon)$. If ε_0 is sufficiently small then $v(\varepsilon) < 0$ [as the initial speed $V < 0$ by assumption (45)]. We will show that for $|\varepsilon|$ sufficiently small the inequality $c'(\varepsilon, \xi) > 0$ holds also for all $\xi \in \mathbb{R}^1$. For simplicity, we will denote the functions $c(\varepsilon, \xi)$ and $h(\varepsilon, \xi)$ by $c(\xi)$ and $h(\xi)$. Because the position of the front profile is fixed by the condition $c(0) = (c_1 + c_3)/2$, therefore on any finite interval $(\mathcal{A}_-, \mathcal{A}_+) \ni 0$, the functions c have positive derivatives for all sufficiently small $|\varepsilon|$, what follows from their continuous dependence on the parameter ε. We will divide our considerations into two parts: for negative and positive values of ξ. We will start from the interval $(-\infty, 0]$. For a fixed $\mathcal{A}_- < 0$ there exists positive $\varepsilon_- \leq \varepsilon_0$, such that for all $|\varepsilon| < \varepsilon_-$ we have the inequality $c'(\xi) > 0$ for $\xi \in (\mathcal{A}_-, 0]$. Our task will be thus to show that the monotonicity property remains valid also for $\xi \in (-\infty, \mathcal{A}_-)$. Let us define:

$\rho = \sup_{\xi \in (-\infty, \mathcal{A}_-)}(|c(\xi) - c_1| + |c'(\xi)|)$. By differentiation of Eq. 98, we obtain

$$D_1(c,0)c''' + [V + O_1(c')]c'' + [(1+S(c))^{-1}]_{,c}[g(c) + \gamma h]c' \\ +[1+S(c)]^{-1}[g'(c)c' + O_2(c')c' + \gamma h'] = 0, \tag{99}$$

where the terms $O_1(c')$, $O_2(c') \to 0$ as $|c'| \to 0$. Suppose that there exists a point ξ_* such that $c'(\xi_*) \le 0$. Thus there exists a point $\xi^*, \xi^* < \xi_* < \mathcal{A}_-$ such that $c'(\xi^*) = 0$. Since $c'(-\infty) = 0$, then there must exist a point ξ_0 such that $|c'(\cdot)|$ has a global maximum on $(-\infty, \xi^*)$. At this point we have $c''(\xi_0) = 0$. By examining the expression for h (see 48) we conclude that there exists constants B_1, B_2 such that

$$|h'(\xi_0)| \le \rho B_1 |c'(\xi_0)| + \varepsilon^2 B_2 \sup_{\xi \in (-\infty, \xi_0)} |c''(\xi_0)|. \tag{100}$$

By means of the above inequality, we can prove the following lemma.

Lemma 9

$$|h'(\xi_0)| \le (\rho + \varepsilon^2) B |c'(\xi_0)|, \tag{101}$$

where B is a constant independent of ε and ρ.

Proof Let the function c'' attain an extremum at $\xi = \xi_1$. Then $c'''(\xi_1) = 0$, so considering Eq. 99 at $\xi = \xi_1$ we can obtain the estimation of $c''(\xi_1)$ by means of $c'(\xi_1)$, $h(\xi_1)$ and $h'(\xi_1)$. Thus, using estimation (9), we obtain the claim of the lemma by choosing $\mathcal{A}_-$ sufficiently large and $|\varepsilon|$ sufficiently small, which implies in ρ being sufficiently small. □

Assuming that the function c' attains a maximum at $\xi = \xi_0$, so $c'''(\xi_0) \le 0$, so Eq. 99 gives the inequality:

$$\mathcal{K}(\xi_0)c'(\xi_0) + \gamma h'(\xi_0) \ge 0,$$

where $\mathcal{K}(\xi_0) = g'(c(\xi_0)) + O(\rho) + O(\varepsilon^2)$ (as $h = O(\varepsilon^2)$). Due to to Assumption 2, $g'(c_1) < 0$, hence $\mathcal{K}(\xi_0) < 0$. Using Lemma 9 we obtain the inequalities:

$$\mathcal{K}(\xi_0)c'(\xi_0) + \gamma h'(\xi_0) \le [\mathcal{K}(\xi_0) + (\rho + \varepsilon^2)B]c'(\xi_0) < 0. \tag{102}$$

Hence, we arrive at contradiction, as for $(\rho + \varepsilon^2)$ sufficiently small $\mathcal{K}(\xi_0) + \rho B < 0$ and $c'(\xi_0) > 0$. If we assume that the function c' attains a minimum at $\xi = \xi_0$ then we arrive at contradiction in the similar way. These contradictions prove that for sufficiently small $|\varepsilon|$ the solution of Eq. 98 satisfies the inequality $c'(\xi) > 0$ for all $\xi \in (-\infty, 0)$.

Now, let us consider the monotonicity property on the interval $(0, \infty)$. In this case we will assume that the function multiplying c' in Eq. 47 is negative close to $c = c_3$. We thus demand that

$$\tau_{,c}(c)K(c) + K_{,c}(c)(\sigma_0 - \tau(c)) < 0. \tag{103}$$

for $0 \leq |c - c_3| \leq r$, $r > 0$. This time for sufficiently small $|\varepsilon|$ we can obtain the estimation $h'(\xi_0) \geq \rho L c'(\xi_0)$ for some constant L independent of ρ and ε. This allows us to repeat the analysis of inequality (102) leading to the obtaining the monotonicity result on the interval $(0, \infty)$.

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