

## A bidomain threshold model of propagating calcium waves

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**Abstract** We present a bidomain fire-diffuse-fire model that facilitates mathematical analysis of propagating waves of elevated intracellular calcium ( $\text{Ca}^{2+}$ ) in living cells. Modeling  $\text{Ca}^{2+}$  release as a threshold process allows the explicit construction of traveling wave solutions to probe the dependence of  $\text{Ca}^{2+}$  wave speed on physiologically important parameters such as the threshold for  $\text{Ca}^{2+}$  release from the endoplasmic reticulum (ER) to the cytosol, the rate of  $\text{Ca}^{2+}$  resequestration from the cytosol to the ER, and the total  $[\text{Ca}^{2+}]$  (cytosolic plus ER). Interestingly, linear stability analysis of the bidomain fire-diffuse-fire model predicts the onset of dynamic wave instabilities leading to the emergence of  $\text{Ca}^{2+}$  waves that propagate in a back-and-forth manner. Numerical simulations are used to confirm the presence of these so-called ‘tango waves’ and the dependence of  $\text{Ca}^{2+}$  wave speed on the total  $[\text{Ca}^{2+}]$ .

**Keywords** Bidomain models · Calcium waves · Stability · Wave bifurcation

**Mathematics Subject Classification (2000)** 92B05

### 1 Introduction

Calcium ions ( $\text{Ca}^{2+}$ ) are an important second messenger in living cells [1]. The diverse physiological roles of intracellular  $\text{Ca}^{2+}$  signals range from the activation of egg

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cells at fertilization [2,3] to the coupling of plasma membrane excitation to cardiac muscle cell contraction [4]. While  $\text{Ca}^{2+}$  influx via voltage-gated  $\text{Ca}^{2+}$  channels of the plasma membrane can lead to increases in intracellular  $[\text{Ca}^{2+}]$ , another important source is the endoplasmic reticulum (ER), a continuous membrane-delimited intracellular compartment with integrative and regenerative properties analogous to the membranes of electrically excitable cells [5–8]. In neurons and many other cell types, activated metabotropic receptors of the plasma membrane stimulate the production of the intracellular messenger inositol 1,4,5-trisphosphate ( $\text{IP}_3$ ) [9].  $\text{IP}_3$  in turn promotes  $\text{Ca}^{2+}$  release from intracellular stores by binding and activating  $\text{IP}_3$  receptor ( $\text{IP}_3\text{R}$ ) channels located on the ER membrane [10]. In addition to this  $\text{IP}_3$ -mediated pathway, a second parallel mechanism for  $\text{Ca}^{2+}$  release is mediated by ryanodine receptors (RyRs)—intracellular  $\text{Ca}^{2+}$  channels on the ER or sarcoplasmic reticulum (SR) that are activated by cyclic ADP ribose [11]. Importantly, both  $\text{IP}_3\text{Rs}$  and RyRs can be activated and/or inactivated by intracellular  $\text{Ca}^{2+}$  leading to ER ‘ $\text{Ca}^{2+}$  excitability’ [6,12]. This  $\text{Ca}^{2+}$  excitability is the physiological basis for  $\text{IP}_3$ - and  $\text{Ca}^{2+}$ -induced  $\text{Ca}^{2+}$  release (IICR and CICR) in excitable and non-excitable cells.

Propagating waves of elevated intracellular  $[\text{Ca}^{2+}]$  have been characterized in the immature *Xenopus laevis* oocyte [13], mature eggs from a variety of species [14–17],  $\text{Ca}^{2+}$ -overloaded cardiac myocytes [18], vascular smooth muscle [19], and many other cell types [20–23]. In many cases intracellular  $\text{Ca}^{2+}$  waves are primarily due to  $\text{Ca}^{2+}$  release from internal stores, that is, they can occur in the absence of influx of  $\text{Ca}^{2+}$  across the plasma membrane. Extensive theoretical work has been carried out in an effort to understand the biophysical mechanisms underlying such waves. In the case of the *X. laevis* oocyte and mature eggs, the focus has been on continuum reaction–diffusion equations in which the release mechanism is modeled in a deterministic fashion [24–34]. For example, in situations where plasma membrane fluxes can be neglected, a one-dimensional continuum model of propagating plane waves of elevated intracellular  $\text{Ca}^{2+}$  might take the form,

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} + J_{\text{rel}}(c, w, c_{\text{er}}) - J_{\text{pump}}(c), \quad (1a)$$

$$\frac{\partial w}{\partial t} = \frac{w_{\infty}(c) - w}{\tau_w(c)}, \quad (1b)$$

$$\frac{\partial c_{\text{er}}}{\partial t} = D_{\text{er}} \frac{\partial^2 c_{\text{er}}}{\partial x^2} - \gamma^{-1} [J_{\text{rel}}(c, w, c_{\text{er}}) - J_{\text{pump}}(c)], \quad (1c)$$

where the cytosolic and ER  $[\text{Ca}^{2+}]$  given by  $c(x, t)$  and  $c_{\text{er}}(x, t)$  are both functions of space and time, and the release and reuptake fluxes,  $J_{\text{rel}}(c, w, c_{\text{er}})$  and  $J_{\text{pump}}(c)$ , are functions of these two concentrations. In such models the  $\text{Ca}^{2+}$  release flux is also a function of a Hodgkin–Huxley-like gating variable ( $w$ ) that represents the fast  $\text{Ca}^{2+}$ -activation and slower  $\text{Ca}^{2+}$ -inactivation of a large number of identical  $\text{IP}_3\text{Rs}$  at fixed  $[\text{IP}_3]$  [35,36]. Note that in (1) the ER is represented as a contiguous compartment with volume fraction  $\gamma$  that is uniformly distributed throughout the cytosol. Spatial whole cell models in which the cytosolic and ER  $[\text{Ca}^{2+}]$  coexist in this manner are often referred to as ‘bidomain’ models [37,38].

The spatial whole cell modelling approach outlined in (1) has suggested or reproduced various distinct modes of transmission of propagating  $\text{Ca}^{2+}$  waves [38]: firstly, solitary and spiral waves that occur when the physiological state of the cytoplasm is excitable [25,29]; secondly, repetitive wave trains and spiral waves that occur when the cytoplasm is oscillatory [28–30]; and thirdly, traveling fronts or ‘tides’ that occur when the cytoplasm is bistable [31,39]. The first two of these mechanisms have been proposed to be responsible for  $\text{Ca}^{2+}$  waves observed in the immature *X. laevis* oocyte, while the third mechanism seems to describe the fertilization  $\text{Ca}^{2+}$  wave in the mature *Xenopus* egg. Interestingly, when the local dynamics of  $\text{Ca}^{2+}$  release and reuptake are spatially heterogeneous, one-dimensional continuum models (1) are also able to produce a fourth wave phenomenon in which fronts of elevated intracellular  $[\text{Ca}^{2+}]$  propagate in a back-and-forth manner that resembles the movement of tango dancers [40] and is reminiscent of the behavior of  $\text{Ca}^{2+}$  waves in nemertean worm [41] and ascidian eggs [42]. While spatial heterogeneity of model parameters may give rise to these so-called ‘tango waves’, the phenomenon can also be observed in models with spatially homogeneous parameters as long as the initial concentration profiles are chosen so that an auxiliary variable known as the total  $[\text{Ca}^{2+}]$  given by

$$c_T = c + \gamma c_{\text{er}}, \quad (2)$$

and satisfying

$$\frac{\partial c_T}{\partial t} = D \frac{\partial^2 c}{\partial x^2} + \gamma D_{\text{er}} \frac{\partial^2 c_{\text{er}}}{\partial x^2}, \quad (3)$$

results in a spatially localized bistable domain [40,43].

One important spatial inhomogeneity known to have a profound impact on propagating  $\text{IP}_3$ -mediated  $\text{Ca}^{2+}$  waves is the distribution of  $\text{IP}_3\text{Rs}$ . In the immature *Xenopus* oocyte, for example,  $\text{IP}_3\text{Rs}$  occur in clusters of 10–100 with inter-cluster spacing on the order of a few microns [8]. Localized  $\text{Ca}^{2+}$  elevations due to the activation of an individual  $\text{IP}_3$ -sensitive  $\text{Ca}^{2+}$  release sites are referred to as ‘ $\text{Ca}^{2+}$  puffs’ [44,45] and under some conditions this organization of  $\text{Ca}^{2+}$  release sites reveals itself in cauliflower-like wave fronts [46]. Similarly, in cardiac myocytes localized  $\text{Ca}^{2+}$  elevations due to intracellular  $\text{Ca}^{2+}$  release mediated by clusters of  $\text{RyRs}$  known as  $\text{Ca}^{2+}$  sparks [47] can merge to form  $\text{Ca}^{2+}$  waves that propagate in a saltatory manner [18].

Although it is possible to modify (1) to include a spatially periodic maximum conductance for  $\text{Ca}^{2+}$  release [48], a more tractable class of ‘fire-diffuse-fire’ (FDF) models introduced in [49–52] are also appropriate for spark- or puff-mediated  $\text{Ca}^{2+}$  waves. FDF models do not include gating variables for the activation and inactivation of  $\text{Ca}^{2+}$ -regulated intracellular channels, but instead model  $\text{Ca}^{2+}$  release as a threshold process in which elevated  $[\text{Ca}^{2+}]$  triggers a prescribed time course of  $\text{Ca}^{2+}$  release. For example, in [51] the cytosolic  $[\text{Ca}^{2+}]$  satisfies

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} + J_{\text{rel}}(x, t), \quad (4)$$

and the release flux is given by

$$J_{\text{rel}}(x, t) = \sum_i f(t - T_i) \delta(x - x_i), \quad (5)$$

where the source amplitude  $f(t)$  upon triggering of  $\text{Ca}^{2+}$  release is a continuous function that is zero for  $t < 0$  and positive for  $t \geq 0$ . In (5)  $T_i$  is the time of the first (and only) release event at release site  $i$  located at  $x_i$  given by

$$T_i = \inf\{t \mid c(x_i, t) \geq c_{\text{th}}\}. \quad (6)$$

That is, at each site  $\text{Ca}^{2+}$  release begins when cytosolic  $[\text{Ca}^{2+}]$  achieves the threshold concentration  $c_{\text{th}}$ . Analytical and simulation based studies using the FDF formalism ((4) and (5)) have illuminated the differences between continuous propagation (as in mature *Xenopus* eggs) and saltatory propagation (as in  $\text{Ca}^{2+}$ -overloaded cardiac myocytes) and have been further extended to include reuptake fluxes [53], stochastic  $\text{Ca}^{2+}$  release [54], diffusion in two dimensions [55], and  $\text{Ca}^{2+}$  release from continuously and uniformly distributed intracellular channels, i.e., channels that are not clustered at  $\text{Ca}^{2+}$  release sites [52], in which case the release flux is given by

$$J_{\text{rel}}(x, t) = f(t - T(x)), \quad (7)$$

where the firing times  $T(x)$  are a function of spatial position that take the form

$$T(x) = \inf\{t \mid c(x, t) \geq c_{\text{th}}\}. \quad (8)$$

To date FDF models with spatially punctate ((5) and (6)) or homogeneous ((7) and (8))  $\text{Ca}^{2+}$  release have been used to reproduce and mathematically analyze the properties of solitary  $\text{Ca}^{2+}$  waves, repetitive wave trains, and traveling fronts, as well as their analogues when release is triggered in a stochastic fashion [49–56].

In spite of these successes, one of the limitations of the FDF models presented up to now is that the dynamics of ER  $[\text{Ca}^{2+}]$  is not included in the model formulation. A single equation (4) governs the dynamics of cytosolic  $\text{Ca}^{2+}$ , rather than the more realistic bidomain equations for concentration balance between the cytosol and the ER such as (1a) and (1c). Because in many cell types  $\text{Ca}^{2+}$  release does lead to significant local depletion of the ER  $\text{Ca}^{2+}$  stores, the range of applicability of prior work analyzing properties of  $\text{Ca}^{2+}$  waves using the FDF formalism is unclear. In particular, the analytical tractability of the FDF formalism has not yet been used to address wave phenomena that require spatial heterogeneity of total  $[\text{Ca}^{2+}]$  (3) to produce spatially localized bistable domains [40, 43].

In order to overcome this limitation of previous FDF models, we have extended the FDF formalism to include concentration balance between the cytosol and ER (Sect. 2) and subsequently present what is to our knowledge the first mathematical analysis of a bidomain threshold-release model of propagating  $\text{Ca}^{2+}$  waves. For clarity, this analysis is developed in two stages. In Sect. 3 we focus on single domain equations (4) with a release term that is proportional to the concentration difference between the

elevated cytosolic  $[Ca^{2+}]$  and a fixed ER  $[Ca^{2+}]$  (i.e., a shunt). By modelling  $Ca^{2+}$  release as a threshold process we explicitly construct traveling wave solutions and perform stability analysis to probe how  $Ca^{2+}$  wave speed depends on the threshold for  $Ca^{2+}$  release and the ER  $[Ca^{2+}]$ . In Sect. 4 we extend this construction and analysis to bidomain equations that include time-dependent depletion of the ER  $[Ca^{2+}]$ , explicitly construct traveling pulse and traveling front solutions, and perform a linear stability analysis that shows the onset of wave instabilities, which lead to the emergence of waves that propagate in a back-and-forth manner [40]. Numerical simulations confirm analytical results such as the dependence of wave speed on the total  $[Ca^{2+}]$  far from the wave front as well as the presence of so-called tango waves.

## 2 The bidomain fire-diffuse-fire model

For clarity, we restrict our analysis and numerical simulation of the bidomain FDF model to the case where intracellular channels are continuously and uniformly distributed. With this assumption, the bidomain FDF model of propagating  $Ca^{2+}$  waves takes the form,

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} + J_{rel}(c, c_{er}) - J_{pump}(c, c_{er}), \tag{9a}$$

$$\frac{\partial c_{er}}{\partial t} = D_{er} \frac{\partial^2 c_{er}}{\partial x^2} - \gamma^{-1} [J_{rel}(c, c_{er}) - J_{pump}(c, c_{er})], \tag{9b}$$

where the release and reuptake fluxes,  $J_{rel}(c, c_{er})$  and  $J_{pump}(c, c_{er})$ , are functions of both the cytosolic and ER  $[Ca^{2+}]$ , and  $\gamma$  is the effective volume fraction of the ER. When written in the most general form that allows for multiple release events from the same spatial location, the release flux in the bidomain FDF model is given by

$$J_{rel}(x, t) = (c_{er}(x, t) - c(x, t)) \sum_m \eta(t - T^m(x)), \tag{10}$$

where the release rate  $\eta(t) = 0$  for  $t < 0$  and  $\eta(t) \geq 0$  for  $t \geq 0$ . The release times  $T^m(x)$  are determined by a threshold process such that

$$T^m(x) = \inf\{t \mid c(x, t) \geq c_{th}, t > T^{m-1}(x) + \tau_R\}, \quad m = 0, 1, \dots, \tag{11}$$

where  $\tau_R$  is the absolute refractory period for  $Ca^{2+}$  release. For simplicity we assume  $T^0(x) < -\tau_R$ , that is, the absolute refractory period does not influence the time of first release,  $T^1(x)$ . To complete the bidomain FDF model formulation, the functional form of the reuptake flux is chosen to be

$$J_{pump}(c, c_{er}) = \frac{c}{\tau} - \frac{c_{er}}{\tau_{er}}, \tag{12}$$

a function that is linear in both the cytosolic and ER  $[Ca^{2+}]$ . This linear bidirectional reuptake flux (12) is equivalent to the low-affinity limit ( $c \ll \kappa$  and  $c_{er} \ll \kappa_{er}$ ) of a

previously published bidirectional SERCA pump model [57],

$$J_{\text{pump}}(c, c_{\text{er}}) = v \frac{(c/\kappa)^n - (c_{\text{er}}/\kappa_{\text{er}})^{n_{\text{er}}}}{1 + (c/\kappa)^n + (c_{\text{er}}/\kappa_{\text{er}})^{n_{\text{er}}}}, \tag{13}$$

when the  $\text{Ca}^{2+}$ -binding is not cooperative ( $n = n_{\text{er}} = 1$ ) and the time constants in (12) are given by  $\tau = \kappa/v$  and  $\tau_{\text{er}} = \kappa_{\text{er}}/v$ .

### 3 Analysis of the fire-diffuse-fire model with shunt

As a first step in our analysis of the bidomain FDF model (9), we consider the associated single domain equations obtained by assuming that the ER  $[\text{Ca}^{2+}]$  is fixed, i.e., we drop (9b) and consider  $c_{\text{er}}$  to be a model parameter. This single domain FDF model is applicable when the ER-to-cytosol volume ratio and the diffusion constant within the ER are both large ( $\gamma \rightarrow \infty$  and  $D_{\text{er}} \rightarrow \infty$ ). Although an approximation of the full bidomain equations, this single domain model with fixed  $c_{\text{er}}$  includes the driving force for  $\text{Ca}^{2+}$  liberation,  $c_{\text{er}} - c(x, t)$ , which decreases upon elevation of intracellular  $\text{Ca}^{2+}$ . This dynamic driving force or ‘shunt’ for  $\text{Ca}^{2+}$  release is potentially important when intracellular  $\text{Ca}^{2+}$  liberation is triggered by cytosolic  $[\text{Ca}^{2+}]$  crossing a threshold, but it has been absent from previously published FDF models, which have instead assumed a time-dependent source amplitude (5) or density (7) that is not influenced by cytosolic  $\text{Ca}^{2+}$  once release is triggered.

#### 3.1 Speed of traveling pulse: arbitrary release shape

We consider a solitary traveling pulse with uniform wave speed  $v$  mediated by a single release event at each spatial location and choose a coordinate system such that the cytosolic  $[\text{Ca}^{2+}]$  crosses the threshold for  $\text{Ca}^{2+}$  release ( $c_{\text{th}}$ ) at  $t = 0$  and  $x = 0$ . Consequently, release at spatial position  $x$  begins at a time given by  $T(x) = x/v$ . To determine the shape and the velocity of the pulse for a release rate that satisfies  $\eta(t) = 0$  for  $t < 0$  and  $\eta(t) \geq 0$  for  $t \geq 0$  but is otherwise arbitrary, it is convenient to work in the co-moving frame. Introducing  $\xi = vt - x$  we may re-write the original equation of motion in which  $c_{\text{er}}$  is a parameter,

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} - \frac{c}{\tau} + \eta(t - T(x))(c_{\text{er}} - c), \tag{14}$$

as  $c = c(\xi, t)$  where  $c$  satisfies

$$\left( \frac{\partial}{\partial t} + v \frac{\partial}{\partial \xi} \right) c = D \frac{\partial^2 c}{\partial \xi^2} - \frac{c}{\tau} + \eta(\xi/v)(c_{\text{er}} - c), \tag{15}$$

and we have used  $\eta(t - T(x)) = \eta(t - x/v) = \eta(\xi/v)$ . Setting  $\partial c/\partial t = 0$  in (15) we find that a stationary profile  $c(\xi, t) = c(\xi)$  in the co-moving frame satisfies the

ordinary differential equation

$$(d_\xi - m_+(\xi))(d_\xi - m_-(\xi))c = F(\xi), \tag{16}$$

where

$$F(\xi) = -\frac{c_{er}}{D}\eta(\xi/v), \quad m_\pm(\xi) = \frac{v \pm \sqrt{v^2 + 4\epsilon(\xi)D}}{2D}, \quad \epsilon(\xi) = \frac{1}{\tau} + \eta(\xi/v). \tag{17}$$

Introducing the auxiliary variable  $z(\xi)$  defined by

$$z = (d_\xi - m_-(\xi))c, \tag{18}$$

we can integrate  $(d_\xi - m_+(\xi))z = F(\xi)$  to find

$$z(\xi) = G_+(\xi, 0) \left[ z(0) + \Theta(\xi) \int_0^\xi G_+(0, \xi')F(\xi')d\xi' \right], \tag{19}$$

where  $\Theta$  is the Heaviside function,  $\Theta(t) = 1$  for  $t \geq 0$  and 0 otherwise, and

$$G_\pm(\xi, \xi') = \exp \left( \int_{\xi'}^\xi ds m_\pm(s) \right). \tag{20}$$

For  $z(\xi)$  to be bounded as  $\xi \rightarrow \infty$  (long after release begins) we require

$$z(0) = - \int_0^\infty G_+(0, \xi')F(\xi')d\xi'. \tag{21}$$

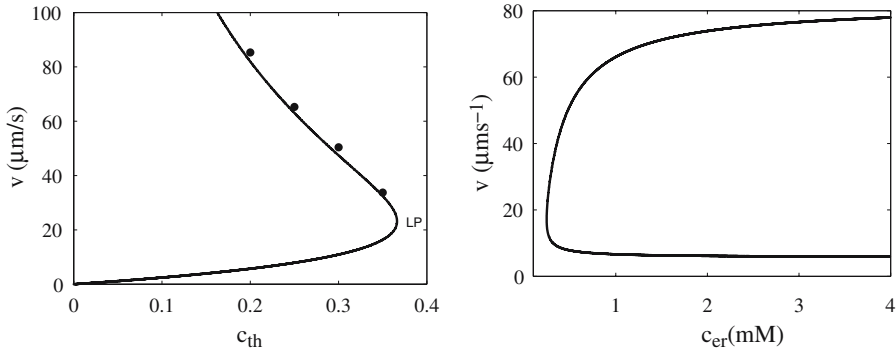
Next, we integrate (18) to obtain the solution  $c(\xi)$  corresponding to  $z(\xi)$  in (19),

$$c(\xi) = G_-(\xi, 0) \left[ c_{th} + \int_0^\xi G_-(0, \xi')z(\xi')d\xi' \right], \tag{22}$$

for which we require

$$c_{th} = z(0) \int_{-\infty}^0 G_-(0, \xi')G_+(\xi', 0)d\xi', \tag{23}$$

for  $c(\xi)$  to be bounded as  $\xi \rightarrow -\infty$  (long before release begins). Note that for  $\xi < 0$  (prior to the initiation of release),  $\eta = 0$  and  $\epsilon = 1/\tau$  in (17) and thus  $m_\pm(\xi) = k_\pm$



**Fig. 1** Speed of a solitary wave as given by (25) with  $\eta(t) = \bar{\eta}\Theta(t)\Theta(\Delta - t)$ . Filled circles denote results from numerical simulations. *Left*  $v = v(c_{th})$ , with  $D = 30 \mu\text{m}^2\text{s}^{-1}$ ,  $c_{er} = 100 \mu\text{M}$ ,  $\Delta = 0.05 \text{ s}$ ,  $\tau = 0.01 \text{ s}^{-1}$  and  $\bar{\eta} = 1 \text{ s}^{-1}$ . *Right*  $v = v(c_{er})$  with  $D = 30 \mu\text{m}^2\text{s}^{-1}$ ,  $c_{th} = 0.2 \mu\text{M}$ ,  $\Delta = 0.05 \text{ s}$ ,  $\tau = 0.01 \text{ s}^{-1}$  and  $\bar{\eta}c_{er} = 100 \mu\text{M s}^{-1}$ . Of the two branches of solutions, the slower is always unstable

where

$$k_{\pm} = \frac{v \pm \sqrt{v^2 + 4D/\tau}}{2D}. \tag{24}$$

Hence, we have the elegant result that the speed of the solitary pulse is determined by the equation

$$c_{th} = \frac{z(0)}{k_+ - k_-} = z(0) \left( \frac{D}{\sqrt{v^2 + 4D/\tau}} \right). \tag{25}$$

### 3.2 Speed of traveling pulse and wave profile: square pulse release shape

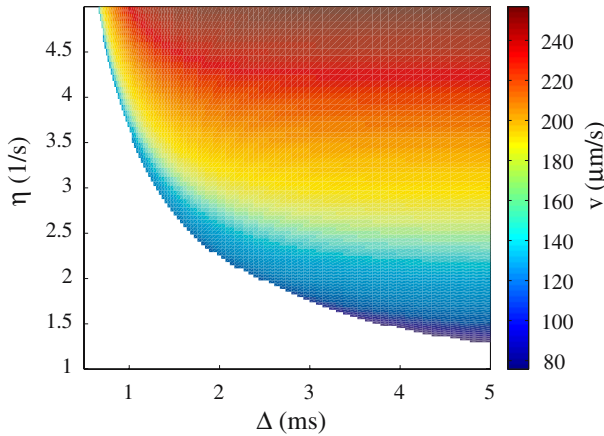
For an example application of the above analysis of traveling pulse speed in the FDF model with a shunt, consider the square pulse release rate with amplitude  $\bar{\eta}$  and duration  $\Delta$  given by  $\eta(t) = \bar{\eta}\Theta(t)\Theta(\Delta - t)$ . In this case  $z(0)$  is easily found from (21) to be

$$z(0) = \frac{\bar{\eta}c_{er}}{Dm_+} (1 - e^{-m_+v\Delta}), \quad \text{where} \quad m_+ = \frac{v + \sqrt{v^2 + 4(\tau^{-1} + \bar{\eta})D}}{2D}. \tag{26}$$

For sufficiently small  $c_{th}/c_{er}$  there are two wave speeds that solve (25) and (26). This is illustrated in Fig. 1 (left) by varying the threshold for release with fixed ER concentration ( $c_{er} = 100 \mu\text{M}$ ) and pulse duration ( $\Delta = 0.05 \text{ s}$ ). Note that Fig. 1 (left) is qualitatively similar to the  $v = v(c_{th})$  plots obtained from FDF models that do not include a shunt [52] and as expected the slower (and lower) branch of solutions is unstable (see Sect. 3.3). The solid dots in Fig. 1 (left) show wave speed calculations obtained from numerical simulations using a finite difference scheme (note agreement with analytical result).

Figure 1 (right) plots the wave speed as a function of the ER concentration for a fixed threshold for release ( $c_{th} = 0.2 \mu\text{M}$ ), pulse duration ( $\Delta = 0.05 \text{ s}$ ), and initial and maximum release amplitude ( $\bar{\eta}c_{er} = 100 \mu\text{M s}^{-1}$ ). As expected, we observe that the





**Fig. 2** Pseudocolour plot of the speed  $v$  ( $\mu\text{m/s}$ ) of a stable solitary wave in the  $(\Delta, \bar{\eta})$  parameter plane, with  $D = 30 \mu\text{m}^2\text{s}^{-1}$ ,  $c_{\text{er}} = 100 \mu\text{M}$ ,  $c_{\text{th}} = 0.2 \mu\text{M}$ , and  $\tau = 0.01 \text{ s}^{-1}$

speed of the stable pulse (upper branch) decreases with decreasing ER  $[\text{Ca}^{2+}]$ . Note that in the limit  $c_{\text{er}} \rightarrow \infty$  with fixed  $\bar{\eta}c_{\text{er}}$  the shunt model (14) is equivalent to a FDF model with pure source term (7) of the form  $f(t) = \bar{\eta}c_{\text{er}}\Theta(t)\Theta(\Delta - t)$ . Consequently, the asymptotic stable and unstable wave speeds shown in Fig. 1 (right) can be found by taking this limit in (25) and (26) and using the identity  $k_+k_- = -1/(D\tau)$ , that is,

$$\frac{c_{\text{th}}}{c_{\text{er}}} = \bar{\eta}\tau \frac{k_-}{k_- - k_+} \left(1 - e^{-k_+v\Delta}\right), \tag{27}$$

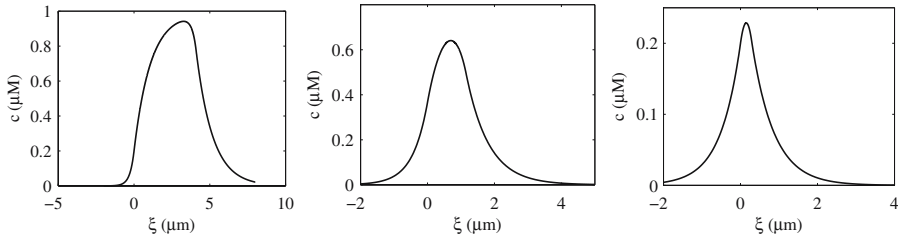
a wave speed result first obtained in [52].

A more comprehensive view is presented in Fig. 2 that plots the stable wave speed in the  $(\Delta, \bar{\eta})$  parameter plane using fixed  $c_{\text{th}}$  and  $c_{\text{er}}$ . Note that the minimum wave speed decreases as the release rate during the pulse  $\bar{\eta}$  decreases. In the limit of a brief pulse with fixed amplitude given by  $\bar{\eta}\Delta = 1$ , the limit  $\Delta \rightarrow 0$  in (25) and (26) such that  $\eta(t) \rightarrow \delta(t)$  yields a unique wave speed

$$v = \sqrt{\frac{4D/\tau}{(c_{\text{er}}/c_{\text{th}})^2 - 1}}, \quad \text{when } c_{\text{er}}/c_{\text{th}} > 1. \tag{28}$$

The corresponding wave profile is simply  $c(\xi) = c_{\text{th}}[e^{k_-\xi}\Theta(\xi) + e^{k_+\xi}\Theta(-\xi)]$ , though using the techniques we develop in the next section it can be shown to be unstable.

Figure 3 shows three wave profiles of the FDF model with shunt calculated from (22) using a square-pulse release rate,  $\eta(t) = \bar{\eta}\Theta(t)\Theta(\Delta - t)$ , and parameters as in Fig. 1 (left). The wave profiles shown in the left and right panels of Fig. 3 both employ  $c_{\text{th}} = 0.2 \mu\text{M}$  and correspond to the upper ( $v = 81.98 \mu\text{m/s}$ ) and lower ( $v = 5.71 \mu\text{m/s}$ ) branches of Fig. 1, respectively, while the wave profile shown in the middle of Fig. 3 corresponds to the limit point in Fig. 1 ( $c_{\text{th}} = 0.366 \mu\text{M}$  and  $v = 23.16 \mu\text{m/s}$ ). When two wave profiles exist for fixed  $c_{\text{th}}$ , the more slowly



**Fig. 3** Three wave profiles corresponding to data on upper branch of Fig. 1 (left) at  $c_{th} = 0.2 \mu\text{M}$  ( $v = 81.98 \mu\text{m/s}$ , stable), the limit point at  $c_{th} = 0.366 \mu\text{M}$  ( $v = 23.14 \mu\text{m/s}$ , neutrally stable), and the lower branch at  $c_{th} = 0.2 \mu\text{M}$  ( $v = 5.71 \mu\text{m/s}$ , unstable)

propagating wave has a smaller pulse width than the more quickly propagating pulse. In the following section we show that the slower solution branch in Fig. 3 (right) is always unstable. The three wave profiles presented in Fig. 3 are nearly identical to profiles obtained from numerical simulations using a finite different scheme (not shown).

### 3.3 Stability of traveling pulse: arbitrary release shape

For the purposes of a linear stability analysis it is more convenient to work in terms of the original variables  $(x, t)$  rather than in the co-moving frame. Our analysis begins by noting that for known release times  $T(x)$  the solution to the FDF model with shunt (14) is

$$c(x, t) = \int_{-\infty}^t ds \int_{-\infty}^{\infty} dy G(x - y, t - s) (c_{er} - c(y, s)) \eta(s - T(y)), \tag{29}$$

where  $G(x, t)$  is the time-translation invariant Green’s function

$$G(x, t) = \frac{1}{\sqrt{4\pi Dt}} e^{-t/\tau} e^{-x^2/(4Dt)} \Theta(t). \tag{30}$$

As discussed in Sect. 3.1, we assume  $c(x, t)$  is a solitary wave solution mediated by a single release event at each spatial location with  $T(x) = x/v$  and  $c(x, T(x)) = c_{th}$ . Consequently,  $c(x, t) = c(vt - x) = c(v[t - T(x)])$  with  $c(\xi)$  given by (22).

Following [52] we consider local perturbations of the release times given by  $\tilde{T}(x) = T(x) + g(x)$  with  $g(x) = \phi(x)$  for  $x \leq 0$  and  $\phi(x)$  a prescribed, bounded function on  $(-\infty, 0]$ . Asymptotic stability then corresponds to the condition  $g(x) \rightarrow 0$  as  $x \rightarrow \infty$  for arbitrary non-uniform initial data  $\phi(x)$ . The perturbed trajectory  $\tilde{c}(x, t)$  is obtained from (29) under the replacement of  $T(x)$  by  $\tilde{T}(x)$ . To compute the perturbed trajectory to first order, we make the natural assumption that the perturbed trajectory can be approximated by a time-translation of the unperturbed trajectory so that we may write  $\tilde{c}(x, t) \approx c(x, t - g(x))$ . Evaluating  $\tilde{c}(x, \tilde{T}(x))$  under this assumption

from Eq. (29) and using  $\tilde{c}(x, \tilde{T}(x)) = c_{th} = c(x, T(x))$  leads to the condition

$$\int_{-\infty}^{x/v} ds \int_{-\infty}^{\infty} dy G(x - y, x/v - s) I'(s - y/v) [g(x) - g(y)] = 0, \tag{31}$$

where  $I(\xi) = (c_{er} - c(v\xi))\eta(\xi)$  is the release flux and the prime denotes differentiation,  $I'(\xi) = dI/d\xi$ . The stability of solutions is then determined by equation (31). More specifically, we now consider perturbations of the firing times of the form  $g(x) = e^{\lambda x}$  to obtain the characteristic equation

$$\mathcal{E}(\lambda) = \mathcal{H}(\lambda) - \mathcal{H}(0) = 0, \tag{32}$$

where

$$\mathcal{H}(\lambda) = \int_0^{\infty} ds \int_{-\infty}^{\infty} dy G(y, s) I'(y/v - s) e^{-\lambda y}. \tag{33}$$

Using the Fourier integral representation

$$G(x, t) = \int_{-\infty}^{\infty} \frac{dk}{2\pi} e^{ikx} e^{-\sigma(k)t}, \quad \sigma(k) = \frac{1}{\tau} + Dk^2, \tag{34}$$

we may also write (33) in the form

$$\mathcal{H}(\lambda) = \int_{-\infty}^{\infty} \frac{dk}{2\pi} \frac{ik \widehat{T}(k)}{\sigma(k/v + i\lambda) + ik}, \tag{35}$$

where we introduce the Fourier transform of  $I(\xi)$ ,

$$\widehat{T}(k) = \int_{-\infty}^{\infty} d\xi e^{-ik\xi} I(\xi). \tag{36}$$

Note that going from Eq. (33) to Eq. (35) requires  $\text{Re} \{ \sigma(k/v + i\lambda) \} > 0$  for all  $k$ . Since a change in stability is indicated by an eigenvalue crossing the imaginary axis, we can restrict our analysis to a region around it where  $\lambda = \nu + i\omega$  and  $\nu^2 < 1/\tau D$ .

Asymptotic stability holds if all non-zero solutions of the characteristic equation (32) have negative real part, while the existence of a solution  $\lambda = 0$  reflects the translation invariance of the underlying dynamical system. Equation (35) can be evaluated by closing the contour in the lower-half complex  $k$ -plane. Since  $I(\xi) = 0$  for  $\xi < 0$  it follows that any poles of  $\widehat{T}(k)$  lie in the upper-half complex plane and thus we only have to consider poles arising from the zeros of the function  $\sigma(k/v + i\lambda) + ik$  (see [52] for a similar calculation). However, when  $\lambda \in \mathbb{R}$  we may establish a more

general result about branch stability. Because there is always a zero eigenvalue by translation invariance, a real instability occurs when there is a repeated root of the characteristic equation, namely  $\mathcal{E}'(0) = 0$ . By differentiating the equation defining wave speed  $c(x, x/v) = c_{th}$  with respect to  $v$  it is possible to show that

$$\mathcal{E}'(0) = v^2 \frac{dc_{th}}{dv}. \tag{37}$$

By contour integration of (35) we find

$$\mathcal{H}(0) = \frac{v^2 k_+ \widehat{I}(-ivk_+)}{D k_+ - k_-}, \tag{38}$$

where  $k_{\pm}$  is given by (24) and

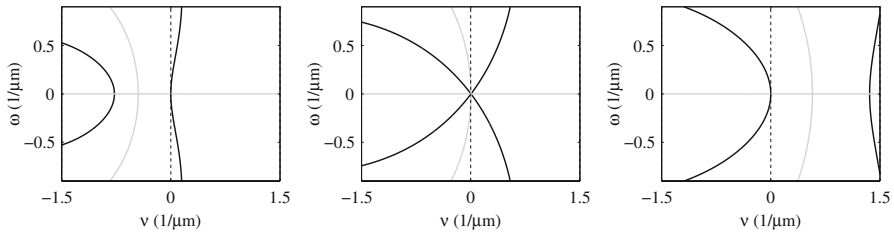
$$\widehat{I}(-ivk_+) = \int_{-\infty}^{\infty} d\xi e^{-vk_+\xi} I(\xi) = \int_0^{\infty} d\xi e^{-vk_+\xi} (c_{er} - c(v\xi))\eta(\xi). \tag{39}$$

Because the release flux  $\eta(c_{er} - c)$  reverses when  $c = c_{er}$  in the FDF model with shunt, we have that  $c(\xi) < c_{er}$  for traveling wave solutions. Using  $c(v\xi) < c_{er}$  in (38) and (39) we see that  $\widehat{I}(-ivk_+) > 0$  and  $\mathcal{H}(0) > 0$ , and hence  $\lim_{\lambda \rightarrow \infty} \mathcal{E}(\lambda) = -\mathcal{H}(0) < 0$ . Consequently, if  $\mathcal{E}'(0) > 0$  there is a positive root of  $\mathcal{E}(\lambda)$  that indicates an unstable solution. Thus we find from Eq. (37) that there is a change of stability at a limit point of a solution branch in the  $(v, c_{th})$  plane. We see that the lower of the two solution branches shown in Fig. 1 (left) is unstable to firing perturbations of the form  $g(x) = e^{\lambda x}$  when  $\lambda \in \mathbb{R}$ .

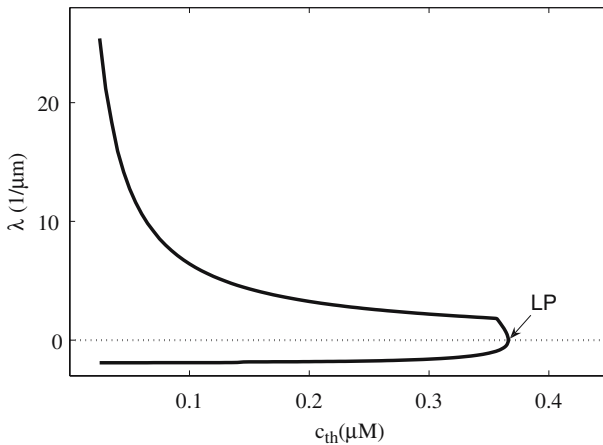
To determine whether there are dynamic instabilities in the traveling wave solution we must establish whether there are any non-zero solutions for  $\omega$  of the equation  $\mathcal{E}(i\omega) = 0$  along a solution branch. A practical way to explore this spectral problem is to introduce  $P(v, \omega) = \text{Re } \mathcal{E}(v + i\omega)$  and  $Q(v, \omega) = \text{Im } \mathcal{E}(v + i\omega)$ . The zero-contours of  $P$  and  $Q$  can then be found numerically and plotted in the  $(v, \omega)$  plane; where the two contours cross determines a zero of the complex function  $\mathcal{E}(\lambda)$  and hence an eigenvalue. Figure 4 uses this approach to show stability functions for the pulse solutions of Fig. 3. Notice that upon lowering the velocity, an eigenvalue crosses from the left to the right in the complex plane along the real axis, indicating a change of stability. Figure 5 summarizes this behavior by plotting the real-valued critical eigenvalue  $\lambda$  as a function of the threshold for  $\text{Ca}^{2+}$  release,  $c_{th}$ . Note that the eigenvalue changes sign at  $c_{th} = 0.366 \mu\text{M}$ , which coincides with the limit point in Fig. 1 (left) as expected.

### 4 The bidomain model

While in the previous section we considered a single domain FDF model that included a shunt for  $\text{Ca}^{2+}$  release, this section focuses on the bidomain FDF model (9) in which the ER  $[\text{Ca}^{2+}]$  is a dynamic variable,  $c_{er}(x, t)$ . Our analysis of the bidomain FDF model includes a derivation of an equation for the speed of a traveling pulse or front



**Fig. 4** Three stability functions, corresponding to data on upper branch of Fig. 1 (left) at  $c_{th} = 0.36 \mu\text{M}$ , the limit point and the lower branch at  $c_{th} = 0.36 \mu\text{M}$ . Solid black lines refer to the zero contour of  $\text{Re } \mathcal{E}(\lambda)$  and solid grey lines to the zero contour of  $\text{Im } \mathcal{E}(\lambda)$ , respectively



**Fig. 5** Critical eigenvalue  $\lambda$  as function of the threshold  $c_{th}$  using parameter as in Fig. 1 (left). As the branch of solutions in Fig. 1 is traversed from the upper to lower branch the critical eigenvalue changes from negative to positive, with a zero at the limit point ( $LP$ ). Hence, the fast (slow) branch of traveling pulse solutions is stable (unstable)

with arbitrary release shape (Sect. 4.1), representative traveling and standing waves mediated by square-pulse  $\text{Ca}^{2+}$  release (Sect. 4.2), and an analysis of the stability of propagating waves (Sect. 4.3).

### 4.1 Speed of traveling pulse: arbitrary release shape

We proceed along the same lines as in Sect. 3.1 and write the original equations in the co-moving frame. Using  $\xi = vt - x$  as above,  $(c, c_{er}) = (c(\xi, t), c_{er}(\xi, t))$  satisfies

$$\left(\frac{\partial}{\partial t} + v \frac{\partial}{\partial \xi}\right) c = D \frac{\partial^2 c}{\partial \xi^2} - \left(\frac{c}{\tau} - \frac{c_{er}}{\tau_{er}}\right) + \eta(\xi/v)(c_{er} - c), \tag{40a}$$

$$\left(\frac{\partial}{\partial t} + v \frac{\partial}{\partial \xi}\right) c_{er} = D_{er} \frac{\partial^2 c_{er}}{\partial \xi^2} - \frac{1}{\gamma} \left(\frac{c_{er}}{\tau_{er}} - \frac{c}{\tau}\right) + \frac{1}{\gamma} \eta(\xi/v)(c - c_{er}). \tag{40b}$$

A stationary profile  $(c(\xi, t), c_{er}(\xi, t)) = (c(\xi), c_{er}(\xi))$  in the co-moving frame satisfies the system of ordinary differential equations  $d_\xi \mathbf{x} = A(\xi)\mathbf{x}$ , where  $\mathbf{x} = (c, z, c_{er}, z_{er})^T$  and

$$A(\xi) = \begin{bmatrix} m_-(\xi) & 1 & 0 & 0 \\ 0 & m_+(\xi) & \beta(\xi) & 0 \\ 0 & 0 & m_-^{er}(\xi) & 1 \\ \alpha(\xi) & 0 & 0 & m_+^{er}(\xi) \end{bmatrix}, \tag{41}$$

with  $m_\pm(\xi)$  given by (17) and  $m_\pm^{er}(\xi)$  given by

$$m_\pm^{er}(\xi) = \frac{v \pm \sqrt{v^2 + 4\epsilon_{er}(\xi)D_{er}}}{2D_{er}}, \quad \epsilon_{er}(\xi) = \frac{1}{\gamma} \left( \frac{1}{\tau_{er}} + \eta(\xi/v) \right), \tag{42}$$

and  $\alpha(\xi)$  and  $\beta(\xi)$  as

$$\alpha(\xi) = -\frac{1}{\gamma D_{er}} \left( \frac{1}{\tau} + \eta(\xi/v) \right), \quad \beta(\xi) = -\frac{1}{D} \left( \frac{1}{\tau_{er}} + \eta(\xi/v) \right). \tag{43}$$

The solution for  $\mathbf{x}(\xi)$  takes the form  $\mathbf{x}(\xi) = G(\xi, 0)\mathbf{x}(0)$  where

$$G(\xi, \xi') = \mathcal{T} \left\{ \exp \int_{\xi'}^{\xi} ds A(s) \right\}, \tag{44}$$

and the symbol  $\mathcal{T}$  denotes the time-ordering operator, that is,

$$\mathcal{T}[A(\xi)A(\xi')] = A(\xi)A(\xi')\Theta(\xi - \xi') + A(\xi')A(\xi)\Theta(\xi' - \xi). \tag{45}$$

As in Sect. 3.1 the traveling wave solution is completed by ensuring that solutions are bounded as  $\xi \rightarrow \pm\infty$  subject to  $c(0) = c_{th}$ . Note that this construction assumes that the diffusion coefficient for  $Ca^{2+}$  in the ER is greater than zero ( $D_{er} > 0$ ) so that (42) is defined. However, traveling pulses with finite velocity can be constructed when  $D_{er} = 0$  by deriving a  $3 \times 3$  analogue of (41) (not shown).

### 4.2 A conserved quantity in the co-moving frame

The structure of  $A$  entails that  $\det A = m_+m_-m_+^{er}m_-^{er} - \alpha\beta = 0$  for all possible release shapes. Consequently, one of the eigenvalues of  $A$  is always zero. Denoting this zero eigenvalue as  $\lambda_1$ , we also note that  $\lambda_2 + \lambda_3 + \lambda_4 = m_+ + m_- + m_+^{er} + m_-^{er} > 0$  and  $\lambda_2\lambda_3\lambda_4 = m_+m_-(m_+^{er} + m_-^{er}) + m_+^{er}m_-^{er}(m_+ + m_-) < 0$  and, therefore, when the remaining three eigenvalues ( $\lambda_2, \lambda_3, \lambda_4$ ) are real, two of them are positive and the other is negative.

The physical significance of the zero eigenvalue of  $A$  is that a conserved quantity exists in the co-moving frame. In the case of square pulse  $Ca^{2+}$  release,  $\eta(t) = \bar{\eta}\Theta(t)\Theta(\Delta - t)$ , we can explicitly compute its value, because calculating the

traveling wave solution from (41–44) simplifies considerably. In this special case,  $m_+$ ,  $m_-$ ,  $m_+^{er}$ ,  $m_-^{er}$ ,  $\alpha$  and  $\beta$  are all piecewise constant, so that  $A(\xi)$  is also piecewise constant. Consequently, we do not have to worry about time ordering. Denoting the right eigenvectors of  $A$  and  $A^T$  by  $\mathbf{v}_i$  and  $\mathbf{u}_i$  respectively, with corresponding eigenvalues  $\lambda_i$ , we may write  $G(\xi) = P e^{\Lambda \xi} P^{-1}$  where  $P = [\mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3, \mathbf{v}_4]$ ,  $P^{-1} = [\mathbf{w}_1, \mathbf{w}_2, \mathbf{w}_3, \mathbf{w}_4]^T$ ,  $\mathbf{w}_i = \mathbf{u}_i / (\mathbf{u}_i^T \mathbf{v}_i)$  and  $\Lambda = \text{diag}[\lambda_1, \lambda_2, \lambda_3, \lambda_4]$ . The right eigenvectors  $\mathbf{v}_i$  and  $\mathbf{u}_i$  are given explicitly by

$$\mathbf{v}_i = \begin{bmatrix} 1 \\ \lambda_i - m_- \\ (\lambda_i - m_+)(\lambda_i - m_-)/\beta \\ \alpha/(\lambda_i - m_+^{er}) \end{bmatrix}, \quad \mathbf{u}_i = \begin{bmatrix} 1 \\ 1/(\lambda_i - m_+) \\ (\lambda_i - m_+^{er})(\lambda_i - m_-)/\alpha \\ (\lambda_i - m_-)/\alpha \end{bmatrix}, \quad (46)$$

for  $i \in \{1, 2, 3, 4\}$ . Because we have set  $\lambda_1 = 0$ , the conserved quantity can be found by considering the first row of the vector  $P^{-1} \mathbf{x}$ , that is,

$$\kappa_T(\xi) = \frac{1}{\mathbf{u}_1^T \mathbf{v}_1} \left[ c(\xi) - \frac{z(\xi)}{m_+} + \frac{m_+^{er} m_-}{\alpha} c_{er}(\xi) - \frac{m_-}{\alpha} z_{er}(\xi) \right]. \quad (47)$$

This function  $\kappa_T(\xi)$  is piecewise constant in the co-moving frame and remains at a fixed level in the ranges of  $\xi$  where  $A(\xi)$  does not change. By rescaling  $\kappa_T(\xi)$  in a piecewise fashion we can construct a quantity  $\kappa(\xi)$  that is constant throughout the co-moving frame:

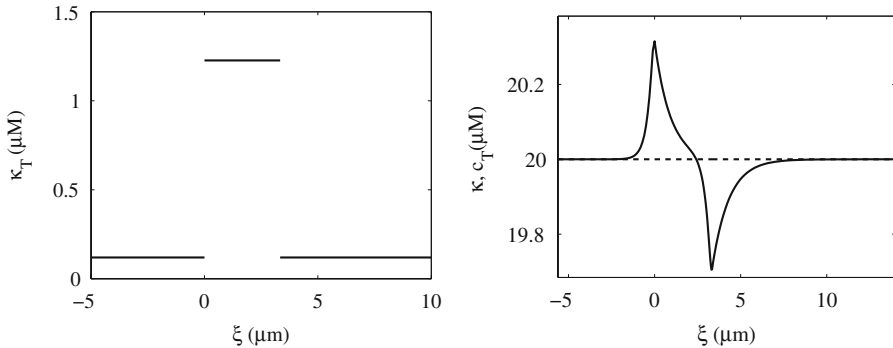
$$\kappa(\xi) = \mathbf{u}_1^T \mathbf{v}_1 \frac{m_+}{m_+ + m_-} \kappa_T(\xi). \quad (48)$$

Using Eqs. (17) and (42) as well as the definitions of  $z$  and  $z_{er}$ , equation (48) can be written as:

$$\kappa(\xi) = \left[ 1 - \frac{D}{v} d_\xi \right] c(\xi) + \gamma \left[ 1 - \frac{D_{er}}{v} d_\xi \right] c_{er}(\xi). \quad (49)$$

For a traveling pulse propagating into a region of the cell where cytosolic and ER  $[\text{Ca}^{2+}]$  are equilibrated,  $d_\xi c$  and  $d_\xi c_{er} \rightarrow 0$  as  $\xi \rightarrow -\infty$ ; similarly, as  $\xi \rightarrow \infty$  (after the wave passes) the derivative of cytosolic and ER  $[\text{Ca}^{2+}]$  in the traveling wave coordinate will be zero. By taking these limits in (49) we see that  $\kappa(\xi) = c_T^\infty$  where the total (cytosolic plus ER)  $[\text{Ca}^{2+}]$  far from the pulse is given by  $c_T^\infty = \lim_{\xi \rightarrow \pm\infty} [c(\xi) + \gamma c_{er}(\xi)] = c^\infty + \gamma c_{er}^\infty$ . For the solitary traveling pulse solutions shown below, we freely choose  $c_T^\infty$  and the parameters of the uptake flux (12), but require  $J_{\text{pump}} = 0$  as  $\xi \rightarrow \pm\infty$  so that  $c_{er}^\infty = c^\infty \tau_{er} / \tau$  and  $c^\infty = c_T^\infty / (1 + \gamma \tau_{er} / \tau)$ .

Figure 6 (left) plots  $\kappa_T(\xi)$  for a solitary traveling pulse using a cytosolic  $[\text{Ca}^{2+}]$  far from the pulse of  $c^\infty = 0.119 \mu\text{M}$ , which employing reuptake flux time constants of  $\tau = 0.01 \text{ s}$  and  $\tau_{er} = 10 \text{ s}$  results in  $c_{er}^\infty = 119.28 \mu\text{M}$  and  $c_T^\infty = 20 \mu\text{M}$ . The piecewise constant function  $\kappa_T(\xi)$  has the same value in the wake as in the front of the pulse due to  $c(-\infty) = c(\infty)$  and  $c_{er}(-\infty) = c_{er}(\infty)$  at a fixed value of  $c_T^\infty$ . The dotted line in Fig. 6 (right) shows the constant function  $\kappa(\xi) = c_T^\infty = 20 \mu\text{M}$ . The solid line in Fig. 6 (right) shows the total  $[\text{Ca}^{2+}]$  in the traveling wave coordinate  $c_T(\xi)$  asymptotically approaching  $c_T^\infty$ . Note that  $c_T(\xi)$  is elevated near the wave front



**Fig. 6** (Left) The piecewise continuous function  $\kappa_T(\xi)$  given by (47). (Right) The total  $\text{Ca}^{2+}$  concentration in the traveling wave coordinate  $c_T(\xi)$  (solid line) is plotted along with the conserved quantity  $\kappa(\xi) = c_T^\infty$  (dashed line) given by (49). Parameters:  $D = 30 \mu\text{m}^2\text{s}^{-1}$ ,  $\Delta = 0.05 \text{ s}$ ,  $\tau = 0.01 \text{ s}^{-1}$ ,  $D_{\text{er}} = 5 \mu\text{m}^2\text{s}^{-1}$ ,  $\tau_{\text{er}} = 10 \text{ s}^{-1}$ ,  $\bar{\eta} = 1 \text{ s}^{-1}$ ,  $\gamma = 0.167$ ,  $c_{\text{th}} = 0.4 \mu\text{M}$ ,  $c^\infty = 0.119 \mu\text{M}$

and depressed near the wave back, consistent with observations in bidomain models with Hodgkin–Huxley-like gating variables [40,43].

### 4.3 Square pulse release: speed of traveling pulse and wave profiles

In order to construct traveling wave solutions mediated by square pulse release, we denote the piecewise constant matrix  $A$  (41) by  $A^\infty$  when  $\xi \notin (0, v\Delta)$  and use similar superscripts to label the associated eigenvectors and eigenvalues. It is also convenient to introduce the sets  $\mathcal{J}_\pm$  defined by

$$\mathcal{J}_- = \{j \mid \lambda_j \geq 0\}, \quad \mathcal{J}_+ = \{j \mid \lambda_j \leq 0\}. \tag{50}$$

In this way we may write a bounded solution as  $\mathbf{x} = (x_1, x_2, x_3, x_4)^T = (c, z, c_{\text{er}}, z_{\text{er}})^T$  where

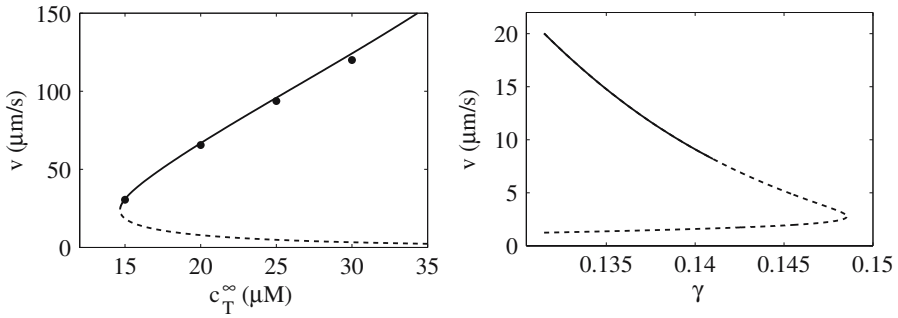
$$x_i(\xi) = \begin{cases} \sum_{j \in \mathcal{J}_-} a_j^- G_{ij}^\infty(\xi), & \xi \leq 0, \\ \sum_j a_j G_{ij}(\xi), & 0 < \xi < v\Delta, \\ \sum_{j \in \mathcal{J}_+} a_j^+ G_{ij}^\infty(\xi), & \xi \geq v\Delta, \end{cases} \tag{51}$$

with the still unknown set of coefficients  $\{a_j^-, a_j, a_j^+\}$ . Note that the components of  $G^\infty(\xi)$  are  $[P^\infty e^{\Lambda^\infty \xi} (P^\infty)^{-1}]_{ij}$ , where  $[e^{\Lambda^\infty \xi}]_{ij} = \delta_{ij} e^{\lambda_i^\infty \xi} \Theta(-\lambda_i^\infty \xi)$ ,  $\Lambda^\infty = \text{diag}[\lambda_1^\infty, \lambda_2^\infty, \lambda_3^\infty, \lambda_4^\infty]$ , and  $P^\infty$  is given by (46) with the substitution of  $\lambda_i^\infty$  for  $\lambda_i$ . To ensure that both  $c(\xi)$  and  $c_{\text{er}}(\xi)$  are  $C^1$  functions we need to match  $x_i$  and  $dx_i/d\xi$  at  $\xi = 0$  and  $\xi = v\Delta$  for  $i = 1, 3$ . Introducing  $H_{ij} = dG_{ij}/d\xi$  and  $H_{ij}^\infty = dG_{ij}^\infty/d\xi$  the eight matching conditions are

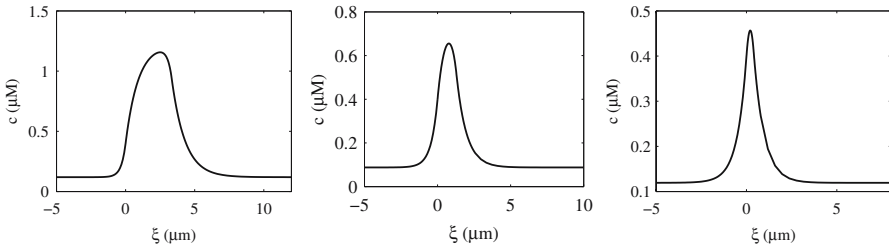
$$\sum_{j \in \mathcal{J}_-} a_j^- G_{ij}^\infty(0) = \sum_j a_j G_{ij}(0), \quad \sum_j a_j G_{ij}(v\Delta) = \sum_{j \in \mathcal{J}_+} a_j^+ G_{ij}^\infty(v\Delta), \tag{52}$$

$$\sum_{j \in \mathcal{J}_-} a_j^- H_{ij}^\infty(0) = \sum_j a_j H_{ij}(0), \quad \sum_j a_j H_{ij}(v\Delta) = \sum_{j \in \mathcal{J}_+} a_j^+ H_{ij}^\infty(v\Delta), \tag{53}$$





**Fig. 7** Speed of a solitary pulse in the bidomain model with square pulse release given by  $\eta(t) = \bar{\eta}(c_{er} - c)$  as a function of total  $[Ca^{2+}]$  far from the pulse ( $c_T^\infty$ , left) and the ER volume fraction ( $\gamma$ , right). Solid and dashed lines denote stable and unstable solutions, respectively. Filled circles indicate simulations results using a finite difference numerical scheme. Parameters (left):  $\Delta = 0.05$  s,  $D_{er} = 5 \mu m^2 s^{-1}$ ,  $\gamma = 0.167$ ,  $c_{th} = 0.4 \mu M$ ,  $\tau_{er} = 10 s^{-1}$ . Parameters (right):  $\Delta = 3$  s,  $\tau = 0.01 s^{-1}$ ,  $D_{er} = 2 \mu m^2 s^{-1}$ ,  $c_T^\infty = 2 \mu M$ ,  $c_{th} = 0.2 \mu M$ ,  $\tau_{er} = 1 s^{-1}$ . In both panels  $D = 30 \mu m^2 s^{-1}$ ,  $\tau = 0.01 s^{-1}$ ,  $\bar{\eta} = 1 s^{-1}$

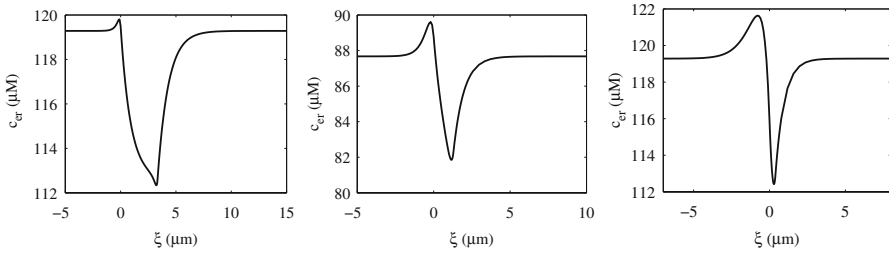


**Fig. 8** Three wave profiles corresponding to data on upper branch of Fig. 7 (left) at  $c_T^\infty = 20 \mu M$  ( $v = 66.75 \mu m/s$ , stable), the limit point at  $c_T^\infty = 14.6712 \mu M$  ( $v = 24.3 \mu m/s$ , neutrally stable), and the lower branch at  $c_T^\infty = 20 \mu M$  ( $v = 7.88 \mu m/s$ , unstable)

for  $i = 1, 3$ . If we demand that  $x_1(0) = c(0) = c_{th}$  then we may regard these nine equations as a linear system in nine unknowns (parameterized by  $v$ ) that may be solved explicitly with, e.g., Cramer’s rule. Imposing the known asymptotic value for  $c_T^\infty$  determines the unknown wave speed. Hence, in this fashion we obtain both the wave profile, given by Eq. (51), and the wave speed  $v$ , as a function of model parameters.

Figure 7 (left) shows the velocity of solitary pulses exhibited by the bidomain model with square pulse  $Ca^{2+}$  release as a function of total  $[Ca^{2+}]$  far from the pulse ( $c_T^\infty$ , left). Recalling the relationship  $c_{er}^\infty = (c_T^\infty - c^\infty)/\gamma$  we see the intuitive result that the velocity of the fast wave (solid line, see Sect. 4.6) is an increasing function of the ER  $[Ca^{2+}]$  being invaded by the wave. Figure 7 (right) shows the velocity of stable solitary pulses is a decreasing function of the ER volume fraction ( $\gamma$ ) for fixed  $c_T^\infty$ .

Figures 8 and 9 depict solitary pulse profiles corresponding to Fig. 7 (left). Note that the ER  $[Ca^{2+}]$  before and after the traveling pulse is reduced in the middle panel of Figs. 9 because the total  $[Ca^{2+}]$  used is less than that of the left and right panels ( $c_T^\infty = 14.67$  and  $20 \mu M$ , respectively).



**Fig. 9** Three luminal wave profiles corresponding to the three panels of Fig. 8

4.4 Traveling fronts with step release

In the case of release events where activated  $\text{Ca}^{2+}$  release sites do not close ( $\Delta \rightarrow \infty$ ), the release rate takes the form  $\eta(t) = \bar{\eta}\Theta(t)$  and the bidomain FDF model exhibits traveling fronts. Traveling fronts with finite velocity and non-zero diffusion coefficient for luminal  $\text{Ca}^{2+}$  ( $D_{\text{er}}$ ) can be constructed in a manner similar to that presented in the previous section. Let  $\{b_j^-, b_j^+\}$  denote a set of still unknown coefficients and  $G_{ij}^\infty$  be defined as after Eq. (51), then a front solution is given by

$$x_i(\xi) = \begin{cases} \sum_{j \in \mathcal{J}_-} b_j^- G_{ij}^\infty(\xi), & \xi < 0, \\ \sum_{j \in \mathcal{J}_+} b_j^+ G_{ij}^\infty(\xi), & \xi \geq 0. \end{cases} \tag{54}$$

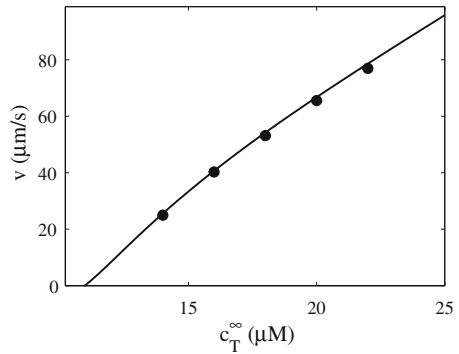
In this construction, we require the release ( $J_{\text{rel}}$ ) and reuptake ( $J_{\text{pump}}$ ) fluxes to be balanced far from the wave front so that  $[c/\tau - c_{\text{er}}/\tau_{\text{er}}] \rightarrow 0$  as  $\xi \rightarrow -\infty$  and  $[c/\tau - c_{\text{er}}/\tau_{\text{er}}] \rightarrow \bar{\eta}(c_{\text{er}} - c)$  as  $\xi \rightarrow \infty$ , that is,

$$\left(\frac{1}{\tau} + \eta(\pm\infty)\right) c(\pm\infty) = \left(\frac{1}{\tau_{\text{er}}} + \eta(\pm\infty)\right) c_{\text{er}}(\pm\infty). \tag{55}$$

Thus, while the cytosolic  $[\text{Ca}^{2+}]$  being invaded by the wave front is a free parameter,  $c(\xi = -\infty) = c^\infty$ , the ER  $[\text{Ca}^{2+}]$  at  $\xi = -\infty$  is constrained by (55) to be  $c_{\text{er}}(\xi = -\infty) = \tau_{\text{er}}c^\infty/\tau$  and the total  $[\text{Ca}^{2+}]$  is thus  $c_T^\infty = c^\infty(1 + \gamma\tau_{\text{er}}/\tau)$ . Because traveling front solutions will have the same total  $[\text{Ca}^{2+}]$  after the wave passes (see Sect. 4.2), we may also write  $c(\xi = \infty) + \gamma c_{\text{er}}(\xi = \infty) = c_T^\infty$ , which combined with (55) implies

$$\begin{aligned} c(\xi = \infty) &= \frac{(\tau_{\text{er}}^{-1} + \bar{\eta})/\gamma}{(\tau^{-1} + \bar{\eta}) + (\tau_{\text{er}}^{-1} + \bar{\eta})/\gamma} c_T^\infty, \\ c_{\text{er}}(\xi = \infty) &= \frac{(\tau^{-1} + \bar{\eta})/\gamma}{(\tau^{-1} + \bar{\eta}) + (\tau_{\text{er}}^{-1} + \bar{\eta})/\gamma} c_T^\infty. \end{aligned} \tag{56}$$

**Fig. 10** Solid line shows solitary traveling front velocity in the bidomain FDF model calculated from (54). Filled circles show results from simulations using a finite difference numerical scheme. Parameters:  $D = 30 \mu\text{m}^2\text{s}^{-1}$ ,  $\tau = 0.01 \text{ s}^{-1}$ ,  $D_{\text{er}} = 5 \mu\text{m}^2\text{s}^{-1}$ ,  $\tau_{\text{er}} = 10 \text{ s}^{-1}$ ,  $\bar{\eta} = 1 \text{ s}^{-1}$ ,  $c_{\text{th}} = 0.4 \mu\text{M}$  and  $\gamma = 0.167$



Thus, in (54) matching  $x_i$  and  $dx_i/d\xi$  at  $\xi = 0$  for  $i = 1, 3$  together with a fixed value for  $c^\infty$  (or, alternatively,  $c_T^\infty$ ) and  $x_1(0) = c(0) = c_{\text{th}}$  determines the profile and the speed of the front.

Figure 10 uses this approach to calculate the traveling front velocity ( $v$ ) as a function of total  $[\text{Ca}^{2+}]$  ( $c_T^\infty$ ). Note that when other model parameters are fixed, traveling fronts exist only above a minimal value of total  $[\text{Ca}^{2+}]$  and  $v$  is an increasing function of  $c_T^\infty$ , a parameter that increases the cytosolic and ER  $[\text{Ca}^{2+}]$  both before and after release.

#### 4.5 Standing waves with step release

In addition to traveling fronts, the bidomain model also supports standing interfaces between states of high and low  $[\text{Ca}^{2+}]$  when the  $\text{Ca}^{2+}$  release rate takes the form  $\eta(t) = \bar{\eta}\Theta(t)$ . Pinned fronts represent stationary solutions of the model equations as expressed in terms of the physical coordinates  $(x, t)$  (9). Writing  $\mathbf{y} = (c, z, c_{\text{er}}, z_{\text{er}})^T$  we find that for a standing wave pinned at  $x = 0$ ,  $d_x \mathbf{y} = B(x)\mathbf{y}$ , where  $B(x)$  has the same structure as  $A(\xi)$  in (41), but with the piecewise constant entries given by

$$m_{\pm}(x) = \pm\sqrt{\frac{1}{D}\left(\frac{1}{\tau} + \eta(x)\right)}, \quad m_{\pm}^{\text{er}}(x) = \pm\sqrt{\frac{1}{\gamma D_{\text{er}}}\left(\frac{1}{\tau_{\text{er}}} + \eta(x)\right)}, \quad (57)$$

and

$$\alpha(x) = -\frac{1}{\gamma D_{\text{er}}}\left(\frac{1}{\tau} + \eta(x)\right), \quad \beta(x) = -\frac{1}{D}\left(\frac{1}{\tau_{\text{er}}} + \eta(x)\right). \quad (58)$$

Note that each of the above expressions takes two different values as  $\eta(x)$  steps from 0 to  $\bar{\eta}$  at  $x = 0$ . It follows that  $B$  possesses two zero eigenvalues and two non-zero eigenvalues  $\pm\sigma$  where

$$\sigma(x) = -\sqrt{(m_+)^2 + (m_+^{\text{er}})^2}. \quad (59)$$

While  $B(x)$  cannot be diagonalized because there is a one-dimensional eigenspace associated with the repeated zero eigenvalue, it is similar to a Jordan normal form.

The matrix  $\tilde{P}$  that contains the generalized eigenvectors of  $B$  is given by

$$\tilde{P} = \begin{bmatrix} 1 & 1 & 0 & 1 \\ \sigma - m_- & -m_- & 1 & -(\sigma + m_-) \\ -\frac{D}{D_{er}\gamma} & \frac{m_- m_+}{\beta} & 0 & -\frac{D}{D_{er}\gamma} \\ \frac{\alpha}{\sigma - m_+^{er}} & -\frac{\alpha}{m_+^{er}} & -\frac{m_+^2}{\beta} & -\frac{\alpha}{\sigma + m_+^{er}} \end{bmatrix}, \tag{60}$$

where  $(\lambda_1, \lambda_2, \lambda_3, \lambda_4) = (\sigma, 0, 0, -\sigma)$  and we have used equation (46) and the identity  $(\sigma - m_+)(\sigma - m_-)/\beta = -D/(D_{er}\gamma)$ . A solution for  $y$  follows from the transformed system  $d_x \tilde{y} = \tilde{\Lambda} \tilde{y}$  where  $\tilde{y} = \tilde{P}^{-1} y$  and

$$\tilde{\Lambda} = \begin{bmatrix} \sigma & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\sigma \end{bmatrix}. \tag{61}$$

It is evident from equation (61) that the third component of  $\tilde{y}$  is constant. Employing

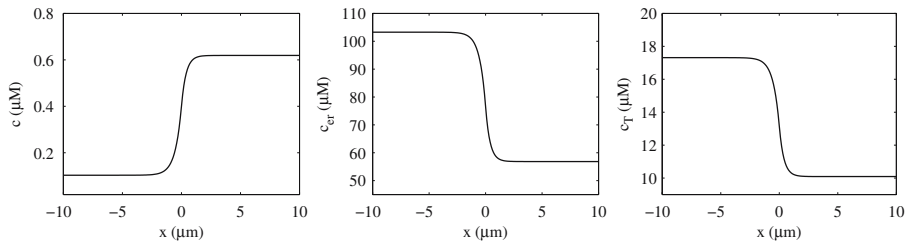
$$\tilde{P}^{-1} = \begin{bmatrix} \frac{m_+^2 (\sigma - m_+)}{2\sigma^3} & \frac{m_+^2}{2\sigma^3} & \frac{\beta(\sigma - m_+^{er})}{2\sigma^3} & \frac{\beta}{2\sigma^3} \\ \frac{(m_+^{er})^2}{\sigma^2} & 0 & -\frac{\beta}{\sigma^2} & 0 \\ \frac{(m_+^{er})^2 m_-}{\sigma^2} & \frac{(m_+^{er})^2}{\sigma^2} & \frac{\beta m_+^{er}}{\sigma^2} & -\frac{\beta}{\sigma^2} \\ \frac{m_+^2 (\sigma + m_+)}{2\sigma^3} & -\frac{m_+^2}{2\sigma^3} & \frac{\beta(\sigma + m_+^{er})}{2\sigma^3} & -\frac{\beta}{2\sigma^3} \end{bmatrix}, \tag{62}$$

we find that  $\tilde{y}_3 = 0$  and, consequently,  $\tilde{y}_2$  is piecewise constant with a step discontinuity at  $x = 0$ , that is,

$$\tilde{y}_2(x) = \frac{1}{\sigma^2} \left[ (m_+^{er})^2 c(x) - \beta c_{er}(x) \right] = \begin{cases} c(-\infty), & x < 0, \\ c(+\infty), & x \geq 0, \end{cases} \tag{63}$$

where the second equality is determined by evaluating  $\tilde{y}_2$  at  $x = \pm\infty$  where the release and reuptake fluxes are assumed to be balanced (55). Note that equation (63) only establishes a relation between  $\tilde{y}_2$  and the cytosolic  $[Ca^{2+}]$  at the boundary, but the latter is still undetermined.

Also note that by multiplying (9b) with  $\gamma$  and then adding the resulting expression to (9a), we see that the stationary solution of (9) satisfies  $Dc + \gamma D_{er}c_{er} = ax + b$  where  $a$  and  $b$  are constants. Assuming no longitudinal fluxes for  $c$  and  $c_{er}$  far from the pinned wave front we have  $a = 0$ . The constant  $b$  can be related to  $c(-\infty)$  by evaluating  $Dc + \gamma D_{er}c_{er}$  as  $x \rightarrow -\infty$  where from (55) we have  $c_{er}(-\infty) = c(-\infty)\tau_{er}/\tau$ , that



**Fig. 11** Front profiles in the cytosol (*left*) and the lumen (*middle*) as well as the total  $\text{Ca}^{2+}$  concentration (*right*) for a pinned wave. Parameter values as in Fig. 10

is,  $b = [D + \gamma D_{er} \tau_{er} / \tau] c(-\infty)$ . But  $b$  can also be related to  $c(\infty)$  by evaluating  $Dc + \gamma D_{er} c_{er}$  as  $x \rightarrow \infty$  where from (55) we have  $c_{er}(\infty) = c(\infty)(\tau^{-1} + \bar{\eta}) / (\tau_{er}^{-1} + \bar{\eta})$ , that is,  $b = [D + \gamma D_{er}(\tau^{-1} + \bar{\eta}) / (\tau_{er}^{-1} + \bar{\eta})] c(\infty)$ . Thus,  $c(-\infty)$  and  $c(\infty)$  are linearly related through

$$\left[ D + \gamma D_{er} \frac{\tau_{er}}{\tau} \right] c(-\infty) = \left[ D + \gamma D_{er} \frac{\tau^{-1} + \bar{\eta}}{\tau_{er}^{-1} + \bar{\eta}} \right] c(\infty). \tag{64}$$

Recalling  $y = \tilde{P}\tilde{y}$ , we immediately find that

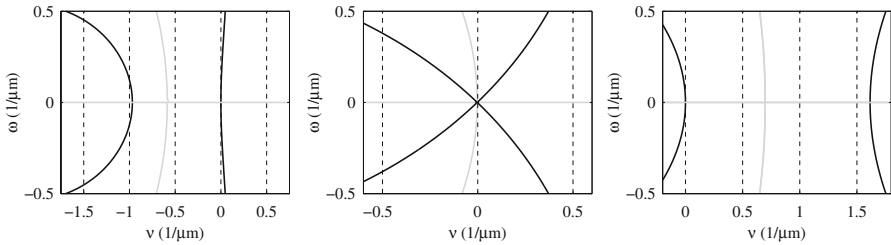
$$c(x) = \begin{cases} c(-\infty) + a^- \exp(-\sigma x), & x \leq 0, \\ c(\infty) + a^+ \exp(\sigma x), & x > 0, \end{cases} \tag{65}$$

with the three unknowns  $c(-\infty)$ ,  $a^-$  and  $a^+$  due to Eq. (64). These three remaining unknowns are determined by demanding that  $c$  is  $C^1$  and  $c(0) = c_{th}$ . Note that for the standing wave solutions there are two distinct total  $\text{Ca}^{2+}$  concentrations far from the pinned front, that is,  $\lim_{x \rightarrow -\infty} c_T(x) \neq \lim_{x \rightarrow \infty} c_T(x)$  where  $c_T = c + \gamma c_{er}$ . For any given threshold concentration  $c_{th}$ , there is exactly one pinned solution of Eq. (9) for nonzero  $D_{er}$ . Figure 11 shows an example for a pinned front that illustrates the different values of the total  $\text{Ca}^{2+}$  concentration in the front and the wake of the wave.

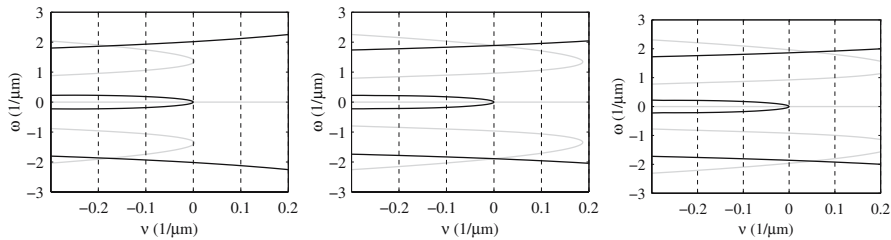
#### 4.6 Stability of traveling waves

Proceeding along similar lines to Sect. 3.3 and linearizing around a traveling wave solution  $(c(\xi), c_{er}(\xi))$  we find that the characteristic equation (32) has the same form as before under the replacement of  $G(x, t)$  by  $G_{11}(x, t) - \gamma^{-1}G_{12}(x, t)$  and  $I(\xi)$  by  $(c_{er}(v\xi) - c(v\xi))\eta(\xi)$  in equation (33). We refer the reader to the Appendix for details and a definition of  $G_{ij}(x, t)$ ,  $i, j = 1, 2$ .

Figure 12 shows three stability functions for the speed curve depicted in Fig. 7 (left). Upon decreasing traveling front velocity  $v$ , an eigenvalue crosses to the right hand of the complex plane along the real axis, signaling a change of stability. As with the shunt model, there is always a zero eigenvalue reflecting translational invariance and, consequently, the point of stability exchange is characterized by a repeated zero eigenvalue.



**Fig. 12** Stability plots for data on upper branch at  $c_T^\infty = 15 \mu\text{M}$  (left), the limit point (middle) and the lower branch at  $c_T^\infty = 15 \mu\text{M}$  (right) of Fig. 7 (left). Solid black lines refer to the zero contour of  $\text{Re } \mathcal{E}(\lambda)$  and solid grey lines to the zero contour of  $\text{Im } \mathcal{E}(\lambda)$ , respectively. Hence, slow pulses in the full bidomain model are unstable

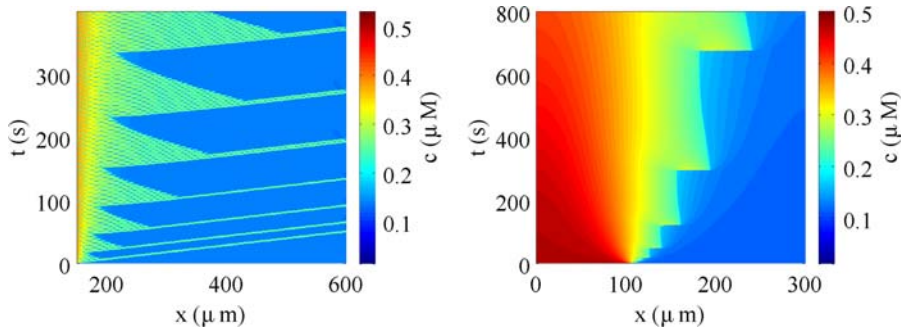


**Fig. 13** Dynamic instability illustrated by stability functions that correspond to the upper branch of Fig. 7 (right) for  $\gamma = 0.1405$  (right),  $\gamma_{\text{crit}} = 0.14098$  (middle), and  $\gamma = 0.1411$  (right). Solid black lines refer to the zero contour of  $\text{Re } \mathcal{E}(\lambda)$  and solid grey lines to the zero contour of  $\text{Im } \mathcal{E}(\lambda)$ , respectively. Hence, fast pulses in the full bidomain model may undergo dynamic instabilities (since a pair of eigenvalues may cross through the imaginary axis)

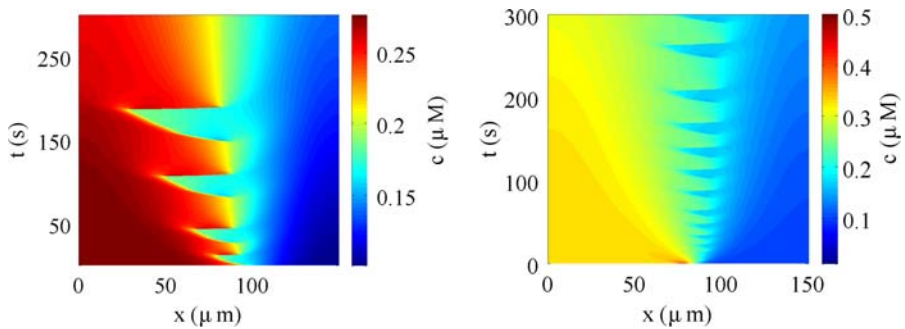
Importantly, the bidomain model also supports dynamic instabilities. For example, Fig. 13 shows three stability functions that correspond to the speed curve of Fig. 7 (right). When the ER to cytosol volume ratio  $\gamma$  is increased, an eigenvalue crosses the imaginary axis at a non-zero value of  $\omega = \text{Im}(\lambda)$ . We therefore expect oscillatory perturbations with a frequency  $\omega$  to grow, leading to solutions with a non-constant profile in the traveling wave frame that periodically vary around the unstable fast wave. This is confirmed in direct numerical simulations, where we see the emergence of ‘back-and-forth’ waves (like those in Figs. 14 and 15). We note that the frequency of oscillations determined from the linear stability analysis is not a strong predictor of the frequencies seen in numerical simulations of the full nonlinear model, suggesting that these wave bifurcations are sub-critical in nature.

#### 4.7 Numerical simulations of tango waves

As mentioned above, many of the analytical results obtained here have been validated against simulations that integrate (9) using a finite difference numerical scheme. For example, the filled circles in Figs. 7 and 10 show numerically calculated wave speeds that closely follow the analytical results (solid lines). Moreover, perturbations of front and pulse solutions that are predicted to be linearly stable were found to decay in numerical simulations, thereby supporting the results of Sect. 4.6 (not shown).



**Fig. 14** Tango waves in the vicinity of the point of instability shown in the right panel of Fig. 7. Parameters as previous figure with  $\tau_R = 0.5$  s (left) and  $\tau_R = 0$  s (right). The pseudocolour plot shows  $c(x, t)$  in  $\mu\text{M}$



**Fig. 15** Reversed tango waves for two different initial  $\text{Ca}^{2+}$  concentration profiles. The pseudocolour plot shows  $c(x, t)$  in  $\mu\text{M}$ . Parameter values are  $D = 30 \mu\text{m}^2\text{s}^{-1}$ ,  $\tau = 0.01 \text{ s}^{-1}$ ,  $D_{\text{er}} = 0.25 \mu\text{m}^2\text{s}^{-1}$ ,  $\tau_{\text{er}} = 0.5 \text{ s}^{-1}$ ,  $\bar{\eta} = 1 \text{ s}^{-1}$ ,  $\Delta = 0.5 \text{ s}$ ,  $\gamma = 0.167$ ,  $c_{\text{th}} = 0.2 \mu\text{M}$ , and  $c_T^\infty = 0.9382 \mu\text{M}$

Interestingly, Figures 14 and 15 show complex cytosolic profiles that result when the same perturbations are applied to the bidomain FDF model with parameters chosen near a point of dynamical instability. In contrast to pulse and front solutions that travel with a constant speed in one direction, in these cases we observe waves that propagate in a back-and-forth manner and are reminiscent of a dynamical phenomenon first reported in [40] and dubbed ‘tango waves’.

Using release duration of  $\Delta = 3$  s and refractory period of  $\tau_R = 0.5$  s, Fig. 14 (left) resembles earlier findings, especially with respect to the wave form and to the emergence of additional pulses. Whenever a tango wave reverses its direction after invading the low  $[\text{Ca}^{2+}]$  region, traveling pulses are released that travel to the right with constant speed. While the first four tango waves initiate only one pulse, the following three tango waves give rise to two pulses each. Figure 14 (right) shows the form of the tango wave changing appreciably when the ER to cytosol volume fraction  $\gamma$  is increased from 0.138 to 0.160 and the refractory period is set to zero. In this case the tango wave front is more compact, the amplitude of the back-and-forth movement is much smaller, and no pulses are released.

Figure 15 illustrates that tango waves possess a larger variety of forms than already suggested by Fig. 14. Although moving in the reverse direction, the shape of the moving edge in Fig. 15 (left) is similar to the one in Fig. 14 (left). A comparison

between the two panels in Fig. 15 reveals that the wave front is moving in opposite directions, that is, the state of low  $[\text{Ca}^{2+}]$  will eventually occupy the whole space in Fig. 15 (left), while the same is true for the state of elevated  $[\text{Ca}^{2+}]$  in Fig. 15 (right). Both simulations are based on the same parameter values, but on different initial conditions.

All initial conditions were set up using the same protocol. We first prepared piecewise constant concentration profiles in the cytosol and the lumen, respectively. In one part, the cytosolic and the luminal  $\text{Ca}^{2+}$  concentrations were determined by  $c_T^\infty$  through  $c^\infty = c_T^\infty / (1 + \gamma \tau_{\text{er}} / \tau)$  and  $c_{\text{er}}^\infty = c^\infty \tau_{\text{er}} / \tau$ . In the other part, we chose a cytosolic  $\text{Ca}^{2+}$  concentration above threshold and put the luminal concentration to a multiple of the of  $c_{\text{er}}^\infty$ . Then, we increased the concentration step in the ER even further by adding or subtracting appropriately chosen exponentials in the high concentration part and low concentration part, respectively. The decay constants of these exponentials were such that the contribution was restricted around the initial step. Different initial conditions varied in the extent and the size of the gap between cytosolic and ER calcium concentration levels.

## 5 Summary and discussion

We have presented and analyzed a bidomain FDF model that extends the formalism introduced in [49–52] to include the effect of shunting  $\text{Ca}^{2+}$  release and depletion of ER  $[\text{Ca}^{2+}]$ . Although the mathematical analysis is more complicated than in the single domain case, modeling  $\text{Ca}^{2+}$  release as a threshold process allows the explicit construction of traveling wave solutions in the single domain model with shunt (Sect. 3) as well as the full bidomain FDF model (Sect. 4). To our knowledge this is first demonstration that the threshold-release formalism can be applied to analyze propagating  $\text{Ca}^{2+}$  waves in a bidomain context.

For the single domain FDF model with shunt, our analytical results indicate that the propagation velocity of stable solitary pulses mediated by square pulse release is a decreasing function of the cytosolic threshold for  $\text{Ca}^{2+}$  release ( $c_{\text{th}}$ ) and an increasing function of the luminal  $[\text{Ca}^{2+}]$  ( $c_{\text{er}}$ ) (Fig. 1). For fixed  $c_{\text{th}}$  and  $c_{\text{er}}$ , we found that the minimum stable wave speed decreases as the release rate  $\bar{\eta}$  decreases even when release duration  $\Delta$  is increased to maintain fixed cumulative release  $\Delta \bar{\eta}$  (Fig. 2). Linear stability analysis of the single domain FDF model with shunt shows that when multiple traveling pulse solutions coexist, the faster wave is stable while the slower wave is unstable (Sect. 3.3).

In the case of the full bidomain FDF model, we found that the propagation velocity of stable solitary pulses mediated by square pulse release is an increasing function of the total  $[\text{Ca}^{2+}]$  ( $c_T^\infty$ ). For fixed background cytosolic  $[\text{Ca}^{2+}]$  ( $c^\infty$ ), the requirement that the cytosolic and ER  $[\text{Ca}^{2+}]$  be in equilibrium in the spatial region being invaded by the wave means that this total  $[\text{Ca}^{2+}]$  is proportional to the ER  $[\text{Ca}^{2+}]$ ; thus, the observation of Fig. 7 (left) is simply that the propagation velocity of stable waves in the bidomain model increases with increasing ER  $[\text{Ca}^{2+}]$ . Linear stability analysis of the bidomain FDF model shows that when multiple traveling pulse solutions coexist, the faster wave is stable while the slower wave is unstable and, furthermore, the faster stable waves have larger pulse width (Fig. 8). In the case of traveling fronts in the



bidomain FDF model we found that the propagation velocity of stable solitary fronts mediated by step release is an increasing function of the total  $[Ca^{2+}]$  ( $c_7^\infty$ ) (Fig. 10). As presented in Sect. 4.5, we were also able to construct standing front solutions in the bidomain FDF model with step release.

Interestingly, the linear stability analysis of the bidomain FDF model presented in Sect. 4.6 shows both saddle-node (Fig. 12) and dynamic (Fig. 13) instabilities (on the fast branch of traveling wave solutions), the latter of which we identify with the emergence of so-called tango waves that propagate in a back-and-forth manner. The presence of tango waves was confirmed in numerical simulations (Figs. 14 and 15).

While the threshold-release framework is somewhat more idealized than the more conventional approach to modelling  $Ca^{2+}$  release by including gating variables for the activation and inactivation of intracellular  $Ca^{2+}$  channels, the FDF scheme has some advantages. For example, the stability analysis presented in Sect. 4.6 explains that the emergence of tango waves does not require any assumptions about the relative size of the cytosolic and ER  $Ca^{2+}$  diffusion coefficients, nor does this analysis assume that the basic wave which tango waves bifurcate from is stationary (cf. [40,43,58,59]). It is also important to point out that some previous bifurcation analysis of stationary pulses that is relevant to bidomain models exhibiting tango waves has been possible only by prescribing a spatially inhomogeneous forcing term or a spatial variation of model parameters [43,58,59]. Notably, the tango waves presented here do not involve spatially inhomogeneous model parameters and, furthermore, the linear stability analysis presented in Sect. 4.6 that explains the emergence of tango waves does so by determining the spatial profiles of cytosolic and ER  $[Ca^{2+}]$  self-consistently. This allows us to make a quantitative connection between bifurcation parameter sets in our analytical work and in numerical simulation.

In the bidomain FDF model we observed an increase in the luminal  $[Ca^{2+}]$  at the leading edge of the wave front which extends as far as the increase in the cytosolic  $[Ca^{2+}]$  that triggers release (Fig. 9), in spite of the fact that the ER diffusion coefficient was 6 times smaller than the cytosolic diffusion coefficient ( $D_{er} = 5 \mu m^2 s^{-1}$  and  $D = 30 \mu m^2 s^{-1}$ , respectively). This observation suggests that the bidomain FDF formalism could be extended to include a threshold for  $Ca^{2+}$  release ( $c_{th}$ ) that is a function of the ER  $[Ca^{2+}]$  ( $c_{er}$ ) and used to analyze the consequences of luminal regulation of  $Ca^{2+}$  release on the properties of  $Ca^{2+}$  waves [60]. In particular, a bidomain FDF model that includes luminal regulation of  $Ca^{2+}$  release threshold might give insight into when (if ever) the traditional concept of  $Ca^{2+}$  wave propagation—waves driven by  $Ca^{2+}$ -induced  $Ca^{2+}$  release at the cytosolic wave front—must be augmented with the idea of ‘sensitization wave fronts’ in which  $Ca^{2+}$  uptake via pumps at the leading edge of a wave and luminal  $Ca^{2+}$  diffusion results in  $Ca^{2+}$  release mediated by sensitization of intracellular channels to cytosolic  $Ca^{2+}$  [61]. This is an area of ongoing research and will be reported upon elsewhere.

## Appendix

Here we present the details of the stability analysis used in Sect. 4.6. Proceeding along the same lines as in Sect. 3.3 we express the cytosolic and the luminal  $Ca^{2+}$  concentration profiles as

$$\begin{bmatrix} c(x, t) \\ c_{er}(x, t) \end{bmatrix} = \int_{-\infty}^t ds \int_{-\infty}^{\infty} dy G(x - y, t - s) \begin{bmatrix} 1 \\ -1/\gamma \end{bmatrix} \times \eta(s - T(y))(c_{er}(y, s) - c(y, s)), \tag{66}$$

where  $G(x, t)$  is now a  $2 \times 2$  matrix with components  $G_{ij}(x, t)$ ,  $i, j = 1, 2$ , that correspond to the Green's function of the matrix operator

$$\mathcal{L} = \begin{bmatrix} \partial_t - D\partial_{xx} + 1/\tau & -1/\tau_{er} \\ -1/(\gamma\tau) & \partial_t - D_{er}\partial_{xx} + 1/(\gamma\tau_{er}) \end{bmatrix}. \tag{67}$$

The matrix Green's function  $G(x, t)$  can be written as an inverse Fourier transform:

$$G(x, t) = \int_{-\infty}^{\infty} \frac{dk}{2\pi} e^{ikx} e^{M(k)t}, \tag{68}$$

where

$$M(k) = \begin{bmatrix} -Dk^2 - 1/\tau & 1/\tau_{er} \\ 1/(\gamma\tau) & -D_{er}k^2 - 1/(\gamma\tau_{er}) \end{bmatrix}. \tag{69}$$

After diagonalising  $M(k)$ ,  $G(x, t)$  takes the computationally useful form

$$G(x, t) = \int_{-\infty}^{\infty} \frac{dk}{2\pi} e^{ikx} P(k)e^{\Lambda(k)t} P^{-1}(k). \tag{70}$$

Introducing  $\sigma(k) = \tau^{-1} + Dk^2$  and  $\sigma_{er}(k) = (\gamma\tau_{er})^{-1} + D_{er}k^2$ , the eigenvalues of  $M(k)$  are given by

$$\lambda_{\pm}(k) = -\frac{1}{2} \left\{ \sigma(k) + \sigma_{er}(k) \pm \sqrt{(\sigma(k) - \sigma_{er}(k))^2 + 4/(\gamma\tau\tau_{er})} \right\}, \tag{71}$$

so that

$$\Lambda(k) = \begin{bmatrix} \lambda_+(k) & 0 \\ 0 & \lambda_-(k) \end{bmatrix}, \tag{72}$$

and

$$P(k) = \begin{bmatrix} 1 & 1 \\ \tau_{er}[\sigma(k) + \lambda_+(k)] & (\tau\gamma[\sigma_{er}(k) + \lambda_-(k)])^{-1} \end{bmatrix}, \tag{73}$$

holds the eigenvectors of  $M(k)$ . Performing a linear stability analysis of (66) around a traveling wave solution in an identical fashion to that of Sect. 3.3 we find

$$\begin{aligned} & \int_{-\infty}^{x/v} ds \int_{-\infty}^{\infty} dy [G_{11}(x - y, x/v - s) - \gamma^{-1}G_{12}(x - y, x/v - s)] \\ & \times I'(s - y/v)[g(x) - g(y)] = 0, \end{aligned} \tag{74}$$

with  $I(\xi) = (c_{\text{er}}(v\xi) - c(v\xi))\eta(\xi)$ . Hence, for the full bidomain model the characteristic equation for stability is given by (32) and (33) under the replacement of  $I(\xi)$  by  $(c_{\text{er}}(v\xi) - c(v\xi))\eta(\xi)$ , and  $G(x, t)$  by  $G_{11}(x, t) - \gamma^{-1}G_{12}(x, t)$ .

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