Using Novel Simplified Models of Excitation for Analytic Description of Initiation Propagation and Blockage of Excitation Waves

I Idris, RD Simitev, VN Biktashev

University of Liverpool, Liverpool, UK

Abstract

We consider applications of a recently suggested new asymptotic approach to detailed ionic models of cardiac excitation. First, we describe a three-variable approximation for the excitation fronts in a detailed ionic model of human atrial kinetics. It predicts not only the speed of the fronts but also a condition for failure of propagation, i.e. gives an operational definition of absolute refractoriness. This prediction is confirmed by direct simulations of the full model. Next, we consider problem of initiation of excitation waves, using a piecewise linear caricature of the I_{Na}-driven excitation front. We identify the unstable propagating front solution ("critical front") as the threshold event between successful initation and decay, which plays a role similar to the "critical nucleus" in the theory of initiation of waves in the FitzHugh-Nagumo system.

1. Introduction

The realism of computer models of excitation propagation in heart is rapidly increasing, and there exists and optimistic view that with the help of detailed cardiac computational models "it will soon be possible to do in silico experiments that would be impossible, difficult or unethical in animals or patients". However, detailed ionic models are immensely complicated, making analytical treatment impossible and simulations costly. Fully resolved three-dimensional models of human heart are still far beyond the power of current computers. Numerous attempts have been made to construct simplified mathematical models of action potentials. However a simplified model can be trusted only if it is derived from an ionic model, rather than fitted to a selected phenomenology such as AP or CV restitution curves as is the case for some popular simplified models. Attempts to use asymptotic methods are complicated by the fact that some of the important small parameters in ionic models appear in non-standard ways.

We are using a novel mathematical approach for deriving simplified models of cardiac excitation from detailed ionic models. It is based on biophysical features of such models, including those that are unsuitable for traditional asymptotic methods, such as large magnitude of the fast sodium current compared to other ionic currents, and nearly perfect switch behaviour of ionic channels.

We propose that such simplified models combine computational simplicity with trustworthiness and therefore can present an attractive alternative to detailed ionic models for large-scale simulations. In this paper, we present two examples. One is a numerically accurate model of the excitation front. It requires numerics, but only of a system of three equations rather than 21 and only of stationary front solutions. The analysis of such solutions leads to a simple operational definition of absolute refractoriness which works in non-stationary simulations of unstable spiral waves in the full ionic model. The other example is a further simplified model, which is not very good quantitatively, but is qualitatively correct and allows exact analytical solution for the stationary fronts. We use these exact solutions to reveal the nature of the critical regimes between successful initiation and decay.

2. Methods

A detailed exposition of our asymptotic approach can be found in [2]. We consider monodomain spatially extended model of human atrial tissue by Courtemanche et al [1]. The asymptotic analysis is based on assumptions about smallness of certain quantities in the equations, formalized with an explicit small parameter ϵ as:

$$\partial_t V = -C_M^{-1}\left(\frac{1}{\epsilon} I_{\mathrm{Na}}(V,m,h,j) + \Sigma'_I(V,\ldots)\right) + D\partial_x^2 V,$$

$$\partial_t m = \frac{(\overline{m}(V;\epsilon) - m)}{\epsilon\,\tau_m(V)}, \quad \overline{m}(V;0) = M(V)\theta(V - V_m),$$

$$\partial_t h = \frac{(\overline{h}(V;\epsilon) - h)}{\epsilon\,\tau_h(V)}, \quad \overline{h}(V;0) = H(V)\theta(V_h - V),$$

$$\partial_t u_a = \frac{(\overline{u_a}(V) - u_a)}{\epsilon\,\tau_{u_a}(V)},$$

$$\partial_t w = \frac{(\overline{w}(V) - w)}{\epsilon\, \tau_w(V)},$$
$$\partial_t o_a = \frac{(\overline{o_a}(V) - o_a)}{\epsilon\, \tau_{o_a}(V)},$$
$$\partial_t d = \frac{(\overline{d}(V) - d)}{\epsilon\, \tau_d(V)},$$
$$\dots \qquad (1)$$

where $\theta()$ is the Heaviside function, representing the nearly perfect switch behaviour of the I_{Na} gates. The rest of the equations are as in [1]. See [2] for further details.

Equation (1) in the singular limit $\epsilon \to +0$ and in the fast time $T = t/\epsilon$ gives a closed system of three equations

$$\begin{aligned} \partial_T V &= -\overline{I_{\mathrm{Na}}}(V) m^3 h j / C_M + \partial_X^2 V, \\ \partial_T m &= \big(M(V)\theta(V - V_m) - m\big)/\tau_m(V), \\ \partial_T h &= \big(H(V)\theta(V_h - V) - h\big)/\tau_h(V). \end{aligned} \qquad (2)$$

where j is slow compared to m and h and remains constant in the fast time T. As this system is obtained by replacing truly small quantities with zero, it is expected to give results numerically close to the full model, as far as fast processes such as fronts are concerned.

Further "caricature" simplification of this model is achieved by replacing functions $M(V)$, $H(V)$, $\tau_h(V)$ and $\overline{I_{\mathrm{Na}}}(V)$ with constants, and assuming additionally the limit of small τ_m so that m always remains close to its quasistationary value $\theta(V - V_m)$ [3]. After a suitable rescaling, this is brought to the system

$$\begin{aligned} \partial_t V &= \theta(V - 1)h + \partial_X^2 V, \\ \partial_t h &= (\theta(-V) - h)/\tau. \end{aligned} \qquad (3)$$

This system has exact solutions for stationary propagating fronts $V = V(x - ct)$, $h = h(x - ct)$. Front speed c satisfies a finite transcendental equation involving the dimensionless parameter τ and the pre-front value of $V(+\infty, t) = V_\alpha$, but this equation admits a complete analytical investigation. In particular, for a fixed value τ, front solutions are possible for a finite range of V_α, and for all but marginal values of V_α there are two front solutions: one stronger and faster and the other weaker and slower. Further, it appears that the stronger faster front is stable and the weaker slower front is unstable [3, 4].

3. Results

3.1. Absolute refractoriness

We have studied stationary front solutions in (2) in the form $V(z)$, $m(z)$, $h(z)$ where $z = x - ct$, numerically as solutions of the boundary value problem with boundary conditions $V(+\infty) = V_\alpha$, $h(+\infty) = 1$, $m(+\infty) = 0$, $V(-\infty) = V_\omega$, $h(-\infty) = 0$, $m(+\infty) = 1$. In this problem, V_α and j are free parameters, and c and V_ω are found as nonlinear eigenvalues. The result is that the solutions exist for $j > j_{\min}(V_\alpha)$ for a certain function $j_{\min}(V_\alpha)$.

Hence $j < j_{\min}(V_\alpha)$ is the condition of the block of propagation of the wave, as far as stationary (in the fast scale) propagation is concerned. Assuming that there have been no fronts and no external currents for some time, then the condition of block simplifies further. This is due to the fact that the recovery phase of an action potential has a great deal of independence of the circumstances of the its initiation. That means, that in the wake of the previous excitation wave and ahead of the next one, $j(t)$ and $V(t)$ at a point are closely related to each other, and so we can say that $j(t) = j_{\mathrm{wake}}(V(t))$ for some function $j_{\mathrm{wake}}(V)$, with a good accuracy. The lines $j = j_{\min}(V)$ and $j = j_{\mathrm{wake}}(V)$ have a unique intersection at a point $(j_{\mathrm{crit}}, V_{\mathrm{crit}})$. For the standard parameters of [1], we have found $j_{\mathrm{crit}} \approx 0.297$ and $V_{\mathrm{crit}} \approx -72.5\,\mathrm{mV}$. This point gives a simple numerical criterion: a front cannot propagate through the tissue where $j < j_{\mathrm{crit}}$ or $V > V_{\mathrm{crit}}$. Of these two criteria, $j < j_{\mathrm{crit}}$ is more convenient for checking in a numerical simulation, as j does not change much during the front itself whereas V does.

Fig. 1 illustrates how this criterion compares with the results of the direct numerical simulation of the full model (1). The colour coding uses V for the red component and $\theta(j_{\mathrm{crit}} - j)$ for the blue component. Hence the front of the exciation wave is red, and the absolutely refractory zone, according to the criterion $j < j_{\mathrm{crit}}$, is blue. Hence the prediction is that the front of the wave should stop propagating if and only if the red front reaches the blue tail. The figure shows one such event. The total duration of the simulation before the self-termination of the spiral wave was about 7.5 sec. During this interval, wavebreaks happened when and only when the red fronts touched the blue tails; there were four such events.

3.2. Initiation problem and critical fronts

There exists a well developed theory of initiation of propagating waves in the FitzHugh-Nagumo of equations, see e.g. [5, 6, 7], in the singular limit when the activator (excitation) variable is much faster than the inhibitor (recovery) variable. The fast subsystem coincides with Zeldovich-Frank-Kamenetsky [8] equation, also known as Nagumo equation [9]:

$$\partial_t u = -(u - u_1)(u - u_2)(u - u_3) + \partial_x^2 u \qquad (4)$$

where $u_1 < u_2 < u_3$, $u_2 < (u_1 + u_3)/2$ and u_1 corresponds to the resting state in the two-variable full FitzHugh-Nagumo system. Initial conditions are considered which are close to u_1 except in a finite "liminal" interval. A key role in this theory is played by the so called

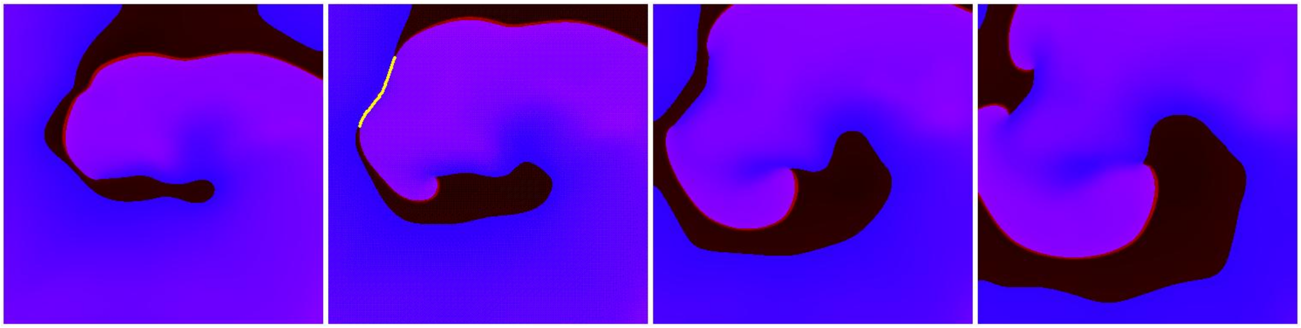

Figure 1. Wavebreak in Courtemanche et al. [1] model. Red component: voltage. Blue component: absolutely refractory region as predicted by asymptotic theory. Box size $75 \times 75\,\mathrm{mm}^2$ with $D = 0.03125\,\mathrm{mm}^2/\mathrm{ms}$, snapshots shown with the interval of $40\,\mathrm{ms}$. The yellow line on the second snapshot indicates the site where the front runs into the absolutely refractory zone.

"critical nucleus" $u_*(x)$, which is a nontrivial stationary solution of (4) such that $u_*(\pm\infty) = u_1$. This solution is unstable, but has only one positive eigenvalue. This means that its center-unstable manifold has codimension one and therefore splits the phase space of (4) into two domains. It appears that one of those domains corresponds to decay of initial perturbation to u_1, and the other to the fronts switching the system to the excitation state u_3.

This property has an important consequence. Consider any continuous one-parametric family of initial conditions, such that some initial generate fronts and some lead to decay. Then the curve in the functional space representing this family, will join the two domains and therefore will cross the center-stable manifold of the critical nucleus. Therefore, initial conditions corresponding to the exact threshold between successful initiation and decay, will give a solution which will neither decay nor initiate a propagating front, but instead will approach, as $t \to +\infty$, the critical nucleus (up to a translation in x).

The problem of determining a threshold for a particular class of initial conditions mathematically reduces, therefore, to the problem of finding the intersection of the corresponding set of initial conditions with this center-stable manifold. Technically this can be done by various means, e.g. Galerkin approximation [7].

Unfortunately, this theory is inapplicable to cardiac models. It easily seen, that unlike (4), the cardiac fast front equation (3) does not have any nontrivial stationary solution, so there is no "critical nucleus" here. However, as we mentioned earlier, this equation has unstable front solutions. According to [4], these unstable solutions have exactly one positive eigenvalue, at least in some range of parameters. We therefore conjecture that the center-stable manifolds of such an unstable front serve as threshold surfaces in the functional space, separating successful excitation from decay. In other words, the "critical front" plays in (3) the same role as the critical nucleus plays in (4).

By the same logic as for critical nuclei, we conclude that any continuous one-parametric family of initial conditions stretching from successful initiation to decay, should have at least one exact threshold initial condition, resulting in a solution neither decaying nor generating the propagating stable front, but instead approaching the unstable front.

Fig. 2 verifies this prediction. We used initial conditions $V(x,0) = V_\alpha + V_{\mathrm{stim}}\theta(x_{\mathrm{stim}} - x)$, $h(x,0) = 1$ on an interval $x \in [0, x_{\max}]$ for a large enough $x_{\max}$. The width x_{stim} of the initial stimulus was fixed, and the amplitude V_{stim} varied. Larger values of V_{stim} initiated propagating fronts, and smaller values led to diffusive spread of V. According to the conjecture, the values of V_{stim} very close to the threshold should lead to solutions approaching the unstable front, before either developing into a stable front or diffusing. This is precisely what is observed. The advantage of (3) is that the unstable front solution and its speed are known exactly, so we can compare the transient front profiles for near-threshold initial conditions with the unstable front solution, as well as their speeds. So Fig. 2 confirms our conjecture. As with ZFK equation, practically useful prediction could be obtained via a suitable approximation for the intersection of the given class of initial conditions with the center-stable manifold of the critical front.

4. Discussion and conclusions

We have shown only two examples how the new asymptotic approach can yield theoretical results which can have useful practical applications. The theory of excitable systems based on the singular asymptotics of the FitzHugh-Nagumo system has been developed for more than forty years and produced remarkable results. Regrettably not all of those results are applicable or even have correct analogies for cardiac models, as solutions of (4) and (3) have sometimes very different properties. Hence further investigation of the asymptotic approach represented by equa-

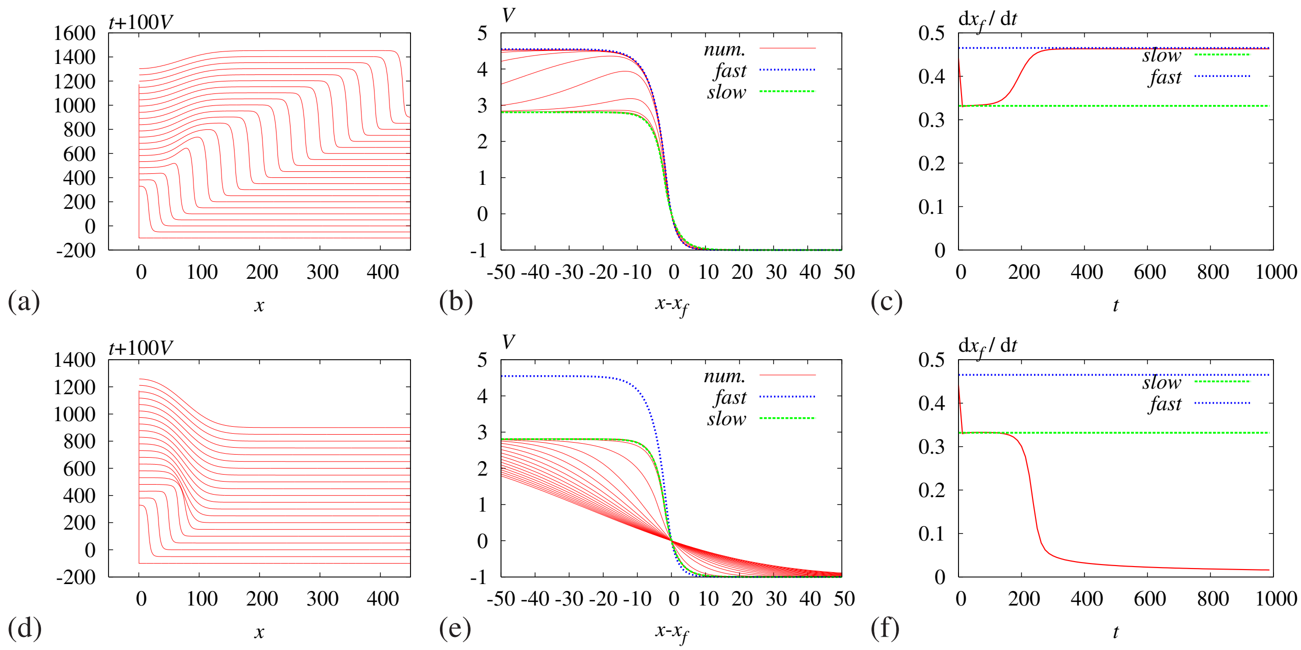

Figure 2. Critical fronts in the caricature model (3). The width of the initial stimulus is $x_{\mathrm{stim}} = 0.3$ and the amplitude is $V_{\mathrm{stim}} = 12.716330706144868$ which is slightly above the threshold for panels (a-c) and $V_s = 12.716330706144867$ which is slightly below the threshold for panels (d-f). (a,d): Evolution of the voltage profiles. Initial stage is similar in both cases, later the upper profile develops into a stable front and the lower profile dissipates. (b,e): Same, in the moving frame of reference with respect to the front point $x_f(t)$ defined via $V(x_f(t), t) = 0$. For comparison, dashed green and dotted blue lines are the exact solutions for the stationary unstable and stable profiles, respectively. Initially profiles are very close to the unstable stationary profile, and evolve towards the stable stationary profile above and homogeneous distribution below. (c,f): Evolution of the speed of the front point $x_f(t)$. For comparison, dashed green and dotted blue lines show the speeds of the unstable and stable stationary profiles, respectively. In both cases, the front point first moves with the speed of the unstable front, and then speeds up towards the speed of the stable front above and drops to zero below.

tions (1–3) is needed.

Acknowledgements

This study has been supported by EPSRC (grant GR/S75314/01) for RDS and VNB and MacArthur Foundation for II.

References

[1] Courtemanche M, Ramirez R, Nattel S. Ionic mechanisms underlying human atrial action potential properties: insights from a mathematical model. Am J Physiol 1998;275:H301–H321.

[2] Simitev RD, Biktashev VN. Conditions for propagation and block of excitation in an asymptotic model of atrial tissue. Biophys J 2006;90:2258–2269.

[3] Biktashev VN. Dissipation of the excitation wavefronts. Phys Rev Lett 2002;89:168102.

[4] Hinch R. Stability of cardiac waves. Bull Math Biol 2004; 66:1887–1908.

[5] Flores G. The stable manifold of the standing wave of the Nagumo equation. J Differential Equations 1989;80:306–314.

[6] Flores G. Stability analysis for the slow traveling pulse of the FitzHugh-Nagumo system. SIAM J Math Anal 1991; 22:392–399.

[7] Neu JC, Preissig RS, Krassowska W. Initiation of propagation in a one-dimensional excitable medium. Physica D 1997;102:285–299.

[8] Zel'dovich YB, Frank-Kamenetsky DA. Towards the theory of uniformly propagating flames. Doklady AN SSSR 1938; 19:693–697.

[9] McKean Jr. HP. Nagumo's equation. Adv Appl Math 1970; 4:209–223.

Address for correspondence:

V. N. Biktashev
Department of Mathematical Sciences
University of Liverpool
Liverpool L69 7ZL
UK
E-mail address vnb@liv.ac.uk