Dissipation of excitation fronts as a mechanism of conduction block in re-entrant waves

Vadim N. Biktashev[1] and Irina V. Biktasheva[2]

[1] Department of Mathematical Sciences, Liverpool University, Liverpool L69 7ZL, UK vnb@liv.ac.uk,
WWW home page: http://www.maths.liv.ac.uk/~vadim
[2] Department of Computer Science, Liverpool University, Liverpool L69 3BX, UK

Abstract. Numerical simulations of re-entrant waves in detailed ionic models reveal a phenomenon that is impossible in traditional simplified mathematical models of FitzHugh-Nagumo type: dissipation of the excitation front (DEF). We have analysed the structure of three selected ionic models, identified the small parameters that appear in non-standard ways, and developed an asymptotic approach based on those. Contrary to a common belief, the fast Na current inactivation gate h is not necessarily much slower than the transmembrane voltage E during the upstroke of the action potential. Interplay between E and h is responsible for the DEF. A new simplified model emerges from the asymptotic analysis and considers E and h as equally fast variables. This model reproduces DEF and admits analytical study. In particular, it yields conditions for the DEF. Predictions of the model agree with the results of direct numerical simulations of spiral wave break-up in a detailed model.

1 Introduction.

Contemporary detailed models of excitation propagation in heart tissue can reproduce many important conduction pathologies, including transient propagation blocks. Such blocks are involved in generation, transformation and termination of re-entrant circuits, the importance of which for cardiac pathologies has been recognized early[1]. In modern detailed models, the relevant phenomena include break-up of spiral waves[2], meandering patterns of spiral waves[3],[4], or spontaneous termination of re-entrant activity[5, 6]. Break-up of spiral waves is thought to be a key mechanism of transition from less dangerous arrhythmia to fibrillation[7, 8, 9]. Thus, it is important to understand, how such break-up, or, more generally, a spontaneous transient excitation conduction block may happen. The detailed mathematical models, in principle, answer this question, in the sense that they can, more or less accurately, reproduce the phenomenon. However, currently there is no other way to see how the possibility of conduction block changes with parameters but to repeat calculations, which may be rather extensive. Situation is even worse if we want to know what changes in parameters are necessary to achieve a certain effect, such as a decrease or an increase in the probability of conduction block in certain conditions in a certain

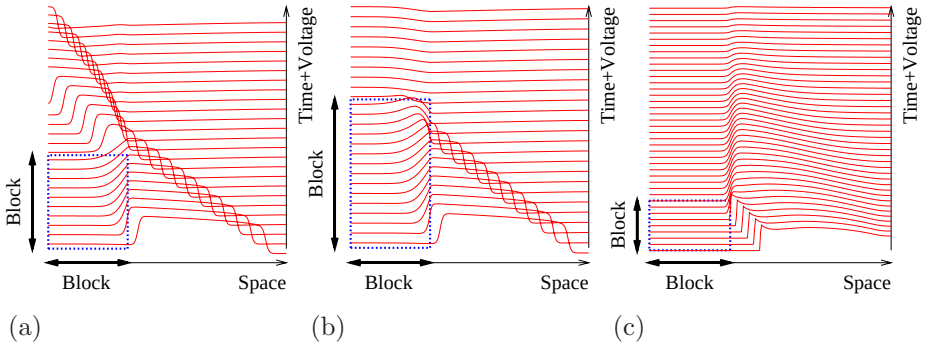


Fig. 1. Propagation block caused by temporary local suppression of excitability in (a,b) the traditionally used simplified mathematical model (FitzHugh-Nagumo) and (c) in a detailed mathematical model of human atrial tissue (Courtemanche et al.[17]). The time and space in the simplified model are in arbitrary units; in the detailed model, the time range is 600ms and space range is 600mm (artificially long for illustration purpose, just to see the whole wave).

model, as the detailed models are not necessarily intuitive in that sense. Thus the motivation of our study: is it possible to predict the conduction block in a simpler way, without running complicated numerical simulations, say but using an explicit analytical formula. The detailed equations describing heart tissue are very complicated and do not to admit exact analytical solutions. Thus we must speak about some simplifications and approximations of those models.

One such approach is well known under the name of slope-1 theory. It gives simple criteria when a stationary re-entrant wave becomes unstable and leads to alternans and break-up[10, 11]. This theory only works as long as its underlying assumptions are true[12, 6], and the relevance of this model to human hearts is a subject of discussions. We must stress, however, that in any case this theory only predicts instability of stationary propagation, and whether this instability will lead to stable alternans or to break-ups is quite another question.

There is an important class of simplified models of excitable tissues, originating from the works by FitzHugh[13] and Nagumo et al.[14]. We call this class FitzHugh-Nagumo-type models. The defining features of this model is one fast variable responsible for the front profile, usually associate with the transmembrane voltage, and bistability of the corresponding fast subsystem. This class is simple enough to allow some analytical study[15, 16]. However, it appears that for the purpose of studying transient propagation block, this type of model is unsuitable. This is illustrated on fig. 1.

It shows what happens if an excitation wave meets a region with temporary suppressed excitability in two different models, in a simplified model (panels a and b) and in a detailed model of atrial tissue (panel c). Suppression of excitability in the simplified models was through replacement of the reaction term in the

activator equation with zero. In the detailed model, it was modelled by replacing the fast sodium current with zero.

In panel (a), the excitability is restored early, before the excitation disappeared completely. Then the wave resumes propagation. In panel (b), the excitability is restored a little later. By that time, the back of the wave caught up with the front, and the excited region disappeared. When excitability is restored, the propagation does not resume as there are not excited cells left.

Such simplified models lead to the popular intuitive understanding that a break-up of an excitation wave occurs when the wavelength reduces to zero, that is, the back catches up with the front[8].

However, this is not what really happens in detailed models. On panel (c), excitability in the detailed model is restored long before the back of the excitation wave reached the front. However, the wave does not resume propagating. Note that while the front is being held back by the obstacle, it becomes smoother, "dissipates". The diffuse excitation front seems unable to resume propagation.

Our aim is to find the simplest way to explain, i.e. to build a mathematical model, of this phenomenon. Our leading hypothesis is that a complete detailed excitation model is not needed, and it can be reproduced in a much simpler model as long as the key factors are included. This would validate our understanding of what are the key factors. As we have seen, the traditional simplified models are unsuitable for this purpose. So we need a new simplified model.

2 The simplified model: the underlying assumptions and the key results.

The new simplified model. We considered Hodgkin and Huxley[18], Noble[19] and Courtemanche et al.[17] models, as three very different representatives of the enormous variety of physiology based models of excitable systems, and identified features common to all of them, in the hope that these features are reasonably universal. We analysed what is large and what is small in these detailed models, and what can be neglected for our purpose. Our purpose is to describe the propagating front. The main player there is the fast sodium current, I_{Na}. In asymptotic approaches, it is customary to involve consideration of relative speed of dynamic variables. Typically the activation gate m is fast, the fast inactivation gate h is slower and its dynamics, especially when dealing with propagation block, are comparable to those of the transmembrane voltage E, and the slow inactivation gate j (not present in Hodgkin-Huxley and Noble-1962 models, of course) is the slowest. However, such considerations were not enough to describe the front dissipation. It has also proved important that I_{Na} is much stronger than other ionic currents, but not always, and only during the upstroke of the action potential, whereas at other stages the "window" component of I_{Na} is comparable or smaller than other currents. To properly represent this property in the dynamic equations of the simplified model, we have to take into account the "almost perfect switch" properties of the I_{Na} channels, i.e the fact that the

I_{Na} ionic gates tend to close well in some ranges of the transmembrane voltage, and the ranges of almost perfect closure of m and h overlap.

These considerations have lead us to a system of only two differential equations describing propagation of excitation, with transmembrane voltage E and the fast inactivation gate h as the key dynamic variables.

$$\begin{aligned} C_m \frac{\partial E}{\partial t} &= I_{\mathrm{Na,max}}(E) j h \theta(E - E_m) + D \frac{\partial^2 E}{\partial x^2} \\ \frac{\partial h}{\partial t} &= \frac{1}{\tau_h(E)} \left(\theta(E_h - E) - h\right) \end{aligned} \tag{1}$$

where E is the membrane capacitance, $I_{\mathrm{Na,max}}(E)$ is the maximal fast sodium current when all gates are open, j is the slow inactivation gate assumed almost unchanged during the front, D is the voltage diffusion coefficient, $\tau_h(E)$ is the characteristic time of the dynamics of the h-gate, E_h and E_m are the switch voltages of the h- and m-gates respectively ($E_m > E_h$), and $\theta()$ is Heaviside's perfect switch function. This is opposed to, say, 21 equations in Courtemanche et al. model. Some further simplification, in the form of replacing $I_{\mathrm{Na,max}}(E)$ and $\tau_h(E)$ with constants, while retaining qualitatively correct behaviour of the solutions, has allowed exact analytical solutions. The details of the solutions have been described elsewhere[20, 21]. For our present purpose, the most interesting result is the excitability, measured say by the local instant value of gate j at the front,[1] that is necessary for propagation of a front with a given speed c:

$$j = \frac{C_m}{\tau_h I_{\mathrm{Na,max}}} g\left(c\sqrt{\tau_h/D}, \frac{E_h - E_{\min}}{E_m - E_{\min}}\right). \tag{2}$$

Here $E_{\min}$ is the pre-front value of the transmembrane voltage, and the dimensionless excitability g is defined as a nonlinear function of the dimensionless front speed

$$\sigma = c\sqrt{\tau_h/D}$$

and the dimensionless voltage load parameter

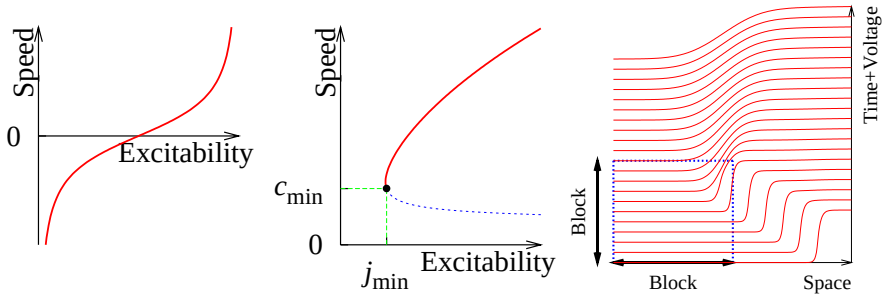
$$\beta = \frac{E_h - E_{\min}}{E_m - E_{\min}}$$

as

$$g(\sigma, \beta) = \frac{1 + \sigma^2}{(1 - \beta)\beta^{1/\sigma}}. \tag{3}$$

Figure 2 illustrates these results, in comparison with the traditional simplified model. Panel (a) shows a typical behaviour of the front propagation speed in

[1] To avoid confusion, we stress here that the terminology we adopt may be different from other authors. Since in our approach gate j is considered as a slow variable, almost unchanged during the front, it is classified as an excitability condition. That is, it characterizes the ability for excitation, which is explicitly opposed to the variables E, m and h which change significantly during the front and thus represent excitation process proper.



(a) (b) (c)

Fig. 2. Some analytical results on excitation propagation fronts, all graphs in arbitrary units. (a) Dependence of the front propagation speed on the instant value of an excitability parameter, in a FitzHugh-Nagumo-type model[15]. (b) Same, in our new simplified model based on detailed equations[20]; here the excitability parameter j is proportional to the product of the local value of I_{Na} conductivity, the slow inactivation gate, and the transmembrane voltage relative to I_{Na} reversal potential. (c) Dissipation of a front at a site with a temporary suppressed excitability and its failure to resume propagation after the excitability is recovered, in our new simplified model, in a setting similar to that on fig. 1.

a traditional FitzHugh-Nagumo-type model, as a function of the instantaneous local value of a slow "excitability" parameter. In that class of simplified models, such parameters usually do not have a straightforward physiological connotation, as there only one slow variable is to represent all slow variables of detailed models at once. An essential feature of dependence shown on fig. 2(a) is that, as the excitability parameter varies, the propagation speed can be arbitrarily low, can be zero, and can even be negative, which corresponds to excitation front turning into a recovery front. Panel (b) illustrates what stands instead of this dependence in our new simplified model, where the excitability is varied via parameter j with other parameters fixed. The key feature of this dependence is that the excitability parameter given by equations (1,2) has a minimum as a function of speed, so for the front to propagate, excitability should not be less than a certain minimum $j_{\min}$. For every value of excitability above that minimum, there are two solutions in the form of stationary propagating fronts. However, it appears that only the solution with the higher speed, shown with a solid line, is stable, while the solution with the lower speed, shown with a dashed line, is unstable [22]. Thus, a propagating front can have a speed no smaller than a certain $c_{\min}$.

The new model describes dissipation of fronts. Thus we deduce that if the front, for any reason, is not allowed to propagate with a speed $c_{\min}$ or higher and/or if the local instant value of the excitability parameter is below $j_{\min}$, then the stationary propagation would not be observed, and the only alternative is the front dissipation, as in the simplified model, this corresponds to a complete

closure of the I_{Na} gates and the evolution of the transmembrane voltage E is described then by simply a diffusion equation.

This conclusion is confirmed by numerical simulations with the new simplified model, which are shown on fig. 2(c). Here the setting is similar to that of fig. 1(c), except now, to be more convincing, we did not use a complete block of excitability in the left half of the medium, but, rather, temporary decreased it to slightly (by 4.3%) below the critical value j_{min}. The excitability in the left half after the temporary "block", as well as all the time in the right half of the medium, was slightly (by 8.7%) above j_{min}. As a result, the excitation front reached the region with suppressed excitability, where it lost its sharp gradient, and after the excitability recovered, the front did not resume propagation but continued to spread diffusively. That is, it has shown exactly the same qualitative properties as observed in the full model (fig. 1c). So, our simplified model does take into account all the key factors involved in the front dissipation.

Application of the propagation condition to the analysis of the breakup of a re-entrant wave. So, our simplified model gives a necessary condition of propagation, in terms of the local excitability and the pre-front voltage. If the condition is not satisfied, the front cannot propagate and dissipates. Figure 3 shows a fragment of a simulation of a re-entrant wave in two-dimensional medium with the kinetics of Courtemanche et al. model[17], which is described in more detail in our recent work[5].

The top row shows distribution of the action potential, as it would be seen by an ideal optical mapping system (dark represents higher voltage). Propagation of a part of the re-entrant wave is blocked by the refractory tail of its previous turn. The wave then breaks up into two pieces, and the net result is there are now three free ends of excitation waves, i.e. three potential re-entry cores in place of one. The second row shows the profile of the transmembrane voltage along the dotted line on the upper panels. One can see first a reduction of the amplitude of the upstroke, and then the loss of the sharp upstroke altogether. The third row shows the profile of the factor of the I_{Na} due to the fast gates; the sharp peaks represent the excitation front. And the bottom row shows the profile of the slow gating variable j, which in our interpretation represents, together with the pre-front voltage, the conditions for the front propagation. The instant maximum of this profile is at the front, as the excitability restores before the fronts and falls after the front. The first shown moment $t = 4100\,\mathrm{ms}$ is when the excitability at the front drops down as low as the critical value, which is designated by a dotted horizontal line on the bottom row panels. If the front went slower at this moment, then excitability ahead of it would recover and it could propagate further. However, as predicted by our simplified model, the front speed cannot decrease below a certain minimum. So the front cannot slow down and "wait" until the excitability is recovered, but has to run further towards even a less excitable area. As a result, the conditions of propagation are no longer met, and the front dissipates, which is seen as the loss of the sharp gradient of $E(x)$, or, clearer, as disappearance of the peak of the $m^3(x)h(x)$ profile. After that, even though excitability j recovers above the critical level, the front does not resume.

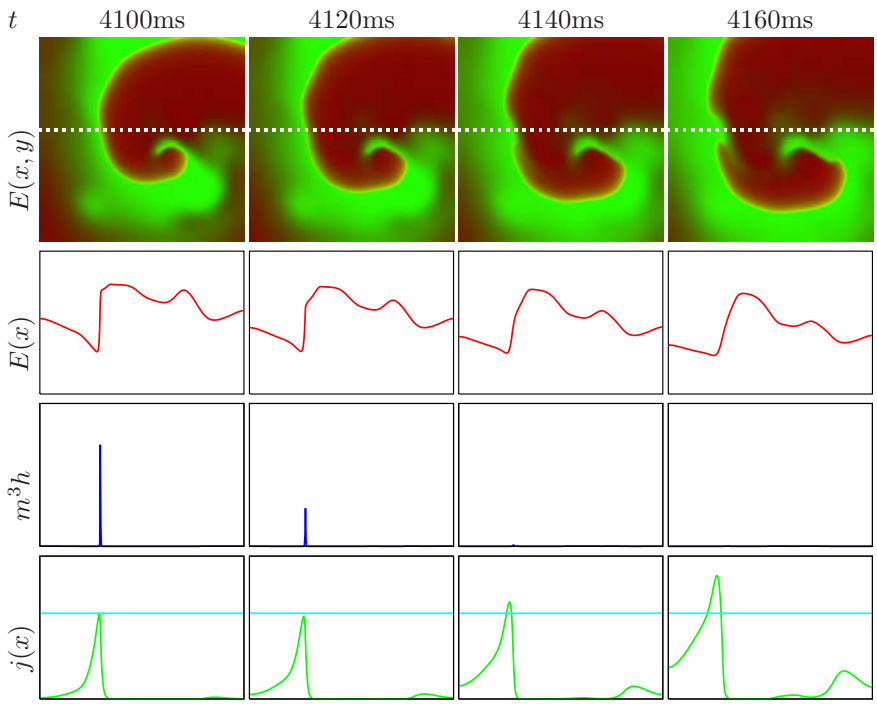


Fig. 3. Analysis of a break-up of a re-entrant wave in a two-dimensional ($75 \times 75\,\mathrm{mm}$) simulation of a detailed model[17]. Top row: snapshots of the distribution of the transmembrane voltage, at the selected moments of time (designated above the panels). The other three rows: profiles of the key dynamic variables (designated on the left) along the dotted line shown on the top row panels, at the same moments of time. Dotted line here represents j_{min}.

Note that this analysis concerns only interaction of the front with the tail of the previous wave, and has nothing to do with the back of the new wave. Front dissipation occurs long before the wavelength reduces to zero. Of course, a break-up of a wave implies that its length vanishes eventually, but it will be long after the crucial events have already happened. Thus, the fate of the front here is determined already at the first snapshot, although it is not at all obvious in the voltage distribution.

3 Conclusions

Summary of results

– For understanding the mechanisms of transient propagation blocks, such as occurring in re-entrant arrhythmia, it is important to bear in mind that the propagation speed in all circumstances has a *positive* lowest critical value, which is determined by the properties of the fast sodium channels. If the

front is not propagated fast enough, say because excitability ahead of it recovers slower after the previous wave, then the front dissipates. After dissipation, the excitation front will not resume propagation even if excitability is restored.

- We have suggested a new simplified model that reproduces this behaviour of the excitation front, thus confirming the main physiological processes responsible for it. The simplified model is based on properties of the fast sodium current. Specifically, the dissipation of the excitation front is related to the simultaneous and mutually dependent dynamics of the transmembrane voltage E and the fast I_{Na} inactivation gate h.
- This particular mechanism of the propagation block is confined to the front, and has nothing to do with the wave back. That is, the propagation is blocked long before the wavelength reduces to zero.
- Apart from the transient propagation block, the new simplified model should be helpful in other cases concerning the margins of normal propagation. This includes initiation of excitation waves, which is the opposite of the propagation block, and the re-entrant waves around functional blocks, which imply juxtaposition of successful and unsuccessful propagation.
- FitzHugh-Nagumo type caricatures, although successfully describing successful propagation, fail to correctly describe propagation failure as it happens in reality or in detailed models. Thus using such models to describe any processes involving initiation of waves, block of propagation, or re-entrant waves, may misrepresent most important features. The new simplified model or its analogue should be used instead.

Limitations and further work Model (1) has been obtained via a number of simplifications: freezing of slow processes, adiabatic elimination of fast processes, replacement of I_{Na} gates with perfect switches and replacement of $I_{\mathrm{Na,max}}(E)$ and $\tau_h(E)$ with constants. Besides, the detailed models themselves are simplified, e.g. they are based on Hodgkin-Huxley description of Na channels rather than the more recent Markovian description. Validity of the results is therefore subject to one's ability to justify the simplifications and show that they do not alter the main properties. This is an ongoing work. We have shown recently that a formal asymptotic limit in Noble-1962 model naturally leads to (1) as a fast subsystem, and reproduces a single-cell action potential with a good accuracy [23]. We have also demonstrated that a similar asymptotic limit works in Courtemanche et al. model, and system (1) obtained in this way gives a reasonable estimate of the critical conditions of front dissipation, which can be further improved by taking into account the dynamics of m-gates instead of adiabatically eliminating them [24]. A Markovian, non-Hodgkin-Huxley description of I_{Na} involves a radically different description of the Na channels. Inasmuch as the old Hodgkin-Huxley description was reasonably accurate phenomenologically, one can expect that the main features should maintain; however, an ultimate answer to that can only be obtained via a further detailed study.

Acknowledgements. This work was supported in part by grants from EPSRC (GR/S43498/01, GR/S75314/01) and by an RDF grant from Liverpool University.

References

[1] V. I. Krinsky. Fibrillation in excitable media. *Cybernetics problems*, 20:59–80, 1968.

[2] A. V. Panfilov and A. V. Holden. Self-generation of turbulent vortices in a 2-dimensional model of cardiac tissue. *Phys. Lett. A*, 151:23–26, 1990.

[3] V. I. Krinsky and I. R. Efimov. Vortices with linear cores in mathematical-models of excitable media. *Physica A*, 188:55–60, 1992.

[4] V. N. Biktashev and A. V. Holden. Re-entrant waves and their elimination in a model of mammalian ventricular tissue. *Chaos*, 8:48–56, 1998.

[5] I. V. Biktasheva, V. N. Biktashev, W. N. Dawes, A. V. Holden, R. C. Saumarez, and A. M.Savill. Dissipation of the excitation front as a mechanism of self-terminating arrhythmias. *IJBC*, 13(12):3645–3656, 2003.

[6] I. V. Biktasheva, V. N. Biktashev, and A. V. Holden. Wavebreaks and self-termination of spiral waves in a model of human atrial tissue, 2005. In this issue.

[7] R. A. Gray and J. Jalife. Spiral waves and the heart. *Int. J. of Bifurcation and Chaos*, 6:415–435, 1996.

[8] J. N. Weiss, P. S. Chen, Z. Qu, H. S. Karagueuzian, and Garfinkel A. Ventricular fibrillation: How do we stop the waves from breaking? *Circ. Res.*, 87:1103–1107, 2000.

[9] A. Panfilov and A. Pertsov. Ventricular fibrillation: evolution of the multuple-wavelet hypothesis. *Phil. Trans. Roy. Soc. Lond. ser. A*, 359:1315–1325, 2001.

[10] J. B. Nolasco and R. W. Dahlen. A graphic method for the study of alternation in cardiac action potentials. *J. Appl. Physiol.*, 25:191–196, 1968.

[11] A. Karma, H. Levine, and X. Q. Zou. Theory of pulse instabilities in electrophysiological models of excitable tissues. *Physica D*, 73:113–127, 1994.

[12] E. M. Cherry and F. H. Fenton. Suppression of alternans and conduction blocks despite steep APD restitution: Electrotonic, memory, and conduction velocity restitution effects. *Am. J. Physiol. - Heart C*, 286:H2332–H2341, 2004.

[13] R. FitzHugh. Impulses and physiological states in theoretical models of nerve membrane. *Biophys. J.*, 1:445–456, 1961.

[14] J. Nagumo, S. Arimoto, and S. Yoshizawa. An active pulse transmission line simulating nerve axon. *Proc. IRE*, 50:2061–2070, 1962.

[15] H. P. McKean. Nagumo's equation. *Adv. Appl. Math.*, 4:209–223, 1970.

[16] J. J. Tyson and J. P. Keener. Singular perturbation theory of traveling waves in excitable media (a review). *Physica D*, 32:327–361, 1988.

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

[18] A. L. Hodgkin and A. F. Huxley. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.*, 117:500–544, 1952.

[19] D. Noble. A modification of the Hodgkin-Huxley equations applicable to Purkinje fibre action and pace-maker potentials. *J. Physiol.*, 160:317–352, 1962.

[20] V. N. Biktashev. Dissipation of the excitation wavefronts. *Phys. Rev. Lett.*, 89(16):168102, 2002.

[21] V. N. Biktashev. A simplified model of propagation and dissipation of excitation fronts. *Int. J. of Bifurcation and Chaos*, 13(12):3605–3620, 2003.

[22] R. Hinch. Stability of cardiac waves. *Bull. Math. Biol.*, 66(6):1887–1908, 2004.

[23] V .N. Biktashev and R. Suckley. Non-Tikhonov asymptotic properties of cardiac excitability. *Phys. Rev. Letters*, 93:168103, 2004.

[24] I. V. Biktasheva, R. S. Simitev, R. Suckley, and V. N. Biktashev. Asymptotic properties of mathematical models of excitability, 2005. Submitted to Phil. Trans. Roy. Soc. A.