V.N. Biktashev. Final Report:
ANALYTICAL APPROACH TO REALISTIC MODELS OF EXCITATION PROPAGATION IN HEART

Background and context

Heart failure is a major cause of death in the industrial world. Major resources in pharmaceutical and biomedical engineering industries are dedicated to development of drugs and devices to tackle heart problems. This entails intensive research into the mechanisms of heart failure. Experiments increasingly provide material for more complicated and accurate mathematical models of subsystems of the heart. The current project has been about mathematical modelling of propagation of electrical excitation in cardiac muscle and its pathologies. Mathematical models of excitation and propagation by now have been developed in remarkable detail. A typical structure of such a model is

$$\partial E/\partial t = D\nabla^2 E + \sum_j I_j(E, \mathbf{y}), \qquad \partial \mathbf{y}/\partial t = \mathbf{Y}(E, \mathbf{y}), \tag{1}$$

where E is transmembrane voltage of the cardiocytes, functions $I_j()$ represent individual transmembrane ionic currents, each conducted by a different sort of transmembrane channels, and the vector $\mathbf{y}$ includes the "gating" variables of the ionic channels and the intra- and extracellular concentrations of ions involved. Some models use 20 or more differential equations per cell [18]. These models are mostly studied numerically, which has well known disadvantages. Attempts of simplication and analytical treatment of the heart models have been made ever since their beginning. The mainstream approach so far was based on systems of equations by van der Pol [19] for an electronic nonlinear oscillator and by Zel'dovich and Frank-Kamenetsky (ZFK) [20] for propagating flames, which have nothing to do with cardiac excitation, but were available when the experiment-based models of cardiac excitation were first created. This direction was set by papers by FitzHugh [21] and Nagumo et al. [22]. The FitzHugh-Nagumo (FHN) class of models has the form

$$\partial E/\partial t = D\nabla^2 E + f(E, \mathbf{g}), \qquad \partial \mathbf{g}/\partial t = \epsilon \mathbf{G}(E, \mathbf{g}), \qquad 0 < \epsilon \ll 1, \tag{2}$$

where $E, f \in \mathbb{R}$, $\mathbf{g}, \mathbf{G} \in \mathbb{R}^k$, $k \geq 1$, and $f(E, \mathbf{g})$ as a function of E, in a relevant range of $\mathbf{g} = \text{const}$ values, has three roots, two stable and one unstable in between. In the original formulation of [21], $k = 1$, $\mathbf{g} = (v)$, $f()$ is cubic, $f(E, \mathbf{g}) = E - E^3/3 - v$ and $\mathbf{G}(E, v) = (E + \beta - \gamma v)$, $\beta, \gamma = \text{const}$. For us most important is the small parameter ϵ, due to which E is (the only) fast variable. The fast equation of (2),

$$\partial E/\partial t = D\nabla^2 E + f(E), \tag{3}$$

with cubic $f(E)$ is known as Zeldovich-Frank-Kamenetsky (ZFK) equation [20, 32]. The limit $\epsilon \to 0$ allowed an attractive and promising asymptotic theory [23]. Alas, it has never been seriously applied to any realistic cardiac excitation models.

In the pilot studies before this project, we have demonstrated that the FHN-type models (2) have a serious and incorrigible fault: they cannot describe an idiosyncratic scenario of block of excitation propagation observed in cardiac models, which we called "front dissipation" [33]. The front is the fast stage of a propagating excitation wave, which in FHN-type systems is described by the fast subsystem like (3). We have suggested in [33, 34] an alternative two-variable fast subsystem that can reproduce the front dissipation phenomenon:

$$\partial E/\partial t = D\nabla^2 E + F(E)h, \qquad \partial h/\partial t = (\bar{h}(E) - h)/\tau(E), \tag{4}$$

where the form of the functions $F(E)$, $\bar{h}(E)$ and $\tau(E)$ is motivated by ionic cardiac excitability equations, with the important property that $F(E)\bar{h}(E) \equiv 0$ and, moreover, that both $F(E)$ and $\bar{h}(E)$ vanish simultaneously in a certain interval of E intermediate between the resting and the excited state. We suggested a "toy" system with these properties, with

$$F(E, h) = \Theta(E - E_m), \qquad \bar{h}(E) = \Theta(E_h - E), \qquad E_m > E_h, \qquad \tau(E) = \tau = \text{const}, \tag{5}$$

where $\Theta()$ is the Heaviside step function. It has exact analytical solution in the form of propagating fronts, and its structure has been motivated by realistic ionic models of cardiac excitation.

The FHN paradigm has been around for over forty years and many important asymptotic results have been obtained within it. As we have learnt that it is of limited use for cardiac excitability, the need appeared in re-doing these results with the new paradigm. The purpose of the current project was to start this and to investigate a few keystone problems, to lay the beginning of the new asymptotic theory of cardiac excitability.

Key Advances and Supporting Methodology

The study proceeded in accordance with the seven tasks laid out in the original grant proposal.

Tasks 1,2: Development of the upstroke/front model and Development of the plateau and recovery model
Derivation of the fast subsystem (4) from the Noble (N62) model of cardiac Purkinje cells [24] and Courtemanche et al. (CRN) model of human atrial tissue [25] was the preliminary work that motivated the current project [34]. The main asymptotic embedding suggested and investigated in this project is formally presented as

$$\partial E/\partial t = D\nabla^2 E + g_{\mathrm{Na}}(E_{\mathrm{Na}} - E)m^3 hj + \epsilon \sum_{j}' I_j(E, \mathbf{y}),$$

$$\partial m/\partial t = (\bar{m}(E) - m)/\tau_m(E),$$
$$\partial h/\partial t = (\bar{h}(E) - h)/\tau_h(E),$$
$$\partial j/\partial t = \epsilon(\bar{j}(E) - j)/\tau_j(E),$$
$$\partial \mathbf{y}/\partial t = \epsilon \mathbf{Y}(E, \mathbf{y}) \qquad (6)$$
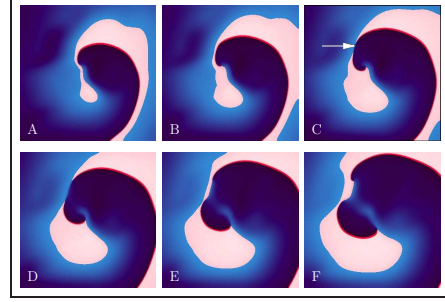

Figure 1: *Local propagation block, dissipation and break-up of the front of a re-entrant excitation wave in CRN model. The arrow indicates the time and place where the propagation block is predicted by the asymptotic theory; it is also where it really happens. From [A6].*

where $\sum_{j}'$ is the sum of all currents except the fast sodium current I_{Na} represented by the previous term, and we are interested in the limit $\epsilon \searrow 0$. We first deduced such embedding for the N62 model (which does not have the j gate) based on a well defined set of axioms, formalizing the asymptotic properties of the model, and identifying parameter regions requiring special treatment [A1, A12]. This study also has led us to suggest an "Archetypal Model" of cardiac excitation, which is a modification of the N62 model inheriting its simplicity but not having peculiar features that are incidental to this model and complicate its analysis, but instead has a structure more typical for other cardiac models. The methdology developed for N62 model, was then applied to Beeler-Reuter (BR) model of mammalian ventricular cells [26] in [A15] and CRN model in [A6, A7].

In [A10] we obtained an analytical front solution of the fast subsystem of (6), and in [A2, A6] we used this subsystem to derive an analytical criterion of front propagation, corresponding to the analogous (but different) criterion in FHN-type systems known as "Maxwell rule". This criterion is in an excellent agreement with direct numerical simulations of the full model.

The particular attention to slow subsystems was paid in [A1, A12] for N62 model, where introduction of further small parameters has allowed a complete asymptotic solution in quadratures (explicit for a "caricature" approximation of some functions). The method has been subsequently applied to the BR model, where the main asymptotic (6) gives a good quantiative approximation of the full model, and involvement of further small parameters allows further simplification to a model similar to the Archetypal Model [A15]. The main asymptotics to the CRN model reproduces well the shape of the action potential; further simplification using further small parameters is possible, some stages of which are significantly hampered by non-standard features in the internal Ca handling part of the model, which are probably unique to the CRN model [A14].

Tasks 3,4: Combining the fast and the slow subsystem, and Validation of the combined model on restitution curves
Combining the slow and the fast subsystem into a joint system leads to a hybrid description of the excitation waves, when the motion of the fronts is described by one sort of equations (front motion equations, ODEs in 1-D systems) and the evolution of the medium in between the
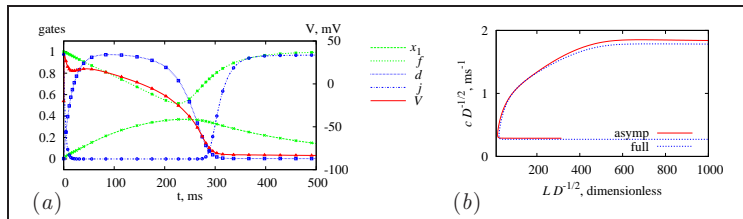

Figure 2: *Asymptotics of the BR model: (a) approximation of a typical action potential solution, lines: full model, symbols: asymptotic. (b) approximation of the conduction velocity restitution curves. From [A15].*

fronts is described by the ODEs for the slow parts of the action potential. We have described the principal formalism of such approach in [A5] and specifically for cardiac models in [A15]. Matching the two asymptotic expansions can be used to calculate the so called Restitution Curves (RCs) of cardiac models,

such as Action Potential Duration (APD) RC and Conduction Velocity (CV) RC, which describe the change of shape of the action potential and propagation velocity of periodic wavetrains depending on their periods. The RCs attract serious attention in cardiac dynamics as some their features correlate with important global characteristics of cardiac tissues, such as propensity to fibrillation. We have obtained RCs for the Archetypal (modified N62) model and the BR model using our asymptotic approach and showed they are in good agreement with the RCs calculated for the full models [A15].

Task 5: Non-stationary processes: initiation and dissipation of the fronts It has been anticipated in the proposal that the new asymptotic approach is particularly important for marginal nonstationary events such as termination and initiation of excitation waves. The termination of the excitation fronts via recently described "front dissipation" mechanisms has proved to be an easier object to study. We have shown that the conditions of existence of excitation fronts coincide with a good precision with the conditions of termination of existing fronts [A6] (fig. 1). The problem of initiation is more complicated: it is an essentially nonlinear, non-stationary and

Figure 3: *(a) "Critical front" in the CRN model. Shown are successive spatial profiles of the transmembrane voltage for initial condition slightly below (left) and slightly above (right) the initiation threshold [A11]. (b) Threshold curve obtained by linear approximation around the critical nucleus in FHN model, compared to the numerical simulations [A16]*

spatially-distributed problem. A few works on this topic done before our project were centered around the concept of the "critical nucleus", which is an unstable spatially-nonuniform solution of the ZFK equation, whose codimension one center-stable manifold serves as the threshold surface between the basins of attraction of the propagating fronts and the resting state. We have demonstrated that this concept is inapplicable to the cardiac equations and should be replaced with the concept of critical front [A9, A11]. The center-stable subspace is a linear approximation of the codimension-1 center-stable manifold and thus provides an analytical answer to the initiation problem [A16] (fig. 3).
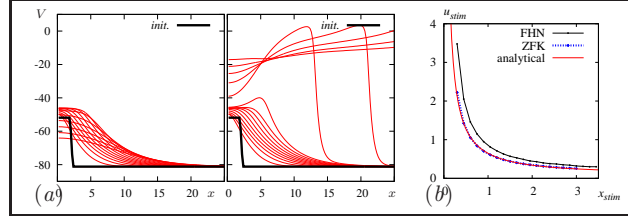
Task 6: Extension to more than one spatial dimension The two- and three-dimensional setting for excitation wave propagation poses two sorts of problems: the movement of fronts and the movement of front breaks. The movement of fronts in FHN-type systems is typically well described by the relationship $V = V_0 - DK$ where V is the local front speed, K is local front curvature and D is a constant of the dimensionality of diffusion coefficient [23, 27, 28]. We have studied the behaviour of curved fronts in fast subsystem of (6); this leads to a parametric con-

Figure 4: *Two-dimensional results. (a) Asymptotic speed-curvature relationship for fronts in the CRN model [A6]. (b) Wavebreak structure in model (4,5). Shown are also: direction of the tip velocity, direction towards centre of rotation and the tip trajectory. (c) Dependence of tip angular velocity on parameter in model (4,5) shows sign of non-unique solution and hysteresis, but all branches are consistent with the non-FHN asymptotic which has been predicted but not seen before [A17].*

tinuation of the 1D boundary-value problem for the front profile, in the parameter K. In CRN model, the resulting dependence is close to linear in a wide range of curvatures, almost up to the point where the curvature arrests propagation (fig. 4(a)).
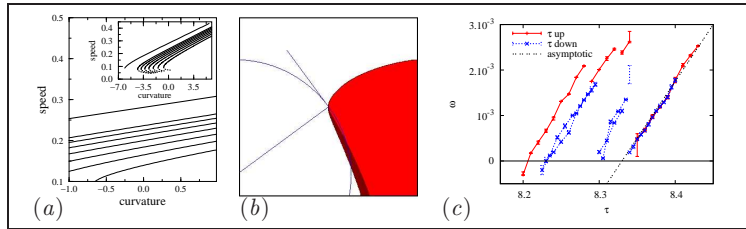
Old asymptotic theories of wavebreak motion (e.g. [28, 29, 35]) demonstrated th key role of the asymptotic of the stationary circular movement, particularly the limit of small turning rate and large trajectory radius. The dependence of tip turning rate ω on any parameter p in this limit is typically $\omega \propto |p - p_*|^n$, as $p \to p_*$. As we have demonstrated in [36], there could be two different types of such asymptotics, with $n = 1$ or $n = 3/2$. According to [30], the FHN-type systems always have $n = 3/2$, whereas the case $n = 1$ *has never been reliably identified before* in any excitable medium. In [A17], we have simulated movement of a front break in the model (4,5). Since this model does not include the processes of recovery, we have used a novel technology of calculation of the quotient system by the Euclidean group of symmetry proposed earlier in [37], in other words in the frame of reference comoving with the

wavebreak point (spiral wave tip). To assess the impact of the co-moving boundaries of the computational domain, apart from the usual comparison of results in different domains, we have calculated "response functions", i.e. eigenfunctions of the adjoint linear operator dual to the symmetry shift modes, using the "causodynamics" method [A4, A8]. We have found that the "large-core" asymptotics in this model does in fact show the non-classical dependence with $n = 1$. However the behaviour of the tip is more complicated than that, as we have discovered there are multiple solutions and hysteresis.

Task 7: Applications Application of the discovery of the front dissipation and methods of its detection is exemplified by [A3] where we have demonstrated that this phenomenon can be an essential underlying mechanism of self-termination of fibrillation in CRN. An application of the theoretical studies to experiments that occurred within the lifetime of this project is illustrated in fig. 5. Experiments with cell cultures of neonathal cardiomyocytes made in the laboratory of N. Sarvazyan, now with George Washington University, are dedicated to a long standing problem: why ischemia can produce re-entrant arrhythmias. The experimental set-up aims to reproduce *in vitro* the dynamic conditions within the border of a recovering ischemic zone. Mathematical modelling using BR model reproduces *in silico*

Figure 5: *A hypothetical mechanims of arrhythmogeneity of infarction. Upper row: generation of a spiral wave via break-up of a wave from an "ectopic nexus" in a dynically recovering ischemic zone. Experiment with neonatal rat cardiocyte culture. Lower row: generation of a spiral wave by a similar scenario and its escape into the bulk of non-ischemic tissue. Simulations of a BR model. From [A13].*

and explains key events, related to marginal non-stationary processes of generation and blocks of excitation waves, such as initiation of ectopic waves, their break-up due to tissue heterogeneity, pinning and drift of resulting spiral waves and their escape from the ischemic border zone into the bulk of the tissue. This provides an entirely plausible, experimentally confirmed and theoretically explained scenario of the genesis of so called reperfusion arrhythmias [A13, 31].

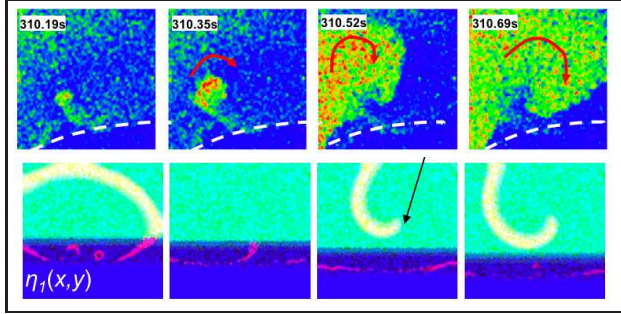So, all the objectives set out in the original plan have been achieved.

Project Plan Review

As expected, minor deviations from the plan depended on the results obtained. For instance, the discovery of multiple solutions for excitation front wavebreaks with different turning rates has been completely unexpected and attracted considerable effort at the final stage of the project at the expense of other tasks; this direction of research will be continued, as it might be of fundamental importance for understanding the movement of excitation wave breaks in realistic ionic cardiac models, which is completely beyond the classical theory based on the FHN-type asymptotics. Another minor deviation was the decision to analyse the BR model, as an intermediate step between the early models (N62) and the modern models (CRN), motivated also by the prospective application [A13].

Research Impact and Benefits to Society

The results of the project lay the foundation of further research into a new area, the realistic asymptotic analysis of ionic models of cardiac excitation. Such analysis leads to a better understanding of excitation phenomena that are of crucial importance for biomedical applications, particularly those involving generation, termination and break-up of excitation waves. Furthermore, correct asymptotic analysis can be exploited in improving the numerical simulation technologies, which could not have been done with the classical FHN-type asymptotics due to their inadequacy for cardiac models. Together, these advances will lead to a better understanding of the mechanisms of cardiac arrhythmias and help development of new means of their prevention and treatment. Thus the biomedical industry, medicine, cardiac patients and the general public are the ultimate beneficiaries.

Extra benefits can emerge via cross-fertilization with other fields, as non-standard asymptotic methods developed for cardiac models are an example for development non-standard approaches for other complex nonlinear systems with small parameters, which in principle spans across the whole of applied mathematics, with all the variety of possible applications.

Explanation of Expenditure

The most significant variations against the original plan, affecting expenditure, were:

• Staffing. The work permit for Dr Simitev was delayed by factors beyond our control. To avoid an unnecessary delay in the start of the project, Ms Suckley (PI's finishing Ph.D. student) was appointed for a short term as a post-graduate RA. In Sept. 2006 Dr Simitev accepted an offer for a permanent academic job and the position became vacant. Dr Vasiev was recruited for the rest of the project; however he was unable to start immediately. To avoid an undesirable break, Mr Idris (PI's second-year Ph.D. student) has been appointed for a short term, as a part-time PGRA. In the end, this allowed to attract extra intellectual resources within the same budget.

• RA salary. The 2005 Pay Modernization required an increase in the RA's salary, the resulting shortfall in the project's budget to be covered by the University. To avoid any (potentially very damaging for the project) controversies, the appointment of the second post-doctoral RA, Dr Vasiev, was at exactly the same spine level as his predecessor. For the same reason, the cost of the interim appointment of Mr Idris (ca £1k) was counted separately from the main salary budget, as otherwise the required contribution from the University would have been unclear and disputable.

• Duration. Dr Vasiev started in the mid-October 2006 with the remaining term of 9 months. However EPSRC advised that the overall duration of the project should be in whole months, so his appointment was extended to the end of August. This was under the same conditions and strictly within the budget.

• Equipment. Soon after the start of the project, the University has installed a new high-performance computing cluster; this has been followed by a purchase of a powerful cluster by the Department of Mathematical Sciences. This has changed our need in computational resources. We delayed the purchase of the workstation closer to the end of the project and got a better value for money. Instead, early in the project we invested in two good Linux boxes for the PI and for the RA, built from parts at low cost thanks to the assistance of the departmental computer officer.

Other variations were less significant and were dictated by current needs.

Further Research or Dissemination Activities

Publications This 3-year project resulted in 17 research papers: 9 appeared in peer-reviewed journals, 1 in peer-reviewed and 1 in not peer-reviewed conference proceedings, 2 accepted in peer-reviewed journals and 4 further papers are in preparation. This list includes *Physical Review Letters* (2 papers) and *Biophysical Journal* (2 papers), the top journals respectively in the nonlinear science community and in the physiology community (its part receptive to mathematical modelling results).

Presentations The results have been presented at (excluding internal Liverpool University events):
2004: CARDIOSTIM, Nice; Physiological Society Focused Meeting "Biocomputation and Modelling in Physiology", Oxford;
2005: Northern Cardiovascular Research Group Meeting, Liverpool; BAMC, Liverpool; Functional Imaging and Modeling of the Heart, Barcelona; European Conference on Mathematical and Theoretical Biology, Dresden; European Cardiac Functional Modelling, Manchester;
2006: Biophysical Society Annual Meeting, Salt Lake City; Kavli Institute of Theoretical Physics miniprogram "Cardiac Dynamics", Santa Barbara; "Computers in Cardiology", Valencia; European Cardiac Functional Modelling, Gandia, Spain;
2007: regional seminar "Complex Nonlinear Processes in Chemistry and Biology", Fritz Haber Institute, Berlin; Applied Mathematics seminar, Leicester; "BIOSIM: Engineering Virtual Cardiac Tissues", Manchester; BAMC, Bristol; International workshop on non-linear dynamics in excitable media, Ghent; European Heart Modelling workshop, Oxford; Applied Mathematics seminars, Glasgow, Newcastle.

Some of the further research directions Participation in the KITP miniprogram (partly supported by a separate EPSRC grant) was a significant evidence of esteem as the theoretician participants were resident through the whole duration of the program and were carefully selected. This has led to a number of perspective collaborations where the results of this project will be applicable, including such nontrival experimentally observed regimes as meandering spirals with discordant alternans (E. Entcheva, Stony Brook) and drifting foci (R. Abraham, John Hopkins Hospital), both observed in different cardiocyte cultures. Collaboration with N. Sarvazyan is to be continued, e.g. to investigate three-dimensional implications of the findings so far. Another perspective research direction is mathematical modelling of hypothetical mechanisms of the "sick sinus syndrome" (H. Zhang , modelling, M. Boyett, experiment, Manchester), a grant application is currently in preparation.

References

Publications resulted from the project   (peer reviewed marked⋆)

[A1] V. N. Biktashev and R. Suckley. Non-Tikhonov asymptotic properties of cardiac excitability. *Physical Review Letters*⋆, 93(16):168103, 2004.

[A2] V. N. Biktashev and I. V. Biktasheva. Dissipation of excitation fronts as a mechanism of conduction block in re-entrant waves. *Lecture Notes in Computer Science*⋆, 3504:283–292, 2005.

[A3] I. V. Biktasheva, V. N. Biktashev, and A. V. Holden. Wavebreaks and self-termination of spiral waves in a model of human atrial tissue. *Lecture Notes in Computer Science*⋆, 3504:293–303, 2005.

[A4] V. N. Biktashev. Causodynamics of autowave patterns. *Physical Review Letters*⋆, 95(8):084501, 2005.

[A5] V. N. Biktashev and M. A. Tsyganov. Solitary waves in excitable systems with cross-diffusion. *Proceedings of the Royal Society of London series A*⋆, 461(2064):3711–3730, 2005.

[A6] R. D. Simitev and V. N. Biktashev. Conditions for propagation and block of excitation in an asymptotic model of atrial tissue. *Biophysical Journal*⋆, 90(7):2258–2269, 2006.

[A7] I. V. Biktasheva, R. D. Simitev, R. Suckley, and V. N. Biktashev. Asymptotic properties of mathematical models of excitability. *Phil. Trans. Roy. Soc. Lond. ser. A*⋆, 364(1842):1283–1298, 2006.

[A8] I. V. Biktasheva, A. V. Holden, and V. N. Biktashev. Localization of response functions of spiral waves in the FitzHugh-Nagumo system. *International Journal of Bifurcation and Chaos*⋆, 16(5):1547–1555, 2006.

[A9] I. Idris, R. D. Simitev, and V. N. Biktashev. Using novel simplified models of excitation for analytic description of initiation propagation and blockage of excitation waves. *Computers in Cardiology*, 33:213–216, 2006.

[A10] R. D. Simitev and V. N. Biktashev. Analytically solvable asymptotic model of atrial excitability. In *Proceedings of The European Conference on Mathematical and Theoretical Biology, Dresden, July 18-22, 2005*⋆, volume 2, pages 313–326, 2007.

[A11] I. Idris and V. N. Biktashev. Critical fronts in initiation of excitation waves. *Physical Review E*⋆, 76(2):021906, 2007.

[A12] V. N. Biktashev, R. Suckley, Y. E. Elkin, and R. D. Simitev. Asymptotic analysis and analytical solutions of a model of cardiac excitation. *Bulletin of Mathematical Biology*⋆, to appear, 2007; arXiv:q-bio/0607047.

[A13] V. N. Biktashev, A. Arutunyan, and N. A. Sarvazyan. Generation and escape of local waves from the boundary of uncoupled cardiac tissue. *Biophysical Journal*⋆, Submitted, 2007; arXiv:0711.2945.

[A14] R. Suckley and V. N. Biktashev. Asymptotics of the action potential in a model of human atrial cells. *In preparation*, 2007.

[A15] R. D. Simitev and V. N. Biktashev. Asymptotic restitution curves for cardiac excitability equations. *In preparation*, 2007.

[A16] I. Idris and V. N. Biktashev. An analytical approach to the initiation of excitation waves. *In preparation*, 2007.

[A17] A. J. Foulkes, B. N. Vasiev, and V. N. Biktashev. Spiral wave dynamics in the symmetry-quotient system: application to large-core and spontaneously drifting spirals. *In preparation*, 2007.

Other references

[18] D. Noble, BioEssays **24**, 1155 (2002).

[19] B. van der Pol, Radio Review London **1**, 701 (1920).

[20] Y. B. Zel'dovich and D. A. Frank-Kamenetsky, Doklady AN SSSR **19**, 693 (1938).

[21] R. A. FitzHugh, Biophys. J. **1**, 445 (1961).

[22] J. Nagumo, S. Arimoto, and S. Yoshizawa, Proc. IRE **50**, 2061 (1962).

[23] J. J. Tyson and J. P. Keener, Physica D **32**, 327 (1988).

[24] D. Noble, J. Physiol. **160**, 317 (1962).

[25] M. Courtemanche, R. J. Ramirez, and S. Nattel, Am. J. Physiol. **275**, H301 (1998).

[26] G. Beeler and H. Reuter, J. Physiol. **268**, 177 (1977).

[27] V. S. Zykov, *Simulation of Wave Processes in Excitable Media* (Manchester University Press, Manchester, 1987).

[28] A. S. Mikhailov, V. A. Davydov, and V. S. Zykov, Physica D **70**, 1 (1994).

[29] F. Fenton and A. Karma, Chaos **8**, 20 (1998).

[30] V. Hakim and A. Karma, Phys. Rev. Lett. **79**, 665 (1997).

[31] A. Pumir, A. Arutunyan, V. Krinsky, and N. Sarvazyan, Biophys.J. **89**, 2332 (2005).

[32] H. P. McKean, Jr., Adv. Appl. Math. **4**, 209 (1970).

[33] V. N. Biktashev, Phys. Rev. Lett. **89**, 168102 (2002).

[34] V. N. Biktashev, Int. J. of Bifurcation and Chaos **13**, 3605 (2003).

[35] Y. E. Elkin, V. N. Biktashev, and A. V. Holden, Chaos Solitons & Fractals **9**, 1597 (1998).

[36] Y. E. Elkin, V. N. Biktashev, and A. V. Holden, Chaos Solitons & Fractals **14**, 385 (2002).

[37] V. N. Biktashev, A. V. Holden, and E. V. Nikolaev, Int. J. of Bifurcation and Chaos **6**, 2433 (1996).