Spatiotemporal Dynamics in Spontaneous Excitable Cells

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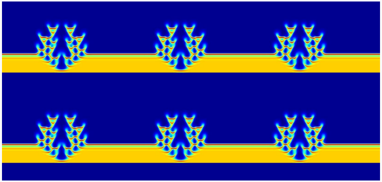


Introduction

- Excitation-contraction coupling (ECC) is the contraction of muscle cell due to its excitation in response to an external stimulation.
- In some muscle cells, for example smooth muscle cell (SMC), ECC activity is spontaneous due to ion fluxes in the cell membrane through the voltage-gated ion channels.
- This type of behaviour is known as *pacemaker dynamics*.

Research goals

Motivation

- *In vivo* studies showed that pacemaker ECC activity observed in a arterial muscle cells depend on transmural pressure.
- Upon elevation of transmural pressure, spontaneous electrical firing is observed and the blood vessel constricts. [1]

Aim

- To investigate mathematically how parameters involved in the equations governing transmural pressure influence the ionic mechanisms and ECC activity of smooth muscle cells in feline cerebral arteries.
- To study the collective behaviour of the SMCs by using a reaction-diffusion system and incorporating gap junction coupling between cells.

[1] Harder 1984

Gap-junction Coupling of SMCs

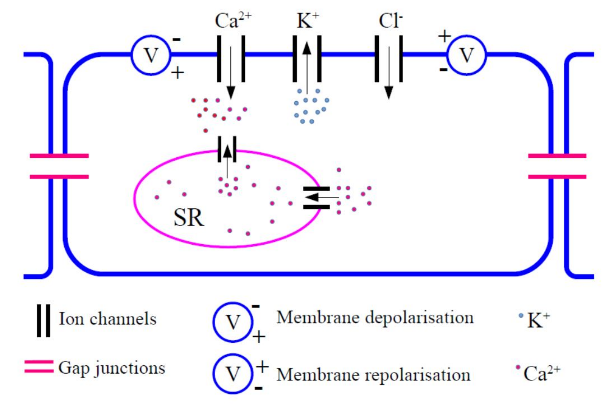


Figure 1: Schematic representation of a smooth muscle cell coupled electrically to adjacent cells

Model Formulation

$$\frac{\partial V}{\partial \tau} = D\frac{\partial^2 V}{\partial X^2} - \bar{g}_L(V - \bar{v}_L) - \bar{g}_K N(V - \bar{v}_K) - \bar{g}_{\mathrm{Ca}} M_\infty(V)(V - 1), \quad (1)$$

$$\frac{\partial N}{\partial \tau} = \lambda_N(V)\big(N_\infty(V) - N\big), \quad (2)$$

where V is the membrane potential, N is the fraction of open potassium channels, and

$$M_\infty(V) = 0.5\left(1 + \tanh\left(\frac{V - \bar{v}_1}{\bar{v}_2}\right)\right)$$

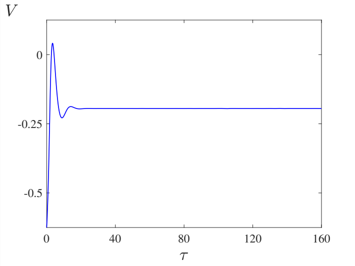
$$N_\infty(V) = 0.5\left(1 + \tanh\left(\frac{V - \bar{v}_3}{\bar{v}_4}\right)\right)$$

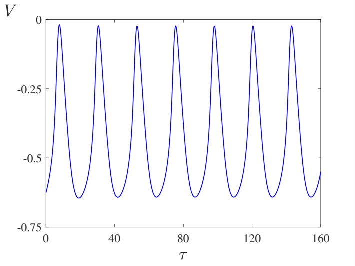
$$\lambda_N(V) = \psi \cosh\left(\frac{V - \bar{v}_3}{2\bar{v}_4}\right),$$

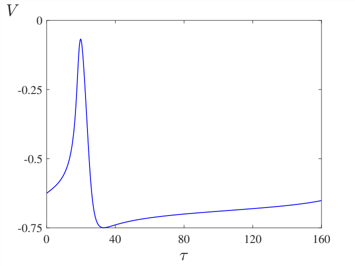
- no-flux boundary conditions
- initial conditions: perturbation around the steady state
- $\bar{v}_1$ and $\bar{v}_3$ are pressure dependent

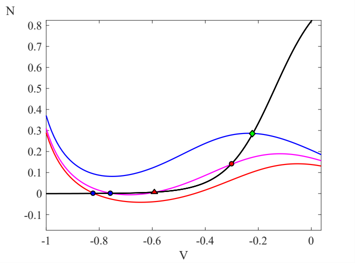
Dynamics of an Isolated Cell

For the range of values of $\bar{v}_1$ and $\bar{v}_3$ considered, the system either converge to a steady state or oscillate.



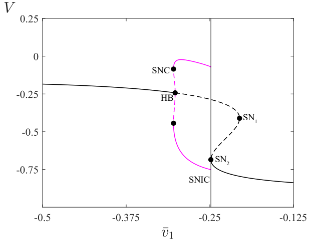


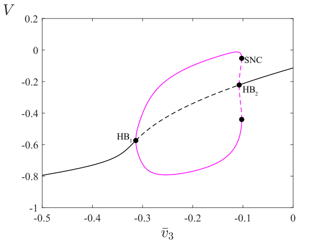


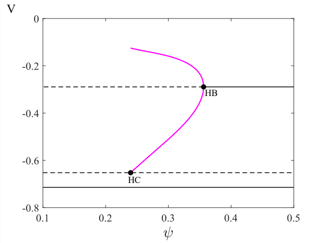


Codimension-1 Bifurcation Analysis

Modulation of model parameter induces type I and type II excitability.







Transition between Type I and Type II Excitability

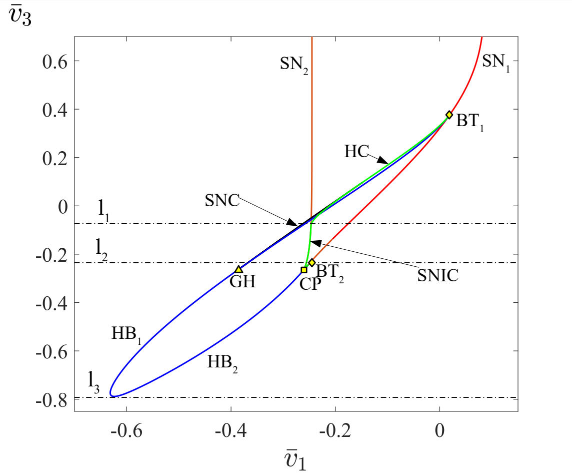


Figure 3: Codimension-2 bifurcation diagram in $(\bar{v}_1, \bar{v}_3)$-plane. The codimension-2 bifurcations are: Bogdanov-Takens-BT, Generalised Hopf-GH, Cusp point-CP

Numerical Simulations of Reaction-Diffusion (RD) Model

- Numerical method: Method of lines
- Initial conditions: $V(0, X) = V_0 + A_0 exp(-(\frac{X - X_0}{\sigma})^2)$
  $N(0, X) = N_0$

where V_0 and N_0 are homogeneous steady states, A_0 is the height of the Gaussian

Variation of model parameters results in wide range of spatiotemporal patterns including

- non-stationary irregular spatiotemporal patterns
- travelling pulses
- fronts with irregular spatiotempoaral oscillations

Spatiotemporal Patterns Varying $\bar{v}_1$

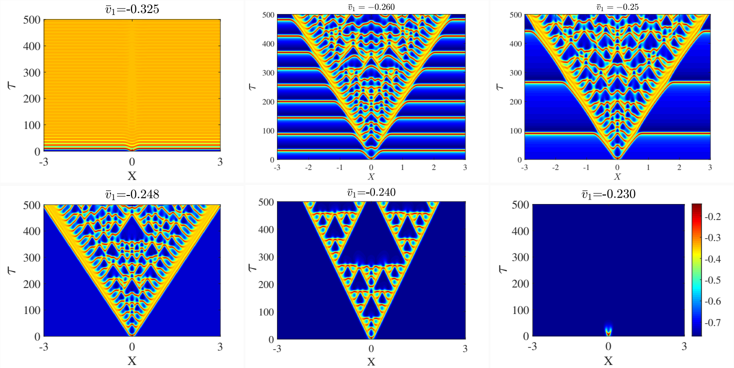


Figure 4: Space-time plot of the membrane potential V for selected values of parameter $\bar{v}_1$

Spatiotemporal Patterns Varying ψ

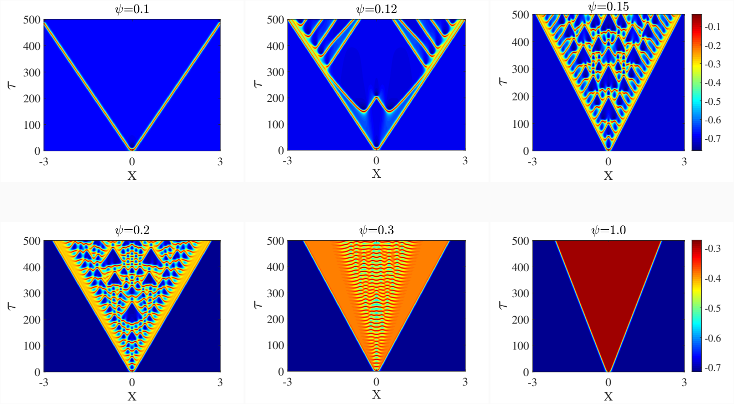


Figure 5: Space-time plot of the membrane potential V for selected values of parameter ψ

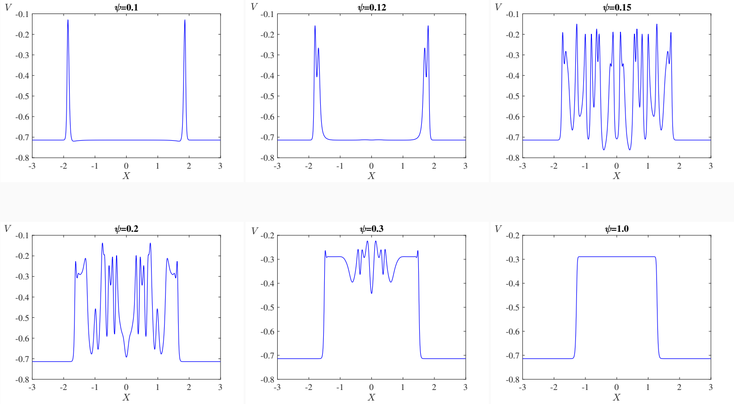


Figure 6: Solution profiles of the membrane potential V at time $\tau = 300$ showing transitions from stable pulses to spatiotemporal chaos and to fronts.

Travelling Wave Analysis

Introducing the travelling wave variable, $\xi = X - c\tau$ such that the RD model in moving coordinate frame becomes

$$\begin{pmatrix} V \\ N \end{pmatrix}_\tau = D \begin{pmatrix} V \\ 0 \end{pmatrix}_{\xi\xi} + \begin{pmatrix} cV \\ cN \end{pmatrix}_\xi + \begin{pmatrix} f(V,N) \\ g(V,N) \end{pmatrix}, \tag{3}$$

where

$$\begin{aligned} f(V,N) &= -\bar{g}_L(V - \bar{v}_L) - \bar{g}_K N(V - \bar{v}_K) - \bar{g}_{\mathrm{Ca}} M_\infty(V)(V - \bar{v}_{\mathrm{Ca}}), \\ g(V,N) &= \lambda_N(V)\big(N_\infty(V) - N\big). \end{aligned}$$

A travelling wave is a stationary solution to the RD which satisfies

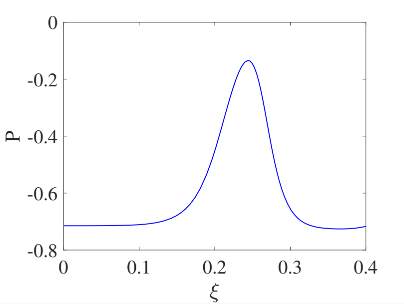
$$D \begin{pmatrix} V \\ 0 \end{pmatrix}_{\xi\xi} + \begin{pmatrix} cV \\ cN \end{pmatrix}_\xi + \begin{pmatrix} f(V,N) \\ g(V,N) \end{pmatrix} = 0, \tag{4}$$

with boundary conditions:

$$\lim_{\xi \to \pm\infty} V(\xi) = V_\pm, \quad \lim_{\xi \to \pm\infty} N(\xi) = N_\pm. \tag{5}$$

Existence of Travelling Pulse

We found numerically a travelling pulse with wave speed $c = 0.00568$



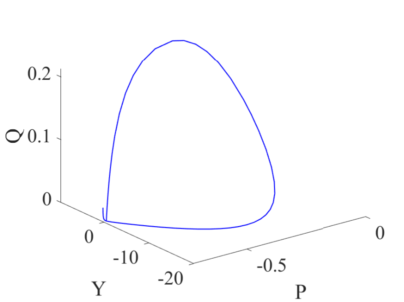


Figure 7: (a) Travelling pulse (b) Homoclinic orbit corresponding to the travelling pulse

Conclusion

- We investigated the role of physiological parameters on ECC in SMCs of cerebral arteries of feline.
- We found that the system can model Type I and II excitability depending on parameter regime.
- The results indicate that in some parameter regimes the coupled cells exhibit spatiotemporal chaos.
- These results could be useful in improving the understanding of physiological responses and disorders in smooth muscle cells.

Ongoing work

- Spectral stability analysis of the travelling wave solutions.

Future Directions

- Investigate the effects on ion conductance on pacemaker dynamics.
- Modification to model by adding the Na^+ inward current.

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ORIGINAL ARTICLE

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Numerical Bifurcation Analysis of Pacemaker Dynamics in a Model of Smooth Muscle Cells

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Abstract

Evidence from experimental studies shows that oscillations due to electro-mechanical coupling can be generated spontaneously in smooth muscle cells. Such cellular dynamics are known as *pacemaker dynamics*. In this article, we address pacemaker dynamics associated with the interaction of Ca^{2+} and K^+ fluxes in the cell membrane of a smooth muscle cell. First we reduce a pacemaker model to a two-dimensional system equivalent to the reduced Morris–Lecar model and then perform a detailed numerical bifurcation analysis of the reduced model. Existing bifurcation analyses of the Morris–Lecar model concentrate on external applied current, whereas we focus on parameters that model the response of the cell to changes in transmural pressure. We reveal a transition between Type I and Type II excitabilities with no external current required. We also compute a two-parameter bifurcation diagram and show how the transition is explained by the bifurcation structure.

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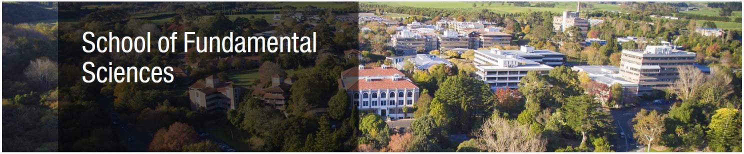

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