THE UNIVERSITY of LIVERPOOL

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Initiation and Block of Excitation Waves: Some Analytical Insights

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Philosophy

- Cardiac equations are difficult for numerical simulations, because of small parameters
- Small parameters are good for doing asymptotics, to obtain
  - simplified models for numerical study, or
  - In some cases, analytical answers or at least qualitative insights

Plan

1. Asymptotic structure of heart excitability: *what are the "correct" small parameters?*
2. Conduction block
3. Initiation
4. Spirals and scrolls

1: What are the correct small parameters?

VNB, RS, RDS

Detailed ionic models: typical structure

$$\partial_t V = D\nabla^2 V - \frac{(I_{\mathrm{Na}}(V,m,h,j) + \Sigma_I'(V,\dots))}{C_M}$$
$$\partial_t m = \frac{(\overline{m}(V) - m)}{\tau_m(V)},$$
$$\partial_t h = \frac{(\overline{h}(V) - h)}{\tau_h(V)},$$
$$\partial_t u_a = \frac{(\overline{u_a}(V) - u_a)}{\tau_{u_a}(V)},$$
$$\partial_t w = \frac{(\overline{w}(V) - w)}{\tau_w(V)},$$
$$\partial_t o_a = \frac{(\overline{o_a}(V) - o_a)}{\tau_{o_a}(V)},$$
$$\partial_t d = \frac{(\overline{d}(V) - d)}{\tau_d(V)},$$
$$\partial_t \mathbf{U} = \mathbf{F}(V,\dots)$$

Is it possible to “simplify”?

Encouraging examples:
Fenton-Karma, Panfilov et al., …

Disadvantages: often “guessed” rather than “derived” => unreliable.

Regular methods?

Hodgkin-Huxley: mother of all cardiac equation

- (Noble 1962, very similar structure)

$$\frac{\partial V}{\partial t} = g_{Na}\,(E_{Na} - V)\,m^3 h + g_K\,(E_K - V)\,n^4 + g_l\,(V_l - V) + D\frac{\partial^2 V}{\partial x^2}$$
$$\frac{\partial m}{\partial t} = (\overline{m}(V) - m)\,/\tau_m(V)$$
$$\frac{\partial h}{\partial t} = (\overline{h}(V) - h)\,/\tau_h(V)$$
$$\frac{\partial n}{\partial t} = (\overline{n}(V) - n)\,/\tau_n(V)$$

These are based on experiments

FitzHugh-Nagumo Equations

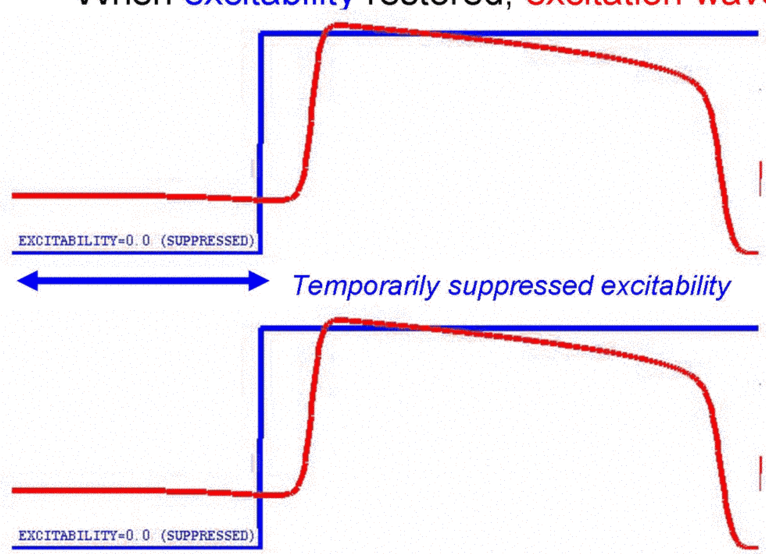
- FHN: would-be simplification of HH and the like

$$\frac{\partial u}{\partial t} = \varepsilon_u(u - u^3/3 - v) + \frac{\partial^2 u}{\partial x^2}$$
$$\frac{\partial v}{\partial t} = \varepsilon_v(u + \beta - \gamma u)$$

Analytically tractable for $\varepsilon_v \ll \varepsilon_u$, BUT:
not derived from real biophysics!

Temporary block in a traditional simplified excitable model (FHN)

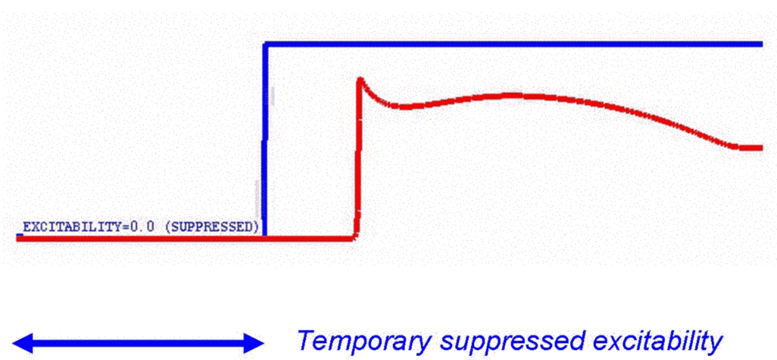
When excitability restored, excitation wave



- resumes if excited region survived
- fails if excited region thinned out to zero

Temporary block in a detailed model (Courtemanche et al, 1998)

When excitability restored, excitation wave



- fails to resume even if the back is still far away from the front!

"Parametric embedding"

- Experiment based models contain *constants*, not *parameters*
- "Small parameters" are ***always*** introduced artificially ("identified")
- How to introduce those parameters: depends on the class of solutions you are interested in

Detailed cardiac excitability models: what is small or large?

- *m*-gate is ultrafast
- *h*-gate is relatively fast

- I_{Na} is large but only when gates are open
- I_{Na} is much smaller when gates are closed (the window current)

}

- **Na gates are near-perfect switches**

(unusual small parameters)

Simplified models should be based on the realistic asymptotics of realistic equations

The fast subsystem (describes onset)

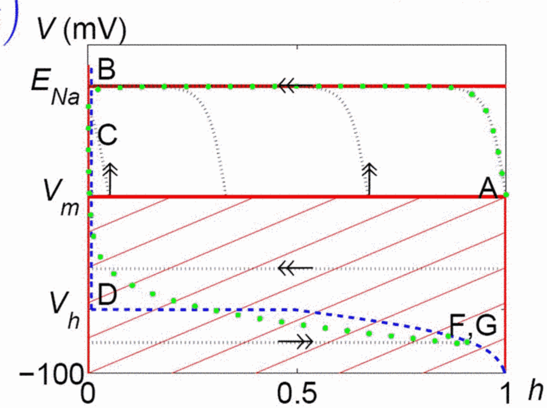
!

$$\frac{\partial V}{\partial T} = g_1(V)\,M(V)\,\theta(V-V_m)\,h\left(+\frac{\partial^2 V}{\partial X^2}\right)$$

$$\frac{\partial h}{\partial T} = f_1(V)\,[H(V)\,\theta(V_h - V) - h]$$

$$\frac{\partial n}{\partial T} = 0.$$

- Rather peculiar mathematically
- Universal across realistic models
- More complicated than the fast system in FHN but still ***can be solved analytically***



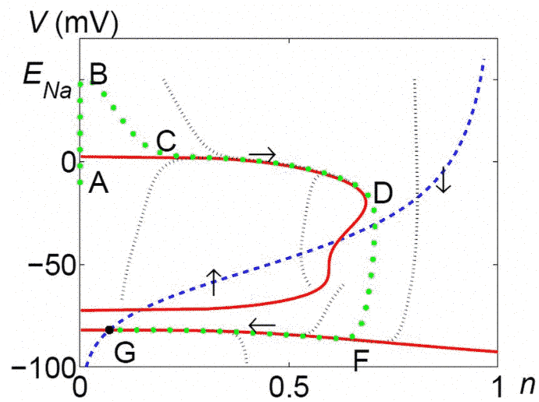
NB: *V* (+∞) depends on *h* (0) => upstroke in single cell AP vs propagating pulse

The slow subsystem (describes plateau/return/recovery)

$$\frac{\partial V}{\partial t} = g_1(V)\,W(V) + g_2(V)\,n^4 + g_3(V)$$
$$h = H(V)\,\theta(V_h - V)$$
$$\frac{\partial n}{\partial t} = f_2(V)\,(\overline{n}(V) - n)$$

- mathematically, more traditional
- less universal across ionic models

Cf Krinsky & Kokoz 1973



Simplified model of a I_{Na}-driven front

- Crude simplifications to fast subsystem:

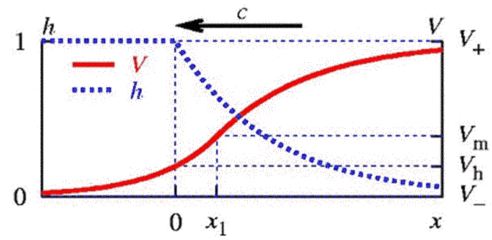
$$\frac{\partial V}{\partial T} = g_1(V)\,M(V)\,\theta(V - V_m)\,h\,\left(+\frac{\partial^2 V}{\partial X^2}\right) \qquad g_1(V)\,M(V) \;\mapsto\; j = \text{const}$$
$$\frac{\partial h}{\partial T} = f_1(V)\,[H(V)\,\theta(V_h - V) - h] \qquad f_1(V) \;\mapsto\; 1/\tau = \text{const}$$
$$\frac{\partial n}{\partial T} = 0. \qquad H(V) \;\mapsto\; 1$$

- Result: very simple system of equations:

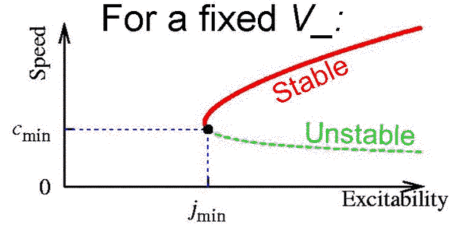
$$\frac{\partial V}{\partial t} = j\,\theta(V - V_m)\,h + \frac{\partial^2 V}{\partial x^2}$$
$$\frac{\partial h}{\partial t} = (\theta(V_h - V) - h)\,/\tau$$

Exact results in simplified model of a I_{Na}-driven front

Front solution



For a fixed $V\_$:

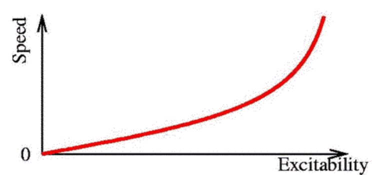


Analytical conditions:

$$j > j_{min}(V_-)$$

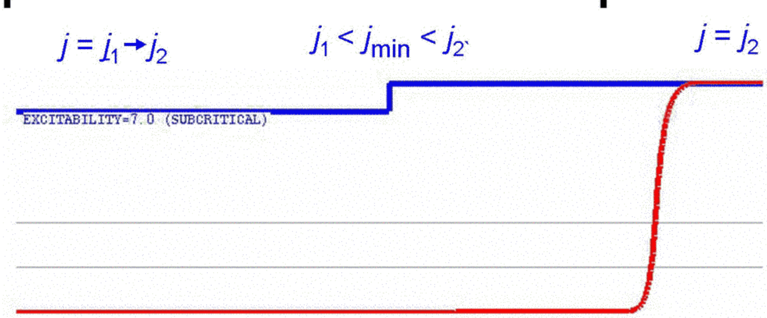
$$c = c(j, V_-) > c_{min}(V_-)$$

Cf the same in FHN:



I_{Na}-driven front cannot propagate slower than c_{min}

The new simplified model reproduces front dissipation



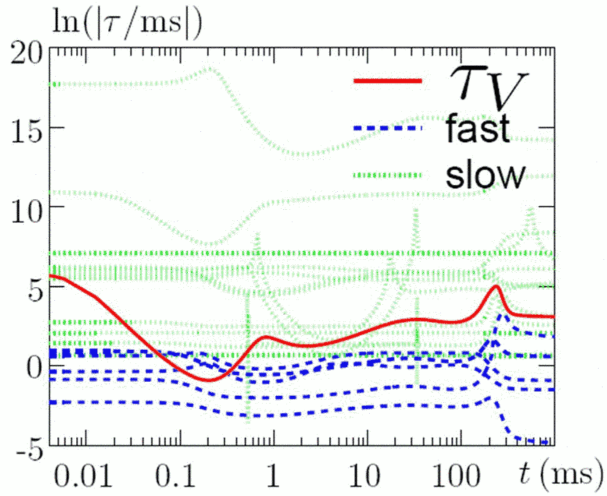
- **Front dissipates if not allowed to propagate fast enough**

(like car engine stalls if the car goes too slowly on gear)

- **It does *not* resume if propagation conditions are restored**

(like stalled engine does not restart by simply releasing the brakes and pressing the accelerator)

Courtemanche et al. 1998: relative speeds of variables



Biktashev et al. 2005

- Definition of τ:

$$\tau_i(x_1, \dots, x_N) \equiv \left|(\partial f_i / \partial x_i)^{-1}\right|.$$

- Speed of variables varies with time and at the various phases of the action potential but on the average
- V, m, h, u_a, w, o_a, d are **fast**
- The rest of the dynamical variables are considered **slow**

Courtemanche et al. 1998: asymptotic structure

$$\partial_t V = D\partial_x^2 V - C_M^{-1}\left(\epsilon_2{}^{-1} I_{\mathrm{Na}}(V,m,h,j) + \Sigma_I'(V,\dots)\right),$$

$$\partial_t m = \frac{(\overline{m}(V;\epsilon_2) - m)}{\epsilon_1\epsilon_2\tau_m(V)}, \quad \overline{m}(V;0) = M(V)\theta(V - V_m),$$

$$\partial_t h = \frac{(\overline{h}(V;\epsilon_2) - h)}{\epsilon_2\tau_h(V)}, \quad \overline{h}(V;0) = H(V)\theta(V_h - V),$$

$$\partial_t u_a = \frac{(\overline{u_a}(V) - u_a)}{\epsilon_1\epsilon_2\tau_{u_a}(V)},$$

$$\partial_t w = \frac{(\overline{w}(V) - w)}{\epsilon_1\epsilon_2\tau_w(V)},$$

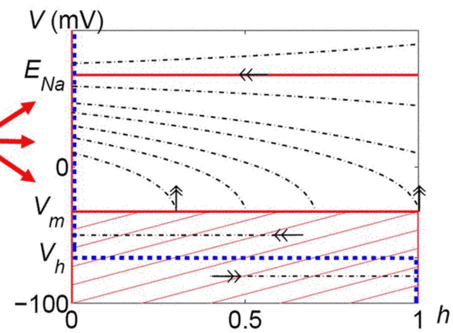
$$\partial_t o_a = \frac{(\overline{o_a}(V) - o_a)}{\epsilon_2\tau_{o_a}(V)},$$

$$\partial_t d = \frac{(\overline{d}(V) - d)}{\epsilon_2\tau_d(V)},$$

$$\partial_t \mathbf{U} = \mathbf{F}(V,\dots)$$

=> fast subsystem similar to N62:

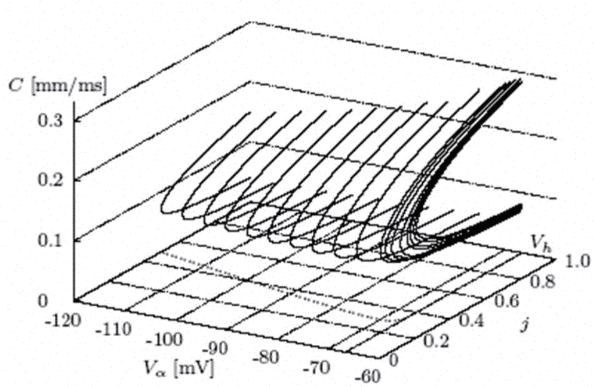
NB: *V* (+∞) depends on *h* (0) => upstroke in single cell AP vs propagating pulse



2: Conduction block

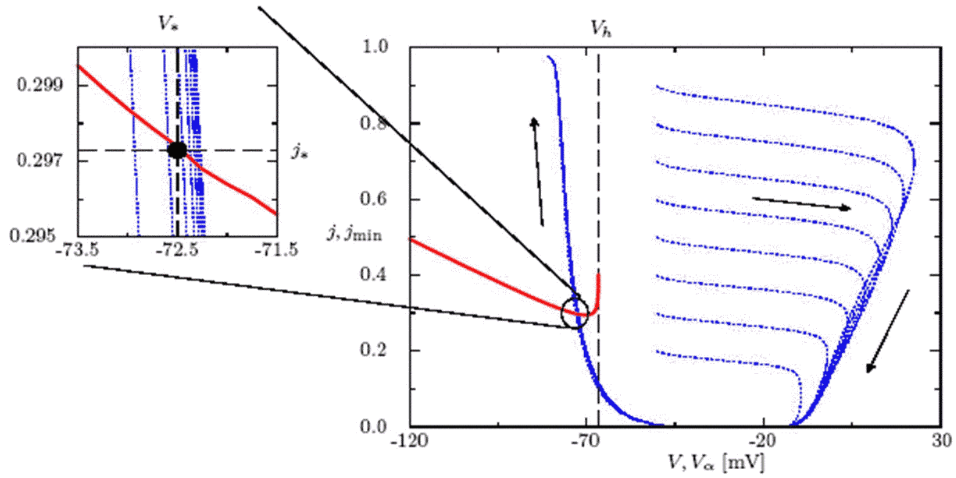
VNB, IVB, RDS

Front velocity in the fast subsystem of Courtemanche et al 1998



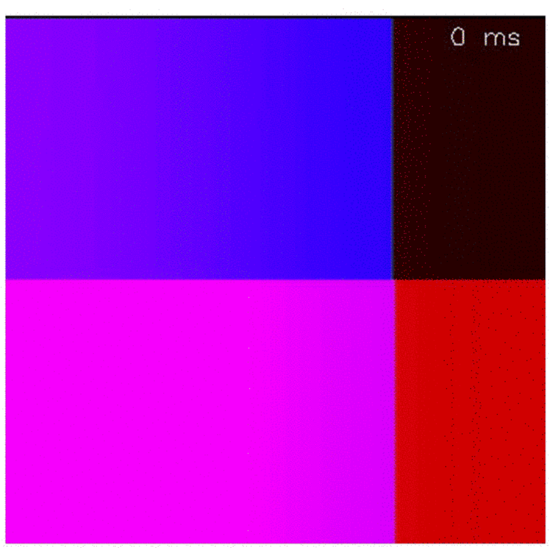
- Accurate numerical solution for fronts in the fast subsystem
- Propagation *c* depends on pre-front voltage V_α and excitability parameter *j*

Prediction: threshold of absolute refractoriness



$$(j_*, V_*) = (0.2975 \pm 0.0015, -72.5 \pm 0.5)$$

Prediction tested in direct numeric simulations



- Red: the voltage
- Blue: $j<j_*$
- Yellow: block, at:
  - 740 ms
  - 1120 ms
  - 3740 ms
  - 3860 ms

Cf Otani's and Salama's talks !

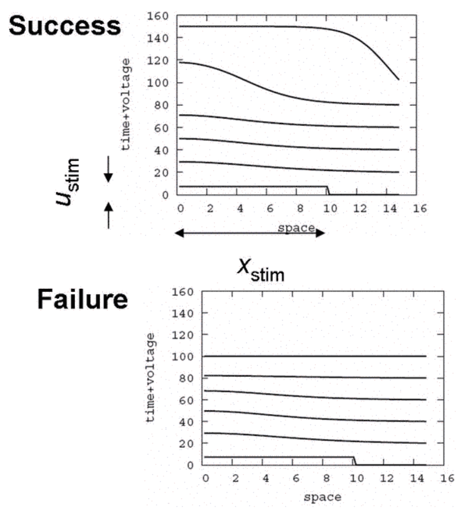
Further goals

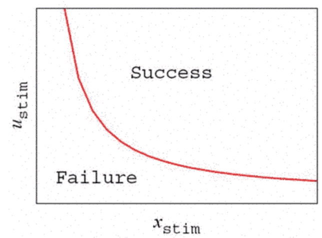
- Simplify the description of the AP shape (further small parameters in the slow subsystem)
- Combine the two to produce “derived” => “reliable” simplified versions of detailed ionic models, hopefully computationally efficient (almost done for Noble-62, CRN in pipeline)
- Should allow *ab initio* derivation of restitution curves etc

3: Initiation

VNB, II

Initiation by a rectangular initial condition, x_{stim} x u_{stim}





- There exist a theory for FitzHugh-Nagumo
- Suspect: cardiac equations are different
- Goal: describe that in a novel simplified model

Critical nucleus in ZFK ("Nagumo") equation

$$u_t = u_{xx} - f'(u) \qquad f'(u) = u(\theta - u)(1-u)$$

- "Critical nucleus":

$$u_{cr}(x) = \frac{3\theta\sqrt{2}}{(1+\theta)\sqrt{2} + \sqrt{(2 - 5\theta + \theta^2)}\cosh(x\sqrt{\theta})}$$

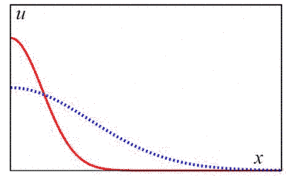
--- stationary, unstable, *one* positive e.v.

- Codim 1 stable manifold = threshold

Galerkin projection of the same

Ansatz:

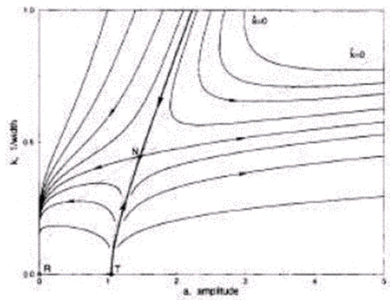
$$u(x,t) \approx a(t)\exp(-(k(t)x)^2)$$



$\Rightarrow$ ODE system in the limit of small θ:

$$\dot{a} = -a(2k^2 + 1 - c_1 a)$$
$$\dot{k} = -k(2k^2 - c_2 a)$$

(Neu, Preissig, Krassowska, Physica D, 1997; also Argentina et al various papers, and others)



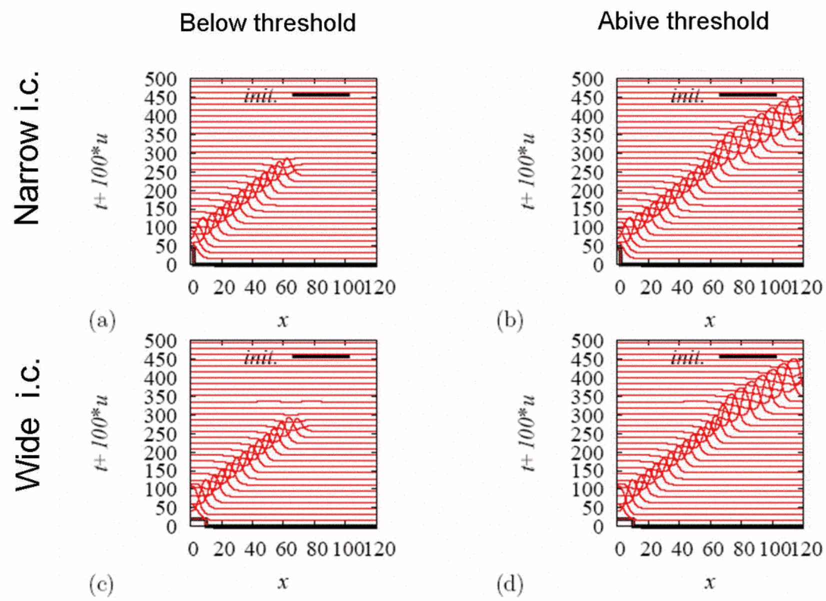
Initiation in FHN: conjecture

$$u_t = u_{xx} - f'(u) - v$$
$$v_t = \varepsilon(\alpha u - v)$$

- No critical nucleus solutions
- Unstable pulse, *one* positive e.v. *(Flores 1991)*
- Its codim 1 stable manifold = threshold?

NB: unstable pulse instead of critical nucleus

Initiation in FHN: confirmation



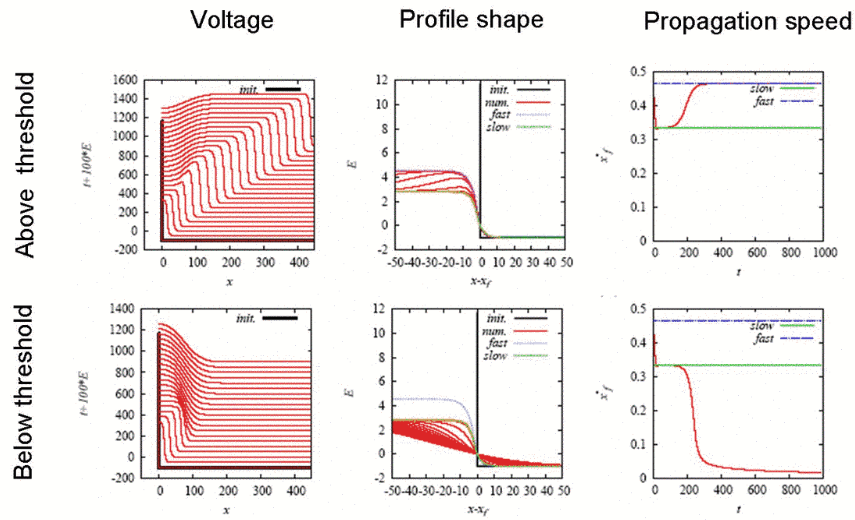
Initiation in front model: conjecture

$$E_t = E_{xx} + \theta(E-1)h$$
$$h_t = (1/\tau)(\theta(-E) - h)$$

- No critical nucleus solutions
- Unstable front, *one* positive e.v. *(Hinch 2004)*
- Its codim 1 stable manifold = threshold?

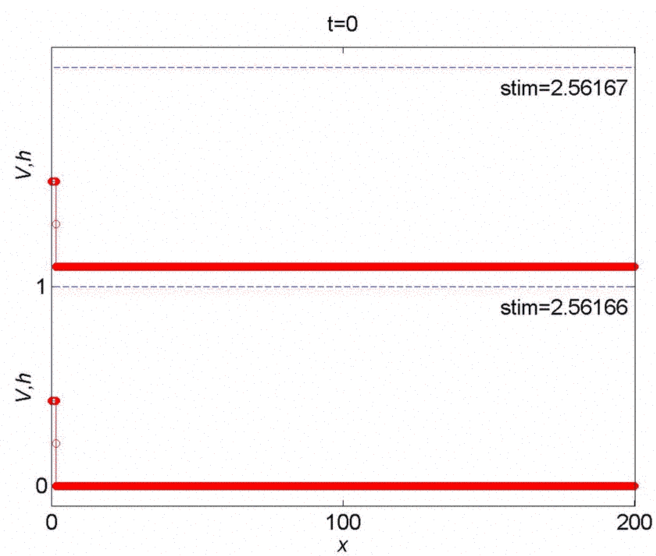
NB: unstable front instead of critical nucleus

Initiation in front model: confirmation

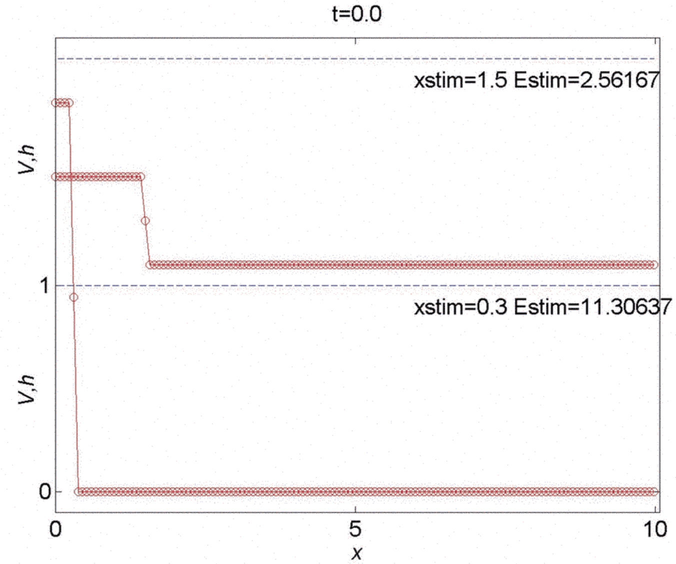


Exact solutions: --- stable --- unstable

Unstable front as the threshold solution



Different initial conditions, same threshold solution



Further goals

- An appropriate approximation of the stable manifold of the unstable front shall therefore produce an analytical criterion of wave initiation
- Apply to “discontinuous propagation”, “ectopic nexus” and other phenomena where initiation thresholds are crucial

Cf Pumir's talk !

4: Drift of spirals and scrolls

VNB, IVB

Phenomenology of spirals and scrolls

Meander of spirals

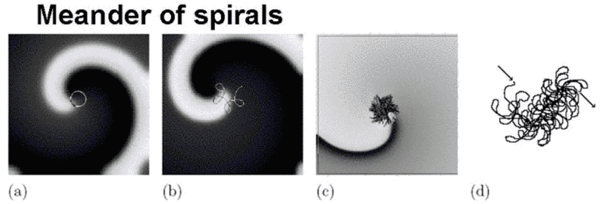


Figure 1. Typical meander patterns. Shown are snapshots of the excitation field with

Drift of spirals

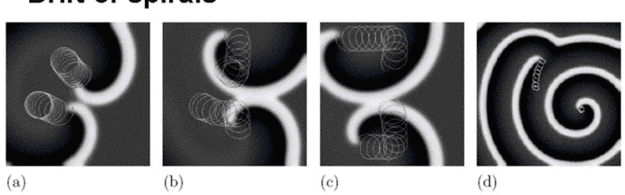
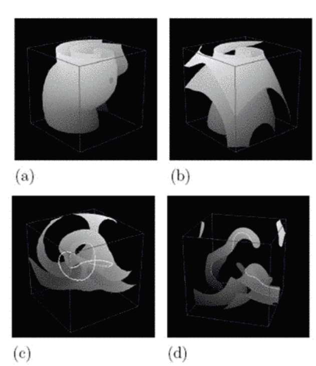


Figure 2. Different drifts of spiral waves. Shown are snapshots of the excitation

Scroll waves



Pictures from "Vortex dynamics in excitable media", *Encyclopedia of Nonlinear Sciences*

Asymptotic theory of drift

- "Unperturbed": infinite, homogenous, time-independent equations, symmetric solution
- Small parameters: spatial inhomogeneity, time-dependent forcing, bending and twisting of scrolls (but NOT small parameters of the kinetics)
- => Equations of motion:

$$\frac{\mathrm{d}\Phi}{\mathrm{d}t} = \bar{\mathbf{F}}_0, \qquad \frac{\mathrm{d}X}{\mathrm{d}t} + i\frac{\mathrm{d}Y}{\mathrm{d}t} = \bar{\mathbf{F}}_1$$

Response functions

The "forces" determining the drift are

$$\bar{\mathbf{F}}_n(t) = e^{in\Phi} \oint_{t-\pi/\omega}^{t+\pi/\omega} \frac{\omega \mathrm{d}\tau}{2\pi} \iint_{\mathbb{R}^2} \mathrm{d}^2\mathbf{r}\, e^{-in\omega\tau} \cdot \left\langle \tilde{\mathbf{Y}}_n \left(\rho(\mathbf{r}-\mathbf{R}), \vartheta(\mathbf{r}-\mathbf{R}) + \omega\tau - \Phi\right), \mathbf{h} \right\rangle$$

where

$$\mathbf{h} = \mathbf{h}(\mathbf{r},\tau), \ \mathbf{R} = \mathbf{R}(t), \ \Phi = \Phi(t),$$

and *response functions* $\tilde{\mathbf{Y}}_n$ are the critical eigenfunctions

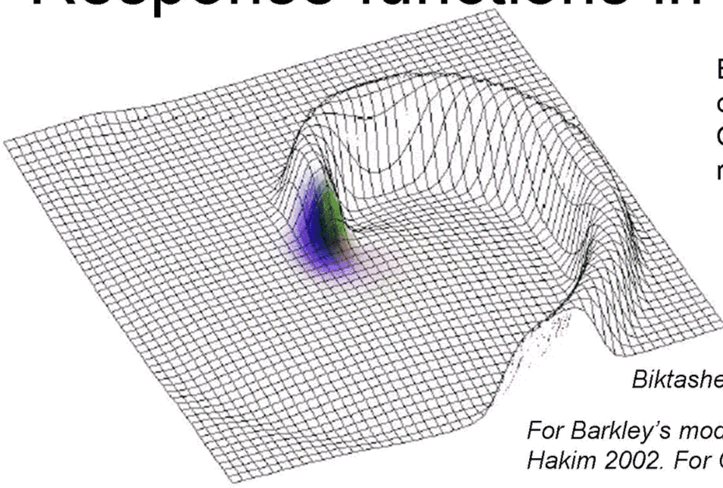
$$\tilde{\mathcal{L}}^{+}\tilde{\mathbf{Y}}_n = -i\omega n \tilde{\mathbf{Y}}_n, \quad n = 0, \pm 1$$

of the adjoint linearised operator

$$\tilde{\mathcal{L}}^{+} = \mathbf{D}\nabla^2 - \omega\partial\vartheta + \left(\frac{\partial \mathbf{f}}{\partial \mathbf{u}}\right)^{+}_{\mathbf{u}=\mathbf{U}(\mathbf{r})}.$$

Biktashev, Holden, 1995 *Cf Zykov's talk* !

Response functions in FHN



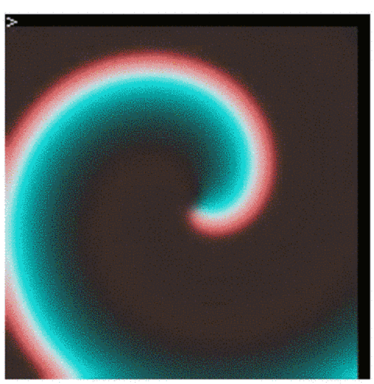
Elevation: the distribution of the voltage.
Colour components: the response functions

Biktasheva, Holden, Biktashev, 2006

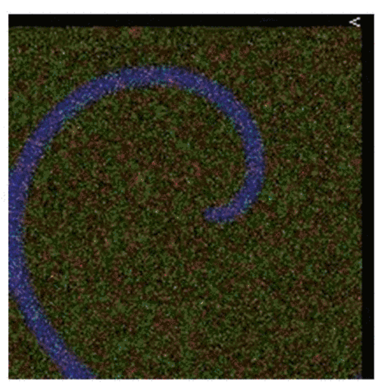
For Barkley's model: Hamm 1997, Henry & Hakim 2002. For CGL: Biktasheva et al 1998

Small parameters can allow some analytical success *(Hakim & Karma 1998, Elkin & Biktashev 1999).* May simplified front model allow finding these analytically for cardiac models?

"Causodynamics" method of calculating the response functions



Spiral wave, calculated ***forward*** in time



RFs,calculated ***backward*** in time

Biktashev 2005

Numerical procedure that reveals parts of a complex system that are most important for subsequent events
(applicable to other problems, e.g. Ca- or V-driven waves, cf. Entcheva's talk?) !

Further goals

- Asymptotics of large-core spirals in ionic models with non-standard embedding
- Asymptotics of Response Functions of such spirals
- "Derive" kinematic description of spiral tip/ scroll filament movement relevant to cardiac equations

Thanks

- EPSRC (UK) (support for VNB, IVB, RS, RDS)
- MacArthur Foundation (support for II)
- KITP and miniprogram organizers for the invitation and
- audience for listening

Postdoc positions available

- *"Response functions for drift of spiral and scroll waves"*, **3 years**, with IVB, VNB and D.Barkley
- *"Analytical approach to realistic models of excitation propagation in heart"*, **9 months**, with VNB

- Check vnb@liv.ac.uk for details!

THE END