Conditions for propagation and block of excitation in asymptotic model of atrial tissue

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Outline of the talk

1) Introduction

a) Cardiac function and physiology

b) Electrical properties of cardiac cells and ionic models

2) Motivation : Examples of break-up and self-termination.

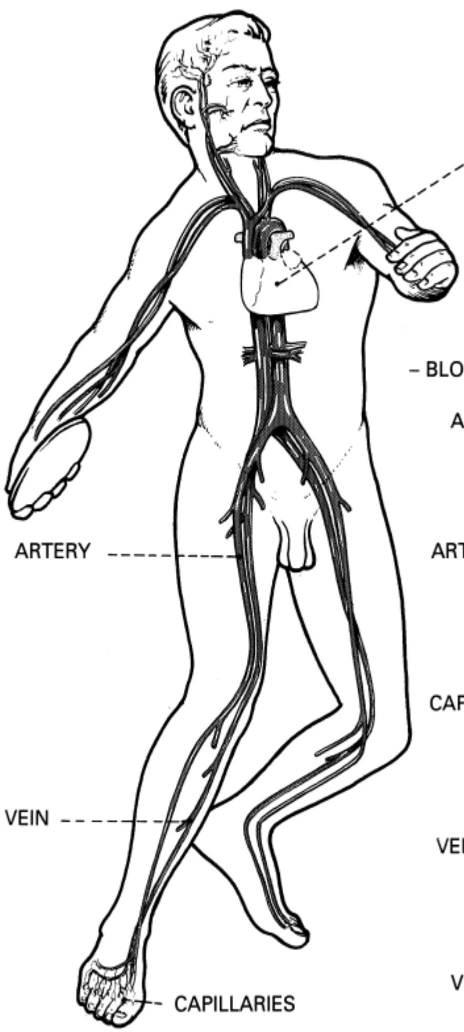
3) Asymptotic simplification of detailed voltage-gated models of cardiac tissue

4) Application: Conditions of propagation in atrial tissue

5) Conclusions

Function of the heart

The **CIRCULATORY** System



Chief **TRANSPORT** System of the body

HEART — Pump which drives –

– BLOOD — a complex fluid containing food materials, respiratory gases, waste products, protective and regulating chemical substances round –

– BLOOD VESSELS — a closed system of tubes:

ARTERIES ... from the 'pump' to the tissues of the body.

branch into

ARTERIOLES ... very small almost microscopic arteries deliver blood to capillaries.

branch into

CAPILLARIES ... where the interchange of gases, food and waste substances occurs.

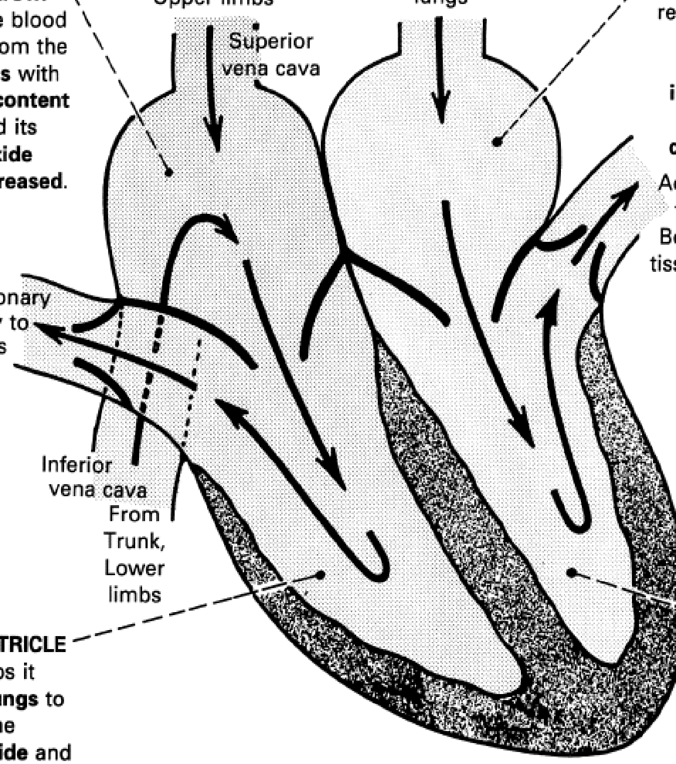
reunite to form

VENULES ... very small veins. Collect blood from capillaries and deliver it to veins.

reunite to form

VEINS ... carry blood back to the 'pump'.

The human heart is really a DOUBLE PUMP i.e. two pumps in series – each pump quite separate from the other.



RIGHT ATRIUM receives the blood returning from the **body tissues** with its **oxygen content reduced** and its **carbon dioxide content increased**.

This blood passes into

RIGHT VENTRICLE which pumps it round the **lungs** to give up some **carbon dioxide** and to take up some **oxygen**.

LEFT ATRIUM receives the blood returning from the **lungs** with its **oxygen** supply **increased** and its **carbon dioxide content reduced**.

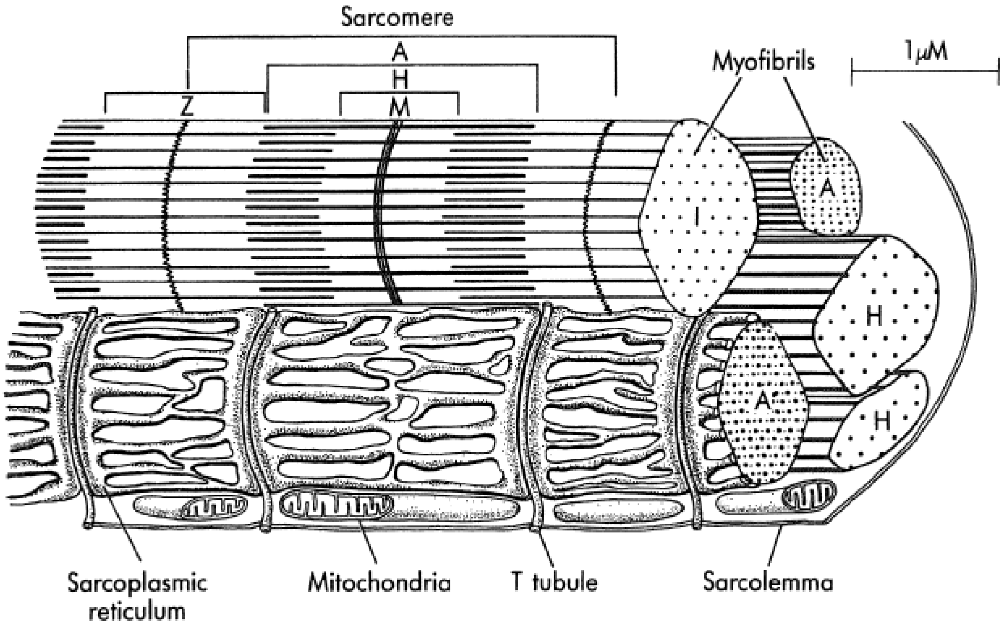
This blood passes into

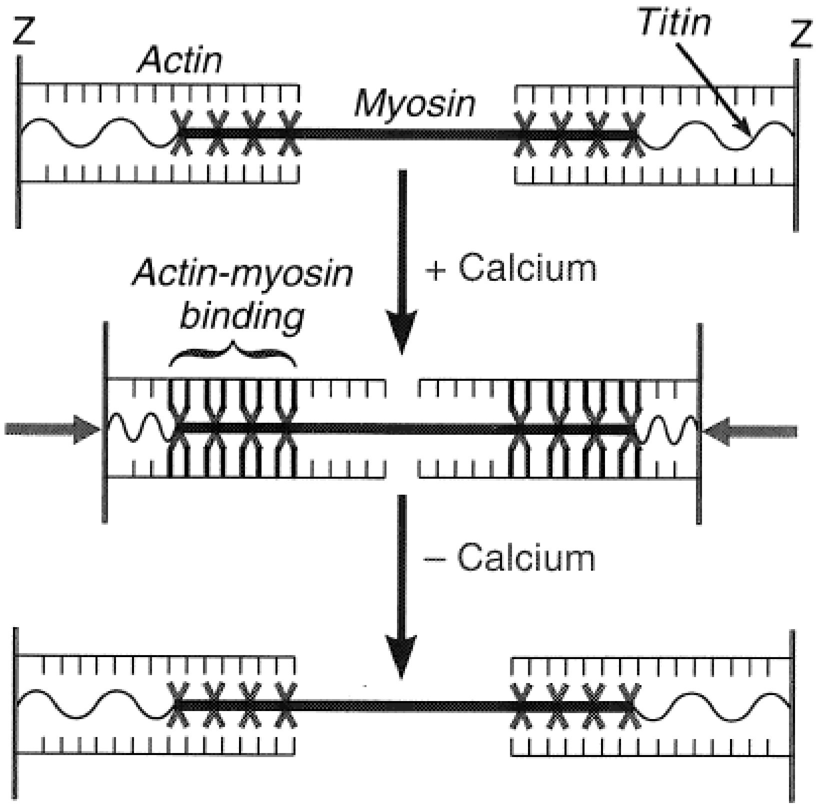
LEFT VENTRICLE which pumps it round the **body** to supply the **tissues** with **oxygen** and to remove **carbon dioxide** from the tissues.

McNaught, Callander; Illustrated Physiology, 1998

Cardiac cell contraction

Contraction of cardiac muscle cells is caused by Ca++ ions.



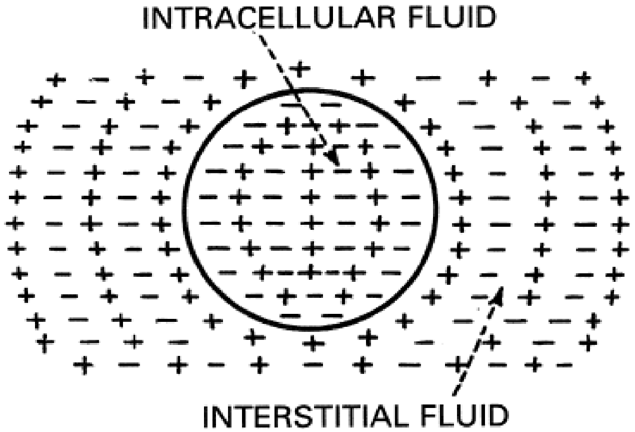


Cardiac cells contain structures called sarcomeres.

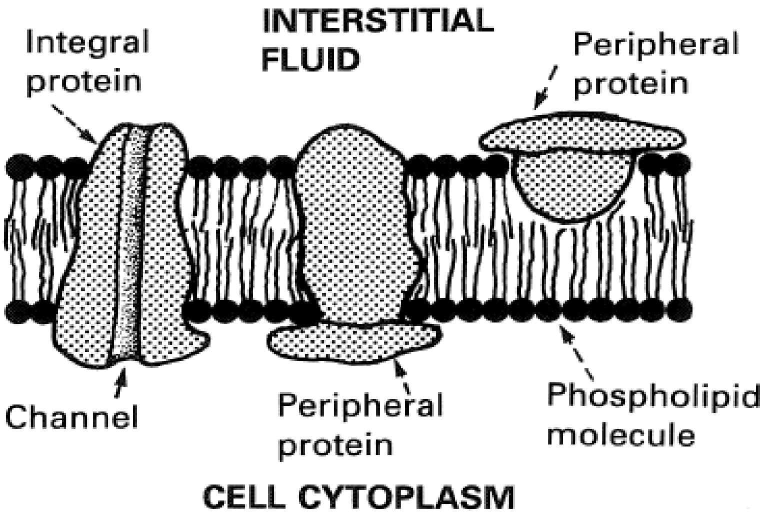
Sarcomeres contain actin and myosin which bind in the presence of Ca++ and slide past each other thus shortening the cell.

Berne, Levi, 1993; Kalbunde 2005

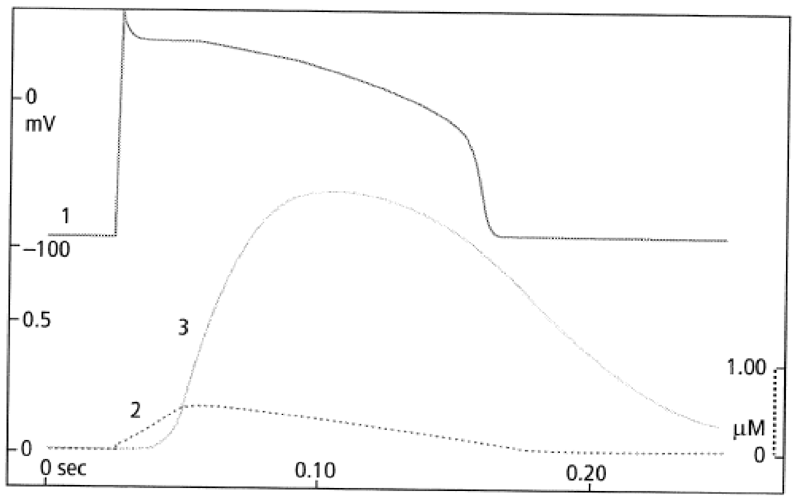
Cardiac electrical excitation and coupling with contraction



Electric potential *across the cell membrane exists because of* ***charge separation*** *between the inside and the outside of the cell. Charge separation is possible due to the* ***semipermeable*** *nature of the* ***cell membrane****.*



Charged ***ions move through the membrane*** *through special* ***channels*** *driven by concentration and electrical gradient. As a result the* ***membrane potential changes in time****.*

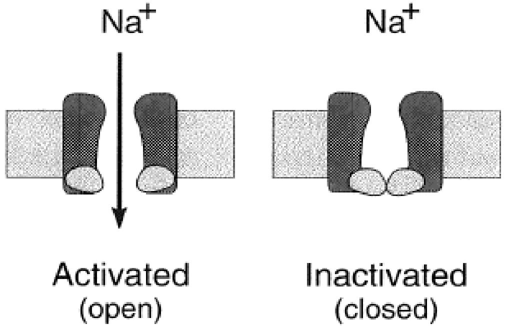


The typical shape of the voltage difference through the membrane is called an ***action potential*** *(curve 1). Note that the plateau is due to* ***increased Ca++*** *concentration in the cell (curve 3) which causes cell* ***contraction*** *(curve 2).*

McNaught, Callander; Illustrated Physiology,1998; Petersen (ed), 2006

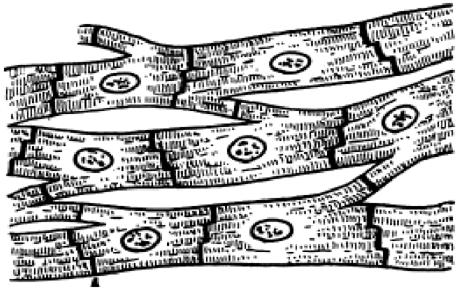
Propagation of action potentials

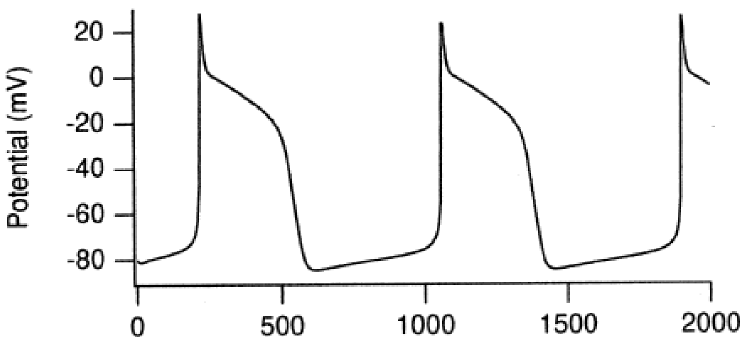
The spatial and temporal movement of action potential coordinates the complex mechanical contraction of the heart.



Ionic **channels are controlled by voltage**. This provides a mechanism for the action potential to change in time and to propagate in space by a **diffusion** like process.

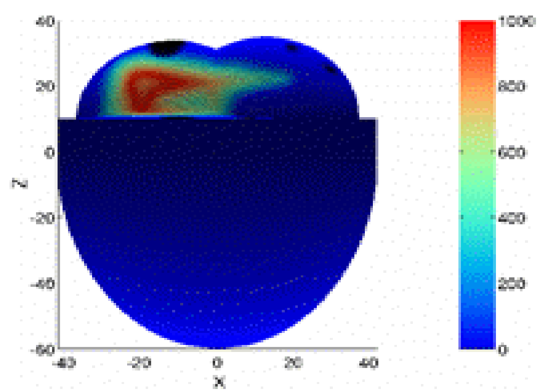
Extracellular propagation is ensured by **gap junctions** - proteins protruding two adjacent cell membranes which are freely permeable to ions.





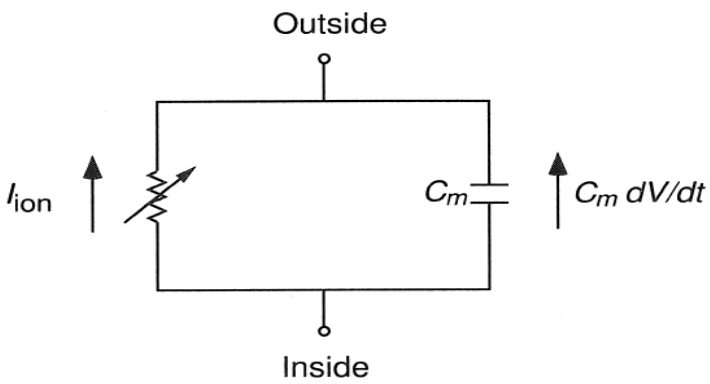
A **wave-train of action potentials** in one-dimension.

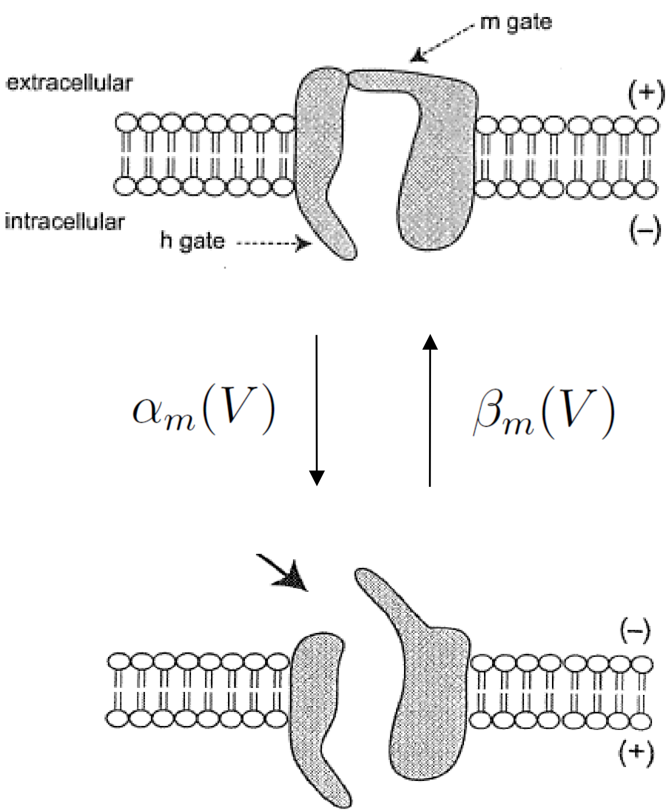
A **beating heart** – electrical excitation propagates at an speed and in a well-defined path and causes controlled contraction and expansion.



G. Buxter, Pitsburg

Basis for cardiac excitation equations





The membrane is modelled as a electrical circuit with a capacitor and a resistor in parallel:

$$C_m \frac{\partial V}{\partial t} + I_{\text{ion}}(V,t) = 0$$

The current through a channel is given by Ohm's law, where **m** is the fraction of open gates of type **m** and **g** is the maximal conductance:

$$i = g\, m\, (V - V_0)$$

The fraction of open **m** gates is given by the rate of change equation:

$$\frac{\partial m}{\partial t} = \alpha_m\,(1-m) - \beta_m m = \frac{\overline{m}(V) - m}{\tau_m(V)}$$

where the alpha-s and beta-s are transition rates.

Detailed voltage-gated model of human atrial tissue Courtemanche et al., (1998)

$$\partial_T V = D\left(\partial_X^2 + \mathcal{K}\partial_X\right)V - \frac{\left(I_{\mathrm{Na}}(V,m,h,j) + \Sigma_I'(V,\dots)\right)}{C_M},$$

$$\partial_T m = \frac{\left(\overline{m}(V) - m\right)}{\tau_m(V)},$$

$$\partial_T h = \frac{\left(\overline{h}(V) - h\right)}{\tau_h(V)},$$

$$\partial_T u_a = \frac{\left(\overline{u_a}(V) - u_a\right)}{\tau_{u_a}(V)},$$

$$\partial_T w = \frac{\left(\overline{w}(V) - w\right)}{\tau_w(V)},$$

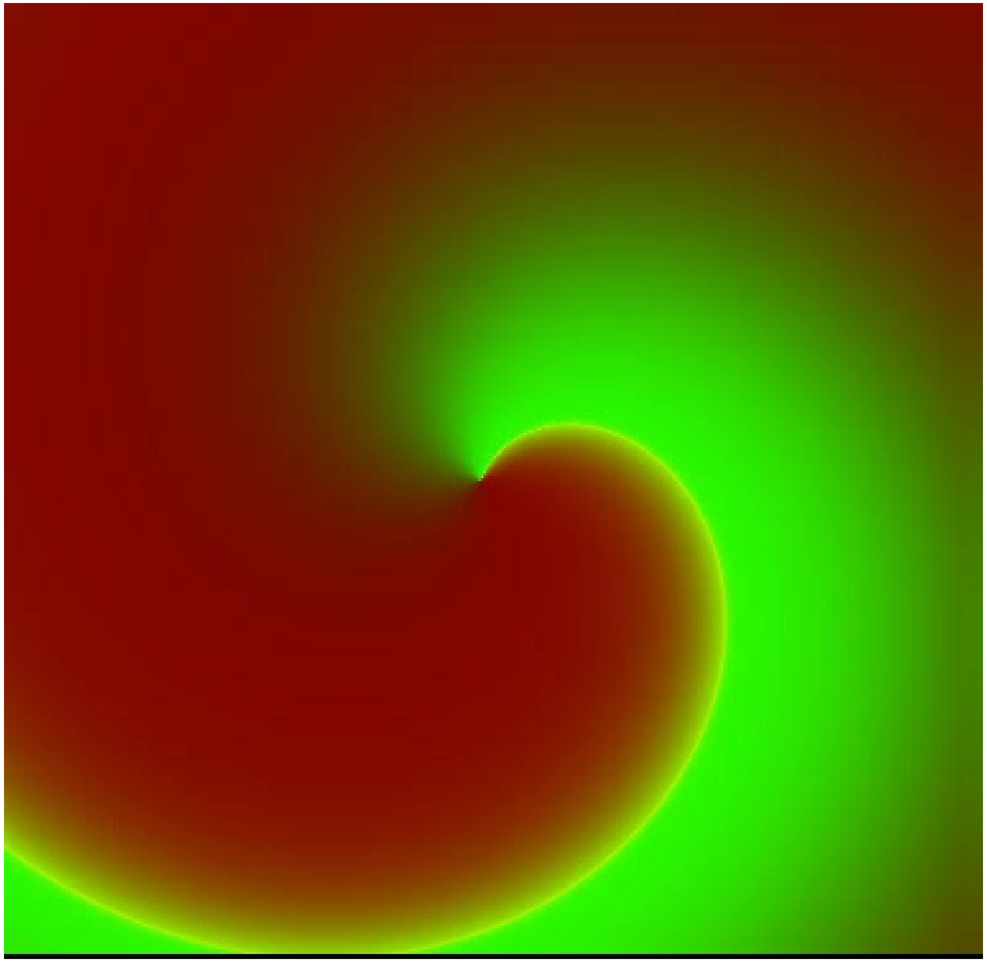
$$\partial_T o_a = \frac{\left(\overline{o_a}(V) - o_a\right)}{\tau_{o_a}(V)},$$

$$\partial_T d = \frac{\left(\overline{d}(V) - d\right)}{\tau_d(V)},$$

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

- ***Detailed ionic single-cell model*** *designed* ***to fit the experimental data. Well-established*** *in the literature.*
- *Consists of 21 coupled reaction-diffusion PDEs*
- *The voltage equation is as a result of various ions passing through the membrane under certain conditions*
- *The gating variables depend on voltage, concentration of substances etc.*

Break-up and self termination: observation in a numerical experiment



- ***Courtemanche et al. (1998)*** *detailed ionic model of human atrial tissue*
- *We need to understand not only the propagation of the wave but also its failure: when and under what conditions the spiralling wave will break-up and self-terminate?*
- *We look for a simplified mathematical model to explain the observed behaviour.*

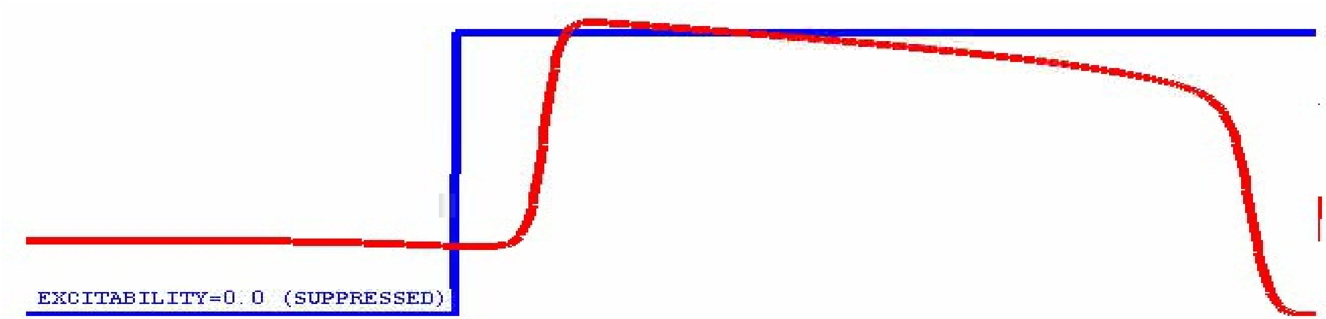
Temporary block of excitability: Standard simplified models of FitzHugh-Nagumo type

$$\partial_T V = D\,\partial_X^2 V + \epsilon_V\,(V - V^3/3 - g),$$
$$\partial_T g = \epsilon_g\,(V + \beta - \gamma g),$$
$$\epsilon_g/\epsilon_V \longrightarrow 0+$$

***FitzHugh-Nagumo equations** are a classical model of cell excitability.*

V – voltage, ε_v – excitation parameter

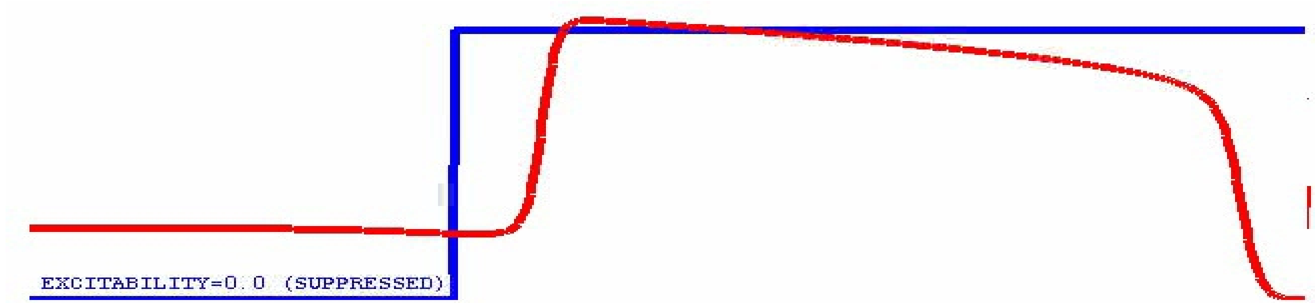
When excitability restored, excitation wave



resumes

if excited region survived

Temporarily suppressed excitability



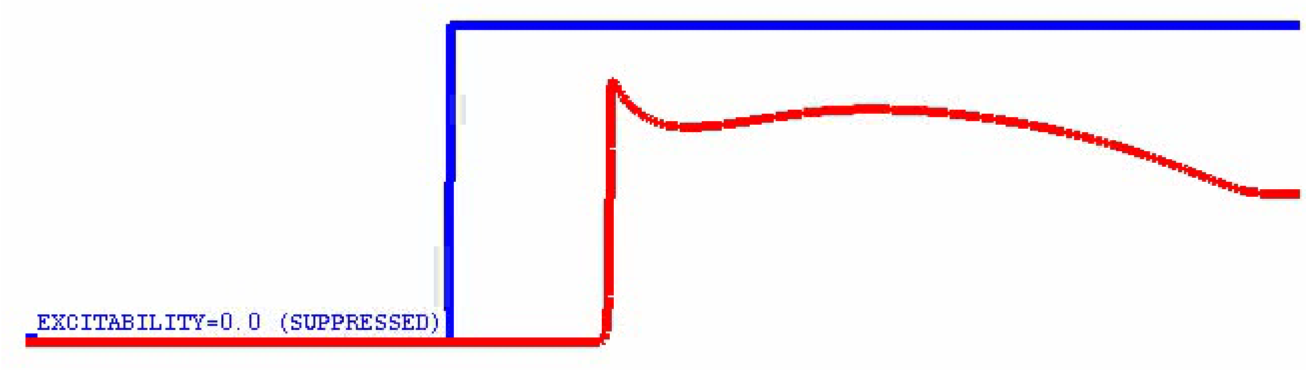
fails to resume

if excited region thinned out to zero

Biktashev. 2002

Temporary block of excitability: Detailed ionic models (Courtemanche et al., 1998)

When excitability restored, excitation wave



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

Biktasheva et al. 2003

Temporary suppressed excitability

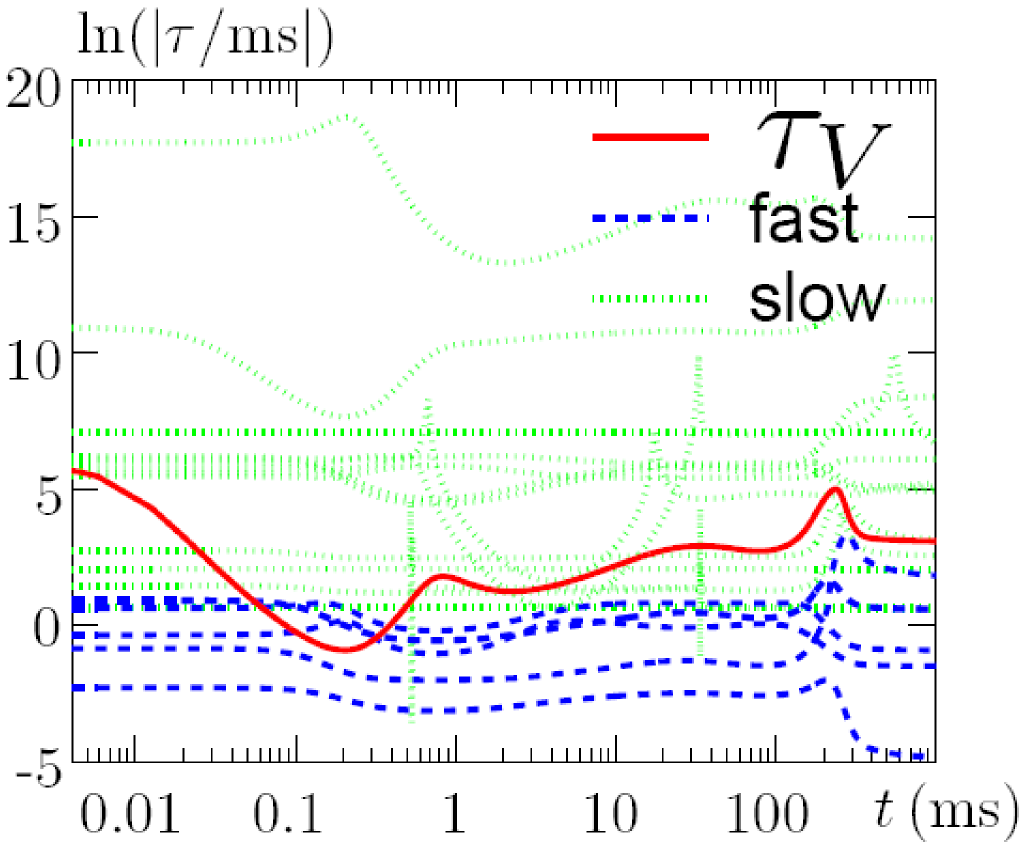
In a similar way standard simplified models of FitzHugh-Nagumo type fail to reproduce:

- *slow re-porarisation,*
- *slow sub-threshold response,*
- *fast accommodation,*
- *variable peak voltage,*
- *front dissipation.*

Need for different simplified models

Relative speed of dynamical variables in Courtemanche's model

Step 1: *Find out which of the variables are fast and which slow.*



Biktasheva et al. 2005

Definition of τ:

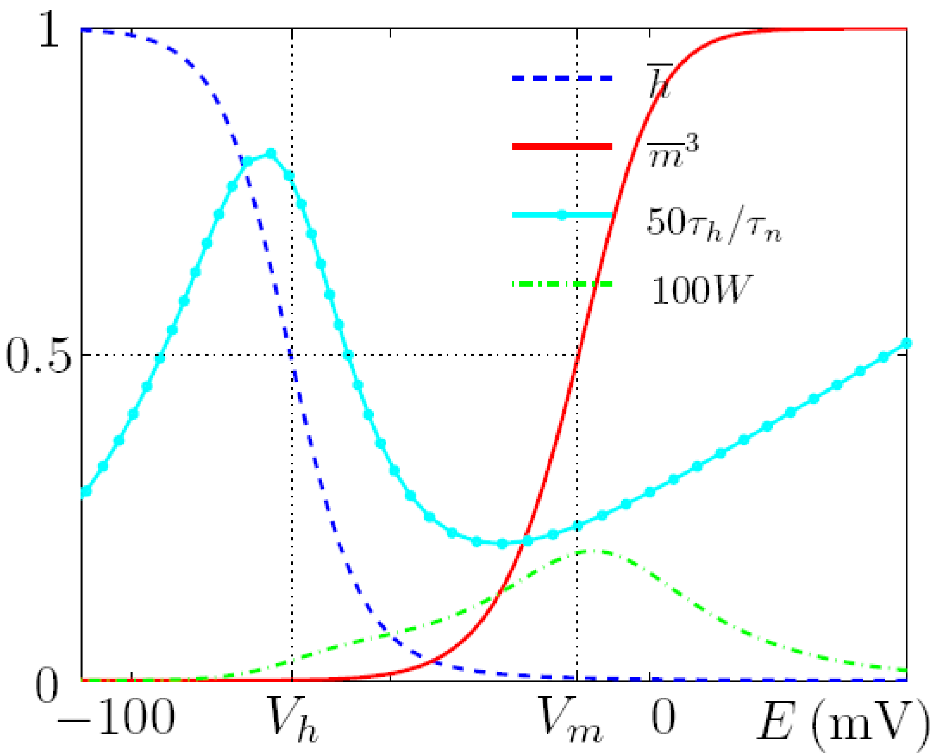
$$\tau_i(x_1, \ldots, x_N) \equiv |(\partial f_i/\partial x_i)^{-1}|$$

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***

Further non-standard asymptotic properties

Step 2: *Take into account any other relevant observations found by numerical experiments.*



Biktashev, Suckley 2004

- *I_{Na} is a **fast current only during the AP upstroke.** In fact it is a "window" current and almost **vanishes outside the upstroke** region.*
- ***All other currents** except I_{Na} **are slow during the AP upstroke**.*

Na gates (m, h) are nearly-perfect switches

and thus require introduction of small parameters in unusual places

Asymptotic embedding of the detailed model of Courtemanche et al., 1998)

Step 3:

$$\partial_T V = D\left(\partial_X^2 + \mathcal{K}\partial_X\right) V - \frac{\left(\epsilon^{-1} I_{\mathrm{Na}}(V,m,h,j) + \Sigma_I'(V,\dots)\right)}{C_M},$$

$$\partial_T m = \frac{\left(\overline{m}(V;\epsilon) - m\right)}{\epsilon\,\tau_m(V)}, \quad \overline{m}(V;\epsilon) = \begin{cases} \theta(V - V_m), & \epsilon = 0 \\ \overline{m}(V), & \epsilon = 1, \end{cases}$$

$$\partial_T h = \frac{\left(\overline{h}(V;\epsilon) - h\right)}{\epsilon\,\tau_h(V)}, \quad \overline{h}(V;0) = \begin{cases} \theta(V_h - V), & \epsilon = 0 \\ \overline{h}(V), & \epsilon = 1, \end{cases}$$

$$\partial_T u_a = \frac{\left(\overline{u_a}(V) - u_a\right)}{\epsilon\,\tau_{u_a}(V)},$$

$$\partial_T w = \frac{\left(\overline{w}(V) - w\right)}{\epsilon\,\tau_w(V)},$$

$$\partial_T o_a = \frac{\left(\overline{o_a}(V) - o_a\right)}{\epsilon\,\tau_{o_a}(V)},$$

$$\partial_T d = \frac{\left(\overline{d}(V) - d\right)}{\epsilon\,\tau_d(V)},$$

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

Asymptotic embedding: *Introduce a small parameter so that in the limit **ε→1 the original model** is recovered while in the limit **ε→0 a simpler system** is obtained.*

*Note: **The small parameter enters in a non-standard way:***
- *A variable can be both fast and slow in the same solution,*
- *Large factor only at some but not all terms in the RHS,*
- *Non-isolated equilibria in the fast system,*
- *Discontinuous RHS of the embedded system even if the original is continuous.*

The standard theory of FitzHugh-Nagumo like systems is not applicable - alternatives in Biktashev et al., 2007

Application to break-up: a simplified model of the front

- *Non-dimensionalize:*

$$t = \frac{T}{\epsilon}, \quad x = \frac{X}{\sqrt{\epsilon D}}, \quad \kappa = \sqrt{\epsilon D}\mathcal{K}$$

- *Take the asymptotic limit*
- *Discard equations for u_a, w, o_a, d which decouple*
- *Arrive at the simplified model for the front*

$$\partial_t V = \left(\partial_x^2 + \kappa\partial_x\right) V + \overline{I_{\mathrm{Na}}}(V)\, j\, h\, m^3,$$

$$\partial_t h = \big(\theta(V_h - V) - h\big)/\tau_h(V),$$

$$\partial_t m = \big(\theta(V - V_m) - m\big)/\tau_m(V),$$

where

$$\overline{I_{\mathrm{Na}}}(V) = g_{Na}(V_{Na} - V),$$

$$\tau_k(V) = \left(\alpha_k(V) + \beta_k(V)\right)^{-1}, \qquad k = h, m,$$

$$\alpha_h(V) = 0.135\, e^{-(V+80)/6.8}\, \theta(-V - 40),$$

$$\beta_h(V) = \left(3.56\, e^{0.079V} + 3.1 \times 10^5\, e^{0.35V}\right)\, \theta(-V - 40) + \theta(V + 40)\, \left(0.13(1 + e^{-(V+10.66)/11.1})\right)^{-1},$$

$$\alpha_m(V) = \frac{0.32(V + 47.13)}{1 - e^{-0.1(V+47.13)}},$$

$$\beta_m(V) = 0.08 e^{-V/11},$$

$$g_{Na} = 7.8, \quad V_{Na} = 67.53, \quad V_h = -66.66, \quad V_m = -32.7.$$

Note:

- *Number of equations reduced from 21 to 3!*
- *Small parameters eliminated – model is not stiff any more!*
- *RHS significantly simpler!*

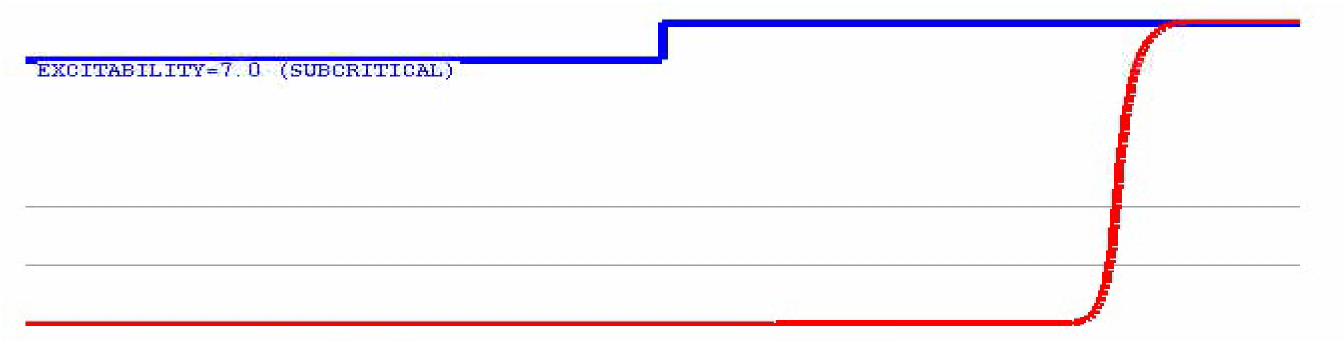
- *j plays the role of **excitability parameter.** The value of j can be found from the slow subsystem.*

Simitev, Biktashev 2005

Quality of the simplified model

1) The simplified model reproduces front dissipation at a a temporary block.

$j = j_1$ $j_1 < j_{min} < j_2$ $j = j_2$



does not resume propagation even if excitability is rapidly restored

2) Quantitative agreement with the detailed model of Courtemanche.

Model	Speed	Peak Voltage	Ralative Error in Speed
Original	0.28	3.6	0.00%
Simplified	0.24	2.89	16.00%

Simitev, Biktashev 2005

The new simplified model agrees quantitatively well with the values of the wave speed and the pre-front voltage on the detailed ionic model of Courtemanche.

Travelling waves

***Travelling wave** ansatz:*

$$F(z) = F(x+ct) \text{ for } F = V, h, m$$

Then:

$$V'' = (c-\kappa)\,V' - \overline{I_{\mathrm{Na}}}(V)\, j\, h\, m^3,$$
$$h' = \left(c\,\tau_h(V)\right)^{-1}\left(\theta(V_h - V) - h\right),$$
$$m' = \left(c\,\tau_m(V)\right)^{-1}\left(\theta(V - V_m) - m\right),$$

***Boundary conditions**:*

$$V(-\infty) = V_\alpha, \qquad V(+\infty) = V_\omega,$$
$$h(-\infty) = 1, \qquad h(+\infty) = 0,$$
$$m(-\infty) = 0, \qquad m(+\infty) = 1.$$

Indication of well-posedness:

- *System with **8 unknown constants** (4th order & **c, j, V_a, V_w**) but only **6 boundary conditions**.*
- *The remaining 2 constants can be chosen arbitrary.*
- *Otherwise their values are fixed by the second half of the problem: the slow system*

Advantages:

- *Conversion from PDE to ODE*
- *Can be solved by standard boundary value problem techniques and numerical schemes.*
- *Immense computational savings.*

Simitev, Biktashev 2005

An exactly solvable toy model

- Replace functions

$$\overline{I_{\rm Na}}(V),\ \tau_h(V)\ \text{and}\ \tau_m(V)$$

with constants, say, by taking their values at ***V=V**$_m$*

- Obtain a piecewise system of linear ODE with constant coefficients

- The equations for **h** and **m** decouple and may be solved separately

- The voltage equation is homogeneous for $z \le \xi$ and with exponential inhomogeneity for $z \ge \xi$

$$\xi = \frac{1}{(c-\kappa)} \ln\left(\frac{V_m - V_\alpha}{V_h - V_\alpha}\right)$$

$$V(z) = \begin{cases} (V_h - V_\alpha)\, e^{(c-\kappa)z} + V_\alpha, & z \le \xi, \\ V_\omega - \overline{I_{\rm Na}}\, j\, c^2 \tau_h^2 \tau_m^2 \sum_{n=0}^{3} A_n(c,z), & z \ge \xi, \end{cases}$$

$$h(z) = \begin{cases} 1, & z \le 0, \\ e^{-z/(c\,\tau_h)}, & z \ge 0, \end{cases}$$

$$m(z) = \begin{cases} 0, & z \le \xi, \\ 1 - e^{(\xi - z)/(c\,\tau_m)}, & z \ge \xi, \end{cases}$$

$$V_\omega = V_m + \overline{I_{\rm Na}}\, j\, (c\,\tau_h\,\tau_m)^2 e^{-\xi/(c\,\tau_h)} \sum_{n=0}^{3} \frac{a_n(c)}{\tau_m + n\,\tau_h},$$

$$0 = (c-\kappa)(V_m - V_\alpha) - \overline{I_{\rm Na}}\, j\, c\, \tau_h \tau_m\, e^{-\xi/(c\tau_h)} \sum_{n=0}^{3} a_n(c),$$

$$A_n(c,z) \equiv \frac{a_n(c)}{\tau_m + n\tau_h} \exp\left(\frac{n\xi\tau_h - (\tau_m + n\tau_h)z}{c\,\tau_h\,\tau_m}\right)$$

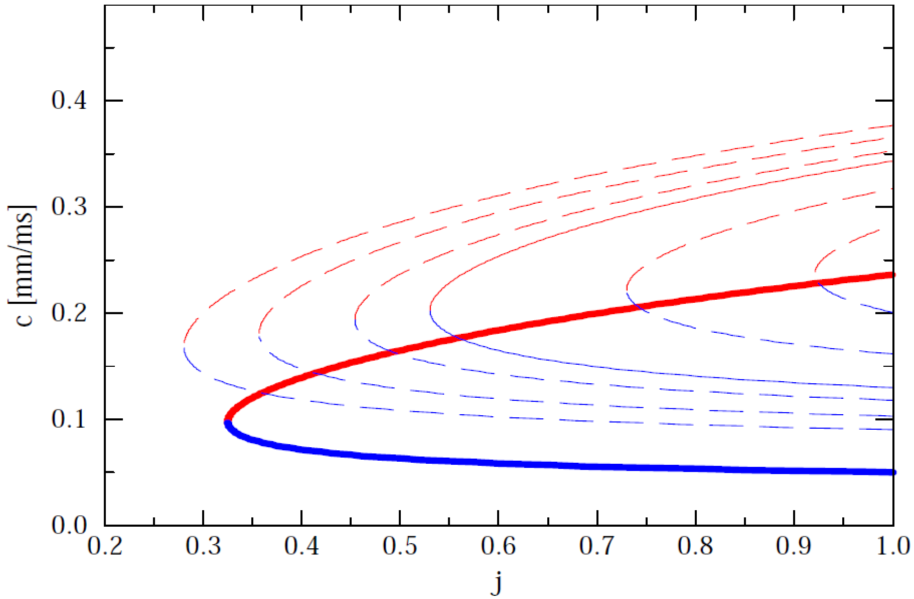
$$a_n(c) \equiv \binom{3}{n} \frac{(-1)^n}{c(c-\kappa)\,\tau_h\,\tau_m + \tau_m + n\,\tau_h}.$$

Simitev, Biktashev 2005

Wave speed as a function of the excitation parameter

- *Of interest are the **conditions at which the excitation wave fails to propagate**.*
- *Thus we seek a **relation between the wave speed and the excitation parameter.***
- *The dispersion relation **cannot be solved for c but can be easily solved for j .***

$$j = \frac{(V_m - V_\alpha)}{6\,\overline{I_{\mathrm{Na}}}\,\tau_h^4\,\tau_m}\, e^{\frac{\xi}{c\,\tau_h}} \prod_{n=0}^{3} \left(c^2\,\tau_h\,\tau_m + \tau_m + n\,\tau_h\right)$$



*The thick solid lines show the **numerical solution** of the true simplified model; the thin lines show **the above expression** for values of τ_m τ_h nd corresponding to V= -28, -30, V_m, -34, -36 -38, from right to left. In both cases V_a = -81.18.*

Turning point bifurcation with increase of excitation parameter.

No propagation below the bifurcation point.

Simitev, Biktashev 2005

The condition for propagation

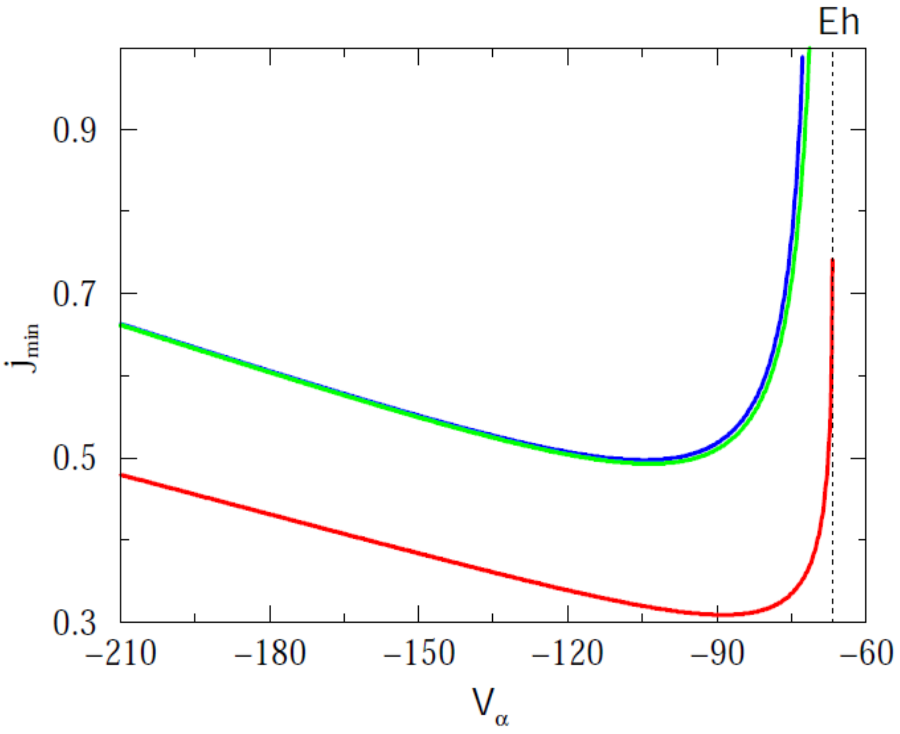
*The excitation waves **can propagate only if the excitation of the tissue is larger than some minimal value**,*

$$j > j_{\min}$$

- ***J_{min}** can be determined as a **minimum of the j as a function of c***

$$j^{(0)}_{\min} = \frac{(V_m - V_\alpha)}{2\overline{I_{\mathrm{Na}}}\tau_h} e^{\frac{2\Theta}{\Theta+\sqrt{\Theta^2+4\Theta}}} \left(\Theta + 2 + \sqrt{\Theta^2 + 4\Theta}\right)$$

$$\Theta = \ln\big((V_m - V_\alpha)/(V_h - V_\alpha)\big).$$

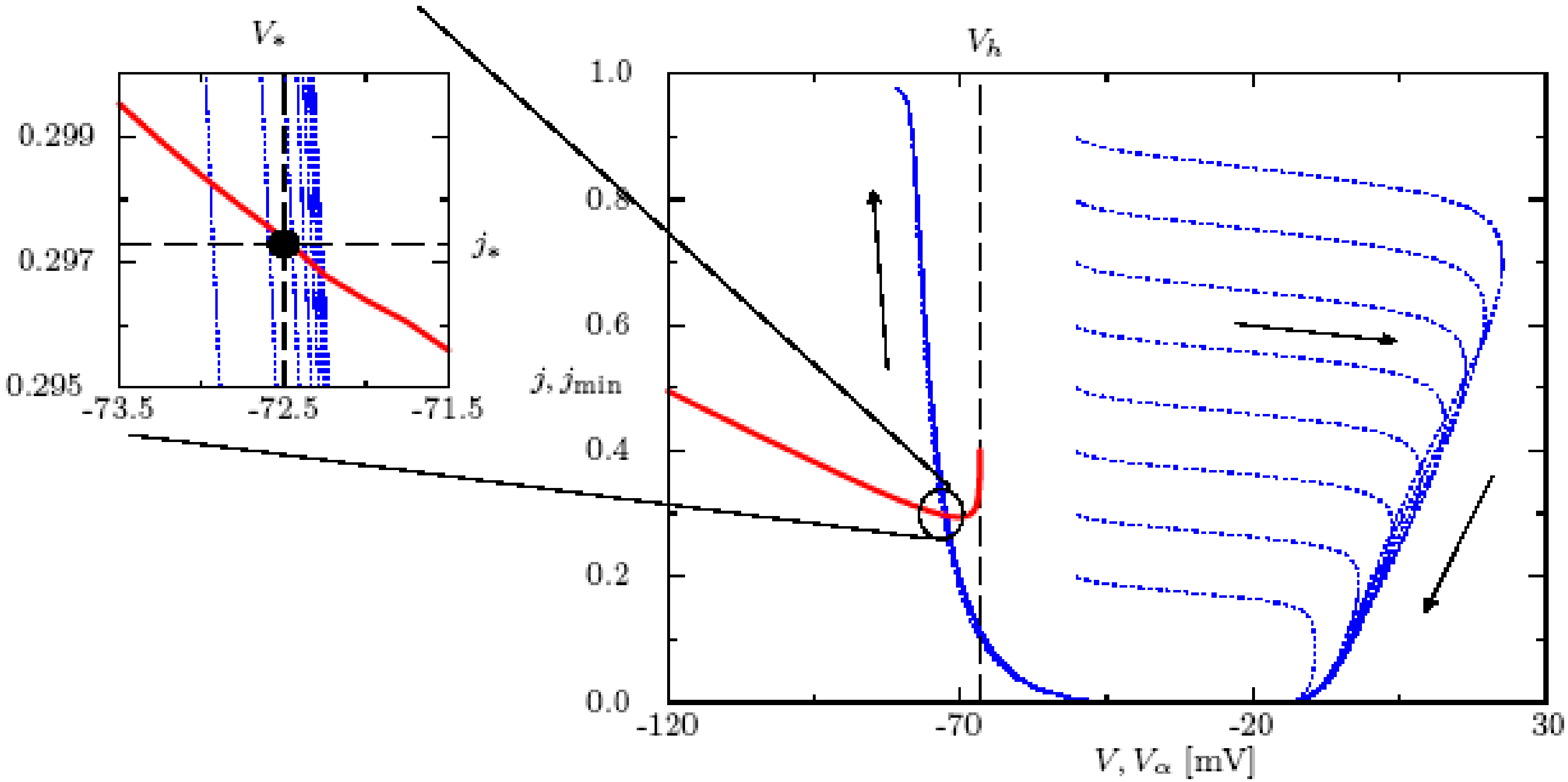


Minimal value of the excitation as a function of the second free parameter, the pre-front voltage. Green and red lines are more accurate approximations.

Simitev, Biktashev 2005

Precise numerical value for the minimal excitability

The precise numerical value of the excitability necessary for propagation is found as an intersection of the minimal excitability curve and typical action potential solutions.



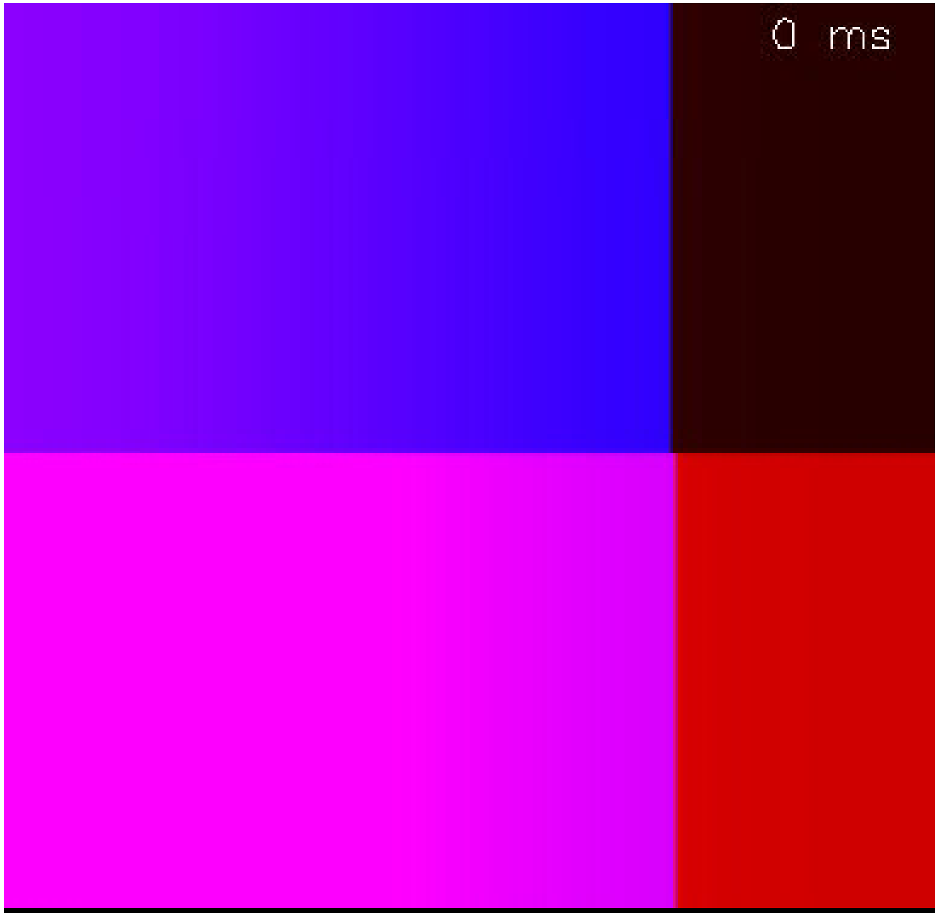
$$(j_*, V_*) = (0.2975 \pm 0.0015, -72.5 \pm 0.5)$$

Simitev, Biktashev 2005

Confirmation in a numerical experiment

CONDITION:

A spiralling wave in the Courtemanche's atrial detailed ionic model will break-up whenever and wherever the value of the j-gating variable decreases below the critical value of 0.298.



- Red: voltage
- Blue: $j < 0.295$
- Yellow: block, at:
  - 740 ms
  - 1120 ms
  - 3740 ms
  - 3860 ms

Simitev, Biktashev 2005

Conclusions

- *Excitation fronts dissipate if not allowed to propagate fast enough*
- Dissipated fronts do not resume if excitability restored
- This is due to I_{Na} and is reproduced by the new simplified model of I_{Na}-driven front
- Propagation can be blocked by front dissipation, long before wavelength reduces to zero
- Novel asymptotic approach applied to derive a simplified model
- Analytical conditions for front dissipation derived
- Accurate numerical values also obtained
- Results tested against the detailed ionic model of atrial tissue and excellent agreement achieved