Electric fields in cardiology :

from clinics to theory and back (perhaps...)

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fibrillation. Transmembrane signals at each site exhibit a strong periodic component centred near 8 Hz. This periodicity is seen as an attractor in two-dimensional-phase space and each site can be represented by its phase around the attractor. Spatial phase maps at each instant reveal the 'sources' of fibrillation in the form of topological defects, or phase singularities[10], at a few sites. Using our method of identifying phase singularities, we can elucidate the mechanisms for the formation and termination of these singularities, and represent an episode of fibrillation by locating singularities. Our results indicate an unprecedented amount of temporal and spatial organization during cardiac fibrillation.

It is still uncertain whether rotors underlie cardiac fibrillation. Self-organized rotors giving rise to spiral waves have been observed in various excitable media[11–13] including cardiac muscle[4]. Although stationary spiral waves occur in isolated thin pieces of cardiac tissue, in the whole heart, as in many excitable media, they tend to move throughout the heart. If these spiral waves move rapidly (at >30% of the wave speed), they give rise to fibrillatory activity[4]. The mechanisms of cardiac fibrillation vary[4,15], however, and fibrillation is usually the result of multiple three-dimensional electrical waves, sometimes described as meandering wavelets, propagating throughout the heart[16,17]. Cardiac fibrillation has been described in terms of

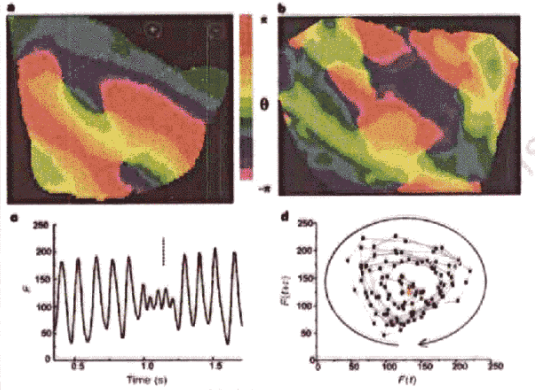


Figure 2 Snapshots of phase from the heart surface of the rabbit and sheep during sustained fibrillation. **a**, Rabbit; **b**, sheep. We classify rotor chirality as '+' for clockwise and '−' for anticlockwise[18]. At these instants, three phase singularities (two clockwise and one anticlockwise) were observed on the rabbit heart and nine (five clockwise and four anticlockwise) on the larger sheep heart. Signals (*F*) demonstrate (**c**) low amplitude and (**d**) remain near the centre of their phase portraits when a spatial-phase singularity site is nearby. Dashed line and red circle indicate the time of the corresponding snapshot. Vertical white line represents 1 cm.

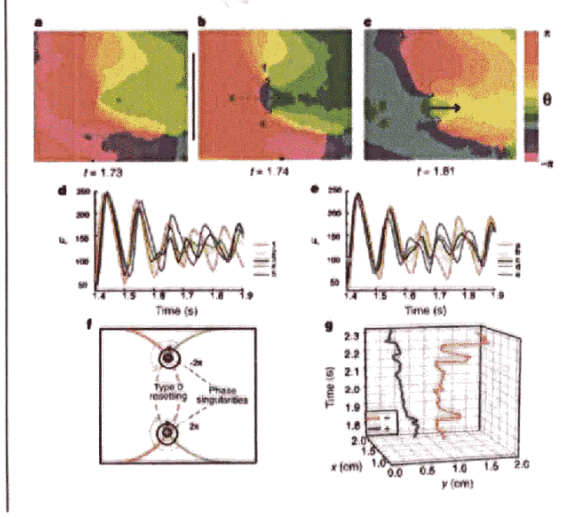


Figure 3 Initiation of a pair of spatial phase singularities. Snapshots of phase before (**a**), during (**b**), and after (**c**) the formation of a pair of spatial phase singularities during sustained fibrillation in the sheep heart. **d**, **e**, Transmembrane signals (*F*) measured at sites a–e and 1–5 labelled in **b**. **f**, A pair of singularities form when the local phase gradient becomes large (in other words, the excitation wave, $\theta = 0$ (green), approaches regions not fully recovered, $\theta = \pm\pi$ (red)). The excitation wave cannot proceed into the recovered region, and hence breaks, forming two phase singularities. The two excitation waves rotate around these newly formed singularities. Sustained rotation in the form of a pair of rotors occurs only if this excitation wave causes type 0, or even, phase resetting at the site of the initial wave break. Type 0 resetting (suprathreshold) advances the phase of this region into a new cycle, generating a new excitation wave (in the opposite direction to the previous wave; see arrow in **c**), resulting in the formation of a pair of self-sustaining rotors. Type 1 resetting (subthreshold) does not create this new excitation wave, and the phase singularity pair lasts less than one rotation. Notice the 'extra' cycle in the central region of block, sites 3 & c in **d** and **e**, indicative of type 0 resetting. **g**, Trajectories of '+' and '−' rotors following their initiation plotted in *x*, *y*, *t* space. Vertical line between **a** and **b** represents 1 cm.

Preliminary

The function of the heart is to *pump blood throughout the body* .

An inadequate pumping of the blood leads to disastrous consequences (death...).

The way a healthy heart is functioning is by contracting *simultaneously* **all** the muscle. This is achieved by an elaborate system : electric waves propagate throughout the muscle and trigger contractions.

A disruption of the electric wave propagation induces a dramatic drop of the pump efficiency, and ultimately to **death** .

The most common source of problems :

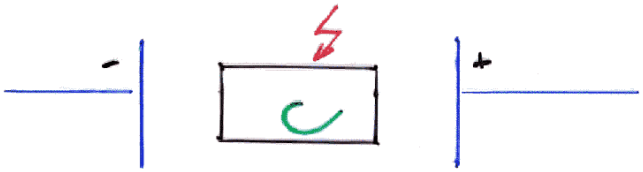
Disruption of the pattern of propagation of electric waves $\Rightarrow$ inefficient contractions.

CLINICAL PROBLEM :
AVOID/CURE THE DISORGANIZED
REGIMES OF ELECTRICAL ACTIVITY

Introduction (1)

Electric fields are widely used in a number of clinical situations in cardiology.

Perhaps the most striking example is *defibrillation* :



Apply a strong shock ($\sim 10 V cm^{-1}$, duration $\sim 5ms$)

Dangerous regimes of wave propagation stop

Elementary questions, such as what happens during defibrillation, or why does defibrillation work at all are not completely answered.

In fact, in many cases, one may suppress dangerous wave activity by sending trains of electrical stimuli of small amplitude. The method is known as *Anti Tachycardia Pacing* (ATP).

In implantable devices, the method leads to a high rate of success ($\gtrsim 80\%$).

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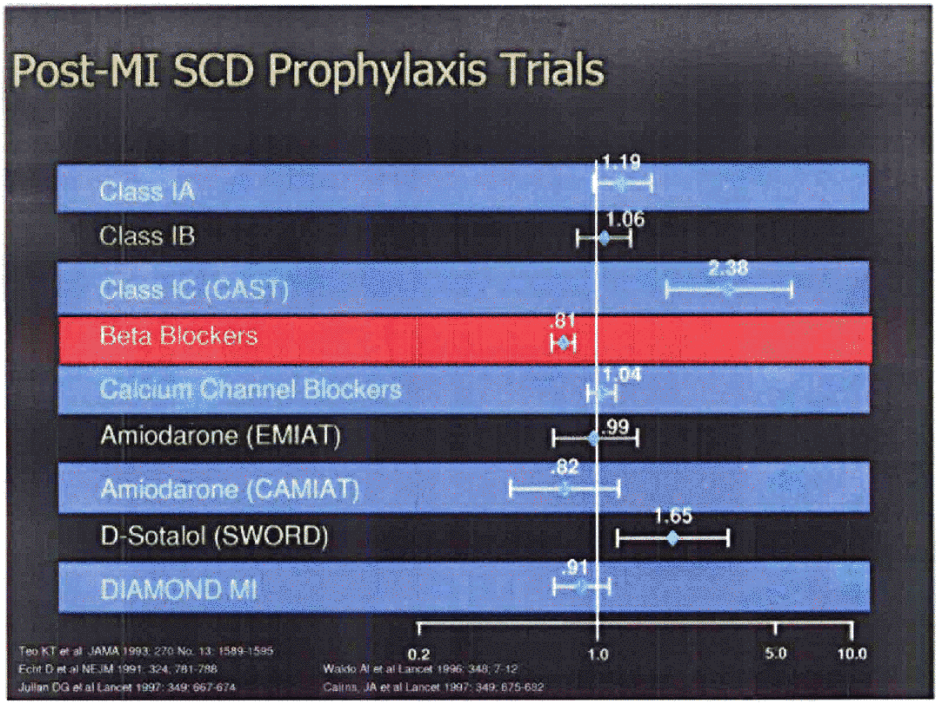

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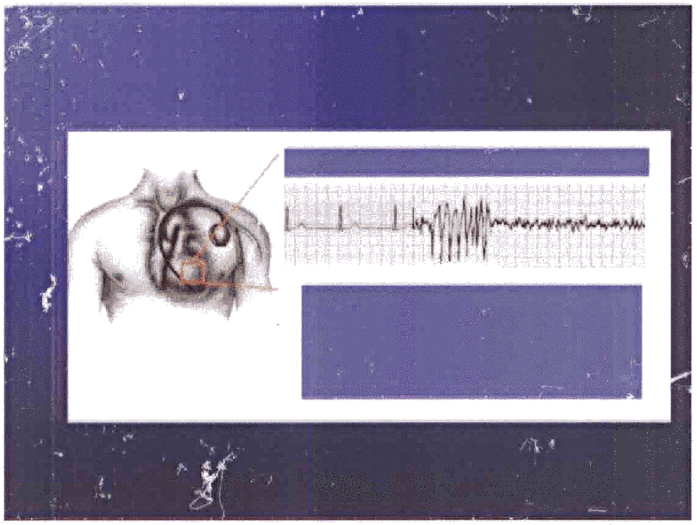

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Introduction (2)

Scientific objectives :

(i) improve the fundamental understanding of the interactions between cardiac tissue and the electric field.

(ii) propose ways to improve the current methods of treatment of cardiac arrhythmias.

Outline of the presentation :

1. Propagation of Action Potential in cardiac tissues : elementary description.
2. Understanding Anti Tachycardia Pacing :

   Spiral wave drift induced by stimulating wave trains.
3. How to detach spiral wave pinned by obstacles ?

   ... how to suppress re-entrant arrhythmias...
4. The problem of spontaneous ectopicity in the heart.

Propagation of Action Potential in cardiac tissue (1)

At rest, the membranes of the nerves, muscles and of the heart are depolarized due to a difference in ionic concentrations.

Muscular contraction is triggered by a wave of electrical activity, consisting in a depolarization of the membrane, similar to what happens in the nerves (Hodgkin & Huxley, 1952).

The muscular contraction happens *after* the electric signal has propagated, and the mechanical process is slow as compared to the electrical one

$\Rightarrow$ focus on the electrical phenomenon.

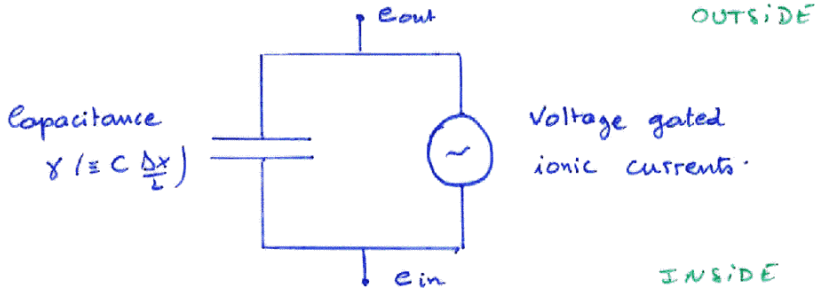
The electric signalling involves exchanges of ions between the cells and the external medium. Schematically,

- propagation is triggered by an influx of Sodium ions, leading to a fast depolarization ($\sim 2ms$).
- the membrane is repolarized thanks to a flux of potassium ions from the cell to the external medium. This is a slow process ($\sim 200ms$).

Propagation of Action Potential in cardiac tissue (2)

The cable theory.

Model a patch of membrane in 1-dimension by :



The patch of membranes are coupled electrically, due to the finite conductivity of the intracellular and extracellular media (electrolytic solutions).

$r_i = R\,\frac{\Delta x}{L}$

Kirchoff's laws (introduce $e = (e_{in} - e_{out})$) :

$$C\partial_t e = -\sum(\text{ionic currents}) + I_{IC} + \frac{d}{dx}\left(\frac{1}{R}\frac{d}{dx}(e + e_{out})\right)$$

Conventions :

- the ionic currents are positive outwards;
- the externally imposed intracellular currents are positive inwards.

Propagation of Action Potential in cardiac tissue (3)

The description of the ionic currents involves an ever growing number of ionic channels : ~ 100 ionic channels have been identified. It is not really feasible, and in fact, not always desirable, to use a very accurate description of the channels.

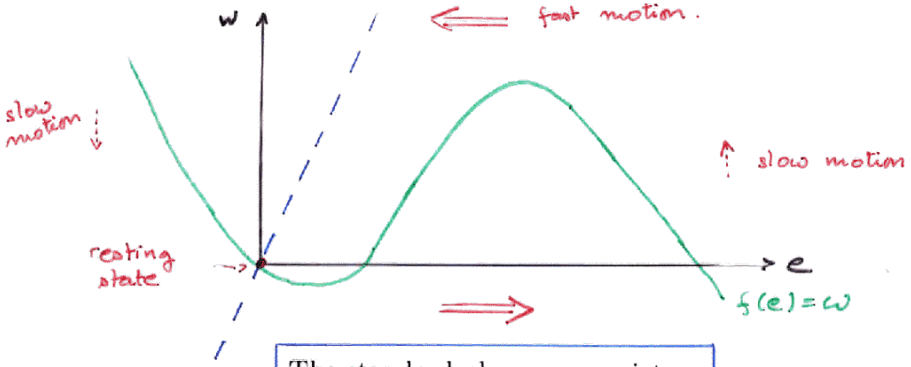
In fact, much can be understood with the help of the (extremely) simplified FitzHugh model, with two variables, e and w.

$$\partial_t e = f(e) - w + D\partial_x^2 e$$
$$\partial_t w = (e - kw)/\tau_s$$

- e represents the difference between the membrane potential and its value in the resting state
- w represents the repolarizing current(s)
- $f(e)$ models in an approximate way the fast (sodium) currents
- τ_s is the slow recovery time scale.

Propagation of Action Potential in cardiac tissue (4)

The FitzHugh model can be understood with the help of qualitative considerations. Case where $f(e) = Ae(1-e)(e-u)$ $(u \sim 0.2)$.



The standard phase space picture

Consequences :

The resting state is stable with respect to perturbations of small amplitude, but unstable with respect to perturbations of finite amplitudes.

Once a perturbation is started, it leads to a characteristic "pulse", which returns in a finite time to the resting state.

$\Rightarrow$ *The heart behaves as an excitable medium*

...analogies with other problems, such as the Belousov-Zhabotinsky chemical reaction and others...

Penetration of an electric field in cardiac tissue

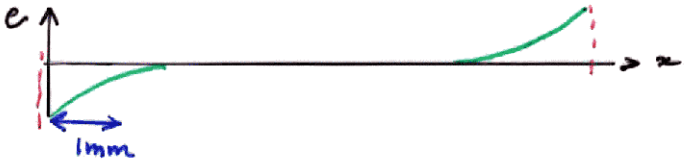
Consider a fiber of cardiac muscle, in a weak externally applied electric field ($e_{out} = Ex$). In the linearized regime, and in the steady state, the equations reduce to :

$$\frac{d^2e}{dx^2} - \frac{e}{\lambda^2} = 0$$

Which implies that near the boundary,

$$e \sim \exp(-x/\lambda), \quad \lambda \sim 1mm$$

Due to the effective resistivity of the membrane, the potential inside the membrane adjusts to the membrane potential outside.



The effect has indeed been observed experimentally (Weidmann, 1970).

Paradoxical situation :

The externally applied electric field does *not* penetrate inside the tissue beyond a "skin depth" of order $\lambda = 1mm$. How then can an electric field act on a muscle which is $\sim 1cm$ thick (left ventricle), and $\sim 10cm$ large ?

Interaction of a spiral wave with a stimulating wave trains

Besides defibrillation, which involves large amplitude electric shocks, the Anti-Tachycardia-Pacing (ATP) method, which uses trains of small amplitude electric pulses, is often sufficient to stop arrhythmias.

Problem :

What happens in reality ? How to model the process... and improve efficiency ?

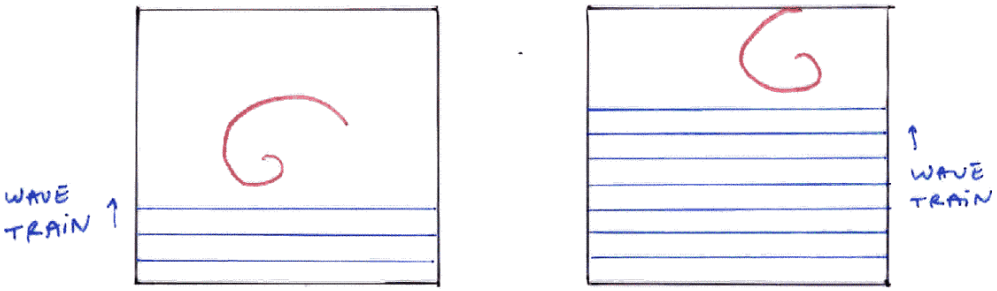
Model problem studied :

Understand the interaction of a rotating wave (vortex) and of a wave train.

- use the analogy between cardiac muscle and simpler excitable media (such as the Belousov-Zhabotinsky reaction)
- rely on the study of simple mathematical models. media (such as the Belousov-Zhabotinsky reaction)

Spiral wave drift induced by stimulating wave trains (1)

The effect :



Experimental realization (B.Z. reaction).

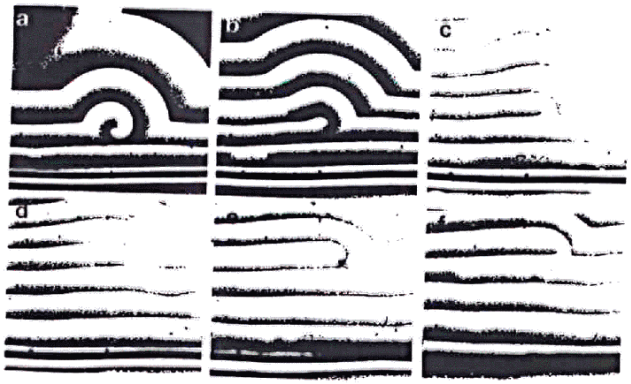
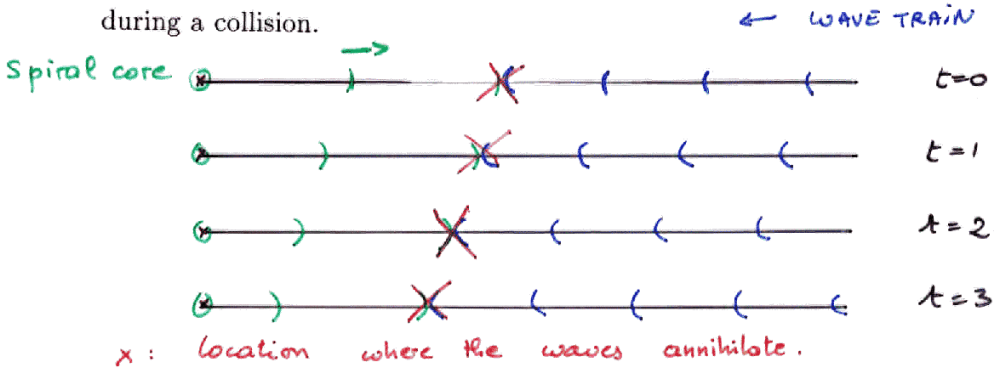


Fig. 3. The drift of spiral wave S_1 induced by high-frequency waves. Plane waves are propagating from the electrode which is seen as a black bar at the bottom of the figure. Plane waves with a higher frequency convert spiral wave a) into a wave-break b). This wave-break closes on the following wave c), which results in the break of this latter d). This process is repeated periodically (compare e and f, b and e), causing a slow drift of the break from the electrode. The period of spiral wave S_1 is 50 s and that of the plane waves is 40 s. The time interval between the frames is 4 min.

Spiral wave drift induced by stimulating wave trains (2)

The main idea (1-dimensional case)

1. Think of the spiral wave as a source radiating waves far away, with a period T_s.
2. Send wave pulses on the spiral wave, with a period T_p.
3. Use the fact that waves in excitable media annihilate each other during a collision.



If the period $T_p < T_s$, ultimately, the wave train reaches the emitting spiral

⇒ *strong interaction with the core of the spiral.*

In 2 dimensions, as a result of the interaction, the spiral wave drifts, until it reaches the boundary of the medium, and disappears.

Spiral wave drift induced by stimulating wave trains (3)

Prediction of the velocity of drift of the spiral ?

Several regimes of spiral waves (dense spirals, sparse spirals, meandering spirals) must be distinguished.

By decomposing the motion of the spiral between two collisions with the incident wave, one may obtain a very good representation of the drift velocity (Gottwald, Pumir and Krinsky, 2001).

n.b. The meandering is not important in this picture.

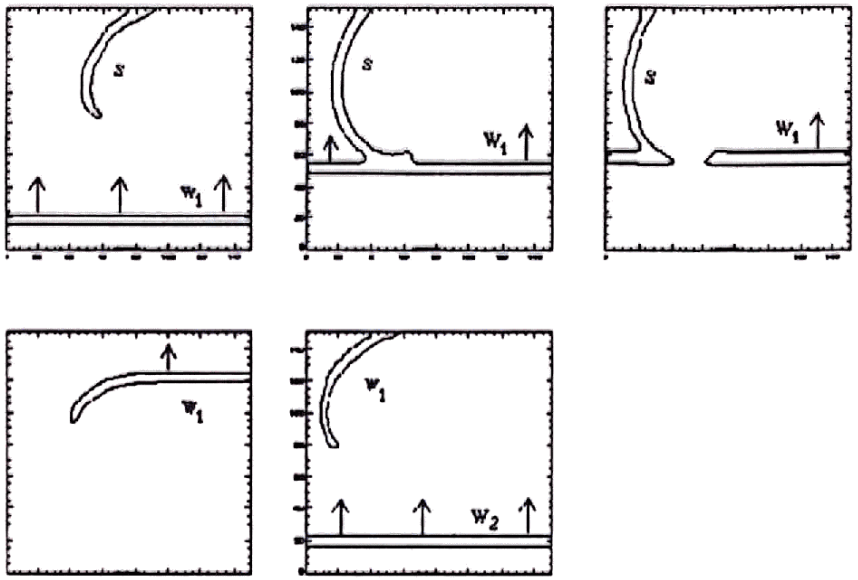


FIG. 1. Dynamics of a spiral wave S induced by a wave train $W_{1,2}$. The activator u is shown. The time increases from left to right. (a) A planar front W_1 is sent towards a spiral wave arm S. (b) Shortly after the collision. (c) Broken front W_1 is created. (d) Broken end W_1 evolves into a new spiral wave arm. (e) The next pulse W_2 of the stimulating wave train is launched. The wave pattern is similar to (a), but the spiral wave appears shifted.

Gottwald, Pumir + Krinsky, 2001.

Sparse spiral

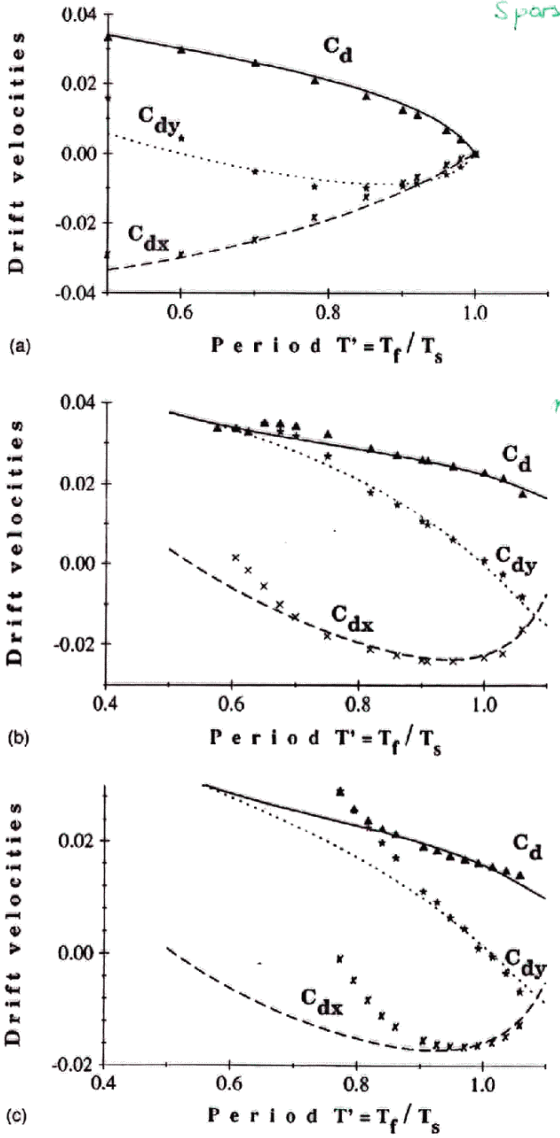


FIG. 6. Comparison of numerical results (points) and the phenomenological model (10) (lines). In (a)–(c) cases A–C from Fig. 1 are shown, respectively. Parameters for the phenomenological model are $\lambda = 0.0$ and $\vartheta = 40.0$ for case A, $\lambda = 7.4$ and $\vartheta = 83.0$ for case B, and $\lambda = 1.7$ and ϑ

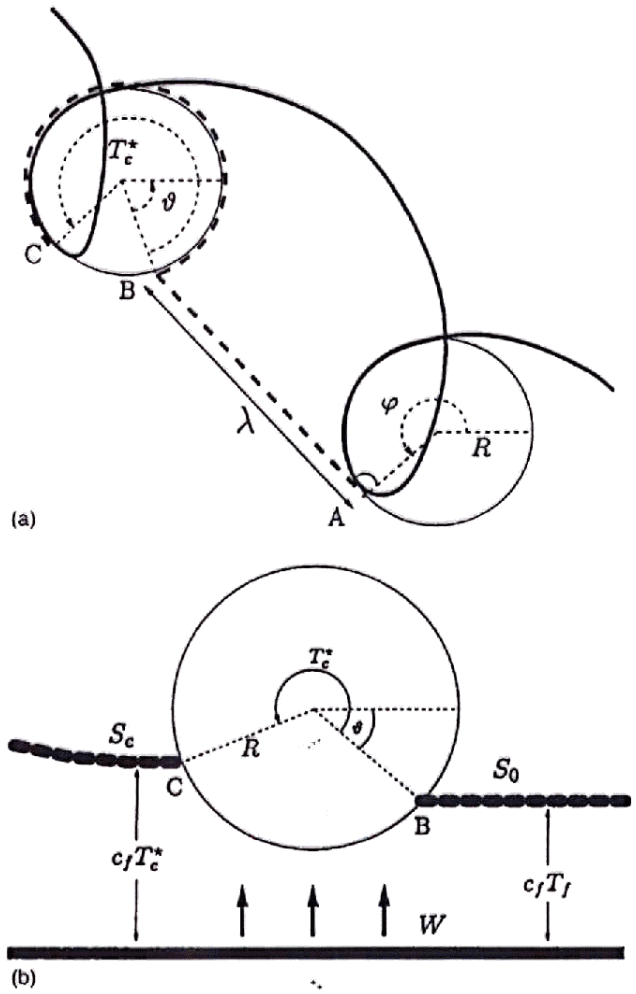


FIG. 5. (a) Illustration of the phenomenological model. (b) Close-up of the tip motion on the circle CB. S is a spiral wave arm moving along the core with radius R. W is a stimulating wave train. S_0 is the spiral wave at the start of its travel time along the core. S_c is the same spiral wave arm at the time of collision.

Gottwald, Pumir, Krinsky, 2001

Effect of an obstacle

In excitable media, an obstacle, such as a hole, or a limited region where the local properties differ from the rest of the medium may lead to a *pinning of a spiral wave*.

Effectively, this may lead to a failure of the methods based on the interaction betweenthe ATP based methods, since once the spiral wave is pinned, the drift induced by the wave train stops.

Practical question : How to unpin the wave ?

Proposed solution :

Apply a small amplitude, properly timed electric shock.

Unpinning of a spiral wave

Physical mechanism :

- The electric field generates on either side of the obstacle a region of size $\sim \lambda$ (the Weidmann length) where the tissue is hyperpolarized/depolarized.

- A wave of excitation is emitted from the depolarized zone.

- When the external stimulation is properly timed, the resulting wave leads to the detachment of the pinned rotating wave.

$\Rightarrow$ With a properly timed excitation, the spiral wave can be detached from the obstacle.

$\Rightarrow$ A *weak field* is enough to unpin the spiral.

($\sim 1\ V cm^{-1}$, instead of $10\ V cm^{-1}$ for defibrillation).

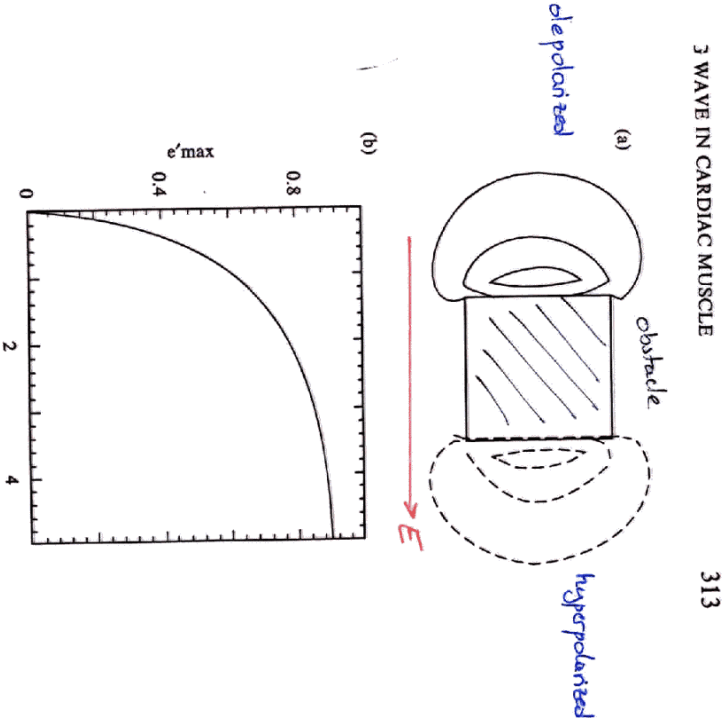
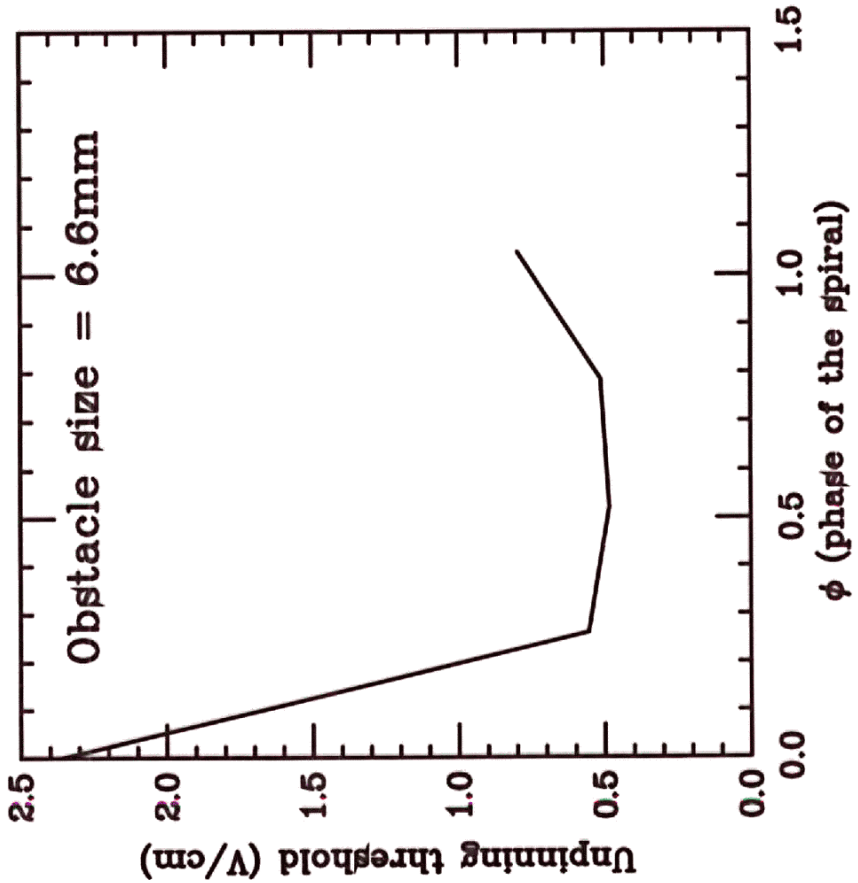


FIG. 1. Electric field creates Weidmann zones near an anatomical obstacle. (a) Potential isolevels around an obstacle of 0.8 mm size. Electric field is 10^{-2} V cm^{-1} (contours from -0.9 to 0.9 mV, contour interval of 0.3 mV). (b) Dependence of the amplitude of the Weidmann zone on the radius of the obstacle. Notation: $e'_{max} = e_{max}/(E_0 \lambda)$, $R' = R/\lambda$.

Defibrillation threshold ~ 10V/cm.



FitzHugh model

Beeler-Reuter model.

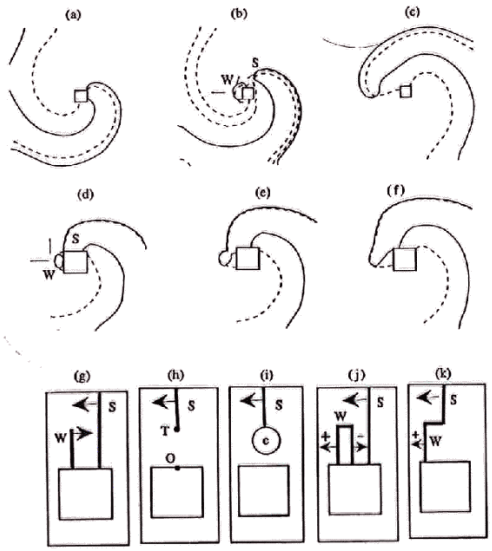
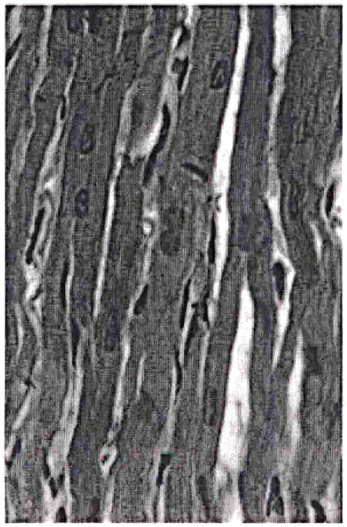


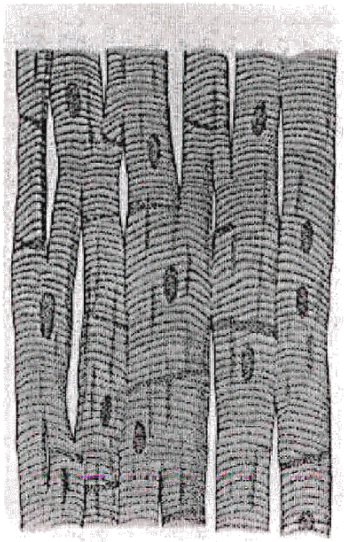
FIG. 2. Unpinning of a rotating wave by a weak electric field in the FH model (a–c), in the BR model (d–f) and schematic (g–k). FH model: (a) a rotating wave pinned to an obstacle, (b) right after the electric shock. W is an excited region created by positive Weidmann zone W+, arrows indicate direction of propagation. (c) The spiral wave S is detached (unpinned) from the obstacle. Solid line—variable $E = 0.5$, dashed line—$w = 0.1$ [$w = 0.05$ is also shown in (b)]. Electric shock amplitude $E_0 = 0.5$, 20 ms duration, directed antiparallel to X-axis ("+" is at the right side). Parameters: $\varepsilon = 7.5\ s^{-1}$, $u = 0.2$, $A = 750\ s^{-1}$, $k = 6$, $\Delta x = 0.6$ mm and $\Delta t = 0.8$ ms. The grid contains 100×100 elements, and the size of the obstacle is 4.8 mm. *BR model*: (d) $t = 10$ ms after the end of the shock, (e) $t = 20$ ms, (f) $t = 30$ ms. Solid lines—potential $E = -50$ mV, dashed line—inactivation $h = 0.5$. Electric shock 0.46 V cm^{-1}, 10 ms duration, obstacle size 6 mm. BR equations, parameters: $g_{Na} = 0.6 g_{Na_2}$, $g_{Ca} = 0.5 g_{Ca_2}$, where g_{Na_2} and g_{Ca_2} are the normal values of conductivities, grid 100×100 elements, $D = 0.1$ mm^2 ms^{-1}, $\Delta x = 0.3$ mm, $\Delta t = 0.5$ ms. *Schematic*: (g–i)—unpinning, (j, k)—no unpinning. (g) Wave W propagates in one direction only (it was created inside VW), (h) after collision and annihilation, wave S is unpinned, (i) the free end of wave S starts rotating around the core C, (j) wave W propagates in all directions (it was created outside VW) and (k) after collision and wave interconnection, wave S is not unpinned.

from Pumir & Krinsky, 1999.

The bidomain model describes the anisotropic electrical properties of cardiac tissue.

Cardiac tissue is very anisotropic.
In mature cardiac tissue, the ratio of the electrical conductivities parallel to and perpendicular to the myocardial fibers is much greater in the intracellular space than in the extracellular space.





The bidomain model

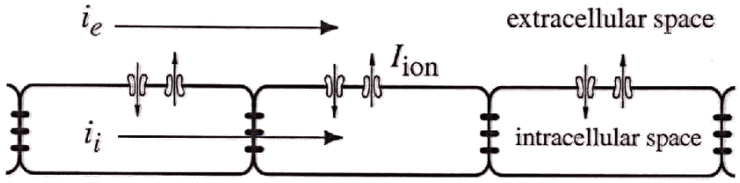
Our study so far was based on very simple assumption about the electric coupling in the cardiac tissue (∼ we were assuming that cardiac tissue was *uniform*.).

Here, we study more precisely the influence of the *structure* of the cardiac tissue.

⇒ Use the *bidomain model* , considered as the proper way to represent the currents inside the tissue.

n.b. : no attempt to use a precise description of ionic currents (not yet).

· The bidomain model



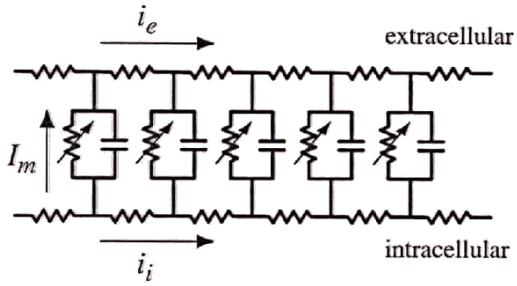
currents

i_e : extracellular space

i_i : intracellular space

I_{ion} : Ionic current.

· Circuit representation



conservation law	Ohm's law
$\nabla \cdot i_e = I_m$,	$i_e = -\underline{\sigma}_e \nabla \phi_e$
$\nabla \cdot i_i = -I_m$,	$i_i = -\underline{\sigma}_i \nabla \phi_i$

$I_m = \beta \left(C_{\text{m}} \dfrac{\partial}{\partial t}(\phi_i - \phi_e) + I_{\text{ion}} \right)$: Trans-membrane current per unit volume.

C_{m} : Membrane capacitance.

β : Surface to volume ratio which converts current per unit area to per unit volume.

ϕ_e , ϕ_i : Potentials in the extra- and intra-cellular space.

$\underline{\sigma}_e$, $\underline{\sigma}_i$: Conductivity tensors in the extra- and intra-cellular space

⚠ : the conductivity tensors are ANISOTROPIC

Potential distribution around an obstacle (1)

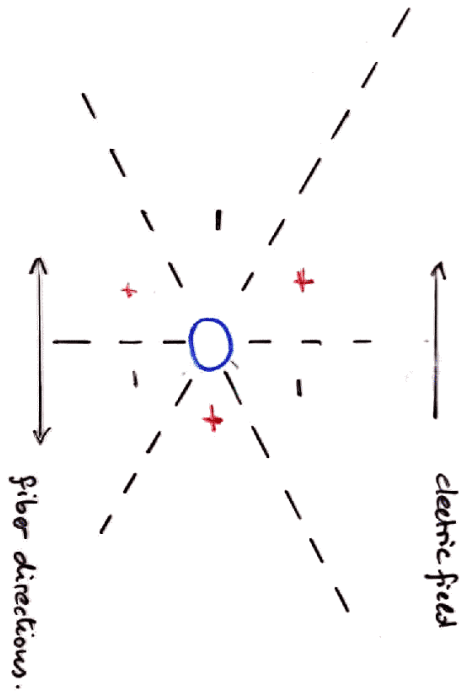
Physical problem : Consider a tissue with an obstacle.

In the obstacle, the cells are uncoupled ($\sigma_i = 0$) and unexcitable.

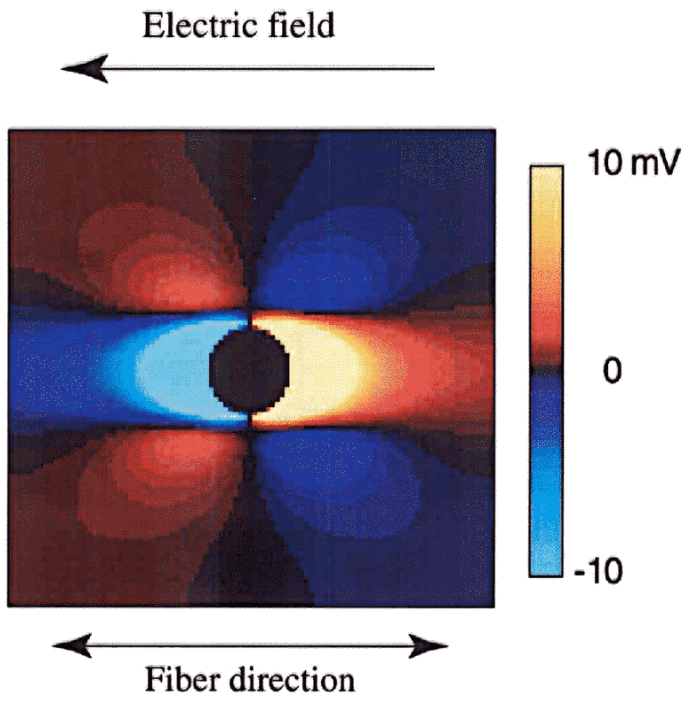
Question : Potential distribution around the obstacle when a uniform current is applied far away from the obstacle ??

Numerical result :

The bidomain model predicts a six-fold angular structure of the membrane potential.



Linear ionic current model : $I_{\text{ion}} \propto \phi_m$



$g_{eL} = g_{eT} = g_{iL} = 10 g_{iT} = \text{const.}$

$\boldsymbol{E}$ = 1.0 V/cm

Potential distribution around an obstacle (2)

Analytic understanding of the solution :

Perturbation analysis of the solution around the "monodomain" solution corresponding to equal anisotropy ratios (Roth, 1997) :

$$\frac{g_{eL}}{g_{eT}} = \frac{g_{iL}}{g_{iT}}$$

Here, do the calculation by assuming

$$g_{eL} = g_{eT} = G_e$$

and take :

$$g_i = G_i \begin{pmatrix} (1+\epsilon) & 0 \\ 0 & (1-\epsilon) \end{pmatrix}$$

$\epsilon << 1$

Potential distribution around an obstacle (3)

Solution at 0th order :

- inside the obstacle :

$$\nabla^2 \phi_e = 0, \phi_m = \text{arbitrary}$$

- outside the obstacle :

$$\nabla^2 \phi_m - \frac{\phi_m}{\lambda^2} = 0$$

$$\nabla^2 \phi_e = -\frac{\phi_m}{\lambda'^2}$$

with $\lambda = ((G_e + G_i)\beta G_m/(G_e G_i))^{1/2}$ and $\lambda' = (\beta G_m/G_e)^{1/2}$.

- boundary conditions at infinity :

$$(\sigma_e + \sigma_i)\nabla\phi_e \rightarrow \mathbf{I} = I(cos(\theta_I), sin(\theta_I))$$

Potential distribution around an obstacle (4)

Solution (outside the obstacle) :

The solution has an angular dependence of the form $\cos(\theta - \theta_I)$.

$$\phi_m^0 = -E\lambda \frac{K_1(r/\lambda)}{K_1'(a/\lambda)} \cos(\theta - \theta_I)$$

$$E = \frac{I}{(G_e + G_i)}\left(1 - \frac{\lambda}{2\lambda'^2}\int_a^\infty \frac{K_1(r/\lambda)}{K_1'(a/\lambda)} dr\right)$$

$$\phi_e^0 = \cos(\theta - \theta_I)(E_1(r) \times r + E_2(r)/r)$$

$\Rightarrow \phi_m^0$ decays exponentially to zero away from the obstacle

$\Rightarrow \phi_e^0$ decays like $1/r$ towards its asymptotic value.

~ dipole like solution -

Potential distribution around an obstacle (5)

Problem at first order in ϵ :

The equation for the correction ϕ_m^1 reads outside of the obstacle :

$$\nabla^2\phi_m^1 - \frac{\phi_m^1}{\lambda^2} + (\partial_x^2 - \partial_y^2)(\phi_m^0 + \phi_e^0) = 0$$

Consequence : the solution ϕ_m^1 has an angular dependence of the form :

$$\phi_m^1(r,\theta) = \varphi_1 \cos(\theta + \theta_I) + \varphi_3 \cos(3\theta - \theta_I)$$

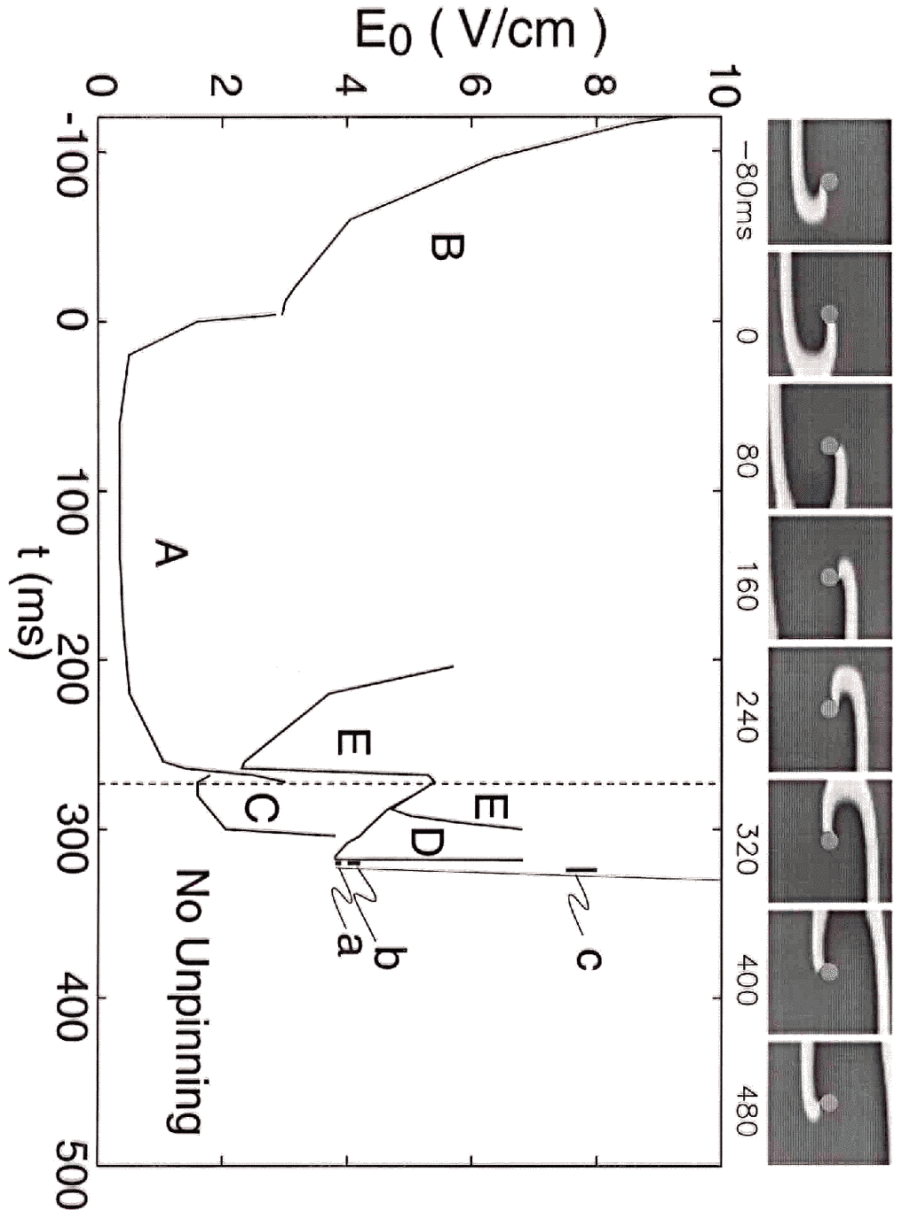
Solution :

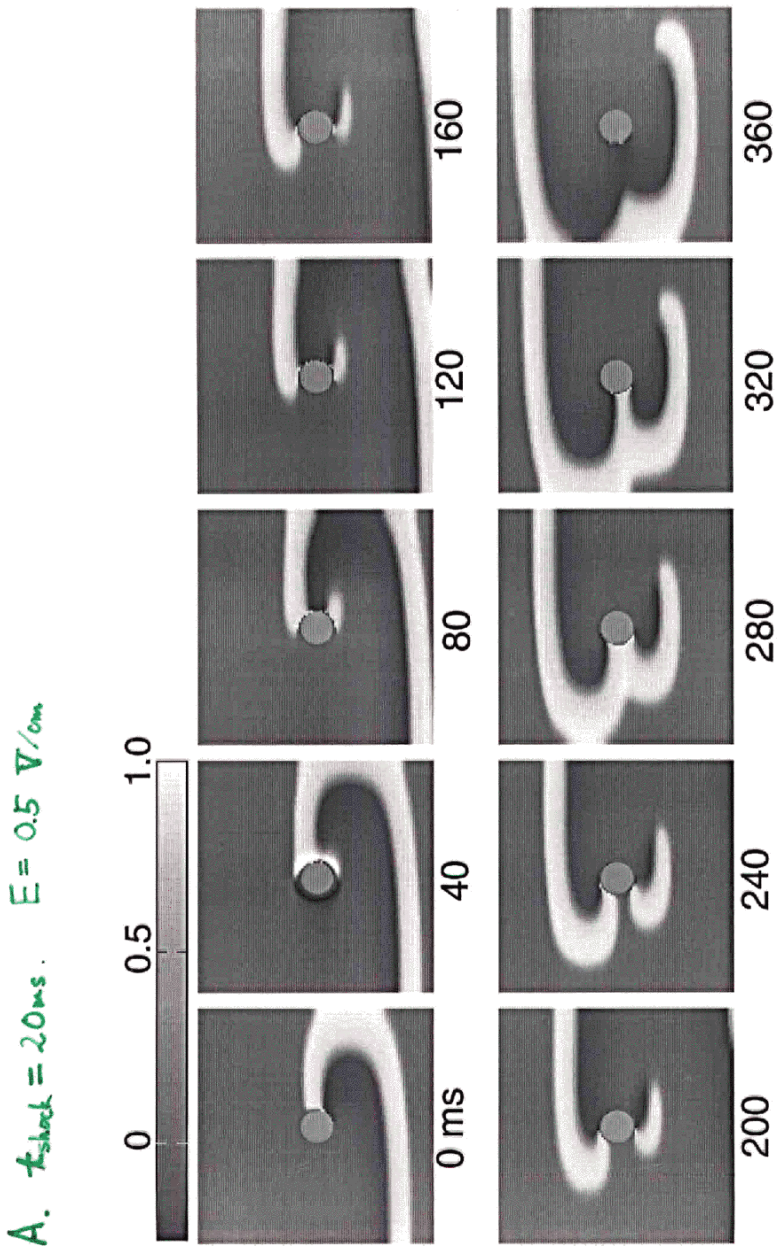
$$\varphi_3(r) \sim \frac{1}{r^3} \quad \text{when} \quad r \to \infty$$

$$\varphi_1(r) \sim \exp(-r/\lambda) \quad \text{when} \quad r \to \infty$$

Implications :

- The solution has a six-fold symmetry
- The membrane potential ϕ_m^1 decay algebraically ($\sim 1/r^3$) away from the obstacle.





The problem of spontaneous ectopicity (1)

An intriguing question, which has serious clinical aspects :

what happens during an infarct ?

Practical importance : many people actually die during (or shortly after) an infarct.

A well-known fact : an infarct results from the obstruction of a blood vessel (clogged by an excess of fat). As a result, the heart tissue is nor properly irrigated, and gets damaged.

It is difficult to see what happens *in-vivo*

⇒ study the problem *in-vitro*

Experimental setup (Arutunyan and Sarvazyan, 2000) :

- Make a 2-dimensional culture of cells.
- Create a well-controlled 'infarct' by perfusing locally the tissue with an 'ischemic solution'. (containing an excess of Potassium and cells' decouplers).

Visualize using Calcium sensitive dyes.

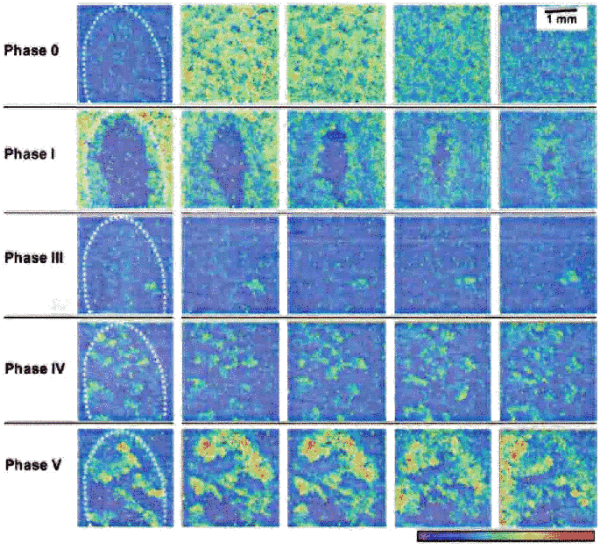
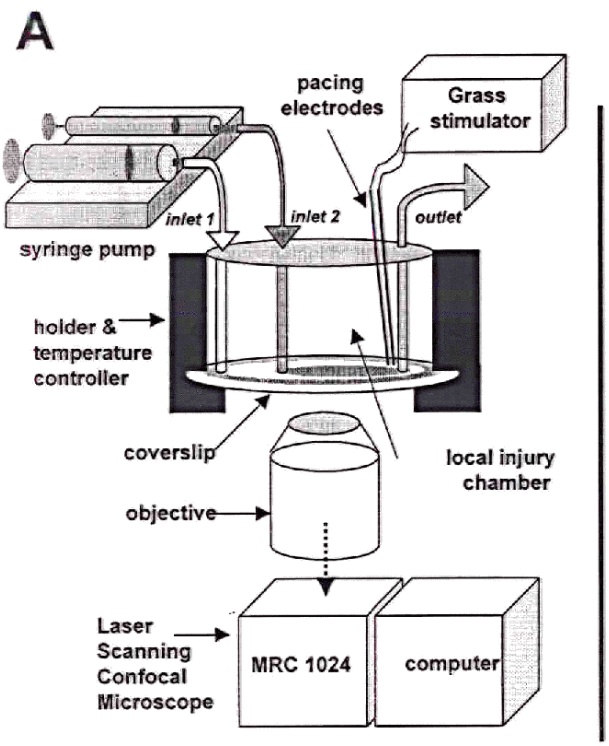

Phase 0
Phase I
Phase III
Phase IV
Phase V
1 mm

Fig.5


A
pacing electrodes
Grass stimulator
inlet 1
inlet 2
outlet
syringe pump
holder & temperature controller
coverslip
local injury chamber
objective
Laser Scanning Confocal Microscope
MRC 1024
computer

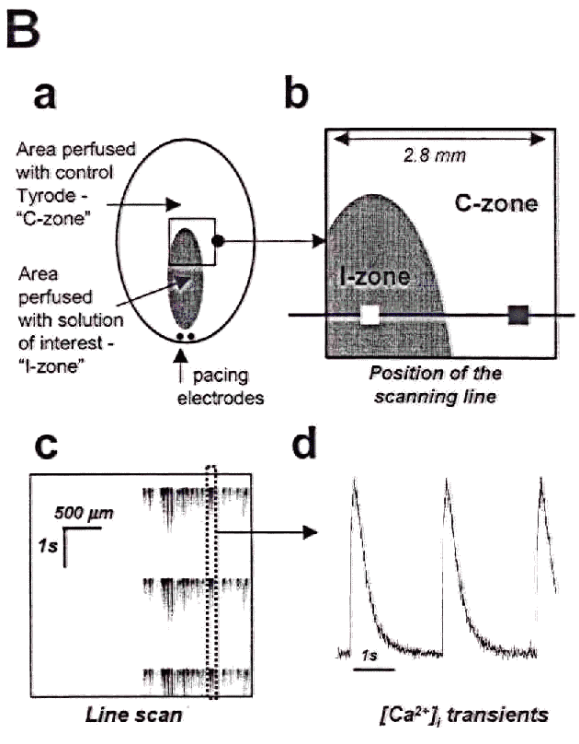

B
a
b
Area perfused with control Tyrode - "C-zone"
Area perfused with solution of interest - "I-zone"
pacing electrodes
2.8 mm
C-zone
I-zone
Position of the scanning line
c
d
500 µm
1s
Line scan
1s
[Ca2+]i transients

Fig.1

"ischemic conditions" "normal conditions"

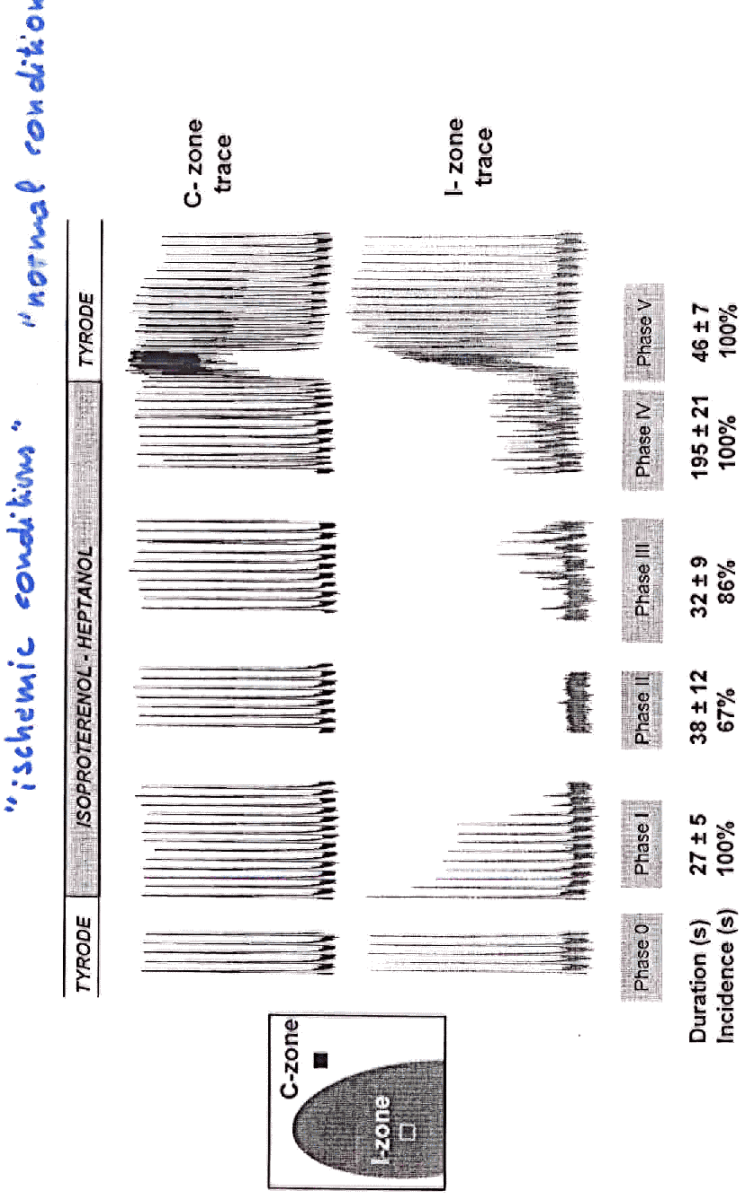


Fig.4

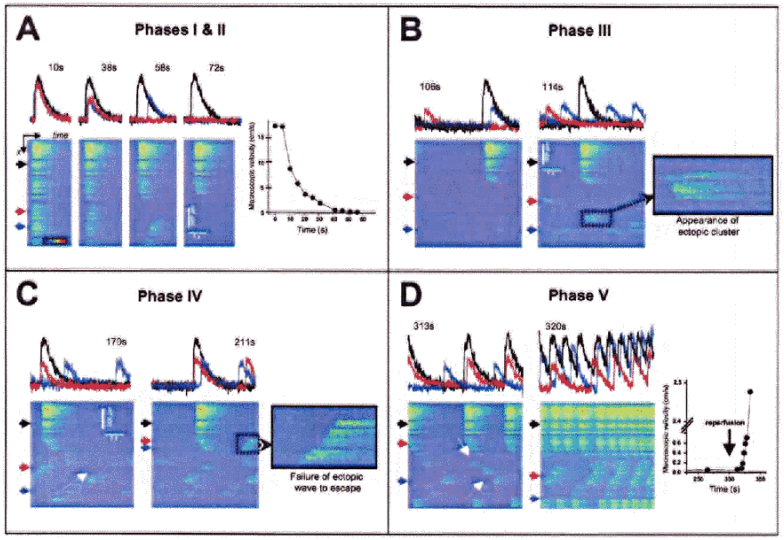


Fig.7

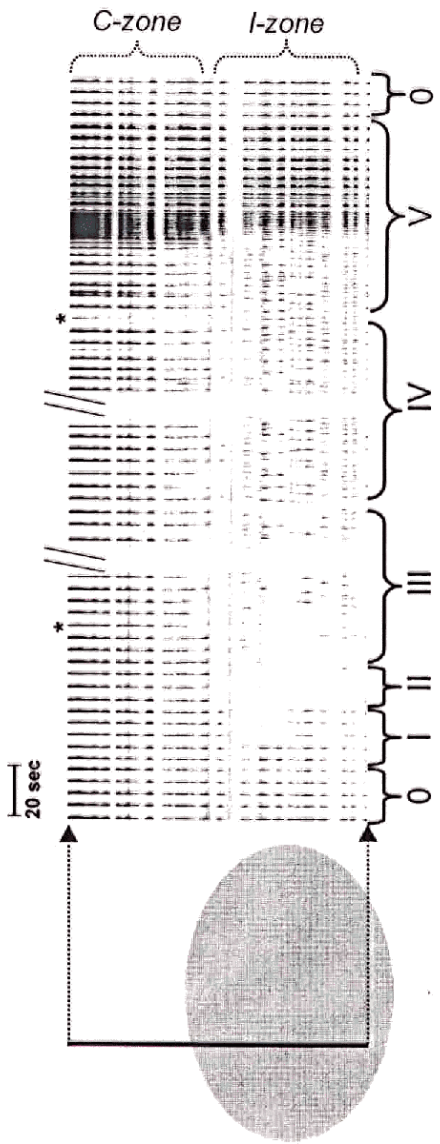


Fig.6

The problem of spontaneous ectopicity (2)

Experimental observations :

After a transient phase,

- Waves generated outside the ischemized region no longer propagate into the ischemized region (effect of uncouplers).

- *Spontaneous activity* is observed inside the infarcted part of the tissue. It leads to the formation of *waves of activity* confined to the ischemized region.

When reperfusing the heart with the normal (healthy) solution, a transient regime is observed when *ectopic waves* can spread out into the healthy part of the tissue.

Relevance : Several clinical studies point to the appearance of lethal arrhythmias a few minutes after an infarct happened.

The problem of spontaneous ectopicity (3)

Mathematical model.

• Consider a tissue made of

1/ Normal tissue

2/ Injured tissue with reduced coupling :

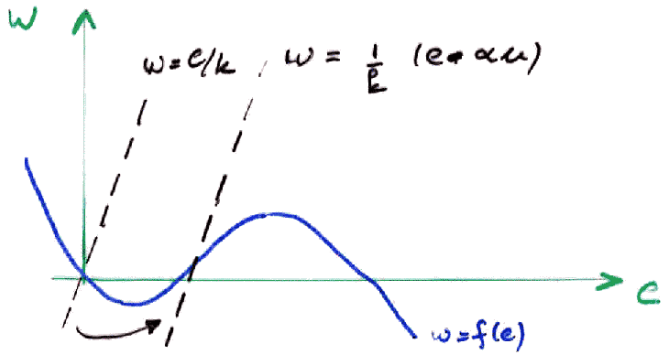
$$D \to D \times f_c(t)$$

and with spontaneous activity. In the FitzHugh Nagumo model, modify the slow nullcline dynamics :

$$\partial_t w = \epsilon \times (e - kw)$$

to

$$\partial_t w = \epsilon \times (e - \alpha u - kw)$$



Take a *random distribution* of values of α.

⇒ cells become spontaneously active, each with a different period.

The problem of spontaneous ectopicity (4)

Numerical results (Arutunyan, Pumir, Krinsky, Swift and Sarvazyan, 2003) :

The model reproduces the main string of events as observed during the experiment, by assuming a 'reasonable choice' of the time dependence of the activity and the coupling.

nb : the results do not depend on the precise nature of the model (FitzHugh-Nagumo, Beeler-Reuter).

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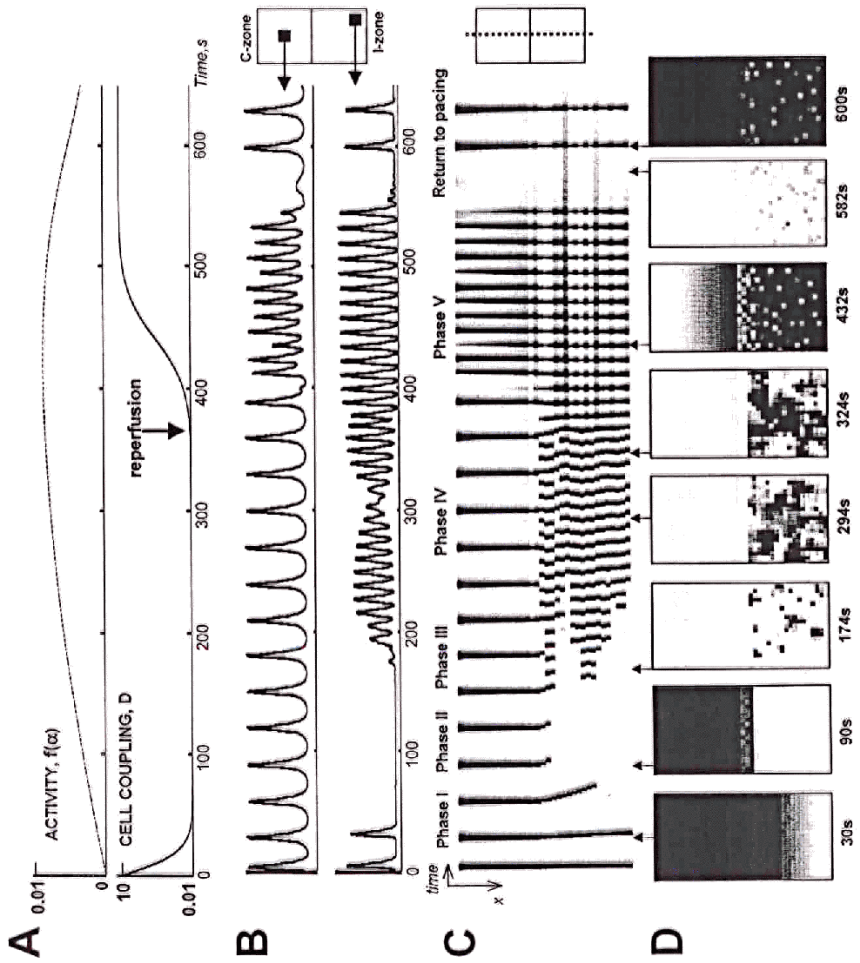

Fig.8

The problem of spontaneous ectopicity (5)

Underlying theoretical problems :

• Wave regimes in a spontaneously active, weakly coupled medium, with a random distribution of activity.

- at very low coupling, each cell oscillates with its own frequency.

- at much higher coupling, all cells tend to synchronize.

what happens at intermediate coupling ?

• Propagation of waves (or lack thereof) from one medium to the other.

Intriguing phenomenon : the waves remain confined to either side of the tissue (ischemized, normal).

Nature of the bidirectional block between the two tissues ?

A related problem : Structure of the AV (Auriculo-Ventricular) node (Keener and Sneyd, Efimov et al).

Conclusions (1)

The methods used in clinics lead to interesting fundamental problems. Solving these riddles is likely to help to devise better ways to treat cardiac arrhythmias.

Some of the examples include :

- How does Anti Tachycardia Pacing work ?

  Simplified model of a spiral wave interacting with an incoming train of pulses : understand the drift of the spiral.

- Problem of unpinning of a spiral wave around an obstacle.

  no need to apply a large electric shock; a small amplitude, properly timed shock is enough.

Conclusions (2)

Importance of the dynamics during an infarct. Interesting new possibilities with a 2-dimensional *in-vitro* experiment ($\sim$ well-controlled infarct).

Observe an interesting set of dynamical phenomena, which can be modelled with simple theoretical tools.

Ultimate goal :

Applications to clinics (devising better algorithm to deliver the electric stimuli).

...Much work is still needed...