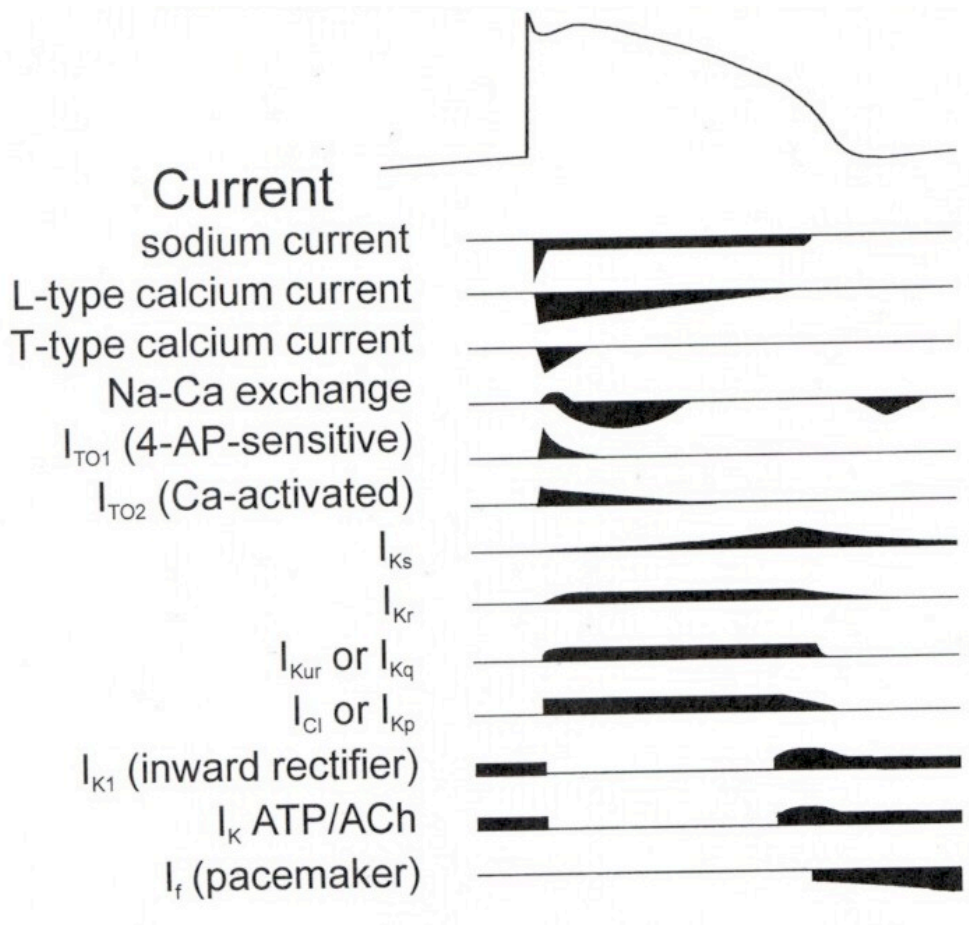
Nonlinear dynamics in biology : cardiac dynamics

Part 2

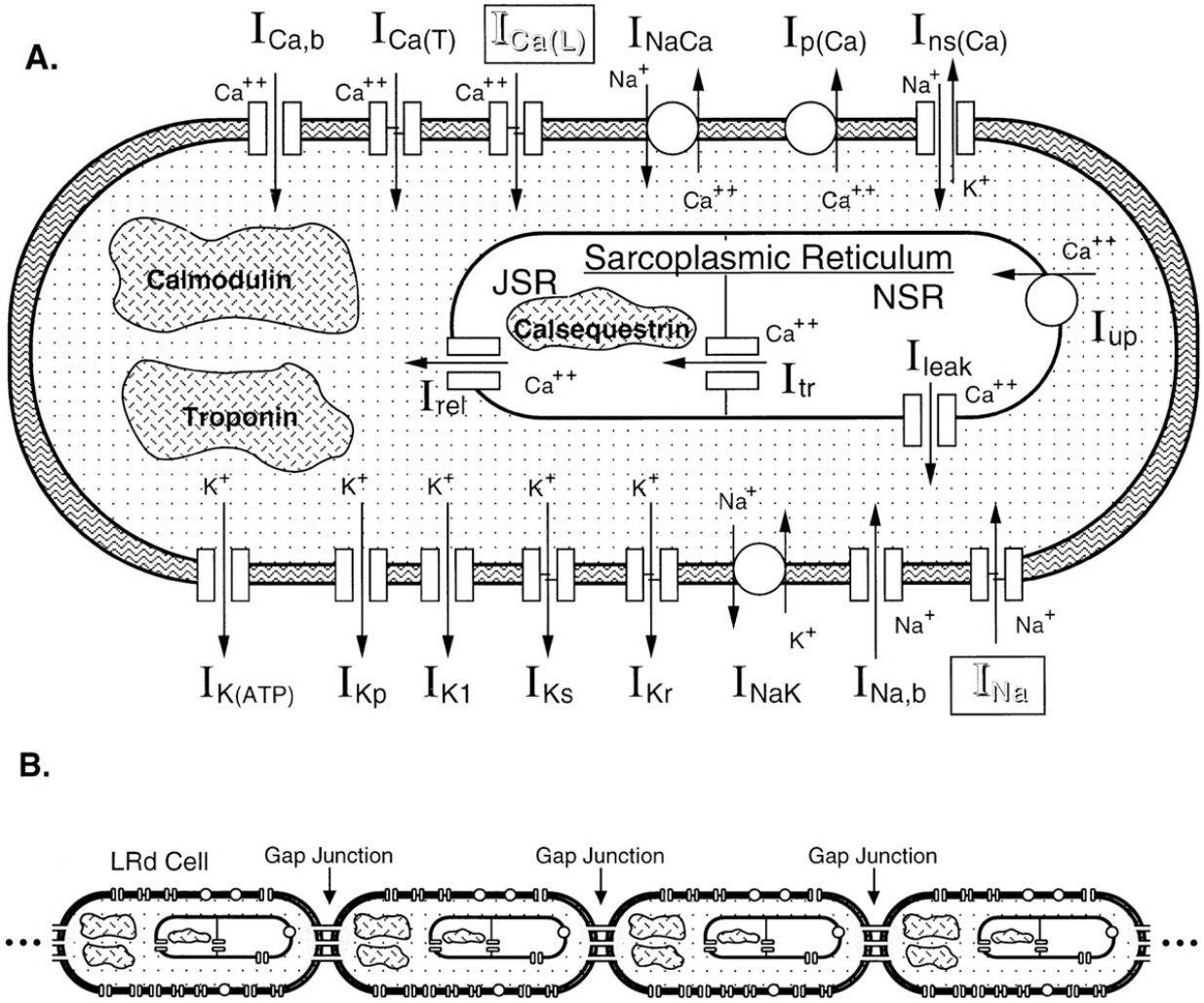
Alain Pumir, ENS Lyon, France.

Electricity in the heart

Cardiac Ion Currents



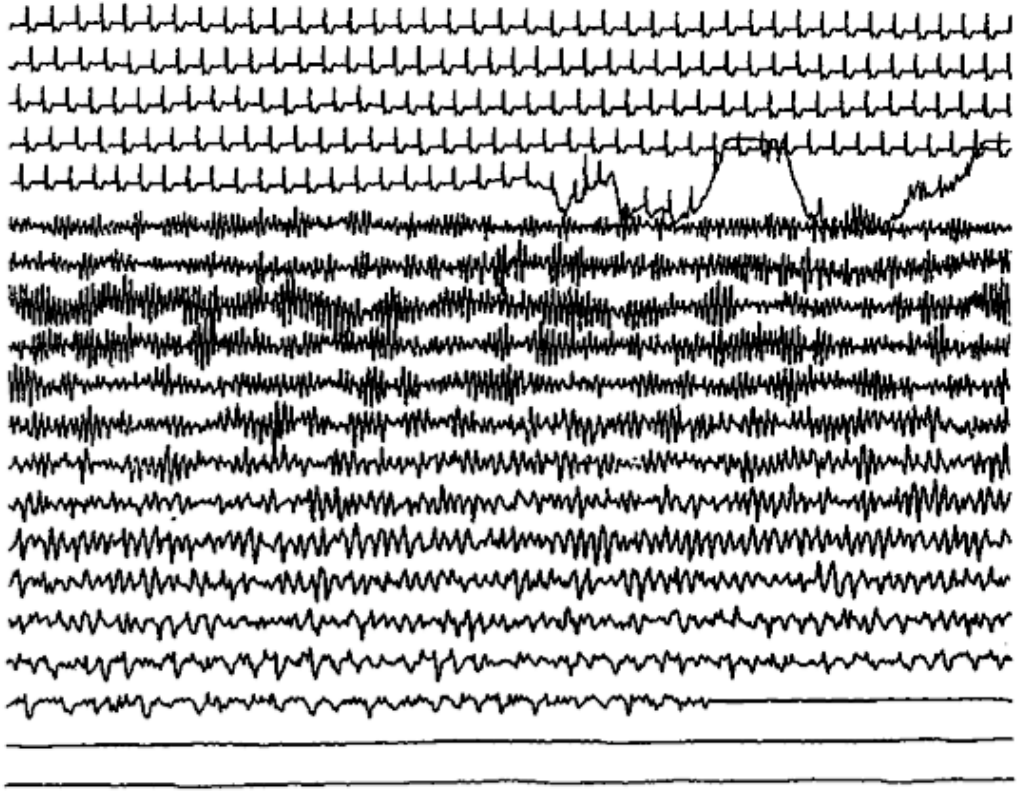
Dynamical model of the heart : the dynamic Luo-Rudy ventricular cell model (LRd)



Shaw, R. M. et al. Circ Res 1997;81:727-741

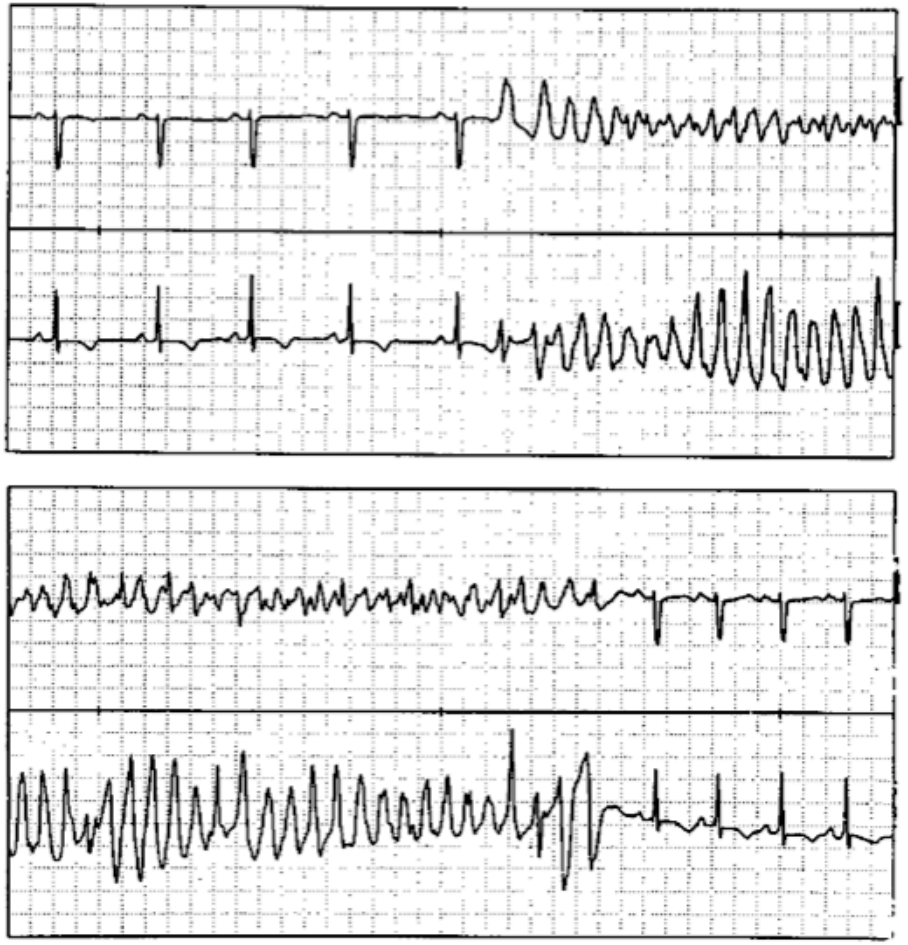
Rhythmic disorders in the heart.

Episode of loss of rhythm followed by death.



Episode of VF and cardiac death, from P.Chen et al, Chaos, 1998

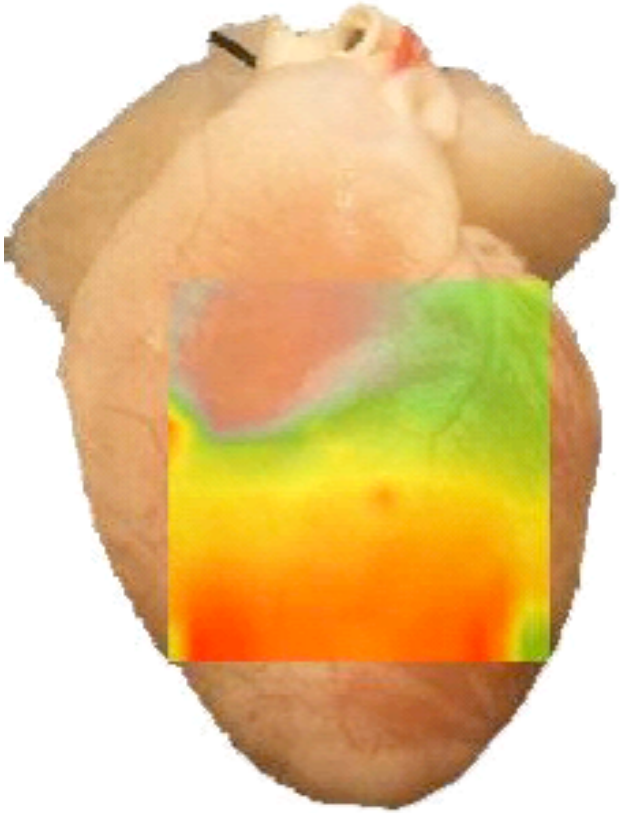
Arrhythmia followed by recovery.



Episode of VT and its spontaneous termination.

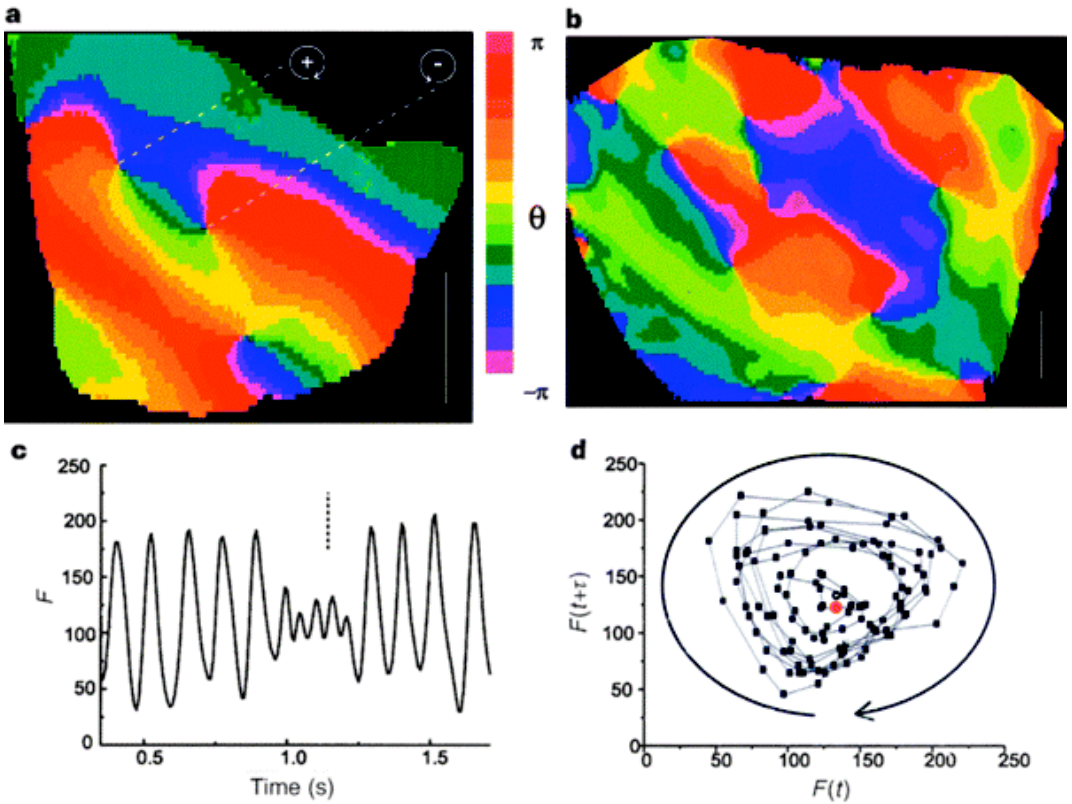
From P.Chen et al, Chaos, 1998

Spatio-temporal chaos on the surface of the heart



Visualisation of waves at the surface of the heart.
Efimov et al. 1998

Patterns of activity at the surface of a fibrillating heart



Spatial chaos in a fibrillating ventricle in a

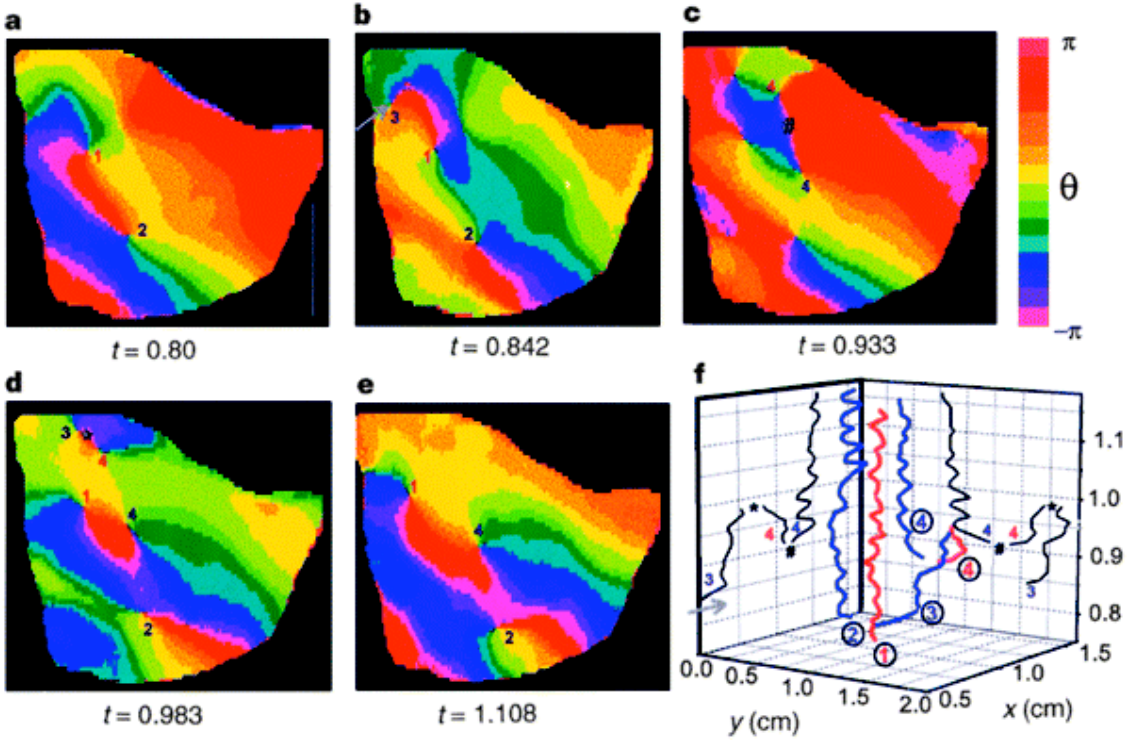
a. rabbit's heart

b. sheep's heart.

c. The tissue is never really excited, hence does not efficiently contracts.

(from Gray et al, Nature 1997).

Patterns of activity at the surface of the heart

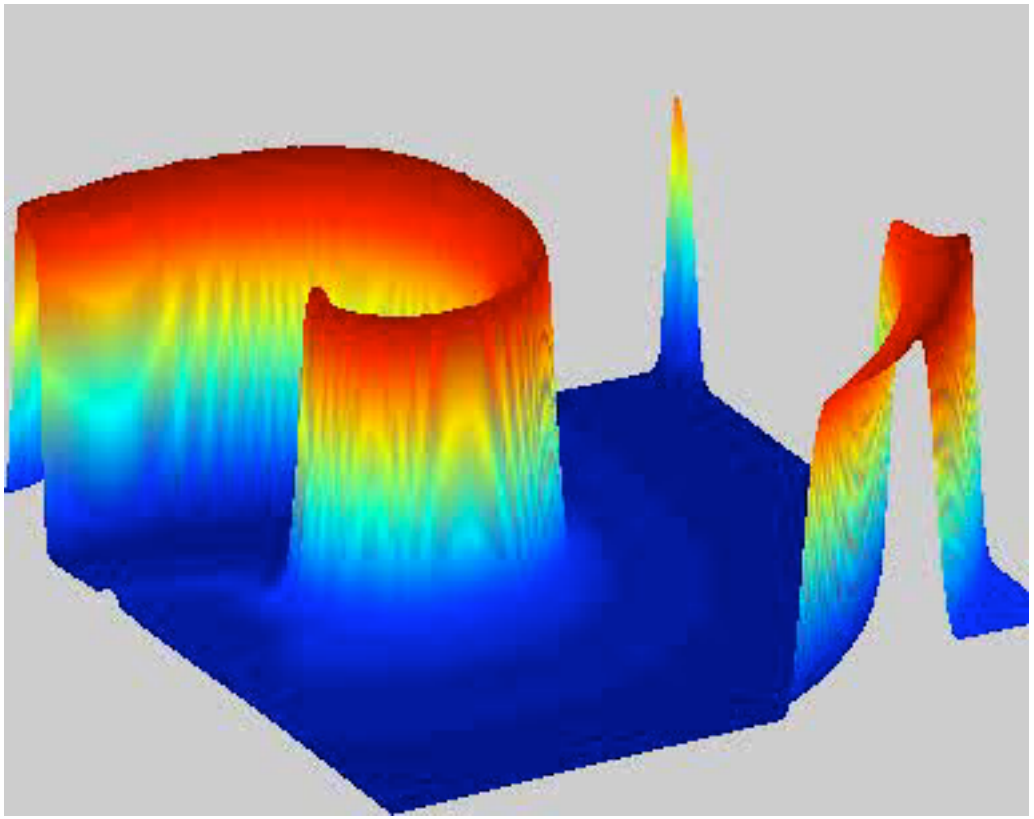


Evolution of the pattern of excitation at the surface of the heart. Phase singularities get created (panel c, # sign).

=> Spatio-temporal chaos

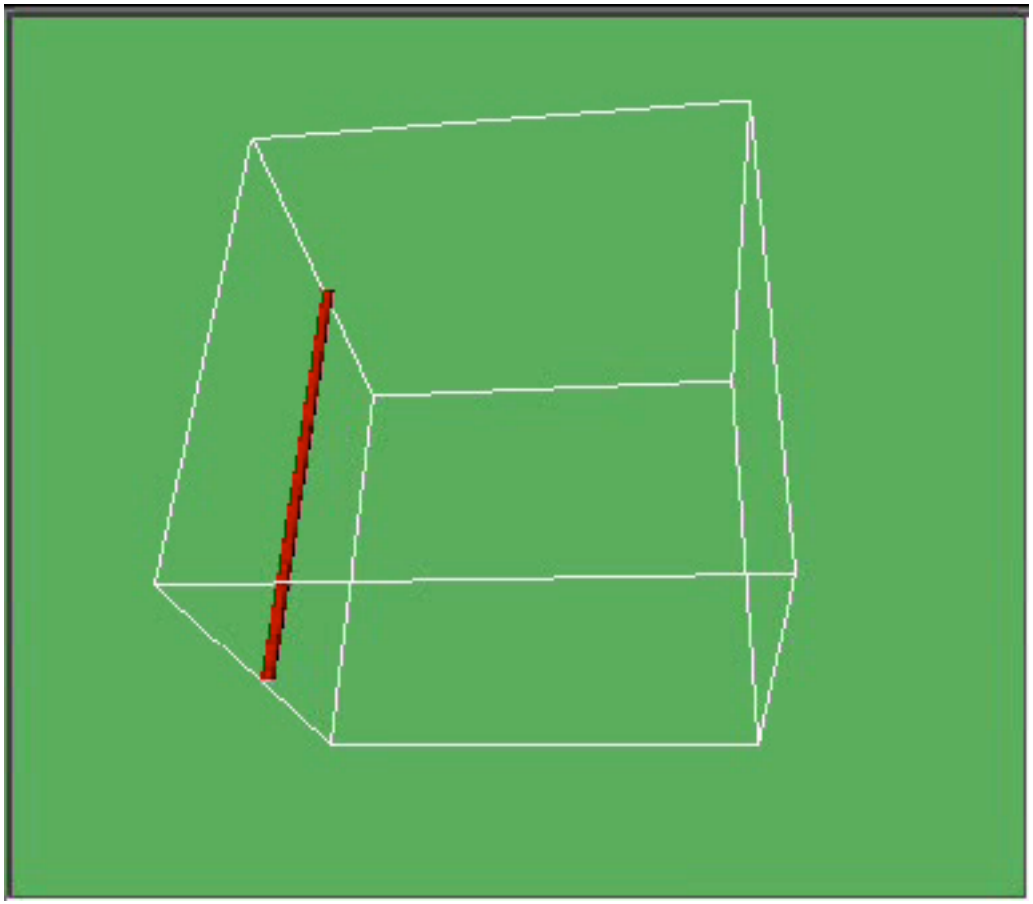
(from Gray et al. Nature 1997).

What is the origin of spatio temporal chaos ? 2d case.



Spatio-temporal chaos is typically a consequence of an instability of the spiral core.

What is the origin of spatio temporal chaos ? 3d case.



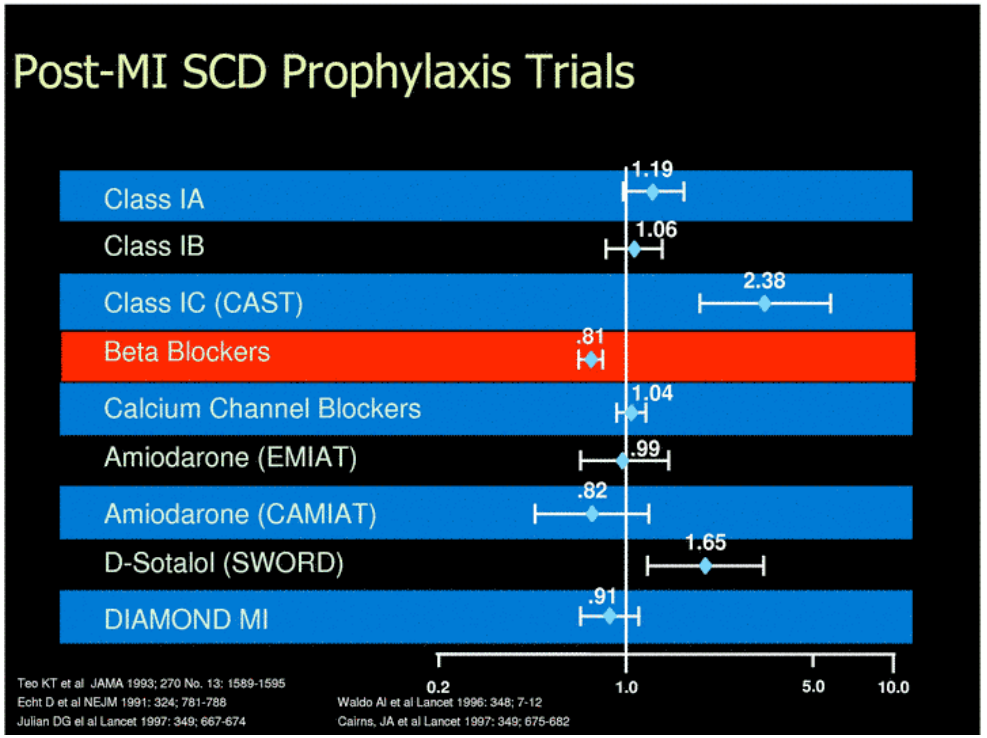
- The ventricle is thick (~1cm); as such, waves may have 3d-instabilities (filament breaking down).

Treatment of rhythmic disorders in the heart.

Treatment of cardiac arrhythmias by pharmaceutical means ?

- Several drugs have been proposed to treat cardiac arrhythmias.
- The standard tests (CAST, SWORD) have shown that the proposed drugs do not work very well …

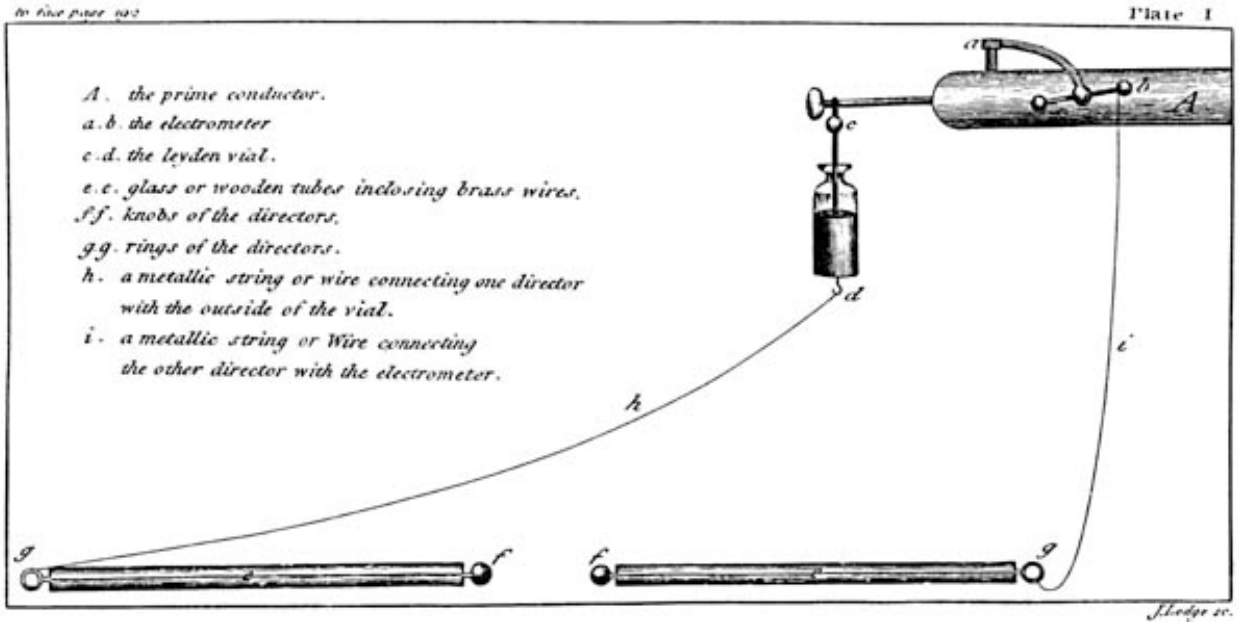
…In fact, some of the proposed drugs even increase mortality…



Another way to treat CVD : use electric shocks !

Charles Kite

An Essay on the Recovery of the Apparently Dead, London, 1788.



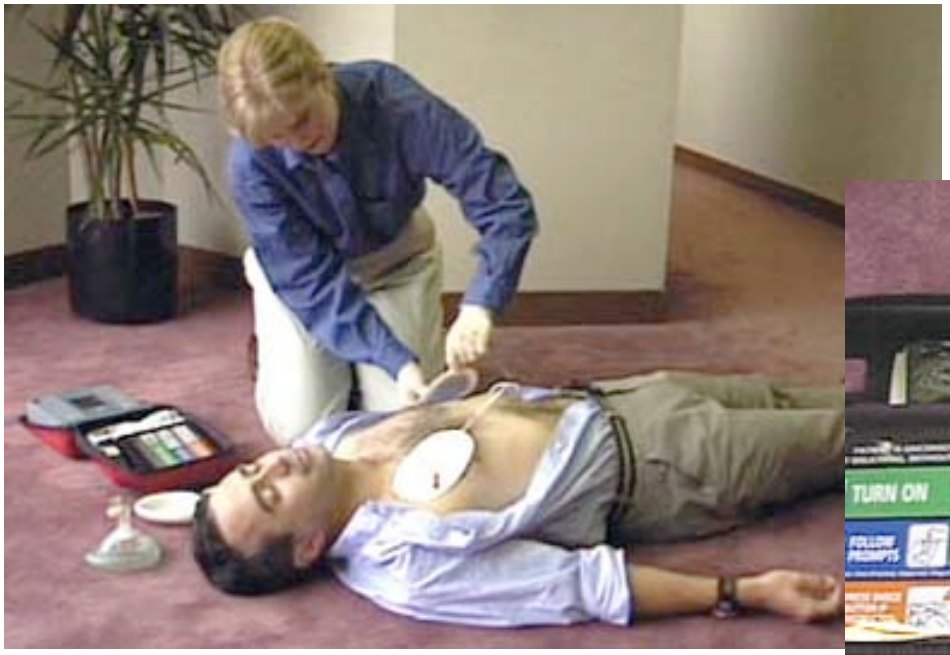
"…Twenty minutes had at least elapsed before he could apply the shock, which he gave to various parts of the body without any apparent success; but at length, on transmitting a few shocks through the thorax, he perceived a small pulsation; soon after the child began to breathe, though with great difficulty. In about ten minutes she vomited. A kind of stupor remained for some days; but the child was restored to perfect health and spirits in about a week".

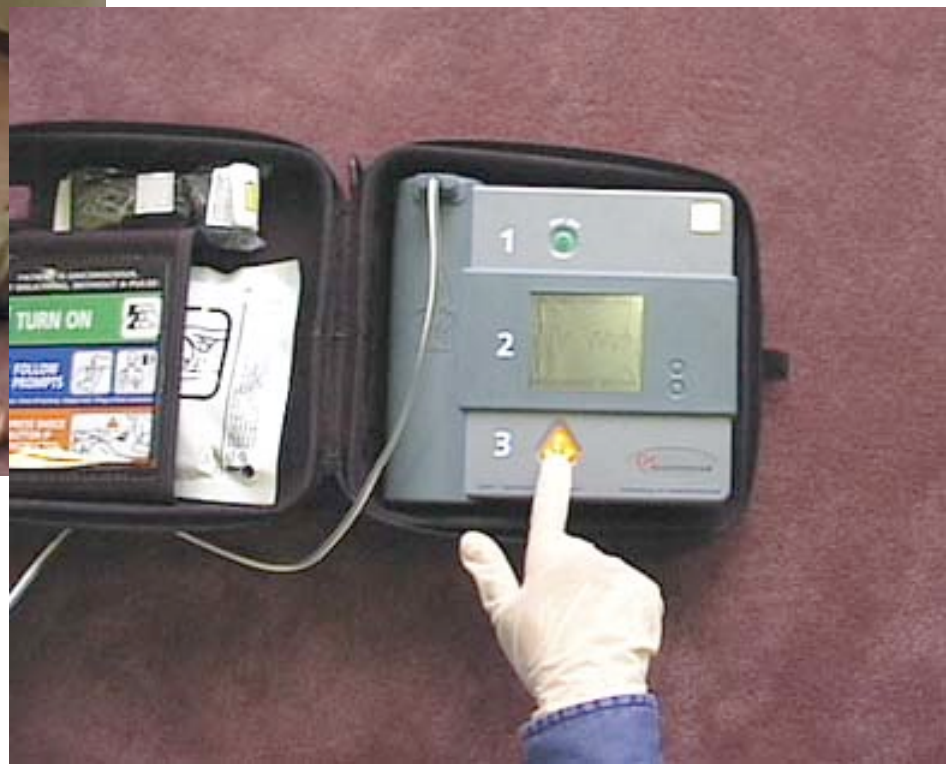
Treatment of cardiac arrhythmias : electric shocks ?

- The scientific part of the story :

- **M. Hoffa & C. Ludwig**, *Einige neue Versuche über Herzbewegung*. Zeitschrift Rationelle Medizin 9:107-144, 1850 [tachycardia can be terminated by electric fields].
- **J.-L. Prevost and F. Battelli**, *La mort par les décharges éléctriques*, Journ. de Physiol., 1: 1085-1100, 1899. [(re)-discovery of 'defibrillation']
- **C.S. Beck, W.H. Pritchard, H.S. Feil**, *Ventricular fibrillation of long duration abolished by electric shock*. JAMA. 135: 985, 1947
- **Zoll PM, Linenthal AJ, Gibson W, Paul M, Norman LR**. *Termination of Ventricular Fibrillation in Man by Externally Applied Electrical Countershock.* New Eng J Med 1956; 254: 727-732.)
- **Gurvich NL, Yuniev GS**. *Restoration of regular rhythm in the mammalian fibrillating heart*. Byulletin Eksper Biol & Med. 1939; 8:55-58. (in Russian)
- **Mirowski M, Mower MM, Staewen WS, Tabatznik B, Mendeloff AL**. *Standby automatic defibrillator: An approach to prevention of sudden coronary death*. Arch Intern Med. 1970; 126:158-161.

Treatment of cardiac arrhythmias : defibrillators.



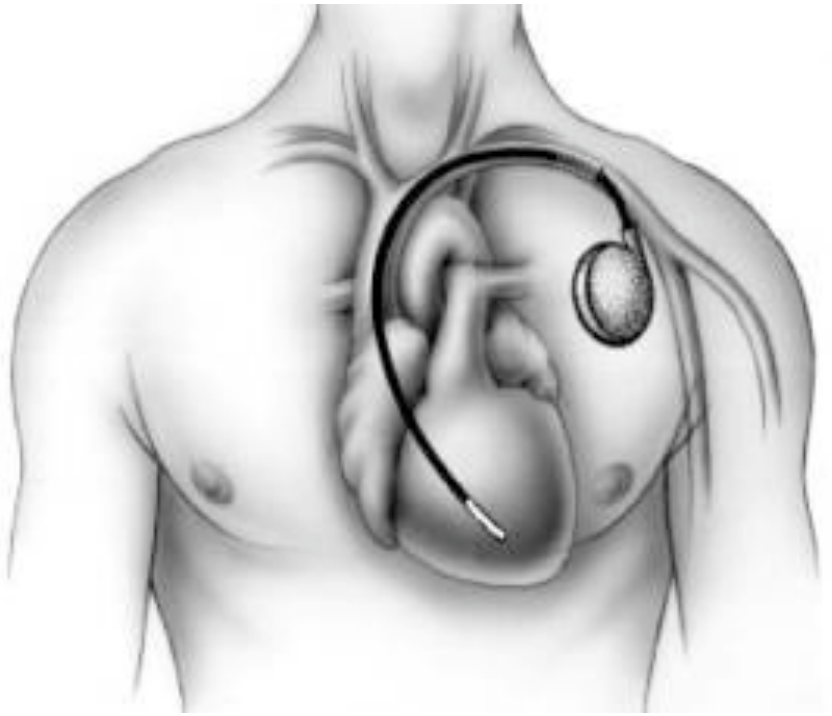


- In case of emergency, apply a very strong electric shock…

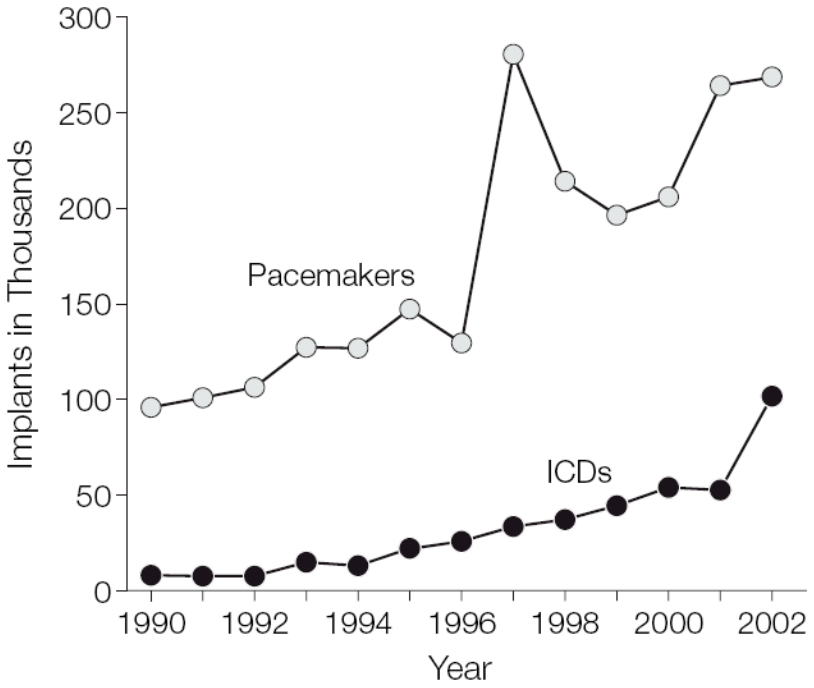
Defibrillators terminate waves in the heart.

The electric field applied from the side terminates the pattern of excitation, and resets the heart.

Implantable Cardioverter Defibrillator (ICD).

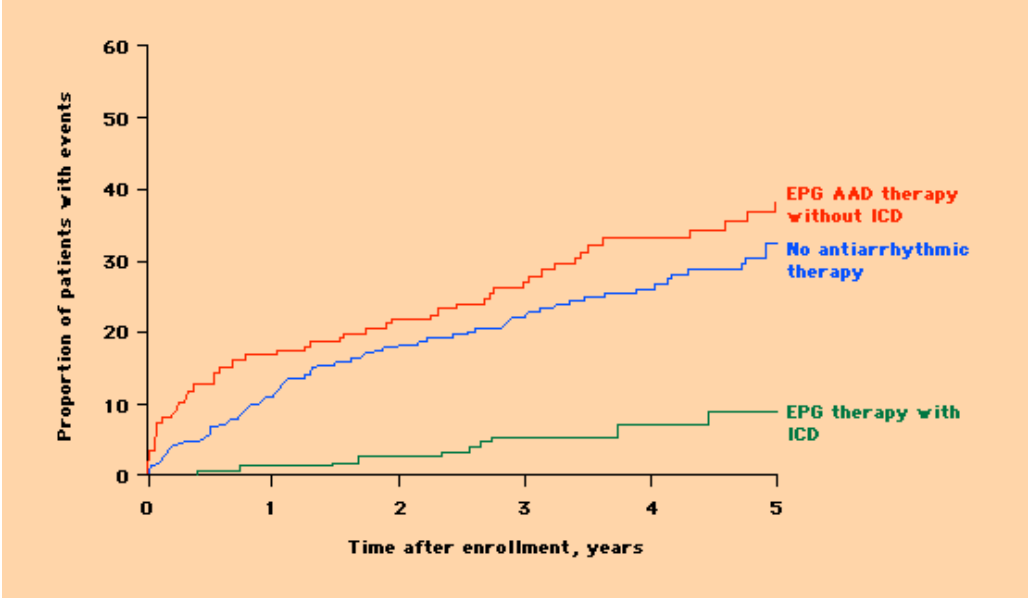


Annual Pacemaker and Implantable Cardioverter-Defibrillator (ICD) Implants in the United States



Maisel et al, Pacemaker and ICD Generator Malfunctions: Analysis of Food and Drug Administration Annual Reports, JAMA, 2006, 295: 1901-6.

Treatment of cardiac arrhythmias : ICDs.



ICD reduces sudden death in MUSTT The MUSTT trial enrolled 704 patients with coronary artery disease, nonsustained ventricular tachycardia (VT) and a left ventricular ejection fraction ≤40 percent who had sustained VT induced during electrophysiologic (EP) study. Kaplan-Meier estimates show that the incidence of cardiac arrest or death from arrhythmia is significantly lower in those receiving an implantable cardioverter-defibrillator (ICD) compared to those receiving no therapy or those with EP-guided (EPG) antiarrhythmic drug (AAD) therapy. (Data from Buxton, AE, Lee, KL, Fisher, JD, et al, N Engl J Med 1999; 341:1882).

ICDs appear as the best existing strategy to save patients' lifes.

Defibrillation : good news and bad news…

- Defibrillation does save life => they are now produced and implanted ‘routinely’ in patients’ chests.

- But it does so at the cost of huge electric fields, that are damaging for the heart… and extremely painful…

How does an ICD function ?

The ICD records the heart rhythm in real time, and **detects anomalies**.

Once an anomaly is detected, the ICD tries pacing from the electrode at a fast frequency.

=> ***Anti-Tachycardia pacing.***

Advantage : low energy, no pain;

Limitation : limited success rate (70-90%).

If it is not enough to restore the normal rhythm, applies a ***defibrillation shock.***

Advantage : very high success rate (~100%)

Limitation : very high energy; pain; damage to the cardiac tissue.

Interaction between an electric field and the cardiac tissue.

- The situation re. defibrillation is not fully satisfactory : it would be desirable to significantly lower the amount of energy used in defibrillation shocks.

Challenges :

Can one come up with better strategies than what is currently available ?

Any improvement requires a better understanding of the interaction between cardiac tissue and the electric field !

Scientifc problem :

Understand the interaction between the electric field and cardiac tissue.

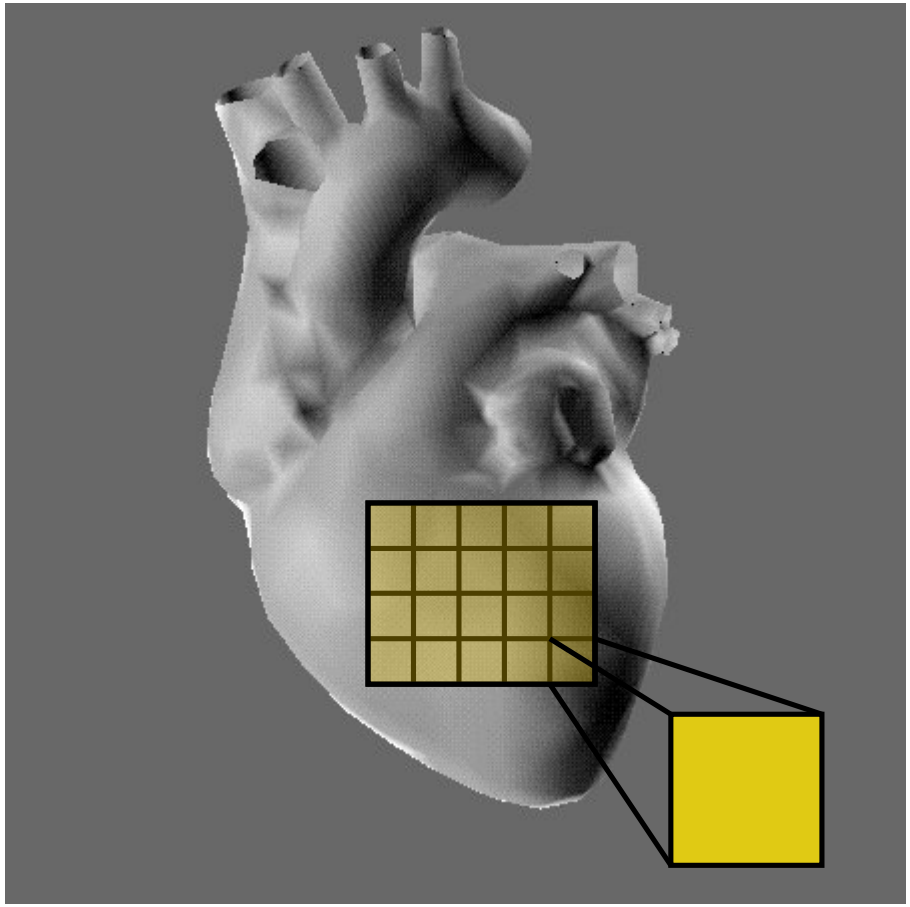
… and propose better way to treat the problem (??).

Suggestions from physics

… several possibilities…

- In a small heart, it is difficult to ‘fit’ a very complex excitation pattern, and to maintain a spatio temporal pattern of excitation going.
- Make the system small, by effectively breaking it in small pieces (Pande et al, 2001).

Operating Principle for the Control Scheme

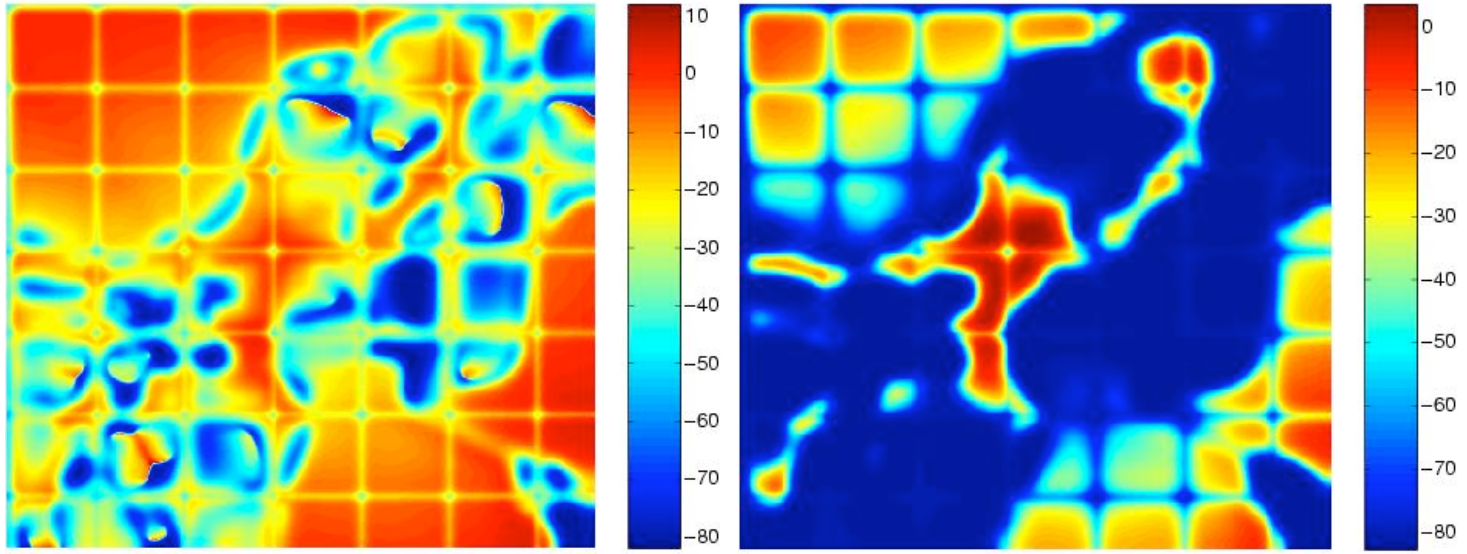


- divide the system ($L \times L$) into K^2 smaller blocks.
- stimulate along block boundaries making them refractory – blocks isolated.
- each block too small to sustain spirals - absorbed by block boundaries.
- control stops after all spirals disappear - block boundaries recover.

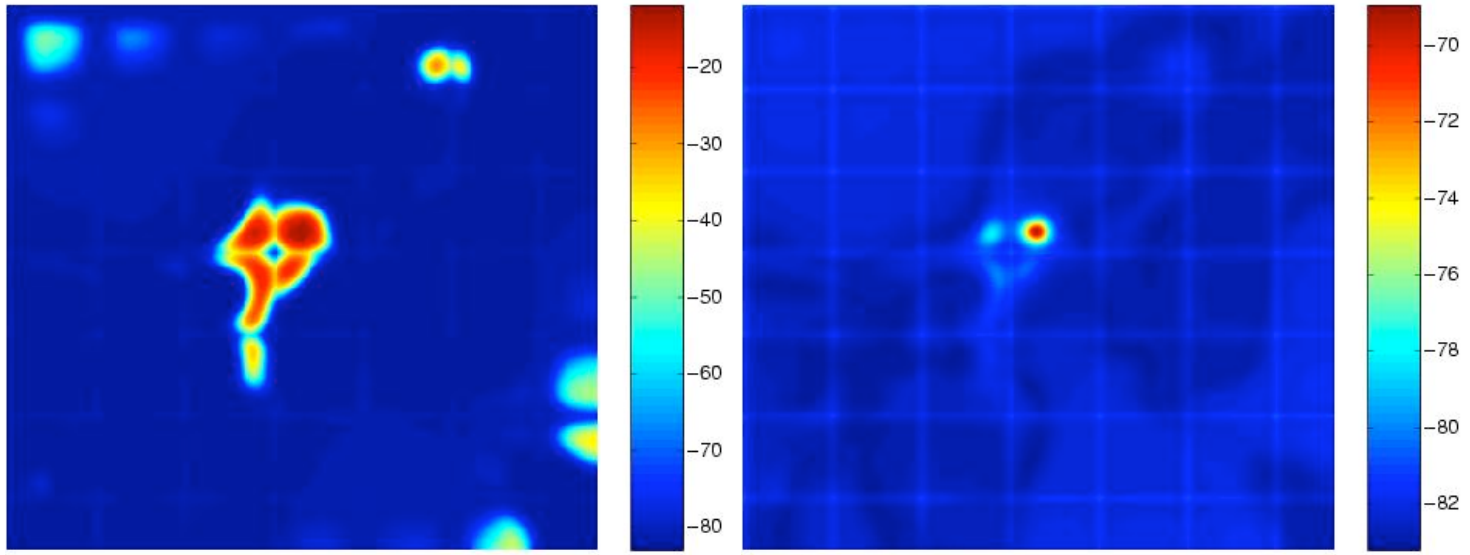
90 mm x 90 mm

Controlling the 2-D L-R I Model

T = 30 ms



T = 90 ms



T = 150 ms

T = 210 ms

Is it the way to go ?

- ✓ Successful defibrillation using very-low-amplitude electrical pulse (~ 10 -100 $\mu A/cm^2$) applied for a brief duration (~ 10 ms) over a mesh electrode.
- ✓ Control successful for simple as well as realistic models with lots and lots of complicated details.
- ✓ Control over 2-D surface is effective even for 3-D control.

But…

… many problems with practical implementation :

- It would require an intricate system of electrodes…

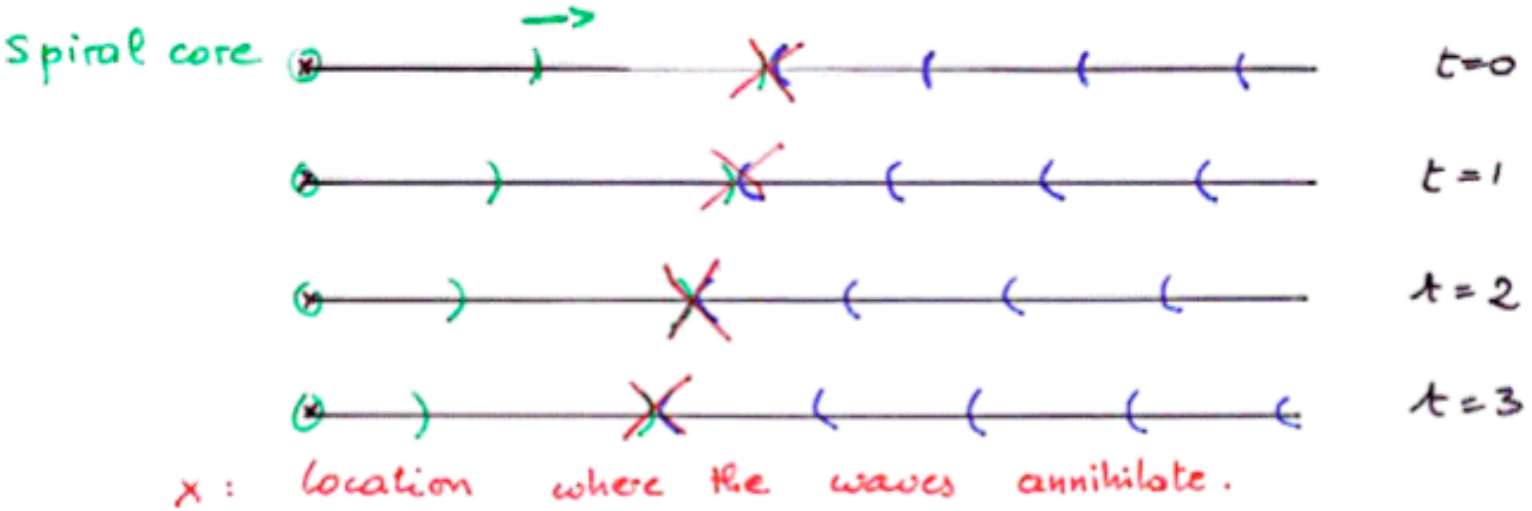
- It would require open-heart surgery to implant the device – a nonstarter given today's surgical constraints.

More realistic objective for now :

Understand the mechanisms involved in the existing methods.

The punchline :
importance of the heterogeneities of the tissue.

Anti-Tachycardia pacing : 1D picture.

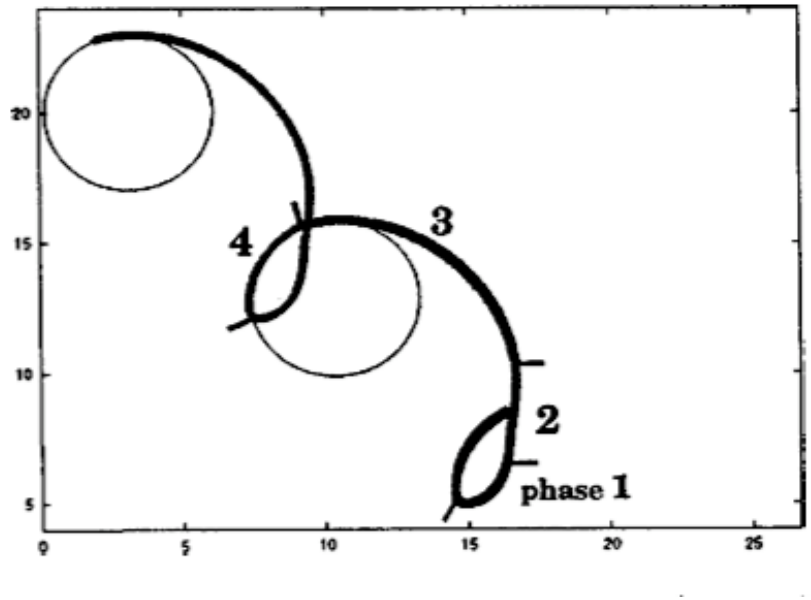


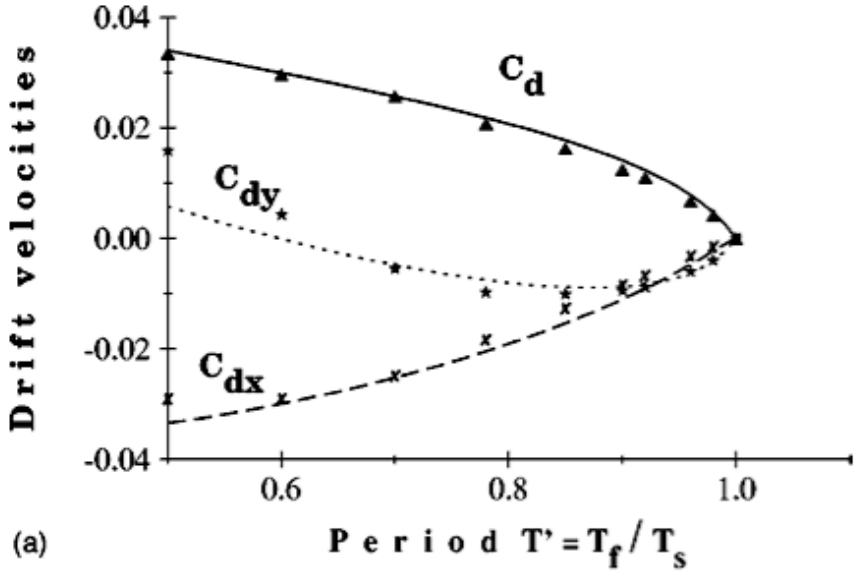
The right part (blue) of a fiber is excited at higher frequency than the left part (green).

The point where the waves collide move towards the source of the slow wave

=> The faster source prevails !

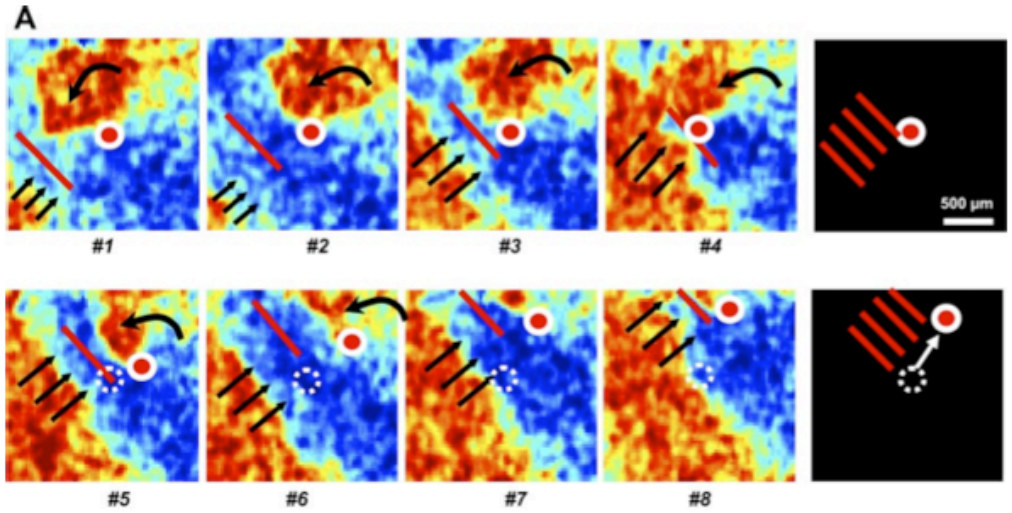
ATP in 2d : theoretical analysis

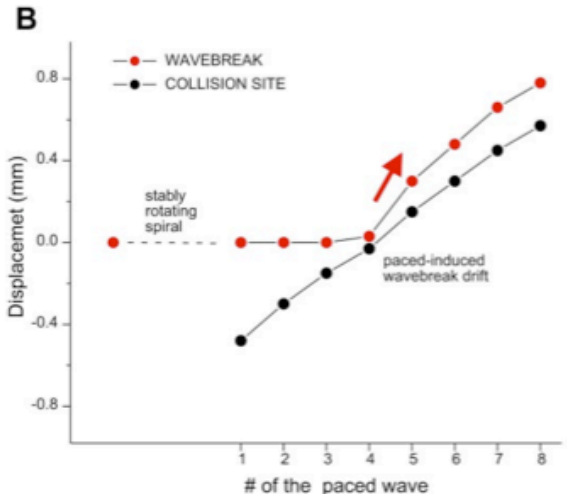




Analyse the motion of the core of the spiral with a pacing wave => successfully predict the drift of the spiral (Gottwald et al, 2001).

ATP in 2d : experiments





Cell culture experiments (Agladze et al, 2007).

=> the fast pacing from the lower left corner induces a drift of the spirals, and eventually terminates the spiral.

Shortcomings of ATP

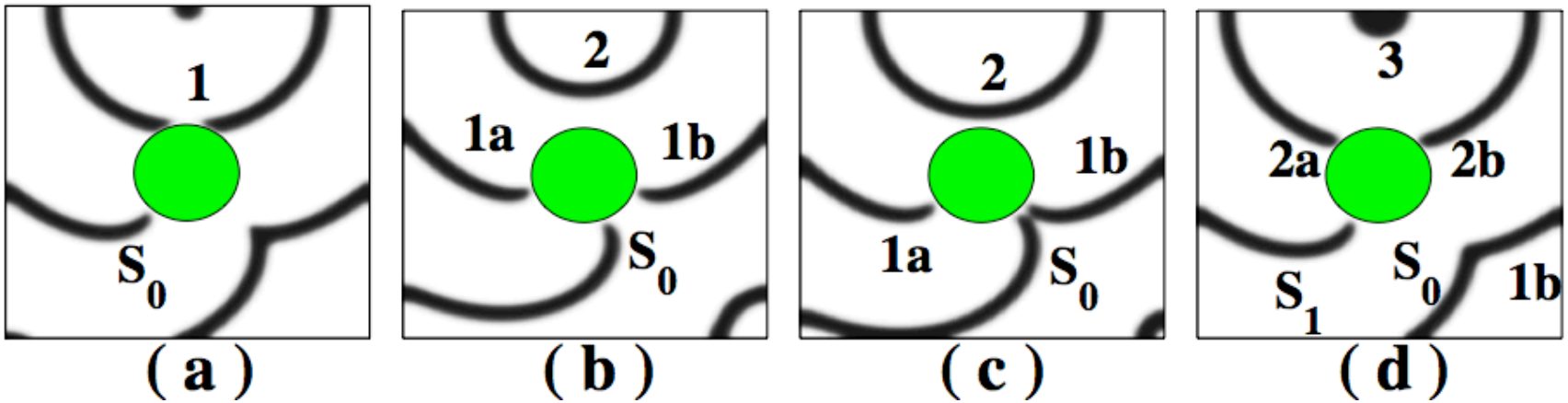
Problem with ATP : **Heterogeneities !**

- Waves may be pinned to large obstacles (anatomical reentries); ATP may or may not be able to pace these spiral away.

Strong attraction of the wave to obstacles such as holes, or pieces of tissue with a significanly lower excitability (Pazo et al, 2004).

- Waves at high frequency may not be able to pass through regions where the refractoriness of the tissue is large.

A wave attached to a large obstacle cannot be detached by a pacing wave.



Topological conservation : $n_+ - n_- = cst.$

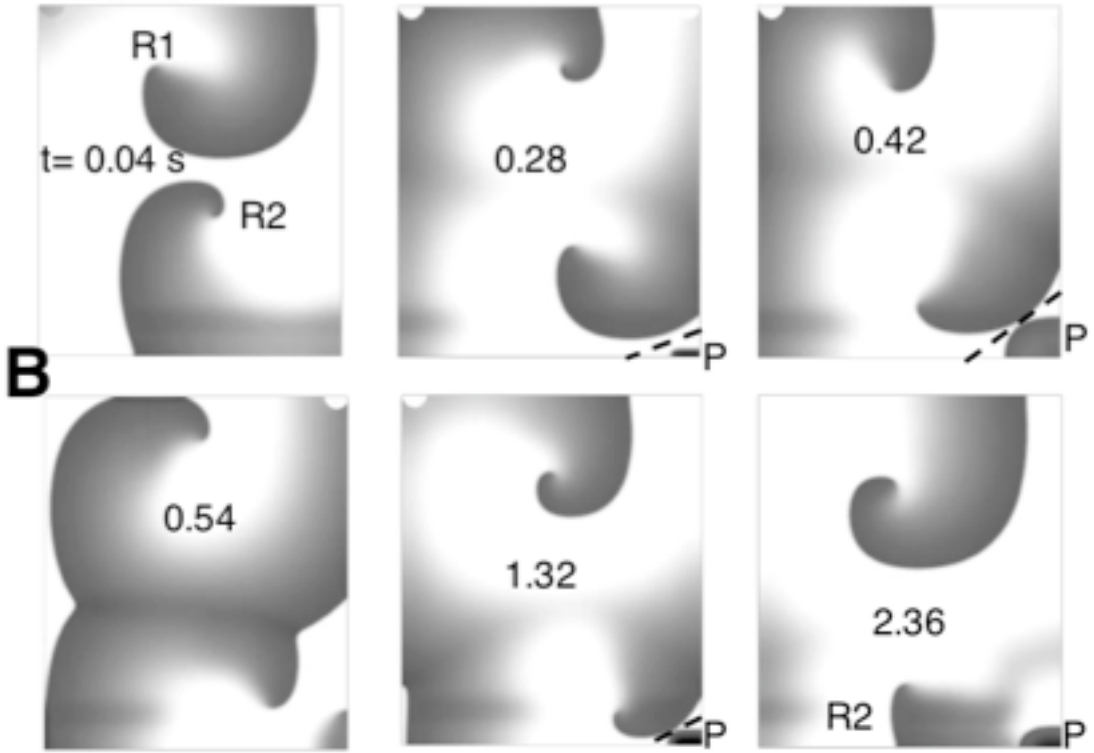
(Wiener and Rosenblueth, 1946)

n_+, n_- = # of waves rotating counterclockwise, clockwise around the obstacle.

In the figure, $n_+ - n_- = 1$

Heterogeneity of the refractoriness.

Problem with ATP : because of the many heterogeneities in the tissue, a pacing wave may be shielded from the arrhythmogenic wave. E.g., by a region with a longer refractory period.



P : Pacing site

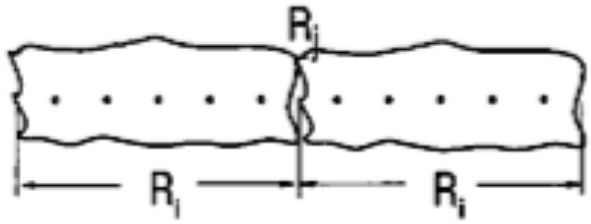
Stripe of tissue with a longer refractory period ↕

Defibrillation mechanism.

The cell coupling hypothesis.

The precise mechanism leading to suppression of all waves (reseting of the tissue) during defibrillation is still not fully elucidated.

One of the proposed scenario is that large electric fields affect the tissue **everywhere** thanks to the fact that cells have strong **coupling heterogeneities** : the conductivity across the membranes is significantly smaller than the intracellular conductivity.



Defibrillation : the sawtooth effect

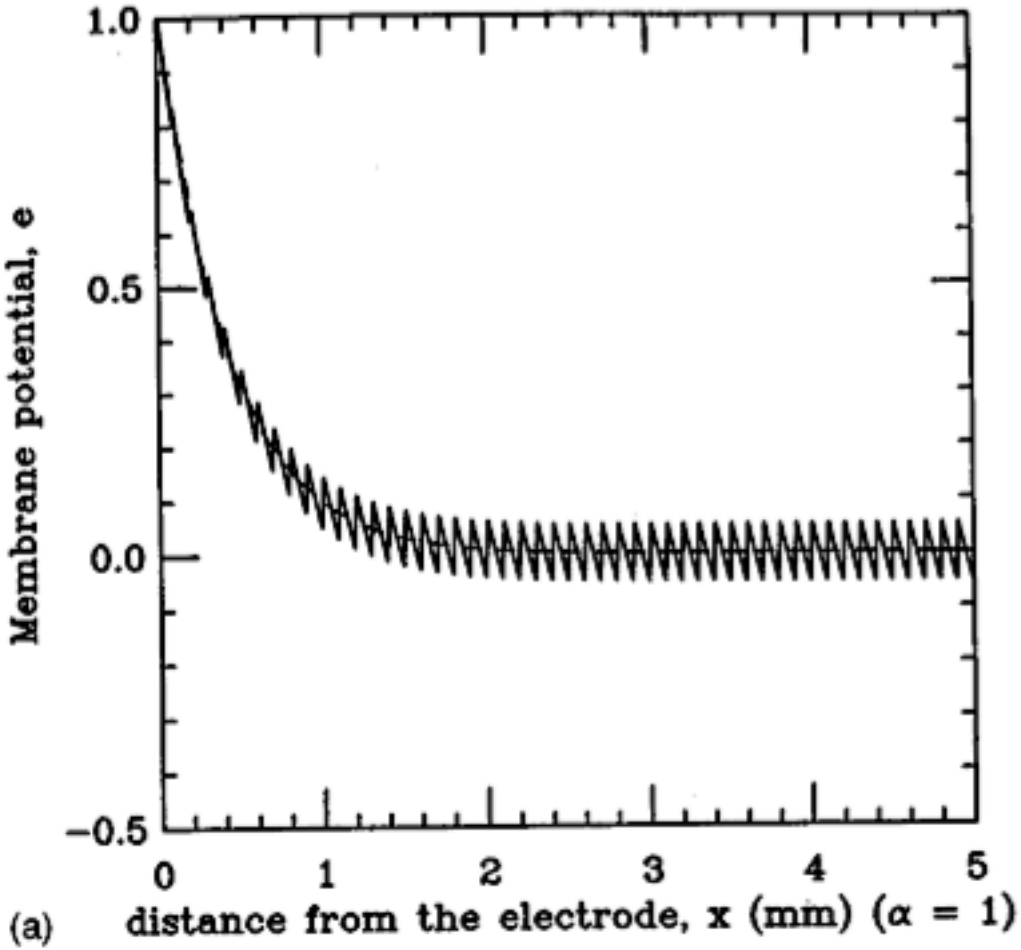
The sawtooth effect :

- Strong depolarization (hyperpolarization) near the end of the tissue over a region of size λ~1mm (electrotonic length).

- Effect persists everywhere in the tissue.

=> Coupling heterogeneities allow to generates Action Potential **everywhere !**

Chaos, Vol. 8, No. 1, 1998



The role of heterogeneities.

According to the scenario above, **defibrillation** works by using all heterogeneities at the smallest scale, to induce waves that can reset all arrhythmic waves (spirals) in the heart.

This picture leads to the **right order of magnitude** for the intensity needed to defibrillate (~ 5V/cm are necessary to terminate arrhythmias).

But other heterogeneities, occurring at larger scales, and documented below, may also play an important role !

Summary :how does ATP/Defibrillation work ?

Summary :

Defibrillation works by generating waves from **heterogeneities** of the medium, even possibly at the very smallest (cellular) scales.

ATP works by pacing the tissue with a **single electrode**. High-frequency is needed, but away from the electrode, the pacing frequency may be diminished due to interactions with highly refractory pieces of tissue.

Interaction of an external electric field with an obstacle.

Obstacle/electric field interaction

The simplest model problem : one hollow circular obstacle in a 2-dimensional piece of cardiac tissue.

Use the **monodomain** model.

V_m = membrane potential

$e = (V_m - V_{m,rest})$: difference between the membrane potential and its resting value.

In the linear regime (weak deviations from resting potential) : $\nabla^2 e - \frac{e}{\lambda^2} = 0$

with the b.c. : $e \to 0$ when $r \to \infty$

$\hat{n}.\nabla(e + \vec{E}.\vec{r}) = 0$ at the obstacle's boundary ($r = R$).

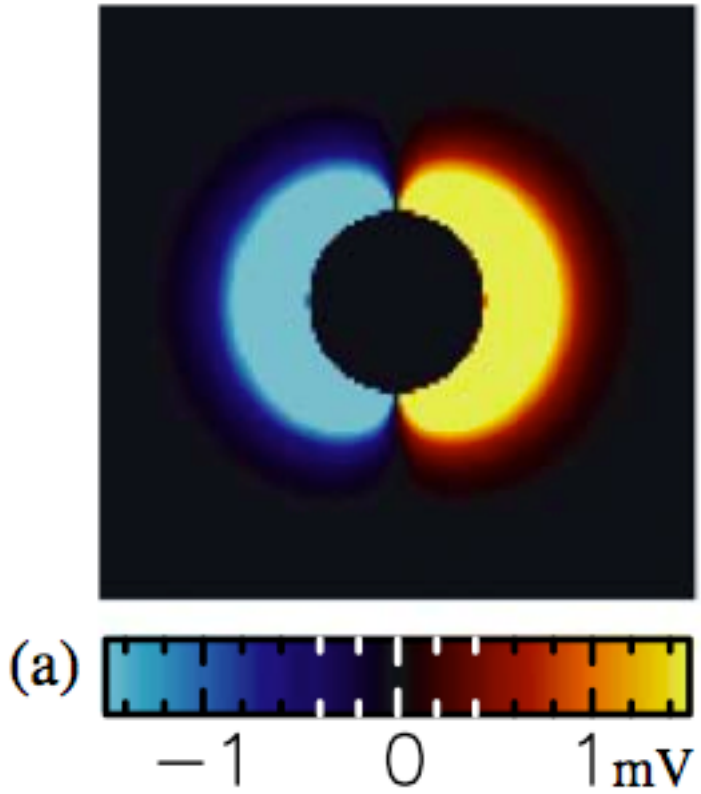
Obstacle/electric field interaction

The solution is obtained in 2d as a simple Bessel function :

$$e(\vec{r}) = -E\lambda \frac{K_1(r/\lambda)}{K'_1(R/\lambda)} \times \cos\theta$$

(θ = angle between E and r)

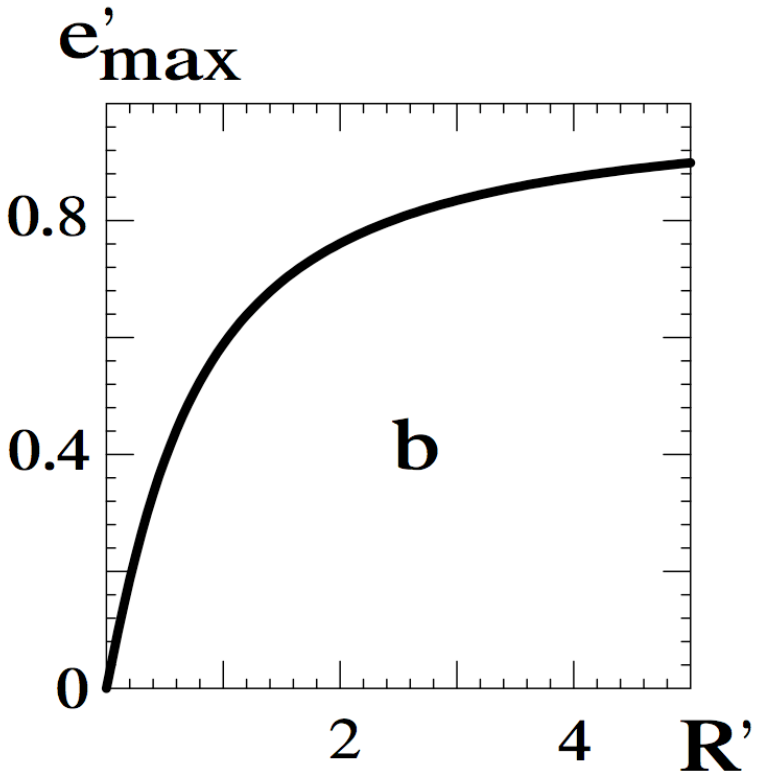
=> Part of the tissue is depolarized (e > 0). If the depolarization **exceeds a threshold**, an Action Potential (wave) may start.



Obstacle/electric field interaction

Maximum depolarization :

$$e'_{\max} = \frac{e}{E} = -\lambda \frac{K_1(R/\lambda)}{K'_1(R/\lambda)}$$



Consequence :
depolarization reaches the stimulation threshold provided the obstacle is large enough, or the field is strong enough.

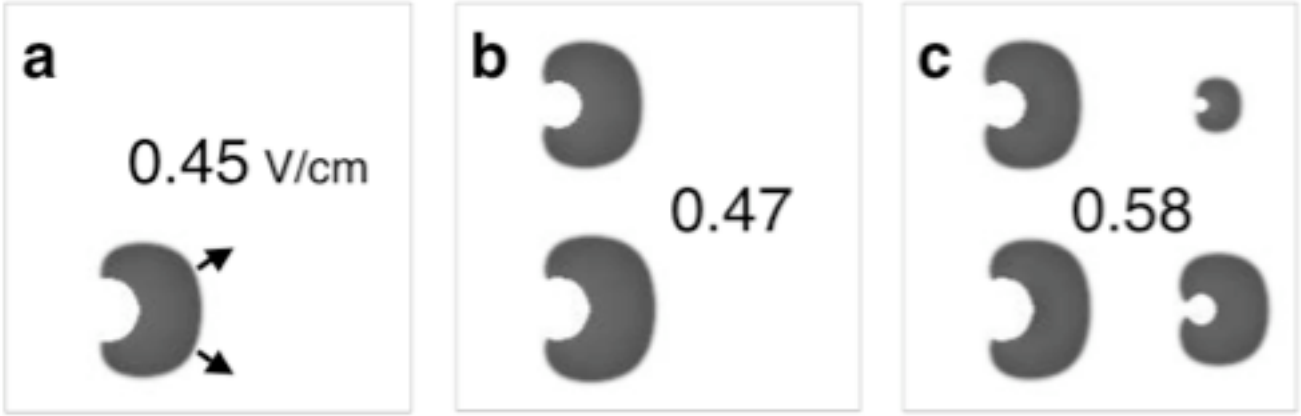
By increasing the external field, one may increase the number of (virtual) pacing electrodes !!

Crucial ingredient !

Obstacle/electric field interaction

Numerical verification :

Integrate numerically the Luo-Rudy 1 model, with several **circular obstacles** of various sizes :



As the externally applied **electric field increases**, obstacles of **decreasing sizes** trigger AP propagation.

Obstacle/electric field interaction

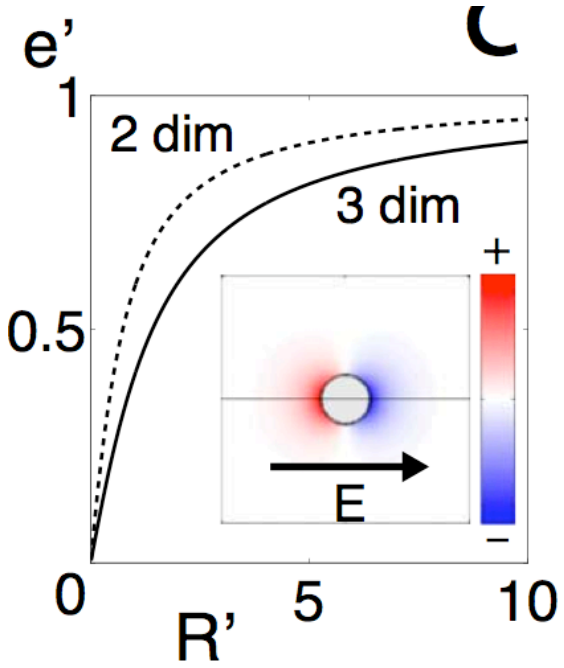
3-dimensional case.

For a simple spherical obstacle of radius R, with a value λ of the electrotonic length :

$$E_{\max} = E \times \lambda \times \left(\frac{1 + \frac{\lambda}{R}}{1 + \frac{2\lambda}{R} + \frac{2\lambda^2}{R^2}} \right) = E \times \lambda \times \left(\frac{\frac{R}{\lambda} + \frac{R^2}{\lambda^2}}{2 + 2\frac{R}{\lambda} + \frac{R^2}{\lambda^2}} \right)$$

$$E_{\max} \propto ER/2 \quad in \quad 3d$$

$$\propto ER \quad in \quad 2d$$



Virtual electrodes and heterogeneities.

- In the presence of an electric field, the heterogeneities in conductivity essentially act as electrode.

- Applying a strong enough field may transform any heterogeneity to a virtual electrode

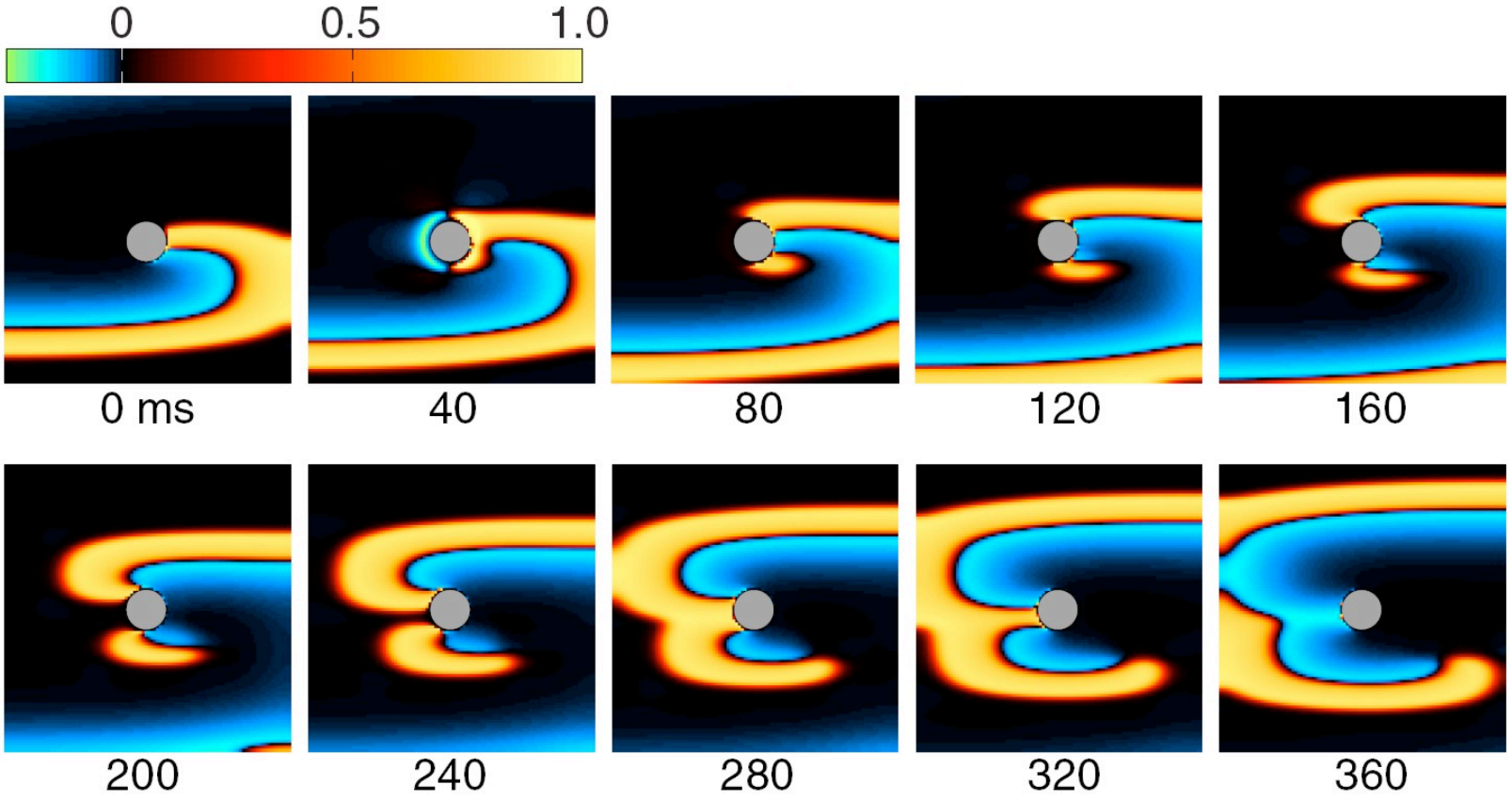
=> possibility to stimulate the heart from these virtual electrodes !

Application : unpinning of waves attached to an obstacle.

Unpinning of a wave attached to an obstacle

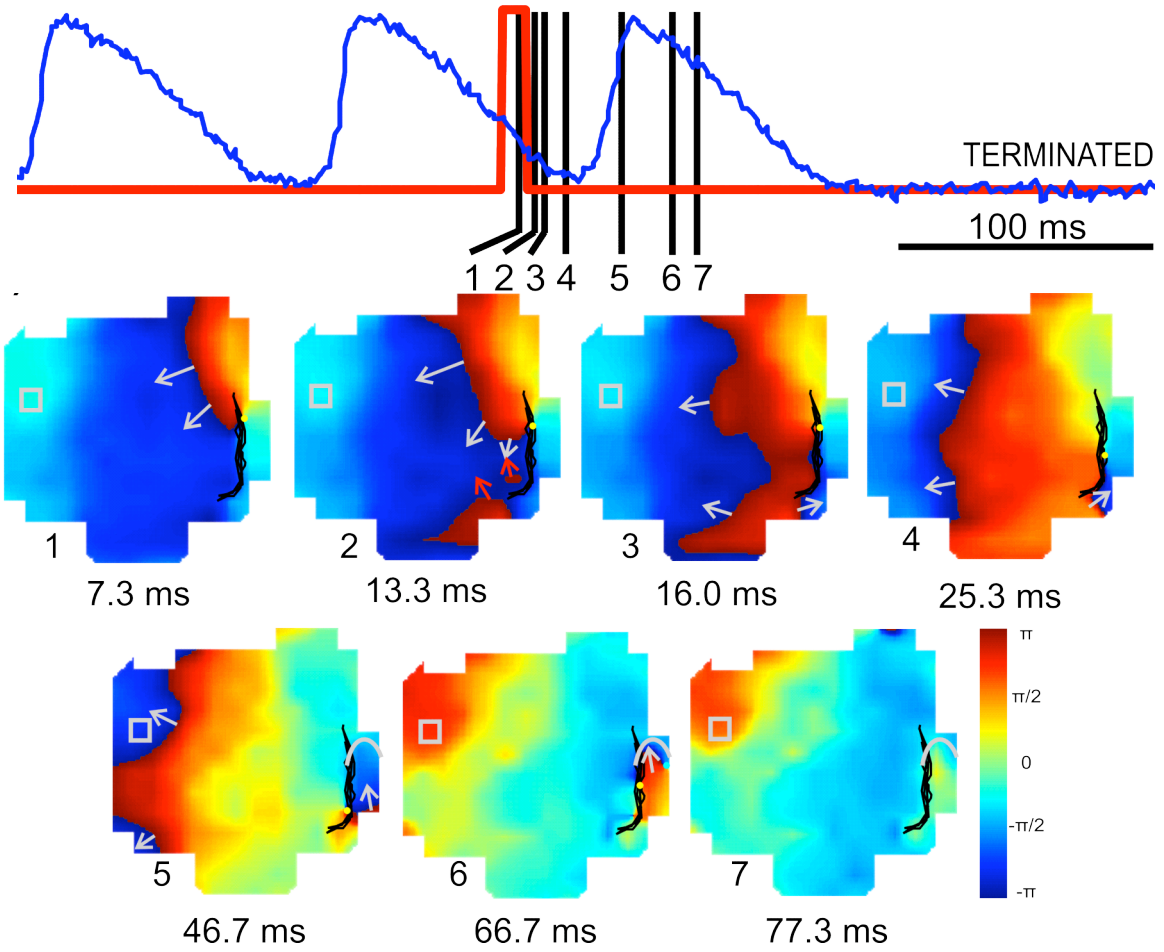
- Pacing may fail to detach a wave attached to an obstacle.
- But ! The virtual electrode effect allows to detach the wave.
- The field amplitude needed is significantly reduced wrt a defibrillation shock.

Reentry "pinning" to a heterogeneity and "unpinning" by a low-energy shock: Mathematical 2D bidomain model



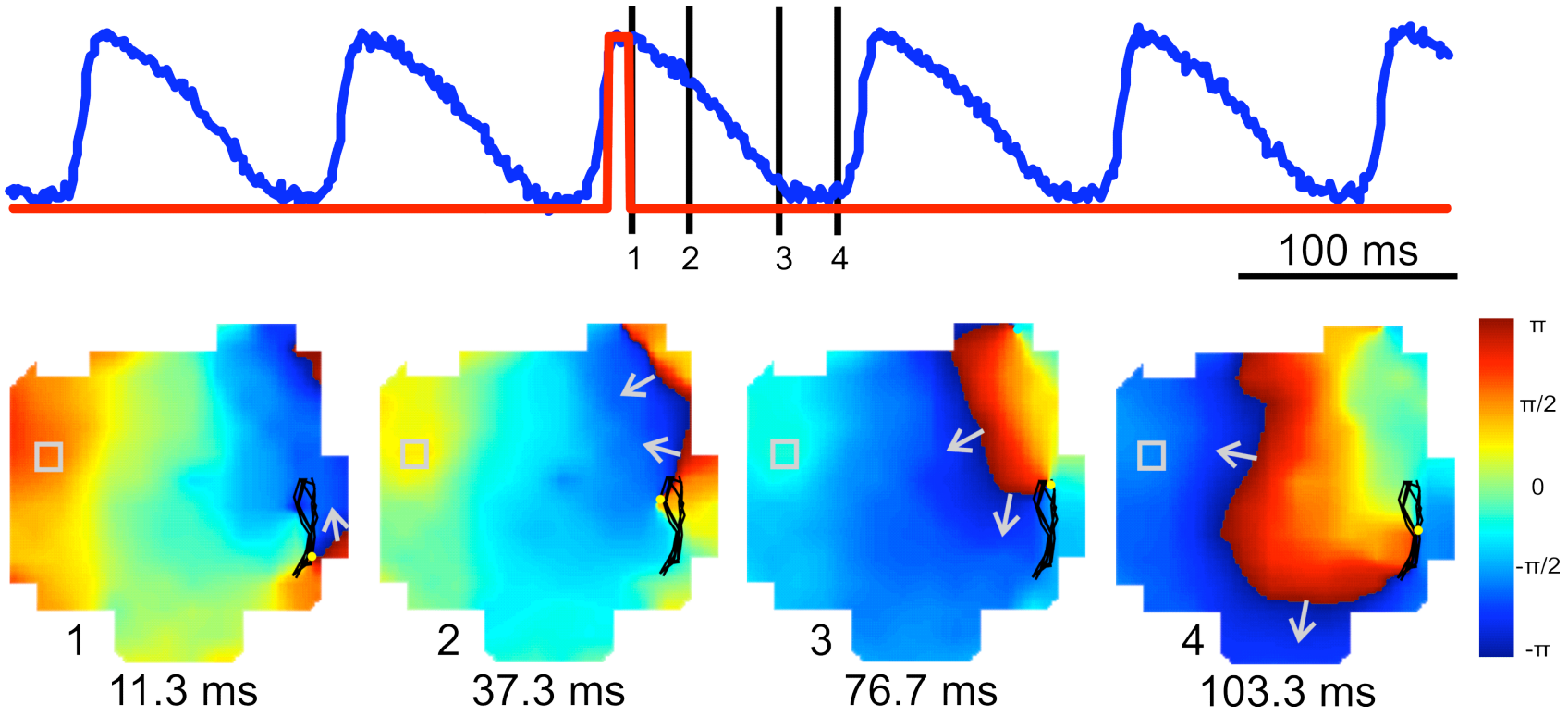
Takagi et al, 2004

Unpinning and termination of reentry by VEP-induced excitation of reentry core: Superfused rabbit right ventricle



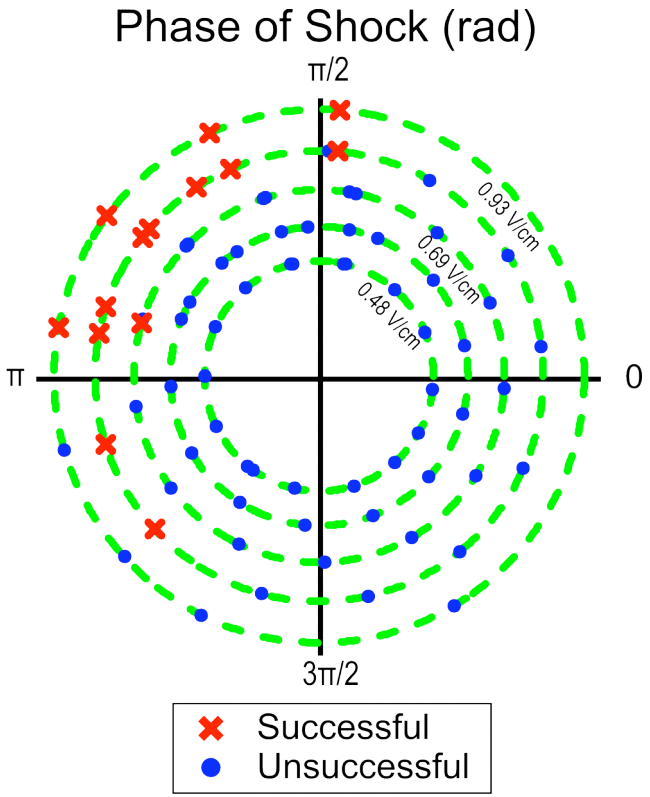
Ripplinger et al., 2006

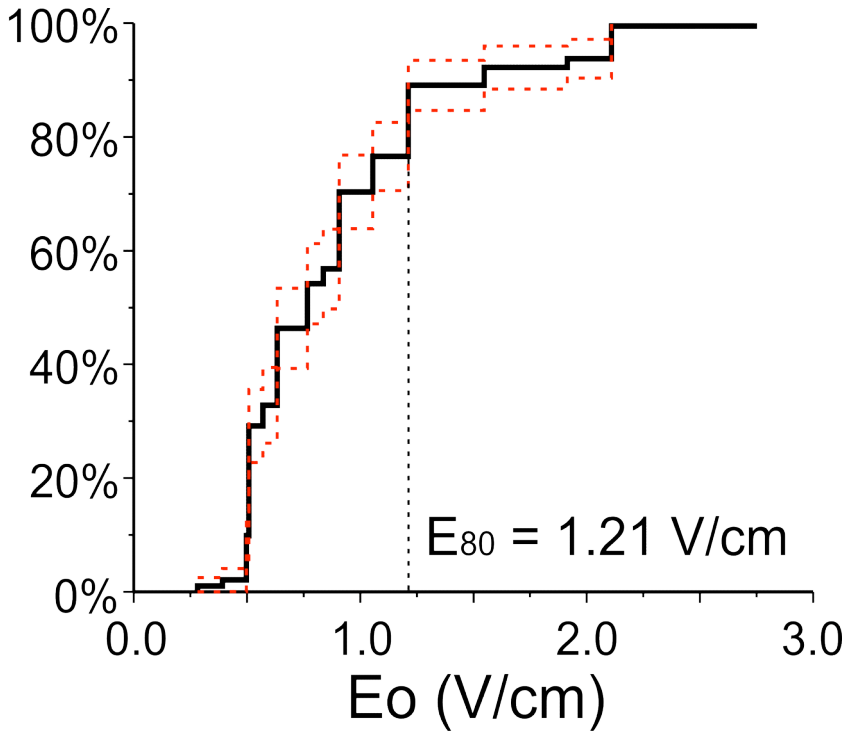
Failed unpinning and termination of VT: Non-optimal timing of the shock



Ripplinger et al., 2006

Phase dependence of low voltage “unpinning” and termination of VT





Ripplinger et al., 2006

Far field pacing : a simple numerical example.

Far field pacing : a simple numerical example

Consider again the tissue with a stripe of tissue with a long refractory time, where ATP was illustrated to fail.

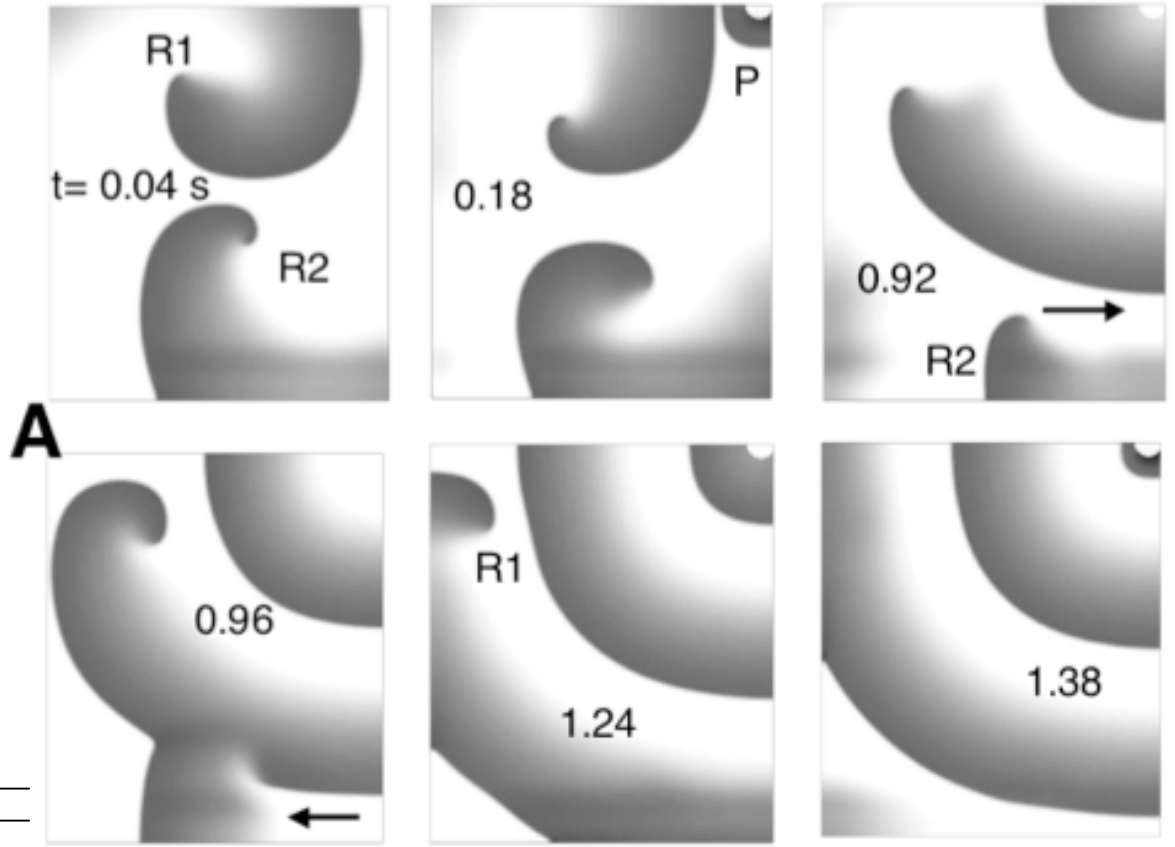
Assume that there exists relatively big obstacle (virtual electrode) not too far away from the cores of the vortices.

Turn on and off the external electric field :

- field on for ~5ms, then off for ~100ms, several times;
- typical values of the field : ~0.5-1 V/cm)

Far field pacing : a simple numerical example

Initial time :
Two vortices



Obstacles (virtual electrode)

Stripe of longer Refractory period

Final time : The pacing waves have swept away the vortices

Far field pacing : a simple numerical example

Remarks :

• For the Luo-Rudy model, the excitation threshold of tissue at rest is **large (~0.4 V/cm)** (larger than in experiments)

• Successful pacing in the previous example was obtained with 8 pulses, and an applied electric field ~ twice larger **(~0.9V.cm)** than the excitation threshold for resting tissue.

• With the same initial condition, one may have several virtual electrodes, which ultimately lead to the same result.

• Results do not depend too much on the initial time where pacing is applied (**phase-independent**).

Far field pacing : a simple numerical example

The entire mechanism is based on the presence of obstacles close to the core of the spiral.

Whether it works in experiments depends on the heterogeneities in the tissue, and on their distribution

=> only experiments can tell !!

First evidence is encouraging (see Fenton et al, Circulation, 2009).

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End of part 2.