Systems Biology Across Scales: A Personal View XXVII. Waves in Biology: Cardiac Arrhythmia

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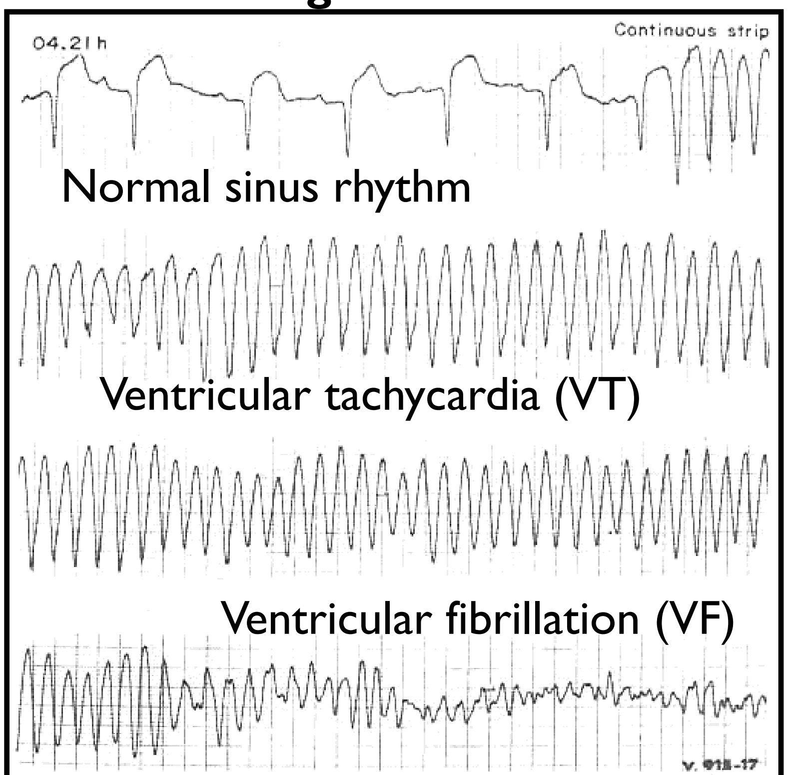
The functional importance of biological waves

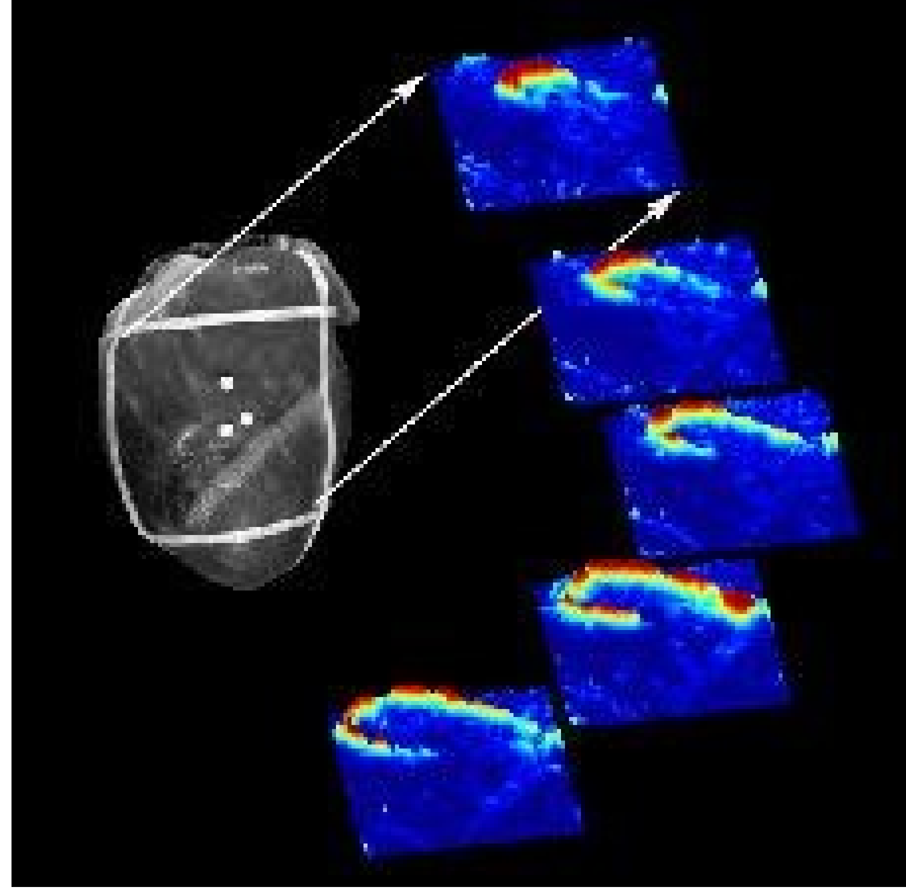
Spiral Waves ≡ Cardiac Arrhythmias

Arrhythmias: disturbances in natural rhythm of heart

ECG recording



Fluorescence imaging of canine ventricle during VT



Color proportional to voltage

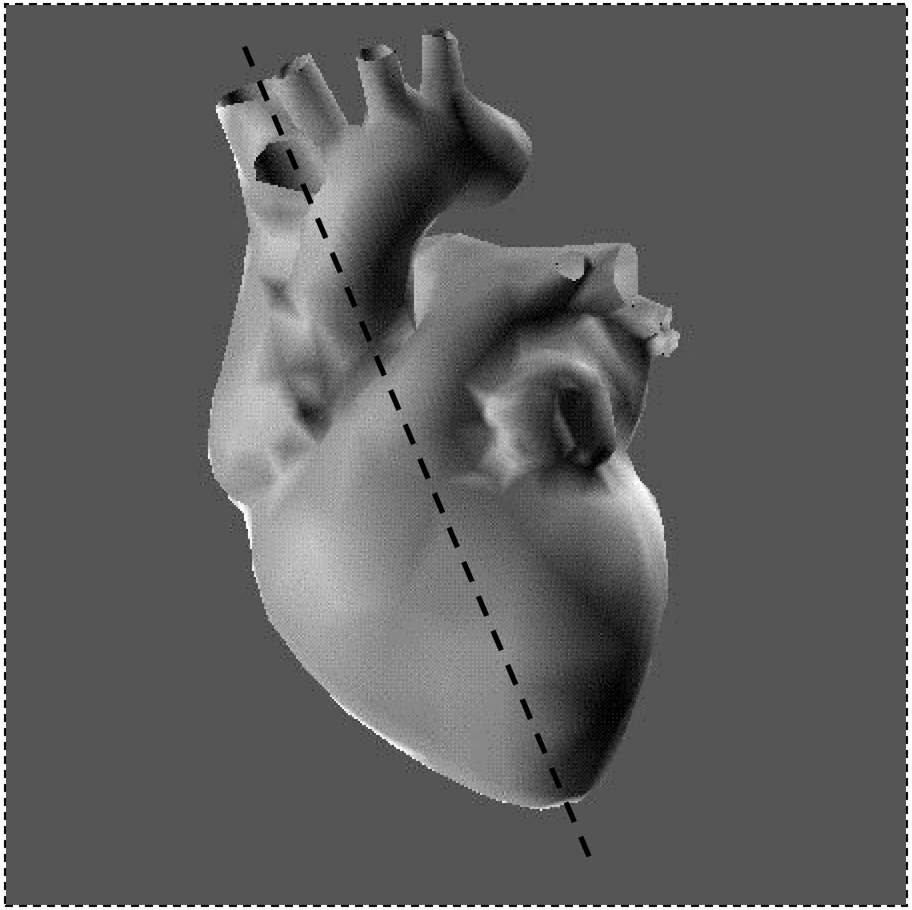
Ditto Lab, Georgia Tech

About half of all cardiac related deaths are due to

Arrhythmias

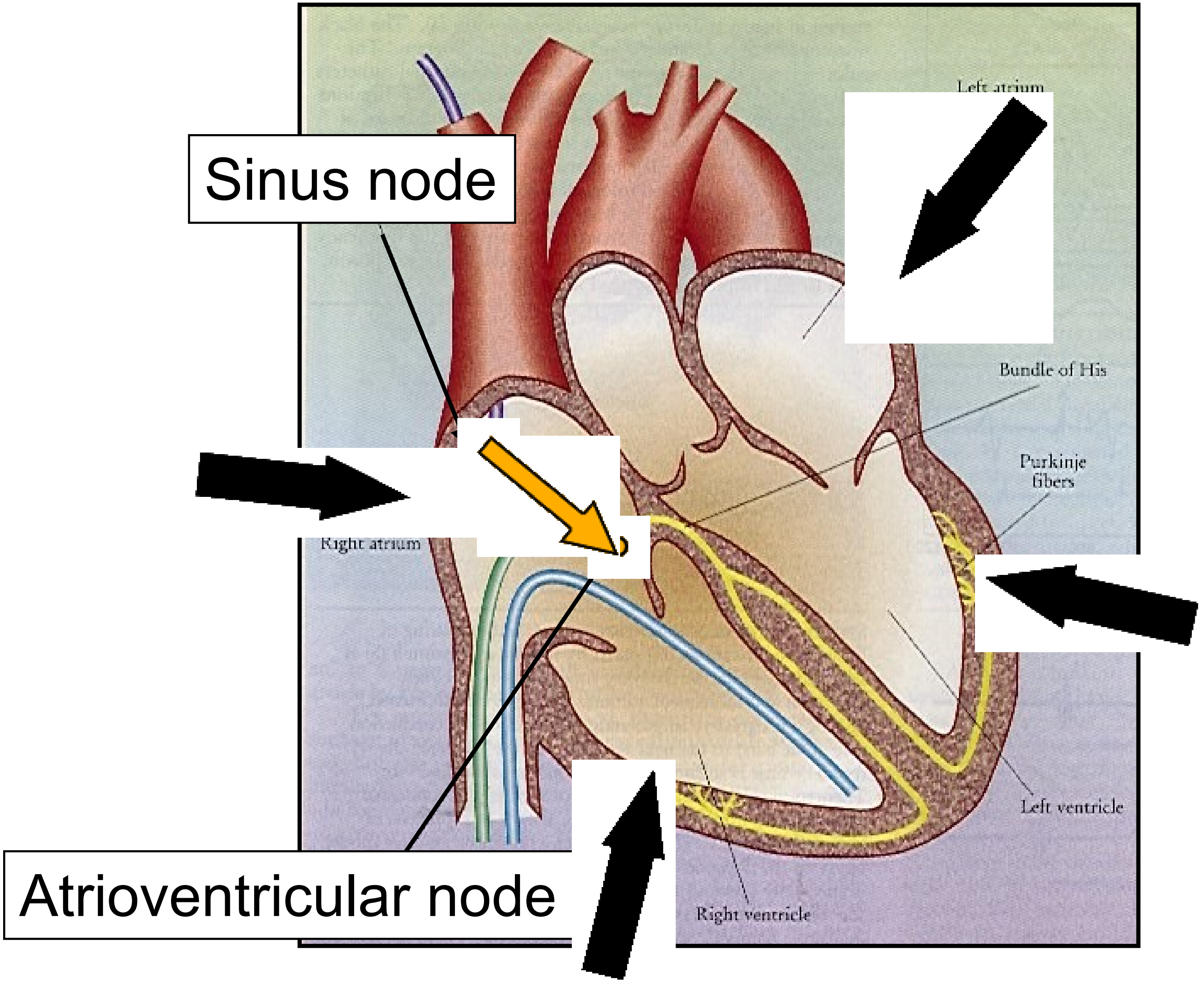
disturbances in the natural rhythm of the heart

A little anatomy lesson



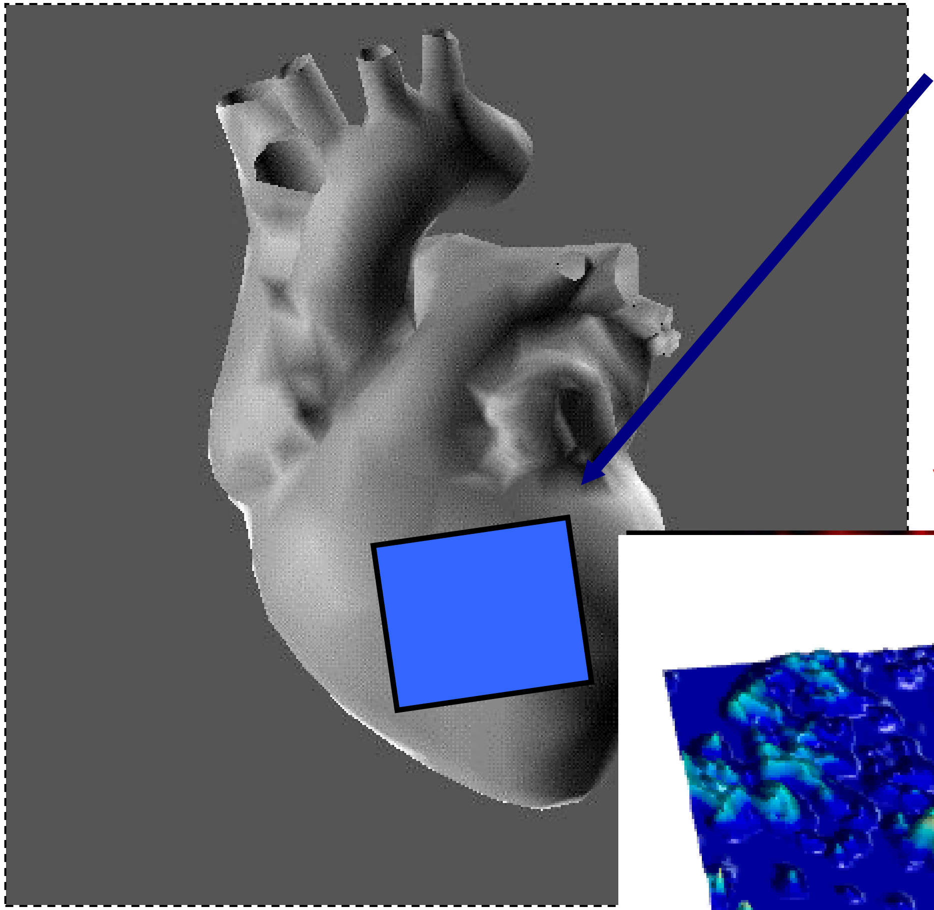
Take a cross section

A little anatomy lesson

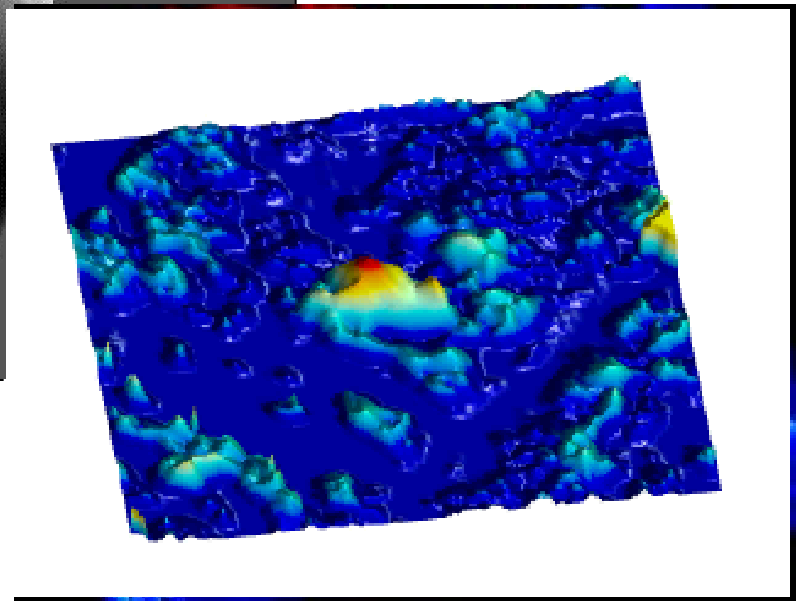


Ventricular Fibrillation: a deeper look

Inject voltage sensitive dye



VF: Spiral breakup



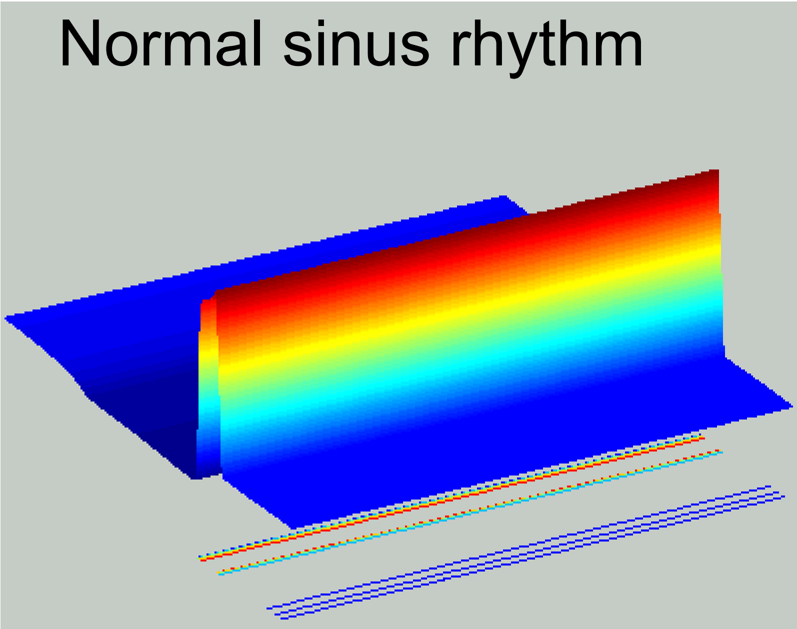
Fluoroscence imaging with CCD camera

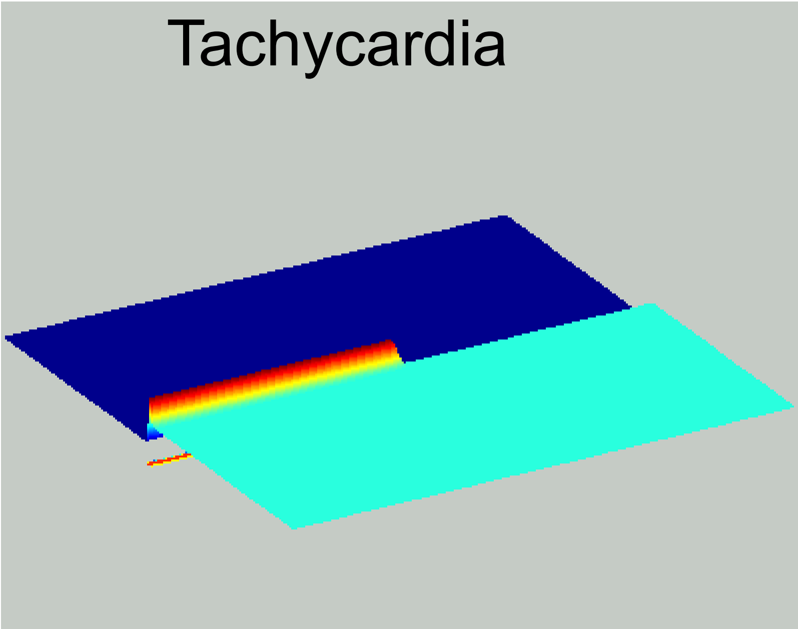
surface of canine ventricle

Color proportional to voltage

VT = Spiral /Pinned Rotating Wave

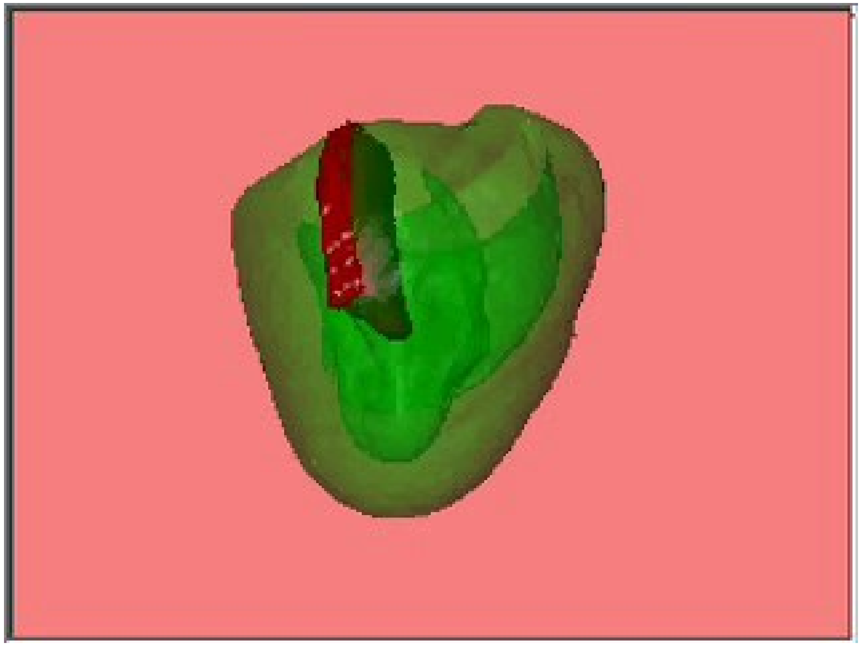
- Underlying cause of VF: formation and subsequent breakup of spiral waves
- Spiral waves: self-sustaining excitations of cardiac tissue
- Leads to tachycardia : abnormally rapid heart beat



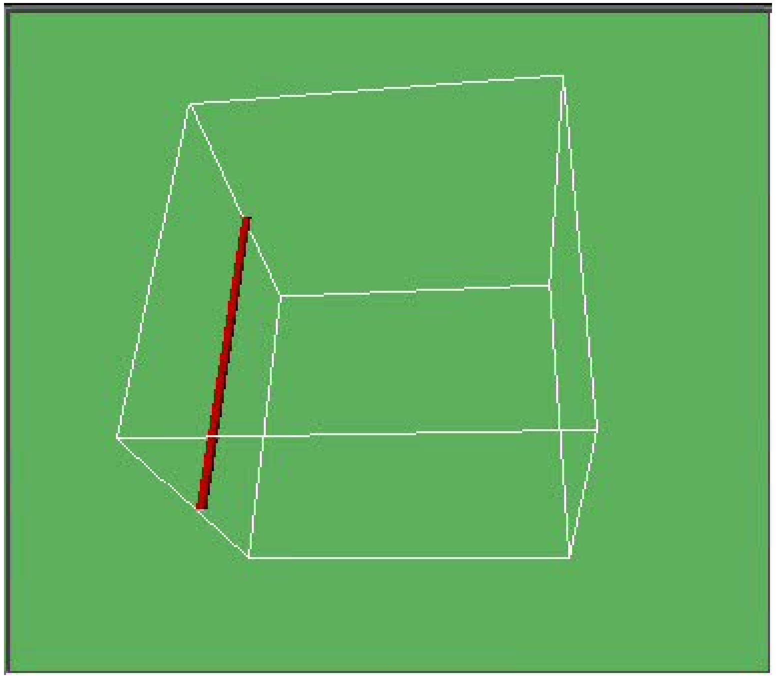


VF = Spatiotemporal Chaos

- If tachycardia is not terminated, a spiral wave may break up into multiple spiral waves: fibrillation
- Self-sustaining activity: only terminated by external intervention



Movie: AV Panfilov



Movie: AV Panfilov

How to model excitation in cardiac tissue ?

For spatially extended systems → reaction diffusion eqn:

$$\frac{\partial V}{\partial t} = -\frac{I_{ion}}{C_m} + D\Delta V$$

Intracellular communication via gap junctions

V	: transmembrane potential
I_{ion}	: ionic currents
C_m	: membrane capacitance
D	: diffusion coefficient

Depending on level of biological realism required, different models for ionic currents, e.g.:

- Panfilov Model (2 variables) – phenomenological
- Luo-Rudy I Model (8 variables) – based on Hodgkin-Huxley

How to model excitation in cardiac tissue?

The simplest model that shows spiral wave breakup

Panfilov Model

$$\dot{e} = D\Delta e - f(e) - g$$

$$\dot{g} = \varepsilon(e,g)\cdot(k\cdot e - g)$$

A piecewise linear variation of Fitzhugh-Nagumo model

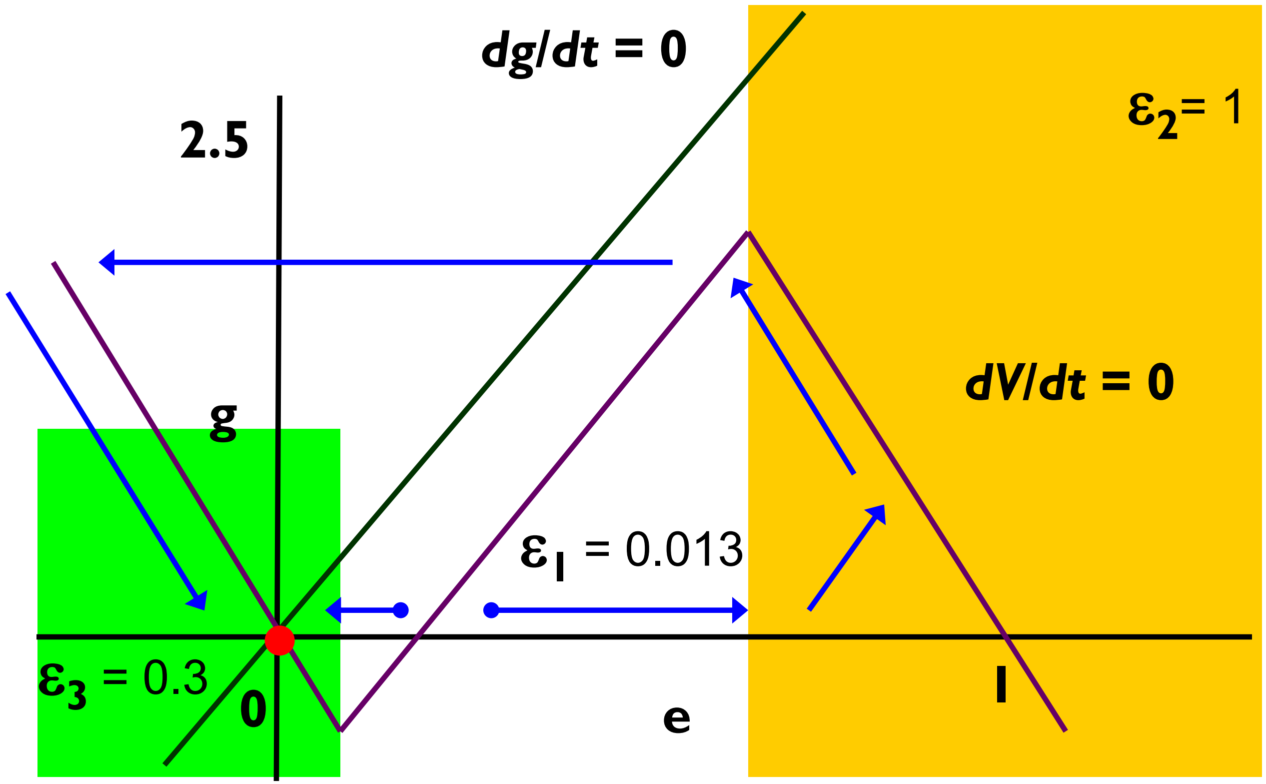
$$f(e) = \begin{cases} C_1 & e < e_1 \\ -C_2 \cdot e + a & e_1 \le e \le e_2 \\ C_3(e-1) & e > e_2 \end{cases}$$

$$\varepsilon(e) = \begin{cases} \varepsilon_1 & e < e_2 \\ \varepsilon_2 & e \ge e_2 \\ \varepsilon_3 & e \le e_1, g < g_1 \end{cases}$$

Other more complicated non-ionic models with increasing realism

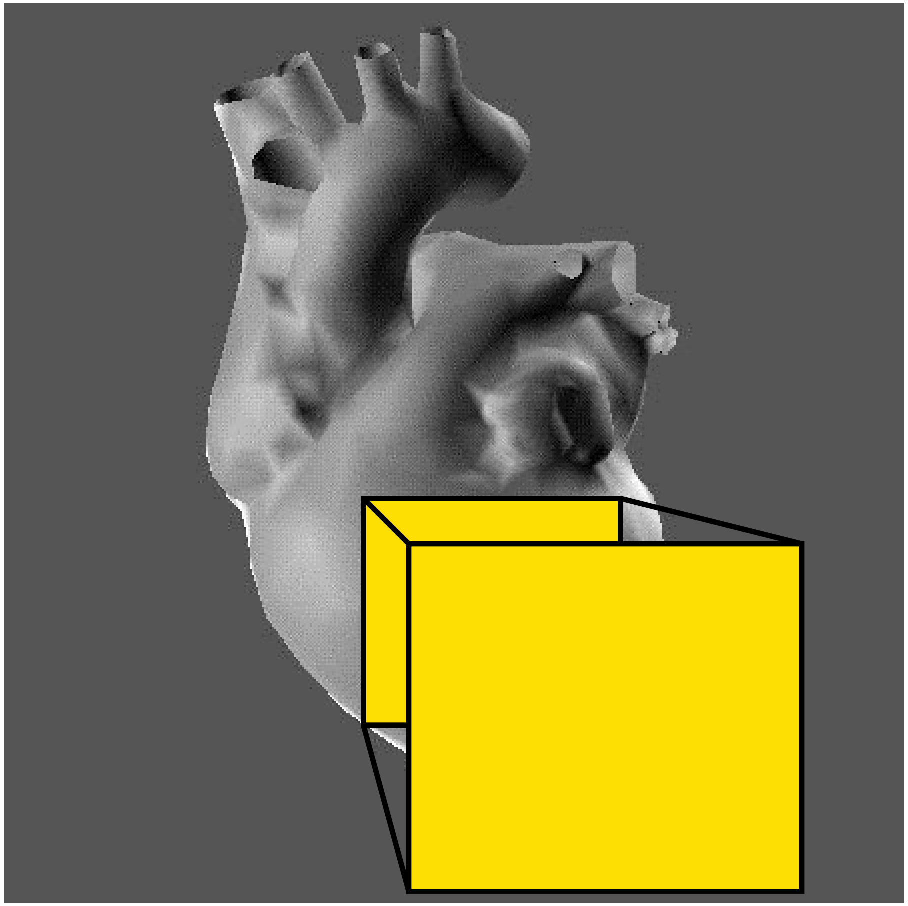
- Karma Model (2 variables) & Fenton-Karma model (3 variables)
- Aliev-Panfilov model (2 variables)

Dynamics of the Panfilov Model

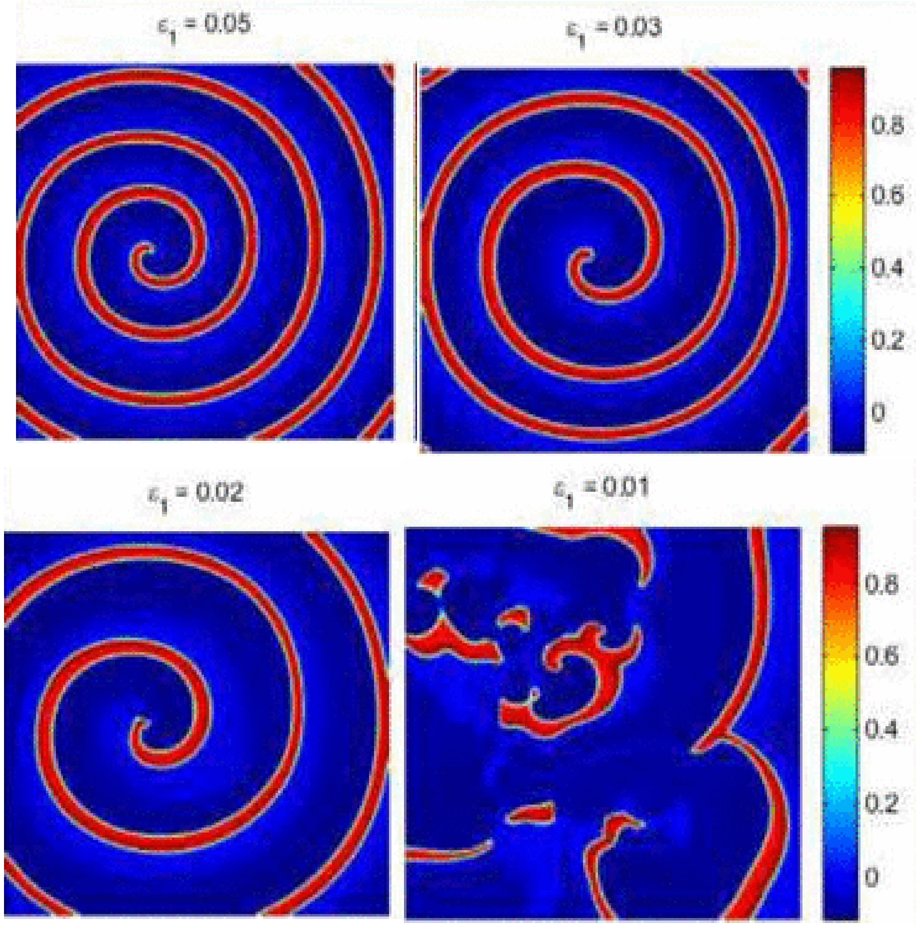


- Quiescent state: V = 0, g = 0 (only stable fixed point)
- Stimulation below threshold: decays to quiescent state
- Stimulation above threshold : action potential

Spiral Turbulence in Panfilov model



Pseudo-color plots of *V* at various values of ε_1 (ε_3 = 0.3)

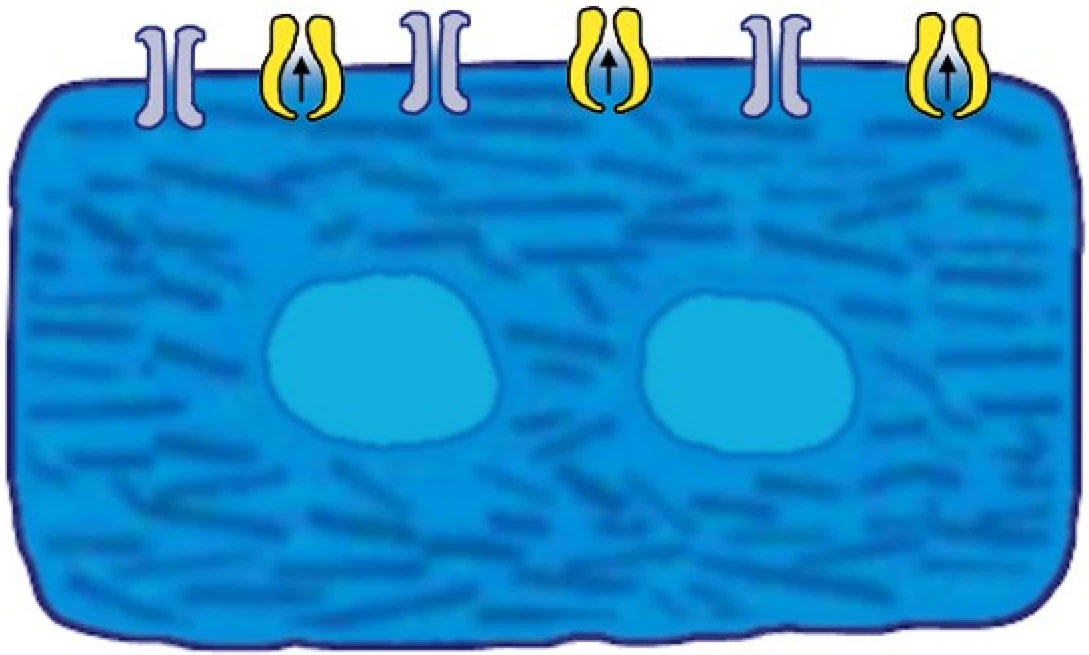


As ε_1 decreases, the pitch of the spiral decreases … ultimately leading to spiral breakup.

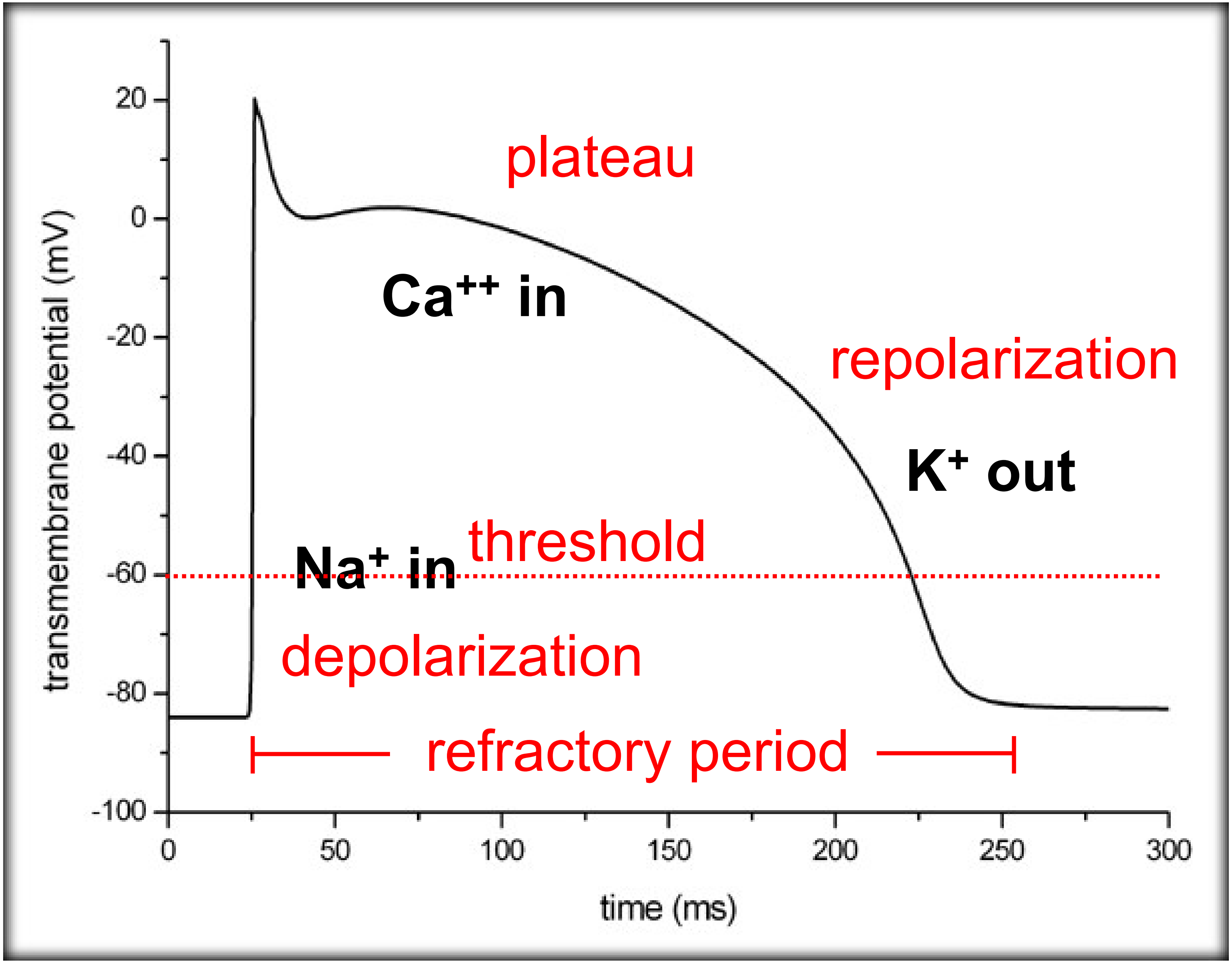
The single cardiac cell

ion pumps

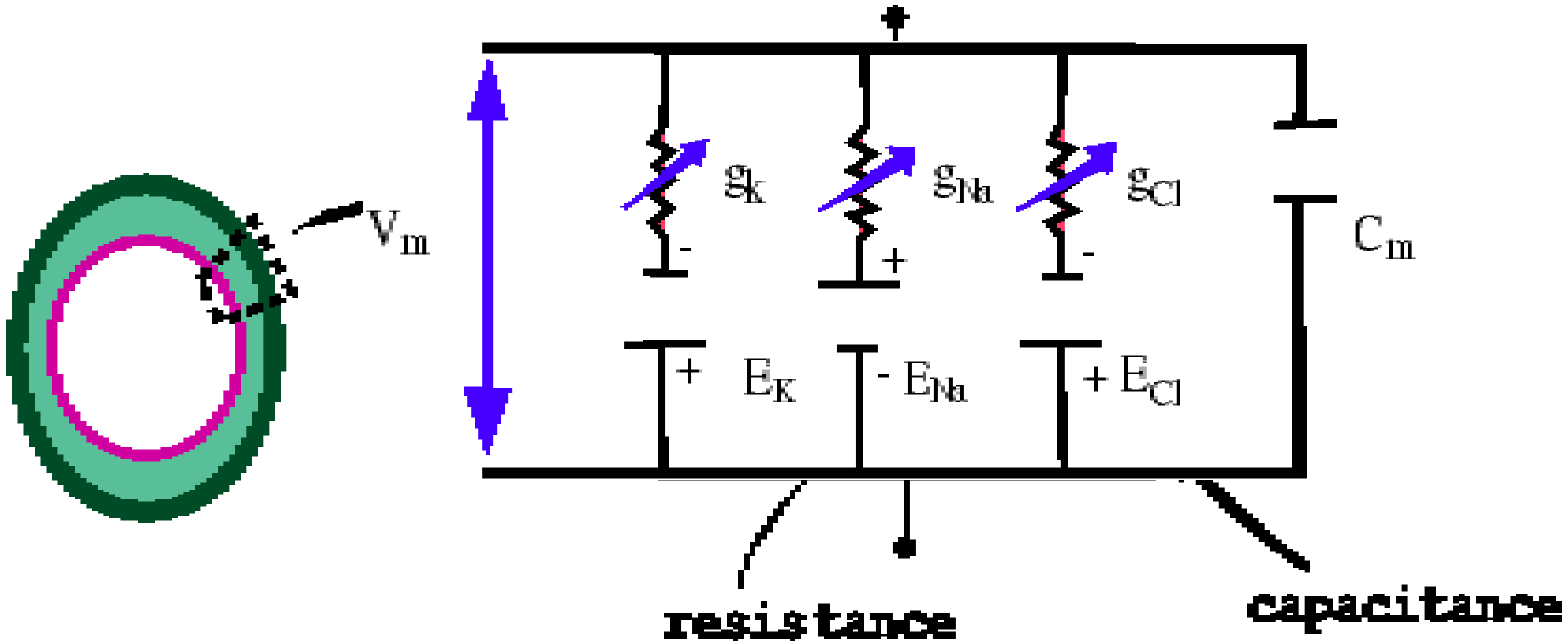
ion transport against the
concentration gradient



Excitation of a cardiac cell: The Action Potential



The ionically detailed models are based on the Hodgkin-Huxley formalism



$$C_m \frac{dV}{dt} = -g_{Na}(V - V_{Na}) - g_K(V - V_K) - g_r(V - V_r) + I_{app}$$

How to model excitation in cardiac tissue?

Luo-Rudy I model (1991)

$$\frac{\partial V}{\partial t} = -\frac{I_{ion}}{C_m} + D\Delta V$$

The LR-I ionic current term:

$I_{ion} = I_{Na} + I_{si} + I_K + I_{K1} + I_{Kp} + I_b$

Inward Currents:

Fast inward sodium current : $I_{Na} = g_{Na}\, m^3\, h\, j\, (V - E_{Na})$

Slow inward calcium current : $I_{si} = g_{si}\, d\, f\, (V - E_{si})$,

Intra-cellular calcium enters the scene: $E_{si} = 7.7 - 13.03 \ln(Ca)$

Calcium density evolves as

$$\frac{dCa}{dt} = -10^{-4} I_{si} + 0.07(10^{-4} - Ca)$$

Outward Currents:

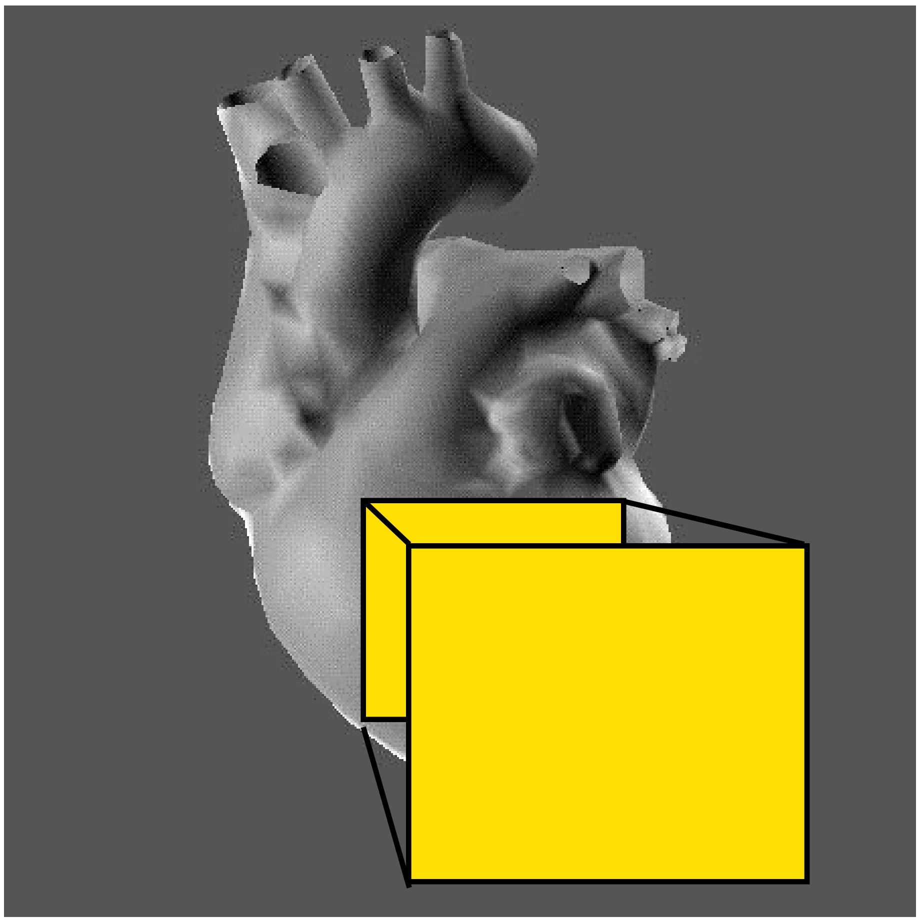
Time-dep outward potassium current : $I_K = g_K\, X\, X_i\, (V - E_K)$

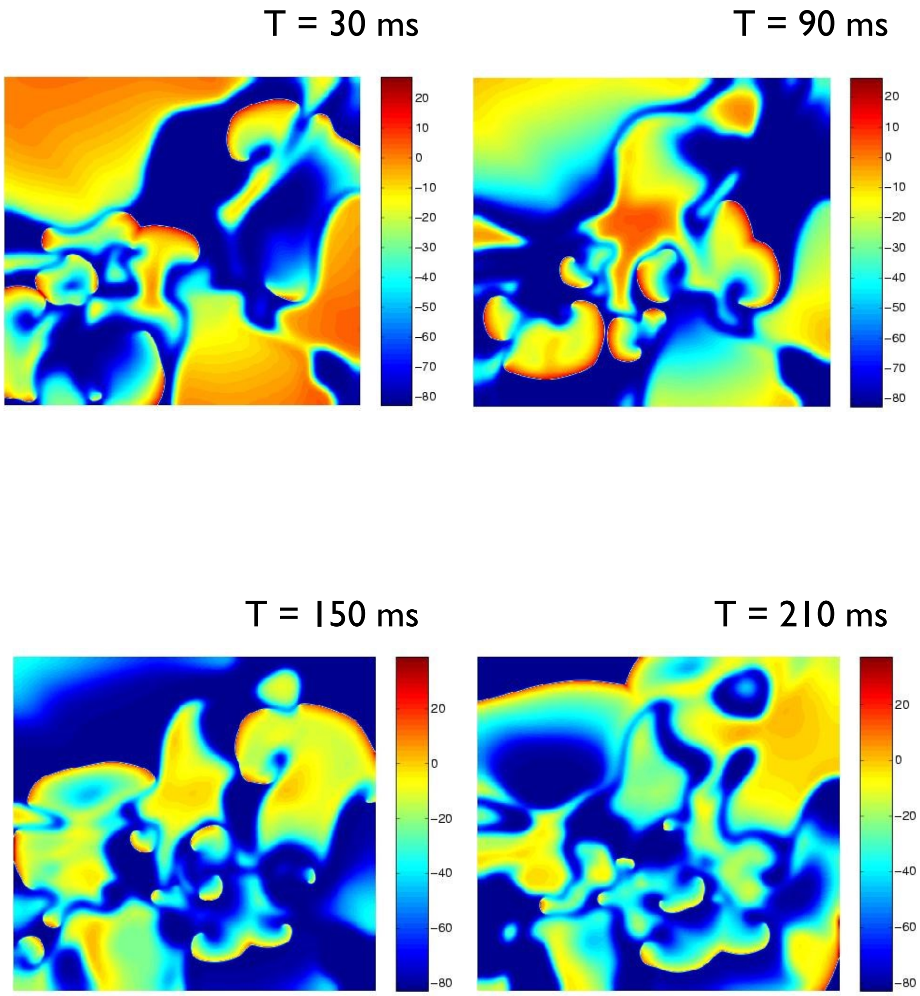
Time-indep outward potassium current : $I_{K1} = g_{K1}\, K_{1\infty}\, (V - E_{K1})$

Plateau outward potassium current : $I_{Kp} = g_{Kp}\, K_p\, (V - E_{Kp})$

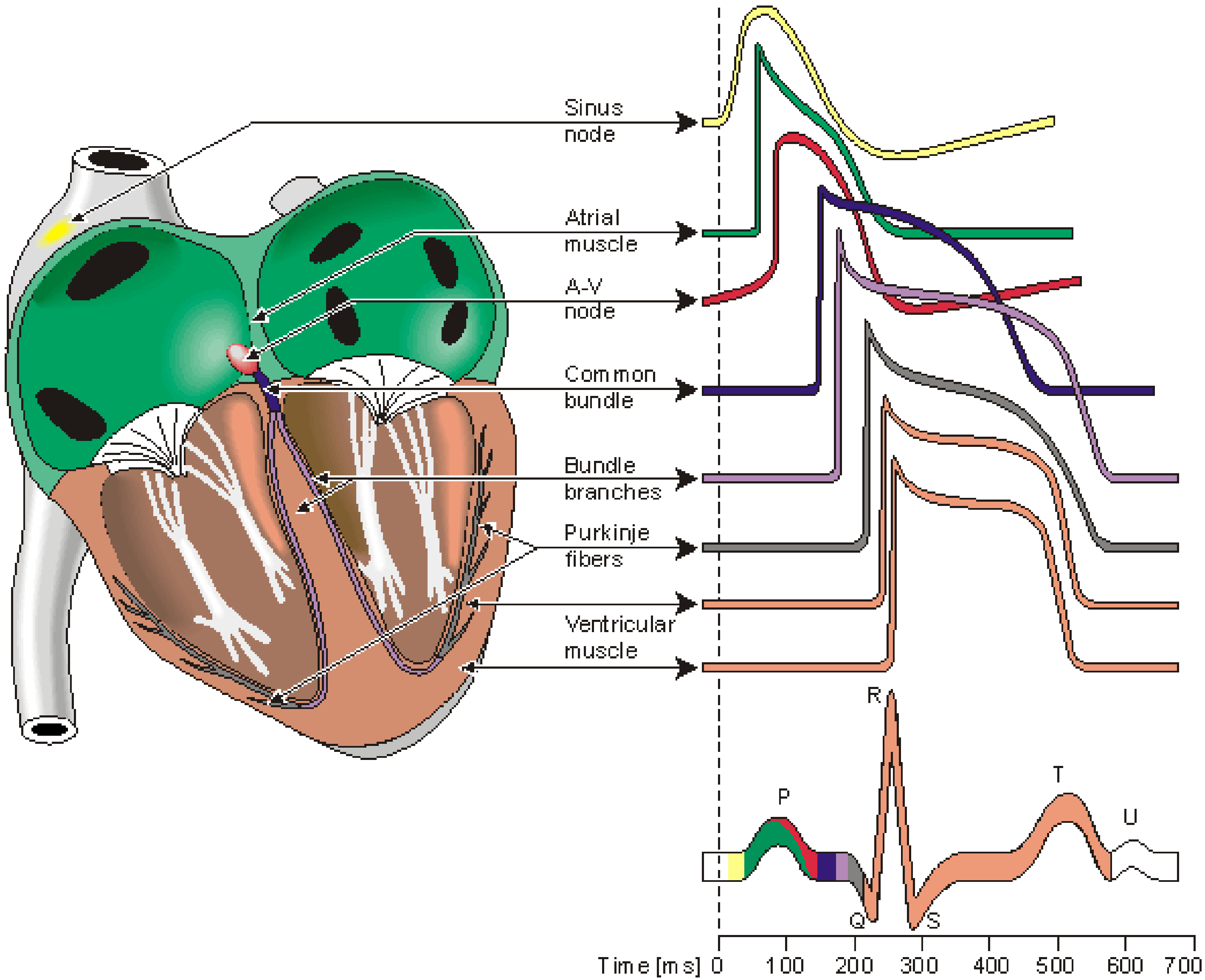
Background current : $I_b = g_b\, (V - E_b)$

Spiral Chaos in the Luo-Rudy model





Cardiac action potential and ECG



http://www.bem.fi/book/

Are there any remedies against cardiac arrhythmia ?

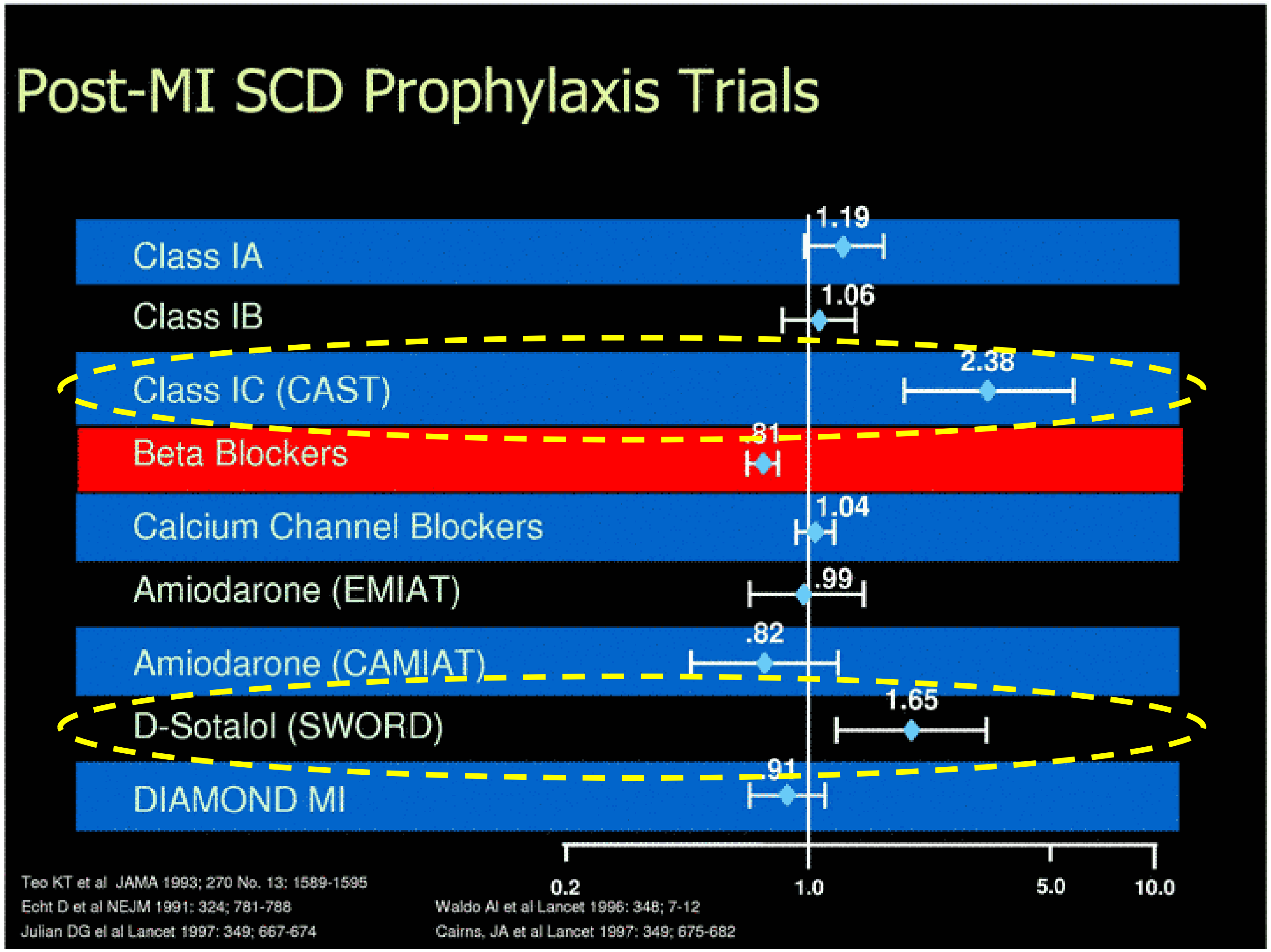
Classes of Anti-arrhythmic drugs

Singh Vaughan Williams classification (1970)

- **Class I** agents interfere with the Na^+ channel.
- **Class II** agents are anti-sympathetic nervous system agents, mostly beta blockers
- **Class III** agents affect K^+ efflux.
- **Class IV** agents affect Ca^+ channels and the AV node.
- **Class V** agents work by other or unknown mechanisms.

Wikipedia

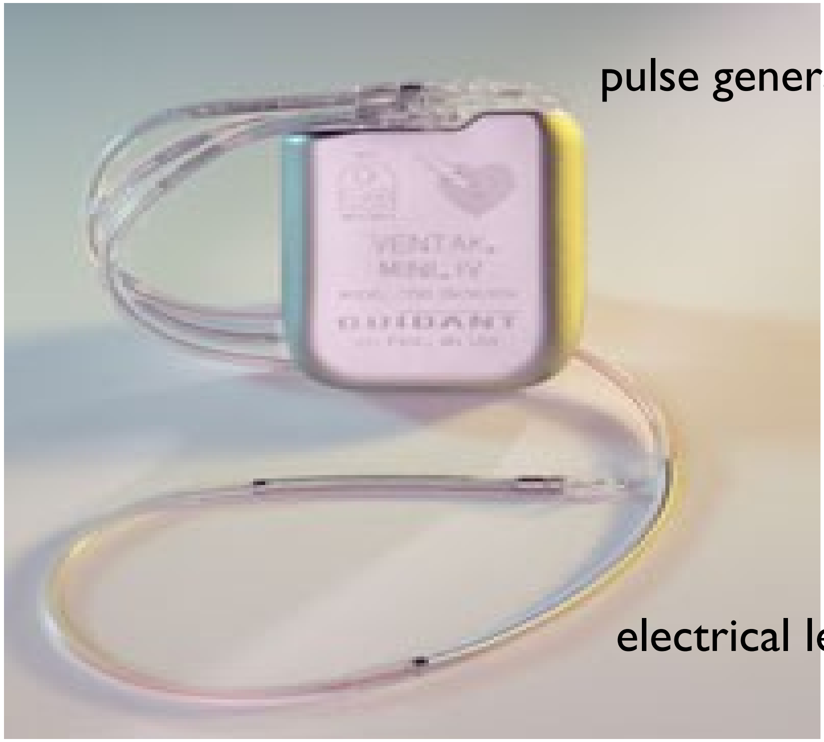
Problem with the Pharmaceutical Approach



Drugs developed to prevent cardiac arrest killed even more people !

Electrical therapy with ICDs

Implantable Cardioverter-Defibrillator



- constantly monitors heart rhythm.
- detects arrhythmia.
- delivers *programmed* treatment.

Variety of possible treatments:

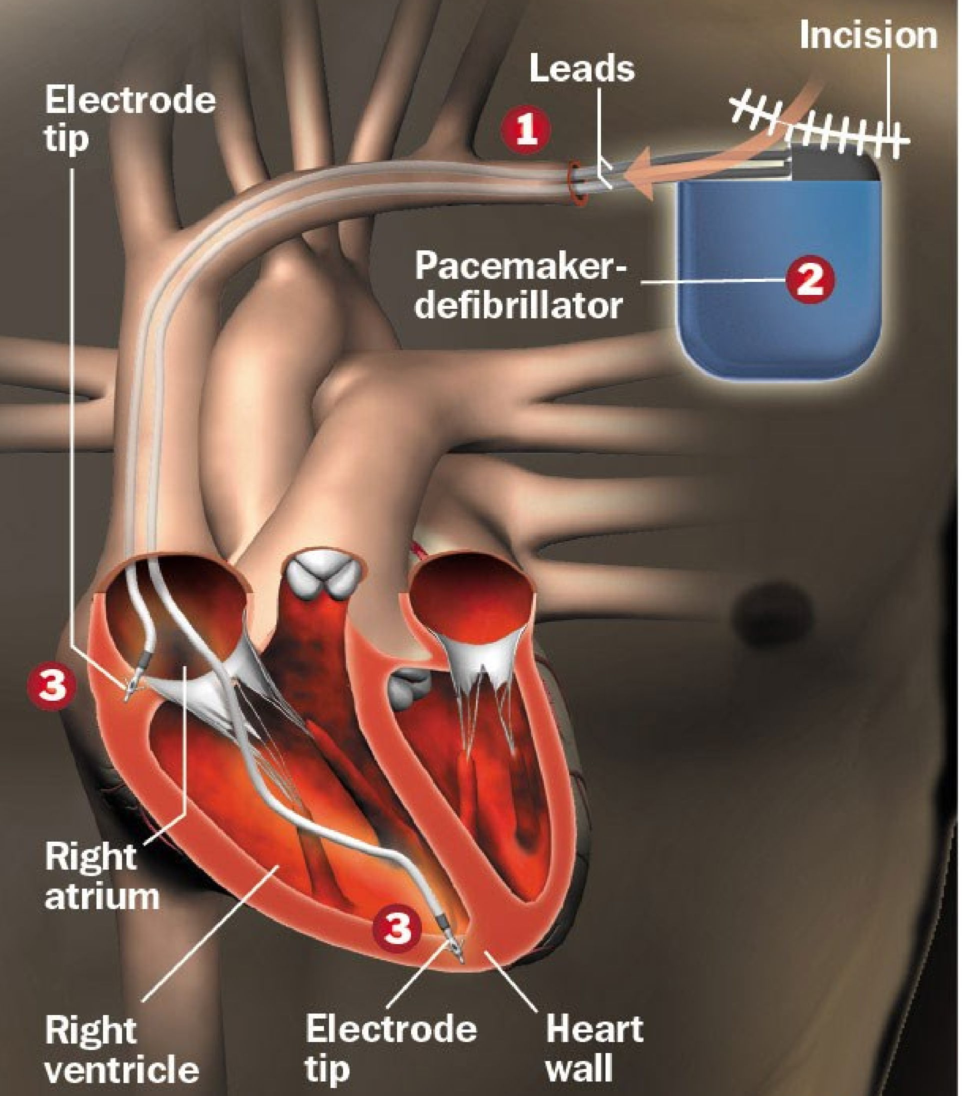
- Pacing: deliver a sequence of low-amplitude pulses.
- Cardioversion: a mild shock (if pacing fails in terminating VT).
- Defibrillation: large shock to terminate VF.

. . . And How It Got There

1. Doctors made a small incision near the collar bone and threaded two thin wire leads through a vein into the heart

2. The pacemaker-defibrillator was implanted under the skin, connected to the leads and tested

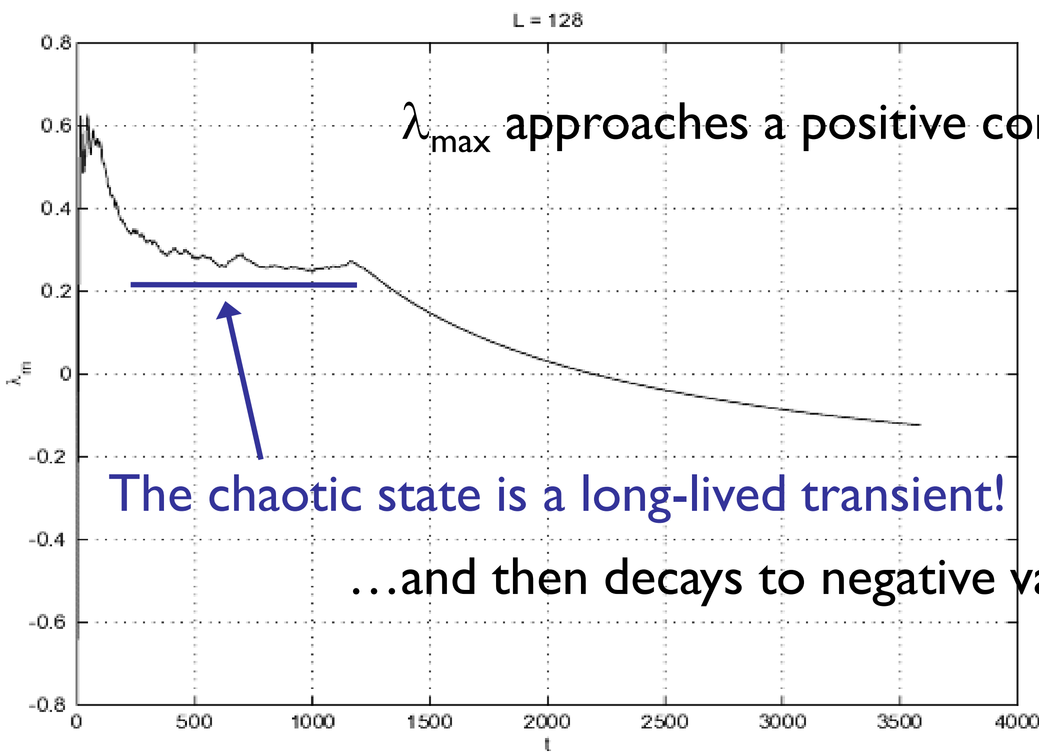
3. Electrodes embedded in the heart muscle will monitor the heartbeat and correct any irregularity with either small pulses or a shock of electricity



TIME Diagram by Joe Lertola

The transience of patterns

The largest Lyapunov exponent (λ_{max}) measures the degree of chaotic activity as a function of time t



λ_{max} approaches a positive constant (~ 0.2)…

The chaotic state is a long-lived transient!

…and then decays to negative values at large t.

Pandit, Pande, Sinha, 2000

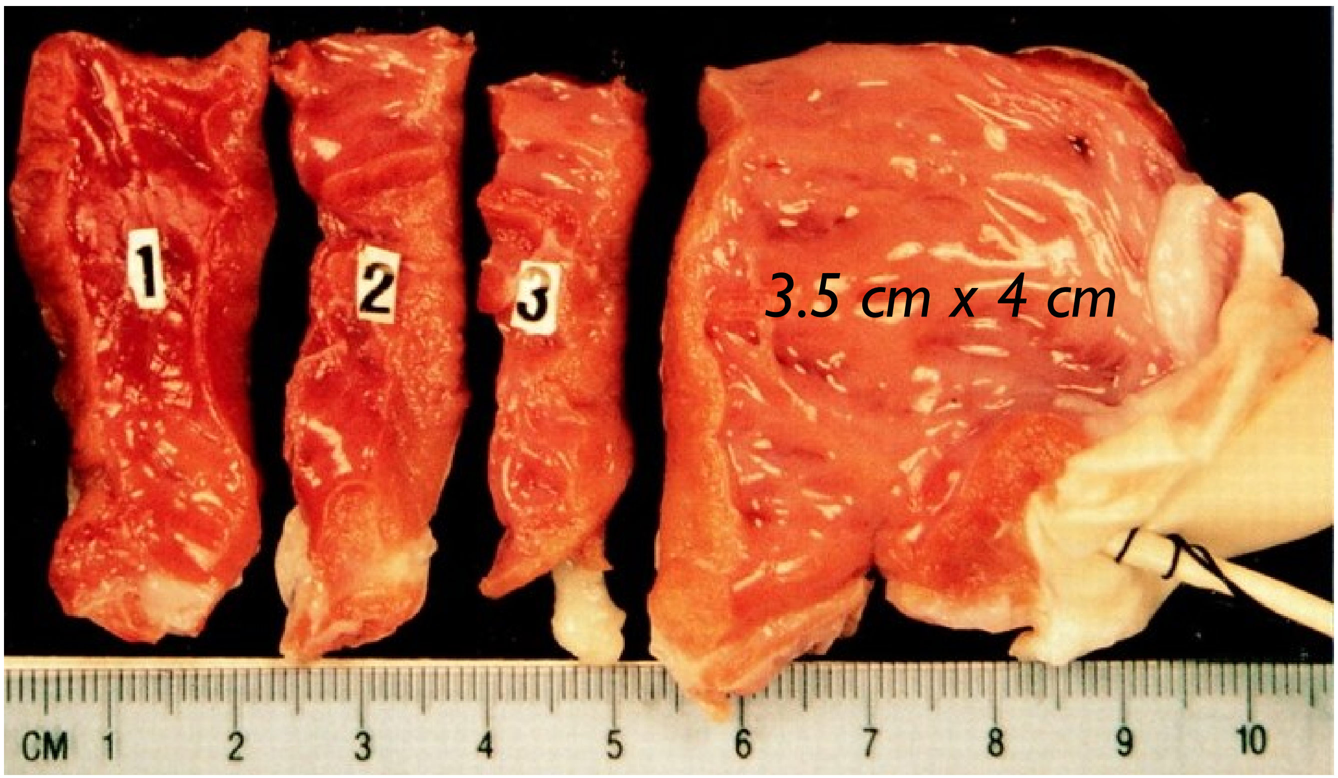
But so what ? Why care ?

The lifetime of the chaotic transient increases with size L.

Size does matter!

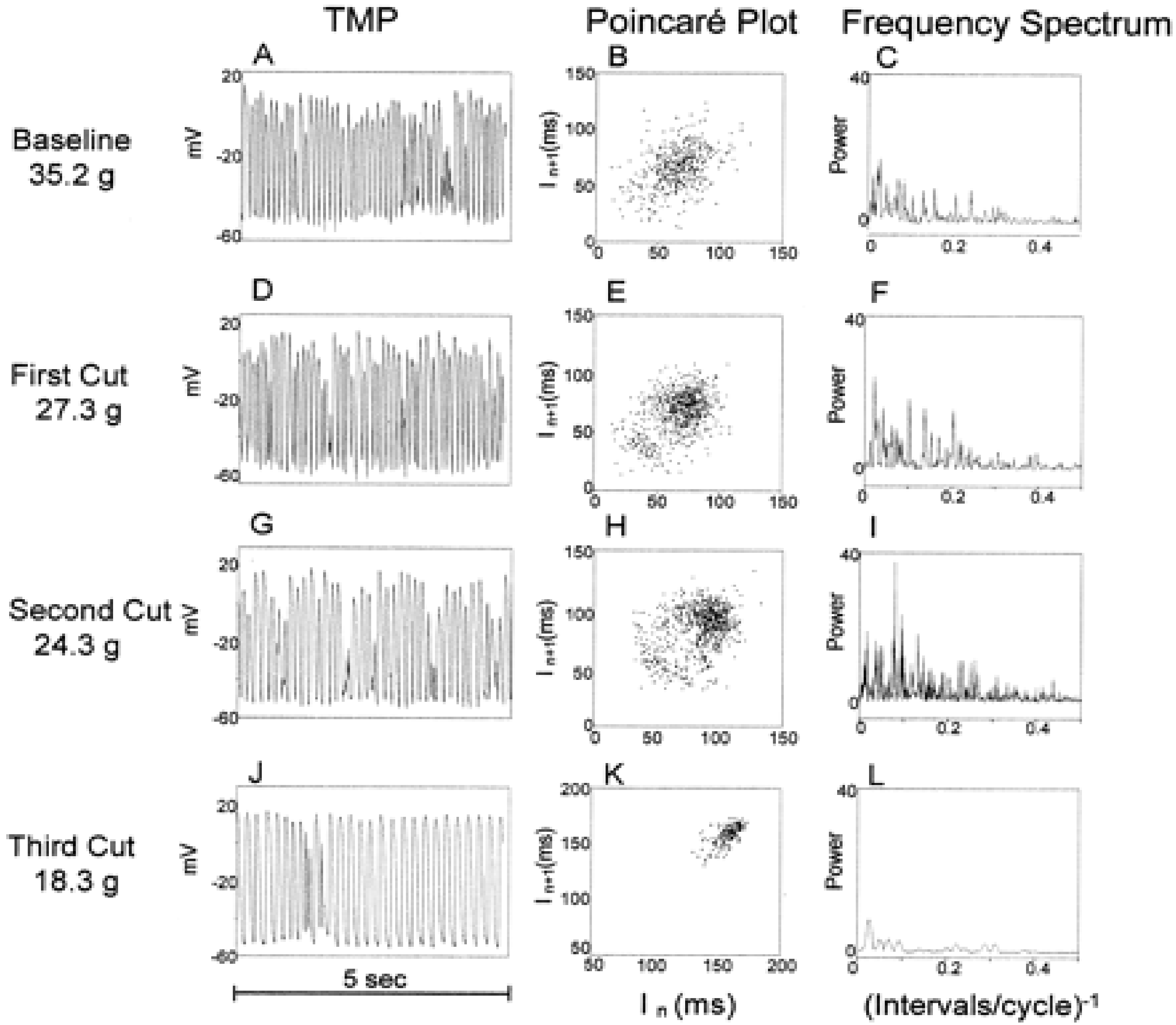
Decreasing the size of heart drastically reduces the duration of the chaotic transient.

Expts: Hearts of smaller mammals less likely to fibrillate.



Y-H Kim et al, *J Clin Invest* 100 (1997) 2486

Tissue mass reduction of swine ventricle by sequential cutting



Y-H Kim et al, *J Clin Invest* 100 (1997) 2486

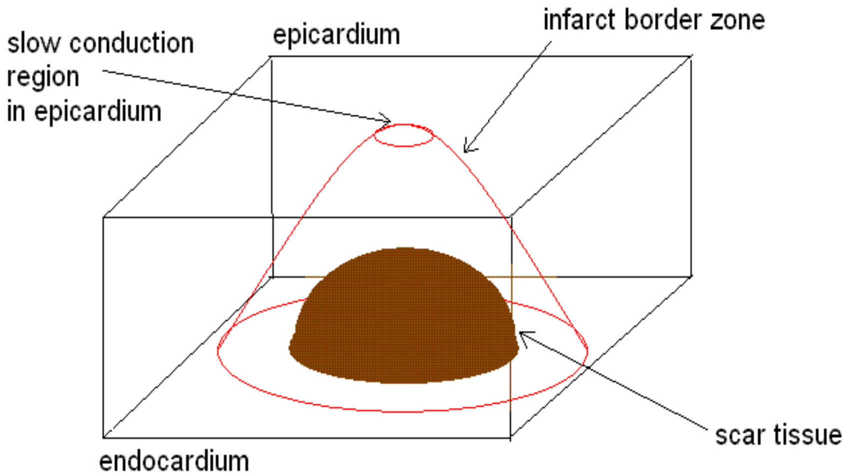
Transition from VF to periodicity with reduction of heart tissue

But…

Life gets even more complicated

Enter disorder (inhomogenity)

Example:
Cardiac tissue damaged by myocardial infarction (heart attack)
Heterogeneities: scar tissue through cell death due to lack of oxygenated blood (structural disorder)



Normal (healthy) tissue: *excitable*

Scar tissue: *Inexcitable*

Recovered tissue: *partially excitable*

In theoretical models, heterogeneity in
- diffusion coefficients (conductivity)
- excitation parameters