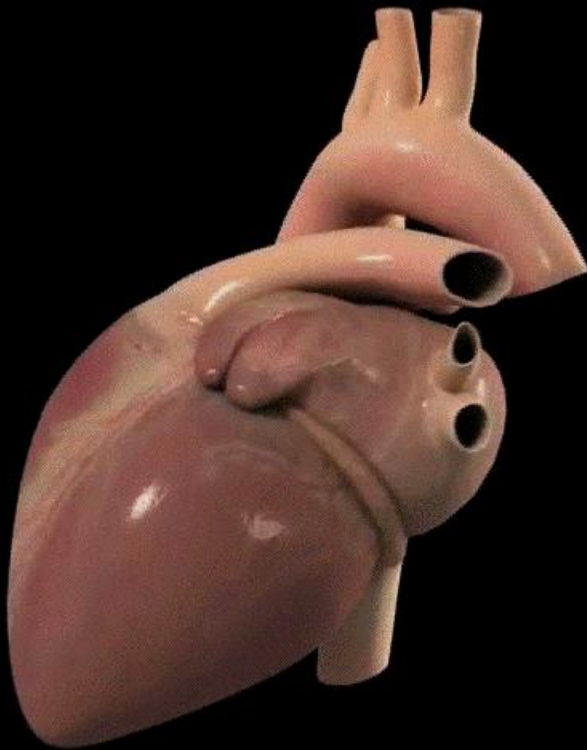
2011 NSF-CMACS Workshop on Atrial Fibrillation (3rd day)



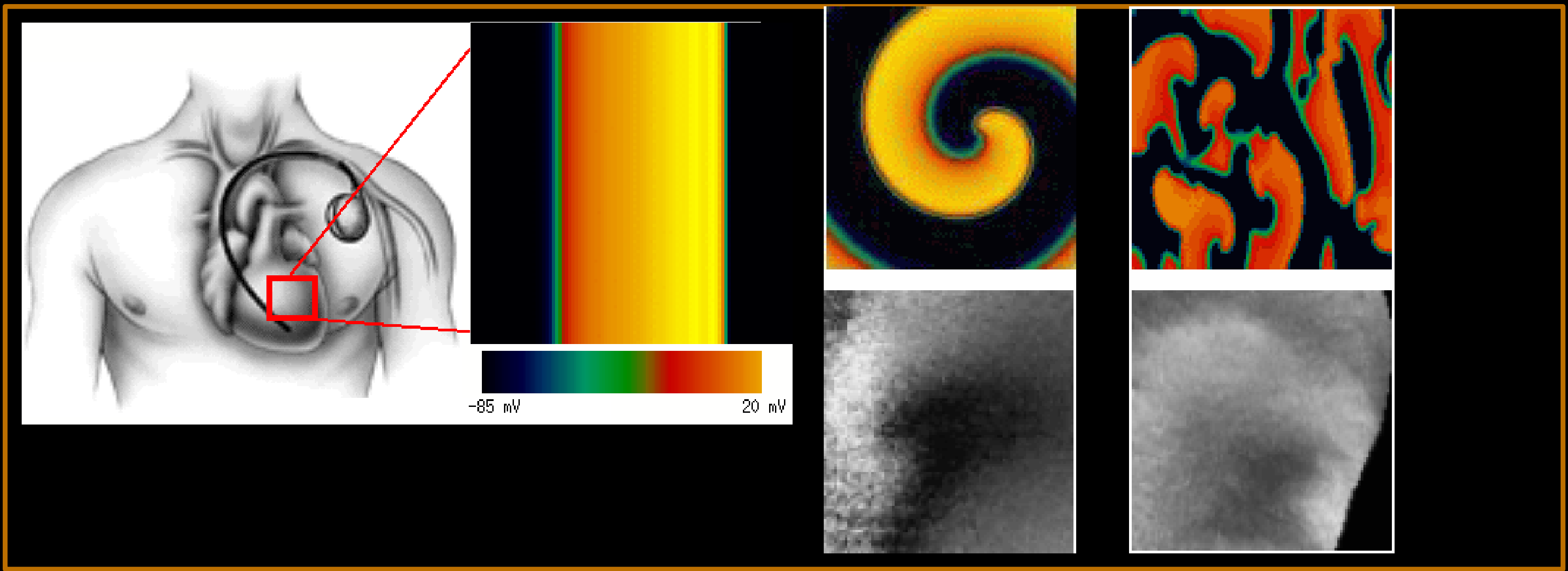
Flavio H. Fenton

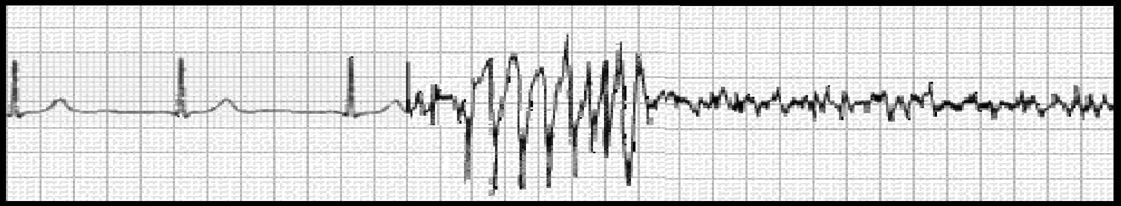
Department of Biomedical Sciences
College of Veterinary Medicine,
Cornell University, NY
and
Max Planck Institute for Dynamics and
Self-organization, Goettingen, Germany

CMACS
Computational Modeling and Analysis for Complex Systems

Lehman College,
Bronx, NY. Jan 3-7, 2011

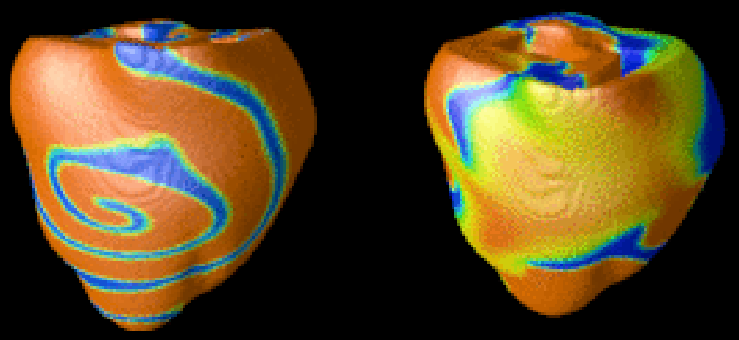
Transition from Sinus Rhythm to Fibrillation





Normal Rhythm VT VF

Sudden cardiac death



Cherry EM, Fenton FH, Am J Physiol 2004; 286: H2332
Cherry EM, Fenton FH, New J. Phys. 2008; 10, 125016

Spiral Waves in the Heart

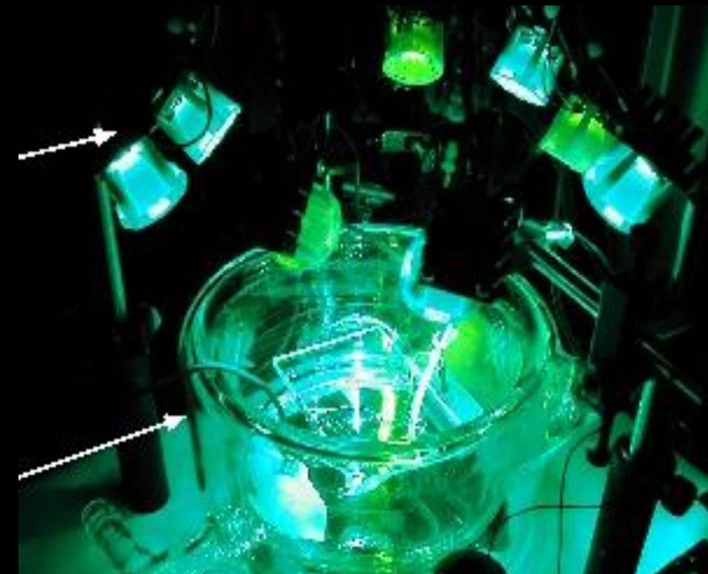
How can we know they are there?

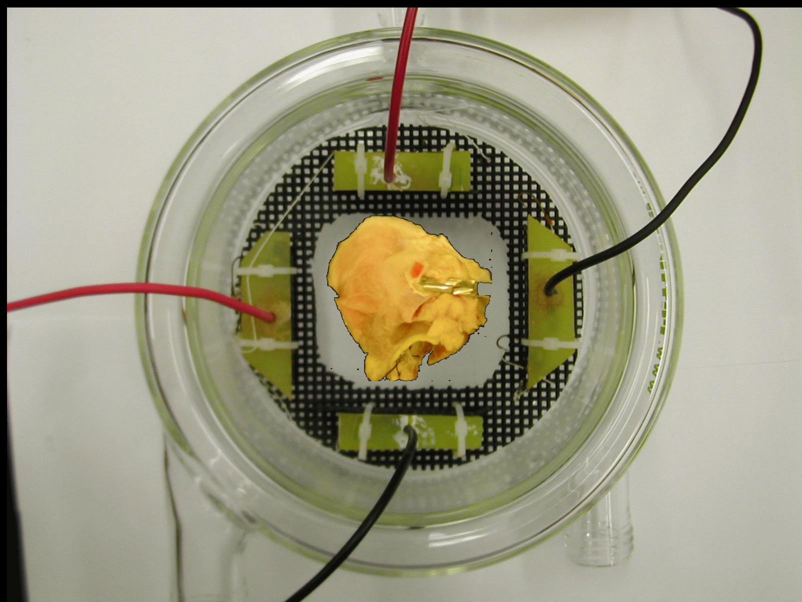
How can we see them?

Visualizing Electrical Activity in Cardiac Tissue

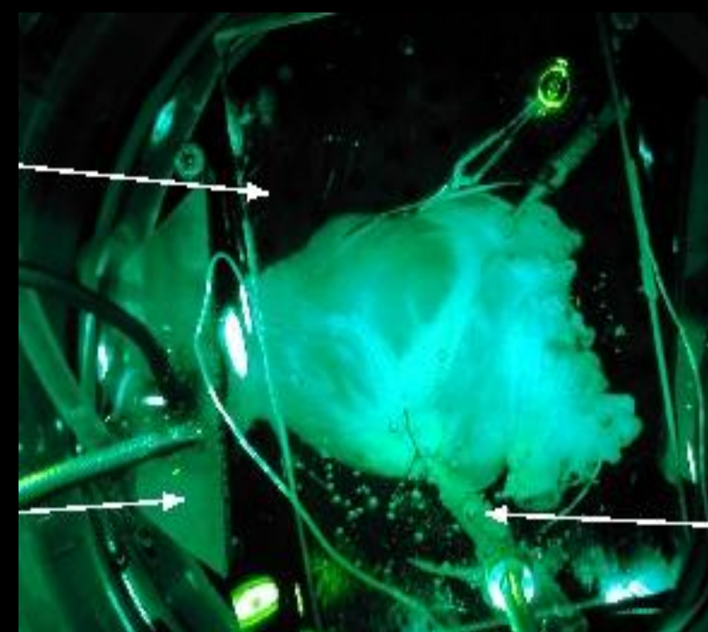
Visualizing Electrical Activity in Cardiac Tissue

Optical Mapping

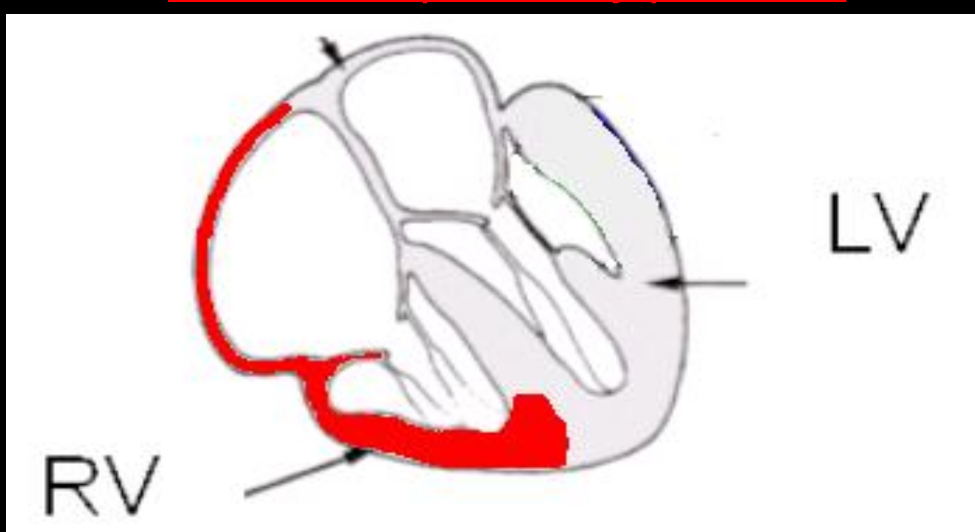




Tissue bath

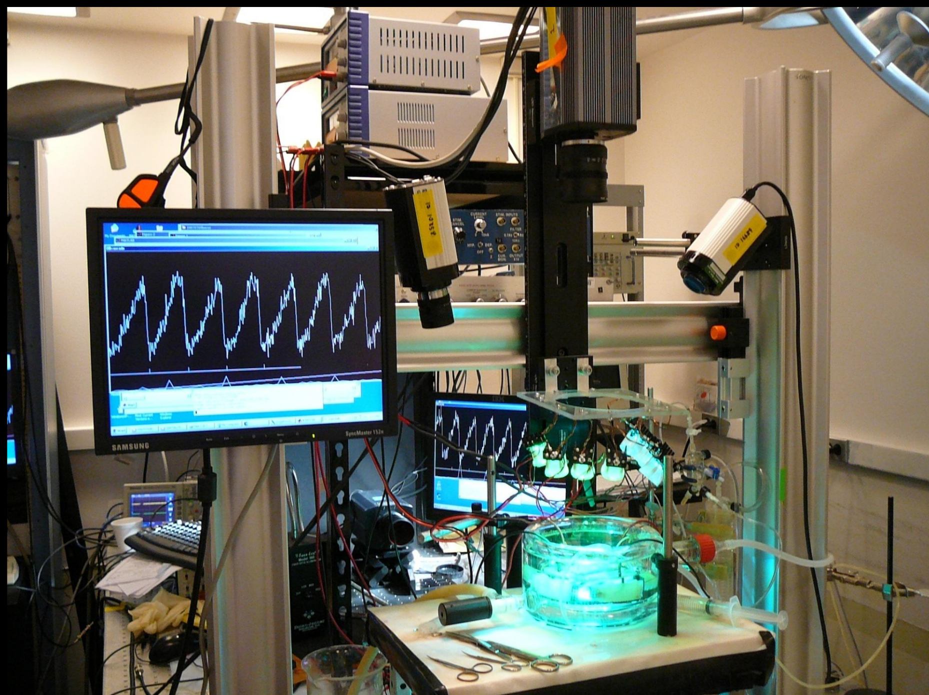


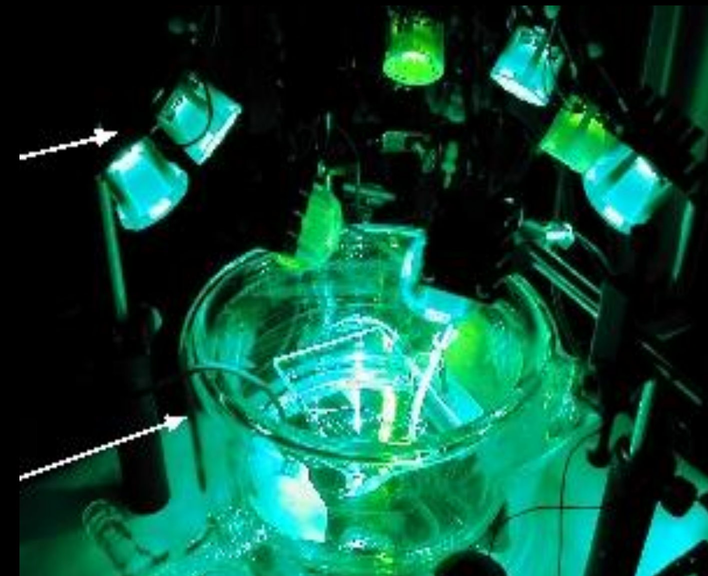
Tissue is kept alive by perfusion

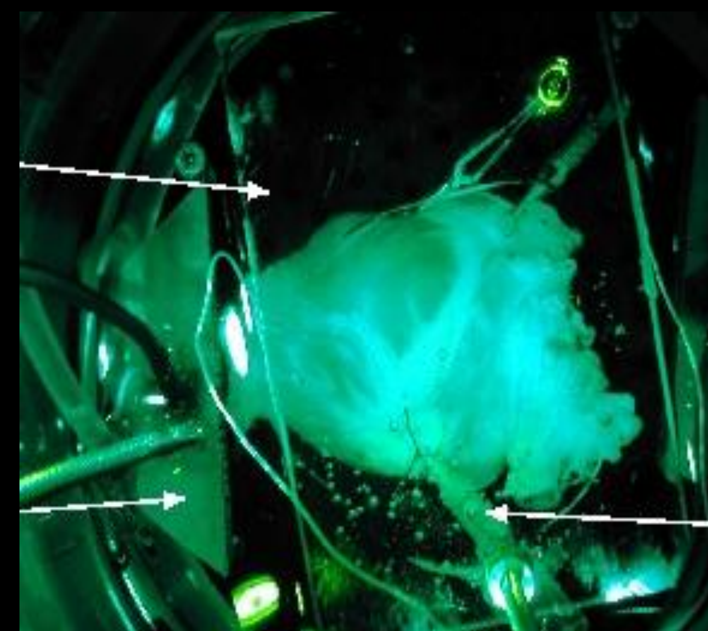


Visualizing Electrical Activity in Cardiac Tissue

Optical Mapping

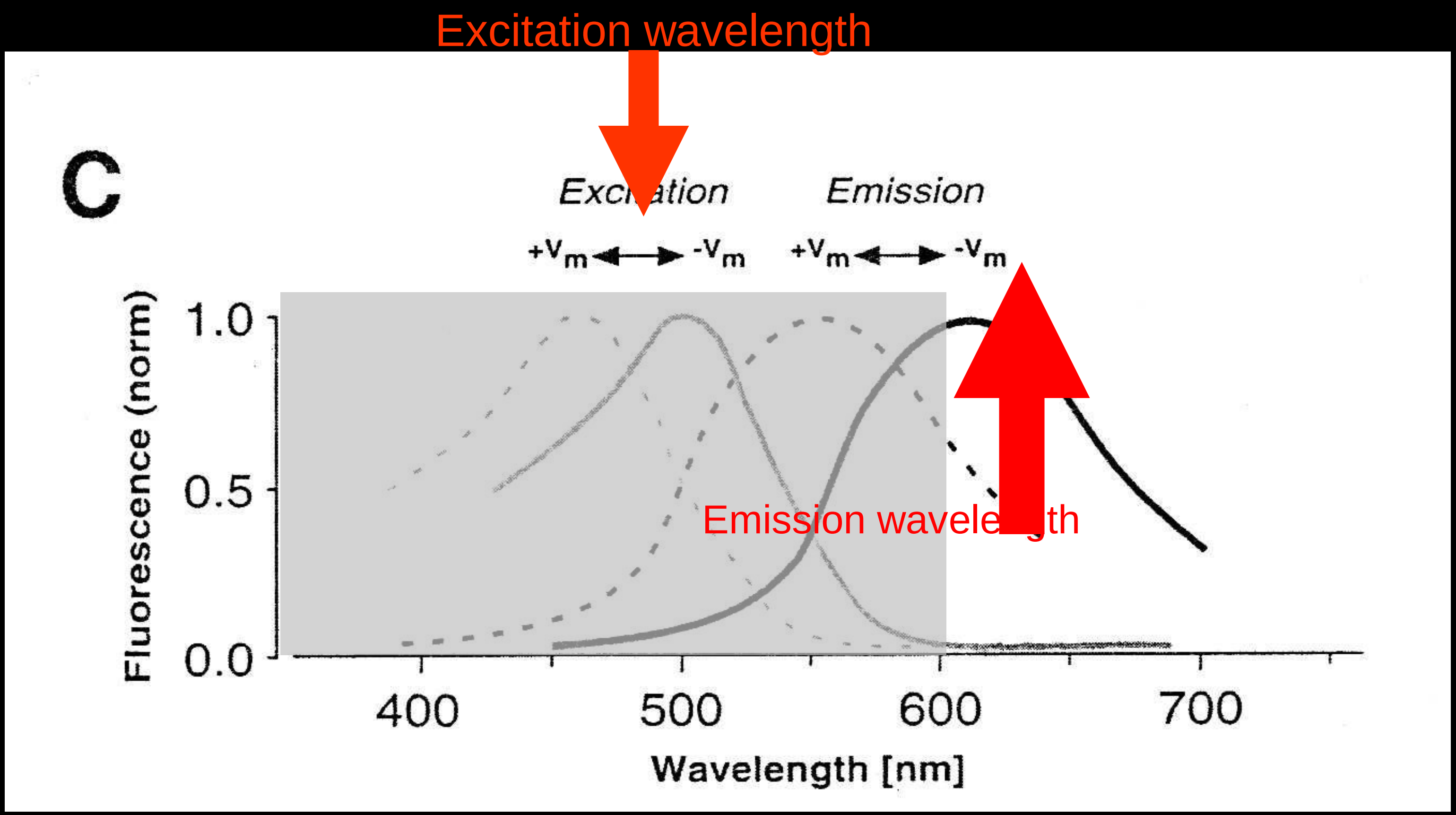






- Di-4-ANEPPS (voltage-sensitive dye)
  Voltage = changes in fluorescence
- Diodes: 530 nm wavelength
- Cascade cameras at 511 Hz
- 128x128 window view

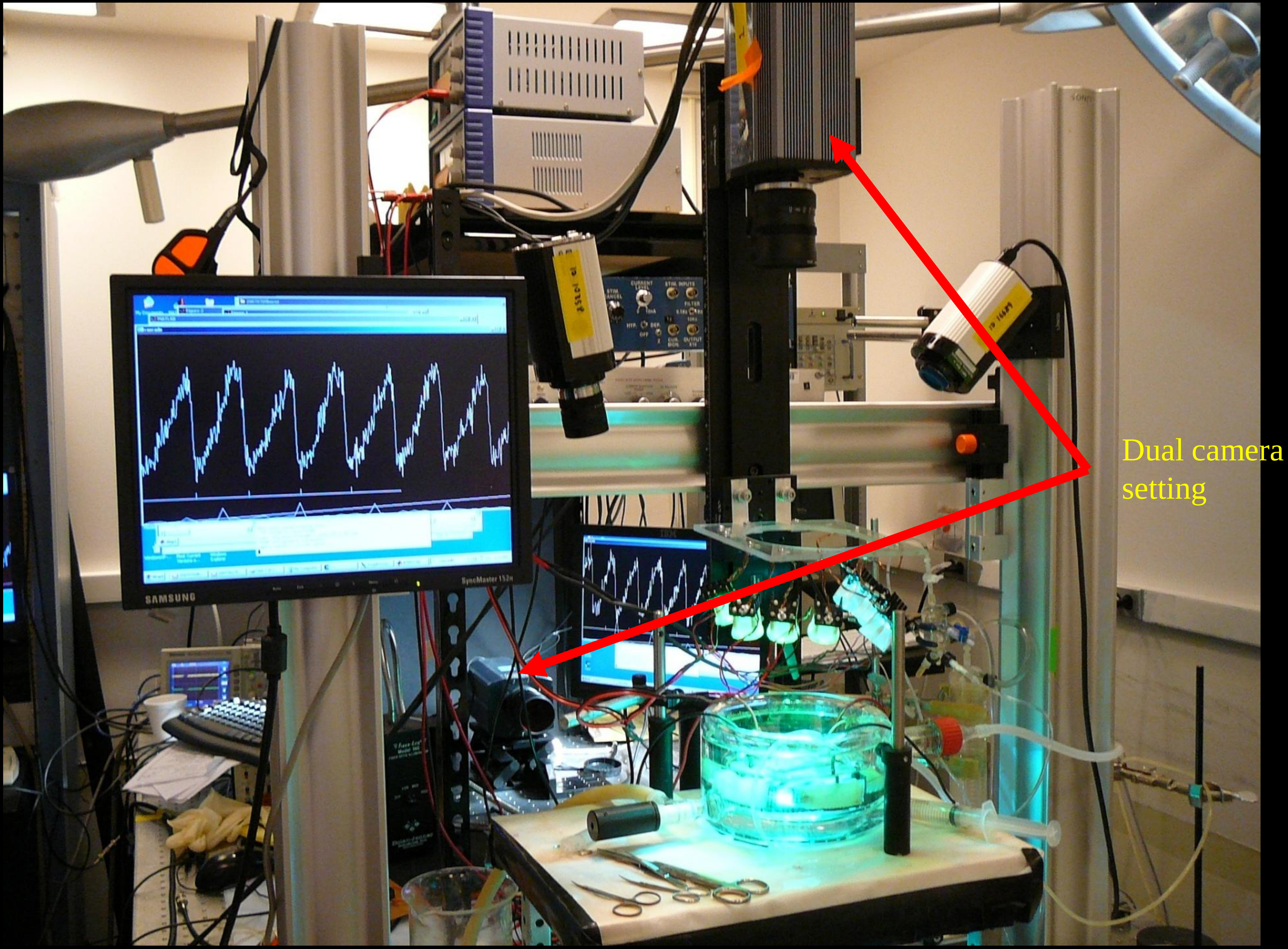
Fluorescence Imaging with di-4-ANNEPS



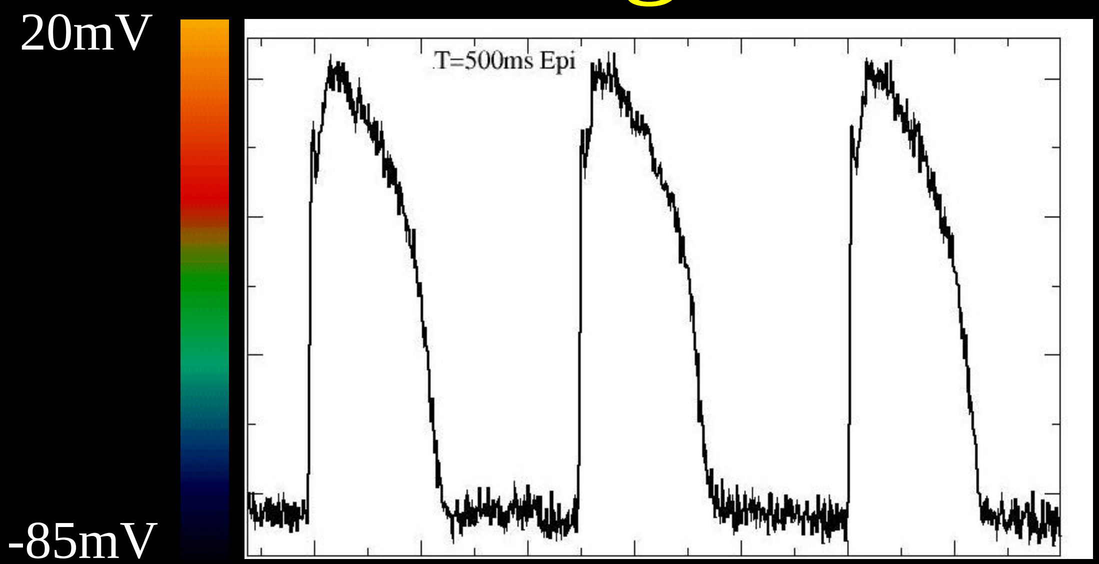
Intensity AND maximum of spectrum change with membrane potential.

Fractional intensity change 1-10% (for a filter cut-off of λ = 600 nm)

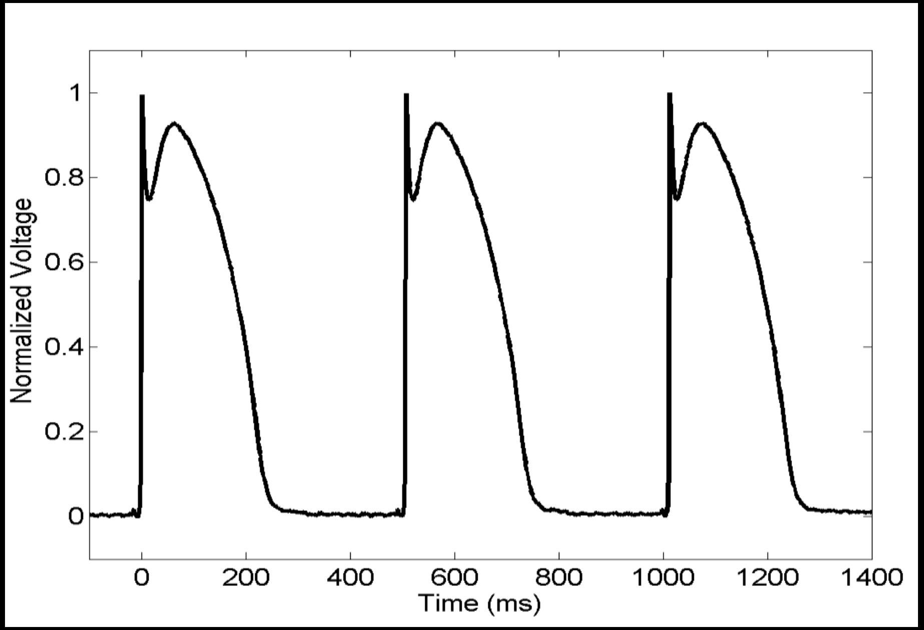
Optical Mapping Setup



Example of Action Potential Recordings in Ventricular Tissue



Optical mapping



Microelectrode Recordings:
Better signal-to-noise
Discontinuous in space
Not for long times

Normal Sinus Rhythm
Plane Waves (Optical Mapping)

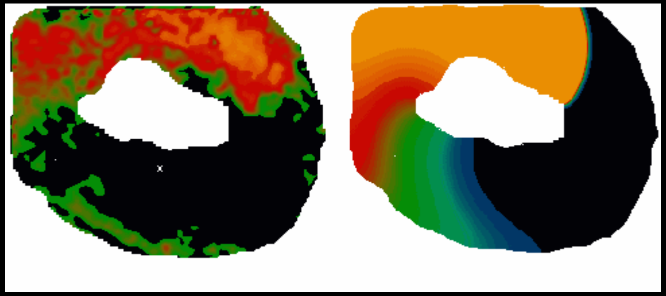
20mV

-85mV

Electrical activity in the atria

Electrical activity in the ventricle

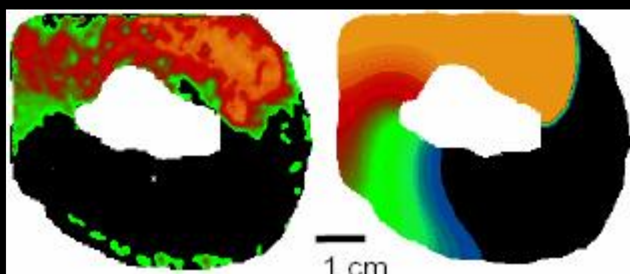
Spiral Waves:
Simulations and Optical Mapping



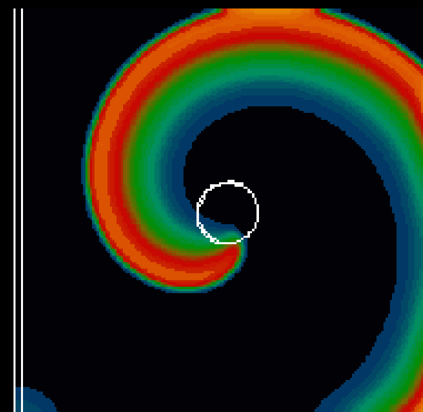
Anatomical
reentry

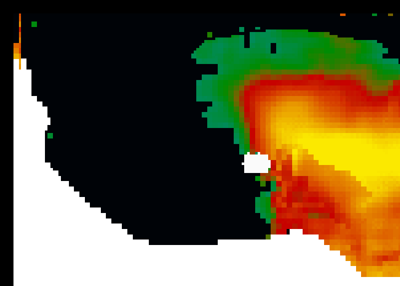
Cherry EM, Fenton FH. New Journal of Physics 2008; 10: 125016

Spiral Waves:
Simulations and Optical Mapping

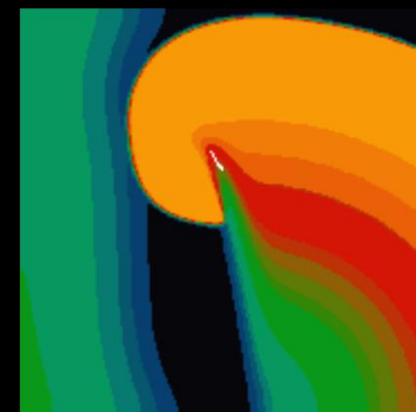


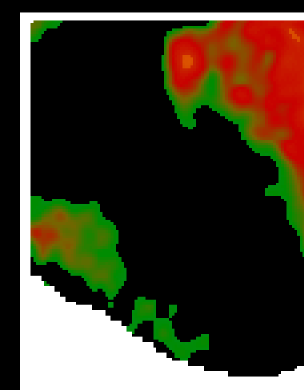
Anatomical
reentry





Circular core
spiral wave



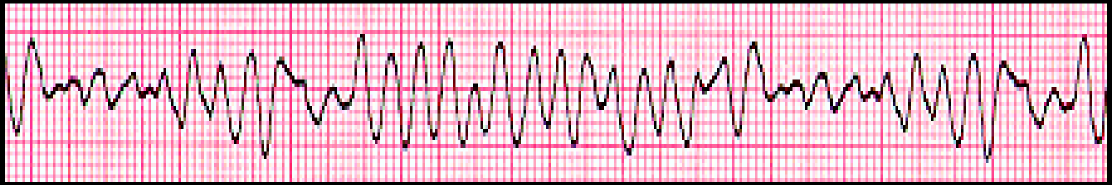


Linear core
spiral wave

Cherry EM, Fenton FH. New Journal of Physics 2008; 10: 125016

Different Types of Arrhythmias

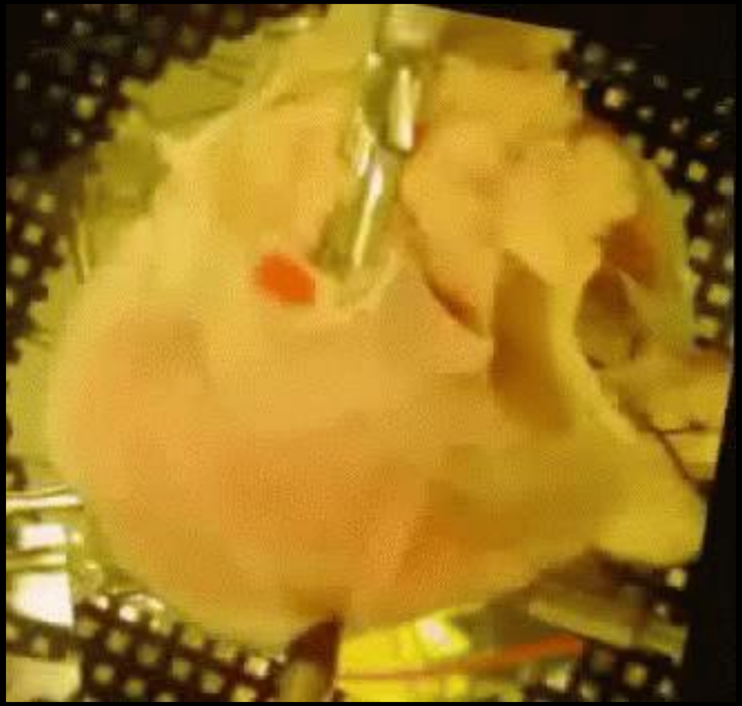
- Ventricular Fibrillation

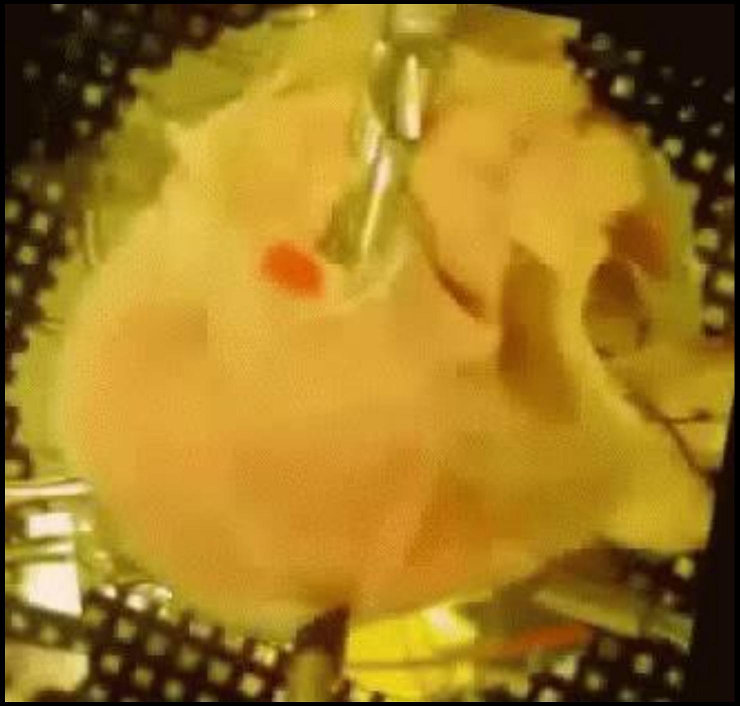


Spiral waves are complicated

The dynamics of multiple spiral waves is not simple, with multiple short lived.

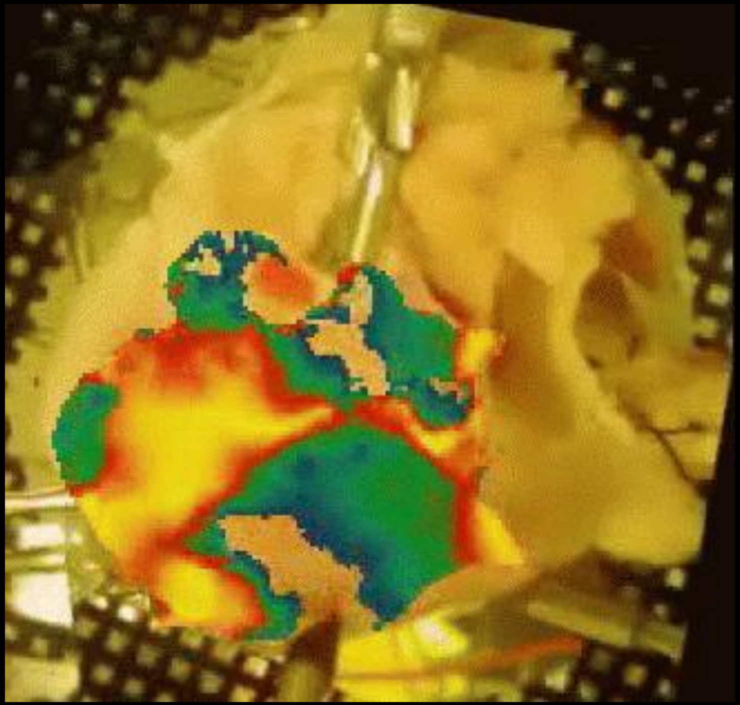
Spiral Wave Instabilities

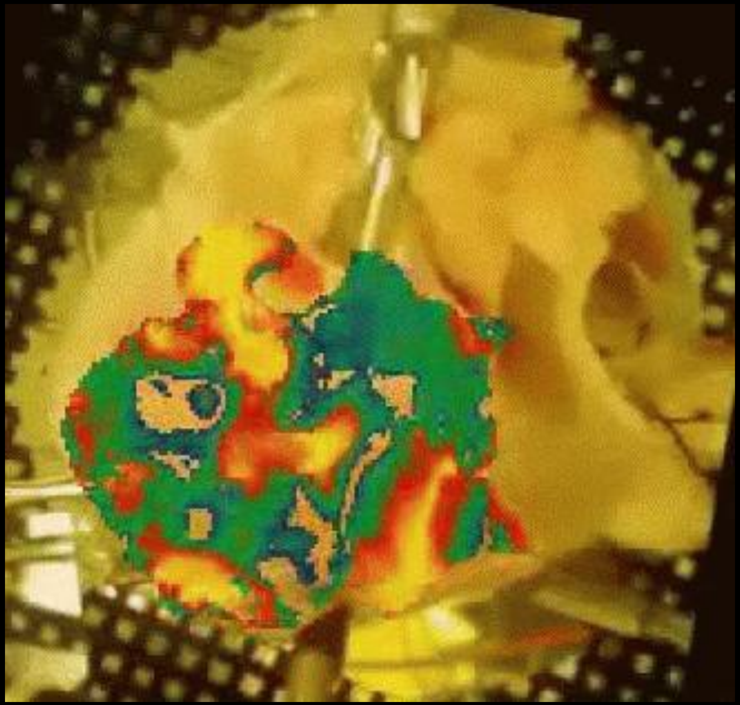


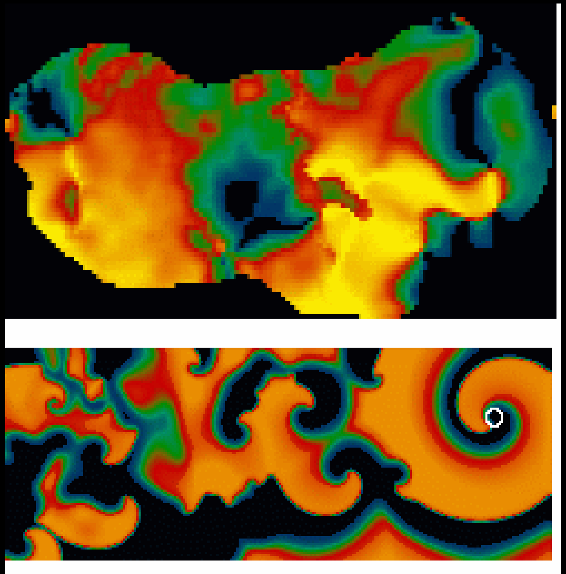


From one spiral to multiple spirals?
How to prevent?
How to terminate?

Spiral Wave Instabilities







Simulation
and
experiment
one spiral
driving
many

In Reality, the Heart Is a 3D System

In Reality, the Heart Is a 3D System

Dual-Surface Optical Mapping

In Reality, the Heart Is a 3D System

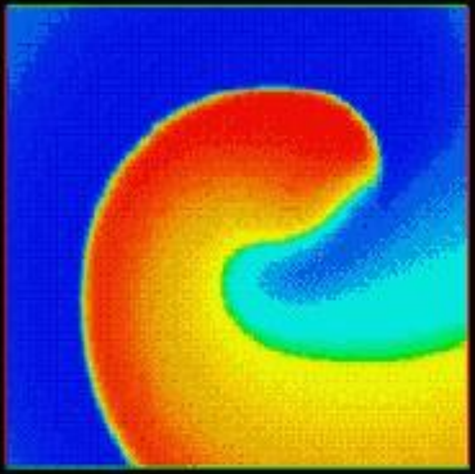
Dual-Surface Optical Mapping

How to Visualize Reentry in 3D?

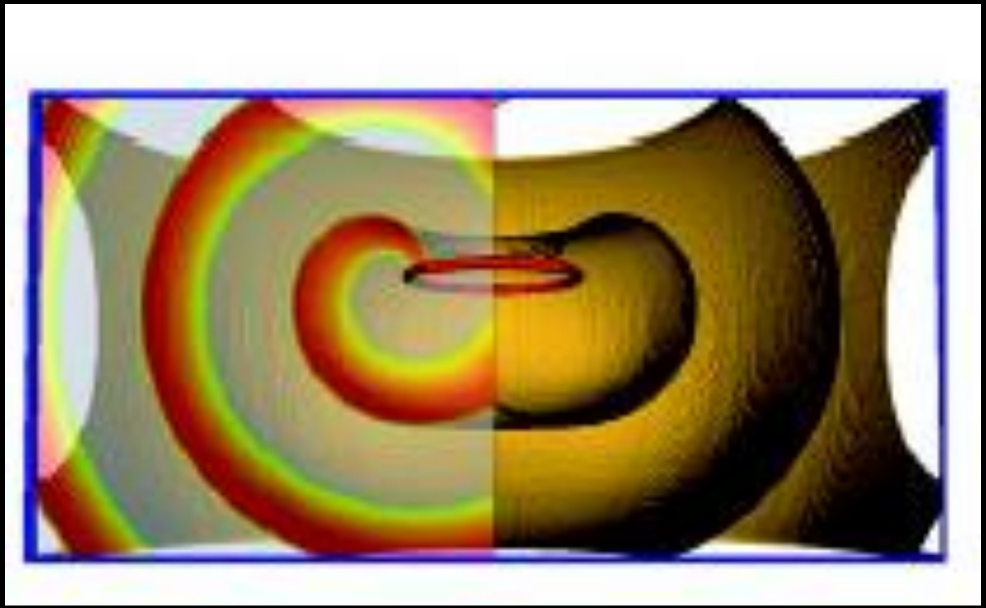
2D → 3D

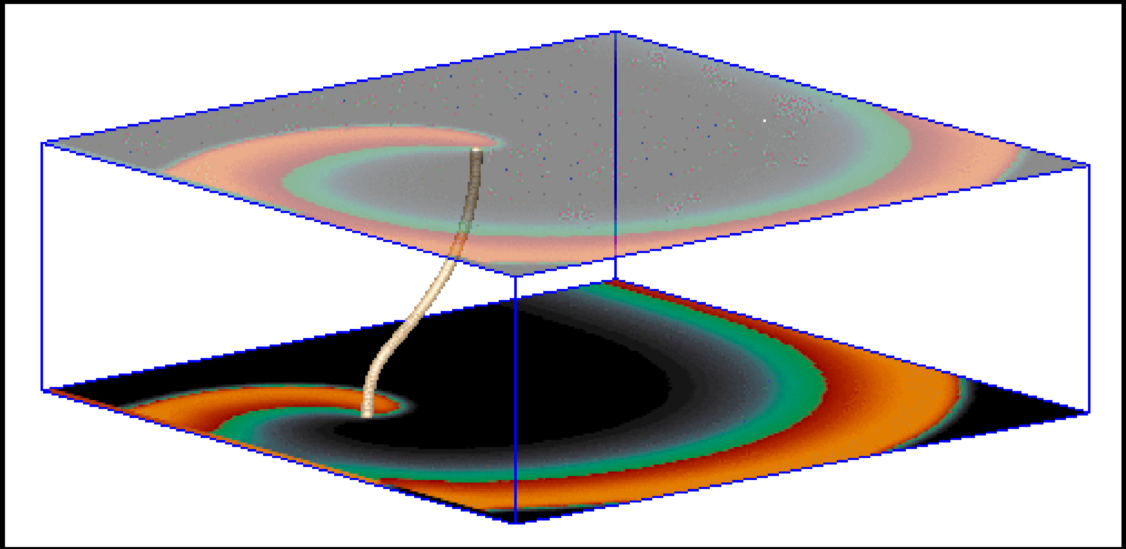
Spiral waves → Scroll waves

spiral tip vortex filament



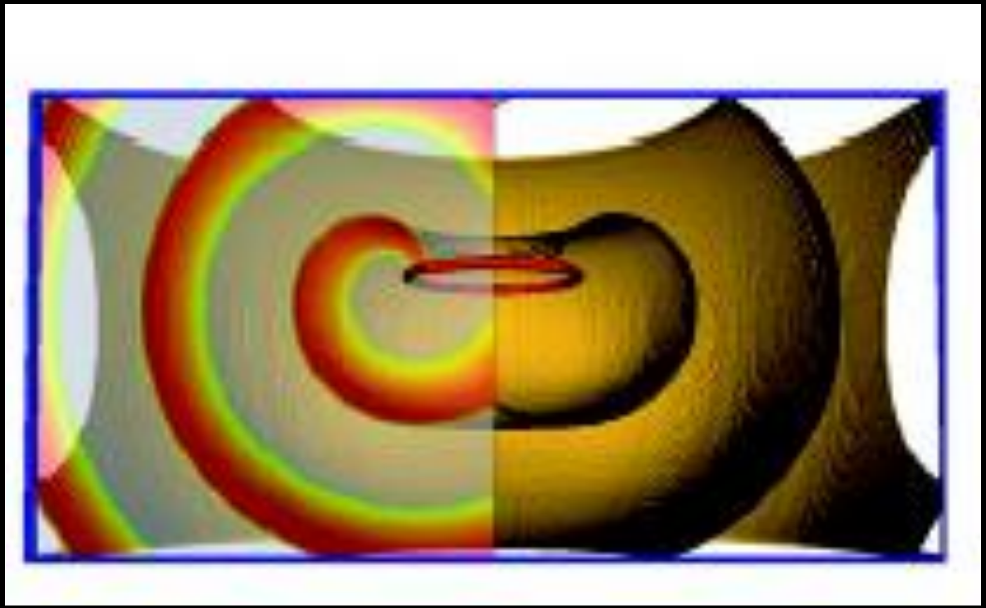
How to Visualize Reentry in 3D?

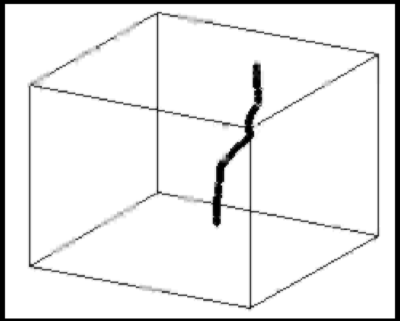


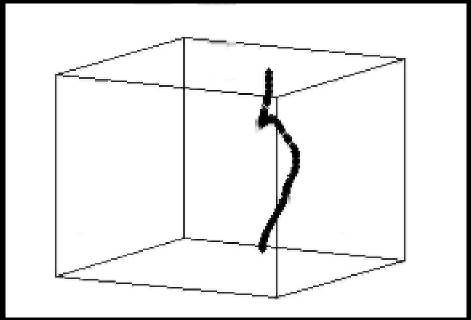


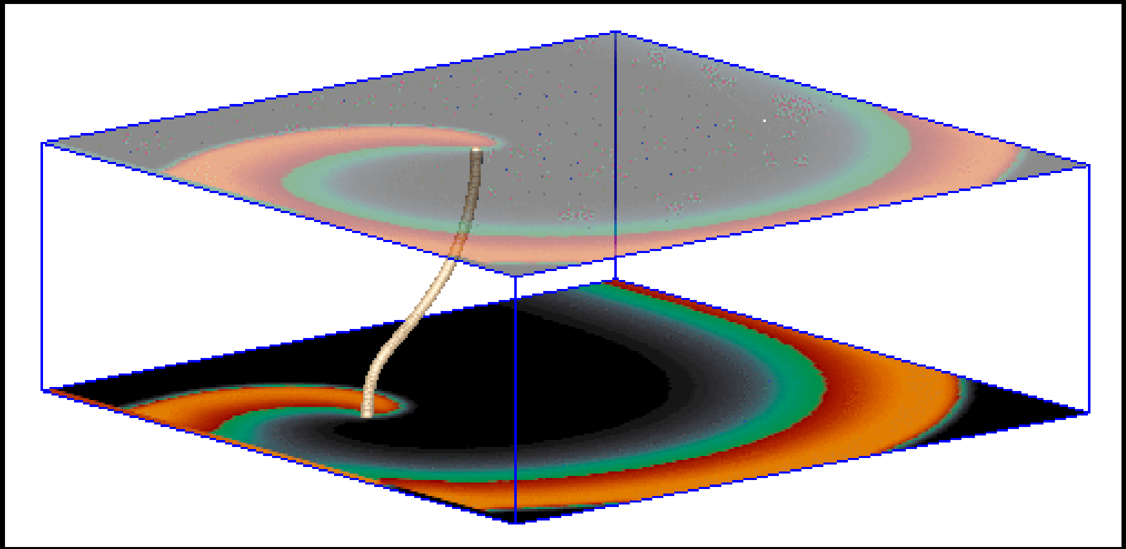
Similar to water spouts

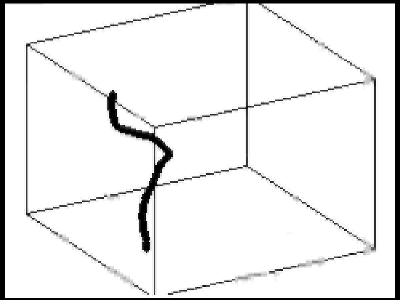
How to Visualize Reentry in 3D?





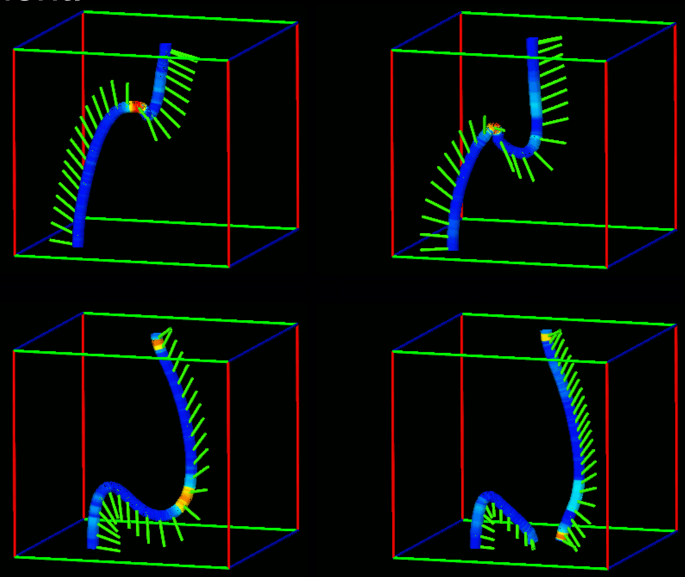


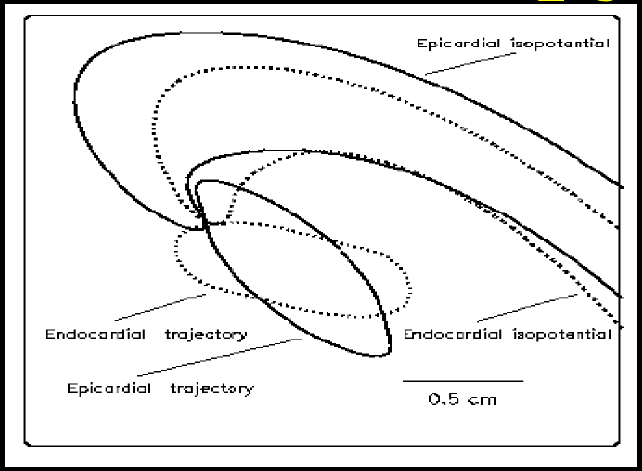




Continuous Rotational Anisotropy

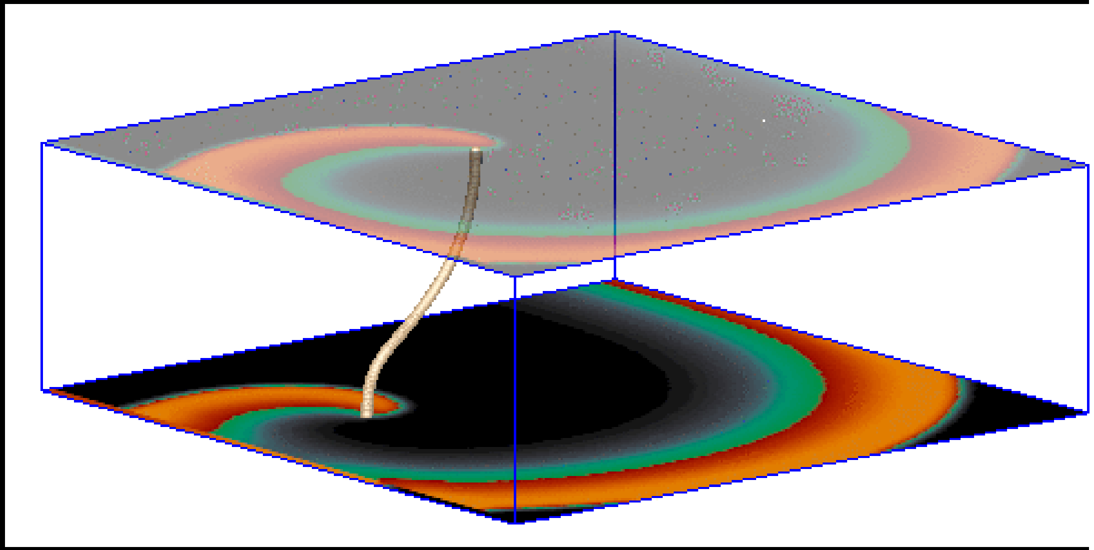
Fiber rotation induces a phase on the wave fronts between layers, producing a localized twist along the filament.

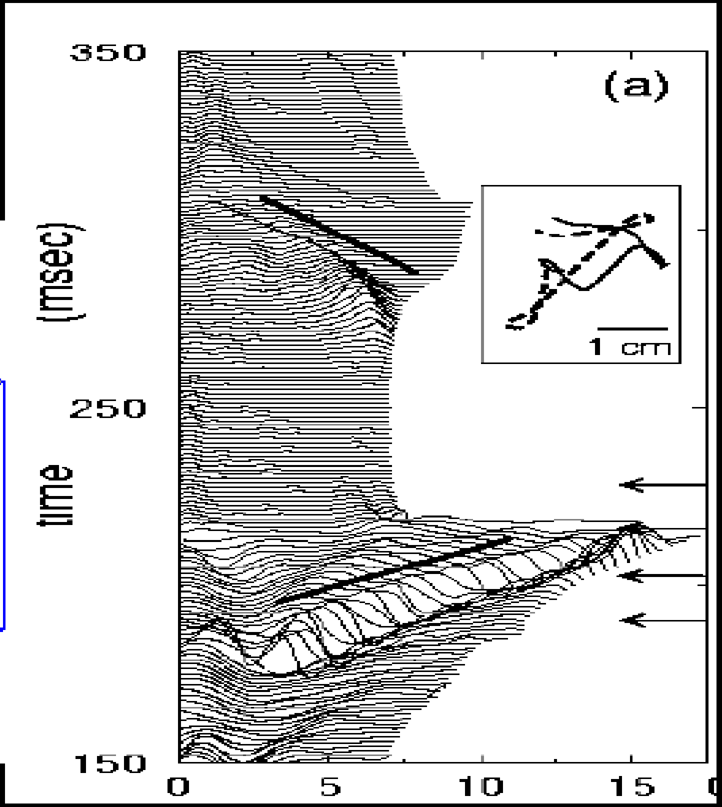




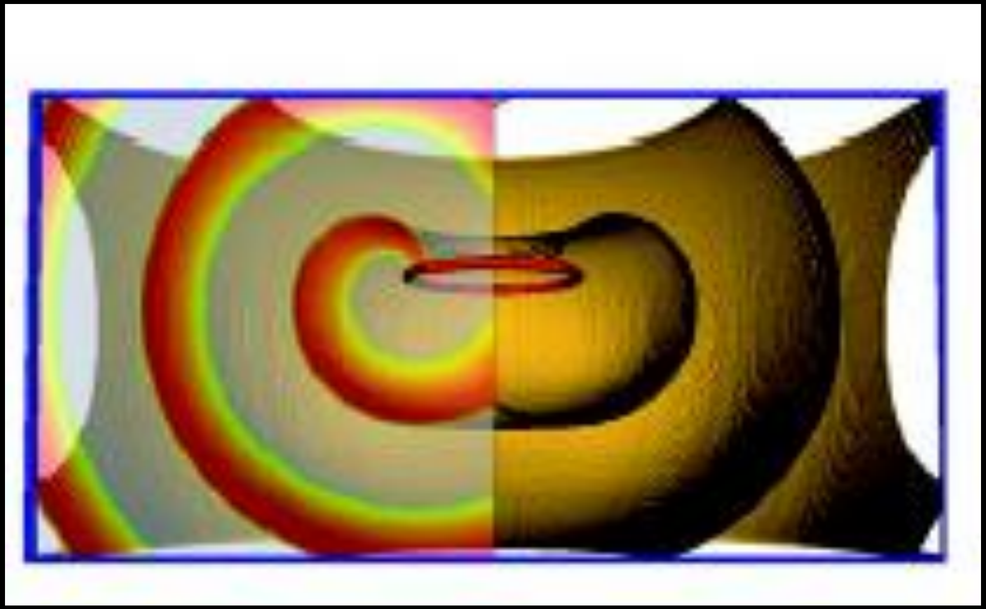
Twist propagation

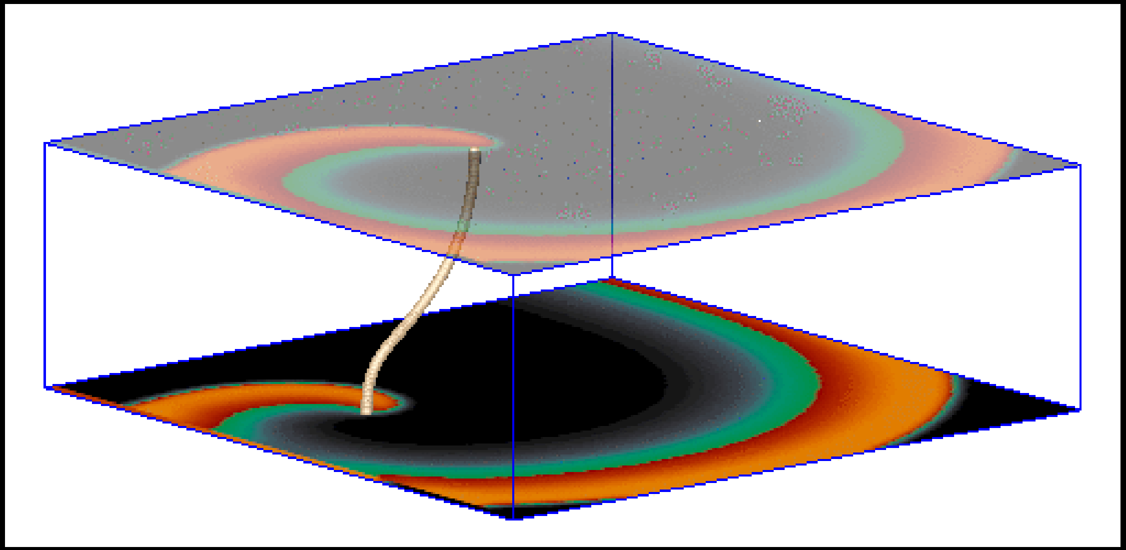
Twist (degree/mm)



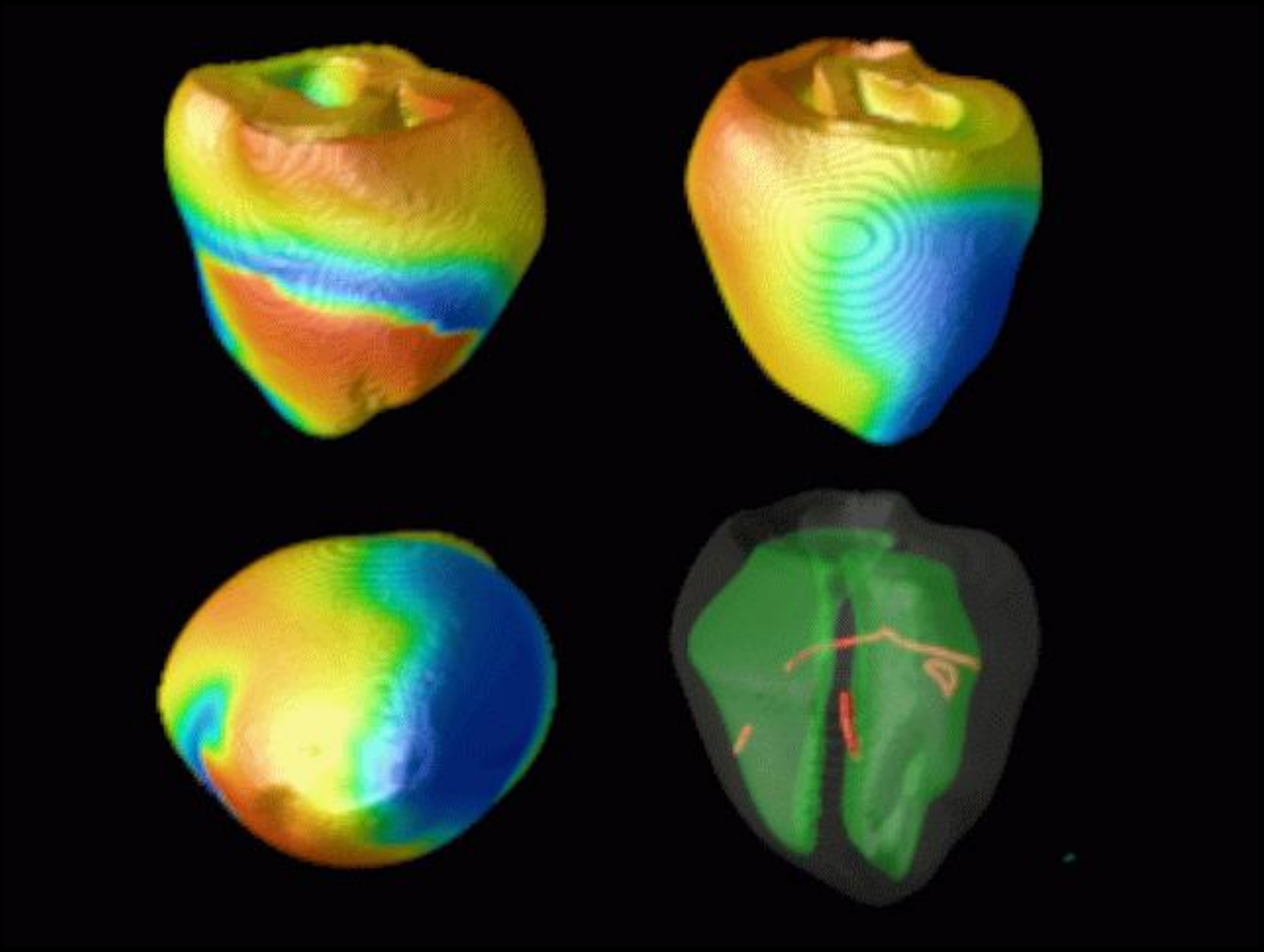


How to Visualize Reentry in 3D?





Ventricular Fibrillation in 3D

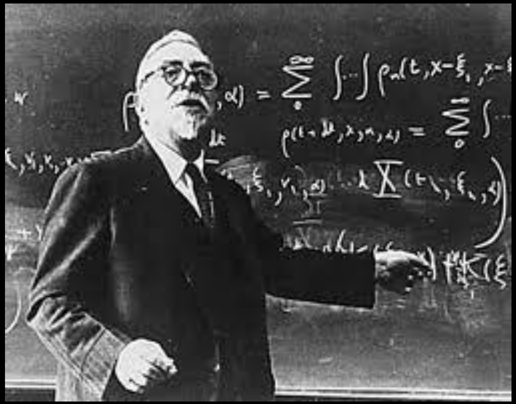


Enough introduction

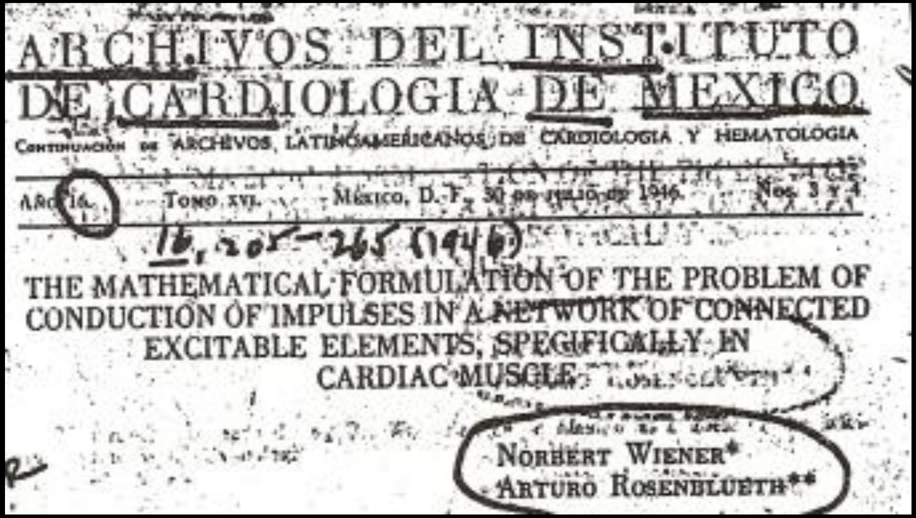
How do we model cell and cardiac dynamics?

The study of cardiac arrhythmias from a computational point of view started in 1946 in Mexico. Fathers of Cybernetics

N. Wiener and A. Rosenblueth, "The mathematical formulation of the problem of conduction of impulses in a network of connected excitable elements, specifically in cardiac muscle," Arch. Inst. Cardiol. Mex **16**, 205–265. 1946



Norbert Wiener



ARCHIVOS DEL INSTITUTO DE CARDIOLOGIA DE MEXICO

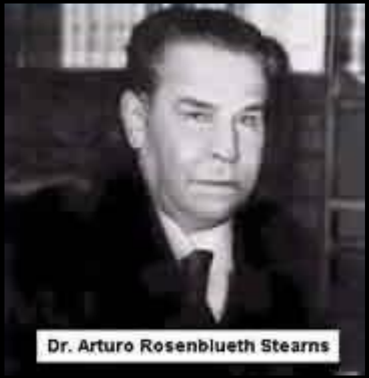
CONTINUACIÓN DE ARCHIVOS LATINOAMERICANOS DE CARDIOLOGIA Y HEMATOLOGIA

Arch. I.C. Tomo XVI. México, D. F., 30 de junio de 1946. Nos. 3 y 4

16, 205–265 (1946)

THE MATHEMATICAL FORMULATION OF THE PROBLEM OF CONDUCTION OF IMPULSES IN A NETWORK OF CONNECTED EXCITABLE ELEMENTS, SPECIFICALLY IN CARDIAC MUSCLE

NORBERT WIENER*
ARTURO ROSENBLUETH**



Arturo Rosenblueth

The best model for a cat is another cat,
Preferable the same cat.

Enough introduction

The first mathematical model of electrical AP

J. Physiol. (1952) 117, 500–544

A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

BY A. L. HODGKIN AND A. F. HUXLEY

From the Physiological Laboratory, University of Cambridge

(*Received* 10 *March* 1952)

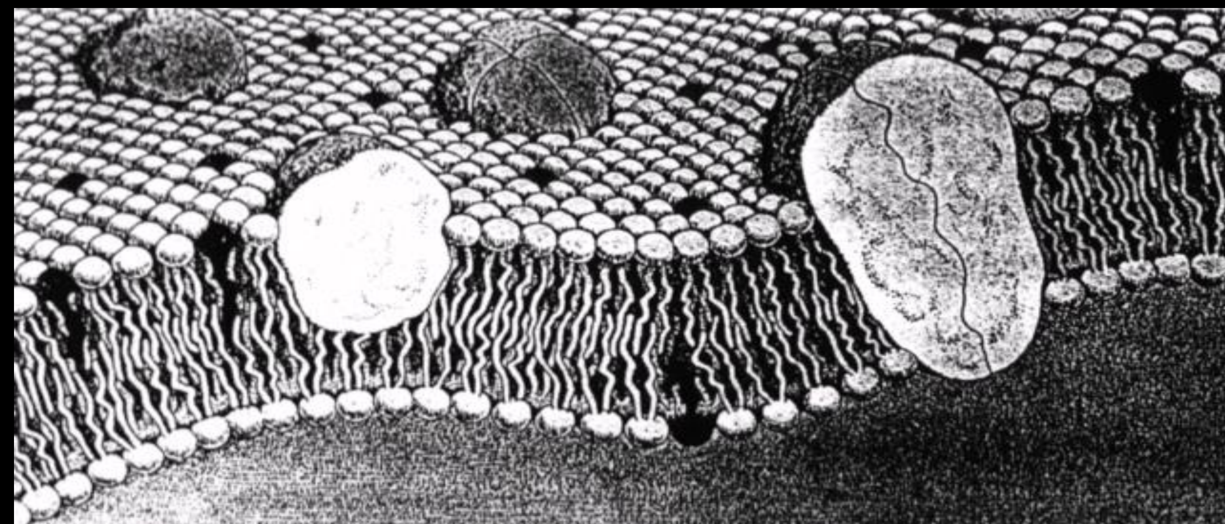
This article concludes a series of papers concerned with the flow of electric current through the surface membrane of a giant nerve fibre (Hodgkin, Huxley & Katz, 1952; Hodgkin & Huxley, 1952 *a–c*). Its general object is to discuss the results of the preceding papers (Part I), to put them into mathematical form (Part II) and to show that they will account for conduction and excitation in quantitative terms (Part III).

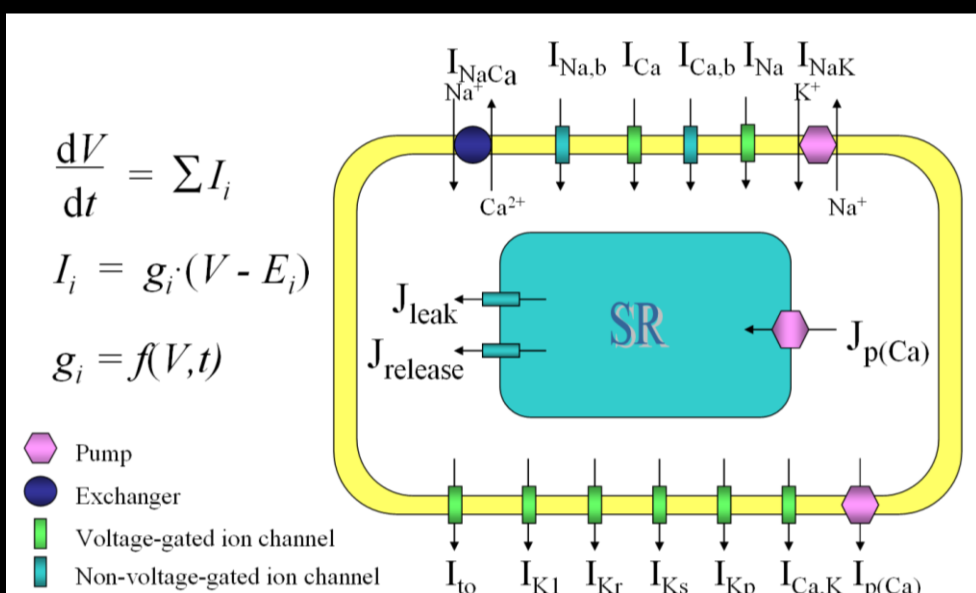
PART I. DISCUSSION OF EXPERIMENTAL RESULTS

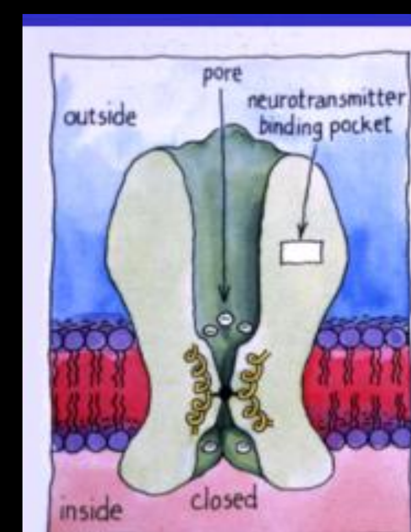
J. Physiol. Vol 117 500-540, 1952 by
A.L. Hodgkin and A.F. Huxley.

Electrical Activity in Myocites

Ca^{2+}, Na^{+}, K^{+}

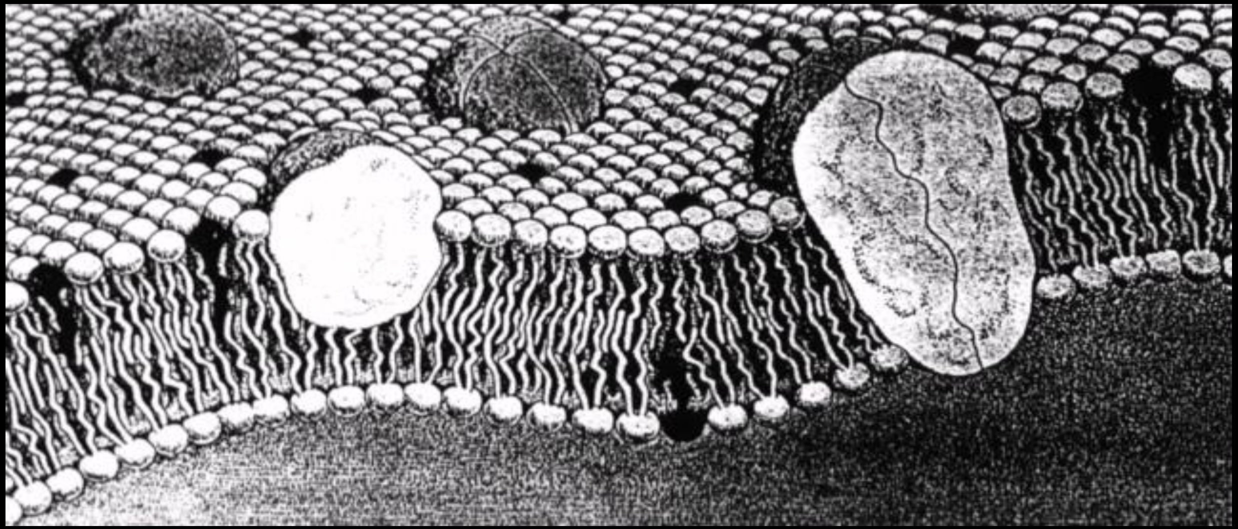






How to model the Neuron AP?

The Hodgkin-Huxley model of four variables for neurons



Capacitance is a measure of the amount of electrical energy stored (or separated) for a given electric potential, where $C = Q/V$

$Q_m = CV_m$; $dQ_m/dt = I_{ion}$; Therefore $I_{ion} = C\, dV_m/dt$

$$dV_m/dt = I_{ion}/C$$

J. Physiol. Vol 117 500-540, 1952 by
A.L. Hodgkin and A.F. Huxley.

How to model the Neuron AP mathematically?

The Hodgkin-Huxley model of four variables for neurons

$$
\begin{aligned}
I_K &= n^4 g_K (V_m - V_K) \\
I_{Na} &= m^3 h g_{Na} (V_m - V_{Na}) \\
I_{Cl} &= g_{Cl} (V_m - V_{Cl})
\end{aligned}
$$

Cell currents for the model (follow Ohms law)

$$dy/dt = \alpha_y(V_m)(1 - y) - \beta(V_m)\, y$$

Ecuaciones para la probabilidad de las puertas

$\alpha_y(V_m)$

$\beta_y(V_m)$

$$
\begin{aligned}
\alpha_m &= 0.1(V_m + 35.0)/(1. - e^{(-(V_m+35.0)/10.0)}) \\
\beta_m &= 4.0\, e^{(-(V_m+60.0)/18.0)}
\end{aligned}
$$

$$
\begin{aligned}
\alpha_h &= 0.07\, e^{(-(V_m+60.0)/20.0)} \\
\beta_h &= 1./(1 + e^{(-(V_m+30.0)/10.0)})
\end{aligned}
$$

$$
\begin{aligned}
\alpha_n &= 0.01(V_m + 50.0)/(1 - e^{(-(V_m+50.0)/10.0)}) \\
\beta_n &= 0.125\, e^{(-(V_m+60.0)/80.0)}
\end{aligned}
$$

J. Physiol. Vol 117 500-540, 1952 by A.L. Hodgkin and A.F. Huxley.

Gating Variables

- Gating variables are time-dependent variables that modify the current conductance.
- Gates vary between 0 and 1; 1 maximizes current and 0 eliminates it.
- Gates follow the following equation:

$$\frac{\mathrm{d}y}{\mathrm{d}t} = \frac{y_\infty - y}{\tau_y}$$

where $y_\infty(V)$ is the steady-state value and $\tau_y(V)$ is the time constant for the gate.

$$dy/dt = \alpha_y(V_m)(1-y) - \beta(V_m)\,y$$

$\beta_y(V_m)$

$\alpha_y(V_m)$

$$y_\infty = \frac{\alpha_i(V)}{\alpha_i(V) + \beta_i(V)}.$$

$$\tau_i(V) = \frac{1}{\alpha_i(V) + \beta_i(V)}.$$

How to model the Neuron AP mathematically?

The Hodgkin-Huxley model of four variables for neurons

$$I_K = n^4 g_K (V_m - V_K)$$
$$I_{Na} = m^3 h g_{Na} (V_m - V_{Na})$$
$$I_{Cl} = g_{Cl} (V_m - V_{Cl})$$

Cell currents
for the model
(follow Ohms law)

$$dy/dt = \alpha_y(V_m)(1-y) - \beta(V_m)\, y$$

Ecuaciones para la probabilidad de las puertas

$$\alpha_y(V_m)$$

$$\beta_y(V_m)$$

$$\alpha_m = 0.1(V_m + 35.0)/(1. - e^{(-(V_m+35.0)/10.0)})$$
$$\beta_m = 4.0\, e^{(-(V_m+60.0)/18.0)}$$

$$\alpha_h = 0.07\, e^{(-(V_m+60.0)/20.0)}$$
$$\beta_h = 1./(1 + e^{(-(V_m+30.0)/10.0)})$$

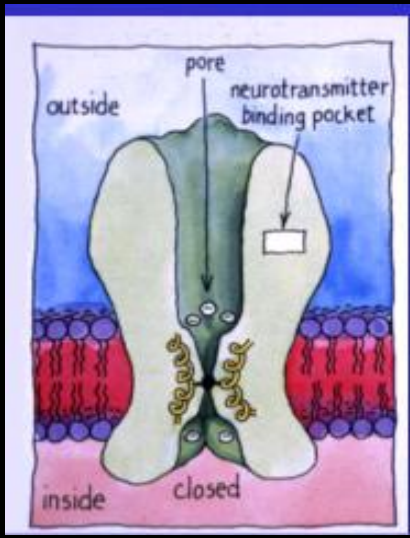
$$\alpha_n = 0.01(V_m + 50.0)/(1 - e^{(-(V_m+50.0)/10.0)})$$
$$\beta_n = 0.125\, e^{(-(V_m+60.0)/80.0)}$$

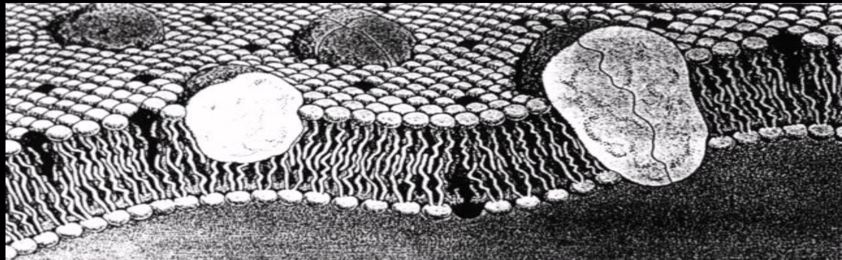
J. Physiol. Vol 117 500-540, 1952 by A.L. Hodgkin and A.F. Huxley.

How to model the Neuron AP mathematically?

Hodgkin-Huxley four variable model

http://thevirtualheart.org/java/neuron/apneuron.html





How to model the Neuron AP mathematically?

Hodgkin-Huxley four variable model

http://thevirtualheart.org/java/neuron/apneuron.html

S2 30,17.6 17.5
13
IS2 -300, -350
-450
N, gna 70, 40

Change Rest Membrane p.
N t=80, gna = 180, 188, 200, 300

How to model the Neuron AP mathematically?

Hodgkin-Huxley four variable model

Even with just 4 variables is hard to understand the dynamics

Ideal to decrease the number of variables to the minimum.

How?

m gate is very fast, make it instantaneous function of Voltage

n ~ 1-h therefore change to an effective variable $w = b - h = a\,n$

$$C\frac{du}{dt} = -g_{Na}[m_0(u)]^3\,(b-w)\,(u-V_{Na}) - g_K\left(\frac{w}{a}\right)^4(u-V_K) - g_L\,(u-V_L)$$

$$\frac{dw}{dt} = \frac{1}{\tau_w}G(u,w)\,,$$

How to model the Neuron AP mathematically?

Hodgkin-Huxley four variable model

Even with just 4 variables is hard to understand the dynamics

Ideal to decrease the number of variables to the minimum.

How?

m gate is very fast, make it instantaneous function of Voltage

n ~ 1-h therefore change to an effective variable $w = b - h = a\, n$

$$\frac{du}{dt} = \frac{1}{\tau}\left[F(u, w) \right]$$

$$\frac{dw}{dt} = \frac{1}{\tau_w} G(u, w) ,$$

The FitzHugh-Nagumo two variable model for neurons

IMPULSES AND PHYSIOLOGICAL STATES IN THEORETICAL MODELS OF NERVE MEMBRANE

RICHARD FITZHUGH
From the National Institutes of Health, Bethesda

ABSTRACT Van der Pol's equation for a relaxation oscillator is generalized by the addition of terms to produce a pair of non-linear differential equations with either a stable singular point or a limit cycle. The resulting "BVP model" has two variables of state, representing excitability and refractoriness, and qualitatively resembles Bonhoeffer's theoretical model for the iron wire model of nerve. This BVP model serves as a simple representative of a class of excitable-oscillatory systems including the Hodgkin-Huxley (HH) model of the squid giant axon. The BVP phase plane can be divided into regions corresponding to the physiological states of nerve fiber (resting, active, refractory, enhanced, depressed, etc.) to form a "physiological state diagram," with the help of which many physiological phenomena can be summarized. A properly chosen projection from the 4-dimensional HH phase space onto a plane produces a similar diagram

$$\frac{du}{dt} = \frac{1}{\tau} [F(u, w)$$

$$\frac{dw}{dt} = \frac{1}{\tau_w} G(u, w) ,$$

$$\frac{\partial V}{\partial t} = \frac{\partial^2 V}{\partial x^2} + (a - V)(V - 1)V - v$$

$$\frac{\partial v}{\partial t} = \epsilon(\beta V - \gamma v - \delta)$$

Biophys. J. Vol 1 445-466, 1961 by R. FitzHugh

The FitzHugh-Nagumo two variable model for neurons

FitzHugh in 1960 made various studies of HH in phase space (fixing values of m,n, h)

Conclusion needed a simpler model to understand the dynamics

He did not do a reduction of HH

Started with Van der Pol relaxation oscillator (1926) and the phase plane model used by Bonhoeffer

$$\ddot{x} + k\dot{x} + x = 0$$

Van der Pol added a damping coefficient

$$\ddot{x} + c(x^2 - 1)\dot{x} + x = 0$$

He used Lineard's transformation

$$y = \dot{x}/c + x^3/3 - x$$

$$\dot{x} = c(y + x - x^3/3)$$
$$\dot{y} = -x/c$$

$\longrightarrow$

Bonhoeffer -Van der Pol (BVP)

$$\dot{x} = c(y + x - x^3/3 + z)$$
$$\dot{y} = -(x - a + by)/c$$

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The FitzHugh-Nagumo two variable model for neurons

$$\frac{\partial V}{\partial t} = \frac{\partial^2 V}{\partial x^2} + (a - V)(V - 1)V - v$$

$$\frac{\partial v}{\partial t} = \epsilon(\beta V - \gamma v - \delta)$$

Four floor to ceiling relay racks,
With vacuum tubes (that failed around twice a week)
And overloaded the air conditining

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The FitzHugh-Nagumo two variable model for neurons

http://thevirtualheart.org/java/fhn24.html

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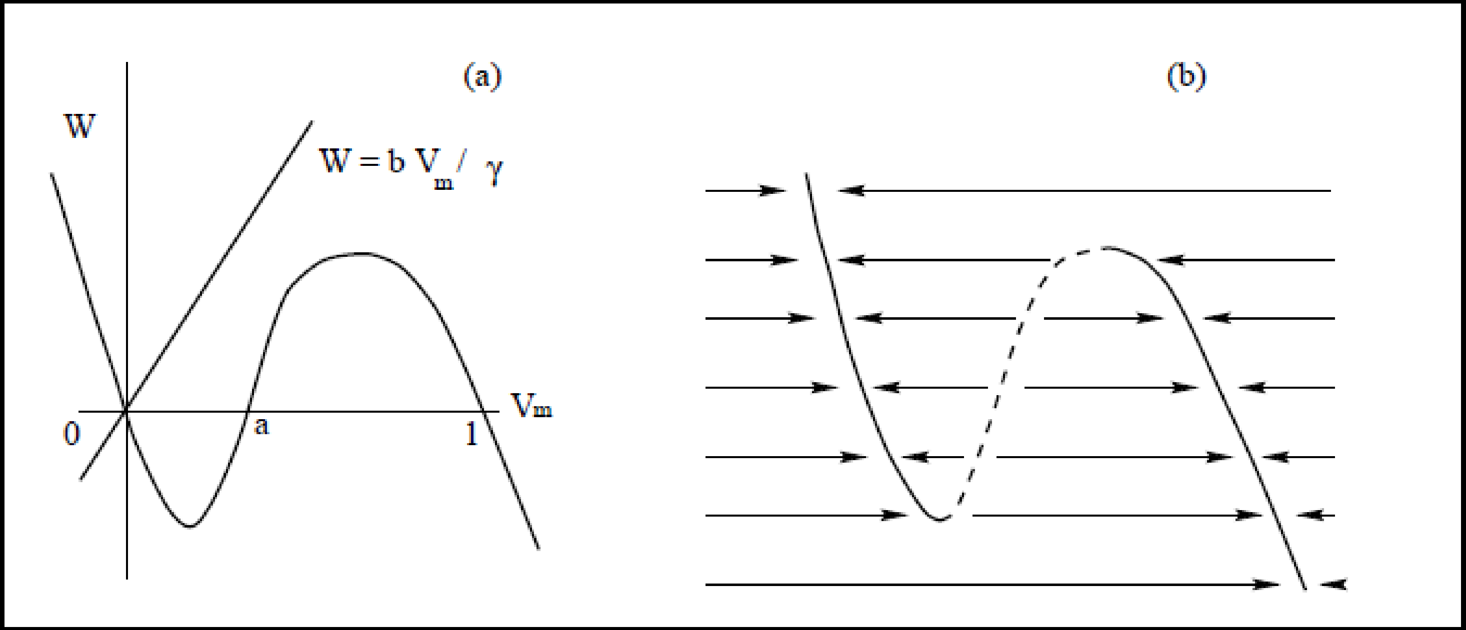
Nullclines and phase space analysis

$$\frac{\partial V}{\partial t} = \frac{\partial^2 V}{\partial x^2} + (a - V)(V - 1)V - v$$

$$\frac{\partial v}{\partial t} = \epsilon(\beta V - \gamma v - \delta)$$



The FitzHugh-Nagumo two variable model for neurons

$$\frac{\partial V}{\partial t} = \frac{\partial^2 V}{\partial x^2} + (a - V)(V - 1)V - v$$

$$\frac{\partial v}{\partial t} = \epsilon(\beta V - \gamma v - \delta)$$

http://thevirtualheart.org/java/fhnphase.html

Phase space:

a .1 .2 .3 .4
.5
Delta .2,.1.5,1.

Eps .01 .02
.03 .04

Eps .01 .005 .002
.001

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The FitzHugh-Nagumo two variable model for neurons

http://thevirtualheart.org/java/fhn25.html

S2 10,9,8,7

a .1 .2 .3 .4 .5
Delta .2,.1.5,1.

Also by
a =-.1
S2 =0

Eps .01 .02 .03 .04

Eps .01 .005 .002 .001
S2 larger

Eps .0001
T 700
S2 464 463

T2000
S2 600, 900 1000 1500

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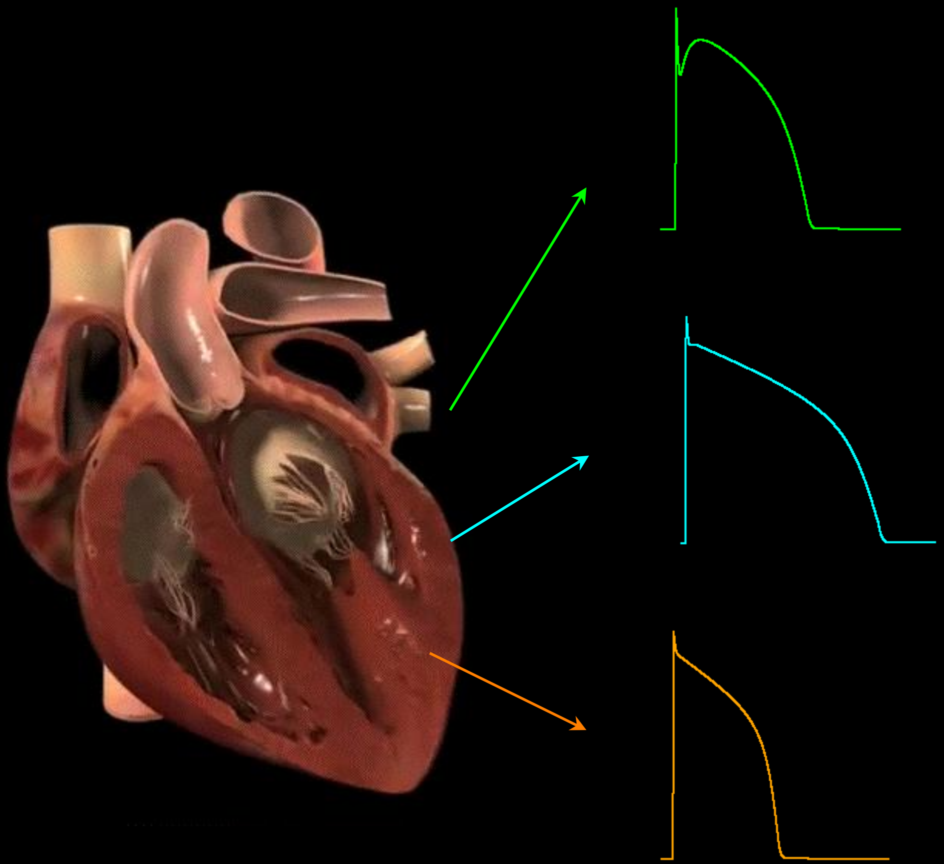
Dynamics of FHN model > 2 h class

Cell models
(for different animals and cell types)



Early Models

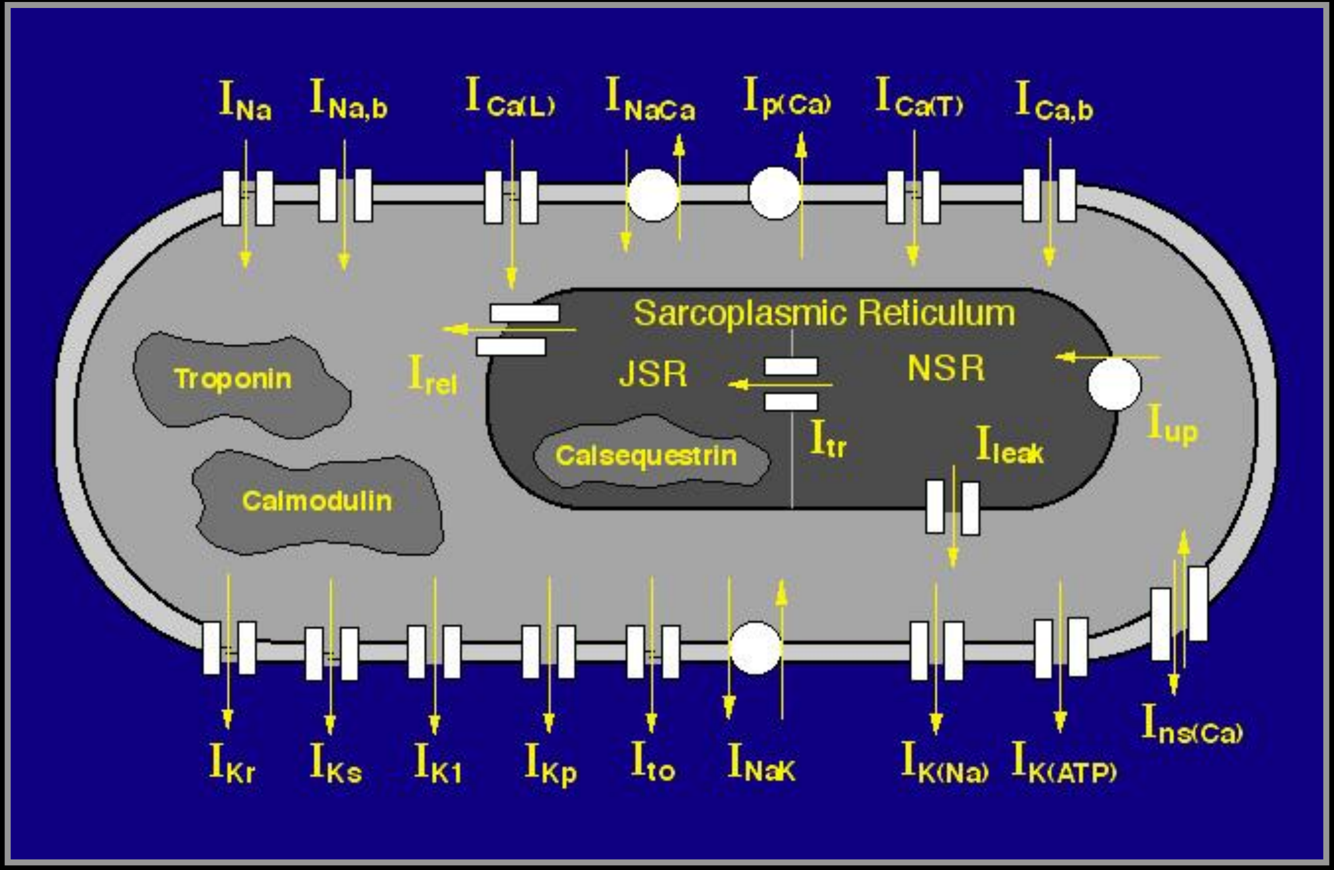
Examples:

- Noble model (1964) (first cardiac model, based on HH model)

  4 variables. 3 currents.

- Beeler-Reuter (1977), Luo-Rudy 1 (1991) 8 vaiables.
- Primary currents:
  - I_{Na}: responsible for upstroke
  - I_{Ca}: responsible for plateau
  - I_K: time-dependent and time-independent components responsible for repolarization
  - Background currents to balance things out (masking unknowns).

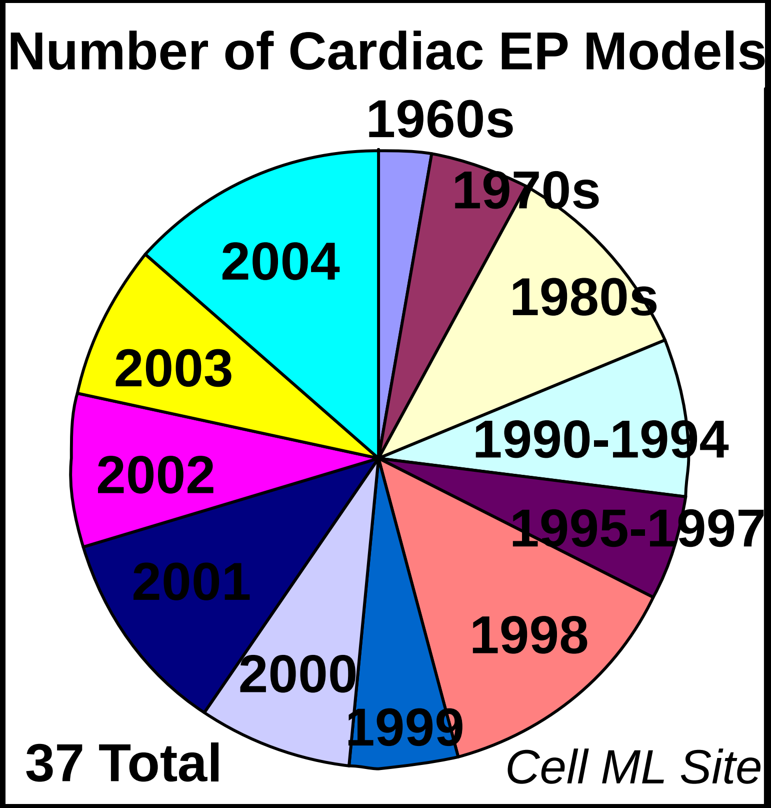
Modeling Cellular Electrophysiology has become more and more complex



Getting very complex:
87 ode + others for stress activated ion channels + contraction equations

Models, Models Everywhere

- Surge in development of models of cardiac myocyte EP over the last 5-10 years.
- 37 models included on Cell ML website through 2004 (not inclusive)
- ~1/3 in most recent 3 years.
- Multiple models for same species/region.



Java applets of 45 different cardiac EP models at scholarpedia (models of cardiac cell)
Google : cell models scholarpedia

Many Models for Different Cell Types and animals

Implemented most (~40) of the published models in single cells and in tissue.