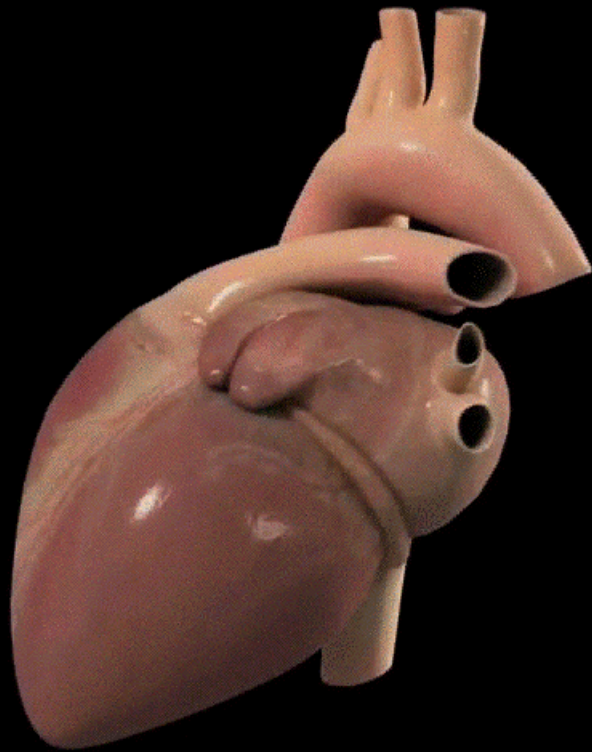# 2013 NSF-CMACS Workshop on Atrial Fibrillation

Flavio H. Fenton

School of Physics
Georgia Institute of Technology, Atlanta, GA
and
Max Planck Institute for Dynamics and
Self-organization, Goettingen, Germany

Lehman College,
Bronx, NY. Jan 14-17, 2013

Outline

- Motivation
- Overview of Excitable Systems
- Cardiac dynamics as an excitable system
- Chaos and tools from nonlinear dynamics can be used to study cardiac arrhythmias.
- Modeling cardiac dynamics
- Initiation, dynamics and instabilities of spiral waves
- Defibrillation and new methods to control arrhythmias using control methods from Chaos theory.
- Get you ready for your projects

Motivation

Heart disease is one of the leading causes of death in the world.

Ranks number one in industrialized countries.

In the USA alone:

- 1 in 5 have some form of heart disease.
- 4.5 million do not die but are hospitalized every year.
- Economic impact: $214 billion a year.
- 1/3 of total deaths are due to heart disease.

As computer science, Mathematics & Statistics and Biology majors : This is a great excitable system with a broad range of dynamical states where you can apply your area of expertise and have an impact, as there are countless of remaining exciting open questions .
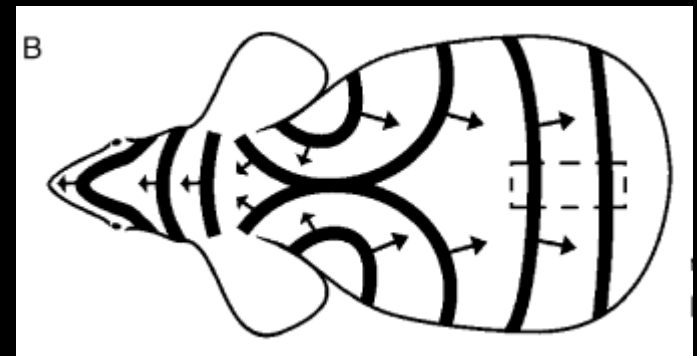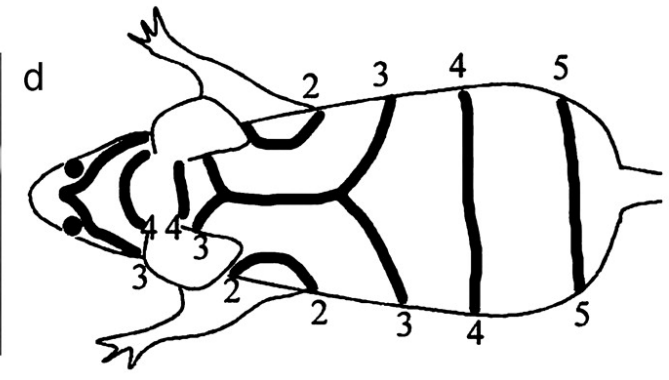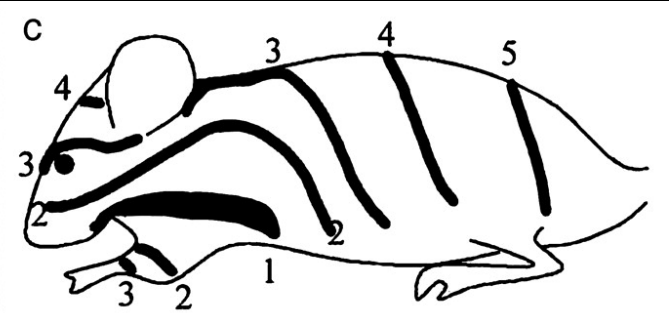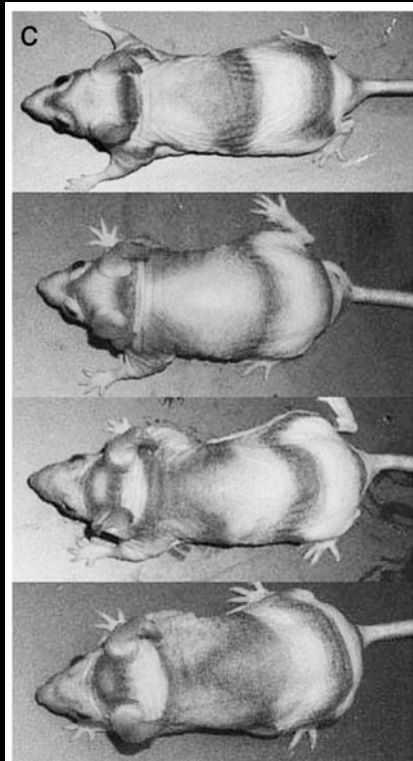
Nonlinear Dynamics: Complex Systems and Pattern Formation

Examples
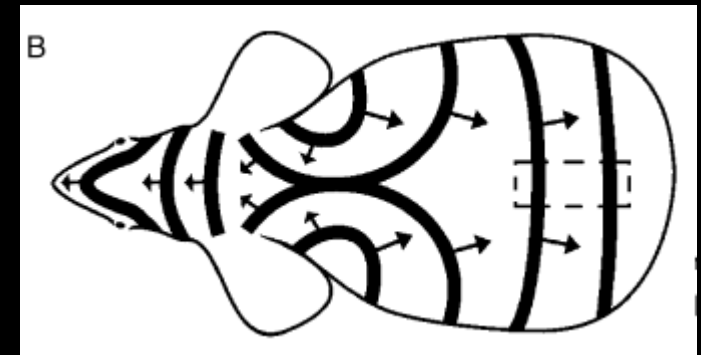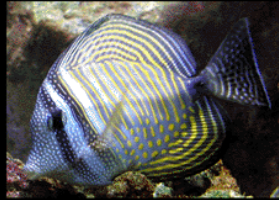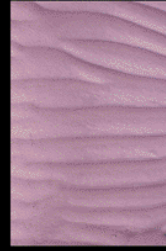
Nonlinear Dynamics: Complex Systems and Pattern Formation

What are excitable systems?

Excitable media can be defined as a system
formed by segments or elemental cells, each
of which has the following properties:

- A well defined steady state (or rest state)
- A threshold for excitation
- An excitation that only a function of the system and independent of the stimulus.
- A refractory period following excitation
- A diffusive coupling with near neighbors (in space)

They can be: Physical, biological, mechanical, electrical, mathematical, chemical, …   and they can lead to chaos.

What are excitable systems?

Example: Mexican Wave

What are excitable systems?

Example: Forest fires

Good example to understand refractory period and collision between waves. (not solitons)

Problem: very long wave length, even longer refractory period

What are excitable systems?

Example: Toilet
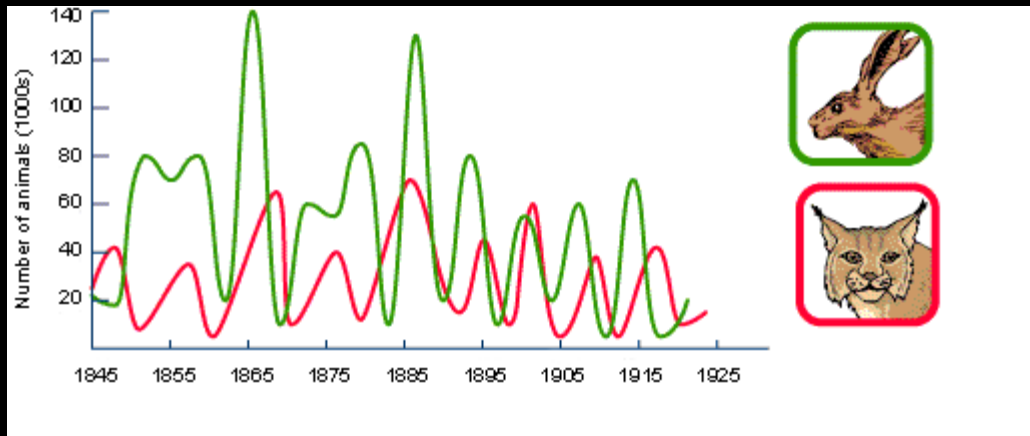
Probably best example: Threshold,
                              Excitation (that is independent of the stimulus)
                              Refractory period
Extras: complex dynamics such as alternans.
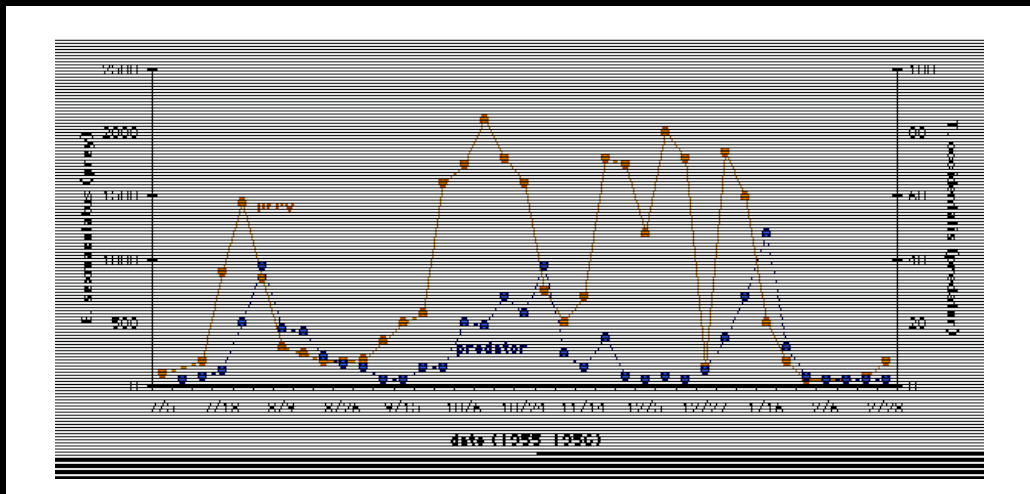Problems: Only good for 0D, difficult to couple in higher dimensions.

What are excitable systems?

Example: Predator-Pray (oscillators)

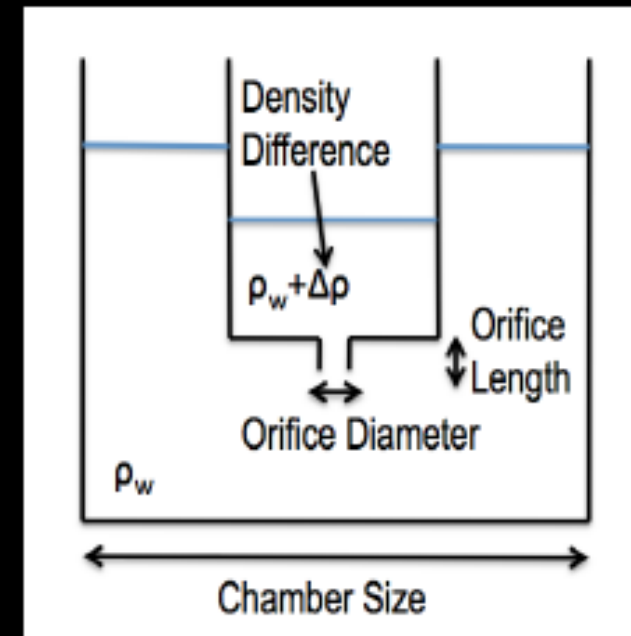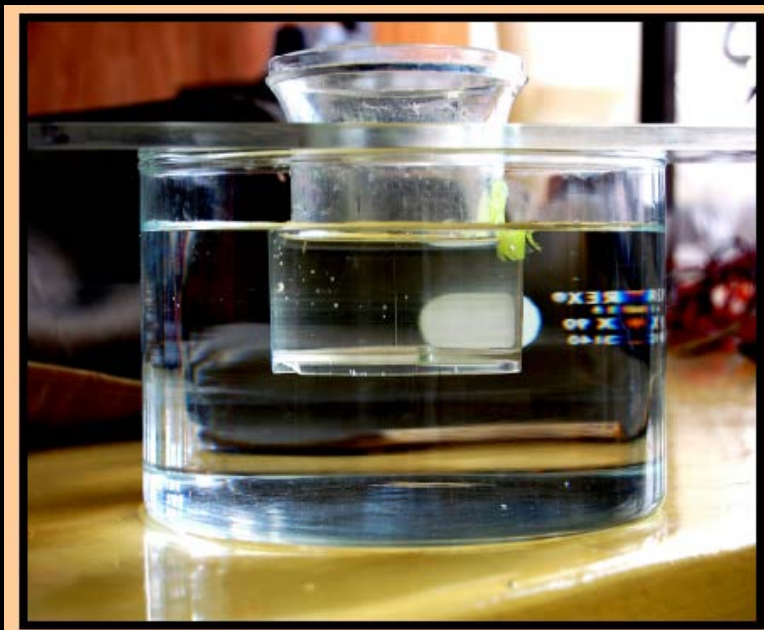Oscillators can be a subclass of Excitable media.

Very useful to understand qualitatively their dynamics

Huffaker (1958) reared two species of mites to demonstrate these coupled oscillations of predator and prey densities in the laboratory. Using *Typhlodromus occidentalis* as the predator and the six-spotted mite (*Eotetranychus sexmaculatus*) as the prey

What are excitable systems?

Example: Saline oscillator (also density oscillator)

Density Difference

$\rho_w + \Delta\rho$

Orifice Length

Orifice Diameter

ρ_w

Chamber Size

(a) EXPERIMENT

0.51T$_O$

2:2

1:1

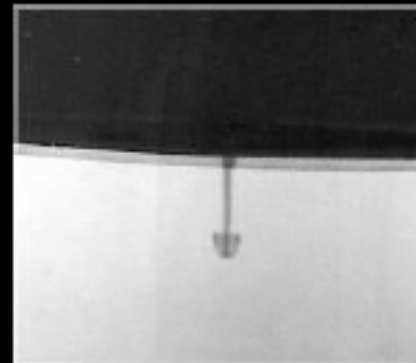Voltage (mV)

40

0

0   100   200   300
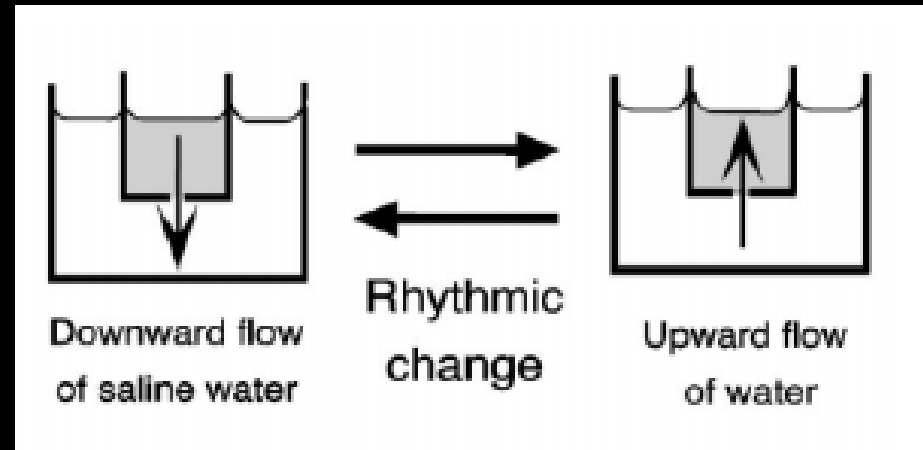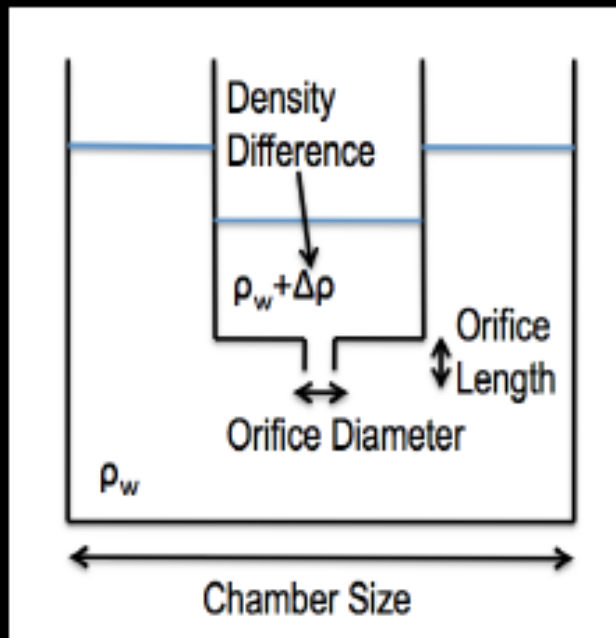
(b)

Oscillators can behave as excitable systems when externally excited at frequencies higher than their Natural oscillation.
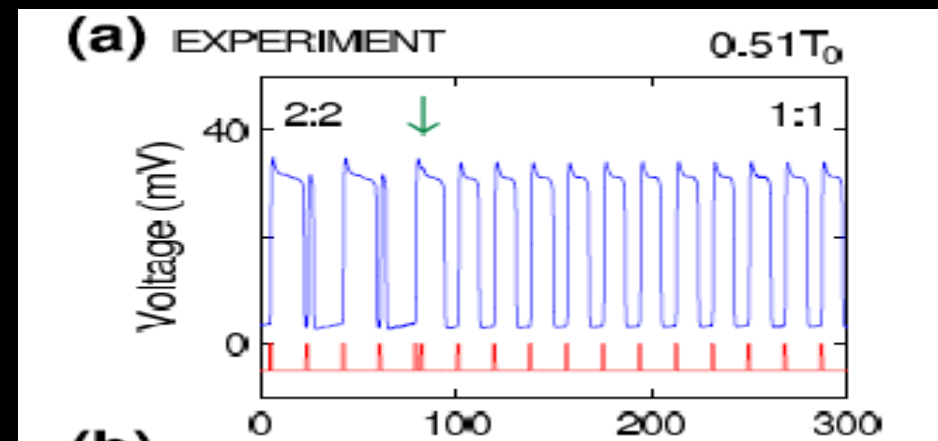
Complex Systems and Pattern Formation

One of the simplest system with complex dynamics

(and the cheapest!)

the Saline Oscillator

Complex Systems and Pattern Formation

One of the simplest system with complex dynamics

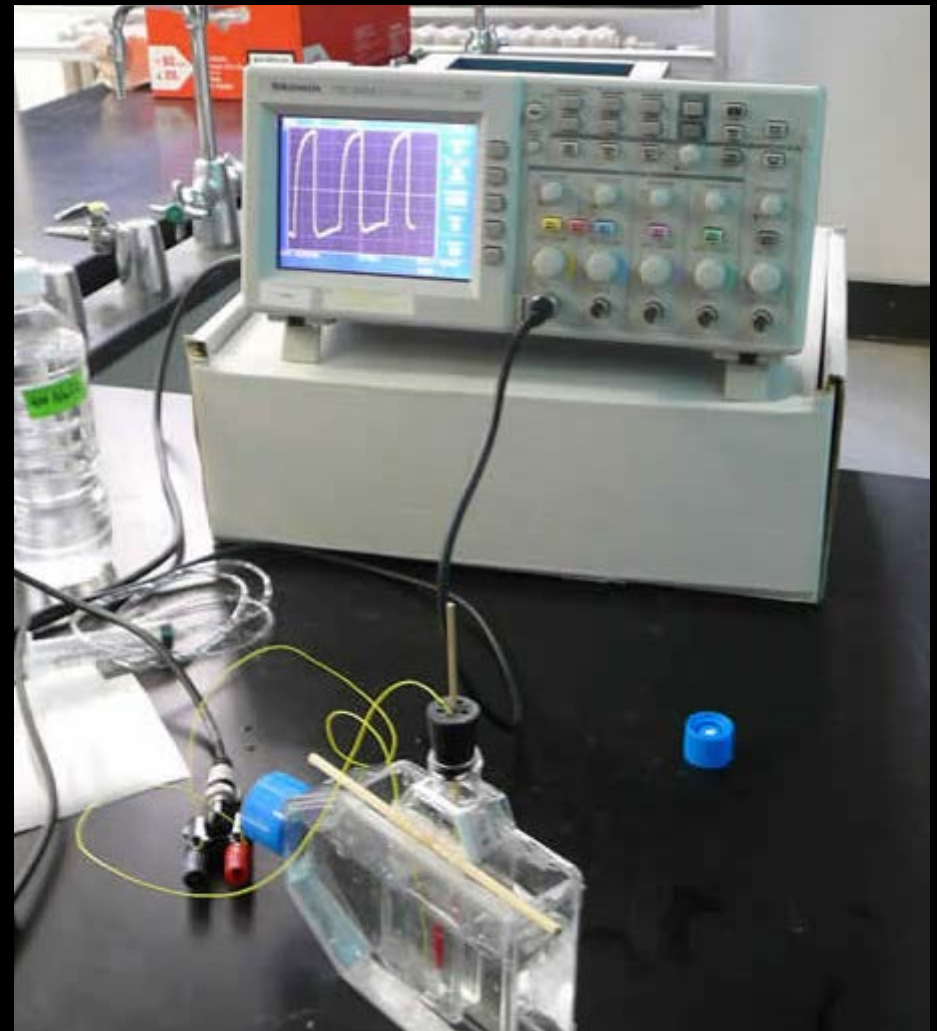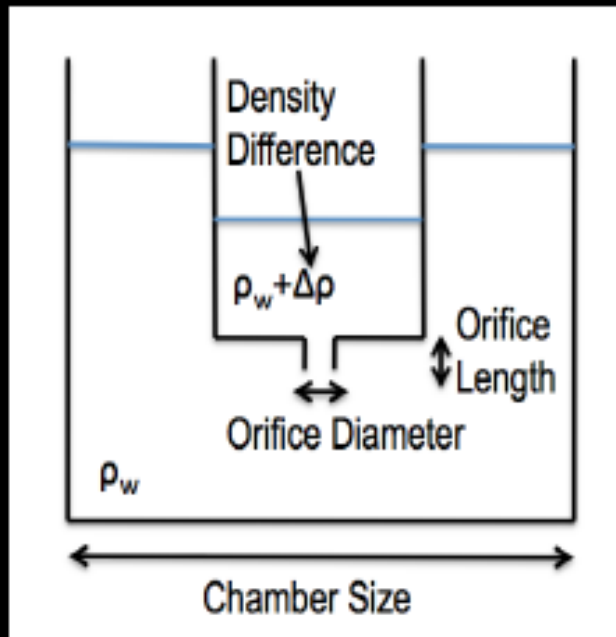(and the cheapest!)

the Saline Oscillator

Complex Systems and Pattern Formation

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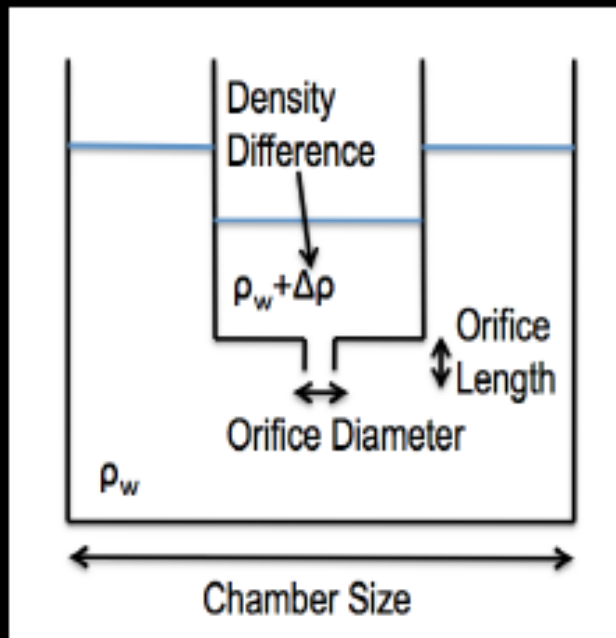
We get to play
with them today!

What are excitable systems?

Example: Chemical oscillators
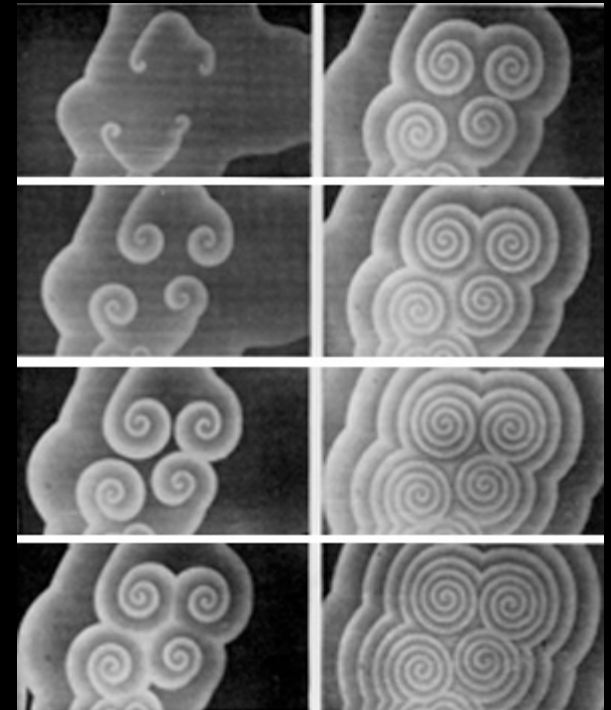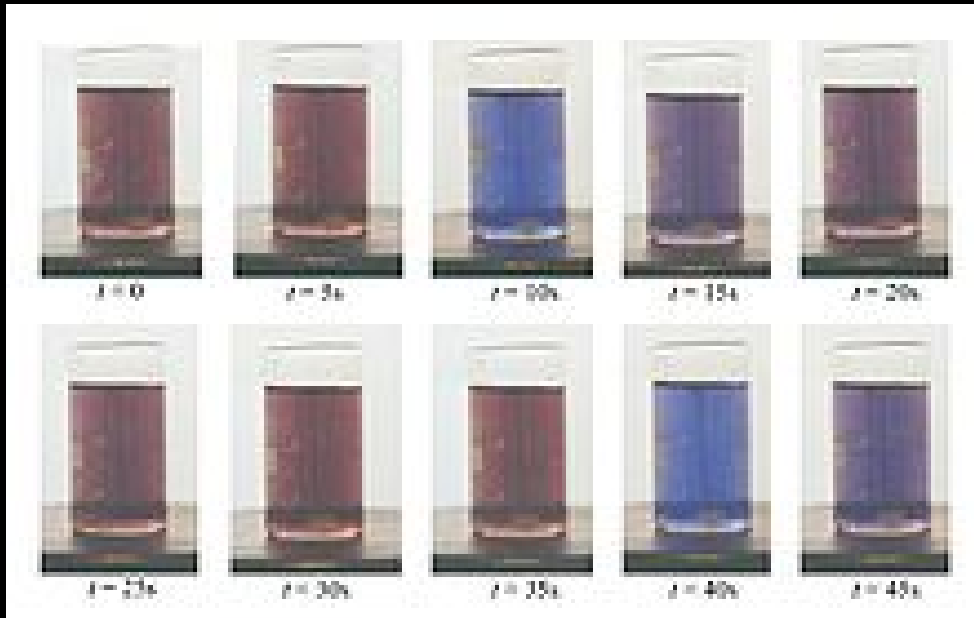
Many types of chemical reactions that oscillate and have interesting dynamics in space.

We get to play with them tomorrow!

What are excitable systems?

Example: excitable biological cells

Neurons
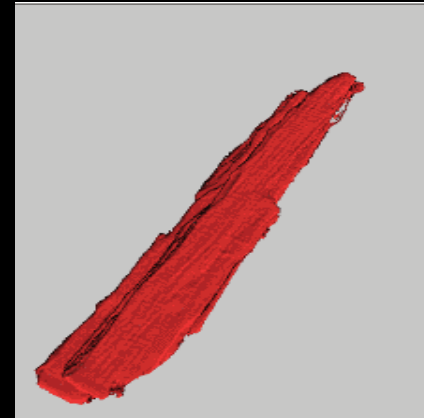
Myocites (cardiac cells)

In these systems, the excitability is a change in voltage

We get to study them the rest of the workshop!

Excitable Biological Cells

In these cells, the voltage is a consequence of a gradient in the cellular membrane due to a difference in concentrations of ions inside and out-side of the cell.
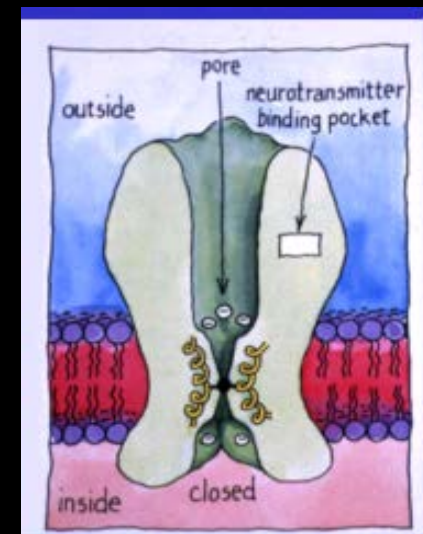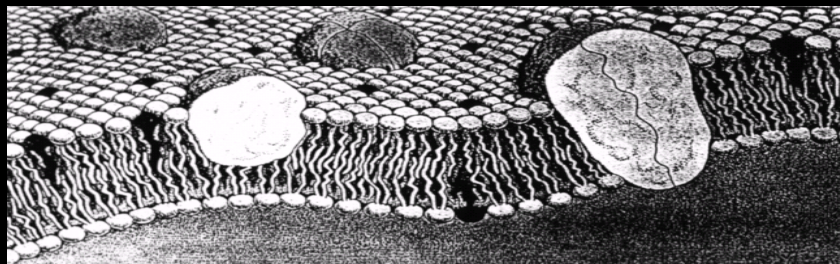
Excitable Biological Cells

The difference in electric potential is a consequence of the intracellular and extracellular ion concentrations.
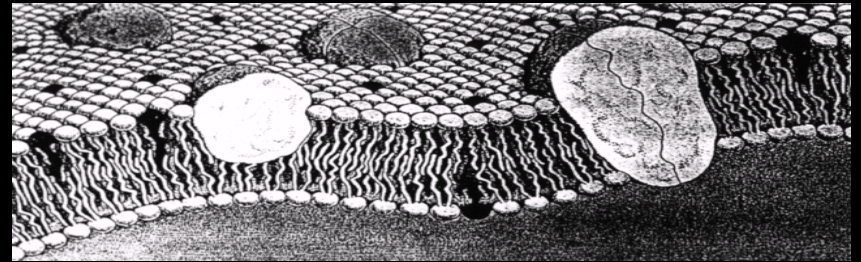
Excitable Biological Cells

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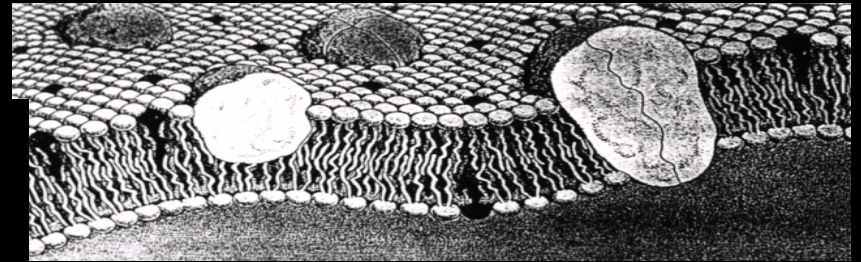
LINK to applet

Resting membrane potential
(Steady State)

Electrical Activity in Cells

How does electricity play a role ?

- The cell membrane: lipid bi-layer 10 nm thick, impermeable to ions except through specialized proteins (ion channels).
- Ion concentration gradient and voltage drop across membrane.
- Movement of ions across the membrane produces an action potential.
- Active transport through pumps and exchangers in the membrane restores original concentrations.
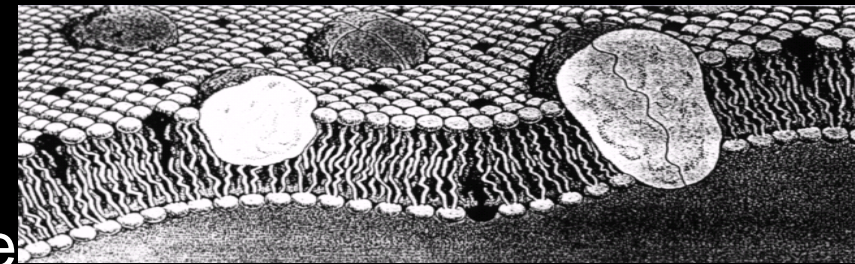
Electrical Activity in Neurons

Na+, K+ ,
Cl-,
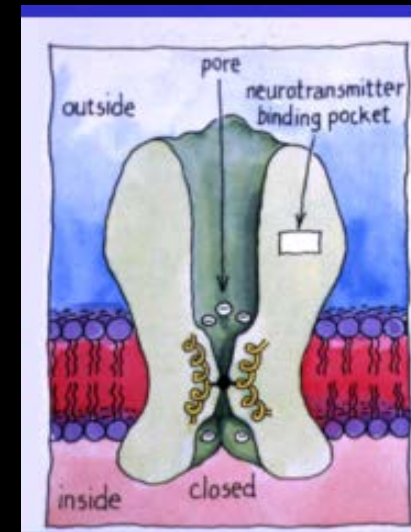
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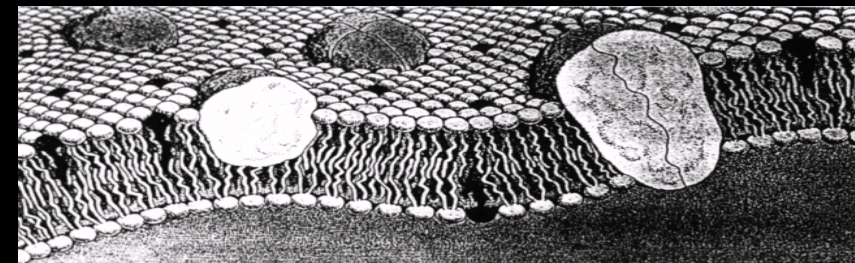
Electrical Activity in Neurons

Transfer of information is the main consequence of electrical activity in neurons.
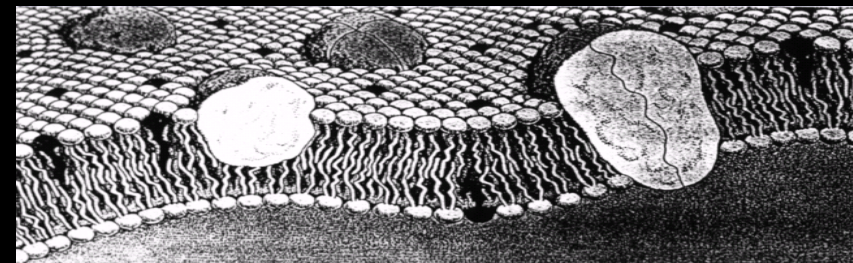
Electrical Activity in Myocites

How does electricity play a role in the heart ?

- Cardiac cells are about 100-150 μm in length, 10-20 μm in diameter.
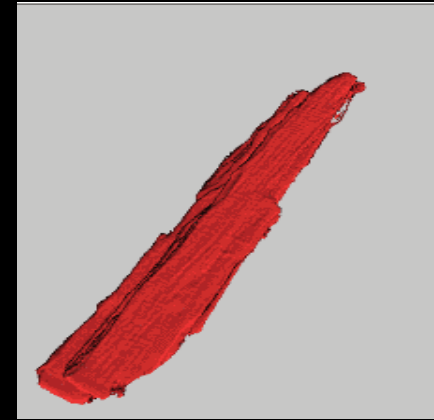
Electrical Activity in Myocites

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

Link to applet

Electrical Activity in Myocites

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

$$\frac{dV}{dt} = \sum I_i$$

$$I_i = g_i \cdot (V - E_i)$$

$$g_i = f(V, t)$$

I_{NaCa} $I_{Na,b}$ I_{Ca} $I_{Ca,b}$ I_{Na} I_{NaK}
Na⁺   K⁺

Ca²⁺   Na⁺

J_{leak}

$J_{release}$

SR

$J_{p(Ca)}$

Pump
Exchanger
Voltage-gated ion channel
Non-voltage-gated ion channel

I_{to} I_{K1} I_{Kr} I_{Ks} I_{Kp} $I_{Ca,K}$ $I_{p(Ca)}$

outside   pore   neurotransmitter binding pocket

inside   closed
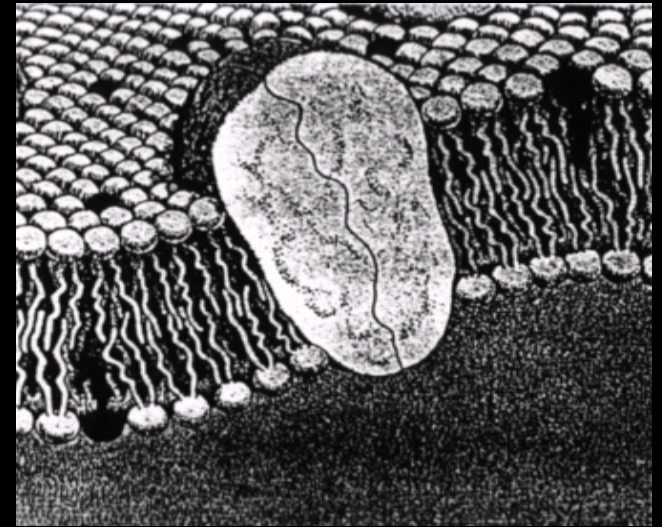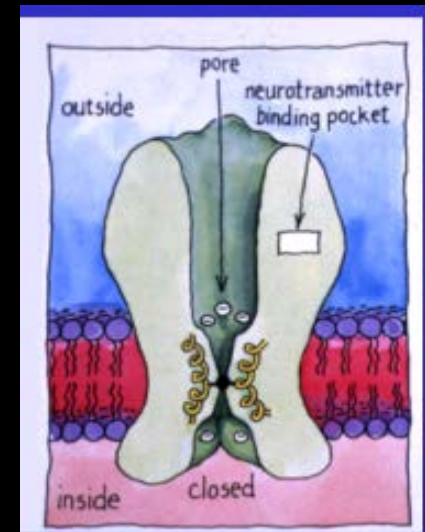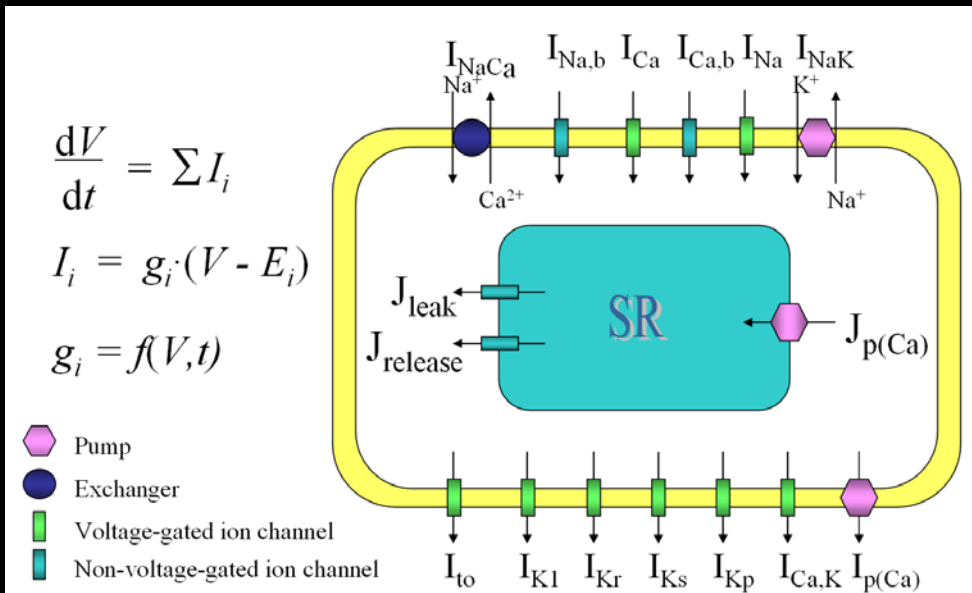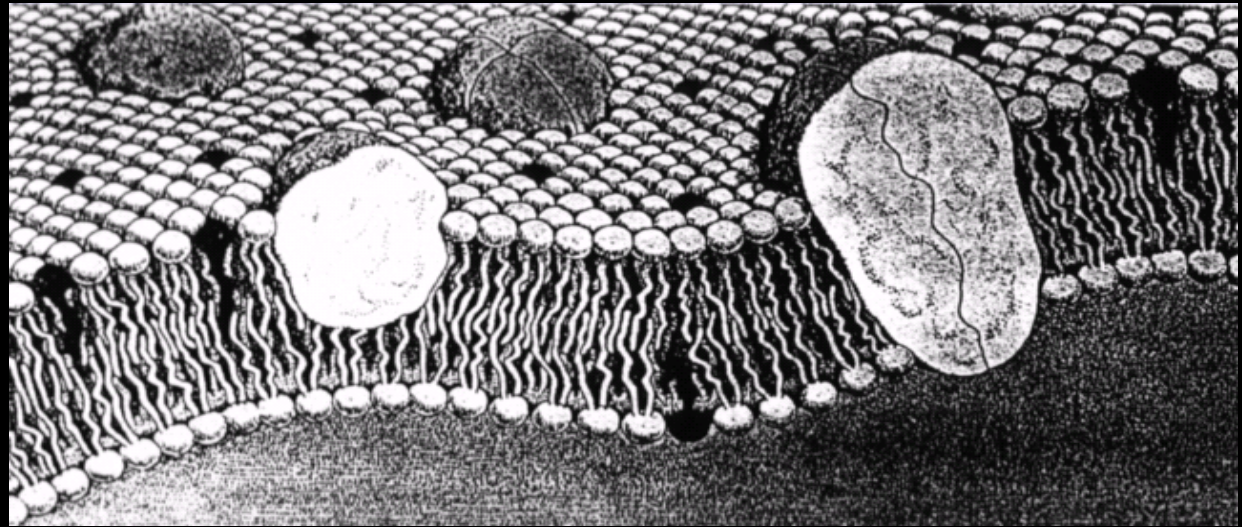
Electrical-Contraction Coupling

- Cellular action potential triggers contraction through calcium processes.

- Increased calcium current stimulates release of intracellular store.

- Transiently increased calcium binds to contraction proteins.

myosin

Bind [Ca]$^{++}$

actin
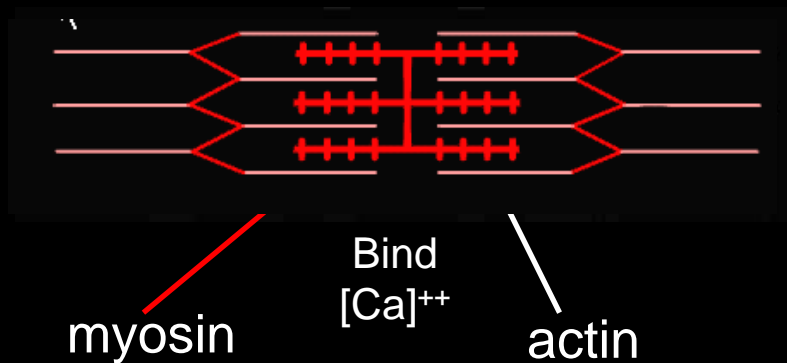
Contraction of the heart occurs because the electrical AP propagate as waves thought the heart.

Electrical Waves in Tissue

Cells connected
in a 2D preparation
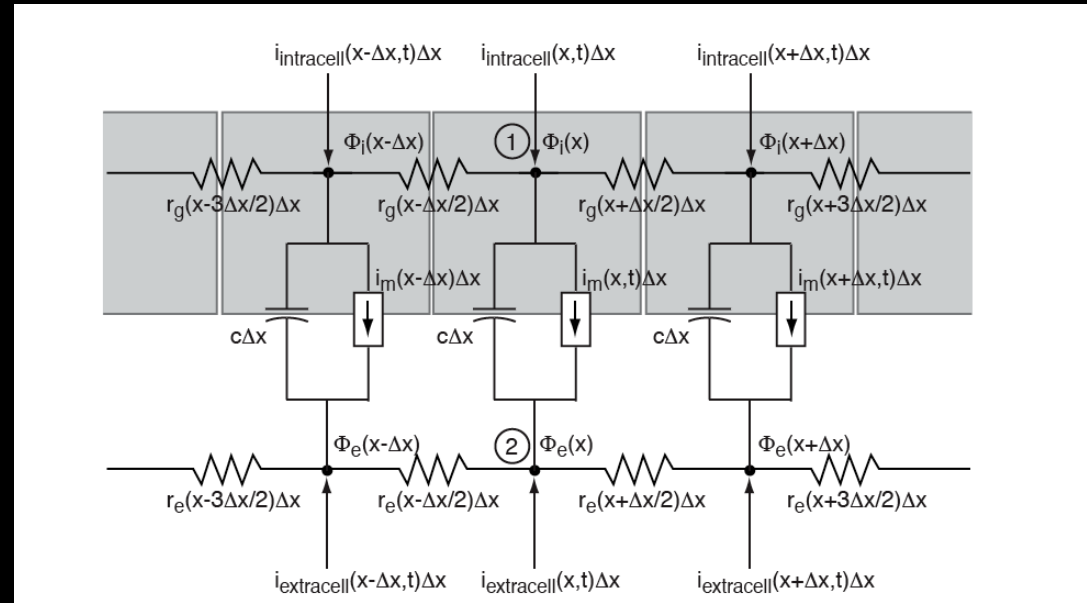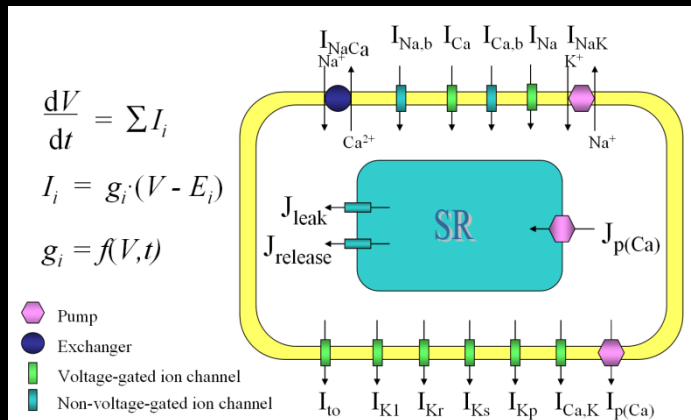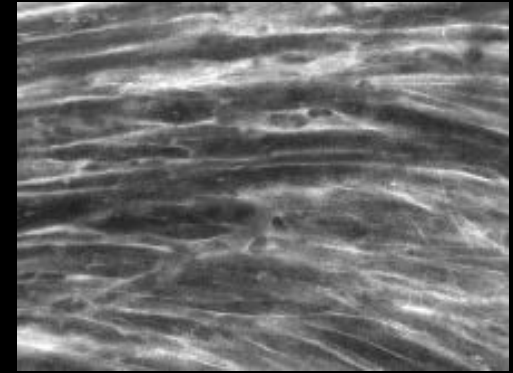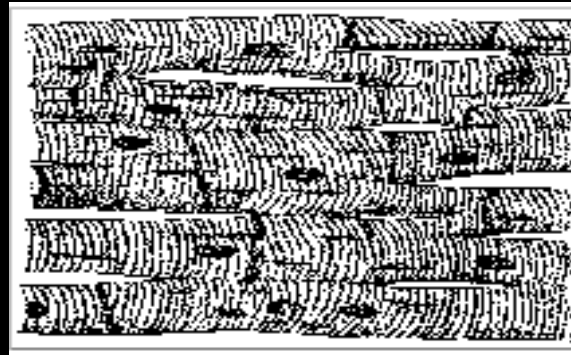
$$C_m \partial V / \partial t = \nabla \cdot D \nabla V - I_{ion}$$

Sum of the ionic currents that make up the action potential.

Tissue connection and structure information is given by the diffusion coefficient D.

The first mathematical model of electrical AP

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

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

Electrical Activity in Myocites

Ca²⁺, Na⁺, K⁺
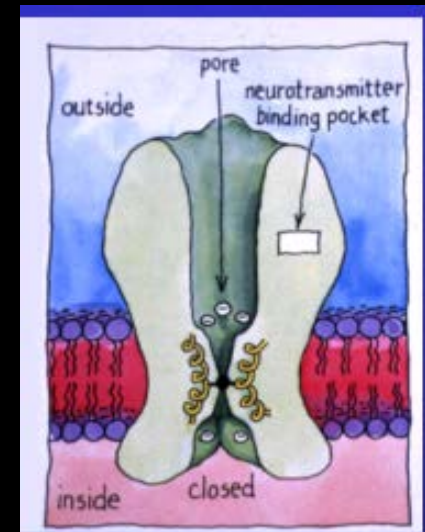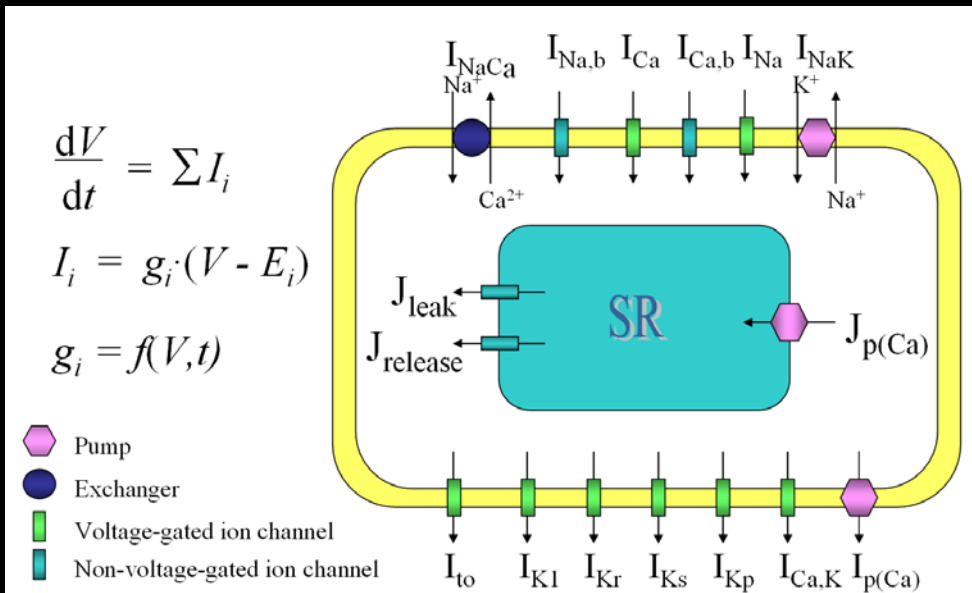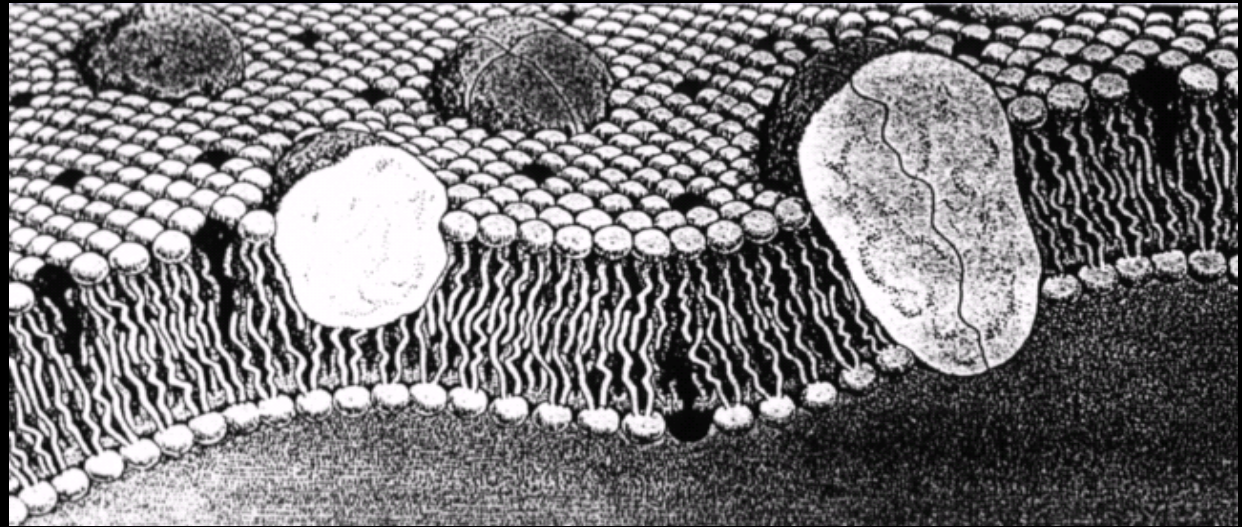
How to model the Neuron AP?

The Hodgkin-Huxley model of four variables for neurons
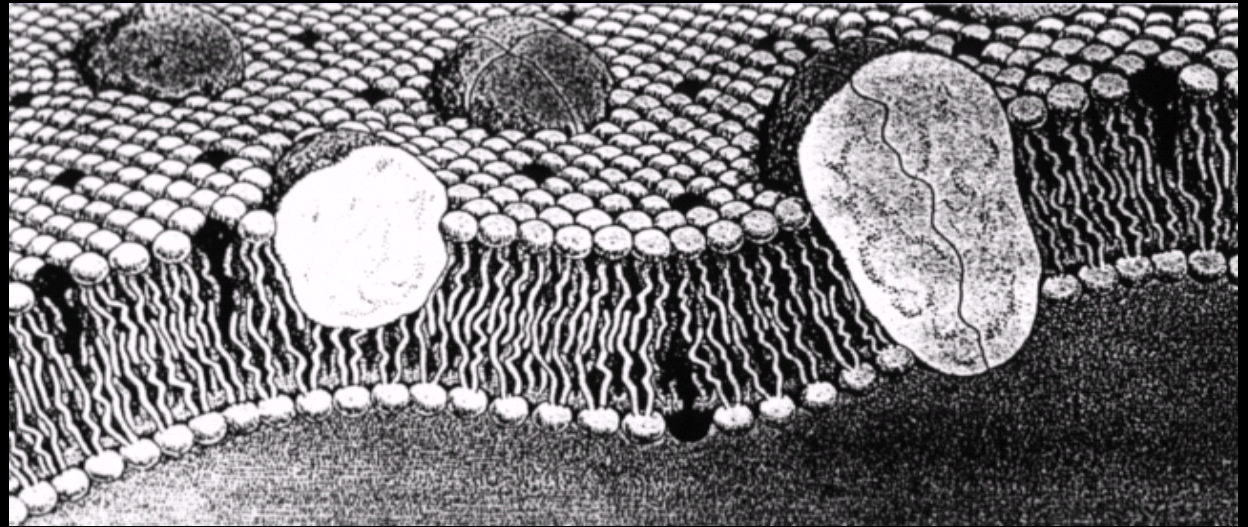
Capacitance is a measure of the amount of electrical energy stored (or separated) for a given electric potential, where $C = Q/V$

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

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

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

$\alpha_y(V_m)$

$\beta_y(V_m)$

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

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

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

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:

$$\frac{dy}{dt} = \frac{y_\infty - y}{\tau_y}$$

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

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Ecuaciones para la probabilidad de las puertas

$$\alpha_y(V_m)$$

$$\beta_y(V_m)$$

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$$\beta_n = 0.125\, e^{(-(V_m+60.0)/80.0)}$$

How to model the Neuron AP mathematically?

Hodgkin-Huxley four variable model

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

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

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

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

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

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

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

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

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

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

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

Bonhoeffer -Van der Pol (BVP)

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

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 conditing

The FitzHugh-Nagumo two variable model for neurons

Nullclines and phase space analysis

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

$$\frac{\partial v}{\partial t} = \epsilon(\beta V - \gamma v - \delta)$$
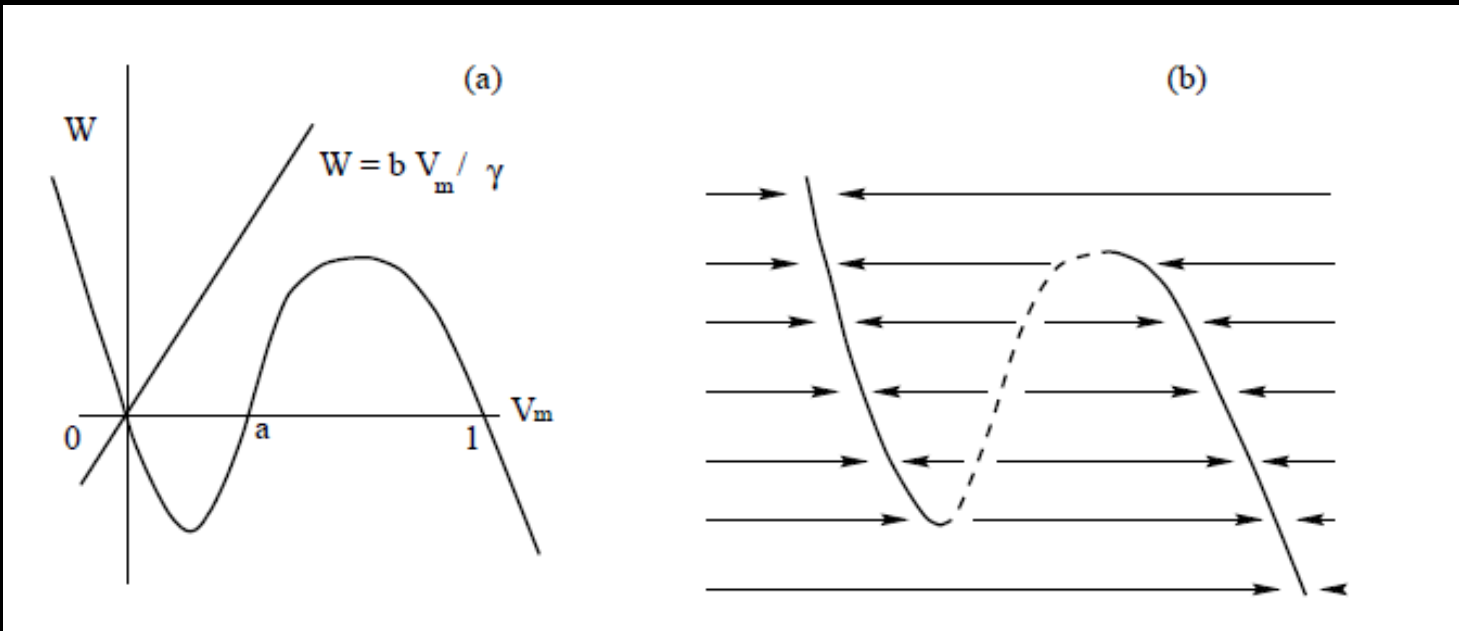
The FitzHugh-Nagumo two variable model for neurons

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

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

Phase space:

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

Eps .01 .02 .03 .04

Eps .01 .005 .002 .001

The FitzHugh-Nagumo two variable model for neurons

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

Dynamics of FHN model > 2 h class