Modelling of physiological and pathological processes

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Lecture 2

A cell must:

•Keep its integrity
•I/O

How?

The answer is:

Membranes with “smart” I/O ports
a.k.a. Ion Channels

What are they?
Ion channels are membrane-bound cellular proteins that permit the flow of ions, including calcium, potassium, sodium, and chloride, into and out of cells.

Where are they?
Ion channels are present in all human cells and effect such vital functions as nerve transmission, muscle contraction, and cellular secretion, to name a few.

Dynamical Systems Theory:

A set of concepts, theorems and tools that allow a unified view of the physical world, both in terms of processes and in terms of systems

Areas of application:

Mathematics
Physics
Chemistry
Biology
Medicine

Zoology
Finance
Economics
Meteorology
Seismology
Genetics
Controls
Electronics
Polymers
Geophysics

Fluid & Plasma Mechanics
Cosmology
Communications
Cardiology
Linguistics
Materials
Optics
Hydrology
Oceanography

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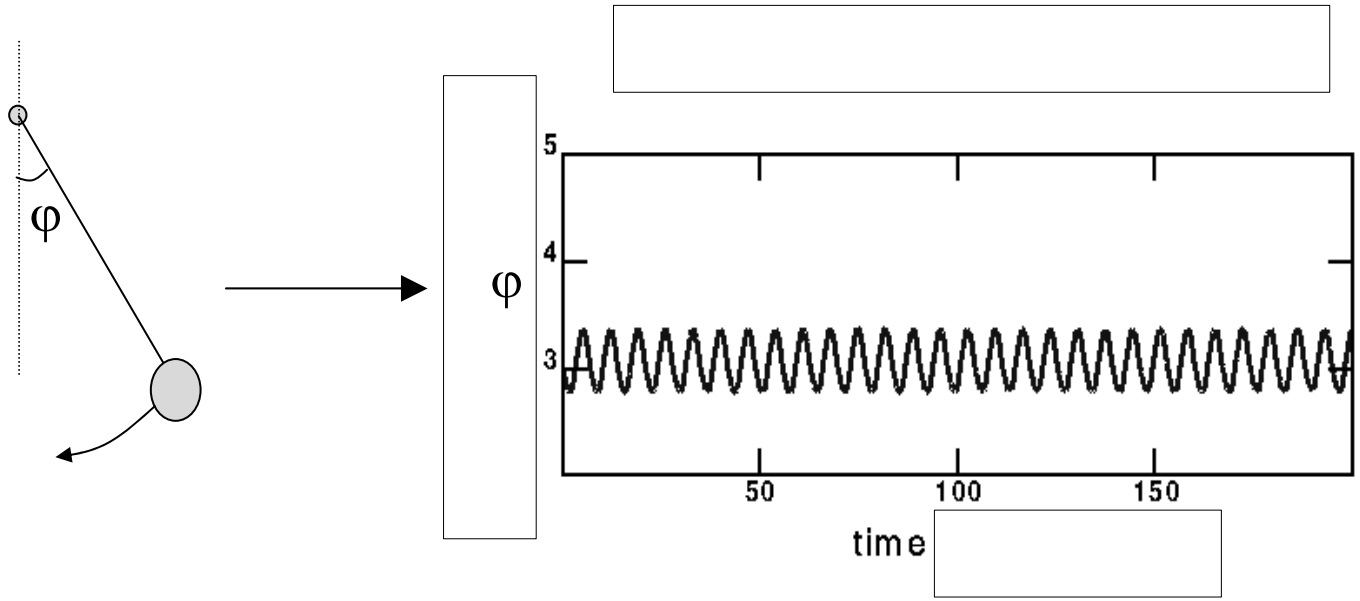
The concept of the Degree of Freedom (DOF)

Assume small angles, perfectly stretched, straight, inelastic and unbreakable string, planar oscillation, constant gravity etc., etc…

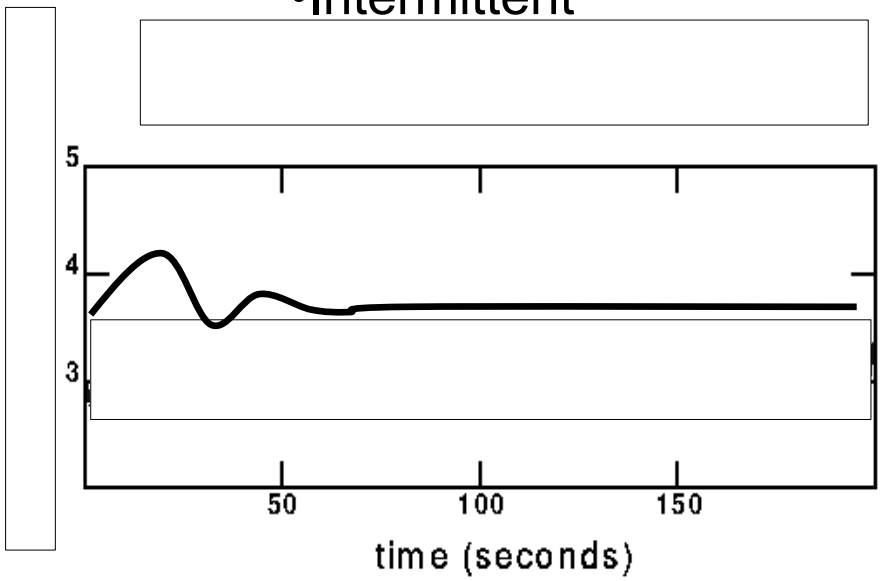


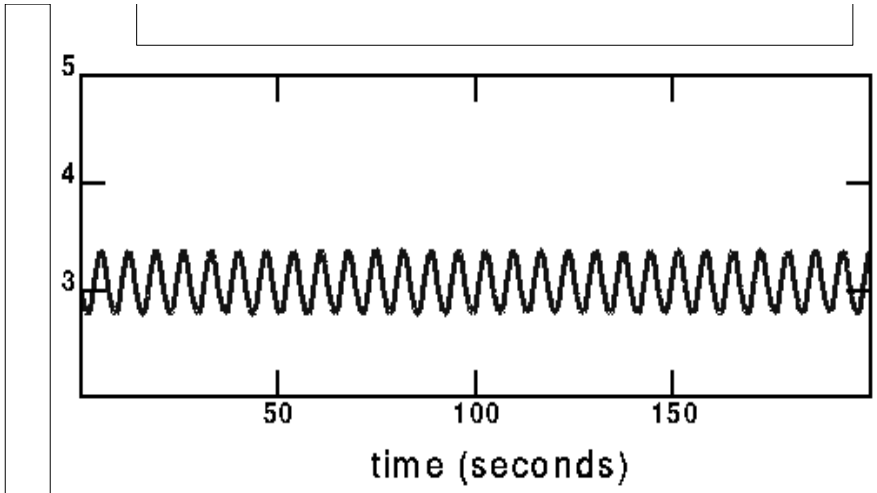
In terms of visualization:
One “variable”, one observable, one degree of freedom: Easy
Two observables: Also easy
Three observables: Easy, with 3D graphics (Lorenz, Ion etc.)

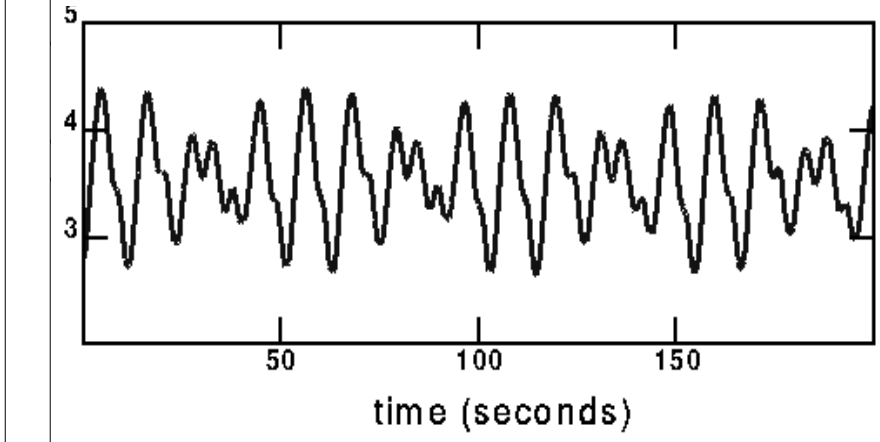
Similarly easy in terms of extracting quantitave information

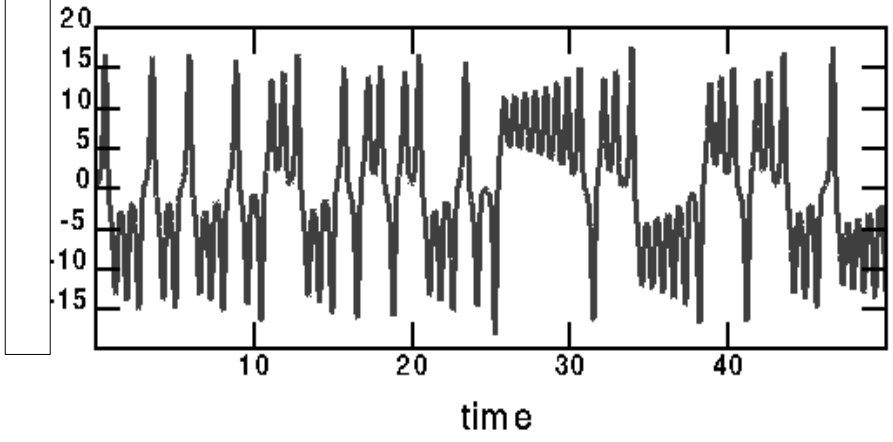
States of a system:

- Steady
- Periodic
  - Single Frequency
  - Many Frequencies
- Quasiperiodic
- Chaotic
  - Intermittent









Generalization of this concept:

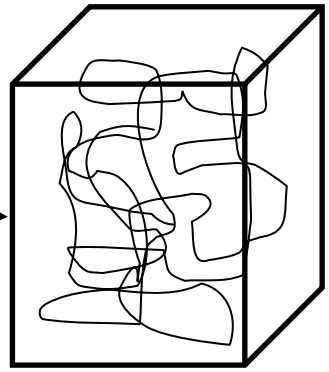
***Phase space* (or state space)**

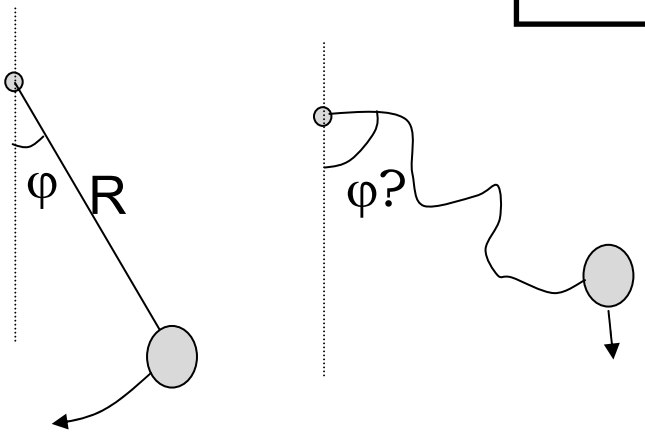
The space (physical or functional) that holds all the possible (and impossible) states or conditions of a system

Two simple examples:

•Fly buzzing in a room (R3)

•Pendulum (?)

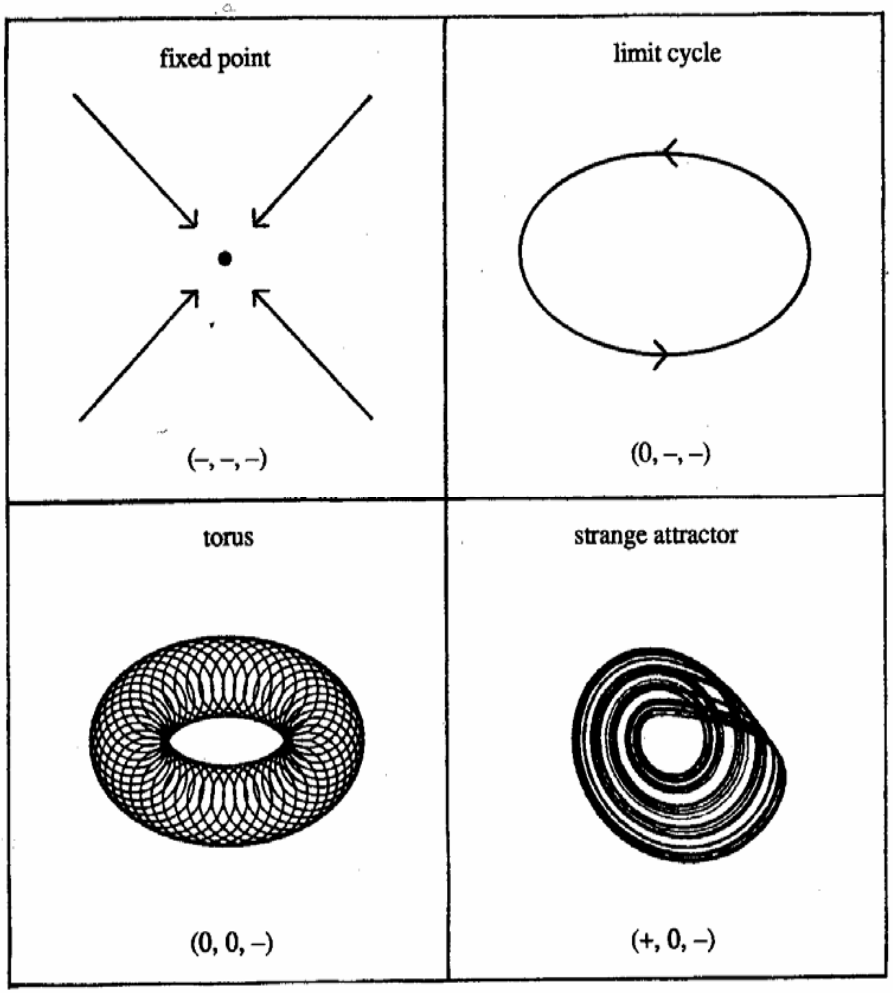




Phase space, or state space:

The “domain” where the state of the system lives!

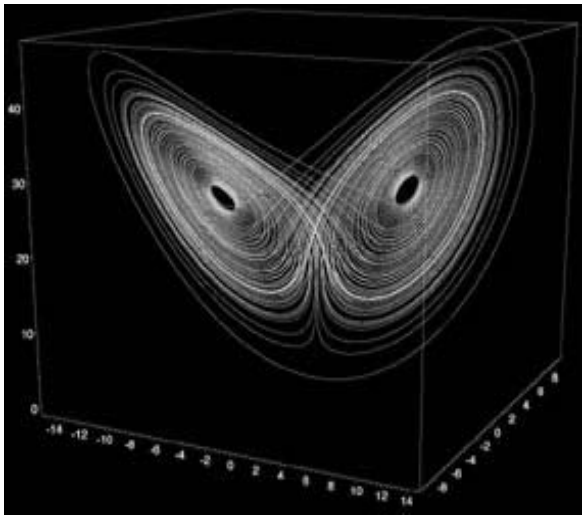
A set, with properties dependent on the nature of the system, that includes a subset corresponding to the loci of the attainable conditions of the system.



A more complex (?) example:

Edward Lorenz, a meteorologist, modeled atmospheric conditions. Starting from the full equations and after serious truncation and simplification, he obtained a system of three differential equations:

$$dx/dt = -10x + 10y$$
$$dy/dt = 28x - y - xz$$
$$dz/dt = -(8/3)z + xy$$



The butterfly shaped “attractor” known as the Lorenz attractor is generated by plotting x-y-z for these equations, which exhibit chaotic behavior. Lorenz saw that slight differences in one variable had profound effects on the outcome of the whole system, a result of "sensitive dependence on initial conditions".
To illustrate what this means, Lorenz is reputed to have said that a butterfly flapping its wings in the Amazon could cause a hurricane in the Caribbean. This sensitivity is now called the "butterfly effect".

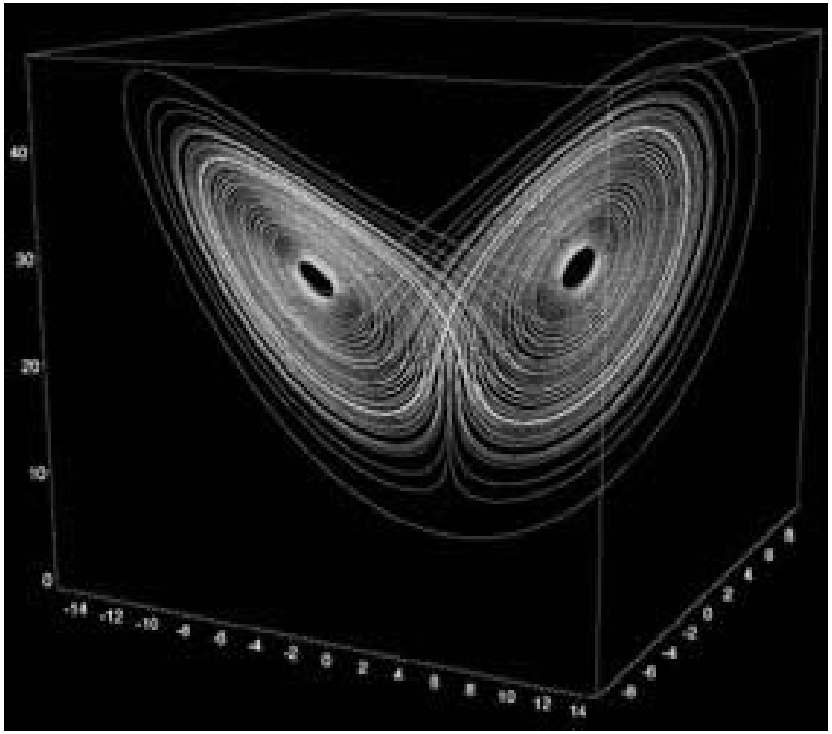
Sensitive dependence from initial conditions: The (re)discovery of E. Lorenz

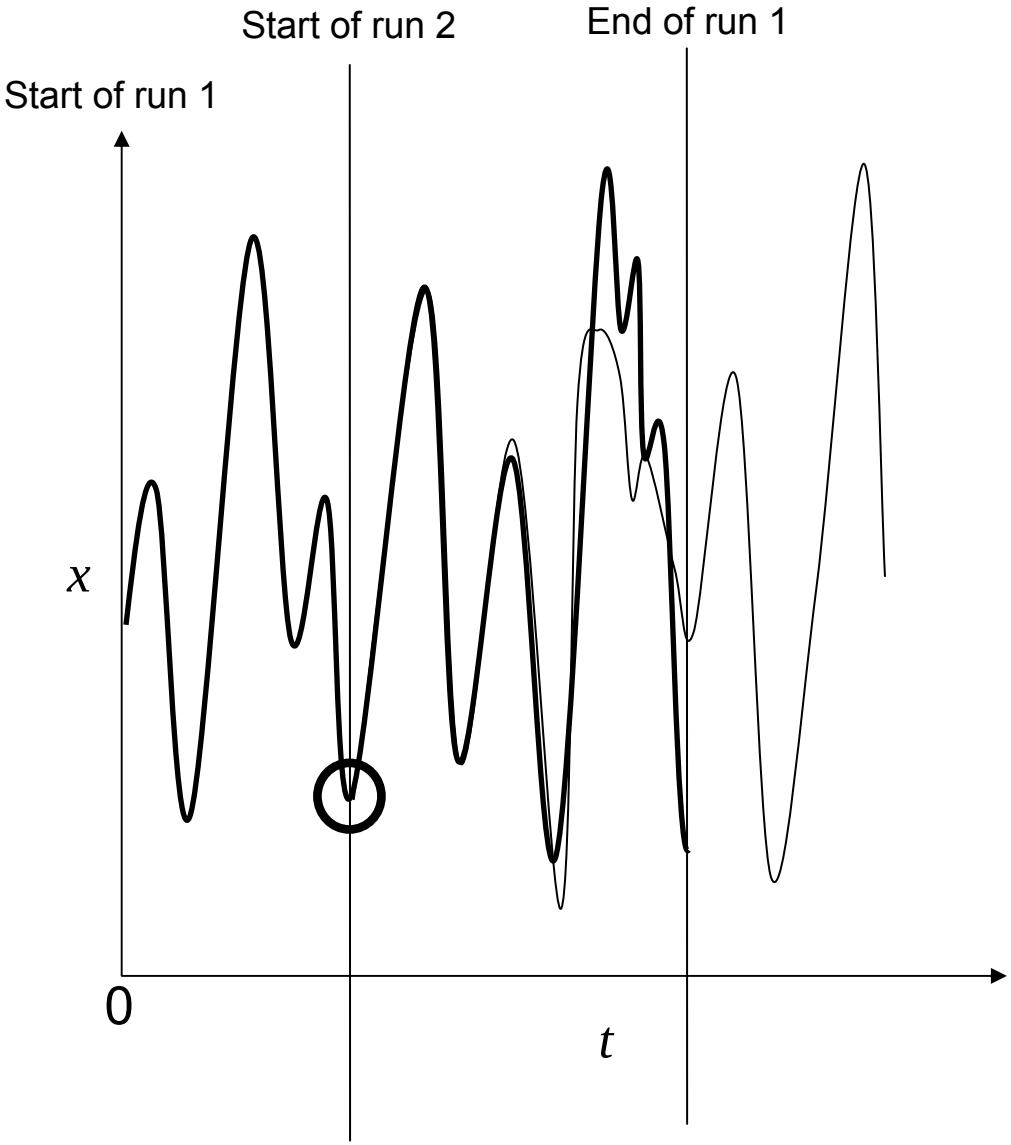
Atmospheric science

$dx/dt = -10x + 10y$

$dy/dt = 28x - y - xz$

$dz/dt = -(8/3)z + xy$

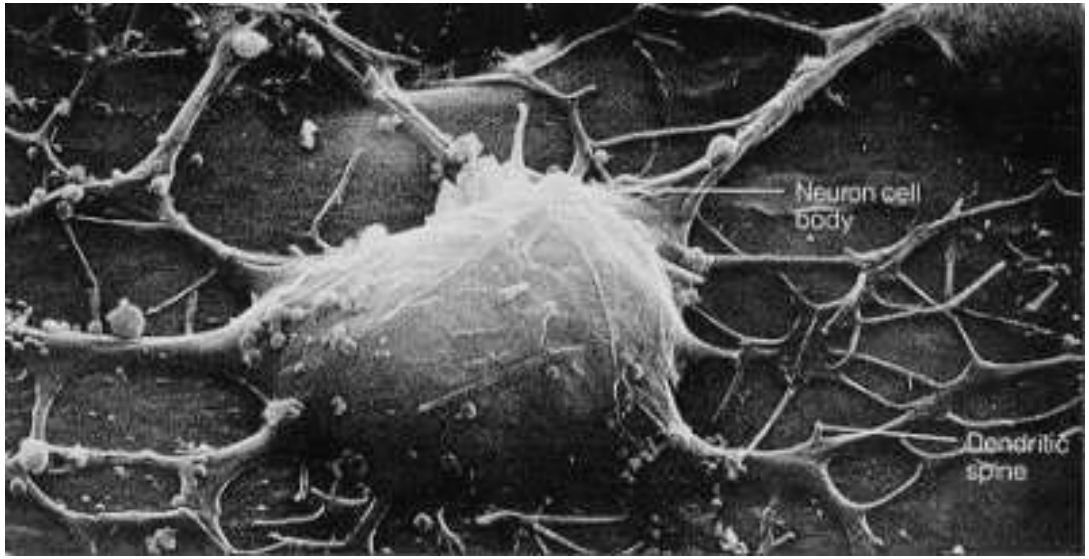


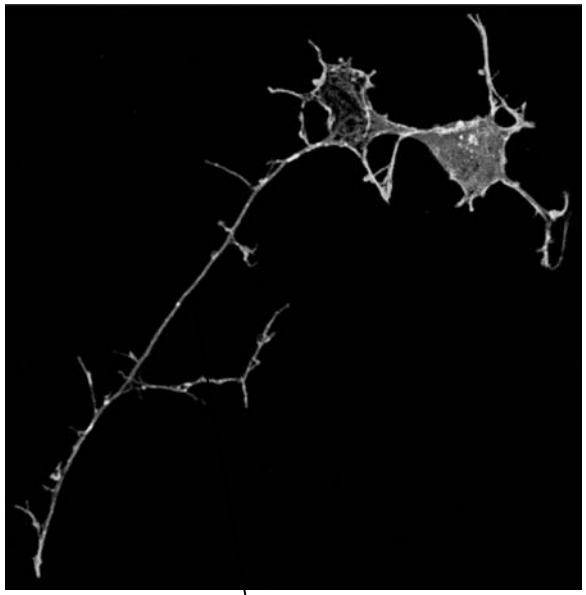


An even more “complex” example !

…Pancreatic β-cells have membranes with voltage-sensitive channels that allow Na^+ and Ca^{2+} ions to enter the cell and voltage-sensitive channels that allow K^+ ions to leave the cell, among others. The membrane potential of such a system seems to obey very complicated dynamics…

Ion Channel Research Started in Nerve Cells





Axon

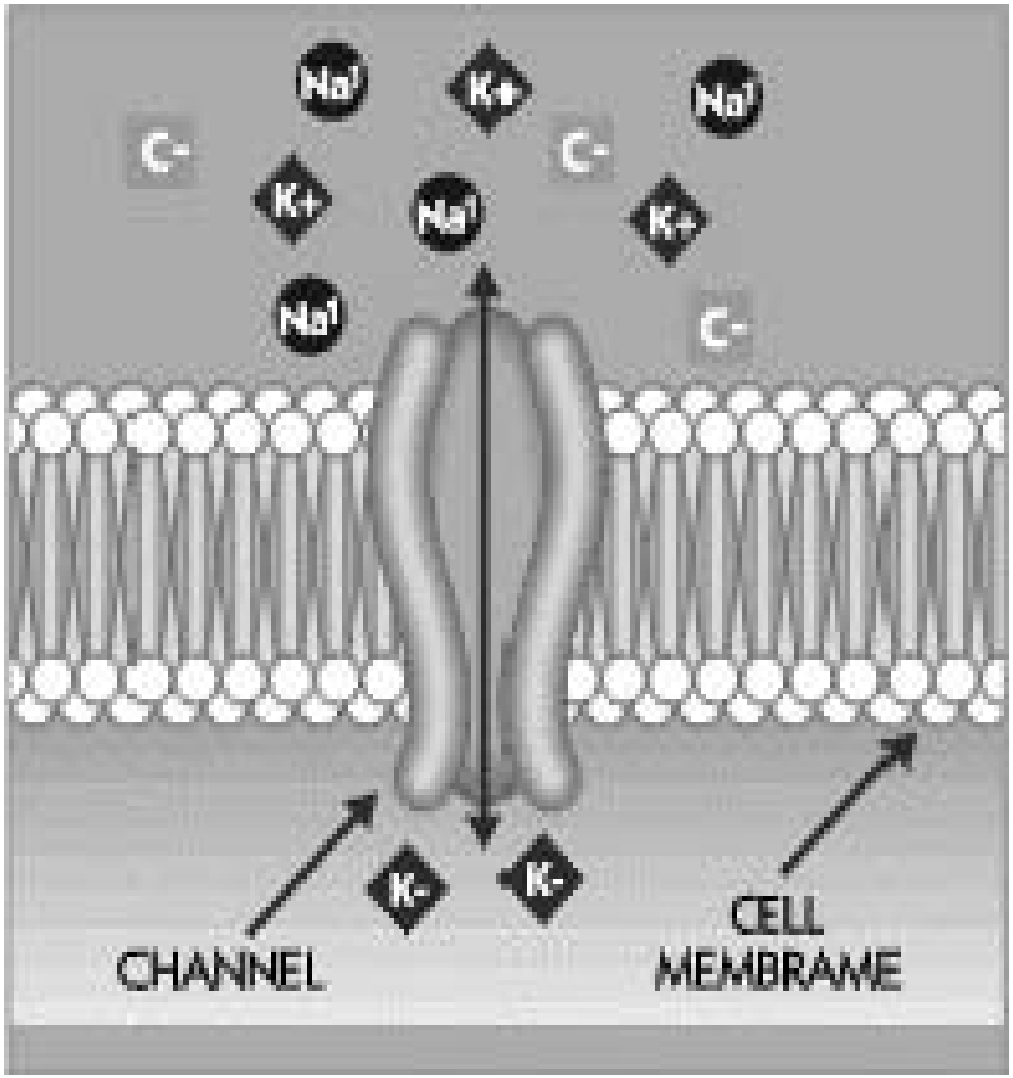
Nerve axons present with great variability:

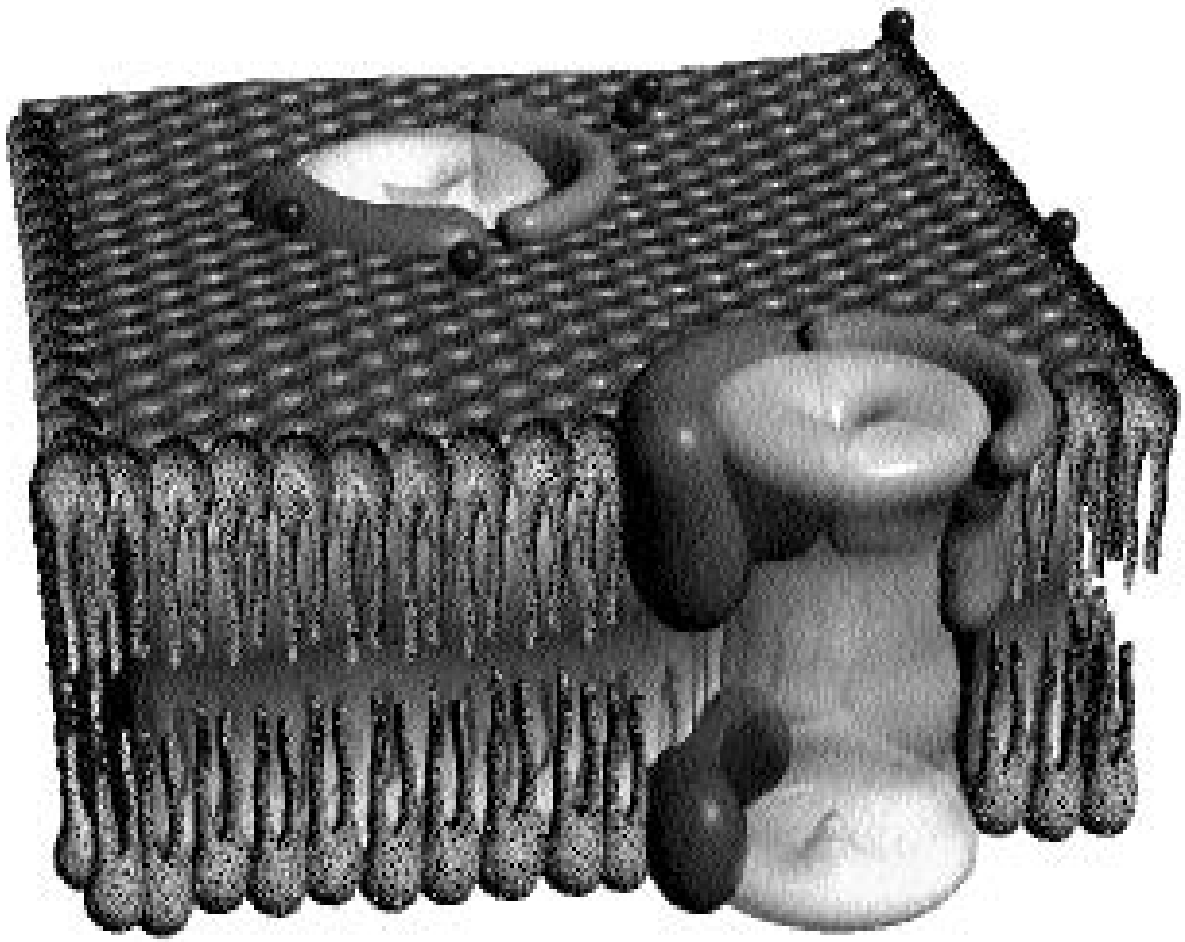
The axon for a giraffe sciatic nerve can be several meters long!

The axon for a squid can be 1 mm in diameter!

Good for manipulation

How does an ion channel “look”?





The cell membrane and ion channels

The cell membrane is a lipid bi-layer. One of its principle functions is to separate the outside of the cell (top) from the inside of the cell (bottom portion).

The red balls represent calcium ions (Ca^{2+}). Ca^{2+} is highly regulated in all cell types and therefore is not allowed to easily diffuse into a cell through the membrane. Instead, Ca^{2+} movement across the lipid membrane is "gated" by a channel called the voltage-gated Ca^{2+} channel (the two bluish units that span across the membrane). Most channels are composed of different protein subunits (green, purple, royal blue and light blue in the drawing) which when embedded together form a pore or gate.

In the example, the Ca^{2+} channel is sensitive to voltage and must open to let Ca^{2+} into the cell. The channel is closed most of the time until a depolarization (change in voltage represented here by a lighting strike inside the membrane) causes a conformational change in the channel structure to let Ca^{2+} through.

Ca^{2+} ion channel dysregulation may be crucial in several disease states, from myocardial dysfunction to brain aging and Alzheimer’s disease. Thus, the importance for tightly regulating the calcium ion.

What are ion channels?
Ion channels are membrane-bound cellular proteins that permit the flow of ions, including calcium, potassium, sodium and chloride into and out of cells:

Cells are usually in contact with “moderately salty” solutions (such as water, body fluids like extracellular fluid, blood plasma etc.). These fluids usually contain a relatively high concentration of ions (lots of sodium Na and chloride Cl, less Calsium Ca and potassium K). Due to the existence of the membrane, a difference in concentrations exist inside and outside of the cell, and thus a chemical gradient is maintained.

Similarly, an electrical potential difference between the cytoplasm and the extracellular medium is sustained.

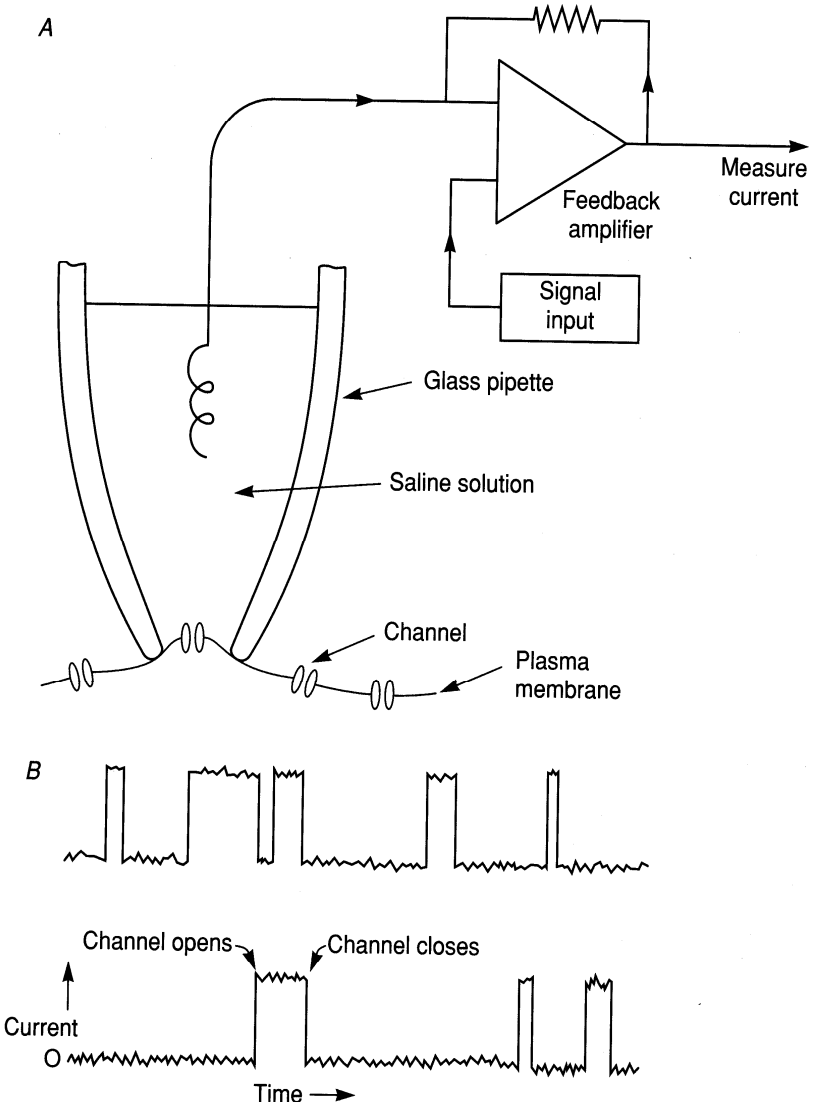
In effect, an electrochemical gradient, for each ion species, is continuously present, for all cells. Cells make good use of this potential for control and signaling, and this is achieved via the ion channels.

Ion channels are only a few (often only 1!) protein molecule ensembles.

They are very fast, 100,000,000 ions per second, and very selective (a K channel may be 10,000 times more permeable to K + than to Na+).

Ion channels are present in all human cells and effect such vital functions as nerve transmission, muscle contraction, and cellular secretion, to name a few.

The patch clamp technique was instrumental in their discovery and in understanding their functionality.

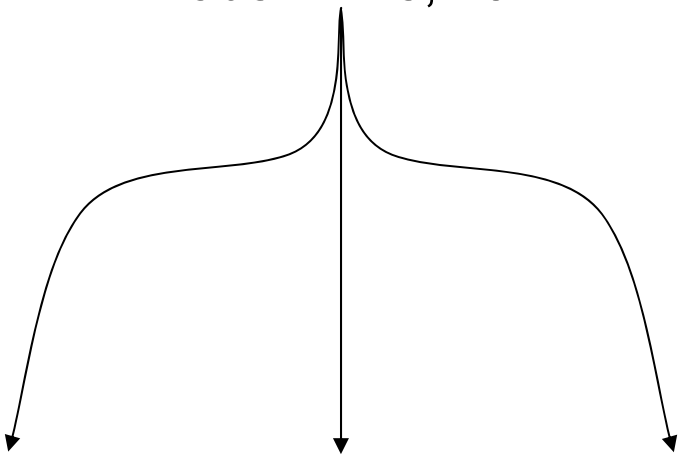


Modeling of Ion Channels:
Easier than Experiments ☺

Took twenty+ years before Armstrong and Bezanilla measured currents connected with the conformational change in the protein connected with the passage of Na^+

But if you combine the two, you might win a cookie:

Hodgkin, A. and Huxley, A.
A quantitative description of membrane current and its application to conduction and excitation in nerve,
J. Physiol. 117: 500-544,.1952
Nobel Prize, 1971



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•Chay TR Effects of extracellular calcium on electrical bursting and intracellular and luminal calcium oscillations in insulin secreting pancreatic beta-cells according to Chay's store-operated model BIOPHYS J 74 (2): A391-A391 Part 2 FEB 1998

•Chay TR Who do pancreatic beta-cells in the islet of Langerhans exhibit complex oscillations? Hypothesis on glucagon oscillation. BIOPHYS J 72 (2): WP248-WP248 Part 2 FEB 1997

•Chay TR The role of endoplasmic reticulum in genesis of complex oscillations in pancreatic beta-cells IEICE T FUND ELECTR E79A (10): 1595-1600 OCT 1996

•Chay TR Modeling slowly bursting neurons via calcium store and voltage-independent calcium current NEURAL COMPUT 8 (5): 951-978 JUL 1 1996

•Chay TR Bifurcations in heart rhythms INT J BIFURCAT CHAOS 5 (6): 1439-1486 DEC 1995

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•Chay TR The Hodgkin-Huxley NA+ channel model versus the 5-state Markovian model
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•Chay TR The effect of compartmentalized CA-2+ IONS on bursting pancreatic beta-cells
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•Lambert MH, Chay TR Cardiac-arrhythmias modeled by cai-inactivated CA2+ channels
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•Chay TR The effect of inactivation of calcium channels by intracellular CA-2+ ions in the bursting
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•Chay TR Chaos in a 3-variable model of an excitable cell PHYSICA D 16 (2): 233-242 1985
•Chay TR, Keizer J Theory of the effect of extracellular potassium on oscillations in the
pancreatic beta-cell BIOPHYS J 47 (2): A489-A489 1985
•Chay TR, Keizer J A minimal model for membrane oscillations in the pancreatic
beta-cell BIOPHYS J 41 (2): A58-A58 1983
•Chay TR A model for biological oscillations P NATL ACAD SCI-BIOL 78 (4): 2204-2207 1981
•Chay TR Proton transport across charged membrane and Ph oscillations BIOPHYS J 30 (1): 99-118 1980

The Nobel Prize in Chemistry 2003

"for discoveries concerning channels in cell membranes"

"for the discovery of water channels"

"for structural and mechanistic studies of ion channels"

Peter Agre

Roderick MacKinnon

Should we care?

Compounds that increase or decrease the flow of ions by selectively blocking or opening specific channels aid in the treatment of many diseases.
(check Xylocaine™ (lidocaine), Diabeta™ (glyburide), and Procardia™ (nifedipine)).

Ion channel modulators can target specific tissues or cells within a tissue. The specificity of these modulators is such that they will differentiate among physiological states (open, closed or inactivated) of the target channels.

Influence of Alcohol:

Although the relaxing effect of alcohol is well known, nobody could explain the mechanism exactly, until recently. Research from Niigata (Japan) & Texas (USA) sheds light:

Alcohol acts upon ion channels in the neuron membrane!

In particular, is was demonstrated that **alcohol opens** a specific type of **ion channel**, called **GIRK**. When open, this channel allows brain cells to **eject potassium**. The **concentration of potassium** in brain cells is known to be connected with the **level of activity of the cells**. Thus, ethanol forces the cells to **reduce their activity**. The result is a slow-down in brain function, perceived as a relaxing sensation by the “drinker”.

Normally, ionic channels in neurons are opened or closed by the action of neurotransmitters or by variations in the electric potential gradient between the interior and exterior of the neurons.

We shall study:

Mixed Na^+ Ca^{2+}
K^+
"Leakage"
} 3 potentials driving the membrane potential V

Exact formulation to follow, but we end up with:
3 ordinary **non-linear** differential equations of the form:

$$\frac{dV}{dt} = f(everything\ \&\ n^4, C)$$

$$\frac{dn}{dt} = g(simple)$$ n is a probability

$$\frac{dC}{dt} = h(also\_simple)$$ C is a concentration

dx/dt = 1 ⟶ x=t+c

Discretization

$$\frac{x_{t+\Delta T} - x_t}{\Delta T} = 1, \Delta T \to 0$$

Taylor Series: $$x(t) = x(t_0) + \left(\frac{dx}{dt}\right)_{t=t_0} (t - t_0) + \frac{1}{2!}\left(\frac{d^2x}{dt^2}\right)_{t=t_0} (t - t_0)^2 + \ldots$$

$$\left(\frac{dx}{dt}\right)_{t=t_0} = \frac{x(t) - x(t_0)}{(t - t_0)} + \frac{1}{2!}\left(\frac{d^2x}{dt^2}\right)_{t=t_0} (t - t_0)^2 + \ldots$$

$$\left(\frac{dx}{dt}\right)_{t=t_0} = \frac{\Delta x}{\Delta T} + \frac{1}{2!}\left(\frac{d^2x}{dt^2}\right)_{t=t_0} (t - t_0)^2 + \ldots$$

An ordinary differential equation:

$$\frac{dx}{dt} = f(x,t,...)$$

Or a system of ordinary differential equations:

$$\frac{dx_1}{dt} = f(x_i,t,...)$$

$$\frac{dx2}{dt} = f(x_i,t,...)$$

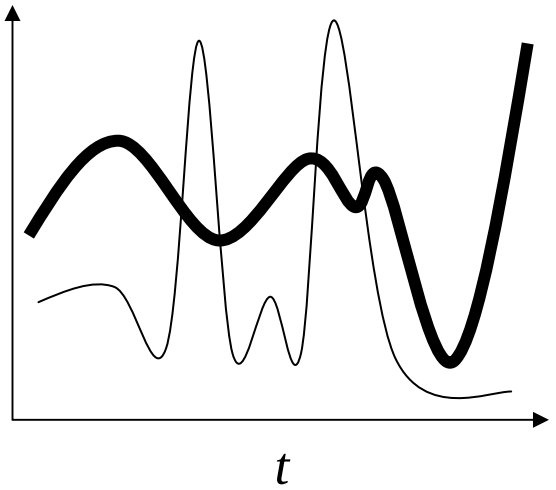
...

$$\frac{dx_n}{dt} = f(x_i,t,...)$$

Numerical Solution

x_i

Time Series



Solution techniques for ODEs:

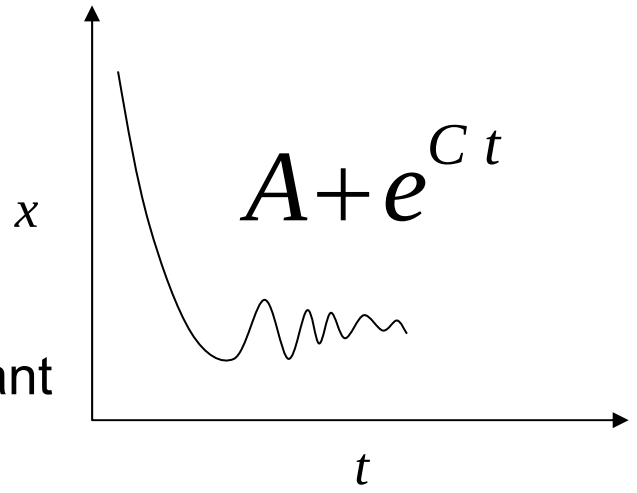
Forward marching Euler (First, second, third, … order)
Higher-order Taylor-based methods
Runge-Kutta (various classes)
Predictor-corrector schemes

Time-stepping:

Constant (intuitive, easy-postprocessing, easy to program)
Variable (computer-time savings, accuracy)

Stability & Stiffness:

Not all schemes converge
The results are not always realistic
“Grid” independence and validation are important



The equation to solve:

$$\frac{dV}{dt} = g_I^* m_\infty^3 h_\infty (V_I - V) + g_{K,V}^* n^4 (V_K - V) +$$

$$+ g_{K,C}^* \frac{C}{1+C} (V_K - V) + g_L^* (V_L - V)$$

Where:

- **C** is a quantity related with the concentration of intracellular Ca^{2+} ions
- **g^*** are the maximal conductances normalized with the membrane capacitance
- **V_L** is the leakage reversal potential
- **V_I** is the combined inward Na^+ -Ca^{2+} reversal potential
- **V_K** is the combined outward K^+ reversal potential
- **m_∞** is the probability of activation of the mixed inwards channel
- **h_∞** is the probability of inactivation of the mixed inwards channel

} Steady-state values, in original HH we solve additional DE for these. Here, we have simple algebraic eqs.

Additionally:

$$\frac{dn}{dt} = \frac{[n_\infty - n]}{\tau_n}$$

$$\frac{dC}{dt} = \rho\{m_\infty^3 h_\infty (V_C - V) - k_C C\}$$

Where:

- **n** is the probability of opening the K^+ channel
- $\mathbf{n}_\infty$ is the steady state value of **n**
- $\tau_\mathbf{n}$ is a characteristic relaxation time
- $\mathbf{k_C}$ is a rate constant for efflux of intracellular Ca^{2+} ions
- ρ is a normalization/proportionality constant
- $\mathbf{V_C}$ is the Ca^{2+} reversal potential

The system closes with:

$$y = \frac{a_y}{a_y + \beta_y},$$

$$where\, y\, is\, m_\infty,\ \ h_\infty\ and\ \ n_\infty$$

Suitable initial conditions:
V=-40mV
C=0.55
n=0.5

$$a_m = \frac{0.1(25+V)}{(1-e^{-0.1V-2.5})}$$

$$\beta_m = 4e^{\frac{-(V+50)}{18}}$$

$$a_h = 0.07e^{-0.05V-2.5}$$

$$\beta_h = \frac{1}{1+e^{-0.1V-2}}$$

$$a_n = \frac{0.01(20+V)}{(1-e^{-0.1V-2})}$$

$$\beta_n = 0.125e^{\frac{-(V+30)}{80}}$$

$$\tau_n = [230(a_n + \beta_n)]^{-1}$$

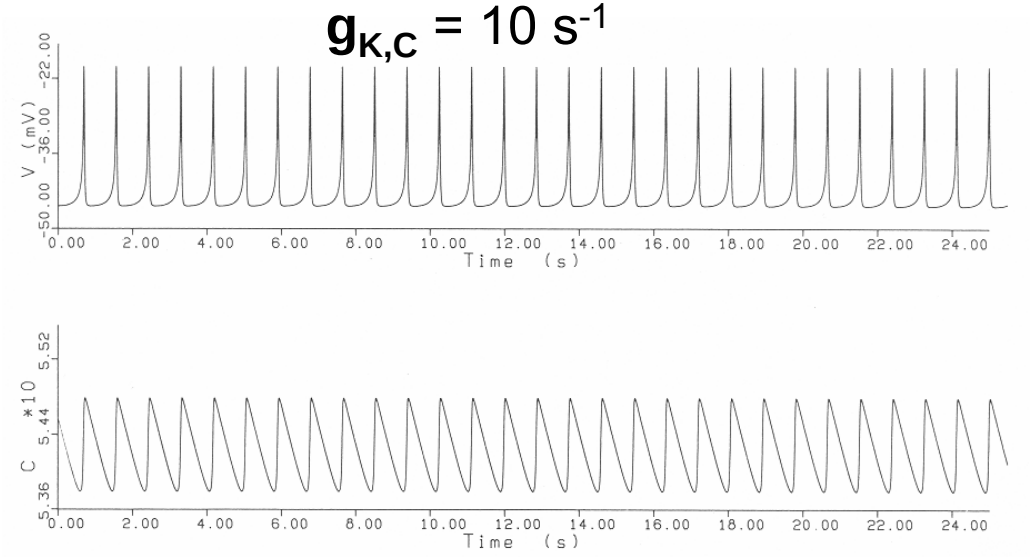
Constant Values for the Model

- $\mathbf{V_I}$ 100 mV
- $\mathbf{V_K}$ –75 mV
- $\mathbf{V_L}$ –40 mV
- $\mathbf{V_C}$ 100 mV
- $\mathbf{g_{K,V}}$ =1700 s^{-1}
- $\mathbf{g_I}$ =1800 s^{-1}
- $\mathbf{g_L}$ =7 s^{-1}
- $\mathbf{k_C}$ =3.3/18 mV
- ρ 0.27 $mV^{-1}s^{-1}$

The forcing:
Vary systematically $\mathbf{g_{K,C}}$ from 10 s^{-1} to 12 s^{-1}

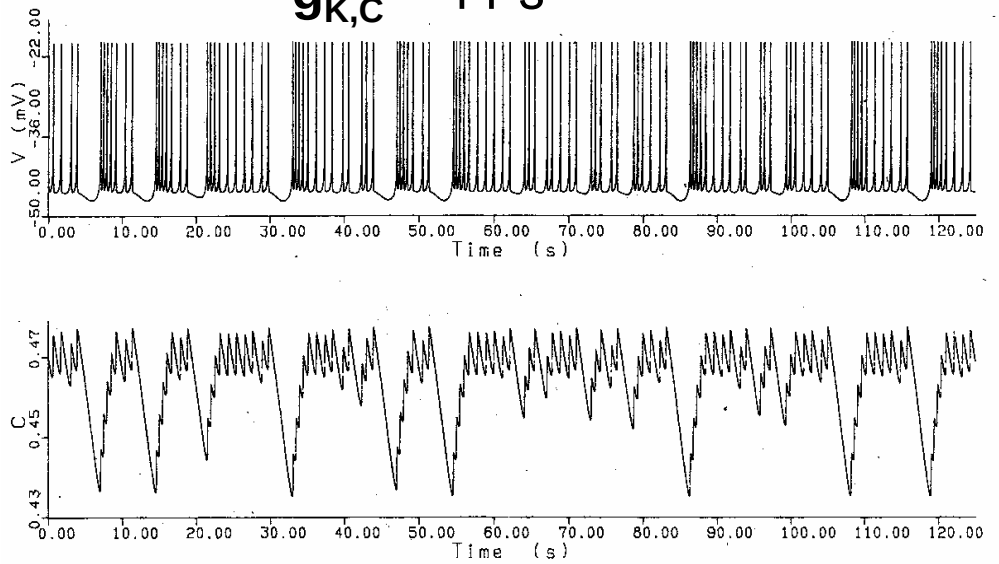
The physics of ion transfer

$g_{K,C} = 10\ s^{-1}$

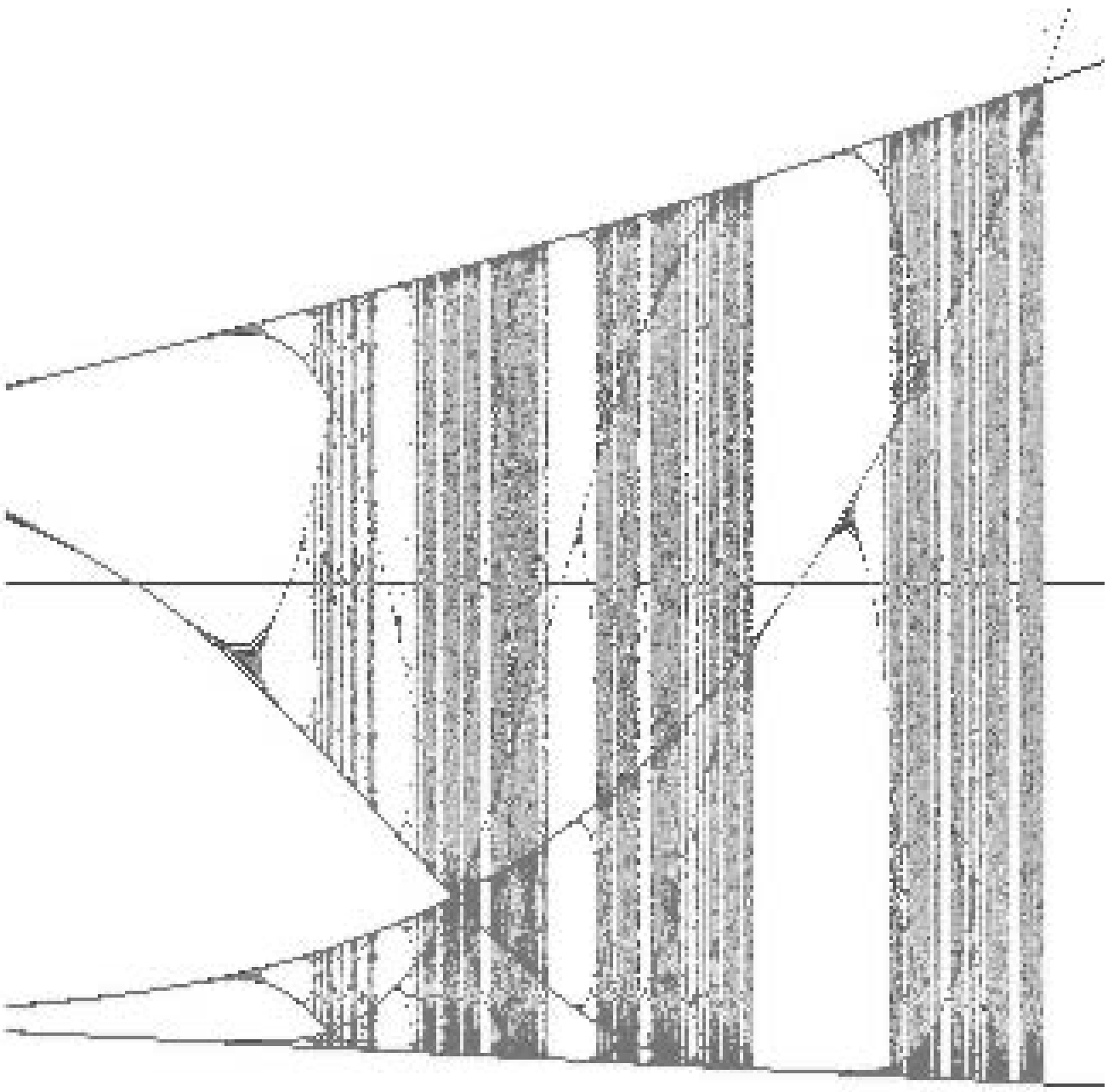


- Cell fires action potentials at regular intervals.
- Calcium concentration increases with each activation, and then drops to the minimum value.

$g_{K,C} = 11\ s^{-1}$

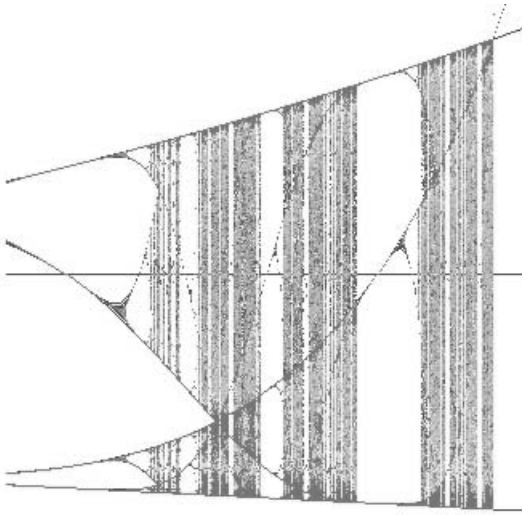


- Cell fires action potentials at bursts, followed by periods or quiescence.
- Calcium concentration increases with each burst, only to drop to the minimum value at the quiescence intervals, if they are long enough.



From Order to Deterministic Randomness:
Routes to Chaos

<u>Period Doubling:</u>
2τ @ $g_{K,C} = 10.7$
4τ @ $g_{K,C} = 10.75$
8τ @ $g_{K,C} = 10.77$
12τ@ $g_{K,C} = 10.8$



Theory and many examples from Science and Technology show that there exists an accumulation point for the successive bifurcations, beyond which the system can be characterized as chaotic. Moreover the intervals at which the bifurcations appear, in many systems, obey a “universal” constant ratio (4.669201609104574), known as the Feigenbaum constant

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