

BIOPHYSICS @ YORK



redefine THE POSSIBLE.

Biophysical models of neurons

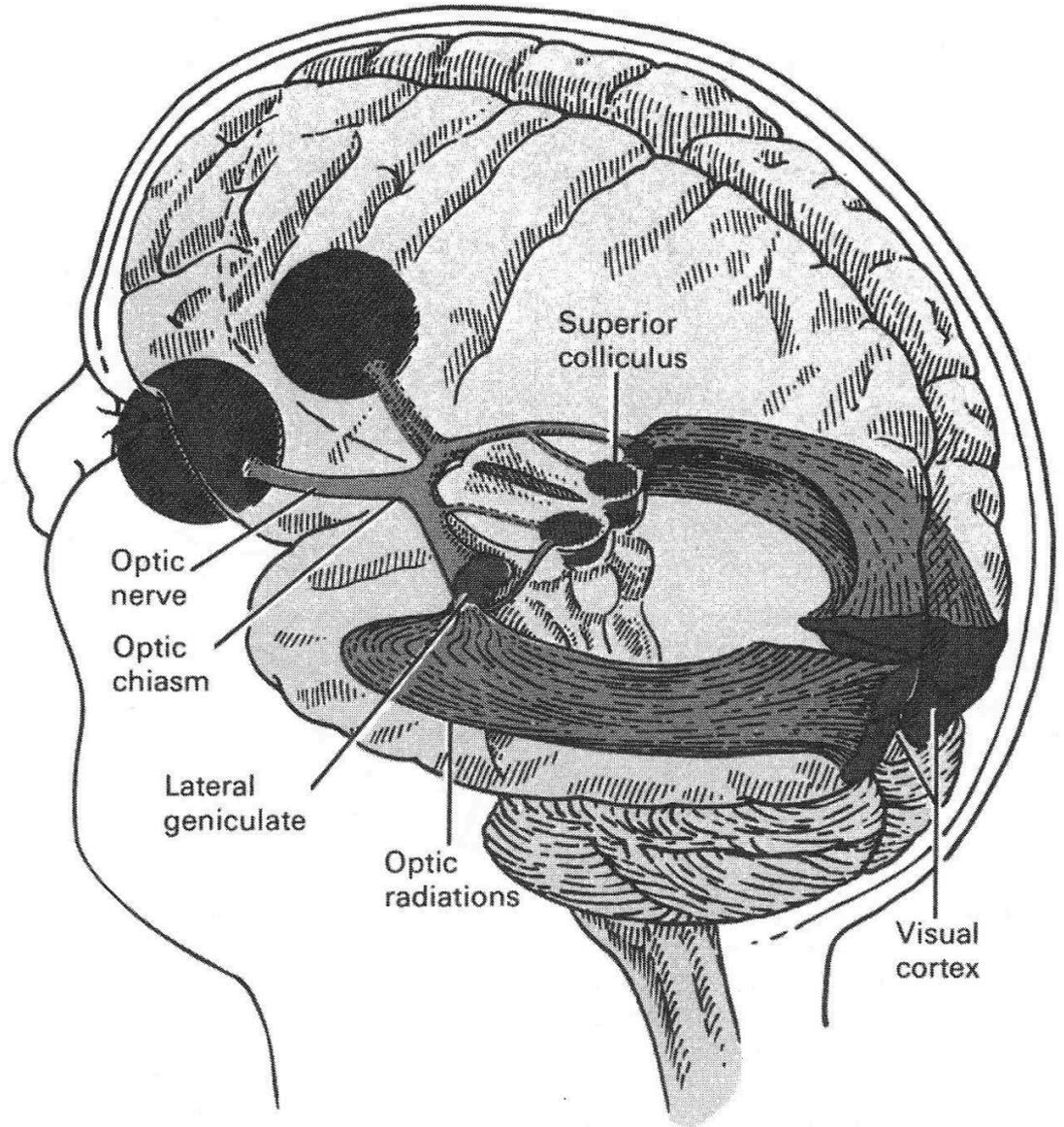
Christopher Bergevin

York University – Dept. of Physics & Astronomy

MoV 2019 (Fields Institute)



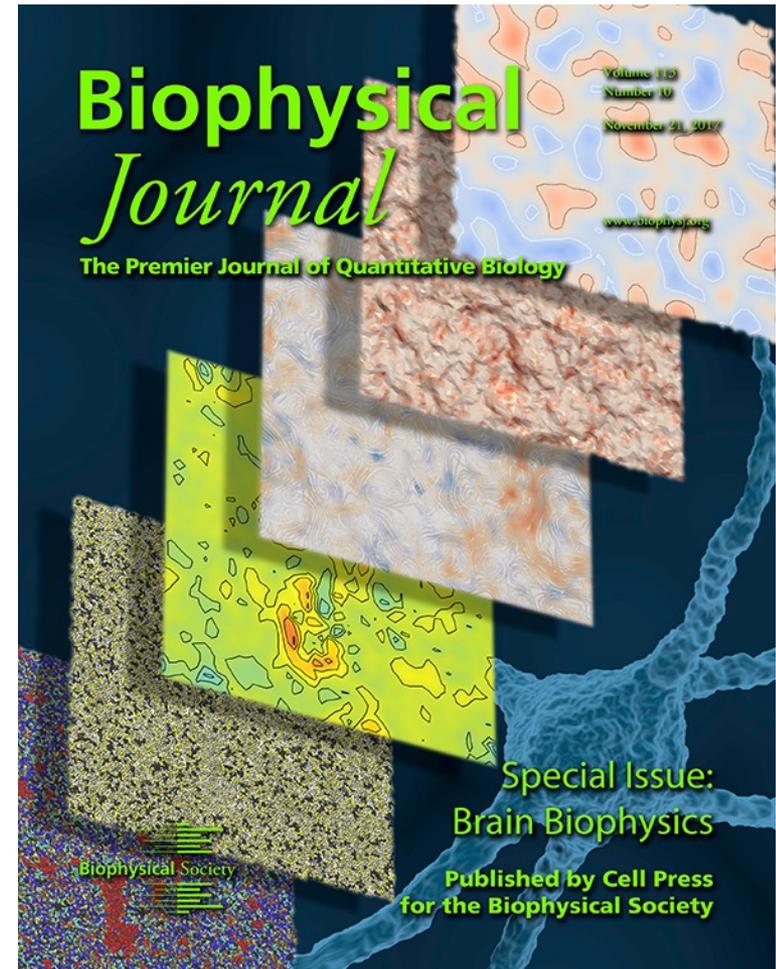
Lennart Nilsson (1966)



Palmer (1999)

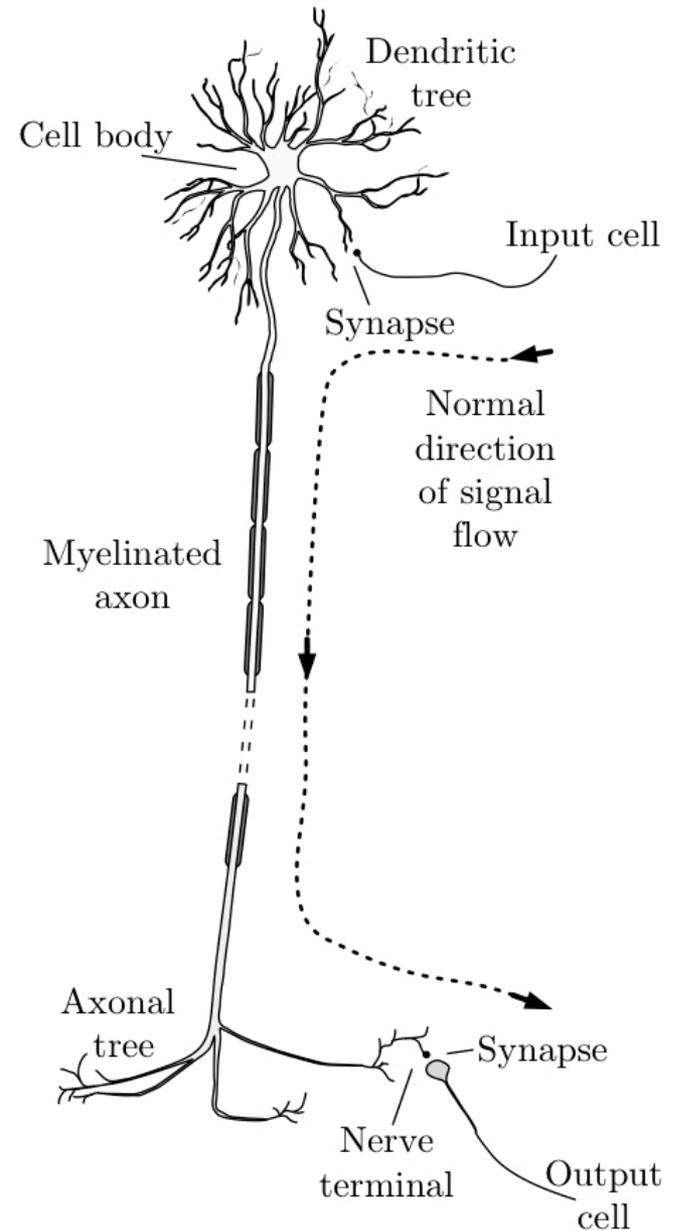
Biophysics of the Brain: From Molecules to Networks

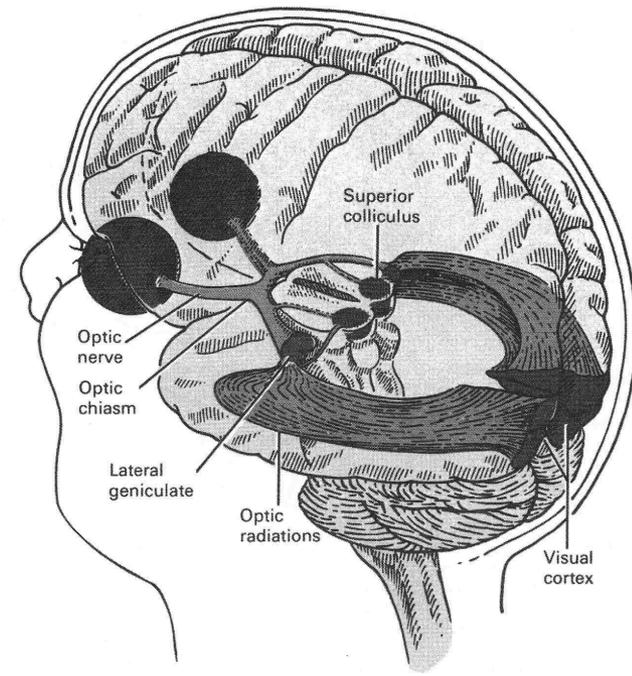
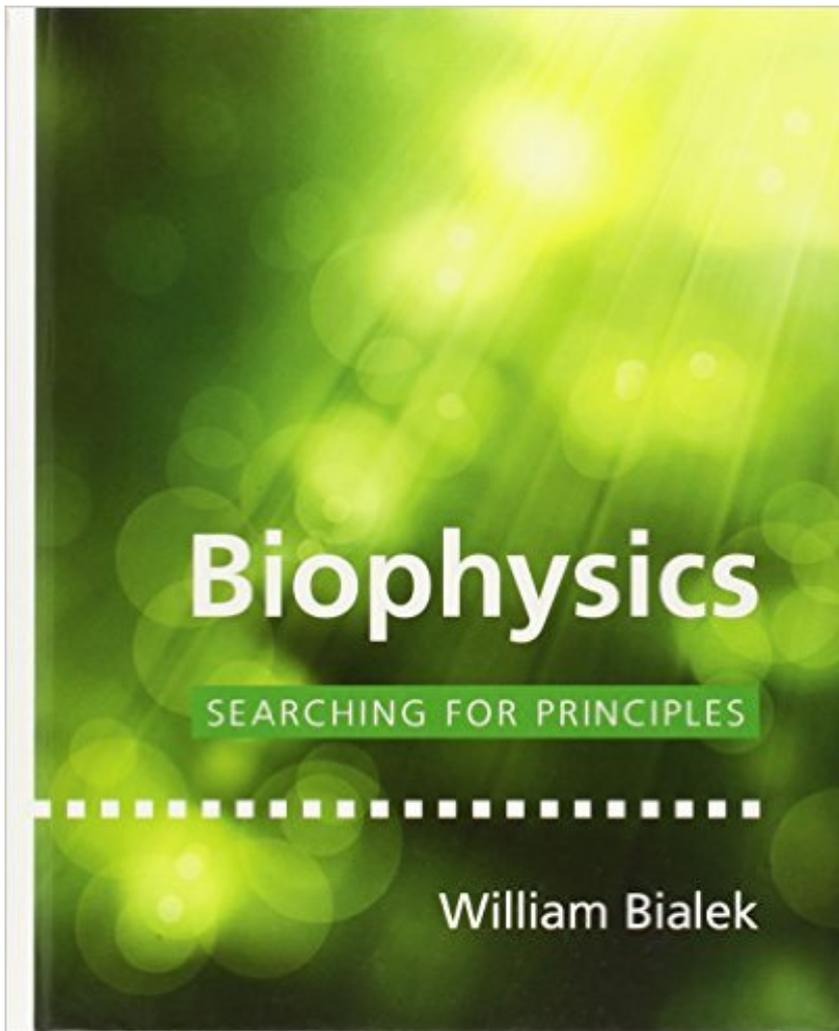
The brain, with billions of neurons making trillions of connections, still largely remains an enigma. The last decade has seen the development of new biophysical tools, including optical methods for mapping neuronal connections and high-resolution imaging. These new biophysical tools, along with electrophysiological, structural, and computational methods, have brought the understanding of the brain into better focus. This special issue of Biophysical Journal on brain biophysics highlights research in these areas.





With 80+ billion neuron and 100+ trillion connections, this is a *hard* problem...





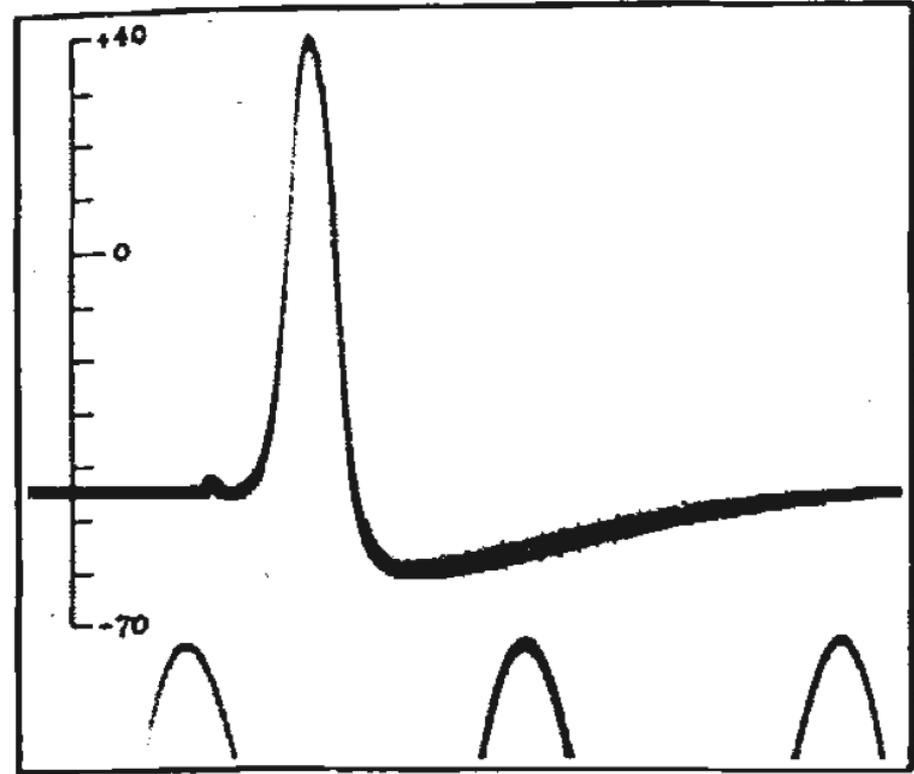
“It is a remarkable thing that, pulling on the threads of one biological phenomenon, *we can unravel* so many general physics questions.”

“No matter how much we may be searching for deep theoretical principles, in the physics tradition, *we do need a grasp of the facts*. But when we teach particle physics we don't start by reading from the particle data book, so similarly I don't start by reciting the ‘biological background.’ Rather, *we plunge right in...*”



Fig. 1.

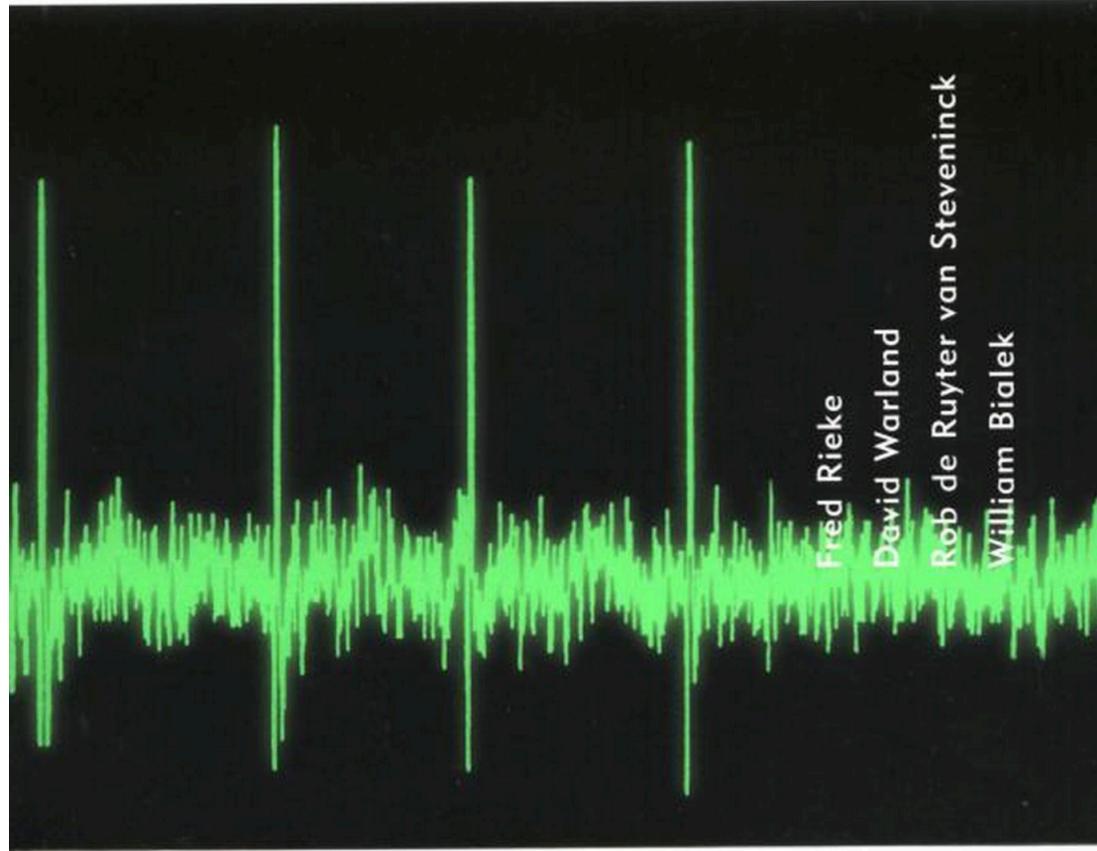
PHOTOMICROGRAPH OF ELECTRODE INSIDE GIANT AXON. 1 SCALE DIVISION = 33 μ .



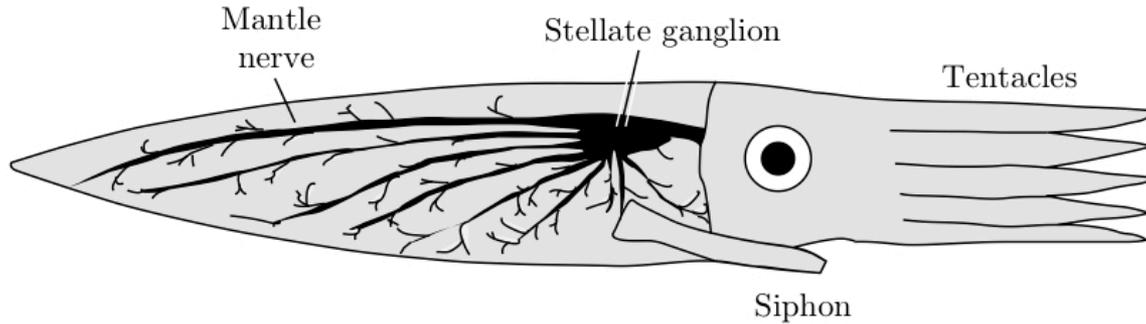
→ 1st intracellular action potential (AP) recording!

SPIKES

EXPLORING THE NEURAL CODE

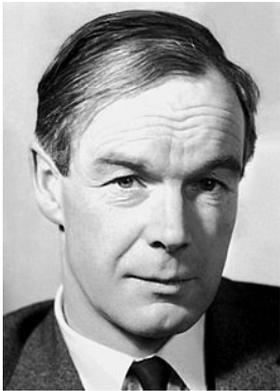


Biophysical model of a neuron

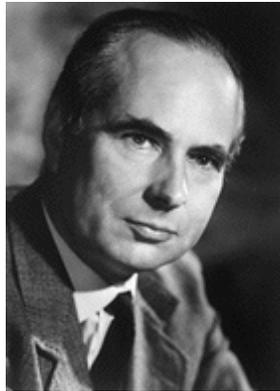


Key Idea #1
Model the cell membrane as an electric circuit

Hodgkin Huxley model

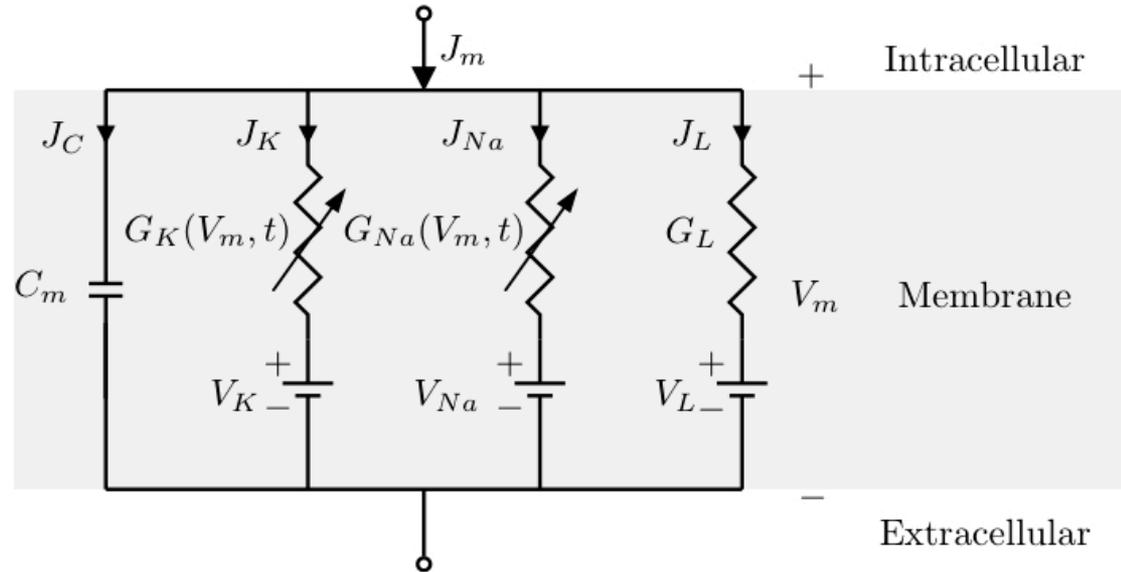


Alan Hodgkin



Andrew Huxley

1963 Nobel Prize



Key Idea #2
Variable Na^+ and K^+ conductances

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).

Hodgkin Huxley model (HH)

$$\frac{1}{2\pi a(r_o + r_i)} \frac{\partial^2 V_m}{\partial z^2} = C_m \frac{\partial V_m}{\partial t} + G_K(V_m, t) (V_m - V_K) + G_{Na}(V_m, t) (V_m - V_{Na}) + G_L(V_m - V_L)$$

$$G_K(V_m, t) = \bar{G}_K n^4(V_m, t)$$

$$G_{Na}(V_m, t) = \bar{G}_{Na} m^3(V_m, t) h(V_m, t)$$

$$n(V_m, t) + \tau_n(V_m) \frac{dn(V_m, t)}{dt} = n_\infty(V_m)$$

$$m(V_m, t) + \tau_m(V_m) \frac{dm(V_m, t)}{dt} = m_\infty(V_m)$$

$$h(V_m, t) + \tau_h(V_m) \frac{dh(V_m, t)}{dt} = h_\infty(V_m)$$

- Linear 1st order ODEs
- Multivariable functions
- Nonlinear PDE
- etc....

Focal Point

What do these equations represent?

$$\tau_x \frac{dx}{dt} + x = x_\infty \quad \frac{dx}{dt} = \alpha_x(1-x) - \beta_x x$$

$$x_\infty = \alpha_x / (\alpha_x + \beta_x) \text{ and } \tau_x = 1 / (\alpha_x + \beta_x)$$

$$\alpha_m = \frac{-0.1(V_m + 35)}{e^{-0.1(V_m + 35)} - 1},$$

$$\beta_m = 4e^{-(V_m + 60)/18},$$

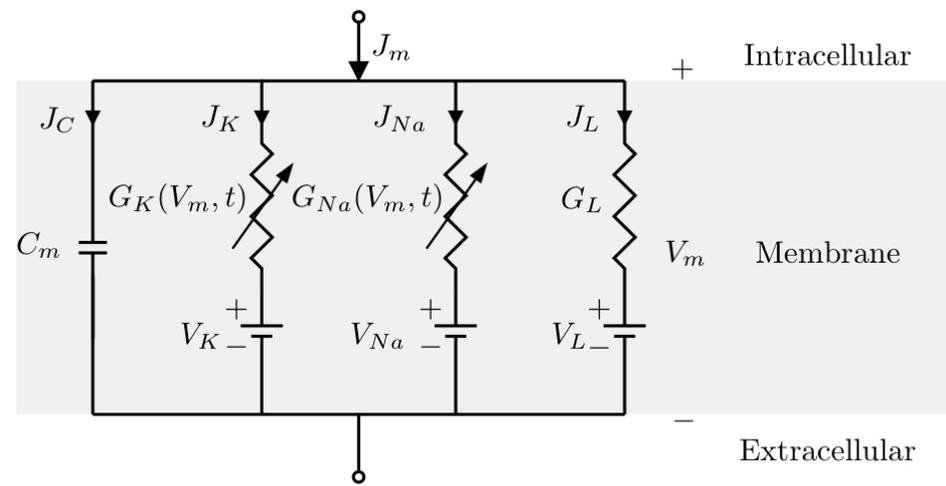
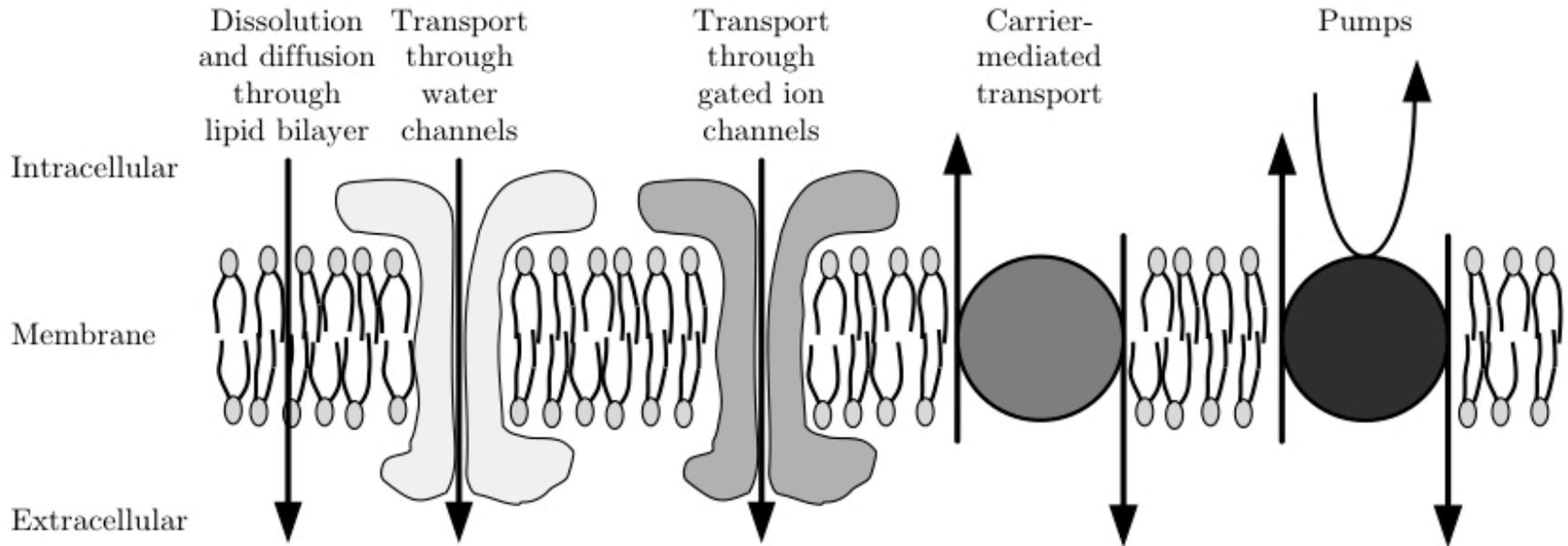
$$\alpha_h = 0.07e^{-0.05(V_m + 60)},$$

$$\beta_h = \frac{1}{1 + e^{-0.1(V_m + 30)}},$$

$$\alpha_n = \frac{-0.01(V_m + 50)}{e^{-0.1(V_m + 50)} - 1},$$

$$\beta_n = 0.125e^{-0.0125(V_m + 60)},$$

Cell membrane (as a foundation)



Unpackaging HH (v1)

Linear 1st order ODEs

$$n(V_m, t) + \tau_n(V_m) \frac{dn(V_m, t)}{dt} = n_\infty(V_m)$$

$$m(V_m, t) + \tau_m(V_m) \frac{dm(V_m, t)}{dt} = m_\infty(V_m)$$

$$h(V_m, t) + \tau_h(V_m) \frac{dh(V_m, t)}{dt} = h_\infty(V_m)$$

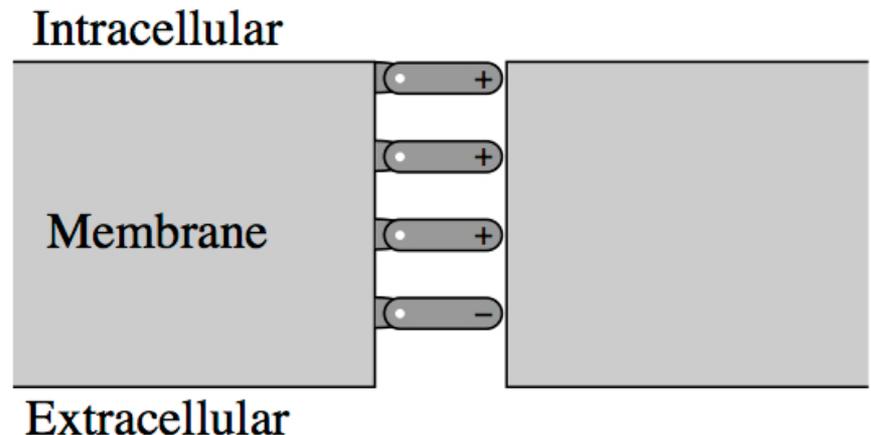
$$\tau_x \frac{dx}{dt} + x = x_\infty \quad \frac{dx}{dt} = \alpha_x(1-x) - \beta_x x$$

$$x_\infty = \alpha_x / (\alpha_x + \beta_x) \text{ and } \tau_x = 1 / (\alpha_x + \beta_x)$$

The mysterious nonlinear bit...

$$G_K(V_m, t) = \bar{G}_K n^4(V_m, t)$$

$$G_{Na}(V_m, t) = \bar{G}_{Na} m^3(V_m, t) h(V_m, t)$$



Caveat: HH is a *macroscopic/deterministic* model, but crucially stimulated development of the *microscopic/stochastic* model of ion channels...

Mathematical tangent: Linear 1st order ODEs

A variable $n(t)$ is described by a first-order linear differential equation with constant coefficients

$$\tau \frac{dn(t)}{dt} + n(t) = n_{\infty}$$

where τ and n_{∞} are constants. Let $n(0) = n_0$.

Exponential growth/decay

$$\frac{dP}{dt} = kP$$

Common examples

$$\frac{dT}{dt} = \alpha(T_o - T)$$

Drag & Terminal velocity

$$m \frac{dv}{dt} = mg - kv$$

Newton's Law of Heating/Cooling

A first-order, linear differential equation with constant coefficients and a constant inhomogeneous (drive or input) term has an exponential solution. Therefore, the solution can be written in the form

$$n(t) = n_{\infty} + \left(n_0 - n_{\infty} \right) e^{-t/\tau},$$

where $n_0 = n(0)$ is the initial value of $n(t)$ and $n_{\infty} = \lim_{t \rightarrow \infty} n(t)$ is the final value of $n(t)$. The form of this solution can be verified by evaluating $n(t)$ at $t = 0$ and $t \rightarrow \infty$. Substitution into the differential equation shows that this solution satisfies the differential equation.

Mathematical tangent: Linear 1st order ODEs

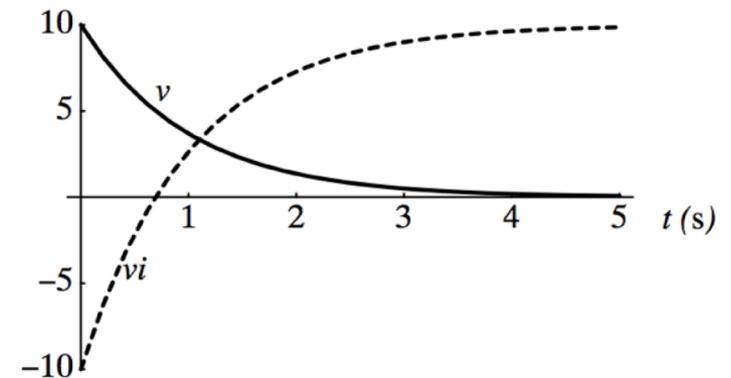
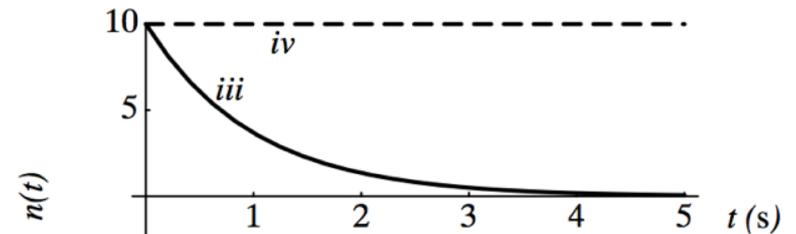
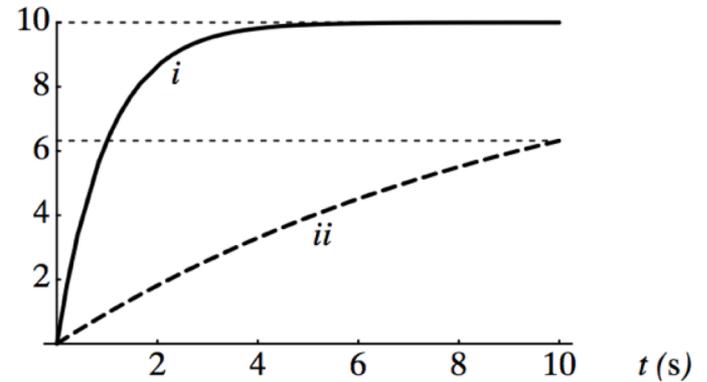
ODE

$$\tau \frac{dn(t)}{dt} + n(t) = n_{\infty}$$

Solution

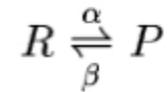
$$n(t) = n_{\infty} + (n_0 - n_{\infty}) e^{-t/\tau}$$

Point to emphasize → Solutions take the form of an **exponential**



Aside: Chemical kinetics

First-order, reversible reaction



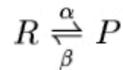
$$\frac{dc_R(t)}{dt} = \beta c_P(t) - \alpha c_R(t) \quad \text{AND} \quad \frac{dc_P(t)}{dt} = \alpha c_R(t) - \beta c_P(t)$$

First-order linear differential equation with constant coefficients

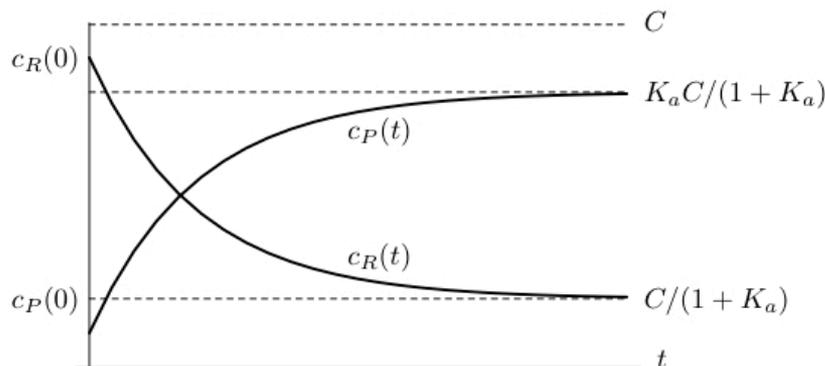
$$c_R(t) = c_R(\infty) - \left(c_R(\infty) - c_R(0) \right) e^{-t/\tau}, \text{ for } t > 0$$

$$c_R(\infty) = \frac{\beta}{\alpha + \beta} C = \frac{1}{1 + K_a} C \quad \text{AND} \quad \tau = \frac{1}{\alpha + \beta}$$

First-order, reversible reaction



$$c_P(t) = C - c_R(t)$$



$$\tau = \frac{1}{\alpha + \beta}$$

→ Not a stretch to scale up to 2nd order reversible (binding) reactions and *Michaelis-Menten kinetics* readily emerges...

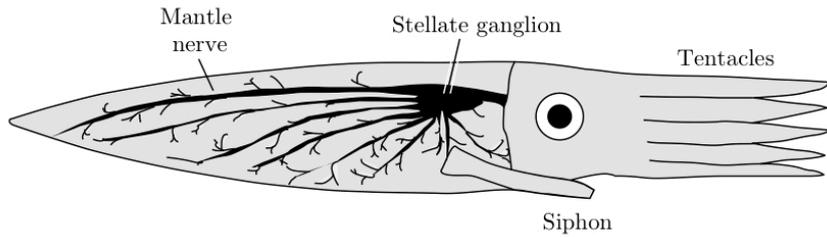


Figure 1.28

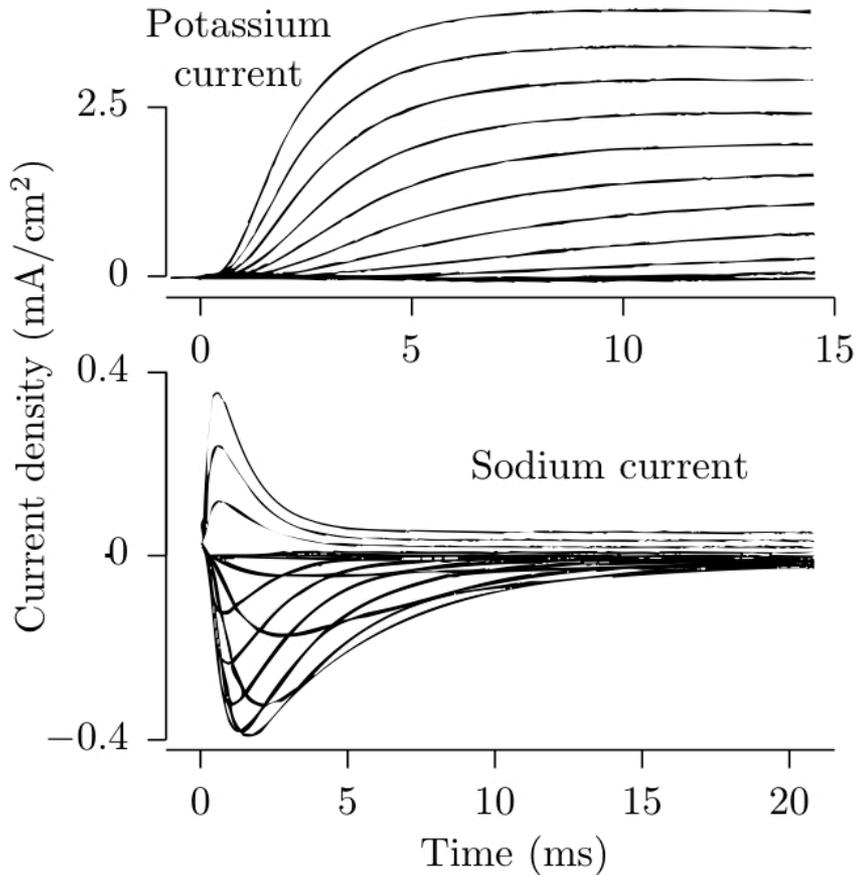
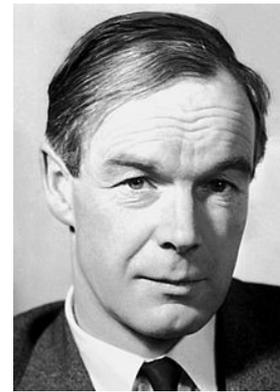
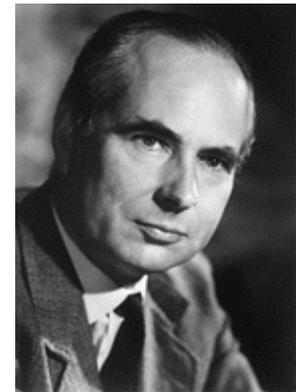


Figure 4.20



Alan Hodgkin



Andrew Huxley

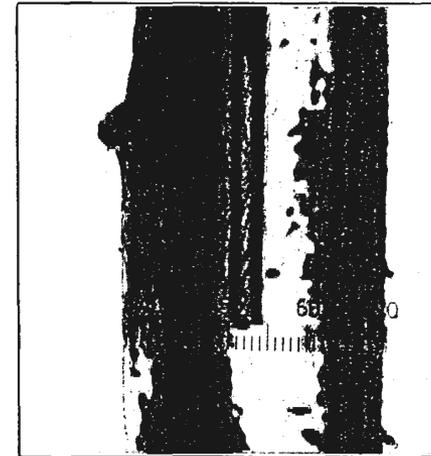


Fig. 1.
PHOTOMICROGRAPH OF ELECTRODE INSIDE GIANT AXON. 1 SCALE DIVISION = 33 μ.

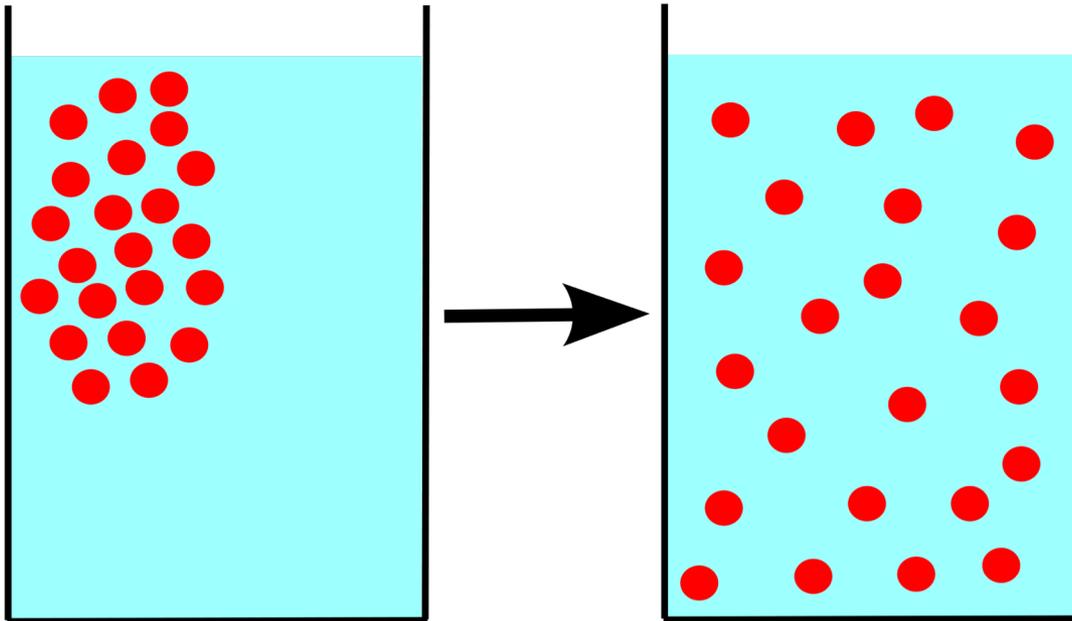
$$G_K(V_m, t) = \bar{G}_K n^4(V_m, t)$$

$$G_{Na}(V_m, t) = \bar{G}_{Na} m^3(V_m, t) h(V_m, t)$$

Unpackaging HH (v2)

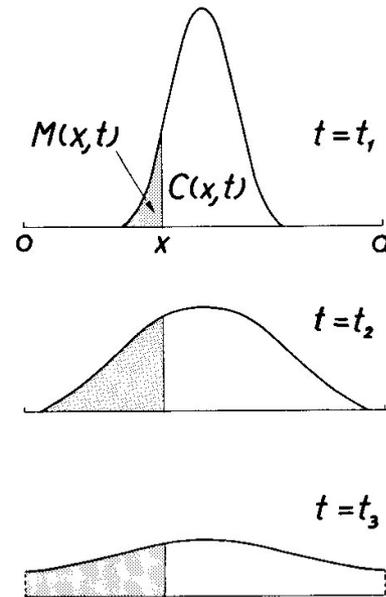
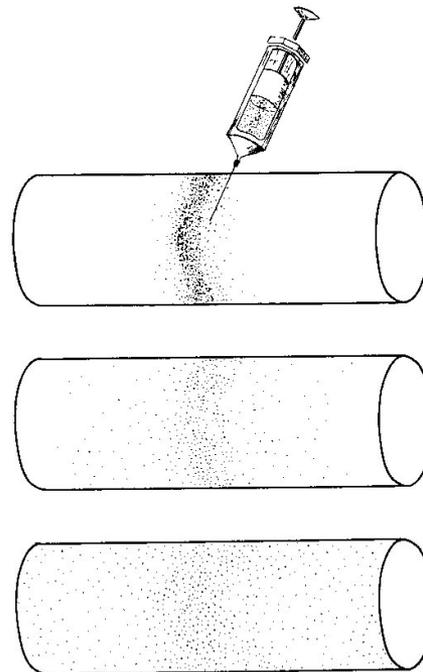
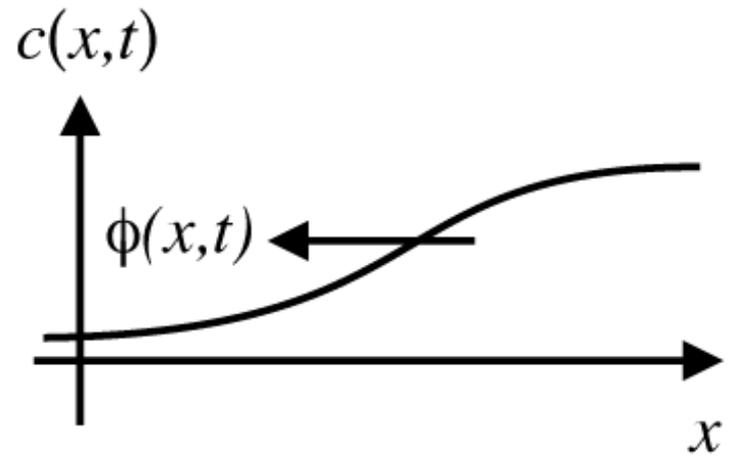
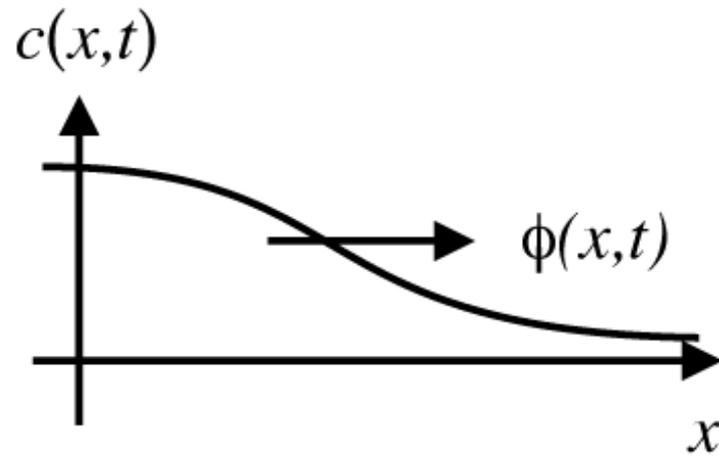
That partial differential equation (PDE)....

$$\frac{1}{2\pi a(r_o + r_i)} \frac{\partial^2 V_m}{\partial z^2} = C_m \frac{\partial V_m}{\partial t} + G_K(V_m, t) (V_m - V_K) + G_{Na}(V_m, t) (V_m - V_{Na}) + G_L(V_m - V_L)$$



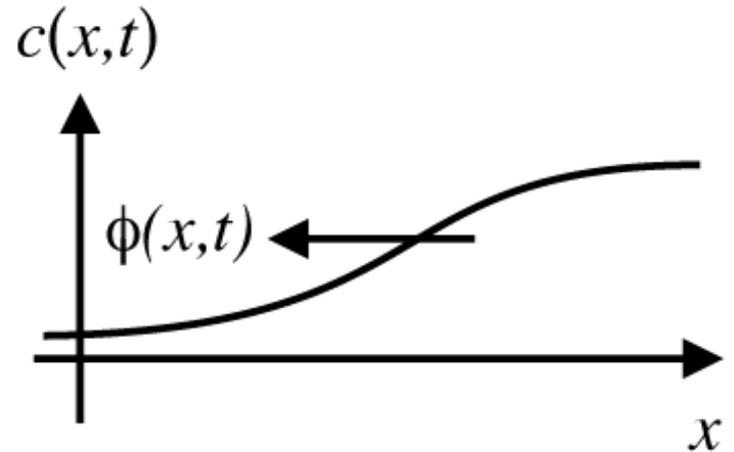
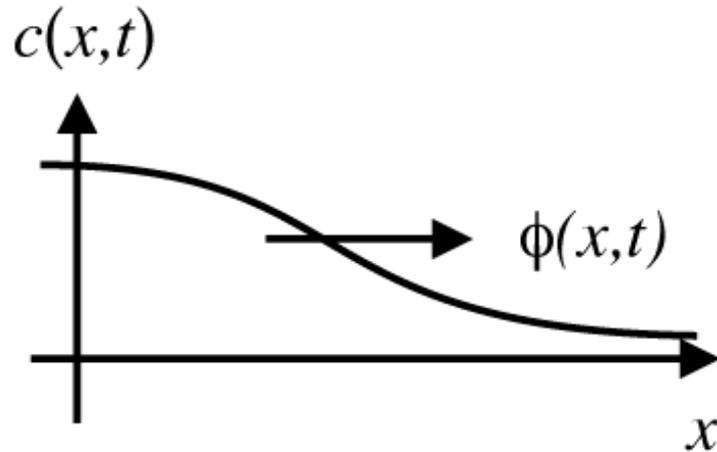
Diffusion (Macroscopic)

Note: These are multi-variable functions.
Will focus on 1-D case here for simplicity



Diffusion (Macroscopic)

Note: These are multi-variable functions.
Will focus on 1-D case here for simplicity



$c(x,t)$

Concentration - of solute in solution [mol/m^3]

$\phi(x,t)$

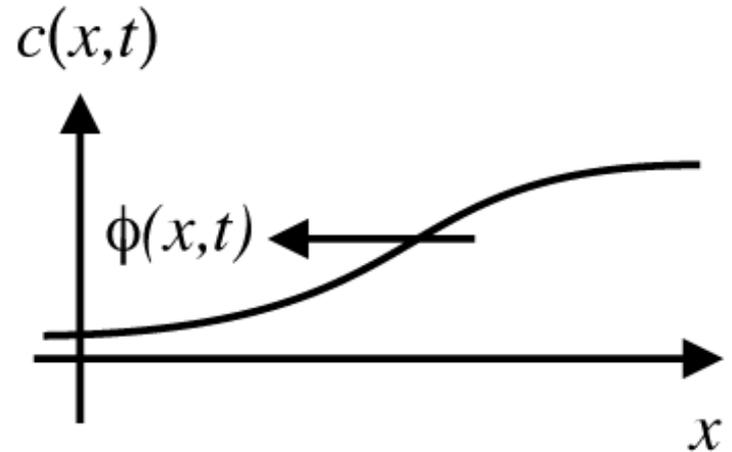
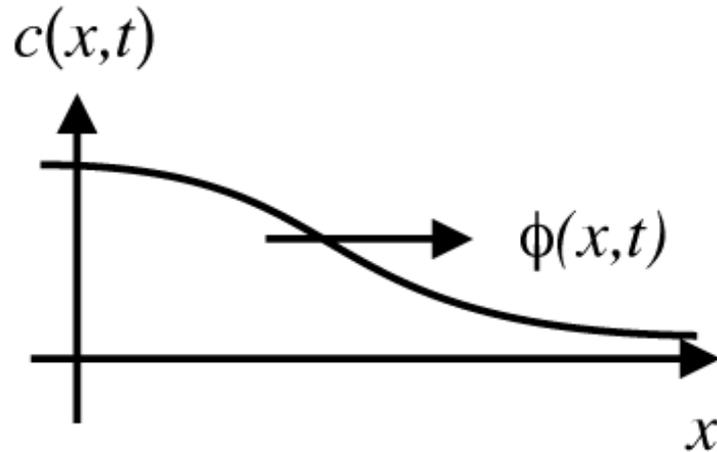
Flux - net # of moles crossing per unit time t through a unit area perpendicular to the tx -axis [$mol/m^2 \cdot s$]

Note: flux is a *vector*!

x, t

Position [m], Time [s]

Diffusion (Macroscopic)



$$\phi(x, t) = -D \frac{\partial c(x, t)}{\partial x}$$

→ *Stuff* moves DOWN a concentration gradient

- Diffusion constant is always positive (i.e., $D > 0$)
- Determines time it takes solute to diffuse a given distance in a medium
- Depends upon both solute and medium (solution)
- *Stokes-Einstein relation* predicts that D is inversely proportional to solute molecular radius

Diffusion: Generalizations

Higher Dimensions:

$$\phi(x, t) = -D \frac{\partial c(x, t)}{\partial x} \longleftrightarrow \vec{\phi} = -D \nabla c$$

$$\text{where } \nabla c = \hat{x} \frac{\partial c}{\partial x} + \hat{y} \frac{\partial c}{\partial y} + \hat{z} \frac{\partial c}{\partial z} = \text{grad}(c)$$

Analogous Flux Laws:

Heat Flow (Fourier): $\phi_h = -\sigma_h \frac{\partial T}{\partial x}$ *heat flow, thermal conductivity, and temperature*

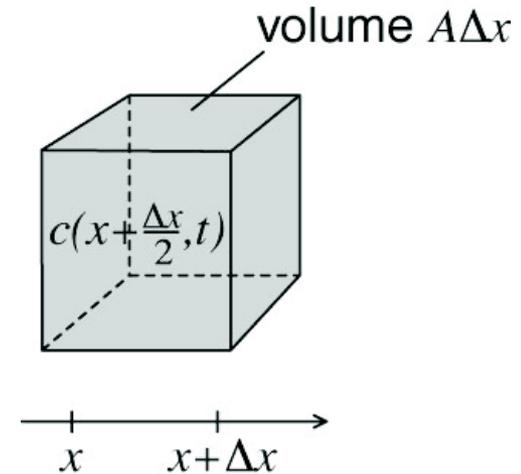
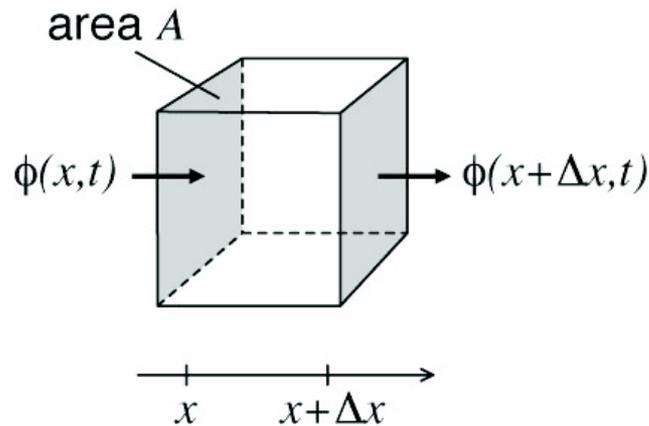
Electric Conduction (Ohm): $J = -\sigma_e \frac{\partial \psi}{\partial x}$ *current density, electrical conductivity, and electric potential*

Convection (Darcy): $\Phi_v = -\kappa \frac{\partial p}{\partial x}$ *fluid flow, hydraulic permeability, and pressure*

Diffusion (Fick): $\phi = -D \frac{\partial c}{\partial x}$

Continuity Equation (1-D)

Imagine a cube (with face area A and length Δx) and a time interval Δt



$$\frac{\partial \phi}{\partial x} = - \frac{\partial c}{\partial t}$$

change in flow
through cube on
each side

change in amount
of stuff inside
cube

Conservation of mass within the context of our imaginary cube yields the *continuity equation*

Diffusion Equation

1. Fick's First Law:

$$\phi = -D \frac{\partial c}{\partial x}$$

+

2. Continuity Equation:

$$\frac{\partial \phi}{\partial x} = -\frac{\partial c}{\partial t}$$

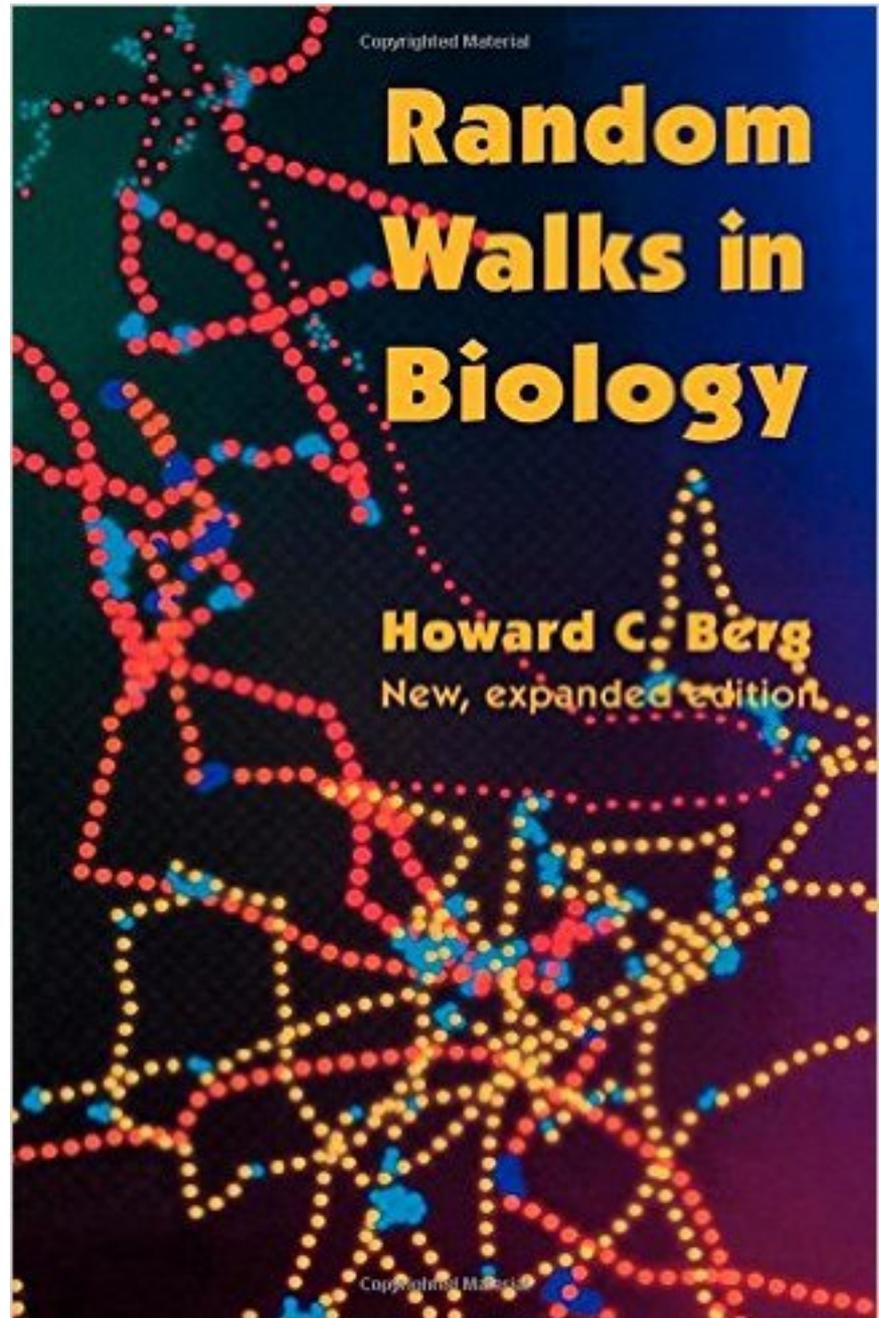
Fick's Second Law

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2}$$

$$\frac{1}{2\pi a(r_o + r_i)} \frac{\partial^2 V_m}{\partial z^2} = C_m \frac{\partial V_m}{\partial t} + G_K(V_m, t) (V_m - V_K) + G_{Na}(V_m, t) (V_m - V_{Na}) + G_L(V_m - V_L)$$

Note

Useful reference re the *microscopic* basis for diffusion



Diffusion processes

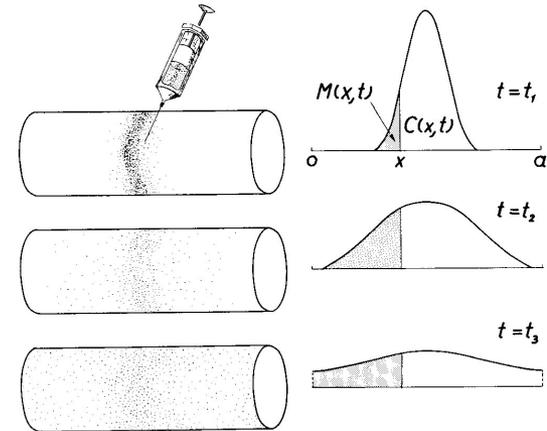
ex. Impulse Response: Point-source of particles (n_o mol/cm²) at $t = 0$ and $x = 0$
[Dirac delta function $\delta(x)$]

given the initial/boundary conditions:

$$c(x, t) = n_o \delta(x) \quad \text{at } t = 0 \quad \text{where} \quad \int_{-\infty}^{\infty} \delta(x) dx = 1$$

need to solve:

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2}$$



Batschelet Fig.12.5

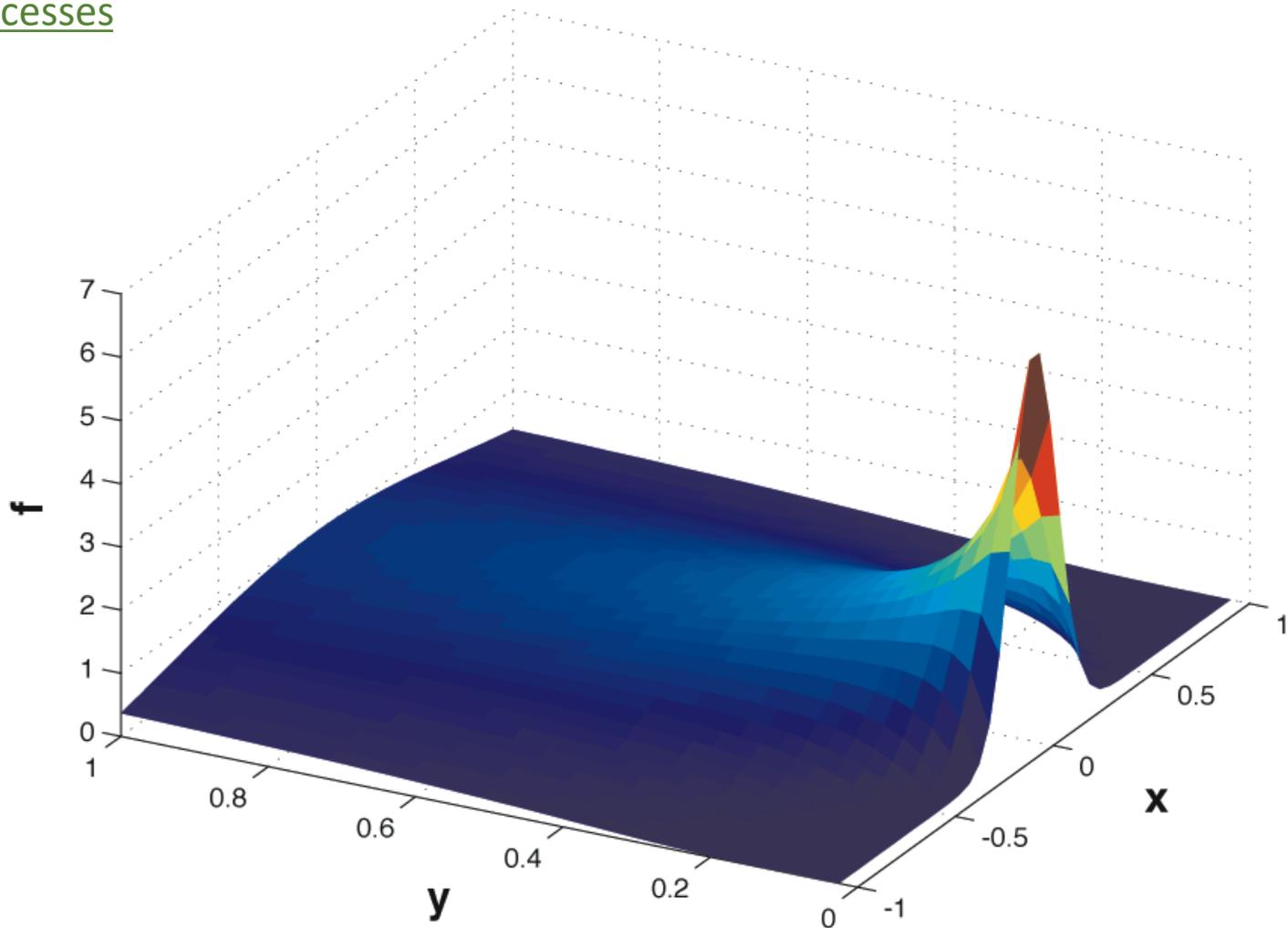
Solution can be found by a # of different methods, one being by separation of variables and using a Fourier transform

Solution
(for $t > 0$)

$$c(x, t) = \frac{n_o}{\sqrt{4\pi Dt}} e^{-x^2/4Dt}$$

Note: Historically, this ties in directly w/ the development of “Fourier analysis”

Diffusion processes



$$f(x, y) = \frac{1}{\sqrt{y}} e^{-x^2/y}$$

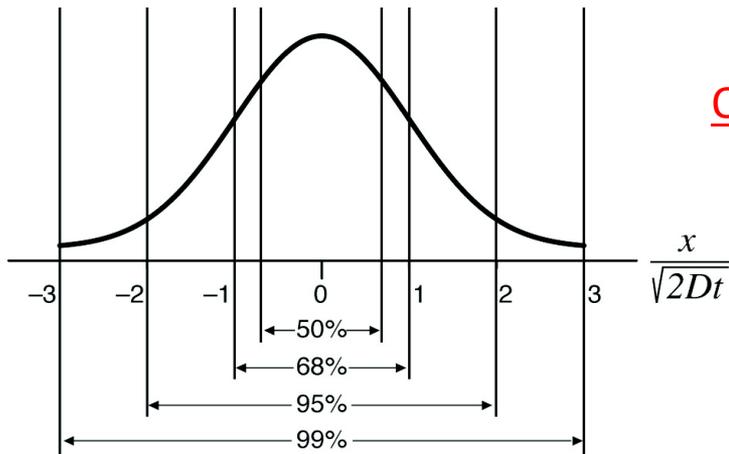
Solution to
diffusion equation

Importance of scale

$$c(x, t) = \frac{n_o}{\sqrt{4\pi Dt}} e^{-x^2/4Dt}$$

Gaussian function with zero mean and standard deviation:

$$\sigma = \sqrt{2Dt}$$



Question: How long does it take ($t_{1/2}$) for $\sim 1/2$ the solute to move at least the distance $x_{1/2}$?

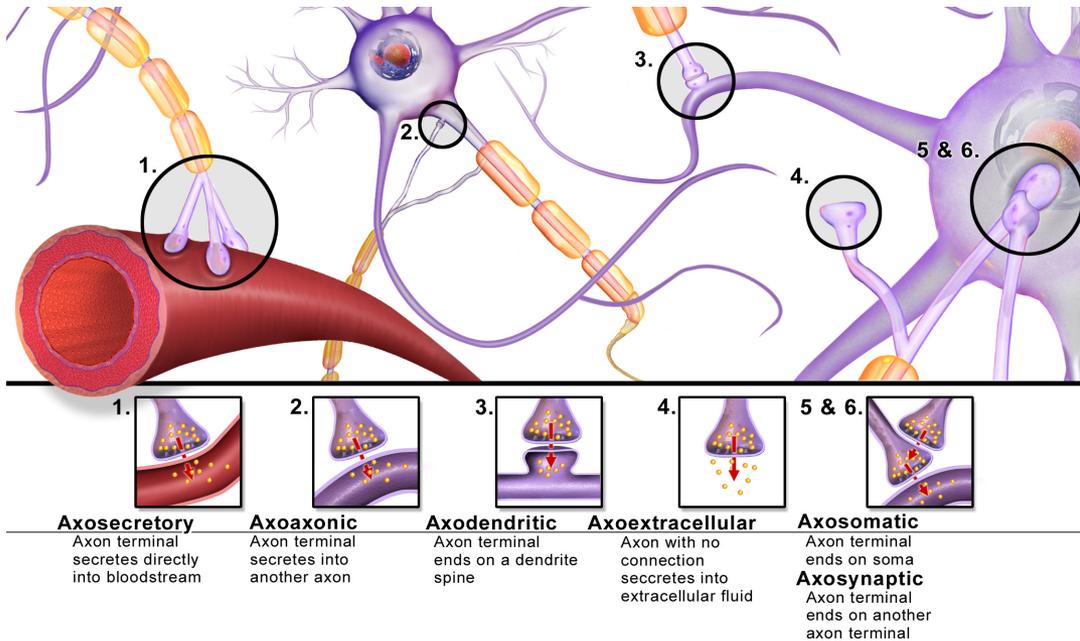
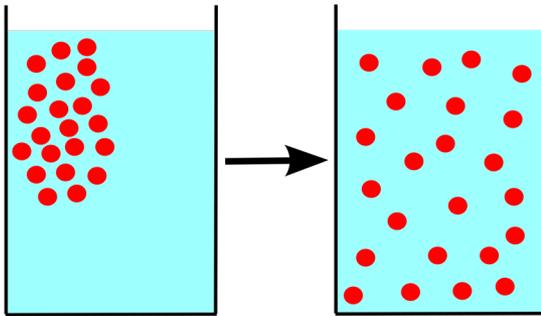
$$\frac{x_{1/2}}{\sqrt{2Dt_{1/2}}} \approx \frac{2}{3} \implies t_{1/2} \approx \frac{x_{1/2}^2}{D}$$

For small solutes
(e.g. K^+ at body temperature) $D \approx 10^{-5} \frac{\text{cm}^2}{\text{s}}$

\rightarrow To 1st order, this is why cells are roughly 10 μm in size!

	$x_{1/2}$	$t_{1/2}$
membrane sized	10 nm	$\frac{1}{10} \mu\text{sec}$
cell sized	10 μm	$\frac{1}{10}$ sec
dime sized	10 mm	10^5 sec \approx 1 day

Key Idea: Diffusion is a fundamental aspect by which neurons “communicate”



Chemical synapses “communicate” via diffusion of neurotransmitter(s)

Rough calculation:

Diffusion across the synaptic cleft (~20 nm) takes ~ 1 μ s

(i.e., diffusion is plenty fast!)

Membrane diffusion

What happens when some of these random walkers are charged (i.e., interacting)?

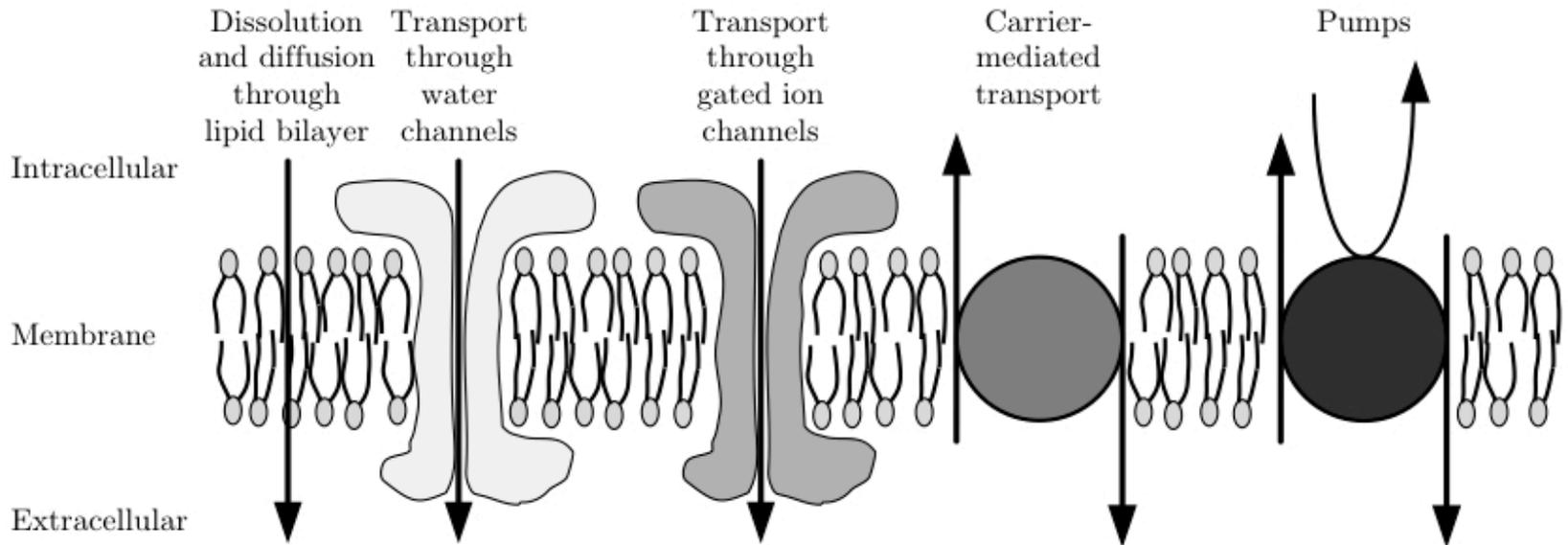
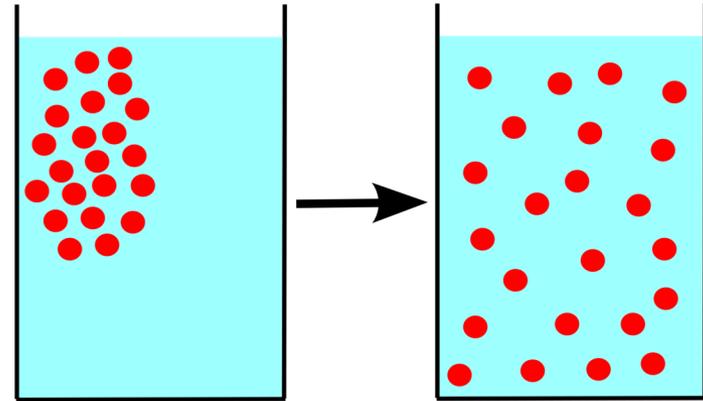


Figure 2.19

Electrodifusion

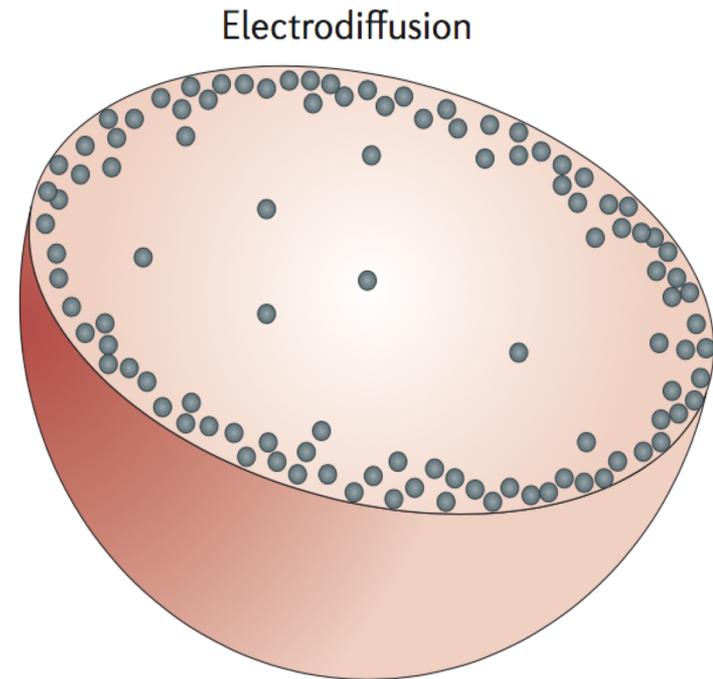
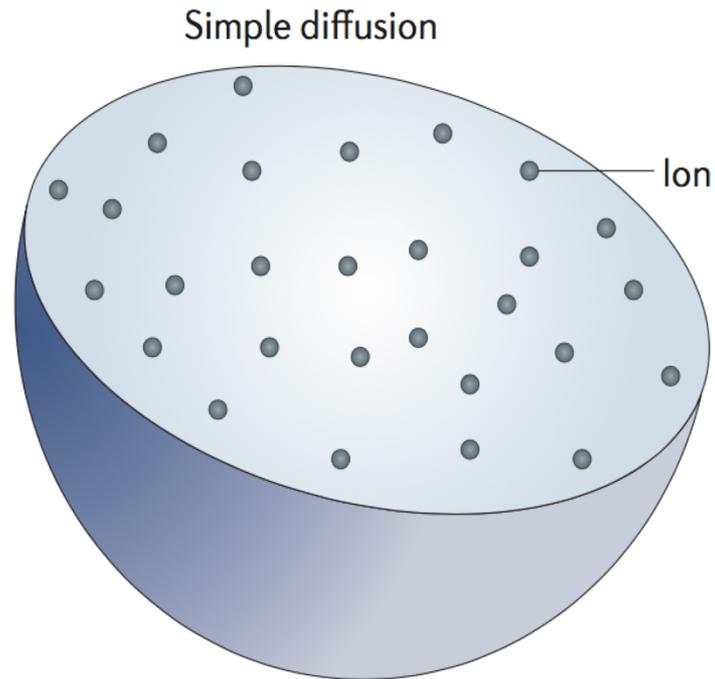
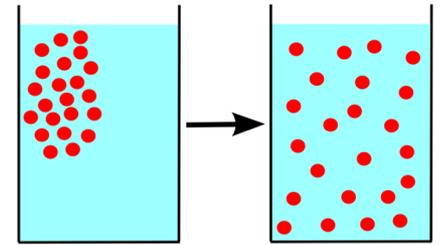


Figure 3 | **Comparison of simple diffusion and electrodiffusion theories.** Traditional diffusion theories and electrodiffusion theories make very different predictions about the distribution of ions within a three-dimensional structure such as a dendritic spine head.

Savtchenko et al

Electrodiffusion phenomena in neuroscience: a neglected companion

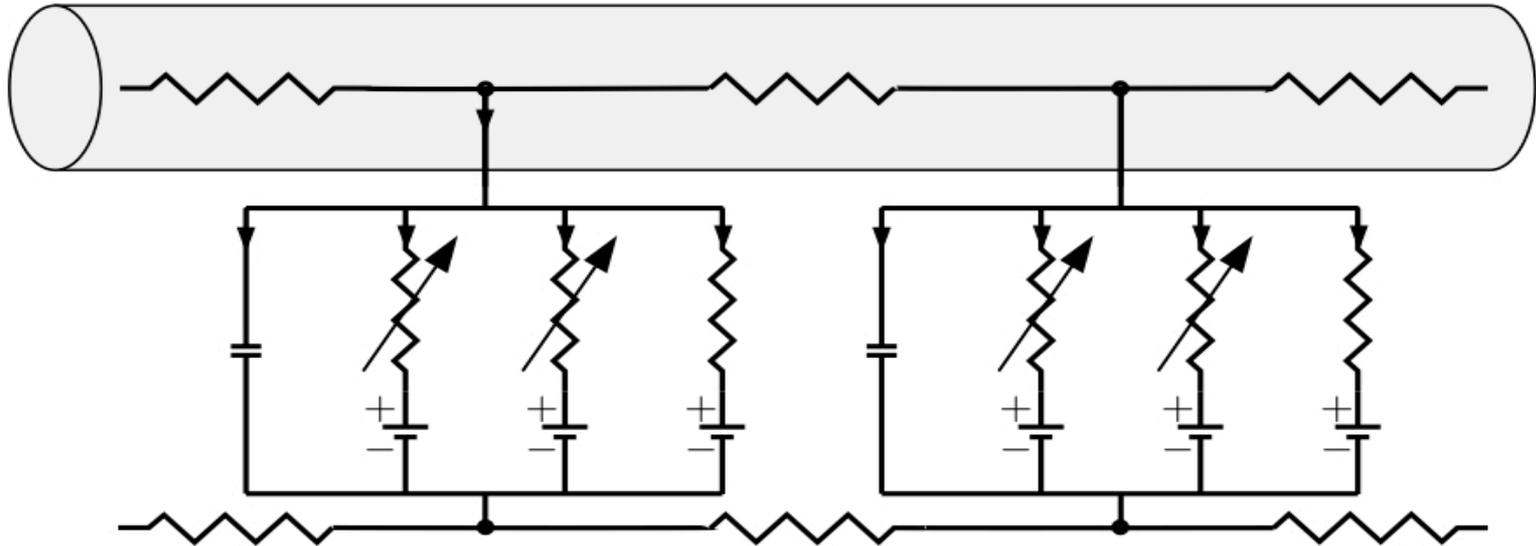
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Abstract | The emerging technological revolution in genetically encoded molecular sensors and super-resolution imaging provides neuroscientists with a pass to the real-time nano-world. On this small scale, however, classical principles of electrophysiology do not always apply. This is in large part because the nanoscopic heterogeneities in ionic concentrations and the local electric fields associated with individual ions and their movement can no longer be ignored. Here, we review basic principles of molecular electrodiffusion in the cellular environment of organized brain tissue. We argue that accurate interpretation of physiological observations on the nanoscale requires a better understanding of the underlying electrodiffusion phenomena.

“We also endeavour to dispel some common misconceptions regarding the nature of the membrane potential while trying not to dwell too much on the well-established electrophysiological postulates.”

“...discuss where and how electroneutrality could be violated and what consequences this may have for our interpretation of empirical observations”

Neurons as "electrically large" cells



Weiss (1996)

Combine HH with a simple electrical model that treats neurons as leaky submarine cables
 → **Propagated** action potentials

Cable Equation

Let $v_m(z, t) = V_m(z, t) - V_m^o$ and $|v_m(z, t)| \ll |V_m^o|$:

$$v_m(z, t) + \tau_M \frac{\partial v_m(z, t)}{\partial t} - \lambda_C^2 \frac{\partial^2 v_m(z, t)}{\partial z^2} = r_o \lambda_C^2 K_e(z, t)$$

$$\frac{1}{2\pi a(r_o + r_i)} \frac{\partial^2 V_m}{\partial z^2} = C_m \frac{\partial V_m}{\partial t} + G_K(V_m, t) (V_m - V_K) + G_{Na}(V_m, t) (V_m - V_{Na}) + G_L(V_m - V_L)$$

Hodgkin Huxley model (HH)

$$\frac{1}{2\pi a(r_o + r_i)} \frac{\partial^2 V_m}{\partial z^2} = C_m \frac{\partial V_m}{\partial t} + G_K(V_m, t) (V_m - V_K) + G_{Na}(V_m, t) (V_m - V_{Na}) + G_L(V_m - V_L)$$

$$G_K(V_m, t) = \bar{G}_K n^4(V_m, t)$$

$$G_{Na}(V_m, t) = \bar{G}_{Na} m^3(V_m, t) h(V_m, t)$$

$$n(V_m, t) + \tau_n(V_m) \frac{dn(V_m, t)}{dt} = n_\infty(V_m)$$

$$m(V_m, t) + \tau_m(V_m) \frac{dm(V_m, t)}{dt} = m_\infty(V_m)$$

$$h(V_m, t) + \tau_h(V_m) \frac{dh(V_m, t)}{dt} = h_\infty(V_m)$$

$$\tau_x \frac{dx}{dt} + x = x_\infty \quad \frac{dx}{dt} = \alpha_x(1-x) - \beta_x x$$

$$x_\infty = \alpha_x / (\alpha_x + \beta_x) \text{ and } \tau_x = 1 / (\alpha_x + \beta_x)$$

$$\alpha_m = \frac{-0.1(V_m + 35)}{e^{-0.1(V_m + 35)} - 1},$$

$$\beta_m = 4e^{-(V_m + 60)/18},$$

$$\alpha_h = 0.07e^{-0.05(V_m + 60)},$$

$$\beta_h = \frac{1}{1 + e^{-0.1(V_m + 30)}},$$

$$\alpha_n = \frac{-0.01(V_m + 50)}{e^{-0.1(V_m + 50)} - 1},$$

$$\beta_n = 0.125e^{-0.0125(V_m + 60)},$$

Question

So do these equations tell us everything about how a neuron *fires*? Or how the brain *works*?

Simplifications v1 – Simpler Neuronal models

HH is certainly too *simple*, but also sometimes too complicated...

Fitzhugh–Nagumo model

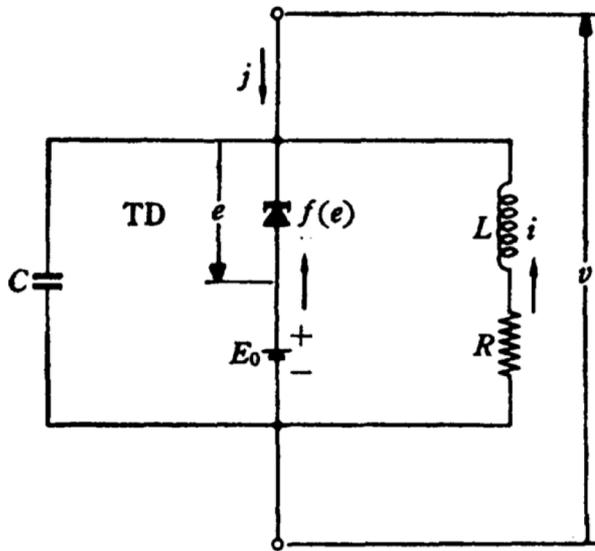
$$\dot{x} = c(y + x - x^3/3 + z)$$

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

Everything should be made as simple as possible, but no simpler.

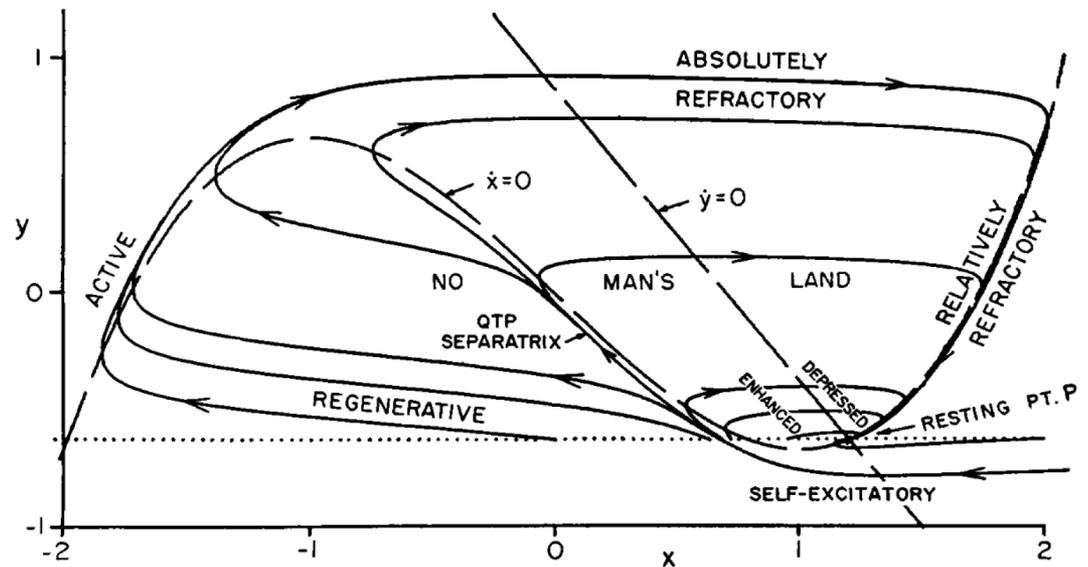
[Roger Session re Einstein]

Circuit representation



Nagumo et al (1962)

Phase space behavior



Fitzhugh (1961)

Simplifications v2 – More than one neuron...

New ideas readily emerge when there are multiple coupled neurons

*"Rather than focus on the microscopic properties of neurons, W&C analyzed the collective properties of large numbers of neurons using methods from statistical mechanics, based on the **mean-field approach**."*

[Destexhe & Sejnowski 2009]

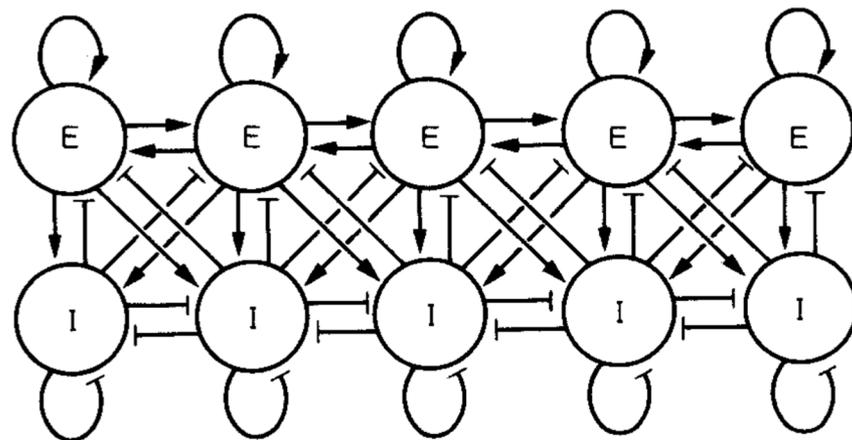
EXCITATORY AND INHIBITORY INTERACTIONS IN LOCALIZED POPULATIONS OF MODEL NEURONS

HUGH R. WILSON *and* JACK D. COWAN

BIOPHYSICAL JOURNAL VOLUME 12 1972

$$\tau \frac{dE}{dt} = -E + \left[1 - \int_{t-\tau}^t E(t') dt' \right] S_e \left\{ \int_{-\infty}^t e^{-\alpha(t-t')} [c_1 E(t') + P(t')] dt' \right\}$$

$$\tau \frac{d\bar{E}}{dt} = -\bar{E} + (1 - r\bar{E}) S_e [kc_1 \bar{E}(t) + kP(t)].$$



Wilson & Cowan (1973)

Simplifications v3 – Limit cycles

Implicit in Fitzhugh–Nagumo and Wilson–Cowan is the notion of a **limit cycle**....

$$\ddot{x} + \gamma \dot{x} + \omega_o^2 x = \frac{F_o}{m} \cos \omega t$$

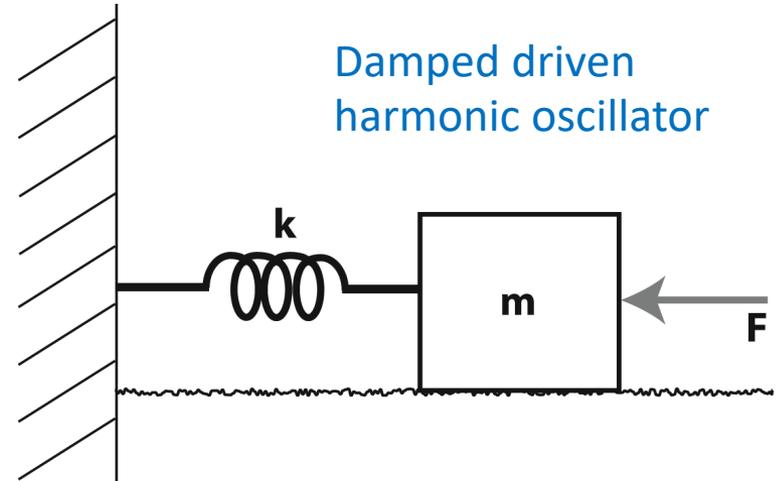
$$z(t) = Ae^{-i(\omega t + \delta)}$$

Steady-state solution as a **complex exponential** (*eigenvalues!*)

$$A(\omega) = \frac{F_o/m}{[(\omega_r^2 - \omega^2)^2 + (\gamma m)^2]^{1/2}}$$

$$\delta(\omega) = \frac{\gamma \omega}{\omega_r^2 - \omega^2}$$

Now what if we allow for negative damping and a nonlinearity to stabilize?

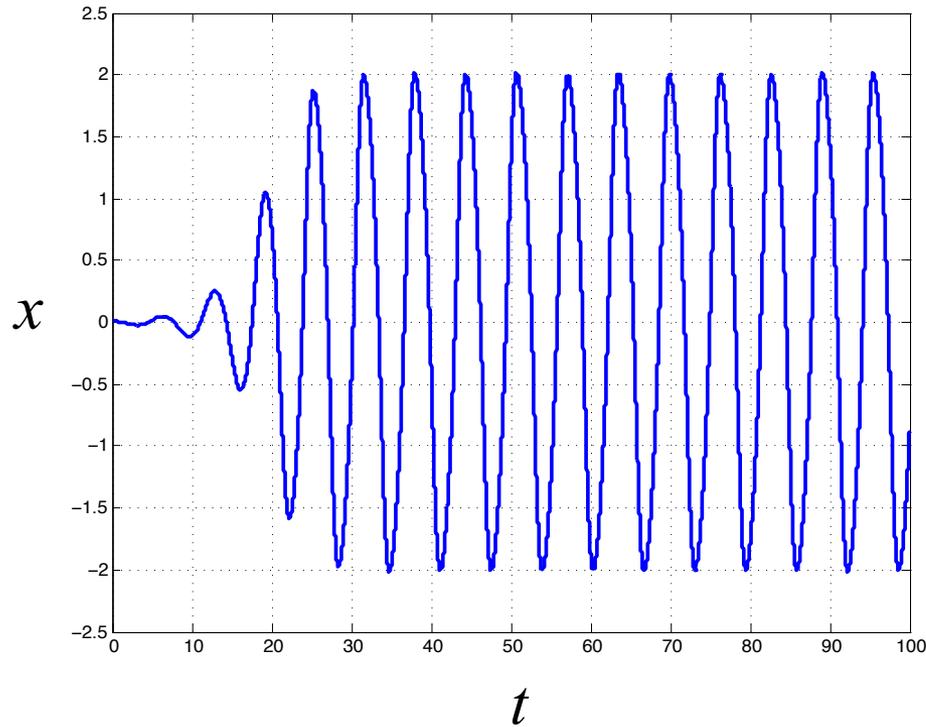


Amplitude and phase provide natural connection point to Fourier analysis

van der Pol equation

$$\ddot{x} = -x - \varepsilon(x^2 - 1)\dot{x}$$

Simplifications v3 – Limit cycles

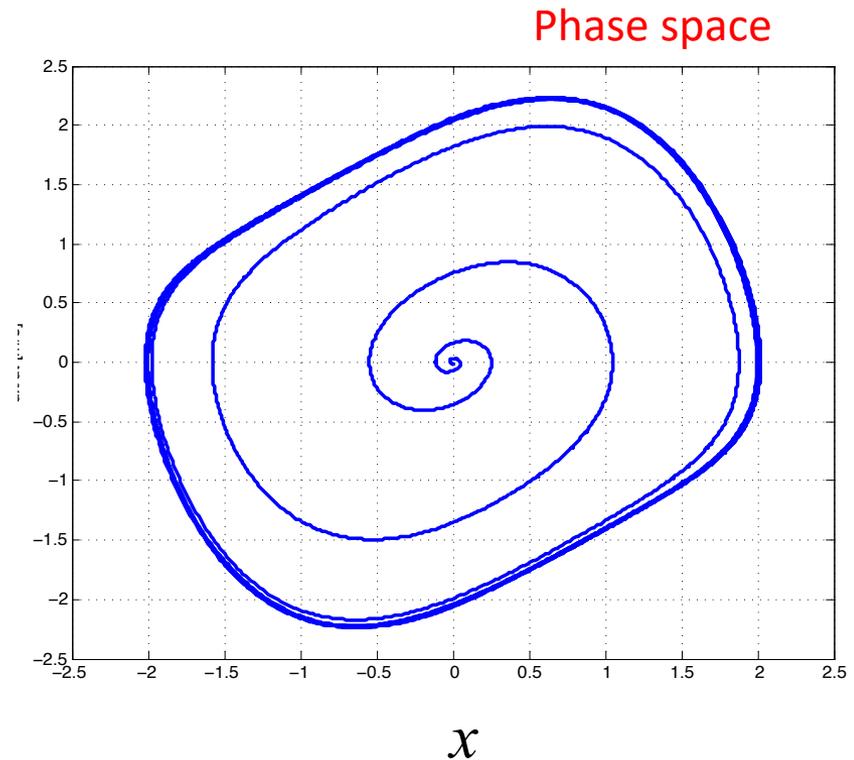


van der Pol equation

$$\ddot{x} = -x - \varepsilon(x^2 - 1)\dot{x}$$

→ Even though there is damping, the system oscillates by itself in a stable fashion (i.e., no external drive!)

dx/dt



Simplifications v4 – Normal forms

van der Pol equation

$$\ddot{x} = -x - \varepsilon(x^2 - 1)\dot{x}$$

"Normal form" = simplified version

$$m\ddot{x} - \mu(a - x^2)\dot{x} + kx = F(t)$$

Note: A single complex differential equation is (more or less) equivalent to a system of two first order real-valued equations

Just like Fitzhugh–Nagumo simplifies HH, can we modify here to make more mathematically tractable for analysis?

$$\rightarrow \dot{z} = -\mu z + i\omega_0 z + z|z^2|$$

This is also a good connection point into *bifurcation analysis*

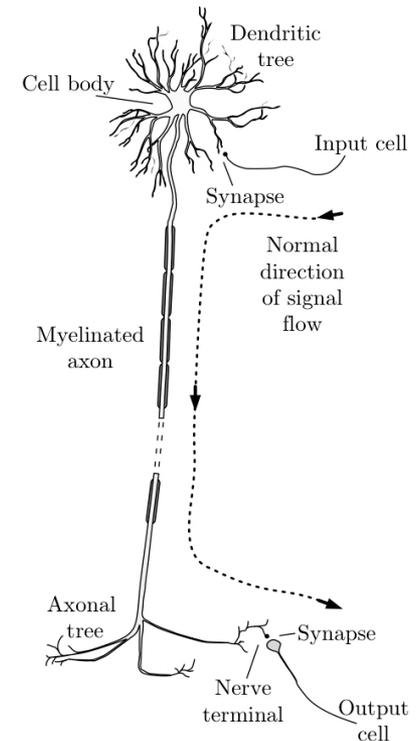
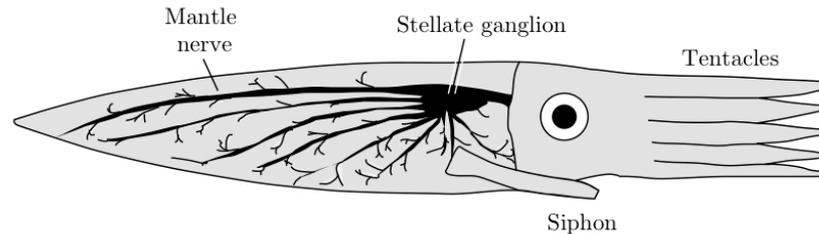
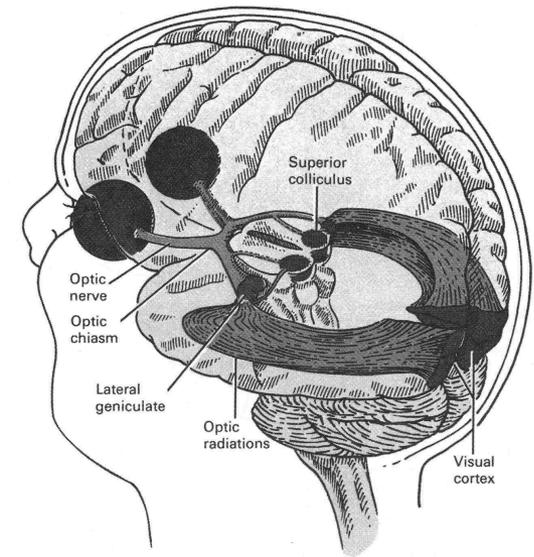
(e.g., how does behavior change with μ ?)

$$z_{n+1} = z_n^2 + c \quad \leftrightarrow \quad \begin{aligned} x_{n+1} &= x_n^2 - y_n^2 + \operatorname{Re}(c) \\ y_{n+1} &= 2x_n y_n + \operatorname{Im}(c) \end{aligned}$$

Summary

Through the lens of neural biophysics, a rich/broad range of mathematical topics emerge:

- Ordinary differential equations (ODEs) → **Change**
- Multivariable functions → **Space & time considered**
- Partial differential equations (PDEs) → e.g., Diffusion
- Linear vs Nonlinear Phenomena → **Complexity**
- Micro- to macro-scopic → **Mean-field approaches, stat mech**
- Complex #s → **Fourier methods, eigenvalues/vectors**
- Normal forms → e.g., **Limit cycle oscillators, bifurcation analysis**



Finally there was the difficulty of computing the action potentials from the equations which we had developed. We had settled all the equations and constants by March 1951 and hoped to get these solved on the Cambridge University computer. However, before anything could be done we learnt that the computer would be off the air for 6 months or so while it underwent a major modification. Andrew Huxley got us out of that difficulty by solving the differential equations numerically using a hand-operated Brunsviga. The propagated action potential took about three weeks to complete and must have been an enormous labour for Andrew. But it was exciting to see it come out with the right shape and velocity and we began to feel that we had not wasted the many months that we had spent in analysing records.

—Hodgkin, 1977





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- Slides available for download: <http://www.yorku.ca/cberge/>
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<http://dpmb.physics.umanitoba.ca/cap%202018%20dpmb101%20slides.html>



Lennart Nilsson (1966)

