Differential equations and their simulation in neuroscience

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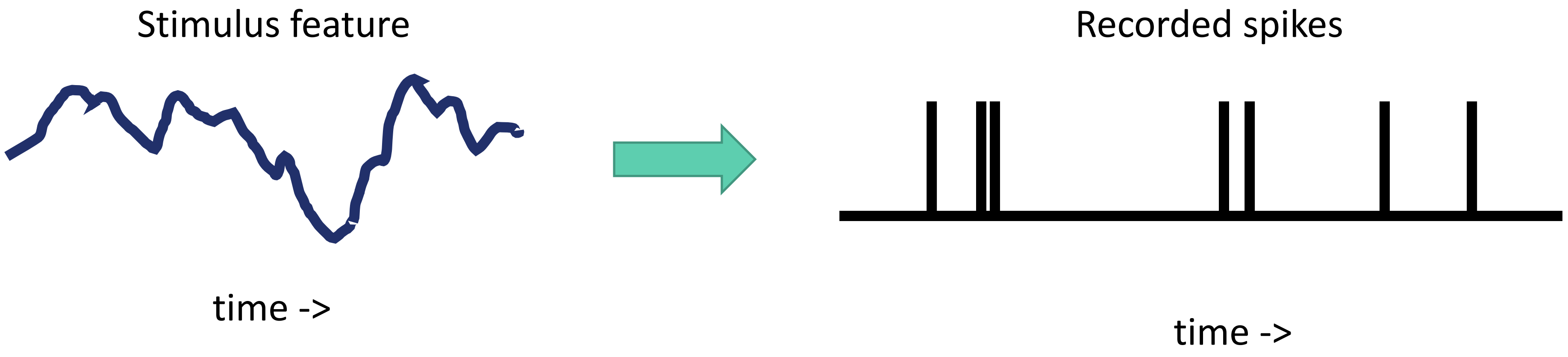
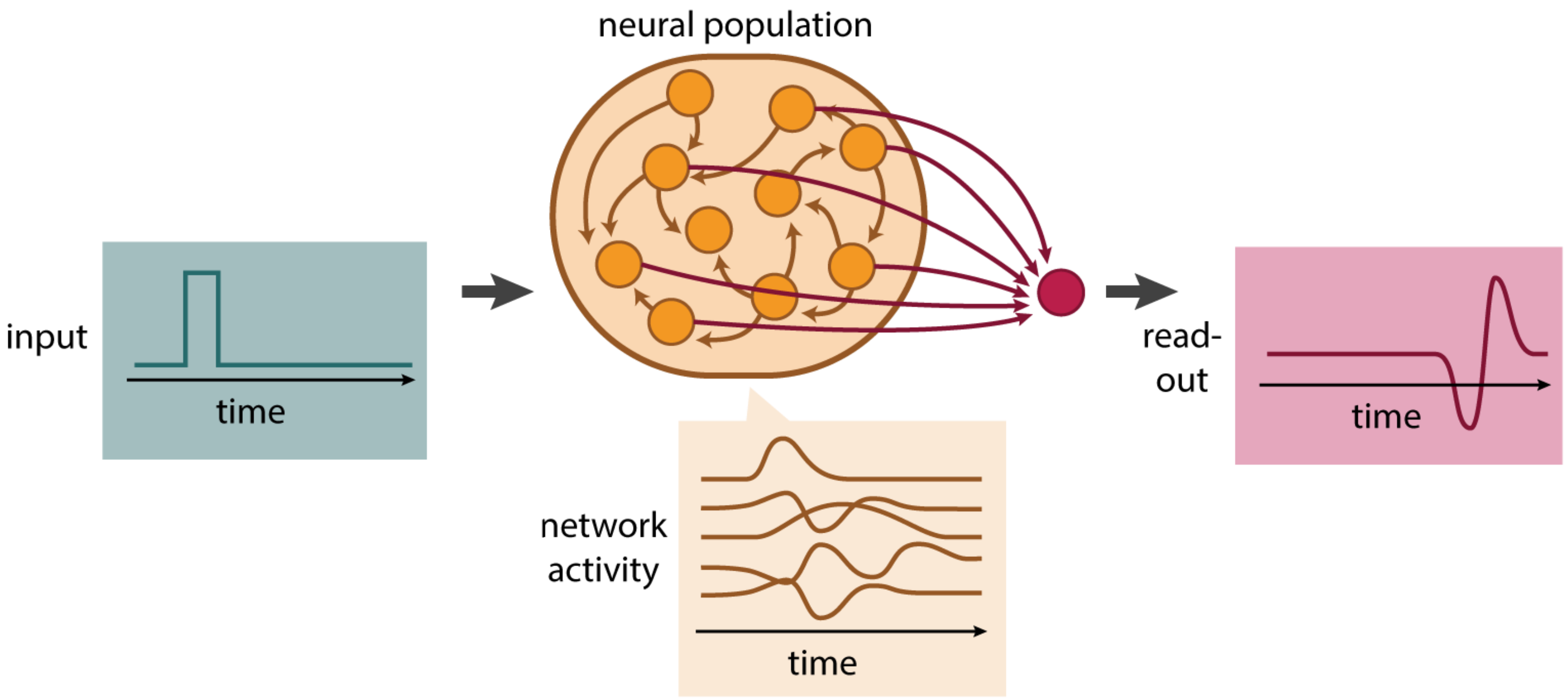
Neuroscience data is time series data



Neuroscience data is time series data



We use two families of tools to deal with time series data

Statistical models and signal processing

- Fit descriptive models of observed neural activity.
- Understand how a neuron filters and transforms its input.

Dynamical systems

- Model behavior of neural populations (or any other system) from first principles.
- Analyze models for interesting structure: attractors, limit cycles, etc.

The neuroscientist’s favorite differential equation

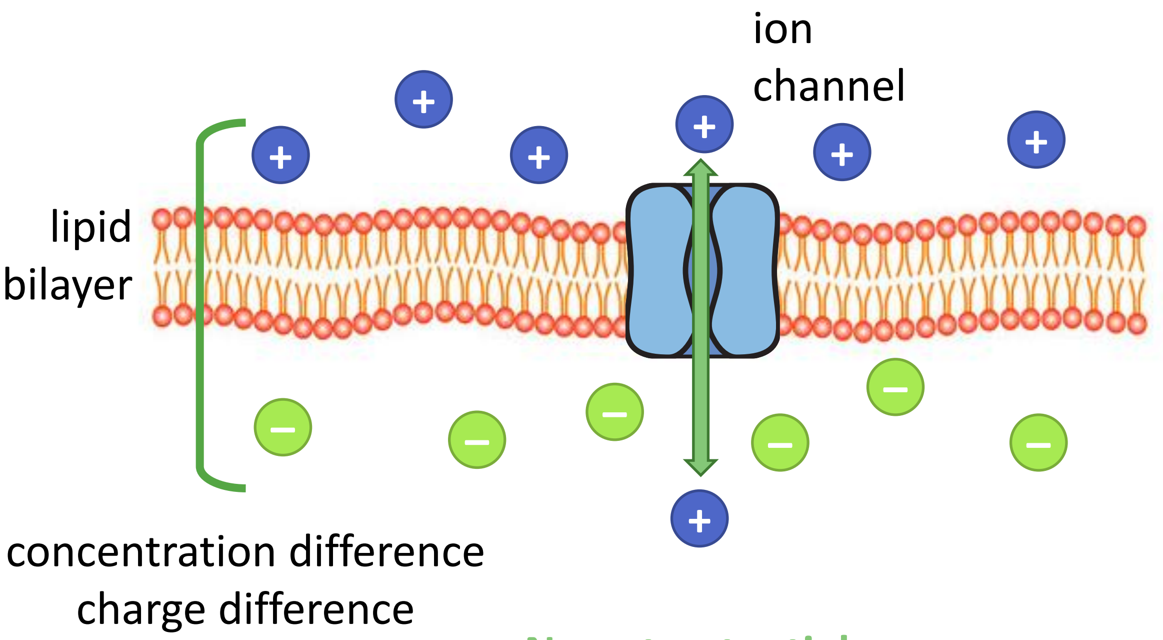
Capacitor dynamics

$$C \, dV/dt = I$$

Ohm’s Law

$$V = I R$$

Neurons store energy in the form of charge and concentration gradients across their membrane



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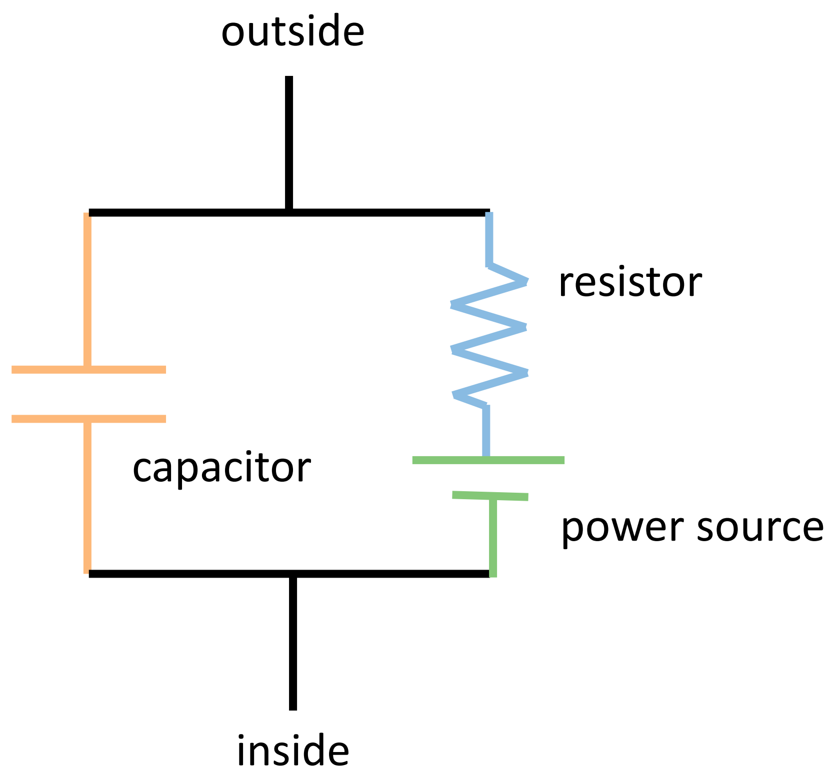


Nernst potential
Combined effect of concentration and charge “forces” on ions

Neurons store energy in the form of charge and concentration gradients across their membrane

Ohm's law

$$V = I\,R$$

$$I = \frac{1}{R}V$$

$$I = g(E_{\mathrm{ion}} - V)$$

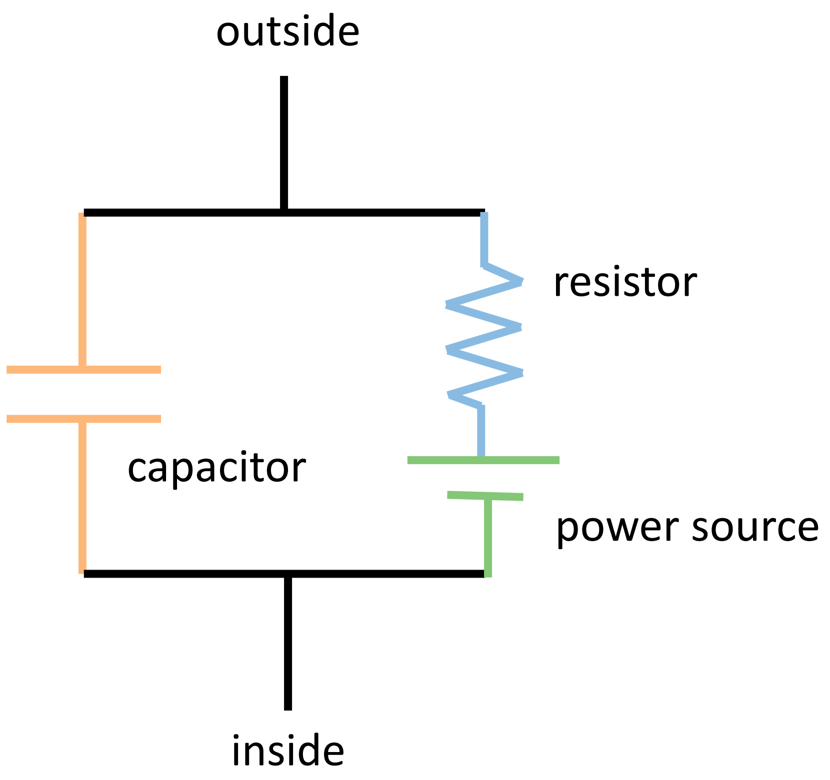
Capacitor dynamics

$$C\,\frac{dV}{dt} = I$$

$$C\,\frac{dV}{dt} = g(E_{\mathrm{ion}} - V)$$

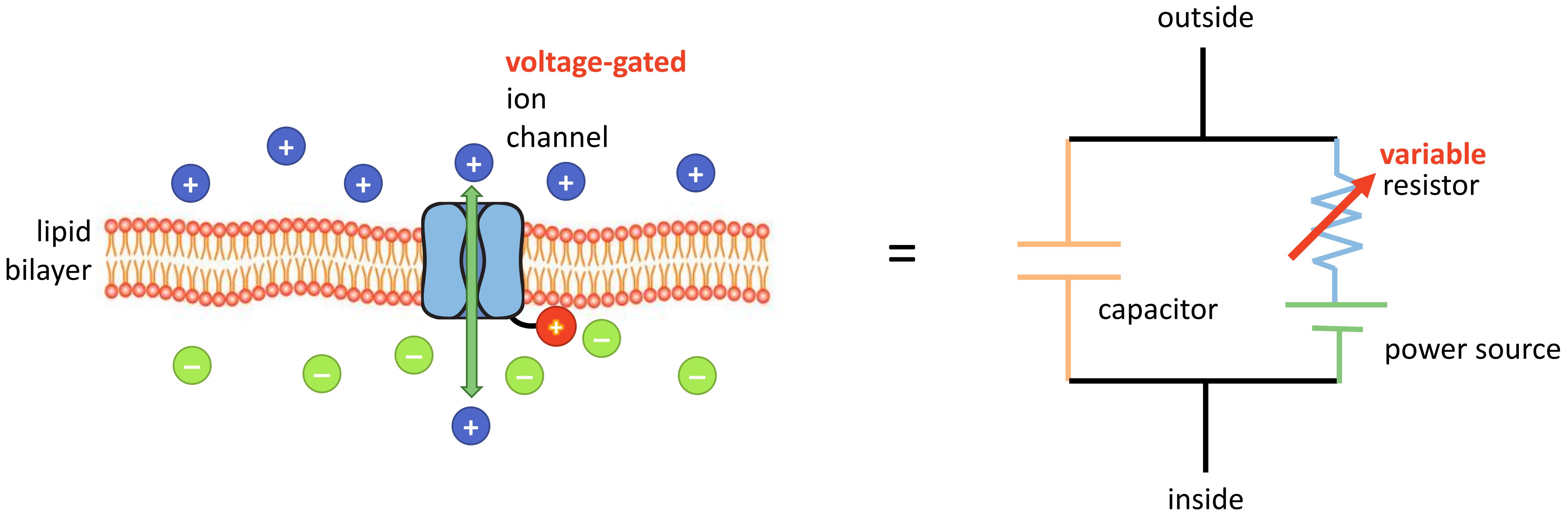
$$\boxed{\frac{dV}{dt} = \frac{1}{RC}(E_{\mathrm{ion}} - V)}$$

First-order linear ordinary differential equation



Note: g = conductance = 1/resistance

Voltage-gated ion channels let neurons generate action potentials



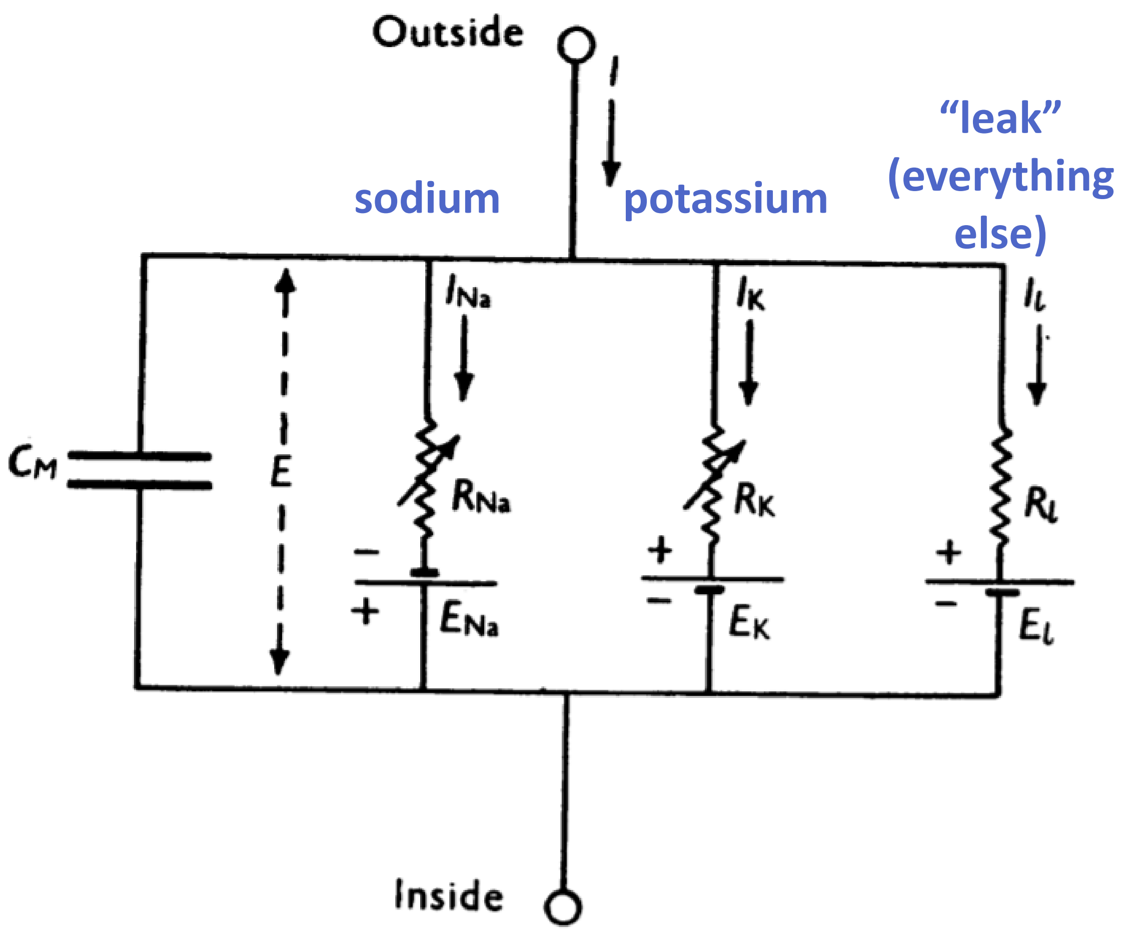
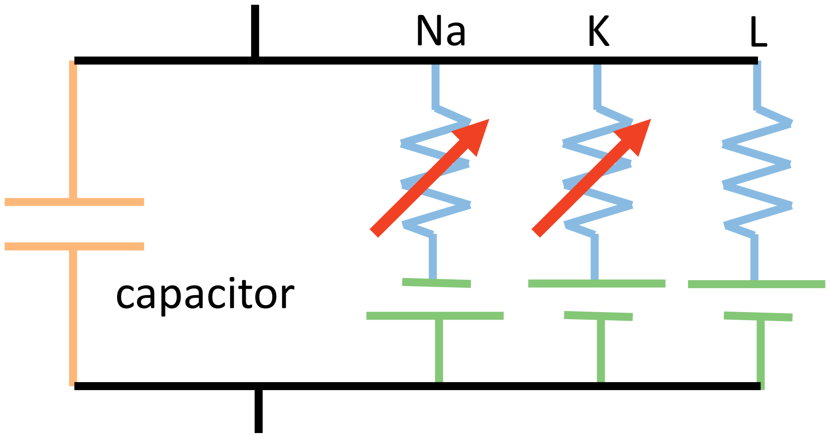


Fig. 1. Electrical circuit representing membrane. $R_{Na}=1/g_{Na}$; $R_K=1/g_K$; $R_l=1/\bar{g}_l$. R_{Na} and R_K vary with time and membrane potential; the other components are constant.

Hodgkin and Huxley (1952) J Physiol.

The Hodgkin-Huxley Model



Ohm's law

$I = g \cdot (E_{ion} - V)$

Capacitor dynamics

$C \cdot dV/dt = I$

$C \cdot dV/dt = I_{Na} + I_K + I_L + I_{ext}$

$$C\frac{dV}{dt} = g_K(V)(V - E_{\mathrm{K}}) + g_{Na}(V)(V - E_{\mathrm{Na}}) + g_L(V)(V - E_{\mathrm{L}}) + I_{ext}$$

functions of voltage and time

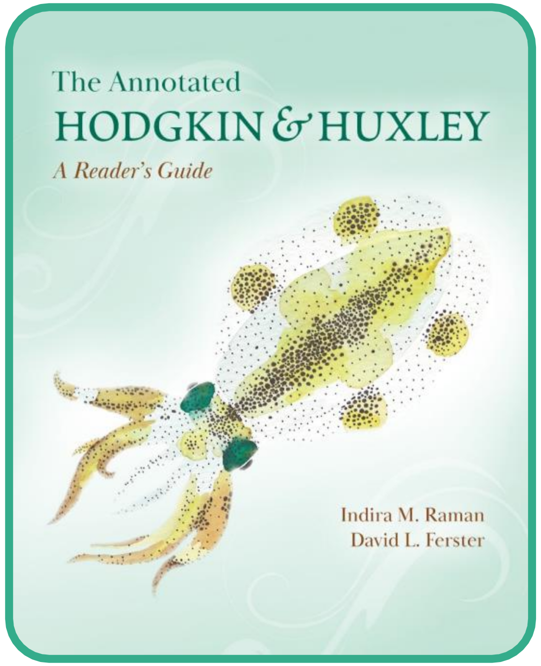
$$g_K(V) = \bar{g}_K n^4$$

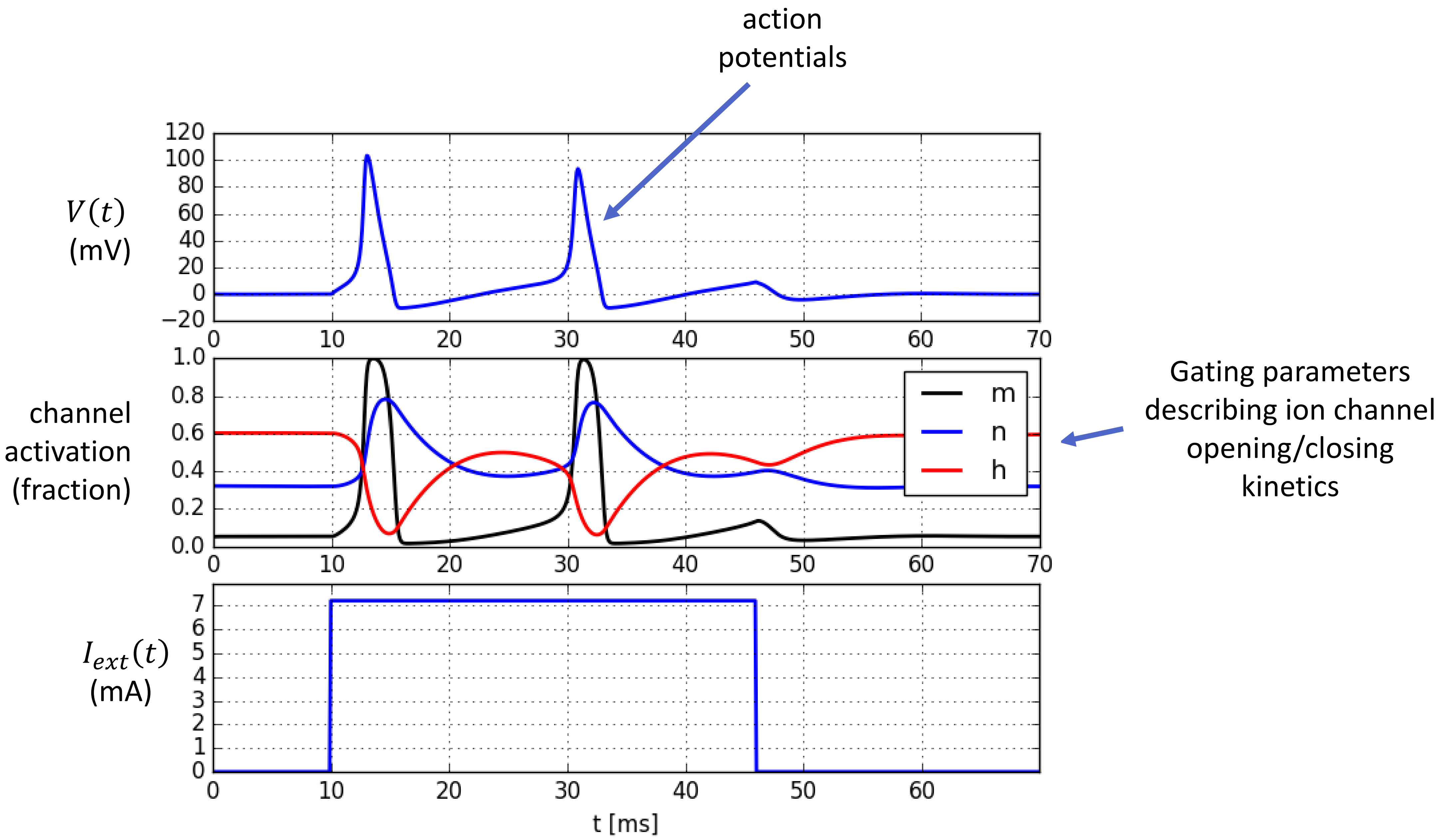
$$g_{Na}(V) = \bar{g}_{Na} m^3 h$$

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n$$

$$\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m$$

$$\frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_n(V)h$$





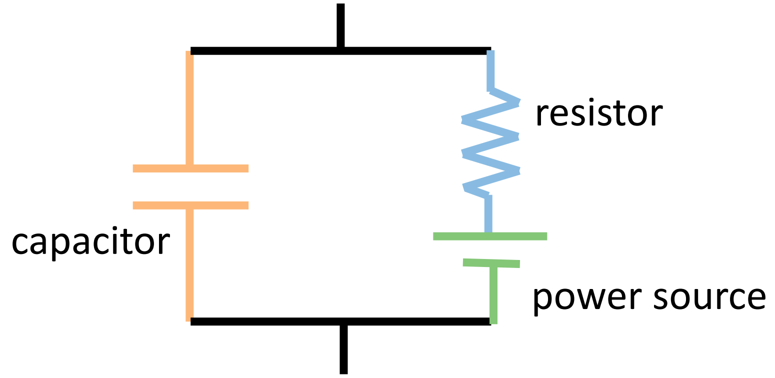
action potentials
$V(t)$ (mV)
channel activation (fraction)
m
n
h
Gating parameters describing ion channel opening/closing kinetics
$I_{ext}(t)$ (mA)
t [ms]

Let's start with the simpler model. How do we study this differential equation?

$$\frac{dV}{dt} = \frac{1}{RC}(E_{\text{ion}} - V)$$

$$0 = \frac{1}{RC}(E_{\text{ion}} - V)$$

$$\boxed{V_{ss} = E_{\text{ion}}}$$

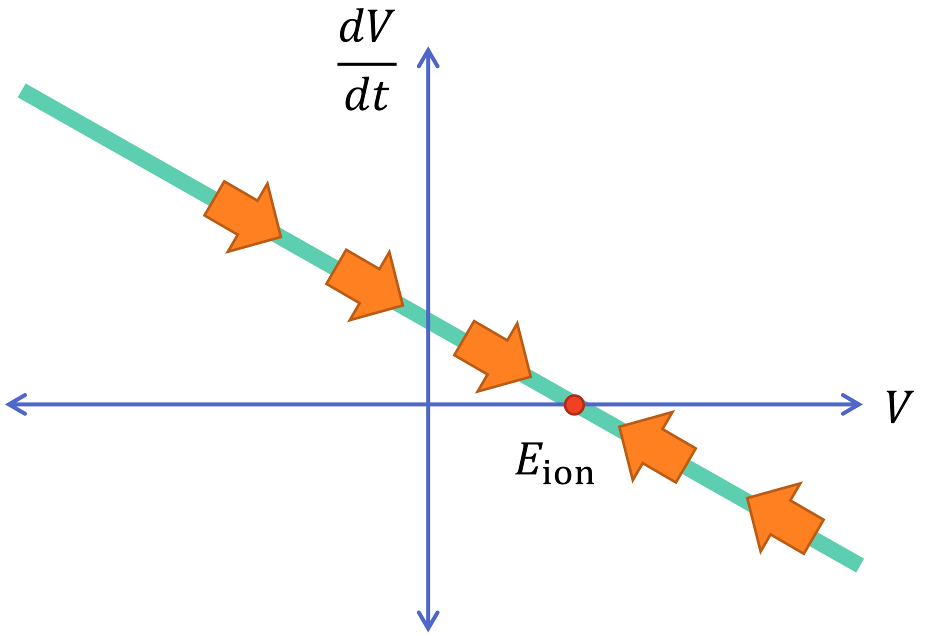


- The membrane potential V has a steady state (ss) value of E_{ion}.
- What happens when $V > E_{\text{ion}}$?

$$\frac{dV}{dt} \sim E_{\text{ion}} - V < 0$$

- What happens when $V < E_{\text{ion}}$?

$$\frac{dV}{dt} \sim E_{\text{ion}} - V > 0$$



We can also try to solve this equation to see how V evolves over time

$$\frac{dV}{dt} = \frac{1}{RC}(E_{\text{ion}} - V)$$

$$\frac{dV}{E_{\text{ion}} - V} = \frac{dt}{RC}$$

$$\int \frac{1}{E_{\text{ion}} - V}\, dV = \int \frac{1}{RC}\, dt$$

$$-\log(E_{\text{ion}} - V) + k_v = \frac{t}{RC} + k_t$$

$$V(t) = E_{\text{ion}} - ke^{-\frac{t}{RC}}$$

$$V(0) = E_{\text{ion}} - ke^{-\frac{0}{RC}}$$

$$k = E_{\text{ion}} - V(0)$$

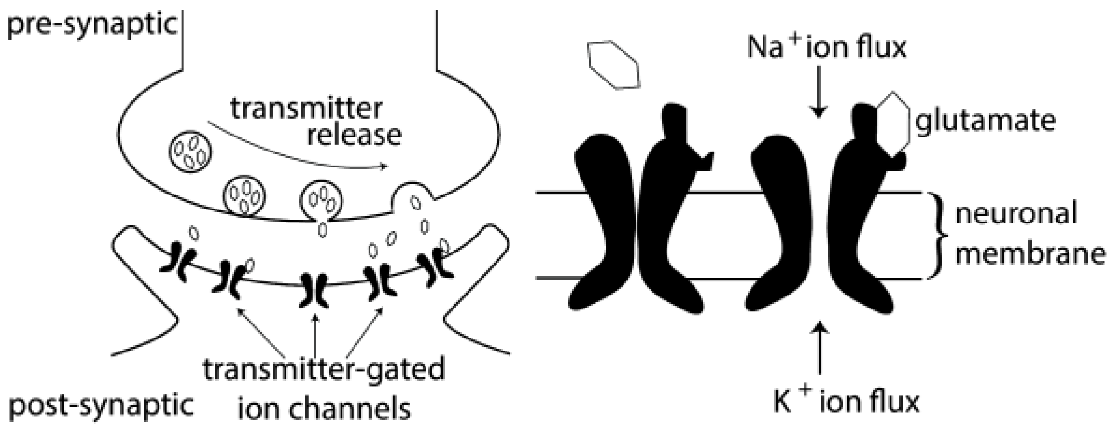
$$\boxed{V(t) = E_{\text{ion}} - \left(E_{\text{ion}} - V(0)\right) e^{-\frac{t}{RC}}}$$

- V approaches its steady state value exponentially, at a rate proportional to **1/(RC)**
  - We often call RC the <u>membrane time constant</u>.

- This equation was simple enough that we could solve it with some integration, aka study it <u>analytically</u>.

How would we model an external input to this system?

$$\frac{dV}{dt} = \frac{1}{RC}(E_{\text{ion}} - V) + I_{ext}(t)?$$



Postsynaptic potentials are typically modeled as an exponential or a difference of exponentials. E.g., given a spike at time T:

$$s_{syn}(t) = \frac{1}{\tau_d - \tau_r}\left(\exp\left(-\frac{t-T}{\tau_d}\right) - \exp\left(-\frac{t-T}{\tau_r}\right)\right)$$

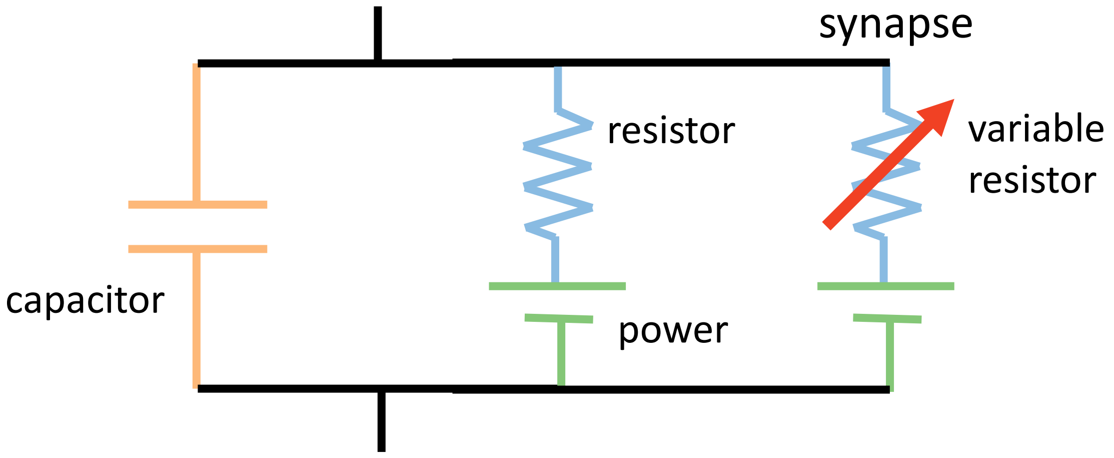
models typically capture the effect of this PSP in one of two ways:

The current-based synaptic model:

$$I_{ext}(t) = J_{syn}\, s_{syn}(t)$$

The conductance-based synaptic model:

$$I_{ext}(t) = \underline{g_{syn}\, s_{syn}(t)}\big(V(t) - V_{syn}\big)$$



Which input model do I use? How realistic does my model need to be?

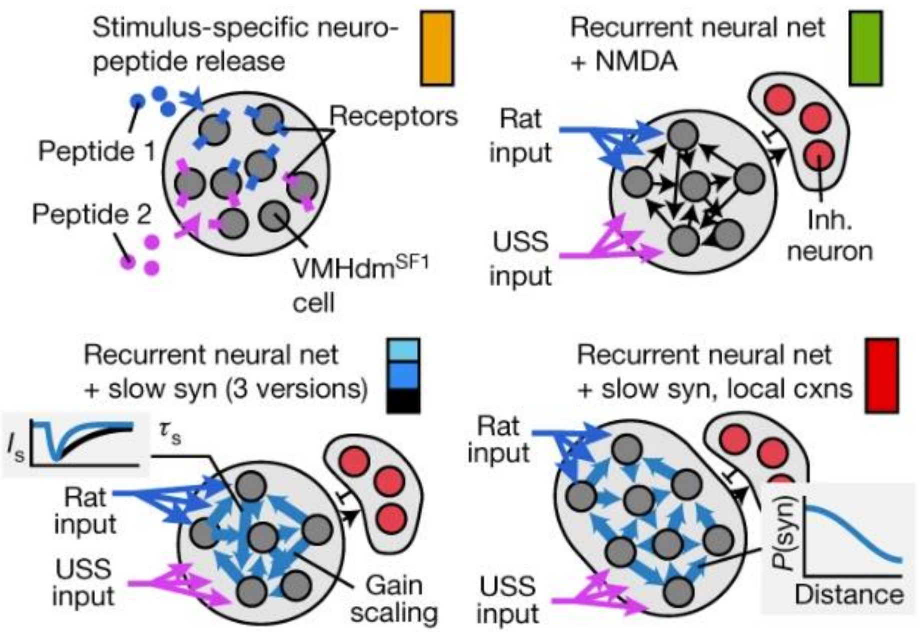
Scientists constantly create models of how they think a system works; these are the narratives that organize Results and Discussion sections of paper.

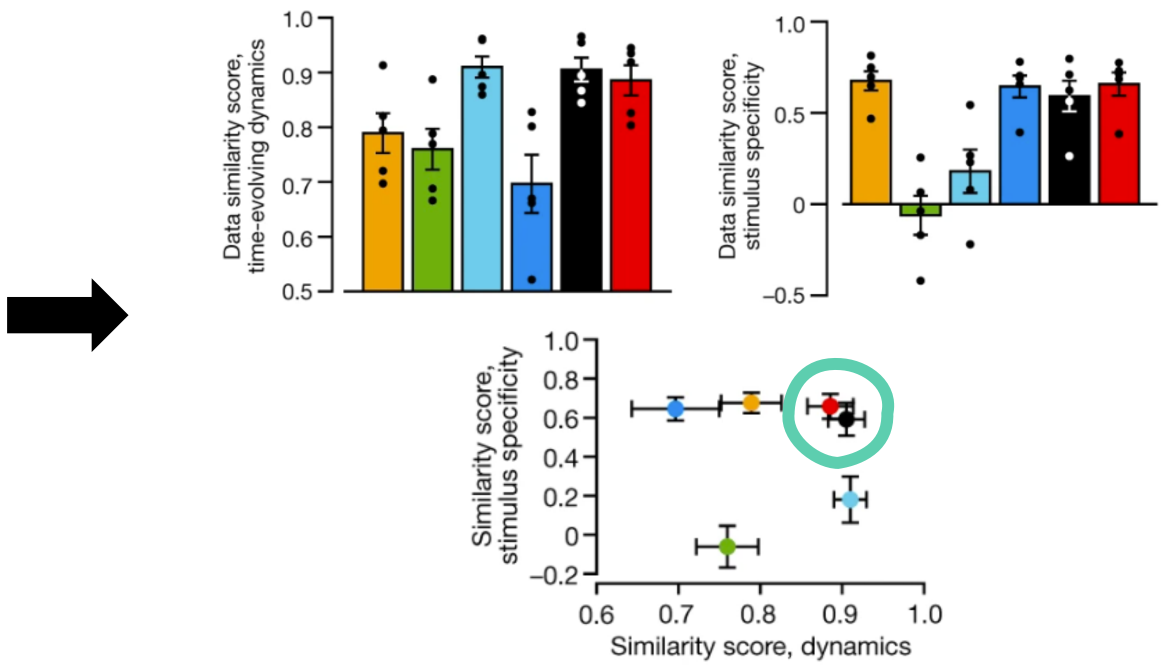
The role of theory is to formalize these “word models” with math, forcing them to be self-consistent.

Theoreticians use math to ask which explanations are consistent with the data and which are not.

A good model can make predictions or postdictions about phenomena (the latter is more common), contributing value to the field by explaining them in a new light, in a way that may inform how we think about other phenomena.

See: “Theoretical Neuroscience Rising”, L.F. Abbott.





Jorge Luis Borges on parametrizing your mathematical models

“In that Empire, the craft of Cartography attained such Perfection that the Map of a Single province covered the space of an entire City, and the Map of the Empire itself an entire Province. In the course of Time, these Extensive maps were found somehow wanting, and so the College of Cartographers evolved a Map of the Empire that was of the same Scale as the Empire and that coincided with it point for point.

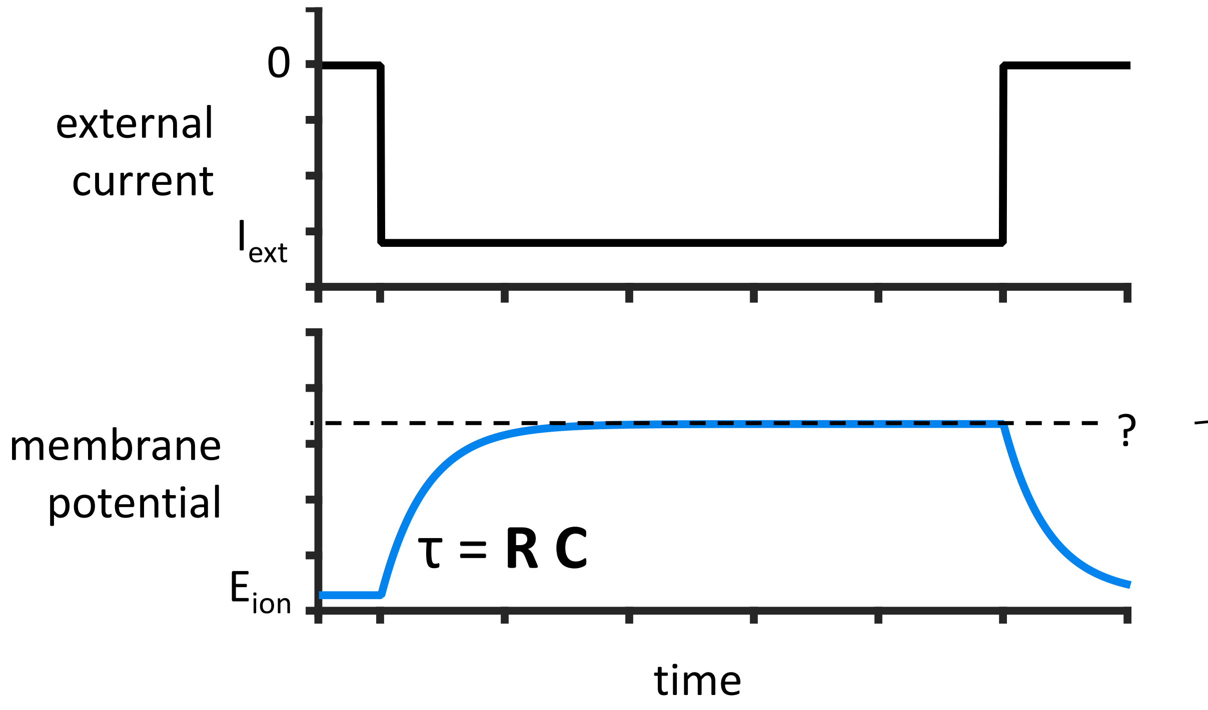
Less attentive to the Study of Cartography, succeeding Generations came to judge a map of such Magnitude cumbersome, and, not without Irreverence, they abandoned it to the Rigours of sun and Rain. In the western Deserts, tattered Fragments of the Map are still to be found, Sheltering an occasional Beast or beggar; in the whole Nation, no other relic is left of the Discipline of Geography.”

—“Del Rigor en la Ciencia”, Jorge Luis Borges

So anyway, let's add a current injection

$$C\,\frac{dV}{dt} = g(E_{\text{ion}} - V) + I_{ext}(t)$$

Non-homogeneous first-order ordinary differential equation



$$0 = g(E_{\text{ion}} - V) + I_{\text{ext}}(t)$$

$$gV = gE_{\text{ion}} + I_{\text{ext}}(t)$$

$$\boxed{V_{ss} = E_{\text{ion}} + RI_{\text{ext}}(t)}$$

We can still use analytical methods to study this system

$$C\frac{dV}{dt} = g(E_{\text{ion}} - V) + I_{ext}(t)$$

$$\frac{dV}{dt} + \frac{V}{CR} = \frac{E_{\text{ion}} + I_{ext}(t)}{CR}$$

define $\tau = CR$ and multiply through by the integrating factor $e^{t/\tau}$:

$$e^{t/\tau}\frac{dV}{dt} + e^{t/\tau}\frac{V}{\tau} = e^{t/\tau}\frac{E_{\text{ion}} + I_{ext}(t)}{\tau}$$

The left-hand side of this equation resembles product rule, $\frac{d}{dt}f(t)g(t) = f(t)g'(t) + f'(t)g(t)$:

$$\frac{d}{dt}\left(e^{t/\tau}V\right) = e^{t/\tau}\frac{E_{\text{ion}} + I_{ext}(t)}{\tau}$$

$$e^{t/\tau}V = \int e^{s/\tau}\frac{E_{\text{ion}} + I_{ext}(s)}{\tau}\,ds + k$$

$$V = e^{-t/\tau}\left(\int e^{s/\tau}\frac{E_{\text{ion}}}{\tau}ds + \int e^{s/\tau}\frac{I_{ext}(s)}{\tau}ds + k\right)$$

$$\boxed{V(t) = E_{\text{ion}} + e^{-t/\tau}\int_{-\infty}^{t} e^{s/\tau}\frac{I_{ext}(s)}{\tau}ds + e^{-t/\tau}k}$$

- In the absence of input, $k = E_{\text{ion}} - V(0)$. So we can set $V(0) = E_{\text{ion}}$ to eliminate that k term.
- Okay to work with when $I_{ext}(t)$ is something simple.
- Kind of gross to deal with in general.

Some quick intuitions for how neurons respond to current pulses

$$V(t) = E_{\text{ion}} + e^{-t/\tau} \int_{-\infty}^{t} e^{s/\tau} \frac{I_{ext}(s)}{\tau} ds$$

Let's make $I_{ext}(t)$ a current pulse starting at time t_{On}. Our integral evaluates to 0 for times before t_{On}, so we get :

$$V(t) = E_{\text{ion}} + e^{-t/\tau} \int_{t_{On}}^{t} e^{s/\tau} \frac{I_{ext}(s)}{\tau} ds$$

If we give $I_{ext}(t)$ a height A and width d, then we can evaluate our integral:

$$V(t) = E_{\text{ion}} + e^{-t/\tau} \left(Ae^{s/\tau}\right)\Big]_{t_{On}}^{\min(t, t_{On}+d)}$$

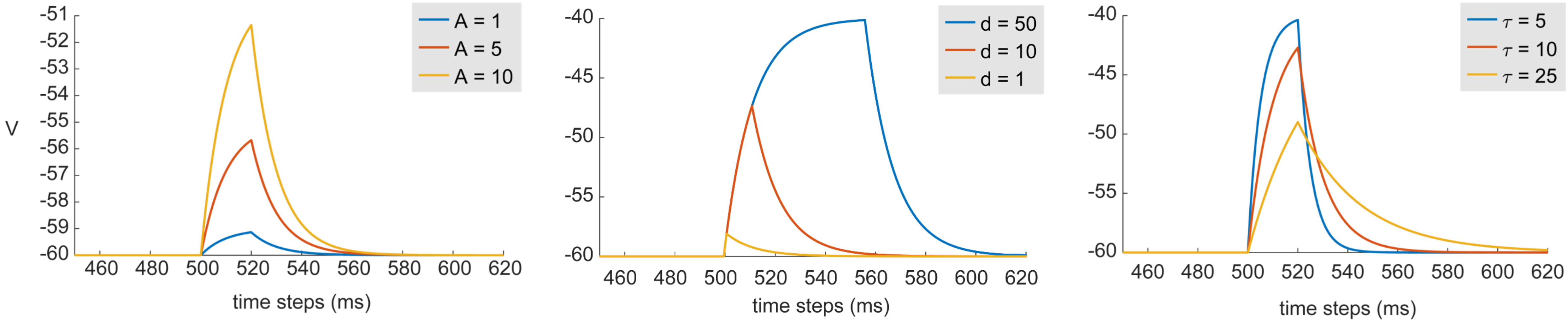
And from this evaluation, we find a piecewise solution for V(t):

$$\boxed{V(t) = \begin{cases} E_{\text{ion}} & t < t_{On} \\ E_{\text{ion}} + A\left(1 - e^{\frac{t_{On}-t}{\tau}}\right) & t_{On} \leq t \leq t_{On} + d \\ E_{\text{ion}} + A\left(e^{\frac{t_{On}+d-t}{\tau}} - e^{\frac{t_{On}-t}{\tau}}\right) & t > t_{On} + d \end{cases}}$$

Some quick intuitions for how neurons respond to current pulses

$$V(t) = E_{\text{ion}} + e^{-t/\tau} \int_{-\infty}^{t} e^{s/\tau} \frac{I_{ext}(s)}{\tau} ds$$

$$I_{ext}(t) = f(x) = \begin{cases} \boldsymbol{A} & t_{On} \le t \le t_{On} + \boldsymbol{d} \\ 0 & \text{otherwise} \end{cases}$$



We can also study the behavior of this system via simulation (aka numerically)

$$C\,\frac{dV}{dt} = g(E_{\text{ion}} - V) + I_{ext}(t)$$

- There are a variety of tools called ODE solvers for numerically computing the trajectory of an ordinary differential equation.

- You can often default to using the first-order Euler method:

$$y_{n+1} = y_n + \Delta t\, f(t_n, y_n)$$

- where Δt is the simulation time step, and $f(t_n, y_n)$ is the update equation of your system, ie $\frac{dV}{dt}$.

- Initialize your system to something reasonable:

$$V(0) = E_{\text{ion}}$$

- Define the update equation for your system:

$$\frac{dV}{dt} = \frac{1}{RC}(E_{\text{ion}} - V) + \frac{1}{C} I_{ext}(t)$$

- Now, iterate! I'm using integer indices for simplicity:

$$V(1) = V(0) + \frac{\Delta t}{RC}\big(E_{\text{ion}} - V(0) + R I_{ext}(0)\big)$$

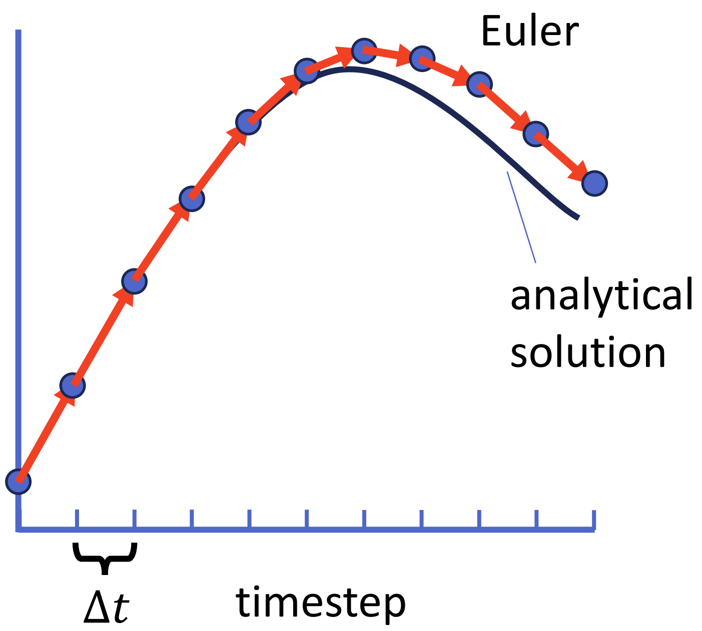
$$V(2) = V(1) + \frac{\Delta t}{RC}\big(E_{\text{ion}} - V(1) + R I_{ext}(1)\big)$$

$$V(3) = V(2) + \frac{\Delta t}{RC}\big(E_{\text{ion}} - V(2) + R I_{ext}(2)\big)$$

…

Best practices for simulating dynamical systems

$$V(t+\Delta t) = V(t) + \frac{\Delta t}{RC}\left(E_{\mathrm{ion}} - V(t) + RI_{ext}(t)\right)$$



- Euler's method can diverge when your timestep is large relative to the rate of change of your system.
  - Avoid by keeping $\frac{\Delta t}{RC}$ sufficiently small.
- V(0) might be difficult to pick.
  - Avoid by <u>burn-in</u>: simulate for a couple τ to reach the steady-state solution to the homogeneous system before adding input.
    - Or if your input has nonzero mean μ, you could burn-in with constant input μ…

Exponential Euler: a niche improvement on the Euler method for neural simulations

$$\frac{dV}{dt} = \frac{1}{RC}\,(E_{\text{ion}} - V) + \frac{1}{C} I_{ext}(t)$$

We can rearrange this equation to take the general form $\frac{dV}{dt} = A(t) - B(t)V(t)$, by setting

$$A(t) = \frac{E_{\text{ion}} + RI_{ext}(t)}{RC}$$

$$B(t) = \frac{1}{RC}$$

Remember slide 15: we found that $V_{ss} = E_{\text{ion}} + RI_{\text{ext}}(t)$, and defined $\tau = RC$. That means we could also write:

$$A(t) = \frac{V_{ss}(t)}{\tau}$$

$$B(t) = \frac{1}{\tau}$$

where $V_{ss}(t)$ is the steady-state solution the system would reach given fixed input $I_{\text{ext}}(t)$.

continued next slide…

Exponential Euler: a niche improvement on the Euler method for neural simulations

$$\frac{dV}{dt} = A(t) - B(t)V(t)$$

Like the first-order Euler method, we will assume that over a small window of time from T to $T + \Delta t$, A and B are constant with $A = A(T)$ and $B = B(T)$. Multiplying through by an integrating factor $e^{B(T)t}$ lets us make use of the product rule:

$$e^{B(T)t}\ \frac{dV}{dt} = e^{B(T)t}A(T) - e^{B(T)t}B(T)V(t)$$

$$e^{B(T)t}\ \frac{dV}{dt} +\ e^{B(T)t}B(T)V(t) = e^{B(T)t}A(T)$$

$$\frac{d}{dt}\left(e^{B(T)t}V(t)\right) = e^{B(T)t}A(T)$$

Which we can then integrate from T to $T + \Delta t$ to find the value of $\mathrm{V}(T + \Delta t)$ given the (known) value of $\mathrm{V}(T)$:

$$\int_T^{T+\Delta t} \frac{d}{dt}\left(e^{B(T)s}V(s)\right) ds = \int_T^{T+\Delta t} e^{B(T)s}A(T)ds$$

continued next slide…

Exponential Euler: a niche improvement on the Euler method for neural simulations

Let's evaluate that integral:

$$\int_T^{T+\Delta t} \frac{d}{dt}\left(e^{B(T)s}\, V(s)\right) ds = A(T)\int_T^{T+\Delta t} e^{B(T)s} ds$$

$$e^{B(T)(T+\Delta t)}V(T+\Delta t) - e^{B(T)(T)}V(T) = \frac{A(T)}{B(T)}\left(e^{B(T)(T+\Delta t)} - e^{B(T)(T)}\right)$$

Multiply both sides by $e^{-B(T)(T+\Delta t)}$:

$$V(T+\Delta t) - e^{-B(T)\Delta t}V(T) = \frac{A(T)}{B(T)}e^{-B(T)(T+\Delta t)}\left(e^{B(T)(T+\Delta t)} - e^{B(T)(T)}\right)$$

$$V(T+\Delta t) = \frac{A(T)}{B(T)}\left(1 - e^{-B(T)\Delta t}\right) + e^{-B(T)\Delta t}V(T)$$

$$V(T+\Delta t) = \frac{A(T)}{B(T)} + e^{-B(T)\Delta t}\left(V(T) - \frac{A(T)}{B(T)}\right)$$

And now the punchline, we plug in our definitions for A and B (and go back to writing t for time):

$$\boxed{V(t+\Delta t) = V_{ss}(t) - e^{-\frac{\Delta t}{\tau}}\left(V_{ss}(t) - V(t)\right)}$$

Exponential Euler: a niche improvement on the Euler method for neural simulations

This is called the Exponential Euler Method, and it works in general for systems of the form $\frac{dx}{dt} = A(x,t) - B(x,t)x(t)$.

Let's think about this equation for a minute.

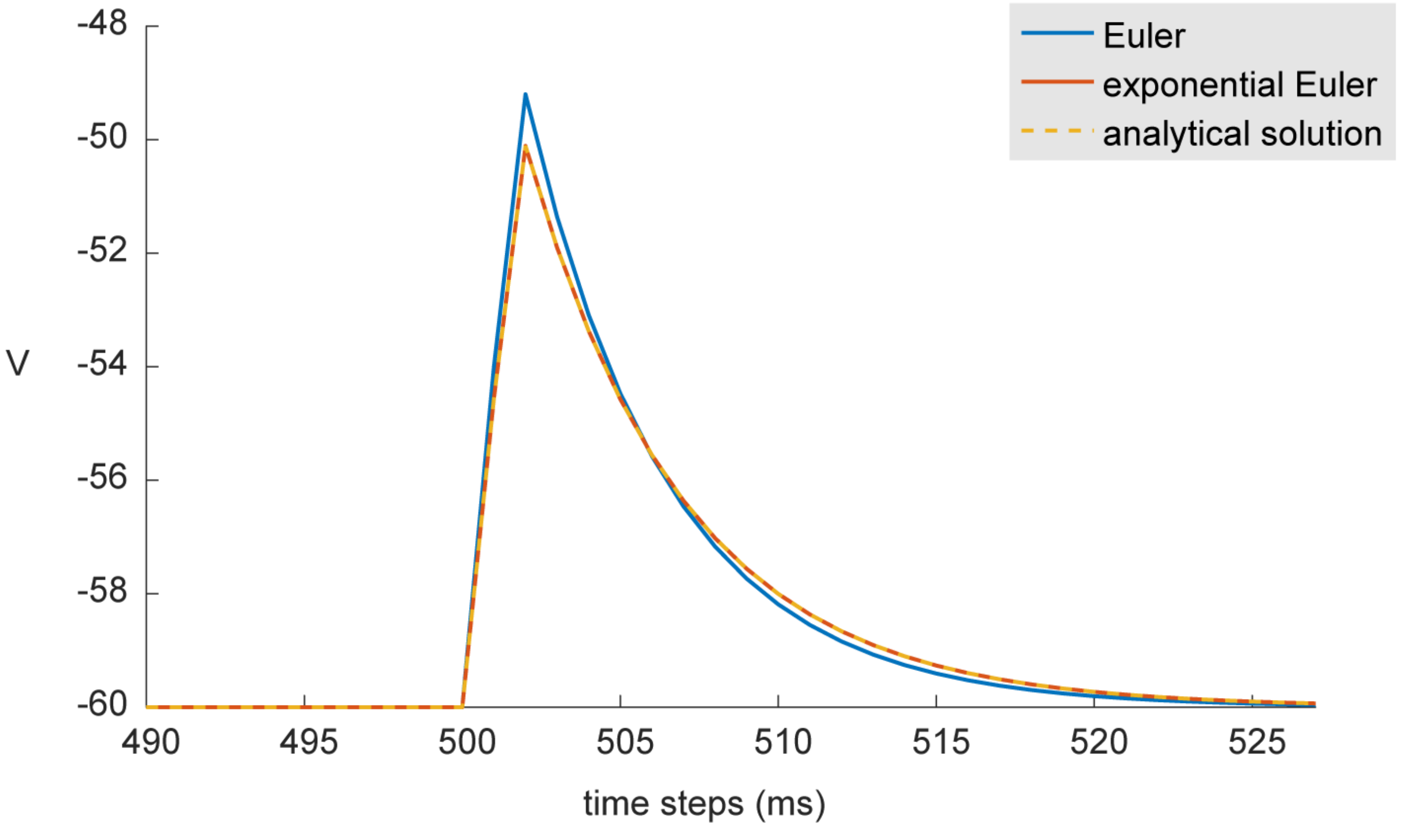
$$V(t + \Delta t) = V_{ss}(t) - e^{-\frac{\Delta t}{\tau}}\left(V_{ss}(t) - V(t)\right)$$

- As $\Delta t \to \infty$, $e^{-\frac{\Delta t}{\tau}}$ approaches 0, giving $V(t + \Delta t) = V_{ss}(t)$.

- We could also think of Exponential Euler as a weighted average of $V(t)$ and $V_{ss}(t)$:

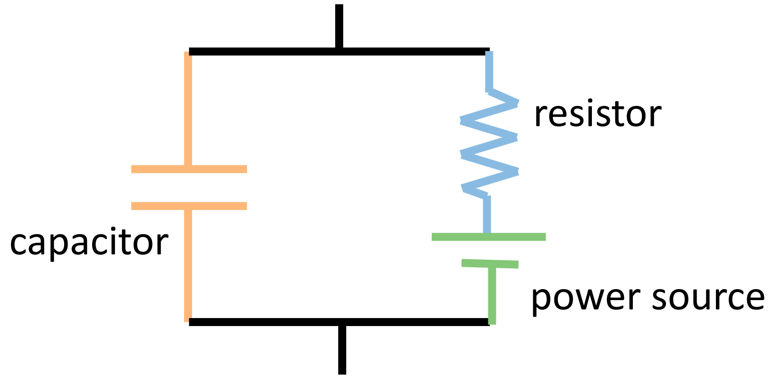
$$V(t + \Delta t) = e^{-\frac{\Delta t}{\tau}} V(t) + \left(1 - e^{-\frac{\Delta t}{\tau}}\right) V_{ss}(t)$$

Exponential Euler: a niche improvement on the Euler method for neural simulations



Let's not forget that neurons also spike

$$\frac{dV}{dt} = \frac{1}{RC}\left(E_{\text{ion}} - V\right) + \frac{1}{C} I_{ext}(t)$$



This is not very interesting- if there's not a spiking mechanism built into our model, we just hard-code it:

If $V(t) > \theta$,

- reset $V(t) = V_{reset}$
- (optional) fix $V(t) \to V(t + \Delta t) = V_{reset}$
- record $S(t) = 1$

Spikes can also update other terms of our model:

- Synaptic facilitation/depression models
- Spike timing-dependent plasticity rules
- Input to other neurons