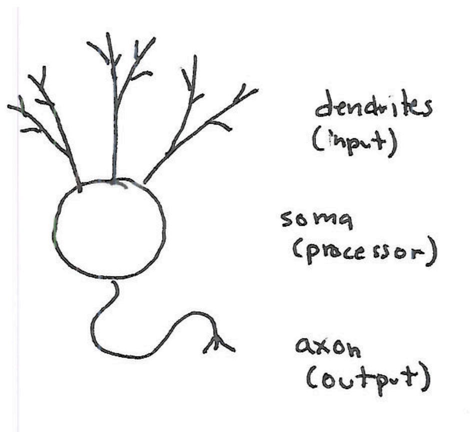
Mathematical Models of Individual Neurons

§I Background

§I(a) Neuron Doctrine



The Neuron Doctrine (∼1890's): the neuron is the basic structural and functional unit of the nervous system

action potential (AP): an electrochemical pulse of activity that serves as the 'signal' between neurons

human brain = a network of $\sim 10^9$ neurons connected by $\sim 10^{14}$ synapses

'bottom-up' approach:

- isolate one neuron from the network
- single compartment models
- study response to (artificial) input signals

the BIG question:

When / How does a neuron create an AP?

§I(b) What exactly are we trying to model?

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- during AP:

aside - some physics terminology
Voltage (V) =

- SI units:
- usually measure voltage relative to an agreed upon $V = 0$ point

Current (I) =

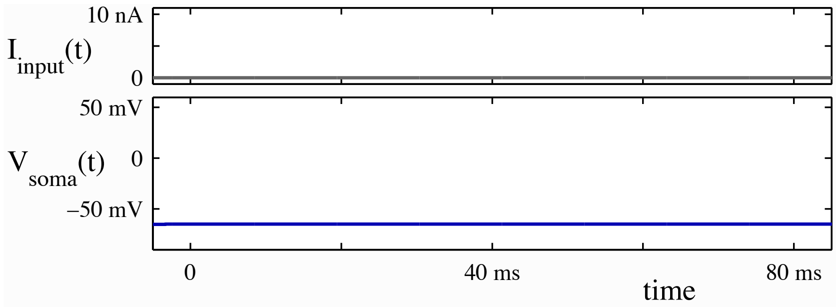
- SI units:

voltage measures a 'push' on the ions, and current measures the response

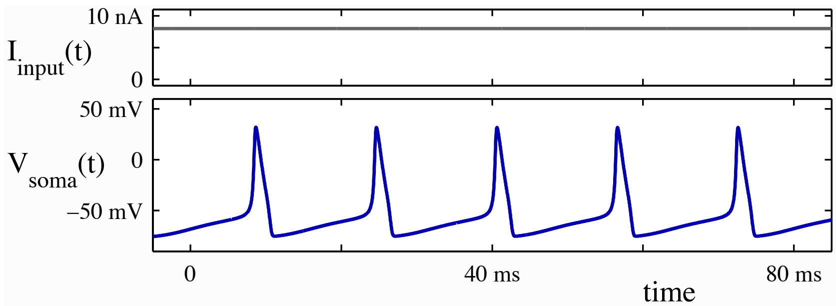
A pretend experiment: inject current into a neuron, and see how the membrane potential changes

- we control I_{input}
- by convention, $V_{\text{outside}} = 0$
- measure the membrane potential: ($V_{\text{soma}} - V_{\text{outside}} = V_{\text{soma}}$)

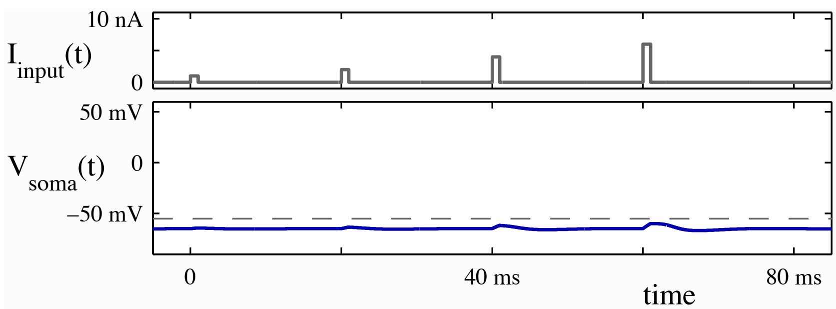
• Experiment 1:



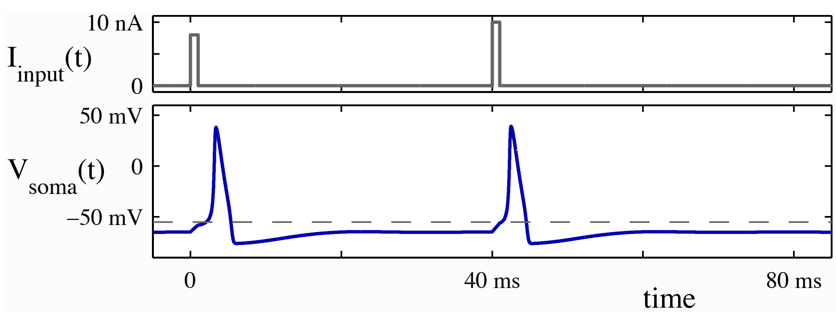
• Experiment 2:



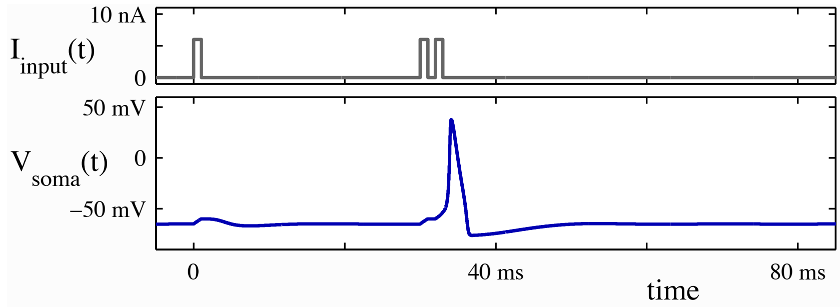
• Experiment 3:



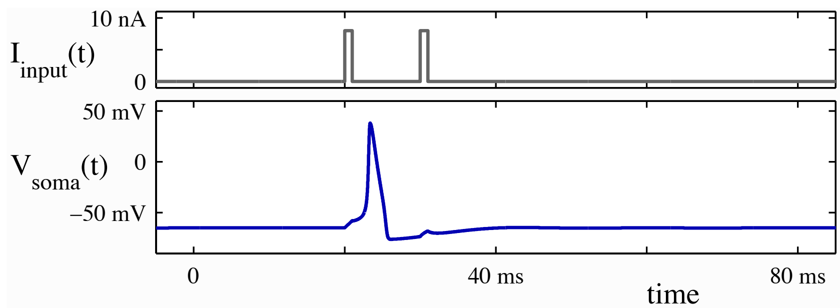
• Experiment 4:



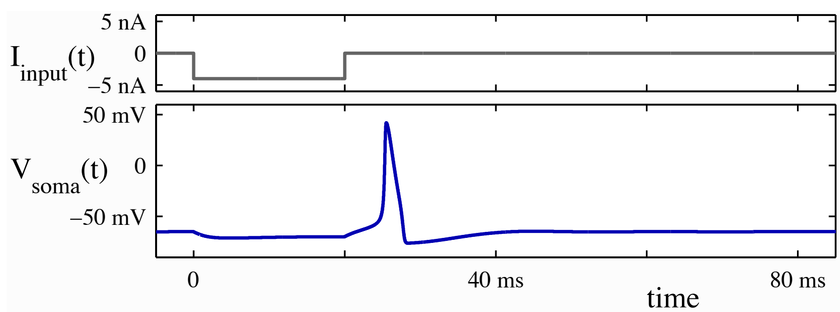
• Experiment 5:



• Experiment 6:



• Experiment 7:



§I(c) What makes a good model?

A model of a dynamical system is

- an imperfect representation of the system (i.e., a picture)
- a mathematical description of the *rules* governing the time evolution of the system (i.e., a differential equation)

Why are there so many models?

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Modeling can involves networks of $1 - 10^{10}$ (or more!) neurons

Conductance based models: motivate our differential equations from electrical circuits which behave like a neuron.

§I(d) background on electrical circuits

An electrical circuit is made of many connected circuit elements, each of which has it's own rules that relate I's to V's

Usually talk about: 'Voltage change across an element' (ΔV)
'current flowing through an element' (I)

(i) wire =

rule: $\Delta V = 0$; i.e. all points on wire are at the same voltage (also I is constant)

(ii) junction =

description: current is conserved
rule: $I_1 = I_2 + I_3$

(iii) battery =

rule: $\Delta V =$ constant (long bar is high voltage side)

(iv) ground =

rule: $V = 0$ at this point

(v) resistor =

description: current flows in proportion to the voltage difference

rule: $V = IR$, where R is a constant called the resistance

(vi) capacitor =

description:
- current deposits charge on the two halves of the capacitor
- this creates a voltage difference in proportion to the charge

rule:
- $Q = VC$, where C is a constant called the capacitance
- also useful to know that $I = dQ/dt$

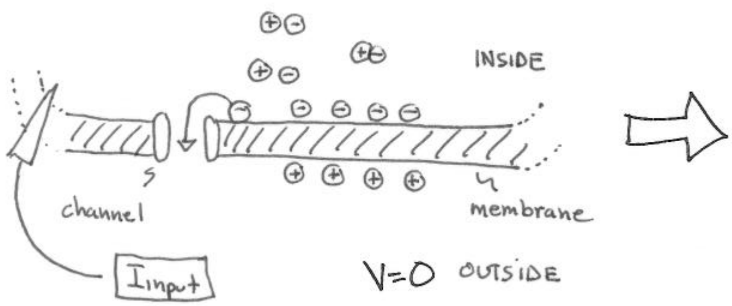
> Given a circuit, we use these rules to develop a differential equation for the evolution of any unspecified V's and I's

§II leaky integrate and fire model (LIF) - early 1900's

- often just called IF (not LIF)
- many LIF-type models, we consider just one

§II(a) motivation

An oversimplified picture of ion flow in a neuron:



The neuron is an integrator:

- fluid (water) inside cell is a conductor
- membrane is an insulator
- excess ions repel, end up on inner wall of membrane (NOT spread throughout the cell body)
- equal and opposite charges on outer membrane wall

  →

The neuron is leaky:

- membrane is mostly an insulator, but...
- there are holes (channels) which slowly let ions pass

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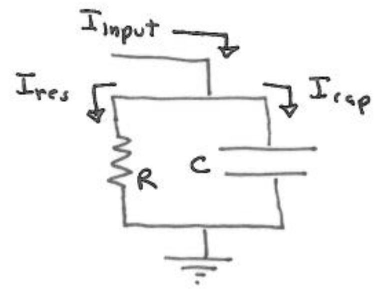
Analysis of RC circuit

- (junction rule) input current splits between resistor and capacitor
  $I_{\text{input}} = I_{\text{res}} + I_{\text{cap}}$



- (ground rule)

- (wire rule) let V = voltage at upper wire
  then V = voltage across resistor
  and V =voltage across capacitor

- (resistor rule)

- (capacitor rule)

Algebra:

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- rearrange:

RC circuit equation is a 'decay-type' equation

- the most important *type* of differential equation in this class

- descriptive solution: V_* is the target voltage
  τ is a time constant (units:)

Question: Where does V go?

Consider three cases:

- $V < V_*$

- $V = V_*$

- $V > V_*$

§II(b) numerical solutions of the LIF model

Question: How does a computer solve the LIF?

Many ways, but here's one ...

In words $$\frac{dV}{dt} = -\frac{V - V_*}{\tau}$$

$dV =$

$V(k) =$

If we know the previous voltage ($V(k-1)$) then we can compute the voltage now ($V(k)$).

§II(c) the LIF model

- model the neuron as an RC circuit
- except, RC circuit has no threshold and does not fire
- so include 'fire' (i.e., threshold and reset) *artificially*

LIF model:

if $V < V_{\text{threshold}}$ then evolve $V(t)$ using $\dfrac{dV}{dt} = -\dfrac{V - V_*(t)}{\tau}$

if $V \geq V_{\text{threshold}}$ then set $V = V_{\text{reset}}$

where $V_{\text{threshold}}$ and V_{reset} are parameters that we choose

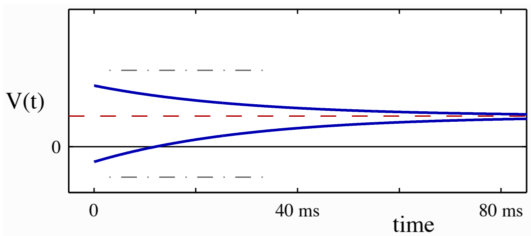
Comments:

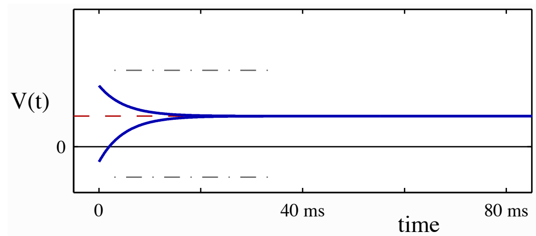
- resting potential is $V = 0$
  why?
- choose $V_{\text{threshold}} \sim +25\text{mV}$ (i.e., wrong *absolute* value, but correct *relative* to resting potential)
- choose $V_{\text{reset}} \sim -10\text{mV}$ (i.e., slightly below resting potential) to mimic refractory period

§II(d) dynamics of the LIF model

recall that V evolves toward the target voltage $V_*(t) = I_{\text{input}}(t)\ R$

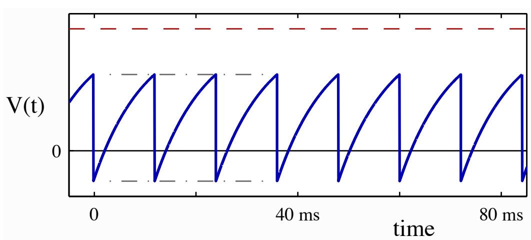
(i) if $I_{\text{input}}(t) = I_0$ is constant and small, then $V_* < V_{\text{threshold}}$ so $V(t) \to V_*$



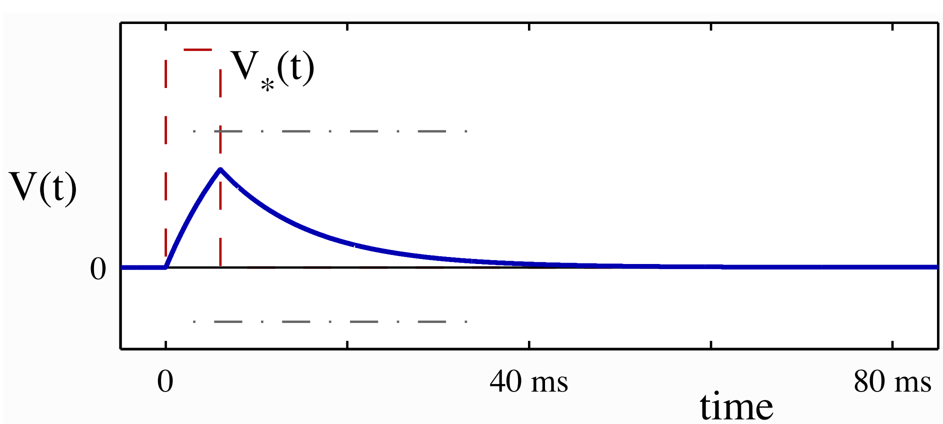


(ii) if $I_{\text{input}}(t) = I_0$ is constant and big, then $V_* > V_{\text{threshold}}$

so $V(t)$ tries to increase to V_* but never gets there because it hits the threshold and resets



(iii) dealing with pulses: piece together the dynamics for $V(t)$ based on the various segments where $I_{\text{input}}(t)$ is constant



§II(e) first order systems

only *one* dependent variable (e.g., voltage) - NOTE: time is the independent variable

- RC circuit is an example of a first order dynamical system
  (a.k.a., one-dimensional dynamical system)
- the associated equation is a first order differential equation

these come in two general classes

- 1^{st} order autonomous differential equation (easier to handle)

- 1^{st} order non-autonomous differential equation (harder to handle)

where u could represent a voltage, concentration, activity, etc.

A very important comment: We focus on autonomous systems. These results can be applied to non-autonomous systems *if* the time dependent parameters (like $I_{\text{input}}(\text{t})$) are pulses, using the trick mentioned above.

Some math notation:

- phase space = all values of u

  NOTE: 'phase' is a confusing word here

- trajectory = motion of a point through phase space
  think 'parametric plot' not 'u vs. t'

- fixed point = a constant value $u(t) = u_{\text{fp}}$, so

  also called stationary point or equilibrium

To ‘solve’ a 1st order differential equation

- (traditional way) given an initial condition $u_0 = u(t = 0)$, find the function $u(t)$

- (geometric way) pictures are better than formulas for describing the important aspects of the behavior of a system - get a lot of important behavior about the dynamics with minimal effort

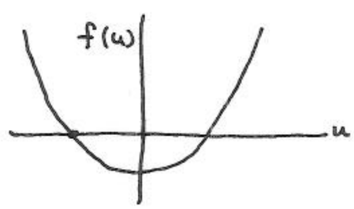
geometric analysis of a 1st order system, in three steps:

(step 1)

(step 2)

(step 3)

Example: $\dfrac{du}{dt} = u^2 - 1$



Returning to the LIF model...

We already saw that the LIF model does not make an AP on its own. But can *any* 1^{st} order systems make an AP?

Question: For what $f(V)$ does $\frac{dV}{dt} = f(V)$ have this solution:

Answer: look at the trajectory of an AP in phase space

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$\rightarrow$ $\boxed{1^{\text{st}} \text{ order systems can NOT make an AP spike!}}$

§II(f) good and bad of LIF model

good:

- physiologically motivated
- offers some insight: *If we force current into a neuron, the excess charge builds up on the inner wall of the membrane, and will leak out, but slowly because the ion channels offer some resistance to the flow.*
- integrator
- tonic spiking, excitable, has a threshold, refractory (sort of...)
- mathematically simple

bad:

- poor modeling of ion variety
- wrong resting potential
- the differential equation does not fire on its own
- the 'conditional' part of the definition is not mathematically satisfying
- offers no insight into AP
- a closer look at some of the 'good' properties shows that they don't quite match real neurons

→ LIF is a good subthreshold model, and a bad model of spiking

What next?