Models of Neurons 3: The Integrate and Fire Neuron

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Computational Neuroscience (Lecture 5, 2023/2024)

Overview of Lecture

- Types of model in neuroscience (abstract vs detailed)
- The leaky integrate and fire (LIF) model
- Models for synapses: conductances and currents

Types of Neuron Model

- Neuron models may be biophysically detailed or simple and abstract
- Detailed models often have many free parameters, cannot be solved mathematically and are difficult to draw general conclusions from when simulated
- Abstract models may overlook important phenomena in real biological neurons
- The level of detail included in a model is typically chosen based on the phenomena we would like to understand

Abstraction in Modelling

- *"Everything should be made as simple as possible, but no simpler."* (Einstein)
- *"All models are wrong; some models are useful"* (George Box)

2.3 Parsimony

Since all models are wrong the scientist cannot obtain a "correct" one by excessive elaboration. On the contrary following William of Occam he should seek an economical description of natural phenomena. Just as the ability to devise simple but evocative models is the signature of the great scientist so overelaboration and overparameterization is often the mark of mediocrity.

2.4 Worrying Selectively

Since all models are wrong the scientist must be alert to what is importantly wrong. It is inappropriate to be concerned about mice when there are tigers abroad.

Types of Neuron Model: Simplified vs Biologically Detailed

Complex/Biophysically Detailed

Hodgkin-Huxley

(Explains action potential biophysically. Computationally expensive and largely unamenable to formal analysis.)

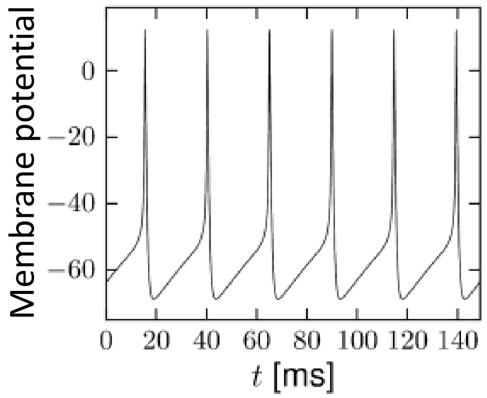
$$I = C_m \frac{\mathrm{d}V_m}{\mathrm{d}t} + \bar{g}_{\mathrm{K}} n^4 (V_m - V_K) + \bar{g}_{\mathrm{Na}} m^3 h (V_m - V_{Na}) + \bar{g}_l (V_m - V_l)$$

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

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

$$\frac{dh}{dt} = \alpha_h(V_m)(1-h) - \beta_h(V_m)h$$

Hodgkin-Huxley



Intermediate Complexity

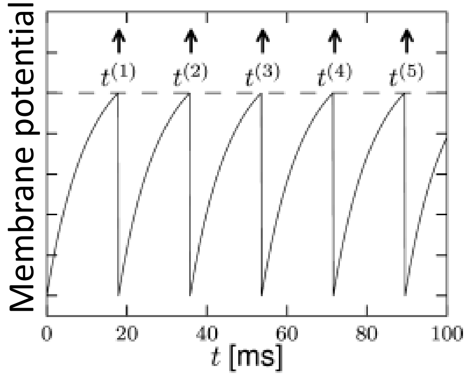
Leaky Integrate and Fire

(Abstracts away biophysics of action potentials. Can be analysed in some cases.)

$$\tau_m \frac{dV}{dt} = -(V - E_m) + I_{ext}/g_m$$

$$V(t) = V_{threshold} \implies \lim_{\epsilon \to 0} V(t+\epsilon) = V_{reset}$$

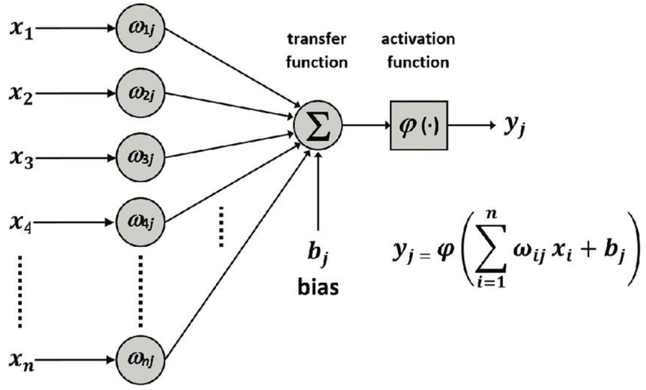
Leaky Integrate and Fire



Simple/Abstract

Transfer Function

(Lacks spiking or dynamics, but easily analysed.)



The Leaky Integrate and Fire Model

- The Hodgkin-Huxley model is computationally expensive and analytically intractable

- Often we don't care about the specific ionic currents or the biophysics of action potential generation

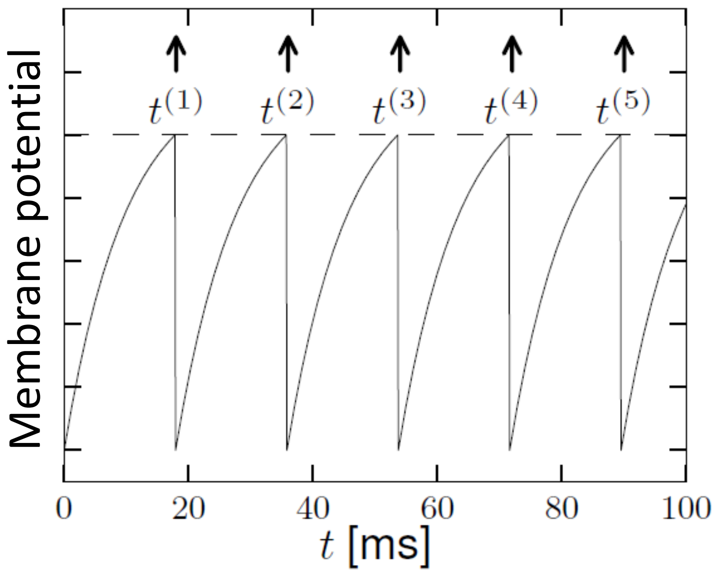
- Can we build a simpler model for the spiking activity of a neuron?

- What details can we throw away? What are the essential properties of the Hodgkin-Huxley model that we want to keep/abstract away?

The Leaky Integrate and Fire Model

Answer: the Leaky Integrate and Fire model. We consider only the passive membrane potential dynamics, and approximate the action potential with a threshold-reset rule

Response to Constant Current Input



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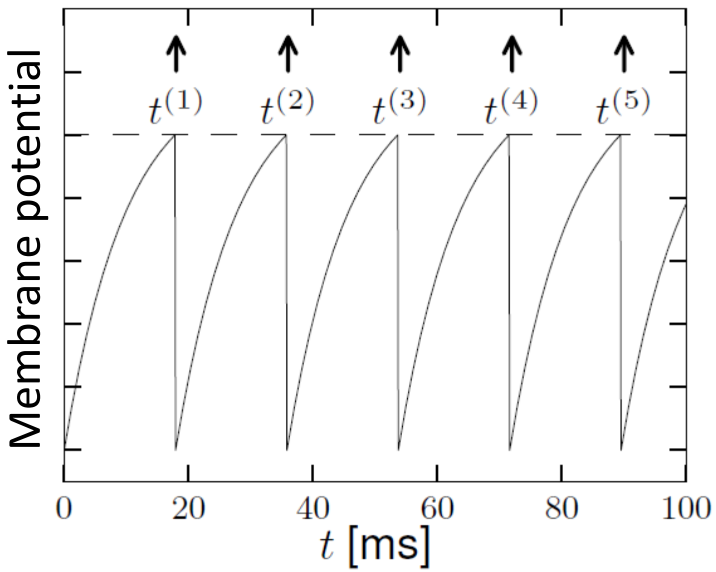
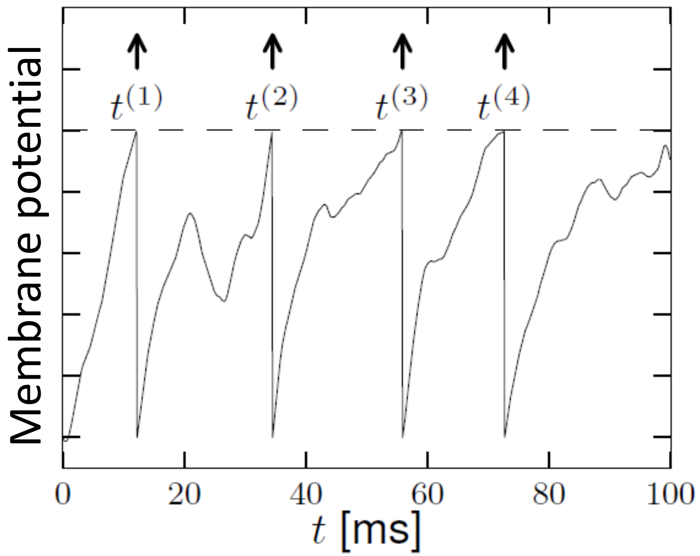


Response to Time-Varying Current



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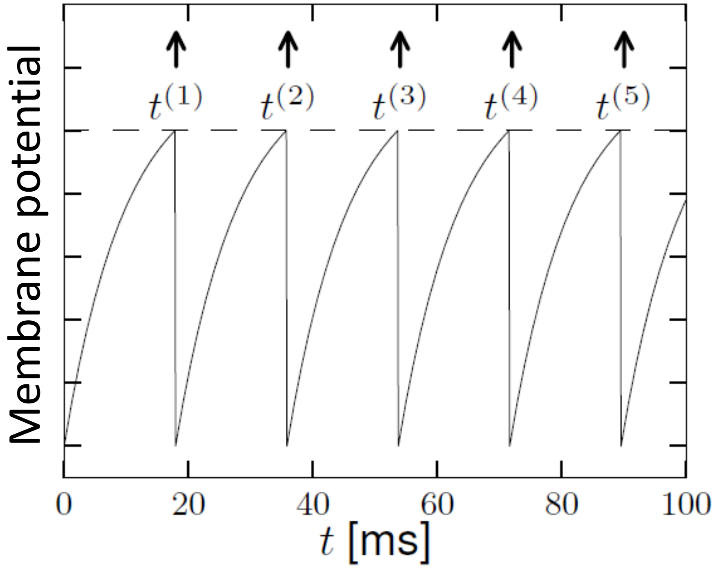

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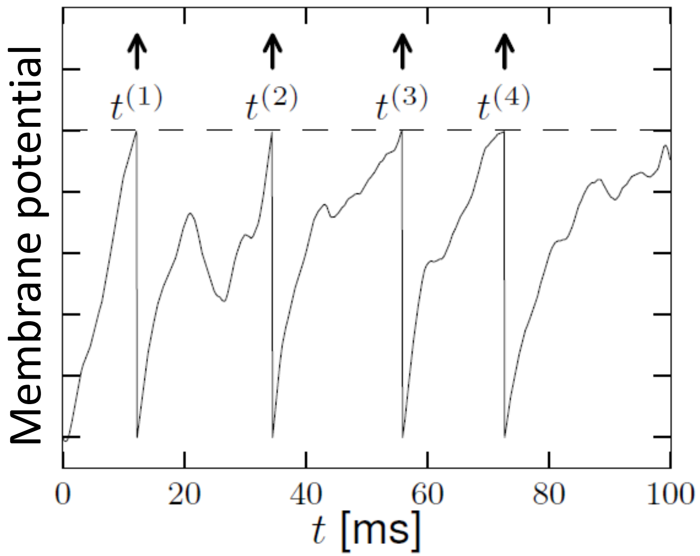
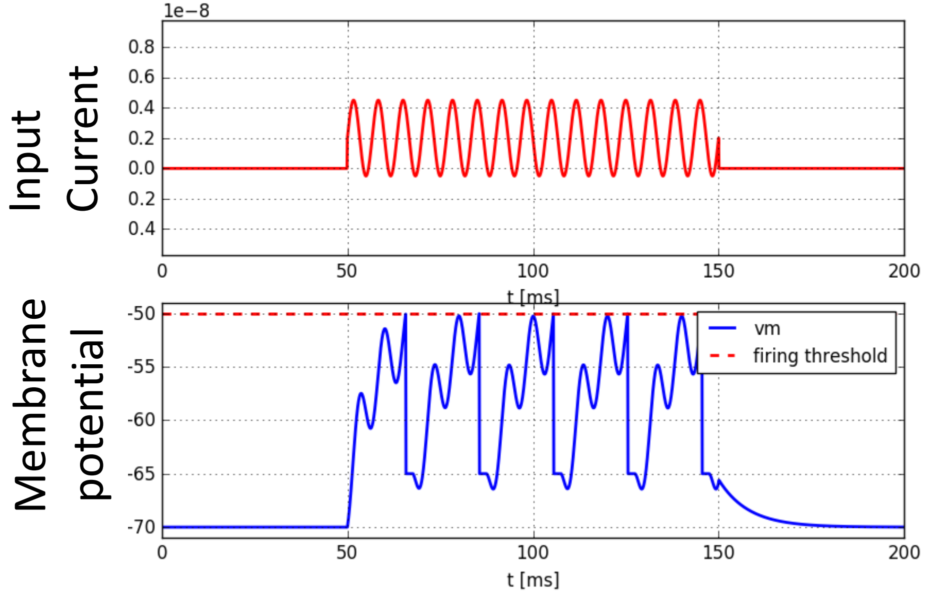


Response to Sinusoidal Current



The Leaky Integrate and Fire Model

- The LIF neuron obeys the following passive dynamics and threshold-reset rule:

Passive Dynamics: $$\tau_m \frac{dV}{dt} = -(V - E_m) + I_{ext}/g_m$$ (while *V* < *Vthreshold*)

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- The dynamics are passive/linear everywhere except at spike times

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- It has a hand-chosen resting potential, spike threshold, and spike reset voltage
- The dynamics are passive/linear everywhere except at spike times
- Every time the neuron resets, we say the neuron has fired a spike:

$$\left\{t^{(1)}, t^{(2)}, ..., t^{(N)}\right\} = \{t : V(t) = V_{threshold}\}$$

The Leaky Integrate and Fire Model

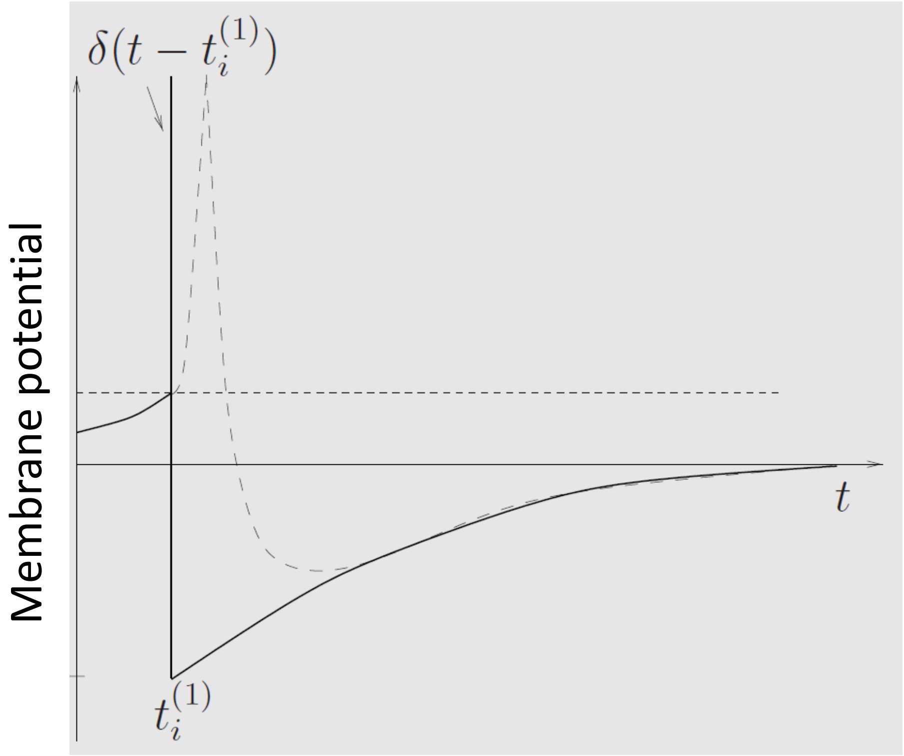
- Although the LIF model doesn't actually exhibit spikes, we often write down the spike train as:

$$s(t) = \sum_{i=1}^{N} \delta(t - t^{(i)}) \qquad \left\{t^{(1)}, t^{(2)}, ..., t^{(N)}\right\} = \{t : V(t) = V_{threshold}\}$$

- In other words, we model spikes as Dirac delta functions

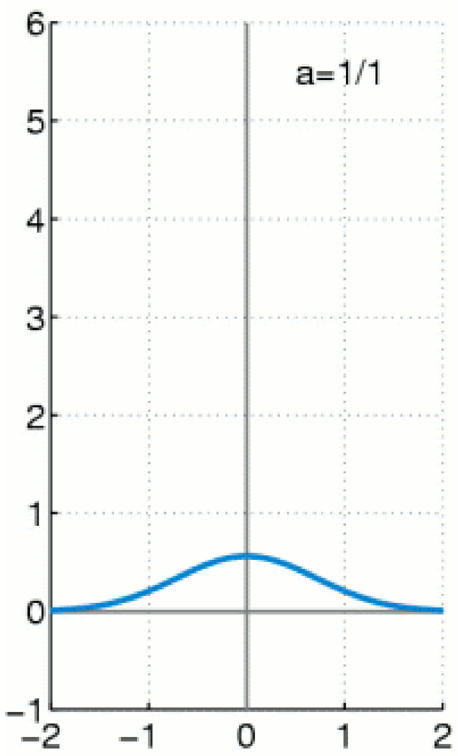
- This is a purely aesthetic choice when plotting the membrane potential

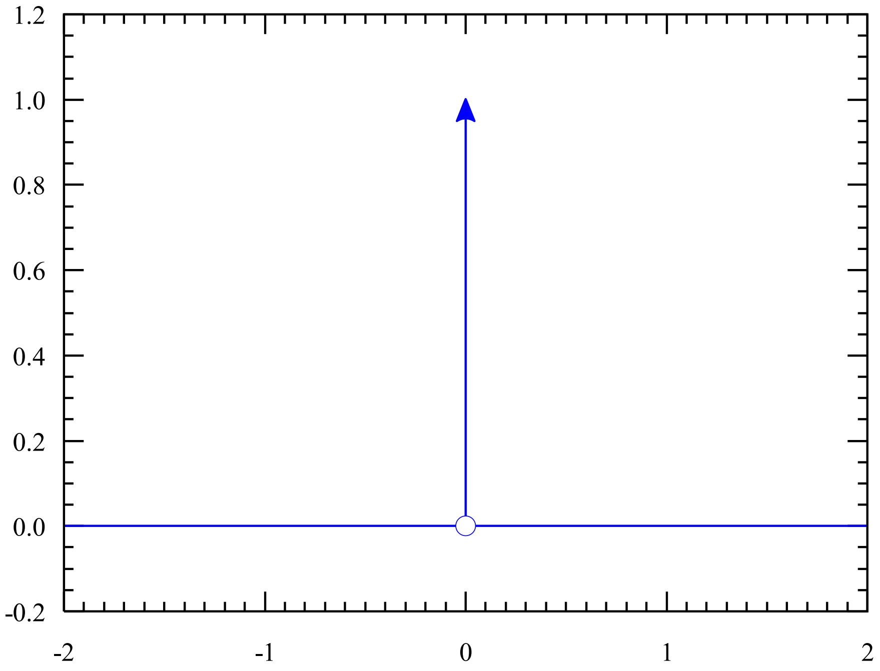
- However, we use this spike train equation often when modelling synaptic currents and firing statistics



The Dirac Delta Function

- The Dirac delta function is the limit of a Gaussian whose width goes to zero and integral remains constant
- It has many nice properties which make it convenient choice for analytical calculations
- Because we generally don't care about the shape of an action potential, it serves as a good approximation when thinking of spikes as identical and instantaneous point events



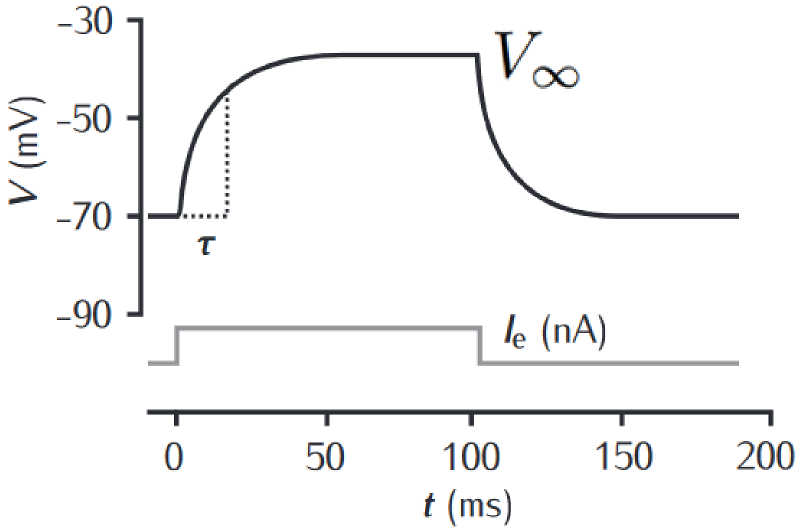


Alternative definition: for any function *f(x)*, delta function gives

$$\int_{-\infty}^{\infty} f(x)\delta(x-a)dx = f(a)$$

The Leaky Integrate and Fire Model – Current Threshold

- How much current does it take to make an LIF neuron spike?



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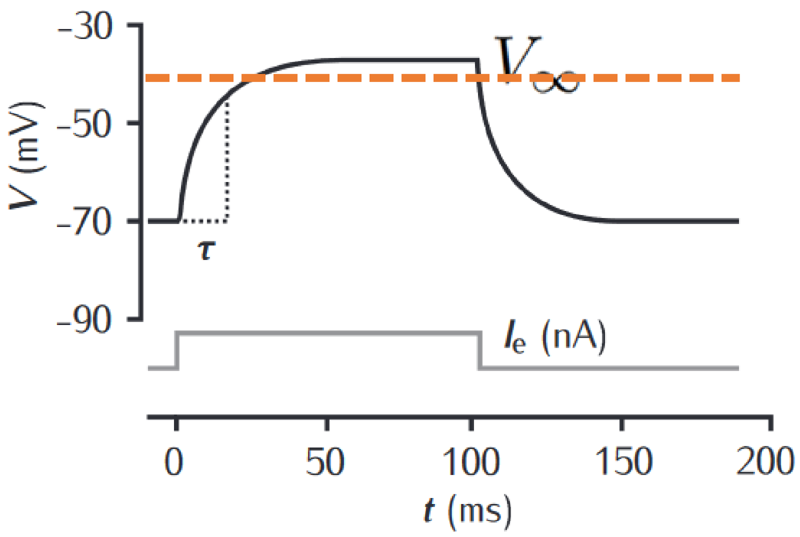

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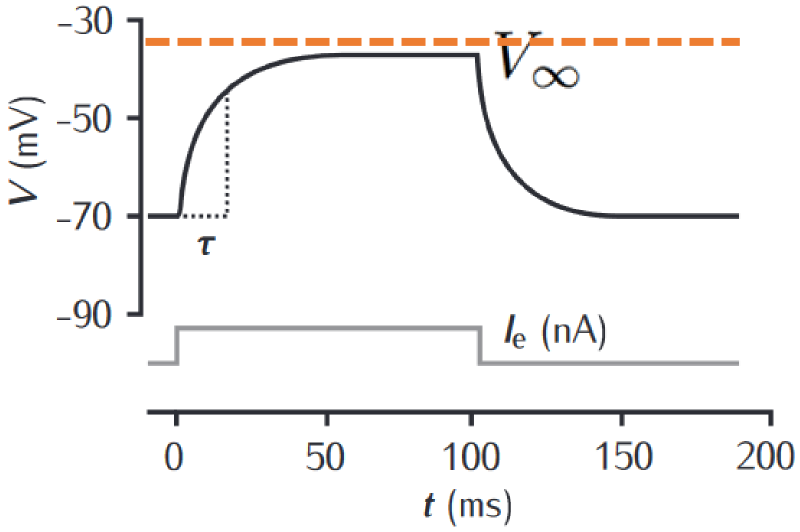
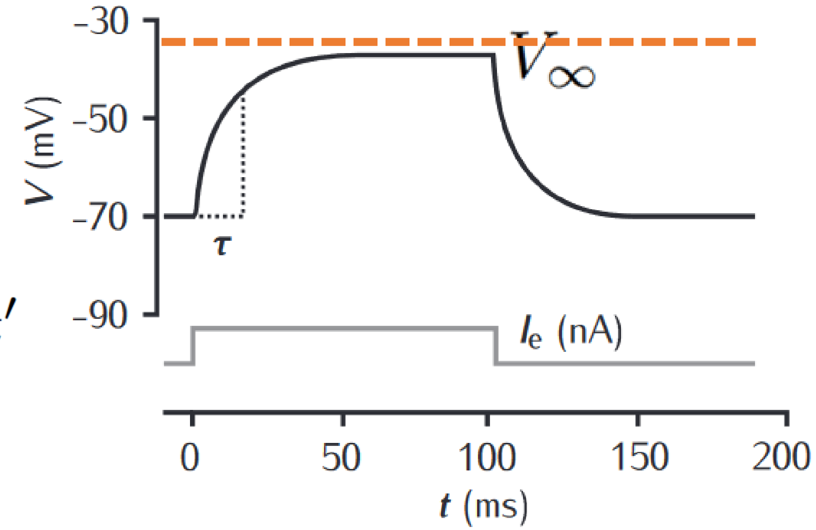


The Leaky Integrate and Fire Model – Current Threshold

- How much current does it take to make an LIF neuron spike?
- For purely passive dynamics (i.e., ignoring voltage threshold):

$$V(t) - E_m = e^{-t/\tau_m}(V(0) - E_m) + \frac{1}{g_m \tau_m}\int_0^t e^{-(t-t')/\tau_m} I_{ext}(t')dt'$$



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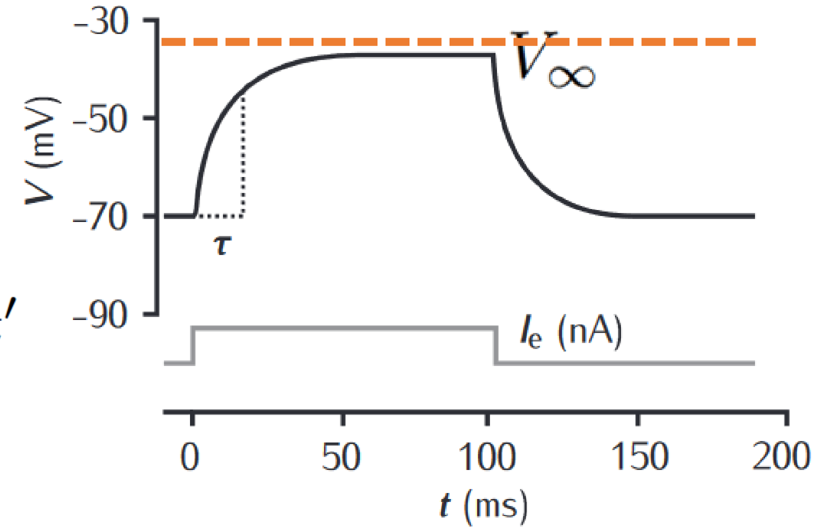

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- For time-independent *Iext* (already derived in previous lecture):

$$V(t) - E_m = e^{-t/\tau_m}(V(0) - E_m) + \frac{I_{ext}}{g_m}(1 - e^{-t/\tau_m})$$

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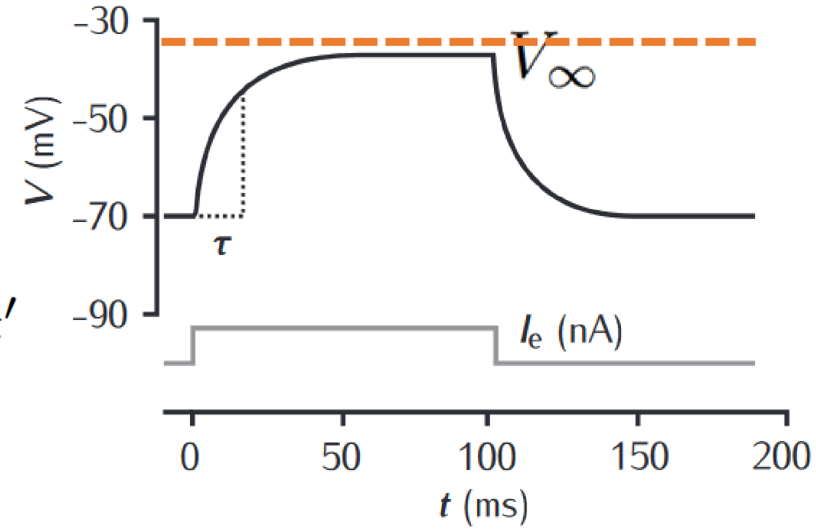

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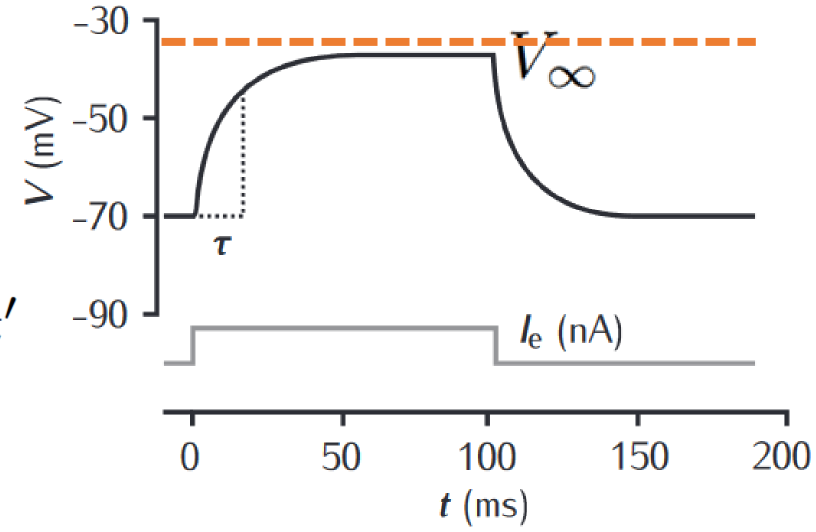

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- Thus, the neuron will *never* spike if the current is below a current threshold:

$$I_{ext} < g_m(V_{threshold} - E_m) \implies V_\infty < V_{threshold}$$

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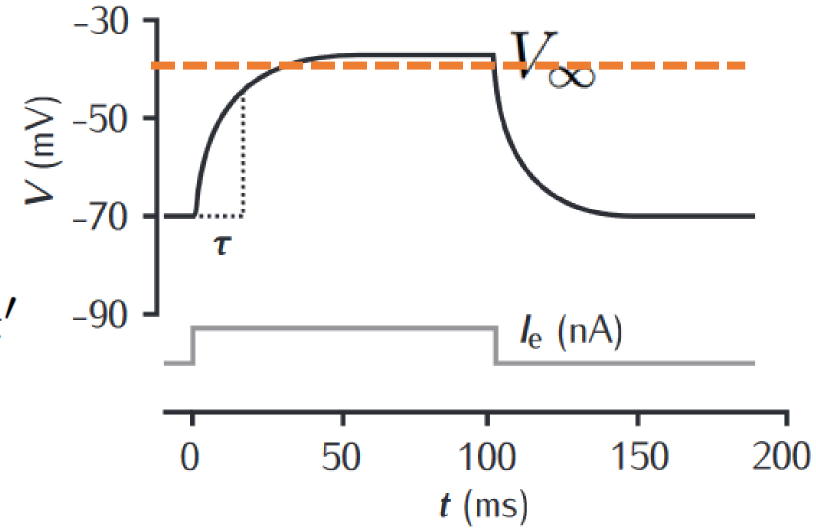

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The Leaky Integrate and Fire Model – f-I Curve

- Given a constant current input, we have the following solution (while under threshold):

$$V(t) - E_m = e^{-t/\tau_m}(V(0) - E_m) + \frac{I_{ext}}{g_m}(1 - e^{-t/\tau_m})$$

- Assume that the current input is strong enough to cause spikes. If the neuron has just spiked at time *t=0*, when will it spike next?

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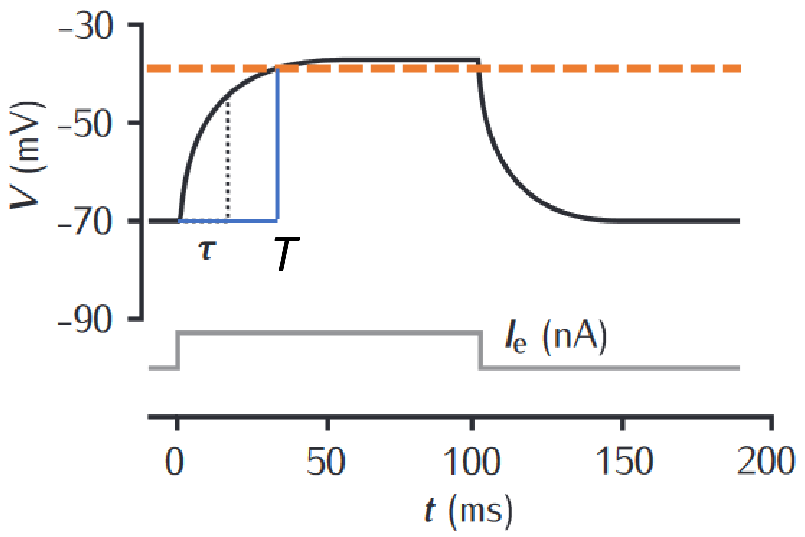
$$V(0) = V_{reset}, V(T) = V_{threshold}$$



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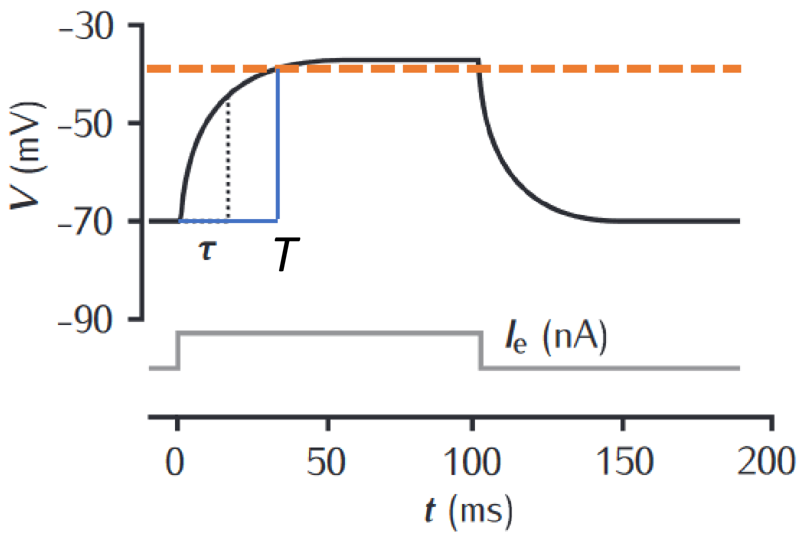
$$V(0) = V_{reset}, V(T) = V_{threshold}$$

$$T = \tau_m \log\left[\frac{I_{ext}/g_m - (V_{reset} - E_m)}{I_{ext}/g_m - (V_{threshold} - E_m)}\right]$$



- *T* is the interspike interval, the firing rate is *f=1/T* – note that the neuron will fire at T, 2T, 3T, etc.

The f-I Curve

For currents above the spiking threshold the interspike interval *T* is:

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For currents below threshold the neuron never spikes….

So the f-I curve must be:

$$f(I_{ext}) = \begin{cases} 0 & \text{if } I_{ext} < g_m(V_{threshold} - E_m) \\ \frac{1}{\tau_m}\left(\log\left[1 + \frac{V_{threshold} - V_{reset}}{I_{ext}/g_m - (V_{threshold} - E_m)}\right]\right)^{-1} & \text{if } I_{ext} > g_m(V_{threshold} - E_m) \end{cases}$$

The f-I Curve – Limiting Behaviour

$$f(I_{ext}) = \begin{cases} 0 & \text{if } I_{ext} < g_m(V_{threshold} - E_m) \\ \frac{1}{\tau_m}\left(\log\left[1 + \frac{V_{threshold} - V_{reset}}{I_{ext}/g_m - (V_{threshold} - E_m)}\right]\right)^{-1} & \text{if } I_{ext} > g_m(V_{threshold} - E_m) \end{cases}$$

- How does this function behave? Does it look like real neurons/the Hodgkin-Huxley model? Useful to look at limiting behaviour (e.g., strong input currents).

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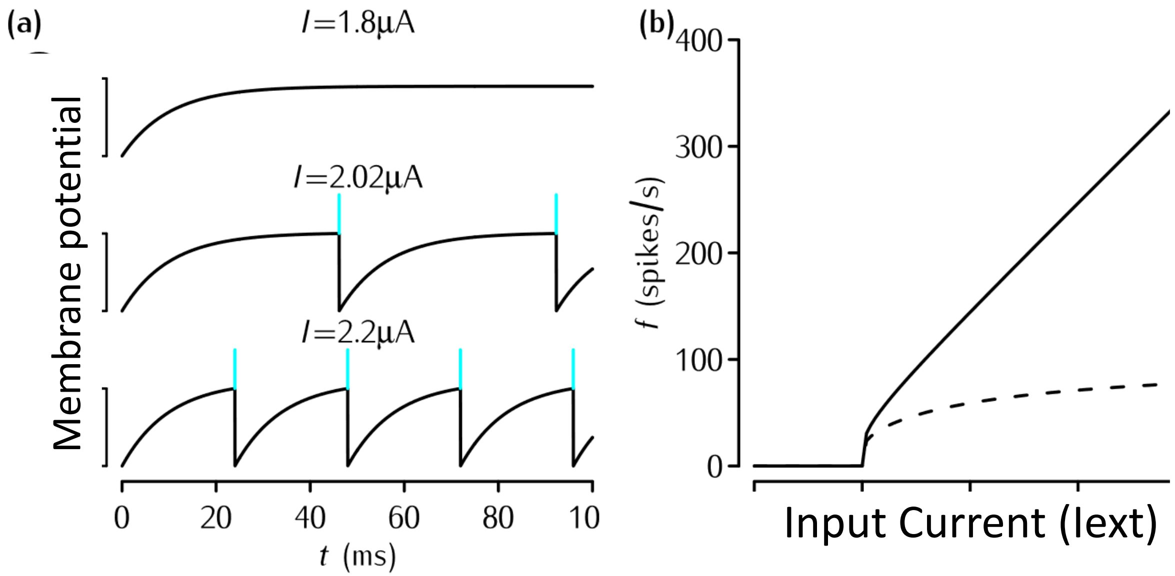
- How does this function behave? Does it look like real neurons/the Hodgkin-Huxley model? Useful to look at limiting behaviour (e.g., strong input currents).

- For strong input currents, using log(1+1/x) = 1/x (for large x): $f(I_{ext}) \approx \frac{1}{\tau_m} \frac{I_{ext}/g_m + E_m - V_{threshold}}{(V_{threshold} - V_{reset})}$

- Firing rate is zero below current threshold and linear for large current input - a bit like a ReLU. But it does something nonlinear in between…

The f-I Curve – LIF vs Hodgkin-Huxley

Leaky Integrate and Fire (Analytical Solution)



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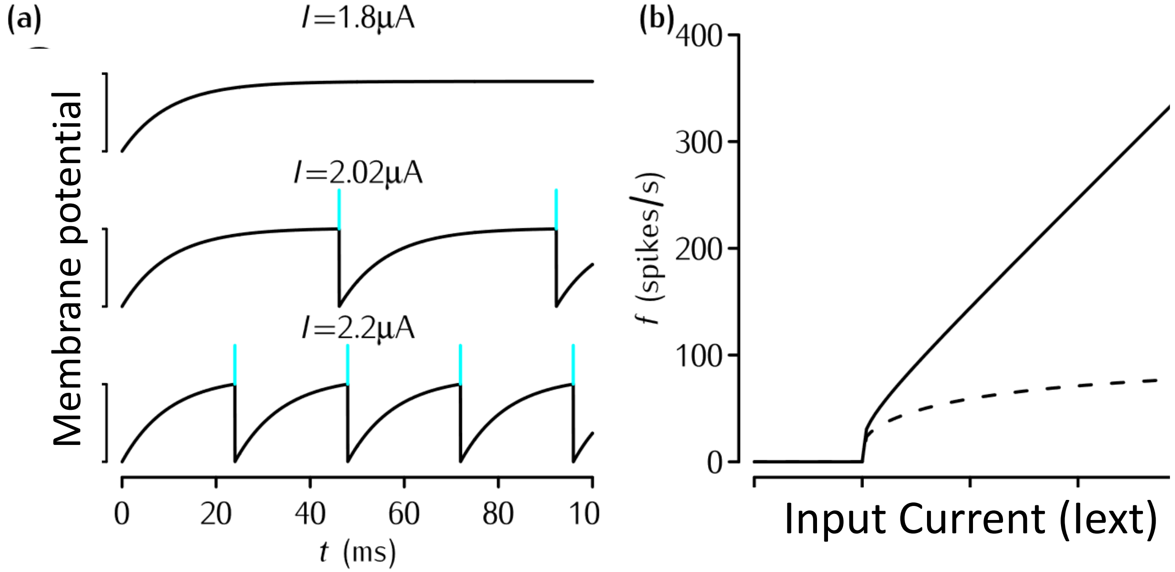
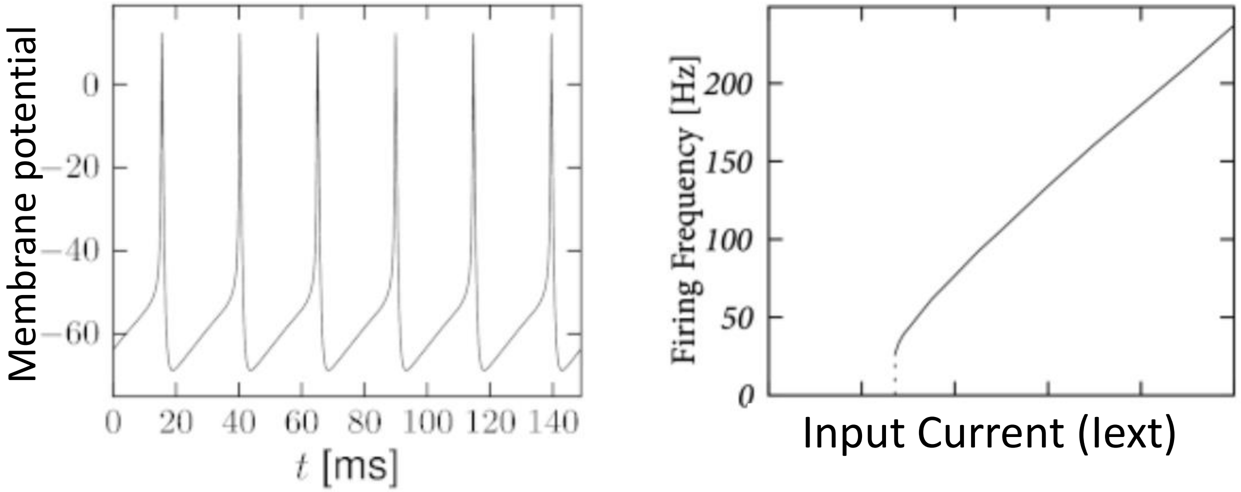


Hodgkin-Huxley (Numerical Calculation)



Simplification/abstraction has allowed to obtain a model in which certain essential features of the Hodgkin-Huxley model can be distilled and understood analytically.

The Leaky Integrate and Fire Model - Summary

- The LIF model combines a mechanistic approach to modelling passive membrane dynamics with a phenomenological approach to modelling action potentials

- This makes it more computationally efficient and analytically tractable compared to the HH model

- The HH model doesn't have a well-defined voltage threshold - the LIF model is unrealistic in that sense. However, both HH and LIF have a well-defined current threshold…

- The basic LIF model is too simple to capture various features of biological neurons, however it can be augmented in order to model relevant features of biological neurons (refractory period, spike rate adaptation, etc.)

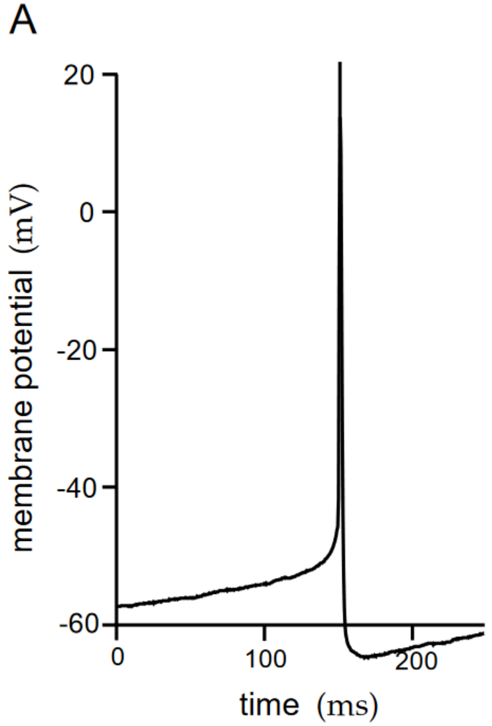
- For most large-scale simulations of spiking networks, variants on the LIF model are the standard choice

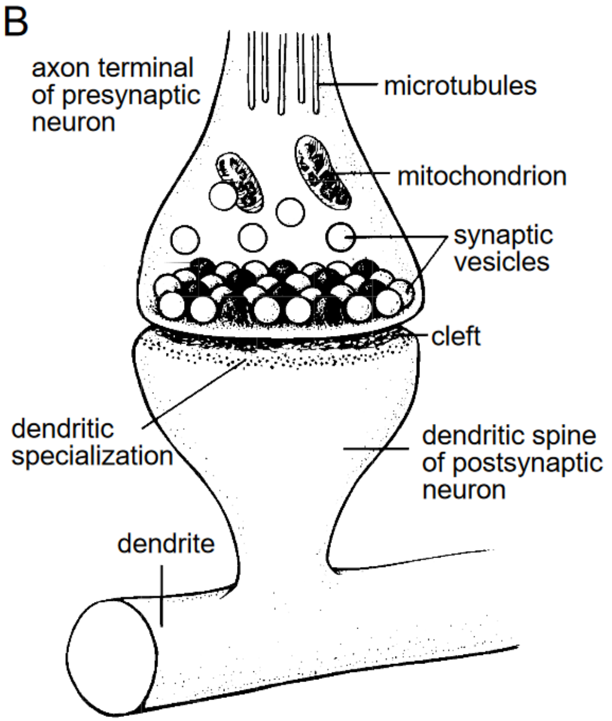
Synapses

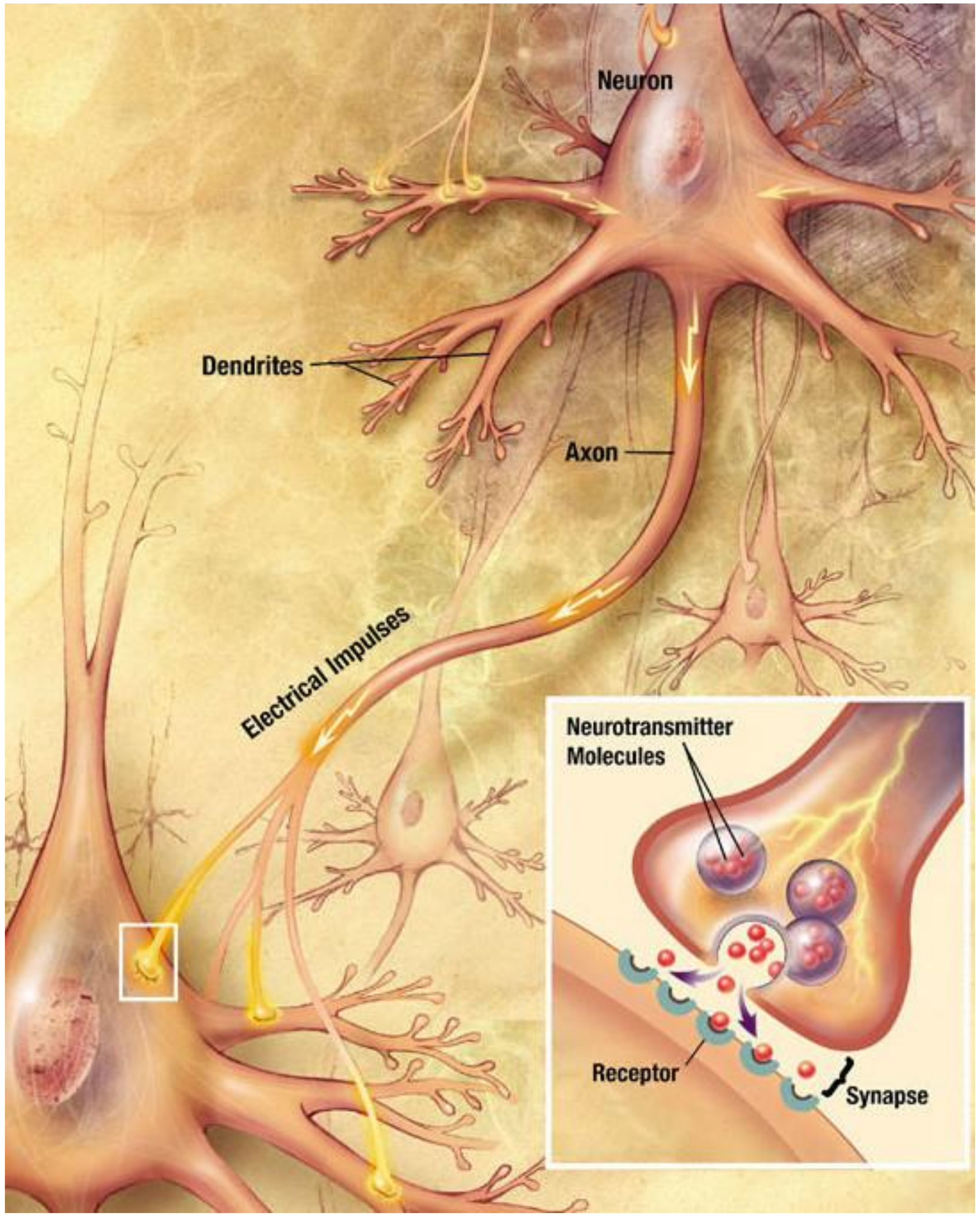
- Neurons communicate via synapses
- Up until now, we have considered current that flows from an electrode into a neuron, or through voltage-gated ion channels
- Do synapses behave like electrodes, or do they behave in a different manner? How can we model them?
- Understanding this is crucial for making sense of how neurons communicate with one another, and how networks of neurons behave

Synapses

- Synapses "connect" one neuron's axon to another's dendrite (usually!) They are the means by which neurons communicate
- They don't physically connect, but instead release neurotransmitter across a small gap called the synaptic cleft.
- The neurotransmitter then binds to the postsynaptic cell membrane, causing currents to flow into the cell







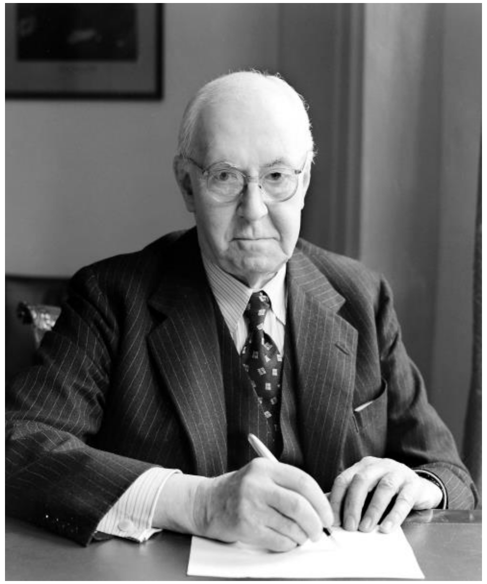
Dale’s Principle

- Each neuron only releases one kind of neurotransmitter across all of its synapses (Dale’s Principle; there are occasional exceptions)

“It is to be noted, further, that in the cases for which direct evidence is already available, the phenomena of regeneration appear to indicate that the nature of the chemical function, whether cholinergic or adrenergic, is characteristic for each particular neurone, and unchangeable” (Henry Dale, 1934)

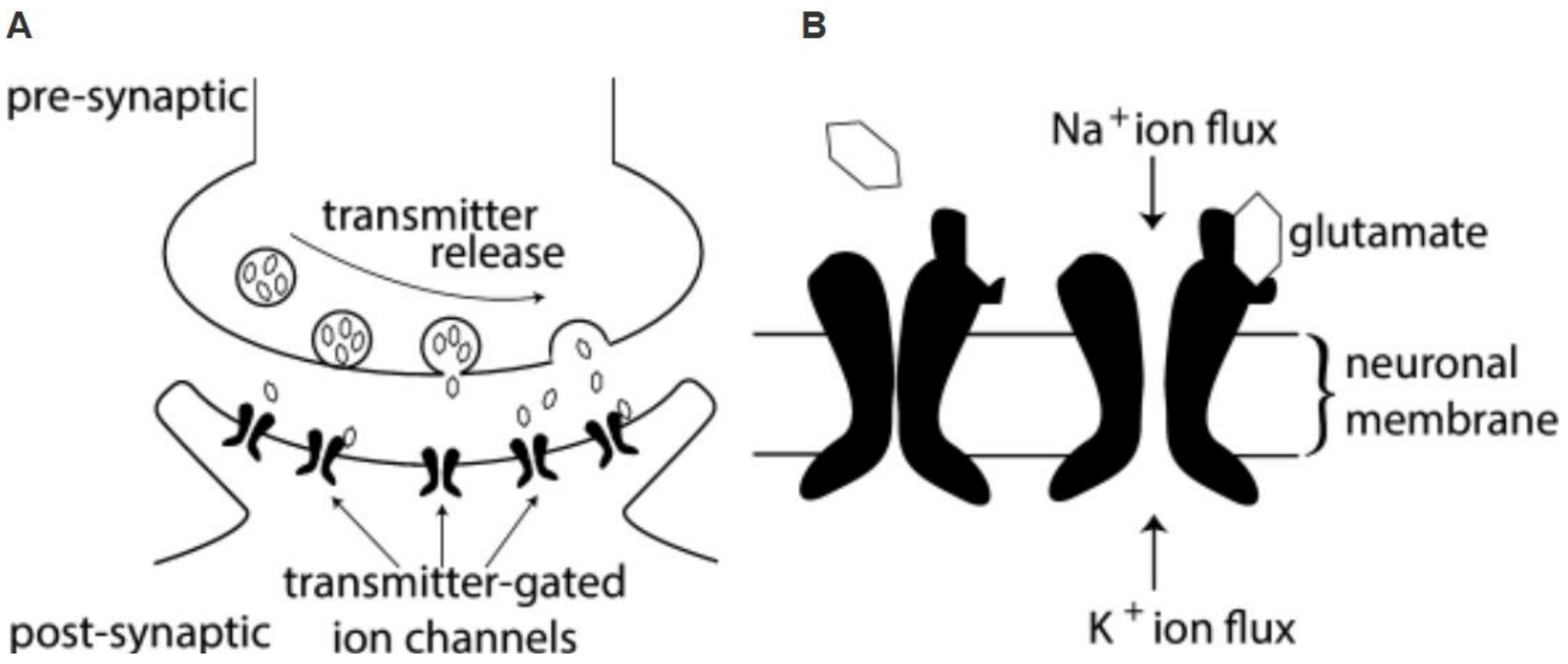
"I proposed that Dale’s Principle be defined as stating that at all the axonal branches of a neurone, there was liberation of the same transmitter substance or substances.“ (John Eccles, 1974)

For our purposes, each neuron is either excitatory or inhibitory!



Modelling Synapses

- Synapses function in a fundamentally different manner to injected currents:



- When an action potential arrives at the pre-synaptic side, molecules called neurotransmitter are released into the synaptic cleft
- The neurotransmitters diffuse across and bind to the post-synaptic cell membrane, which causes ion channels to open and current to flow into the post-synaptic cell

Synaptic Currents – Conductance-Based Models

- A simple model for the synaptic current is:

$$I_{syn}(t) = g_{syn}(t)(V(t) - E_{syn})$$

- *gsyn(t)* is the post-synaptic membrane conductance, *V* is the post-synaptic membrane potential, *Esyn* is the postsynaptic reversal potential

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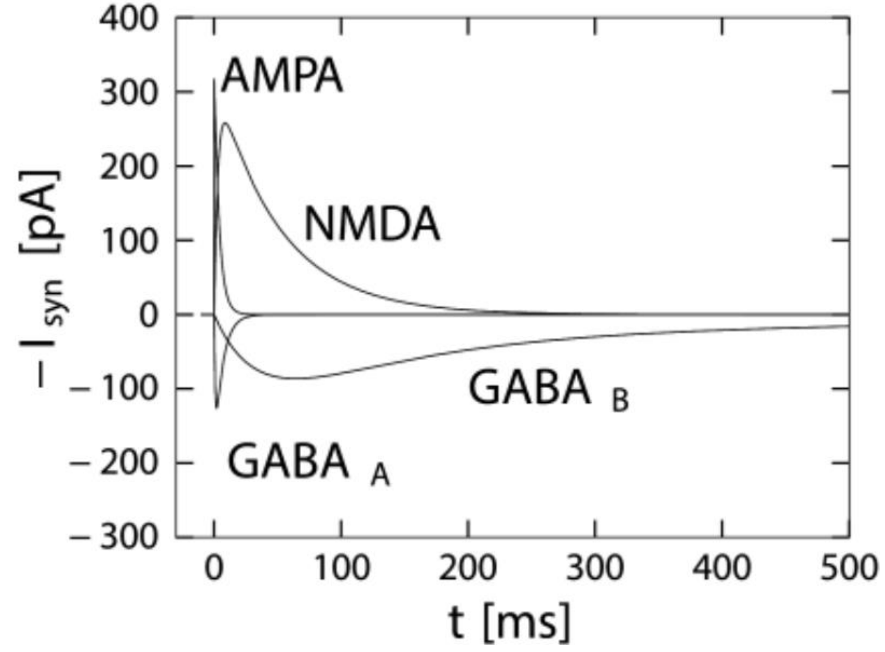
- For example, excitatory synapses have a reversal potential of *0 mV*, because they let both potassium (*-80 mV*) and sodium (*+50 mV*) flow through. Inhibitory synapses have a reversal potential of around *-80 mV*, because they let chloride (*-75 mV*) or potassium (*-80 mV*) flow through.

The Main Synaptic Currents/Receptors

Neurotransmitter	Receptor	Time constant	Ions
Glutamate	AMPA	fast ($\sim$ 1ms)	cations
	NMDA	slow	cations, including Ca^{2+}
GABA	$GABA_A$	fast	Cl^- conductance
	$GABA_B$	slow	K^+ conductance



Synaptic Currents – Conductance-Based Models

- We modelled the synaptic current as:

$$I_{syn}(t) = g_{syn}(t)(V(t) - E_{syn})$$

- A neuron with passive membrane potential dynamics will respond to this synaptic current as:

$$\tau_m \frac{dV}{dt} = -(V - E_m) - I_{syn}(t)/g_m$$

- But we haven't specified *gsyn(t)* yet. As usual there are many possible models, ranging from biologically detailed to heavily simplified approximations.

- Note also that we could use a Hodgkin Huxley model for the membrane dynamics.

Synaptic Currents – Delta Models

- One way to model synaptic conductances is to model all of the complicated biophysics of ion channels, vesicles, diffusion across the synaptic cleft, etc. Usually we opt for much simpler models.

- One of the simplest models for the synaptic conductance is the Dirac delta function (an instantaneous pulse):

$$g_{syn}(t) = \sum_{i=1}^{N} \bar{g}_{syn} \delta(t - t^{(i)})$$

where $t^{(i)}$ are presynaptic spike times and $\bar{g}_{syn}$ is the magnitude of post-synaptic conductances

This model is useful for analytical calculations, but is too simple to capture many interesting phenomena (such as the slow timecourse of NMDA or GABAb conductances)

Synaptic Currents – Exponential Model

- An alternative model treats the conductance as:

$$\tau_{syn}\frac{dg_{syn}}{dt} = -g_{syn} + \bar{g}_{syn}\sum_i \delta(t - t^{(i)})$$

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Heaviside step function:
$$\Theta(t) = \begin{cases} 0 & \text{if } t < 0 \\ 1 & \text{if } t > 0 \end{cases}$$

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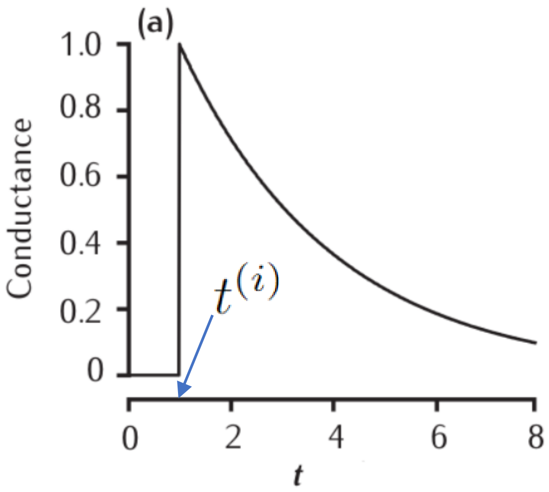


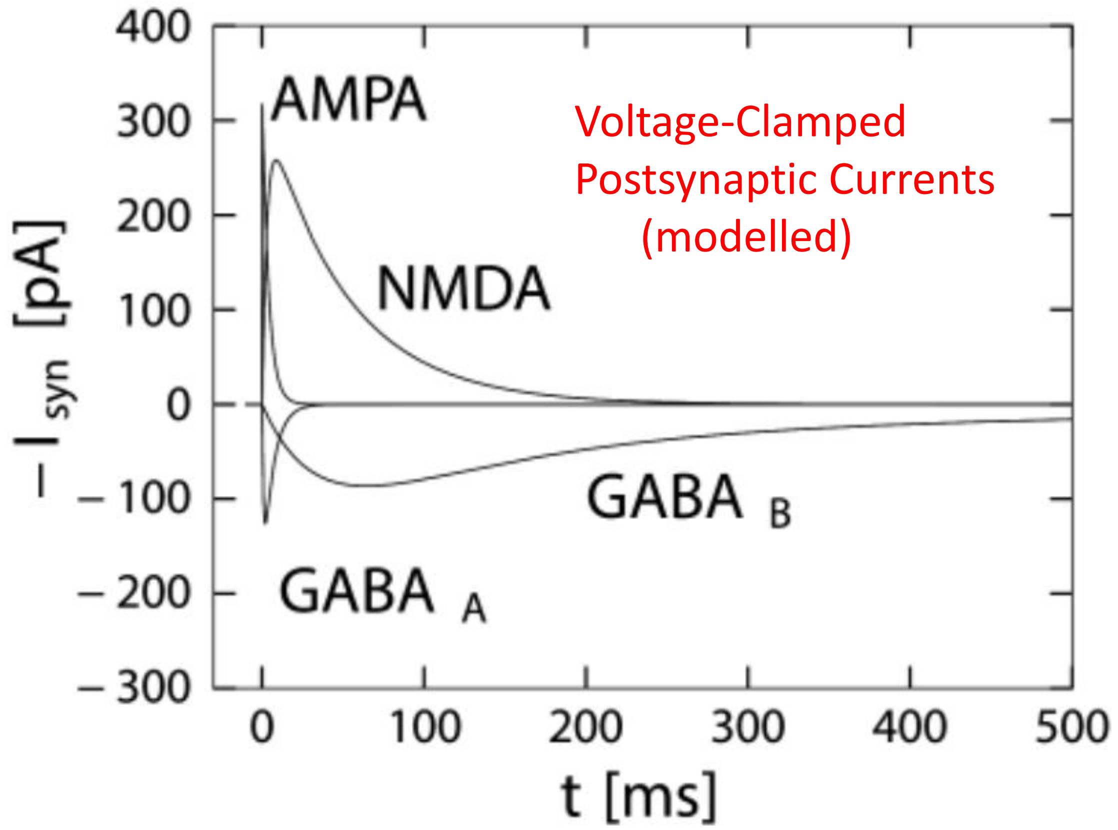
Heaviside step function:

$$\Theta(t) = \begin{cases} 0 & \text{if } t < 0 \\ 1 & \text{if } t > 0 \end{cases}$$

- This models synaptic conductance as an instantaneous rise followed by an exponential decay for each spike
- This makes some sense – neurotransmitter will be quickly released and bind to the postsynaptic cell membrane, causing ions to transiently flow through, with a roughly exponential time course
- It’s a reasonable approximation for AMPA or GABAa (which are fast)

Synaptic Currents – Rise and Decay Times

- Not all synaptic currents can be fit to a simple exponential. Some have slow rise times and/or multiple decay times



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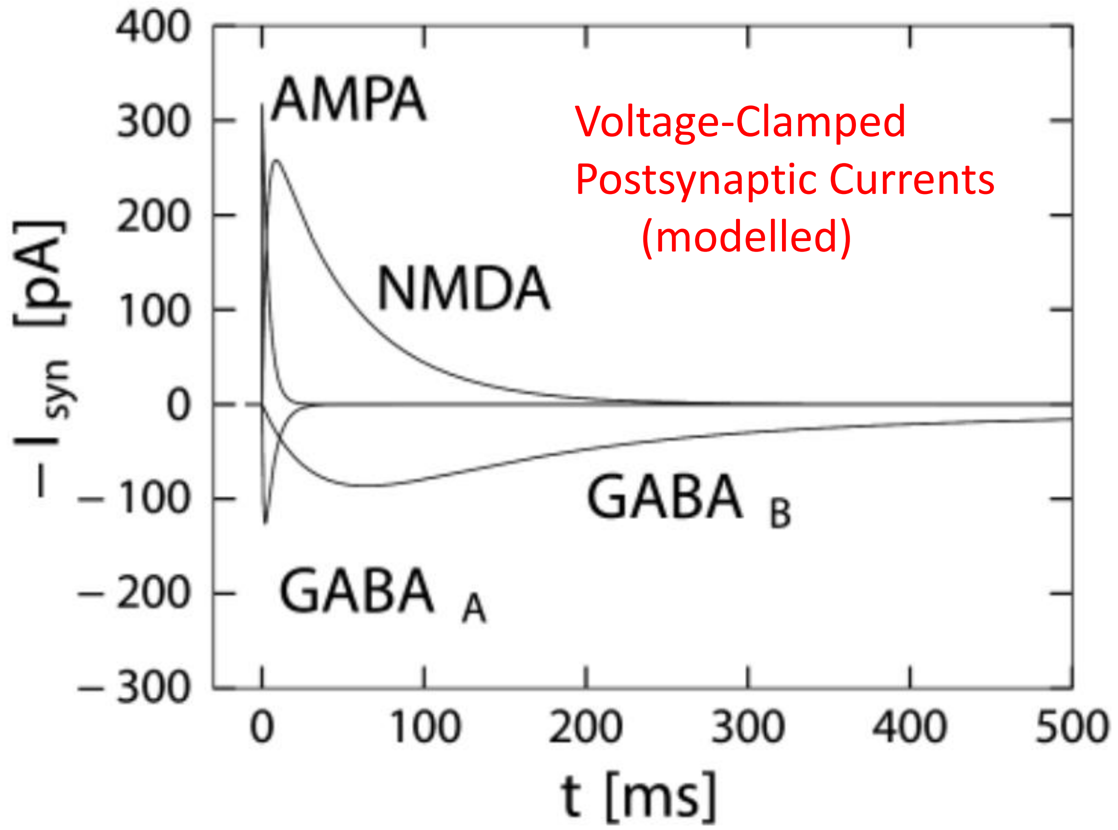
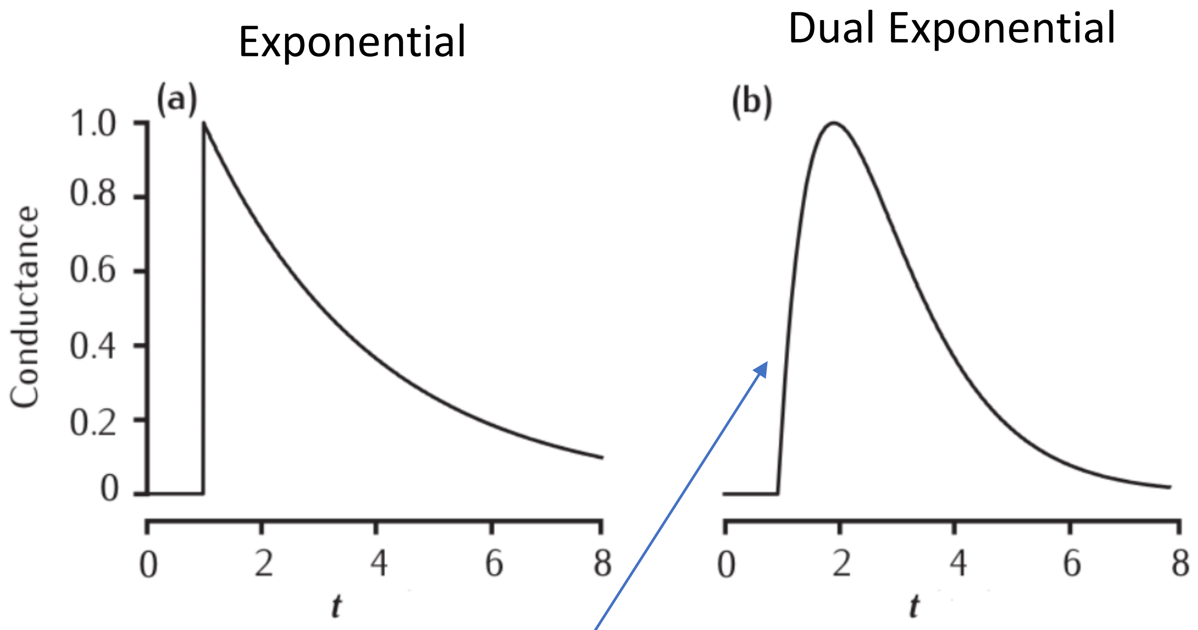




$$g_{syn}(t) = \sum_i \bar{g}_{syn} \left[e^{-(t-t^{(i)})/\tau_1} - e^{-(t-t^{(i)})/\tau_2} \right] \Theta(t - t^{(i)})$$

Accounting for Multiple Rise and Decay Times

- A yet more flexible model assumes three separate time constants (1 rise + 2 decay):

$$g_{syn}(t) = \sum_{i=1}^{N} \bar{g}_{syn} \underbrace{(1 - e^{-(t-t^{(i)})/\tau_{rise}})}_{\text{rise of conductance}} (\underbrace{a e^{-(t-t^{(i)})/\tau_{fast}}}_{\text{fast decay}} + \underbrace{(1-a) e^{-(t-t^{(i)})/\tau_{slow}}}_{\text{slow decay}}) \Theta(t - t^{(i)})$$

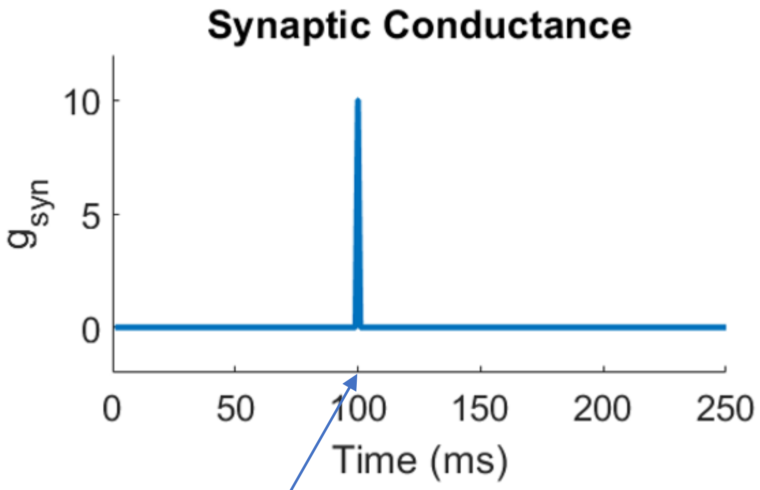
- This model can replicate the time courses of the main excitatory (AMPA, NMDA) and inhibitory (GABAa, GABAb) synaptic currents

- Note: the models we have considered are phenomenological – they fit a curve to the observed time courses without positing a biological/physical mechanism

- More complex mechanistic models consider voltage-dependence of synaptic conductances, vesicle release, diffusion of neurotransmitter, and many other details (we won't cover these in this course!)

Example - Delta Synapse (Excitatory)

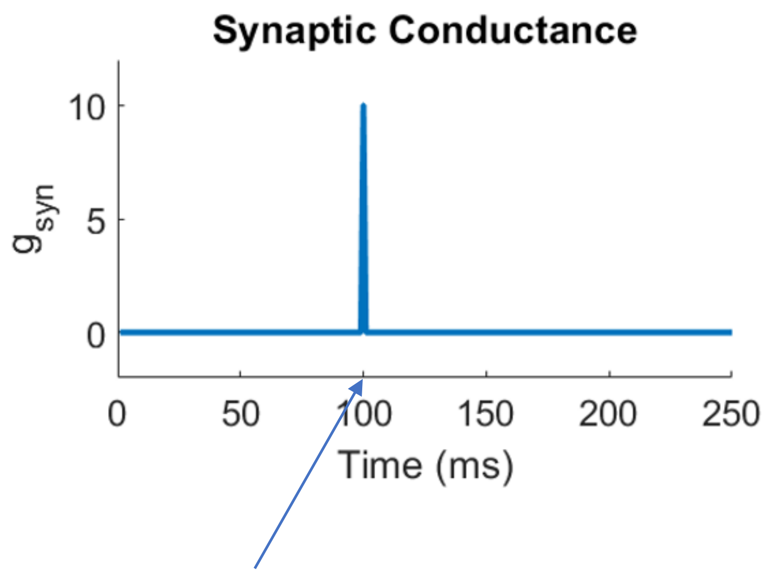
$$g_{syn}(t) = \bar{g}_{syn}\delta(t - 100ms)$$

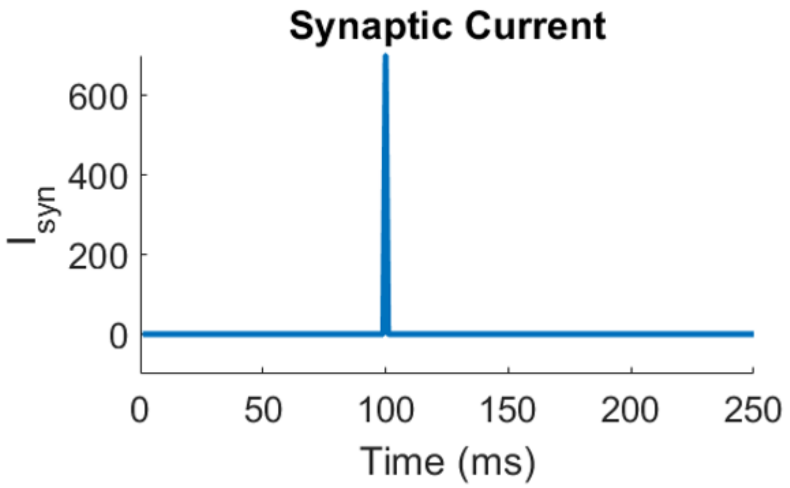


presynaptic spike time

Example - Delta Synapse (Excitatory)

$$g_{syn}(t) = \bar{g}_{syn}\delta(t - 100ms) \qquad I_{syn}(t) = g_{syn}(t)(V(t) - E_{syn})$$





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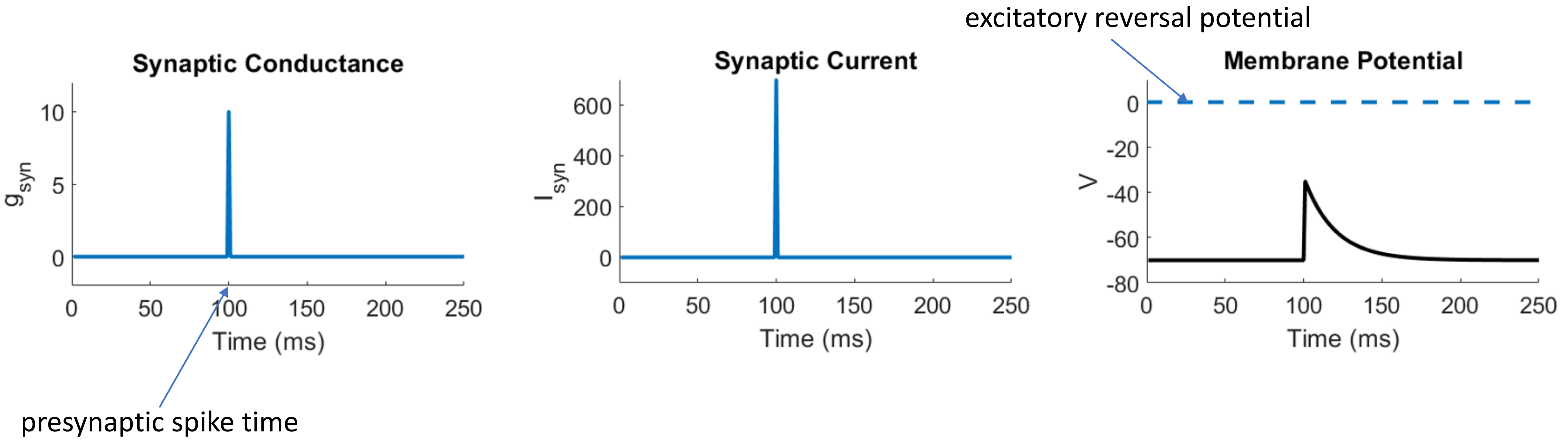
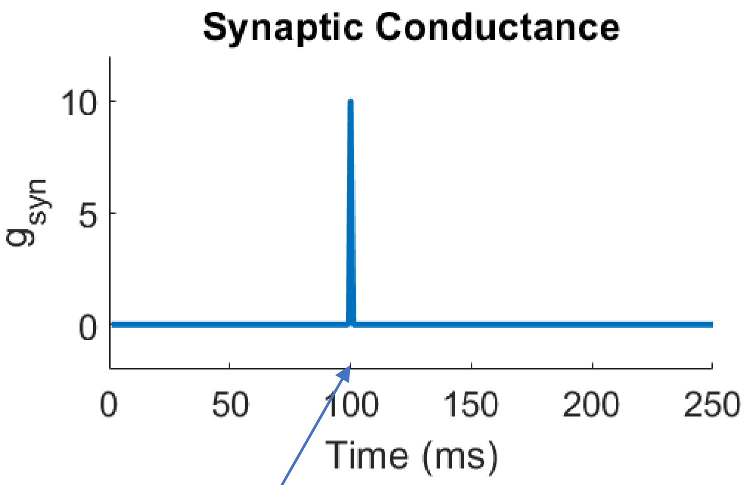


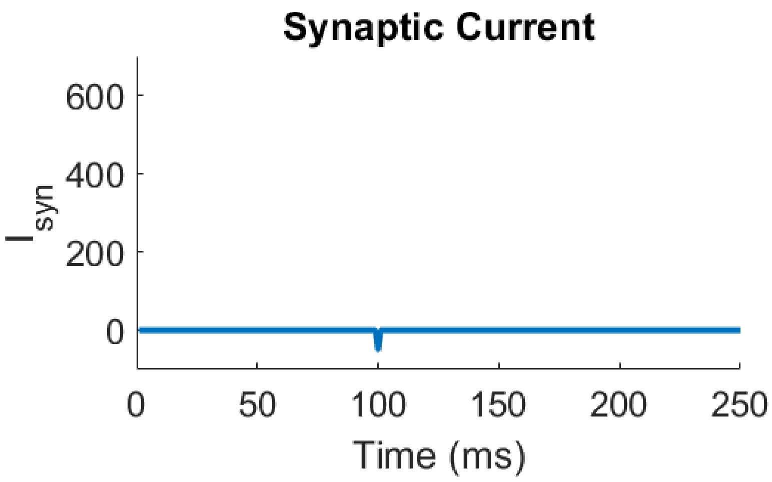
Example - Delta Synapse (Inhibitory)

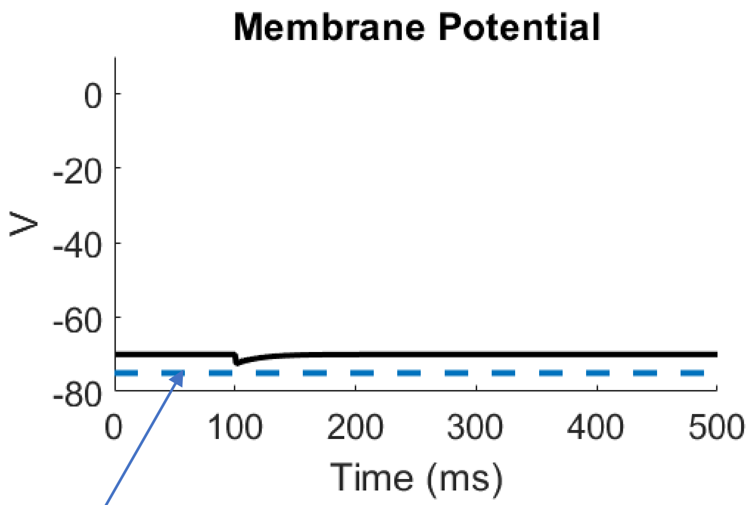
$$g_{syn}(t) = \bar{g}_{syn}\delta(t - 100ms)$$

$$I_{syn}(t) = g_{syn}(t)(V(t) - E_{syn})$$

$$\tau_m \frac{dV}{dt} = -(V - E_m) - I_{syn}(t)/g_m$$







presynaptic spike time

inhibitory reversal potential

Example - Delta Synapse (Inhibitory)

What happens if you hold the membrane potential at the excitatory reversal potential (e.g., via voltage clamp)?

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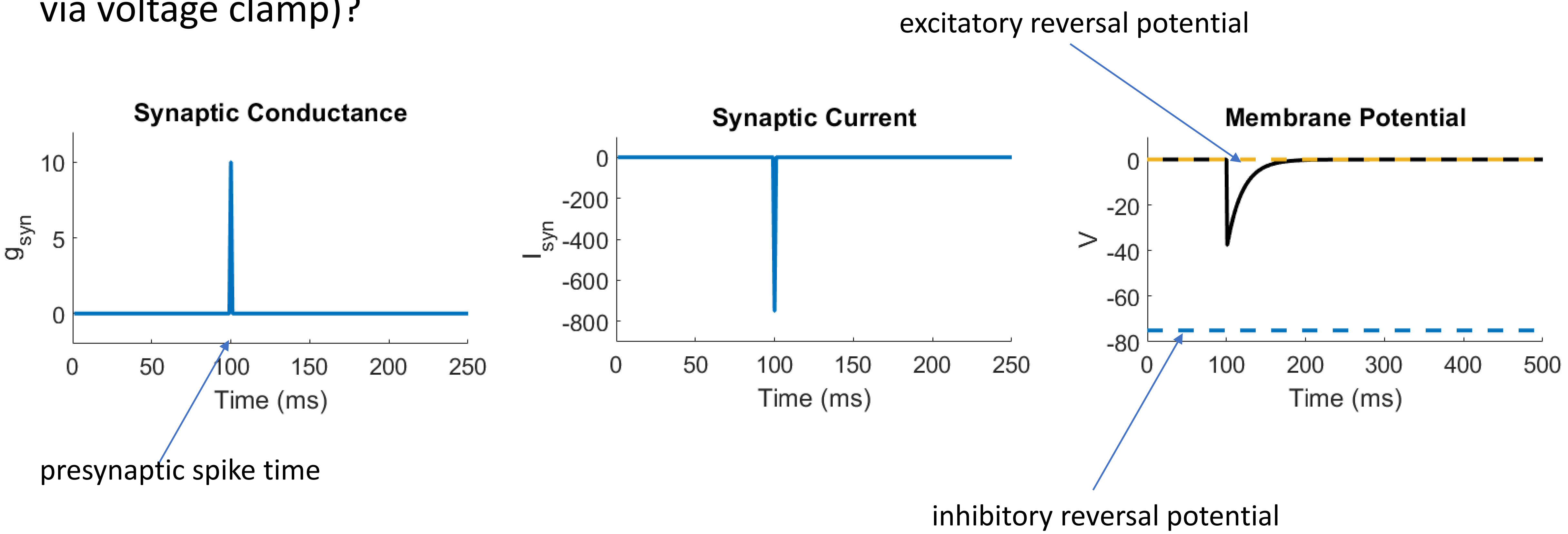

This voltage clamp technique is used experimentally to infer excitatory and inhibitory synaptic currents entering a neuron!

Summary - Synapses

- Neurons communicate via synapses
- When an action potential arrives at the pre-synaptic side, a cascade of biochemical events causes molecules called neurotransmitters to be released into the synaptic cleft
- These molecules bind to the post-synaptic cell membrane, causing ion channels to open
- There are two main types of synapse, excitatory and inhibitory, that release different kinds of neurotransmitter that elicit positive or negative currents
- There are a wide range of models for synapses, ranging from complex biophysical models to extremely simple phenomenological models

Summary – Combining Neuron and Synapse Models

- We have so far considered two neuron models: Hodgkin-Huxley and leaky integrate and fire
- We have also considered multiple synapse models at varying levels of abstraction
- How do we choose an appropriate set of models for a given application?
- Answer: use the simplest possible models that can capture the phenomena in question
- It is rare to see a large-scale network models using Hodgkin-Huxley neurons and/or biophysically-detailed synapses (but see e.g. the Human Brain Project for a counterexample)
- The notion of biological plausibility is subjective – to an AI researcher deep networks are biologically plausible, but to a molecular biologist the Hodgkin-Huxley model is overly simplified…

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