Lecture 1. Introduction to Computational Neuroscience
Single-cell models

Before we begin: Admin

- Main course text: Theoretical Neuroscience (P. Dayan and L.F. Abbott). `http://neurotheory.columbia.edu/~larry/book/`
- Other books: David Mackay: ITILA; Hugh Wilson: Spikes (`http://www.cvr.yorku.ca/webpages/wilson.htm#book`). Thomas Trappenberg: FCNS. Copies available in BGM library.
- `http://github.com/sje30/cn2019` for lecture notes, assignments, papers.
- Office hour (Fri 12:00–13:00) for any enquiries.

Key questions in neuroscience

- How do we perceive (sensory system) and act (motor system)?
- What is the neural substrate of cognition?
- How do neurons encode memories?
- How does the nervous system develop?
- ...

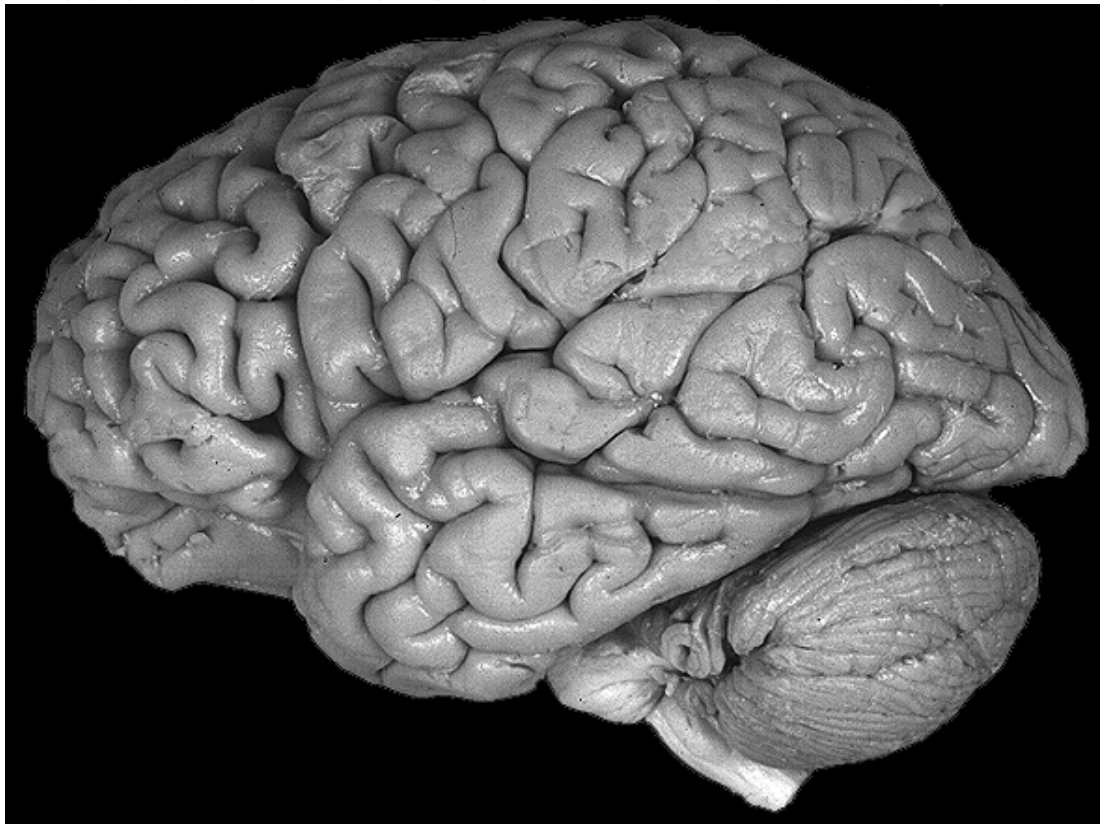
Mostly approached by experimental techniques.
Experiments test for necessity, models test for sufficiency ...

What is Computational Neuroscience?

- Computational neuroscience has two meanings:
  1. Using computers to study neuroscience questions (visualisation, analysis, modelling).
  2. What computations does the brain perform?
- We will examine several themes:
  1. Modelling of single neurons.
  2. Short/long-term memories in networks.
  3. Complex brain networks (4 lectures by Rafael Romero-Garcia).
  4. Development of connectivity (unsupervised mostly – see deep learning course).

Brain organisation

Structural and functional divisions of mammalian brain.



Neurons are the building blocks of the brain. $\sim 10^{11}$ in human brain; each may make $10^0 - 10^3$ connections. Not encoded in the genome!
Vastly distributed architecture exhibiting *parallel processing* and *graceful degradation*.

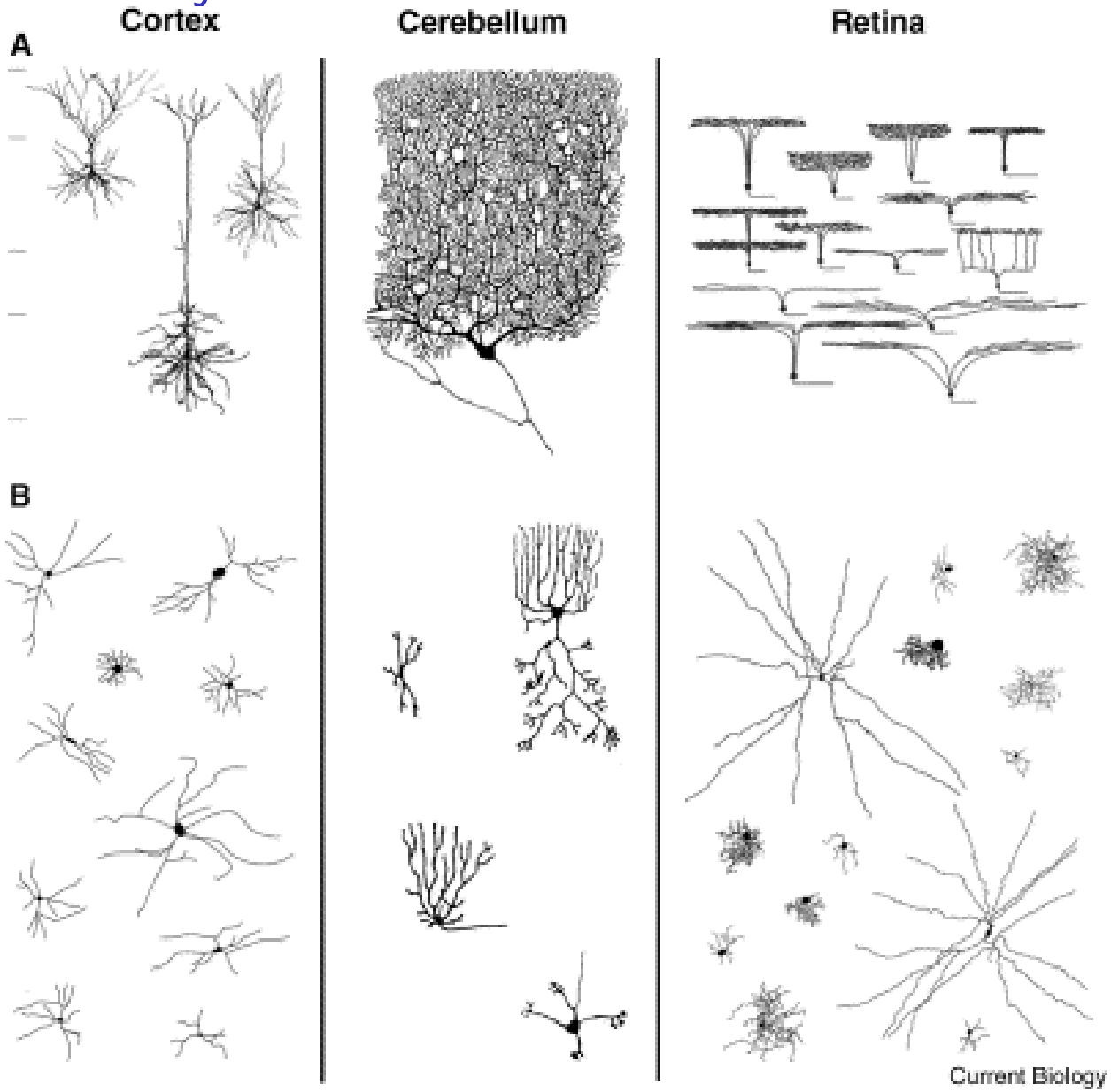
Phineas Gage

http://www.deakin.edu.au/hmnbs/psychology/gagepage/

http://www.interscoop.com/media/phine.jpg

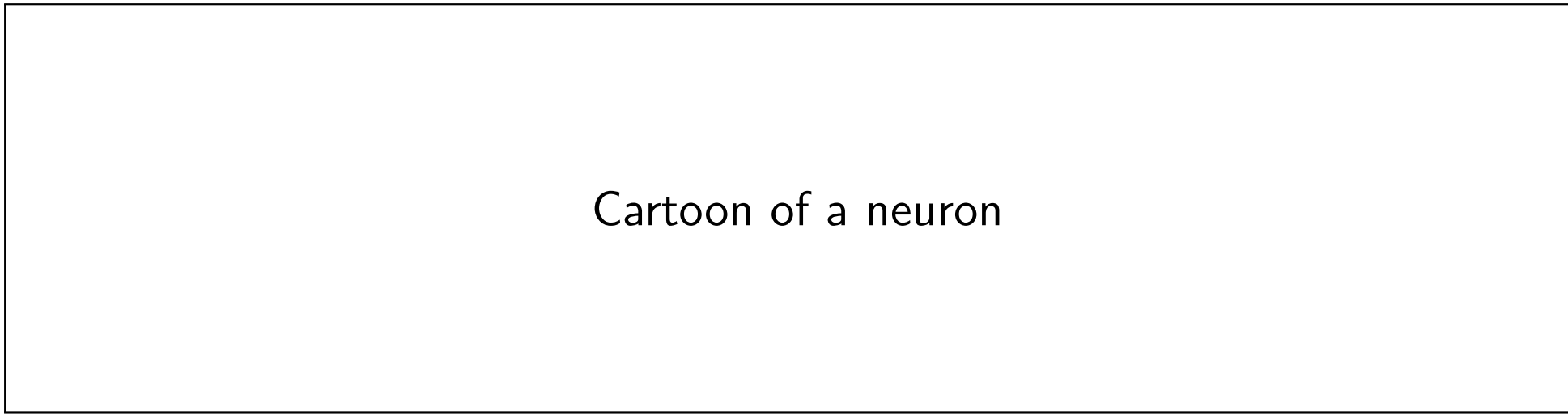
"On 13th. September 1848, an accidental explosion of a charge he had set blew his tamping iron through his head. The tamping iron was 3 feet 7 inches long and weighed 13 1/2 pounds. It was 1 1/4 inches in diameter at one end (...) and tapered over a distance of about 1-foot to a diameter of 1/4 inch at the other. The tamping iron went in point first under his left cheek bone and completely out through the top of his head, landing about 25 to 30 yards behind him. Phineas was knocked over but may not have lost consciousness even though most of the front part of the left side of his brain was destroyed. Dr. John Martyn Harlow, the young physician of Cavendish, treated him with such success that he returned home to Lebanon, New Hampshire 10 weeks later."

Neuronal diversity



Masland (2004).

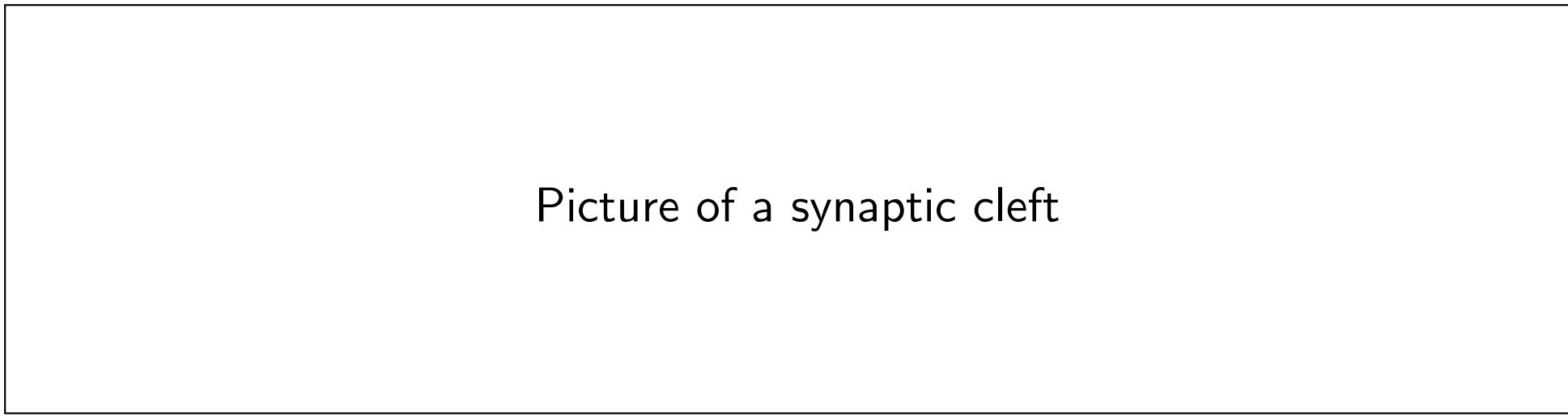
Components of a neuron



- Dendritic tree
- Cell body
- Axon
- Axon terminal
- synapses

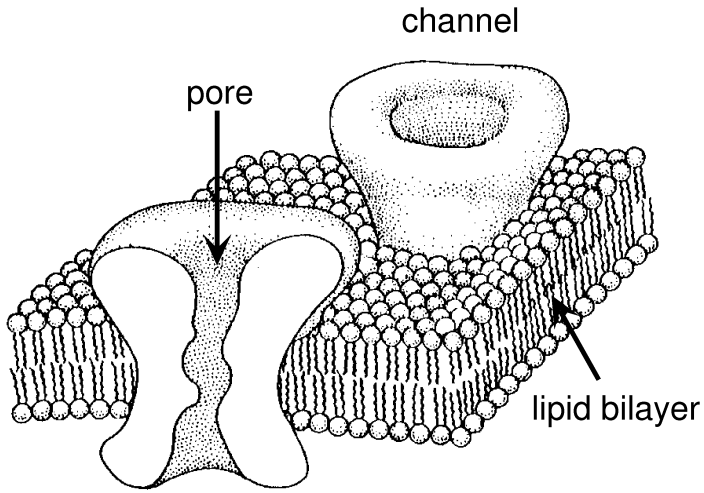
Action potentials ("spikes") travel along the axon when cell reaches threshold. All-or-none events.

Synapses



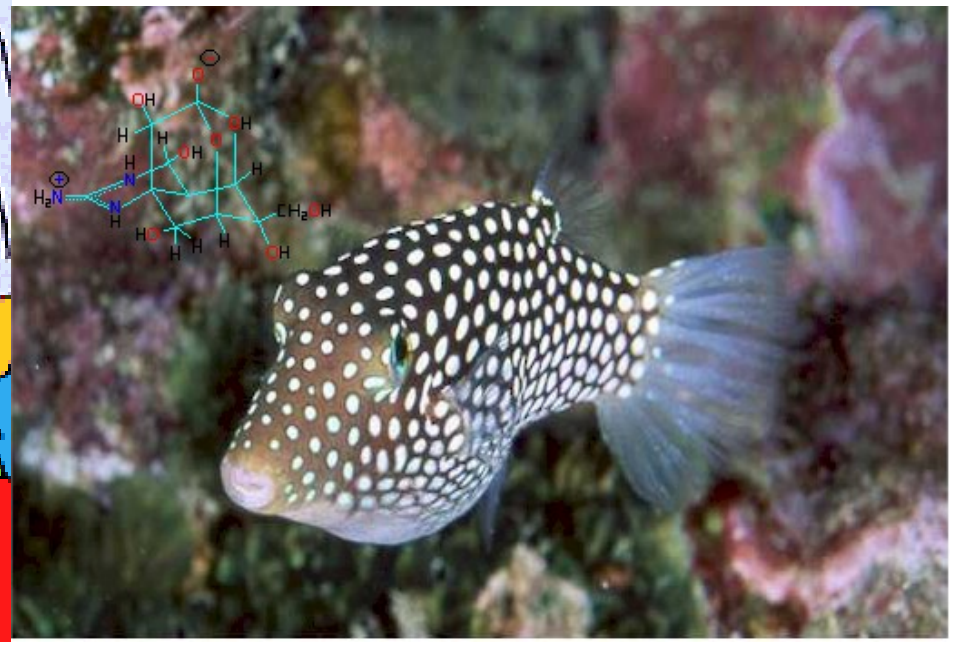
- presynaptic neuron
- postsynaptic neuron
- vesicles
- neurotransmitters (Glutamate, ACh, GABA)
- receptors (type of ion channel; next slide)
- cf. gap junctions for electrical transmission.

Ion channels



- Ion channels (ICs) allow specific ions to selectively diffuse across membrane when channels are "open".
- State of channel can be modulated by sensing voltage (voltage-gated) or by sensing internal/external concentration of e.g. messengers (Ca) or neurotransmitters (ACh). Ionotropic (fast) vs Metabotropic (slow).
- Typically $10^2 - 10^6$ per μm^2 channels of each type in membrane; each channel about 10 nm high.

Tetrodotoxin (TTX) will block your sodium channels . . .



Ionic basis of action potential Hodgkin and Huxley

- Principal ions Na^+, K^+. Imbalance in numbers across membrane causes electrical gradient and concentration gradient.
- Ion channels *selectively* allow ions to flow down concentration gradient.
- Ion pumps actively move ions against concentration gradient.
- Electrical gradient acts against concentration gradient. Each ion has its own resting potential when two gradients balance. ($E_{\mathrm{Na}} = +50mV, E_{\mathrm{K}} = -77mV$).
- This is determined by Nernst potential $E = (RT/Fz) \ln[X_o]/[X_i]$ (RT/F = 25 mV at 25C)
- At rest (-70 mV; inside relative to outside), voltage-gated ion channels are closed.

Threshold behaviour

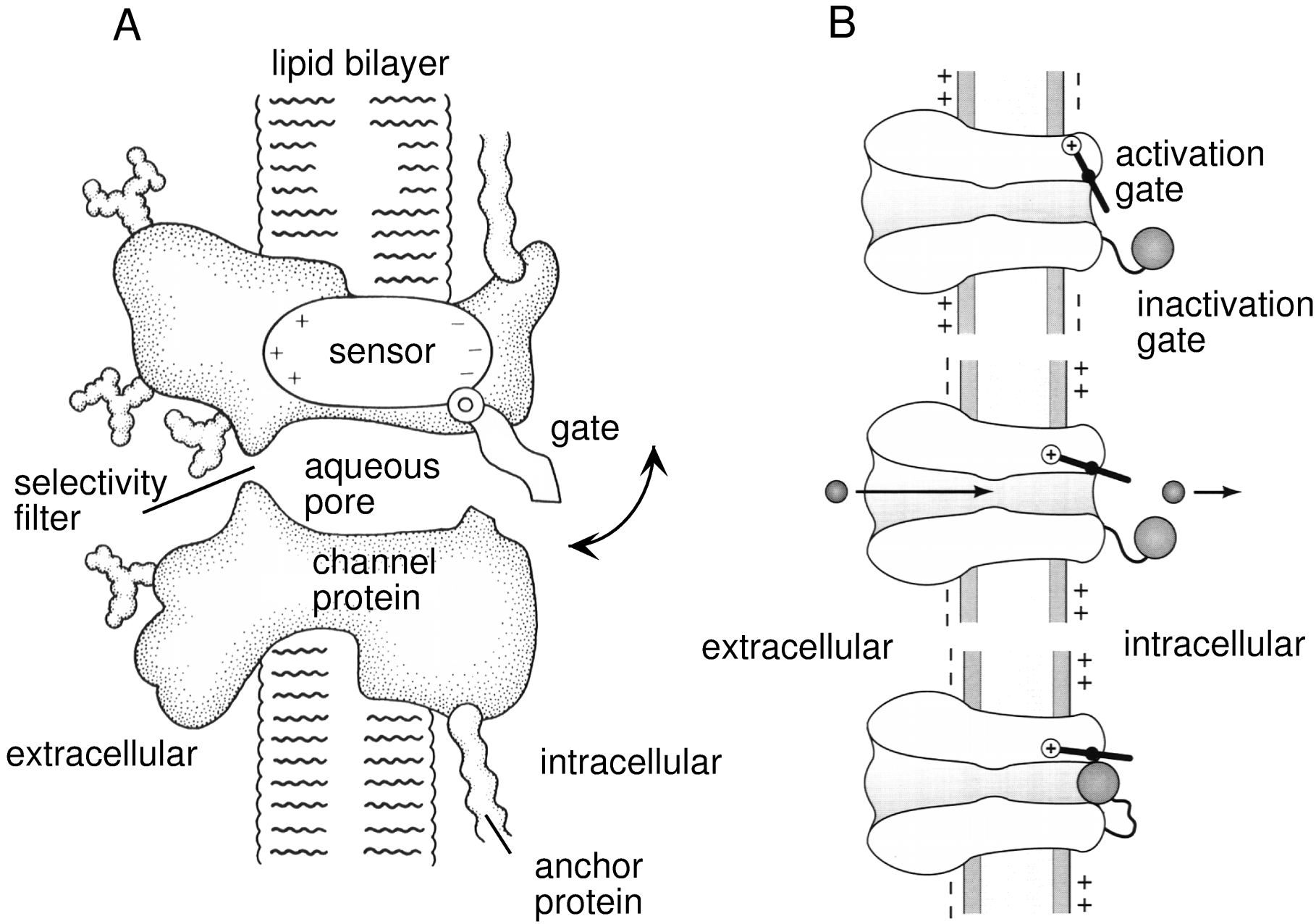
Action potential with phases marked.

- For small depolarizations, ion channels open and Na^+flow in is balanced by K^+flow out. Ion channels are voltage-gated.
- For larger depolarizations ($\sim$ 10–15 mV), Na^+flow faster.
- On fast timescale, more Na^+channels open, causing more depolarization... action potential. Na^+inactivates.
- On slower timescale, K^+channels open, causing hyperpolarization, undershoot (refractory period) and back to resting.
- Action potential ("spikes") travels as a wave down axon; passively diffusing and then regenerating at Nodes of Ranvier (unmyelinated).
- `http://tinyurl.com/matthews-channel`

Propagation of action potential

- Local depolarization causes passive intracellular spread of current, causing local depolarisation. This opens neighbouring channels, causing AP to actively regenerate.
- This is slow. Myelin acts as insulator so that signal (passively) propagates quickly down axon, regenerating at nodes of Ranvier.
- `http://tinyurl.com/matthews-prop`

Persistent vs transient channels (TN fig 5.8)



Mathematical description of ion channels

Voltage-gated channels: gating variables [0,1] modulate flow of ions.
m,n increase with voltage; h (inactivating) decreases with voltage.
For given voltage, e.g. K^+channel activation, gated by *n*:

$$\underset{\text{1-n}}{\text{Closed}} \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} \underset{\text{n}}{\text{Open}}$$

leading to:

$$\tau_n(V) = \frac{1}{\alpha(V) + \beta(V)}$$

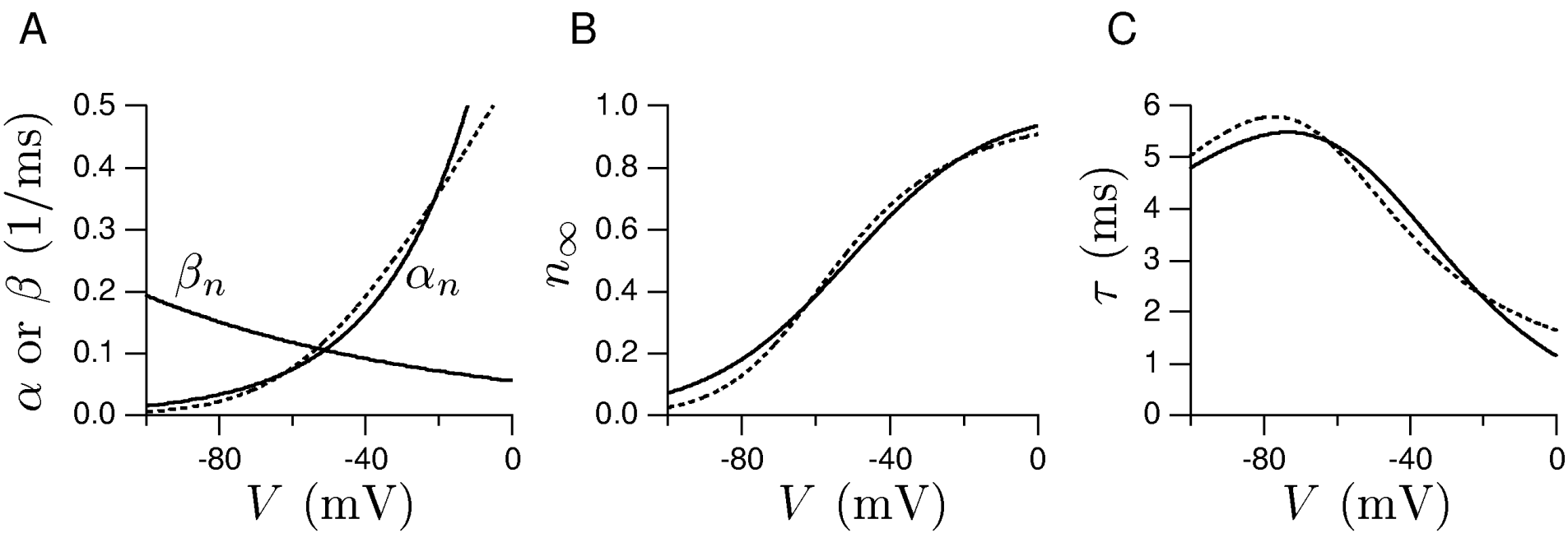
$$\tau_n(V)\frac{\mathrm{d}n}{\mathrm{d}t} = n_\infty - n$$

Fitting $\alpha(V)$ and $\beta(V)$ for a channel

Thermodynamic arguments led to suggestions of exptl fits for $\alpha(V)$, $\beta(V)$; e.g. for K^+:

$$\alpha_n(V) = \frac{.01(V+55)}{1-\exp[-(V+55)/10]}$$

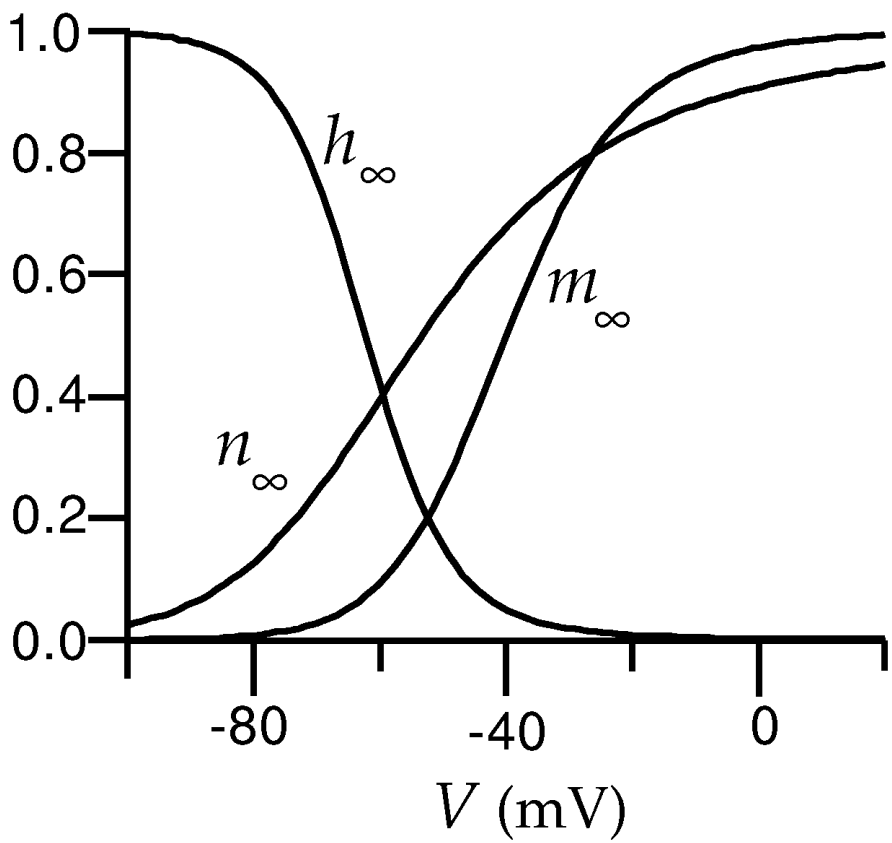
$$\beta_n(V) = .125\exp[-.0125(V+65)]$$

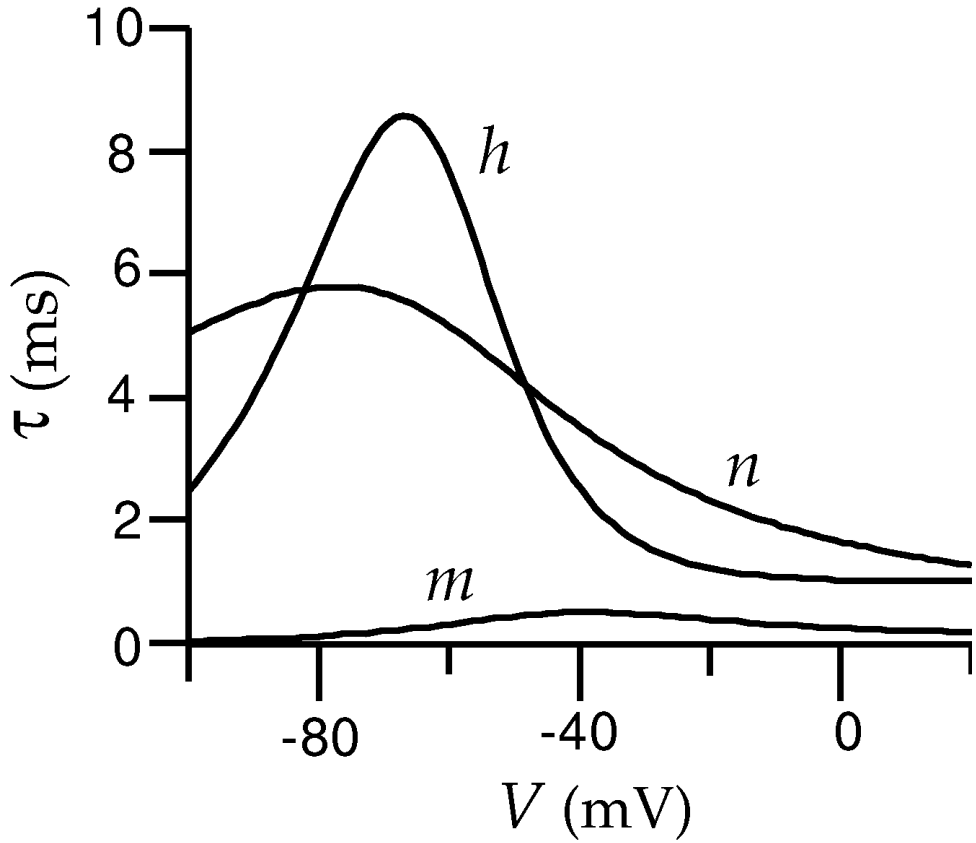


Dayan and Abbott (2002) fig 5.9. Solid line: exptl data; dotted line: fits. For β_n, theory and fit overlap.

Voltage-dependence channel openings for $K^+$and Na^+

Steady-state levels of activation and inactivation (n: activation of K^+; m: activation of Na^+; h: inactivation of Na^+).





Dayan and Abbott (2002) fig 5.10.

Notation and units

Term	meaning	typical value
E_{Na}	Reversal potential (for sodium)	50 mV
A	neuronal surface area	0.01–0.1 mm^2
c_m	specific membrane capacitance	10 nF mm^{-2}
C_m	total capacitance $= c_m A$	
g_{Na}	specific conductance (i.e. per unit area) for sodium	1.2 mS mm^{-2}
r_m	specific membrane resistance (= inverse of membrane conductance)	$\approx 1 M\Omega$ mm^2
R_m	total membrane resistance $= r_m/A$	
m,n,h	gating variables	0–1
α, β	open/close rates	ms^{-1}
τ_m	membrane time constant $(= r_m c_m)$	10–100 ms

Putting it together: Hodgkin-Huxley equations

$$c_m \frac{\mathrm{d}V}{\mathrm{d}t} = -i_m + I_e/A$$

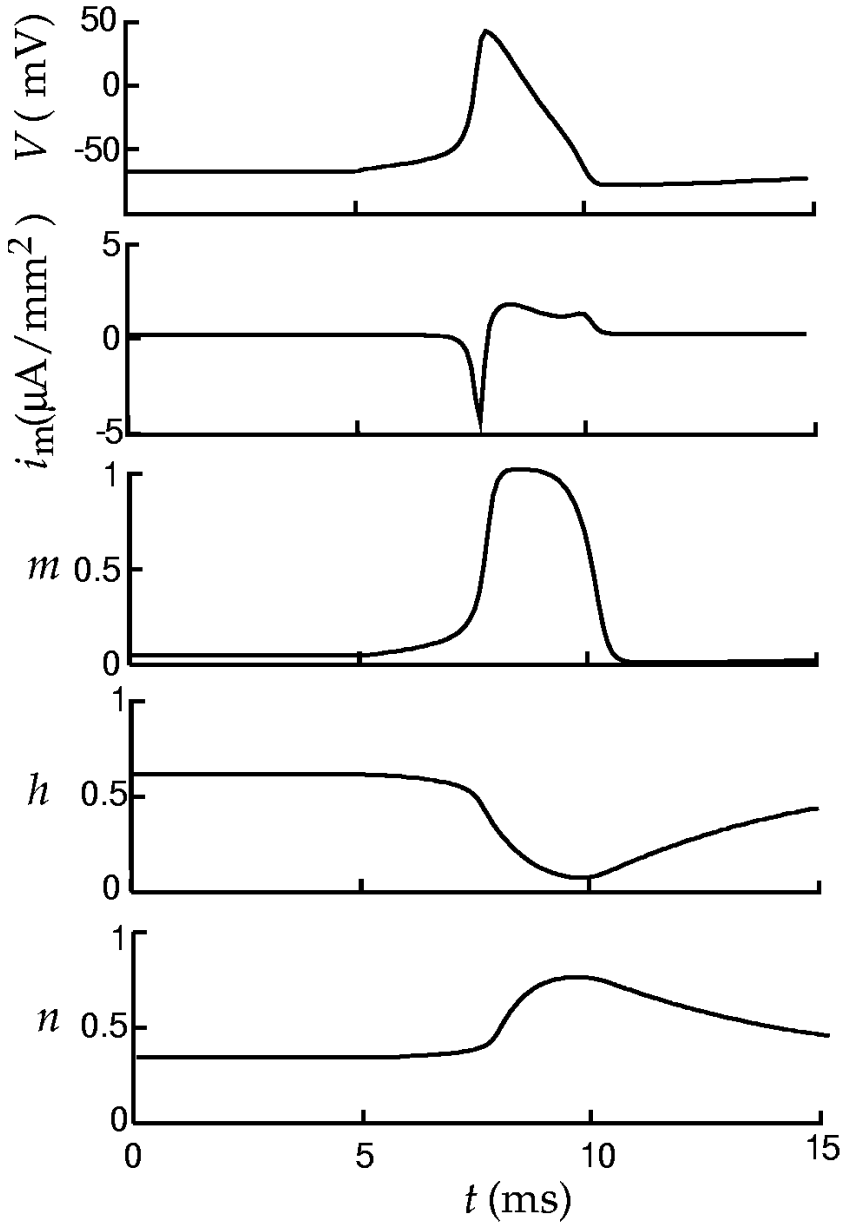
Each ion produces a current which can be summed:

$$i_m = \sum_i g_i[\text{gating}](V - E_i)$$

$$c_\mathrm{m} \frac{\mathrm{d}V}{\mathrm{d}t} = g_L(E_\mathrm{L} - V) + g_\mathrm{Na} m^3 h(E_\mathrm{Na} - V) + g_\mathrm{K} n^4 (E_\mathrm{K} - V) + I_\mathrm{e}/A$$

Plus we have equations for $\frac{\mathrm{d}n}{\mathrm{d}t}, \frac{\mathrm{d}m}{\mathrm{d}t}, \frac{\mathrm{d}h}{\mathrm{d}t}$.
(Notes: this is space-clamped; note I_e defined as positive inward, whereas i_m are defined as positive-outward.)

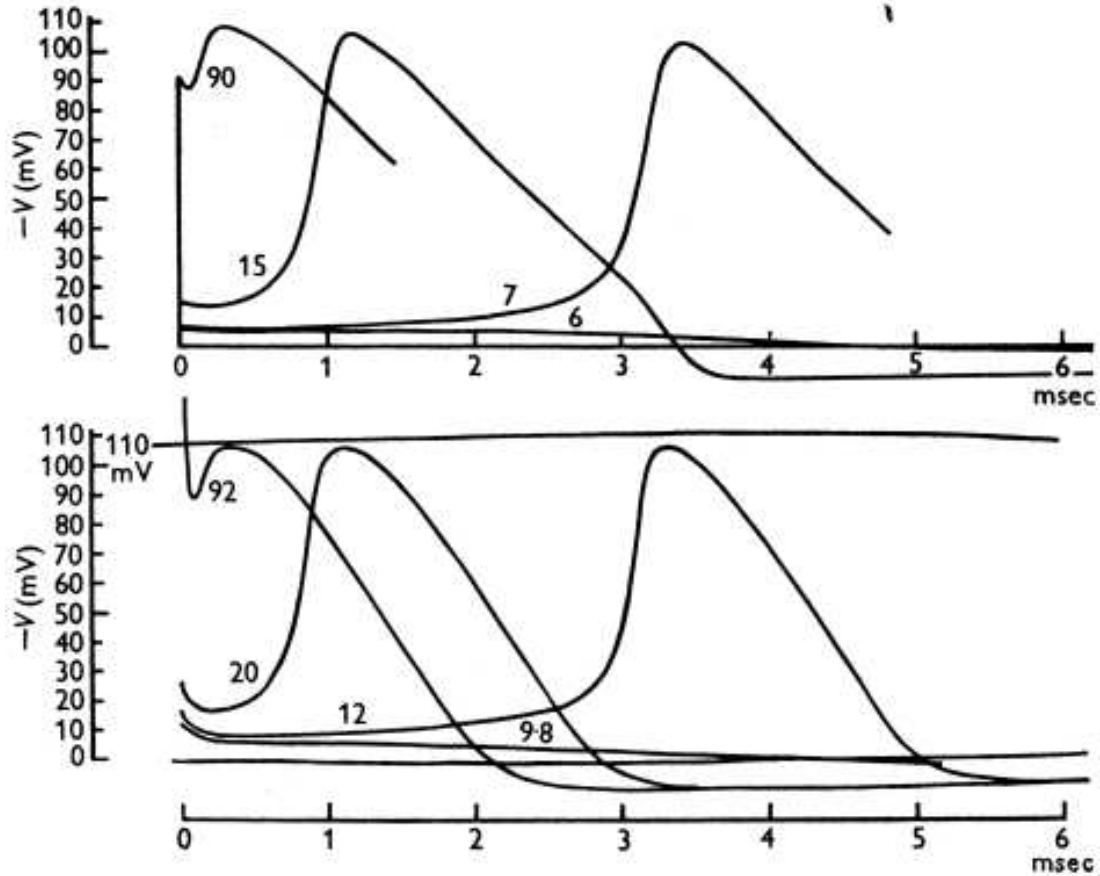
Evolution of a model action potential



Dayan and Abbott (2002) fig 5.11.

HH: model vs experiment

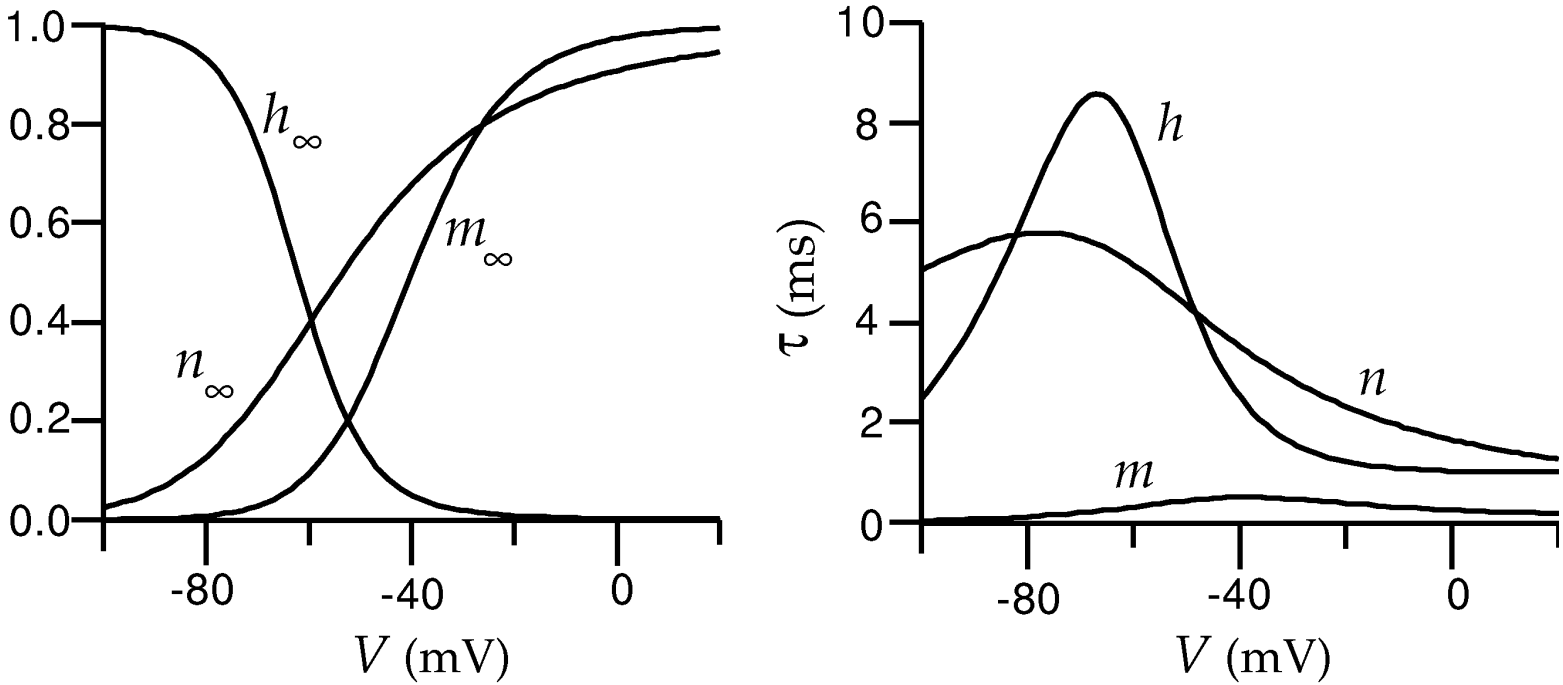
Data taken from squid giant axon; much wider axonal diameter (800 μm) than normal (2 μm) for rapid signal propagation [escape behaviour].



(Hodgkin and Huxley, 1952). Reproduced from David Sterratt. Upper trace: model; numbers give initial depolarisations (in mV); recordings at 6 C.

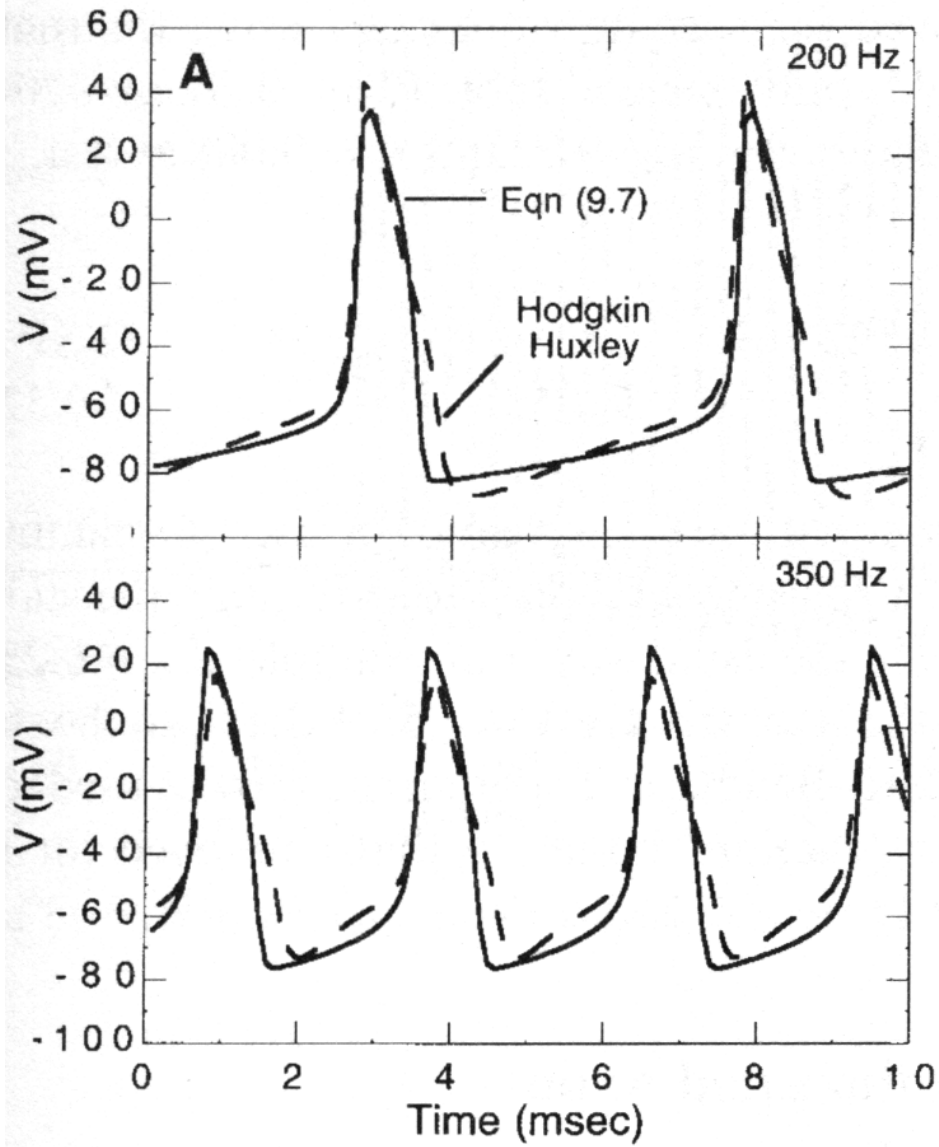
Simplifications to HH

Two observations (Rinzel, 1985) from this picture (seen before):



1. τ_m is pretty small; so assume m immediately reaches steady-state m_∞. Na^+activates quickly. Eliminate $\frac{dm}{dt}$.
2. h_∞ and $1 - n_\infty$ have similar voltage dependence, and $\tau_h \approx \tau_n$. i.e. Na^+channel inactivation, h, occurs at same rate (but in opposite direction) as K^+channel opening, n. Eliminate $\frac{dh}{dt}$.

Rinzel simplification vs HH model



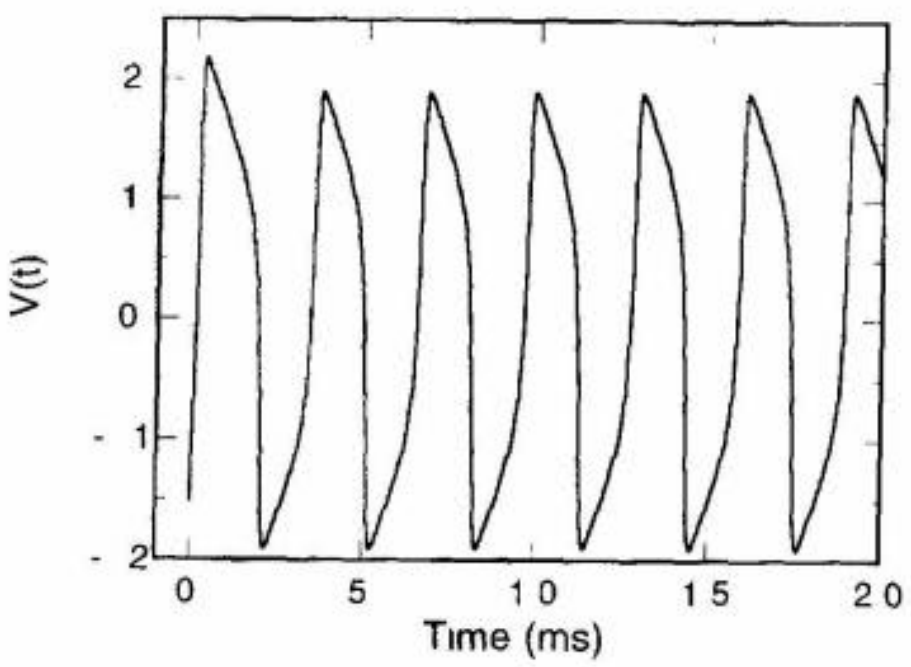
Wilson (1999) Fig 9.3. Comparison of HH model with Rinzel approximation (eqn 9.7). Both systems produce a reduced spike amplitude at higher frequencies.

FitzHugh-Nagumo (FHN) model

Alternative simplification of HH system, for analytical tractability.
Space-clamped version (I is external input to neuron):

$$\frac{\mathrm{d}u}{\mathrm{d}t} = u(1-u)(u-a) - w + I \qquad \text{Membrane voltage}$$

$$\frac{\mathrm{d}w}{\mathrm{d}t} = bu - \gamma w \qquad \text{Recovery variable}$$



Examine nullclines and behaviour of system.

Hopf bifurcation theorem (we will return to this)

For an N-dimensional system, where:

$$\frac{\mathrm{d}\mathbf{x}}{\mathrm{d}t} = F(\mathbf{x}, \beta)$$

$\mathbf{x}_0$ is an isolated equilibrium point. Assume $\beta = \alpha$ is a critical value with properties determined from Jacobian $\mathbf{A}(\beta)$:

1. $\mathbf{x}_0$ is asymptotically stable for some finite range of values $\beta < \alpha$.
2. At $\beta = \alpha$, $\mathbf{A}(\beta)$ has one pair of eigenvalues $\pm i\omega$; all other eigenvalues have negative real part.
3. $\mathbf{x}_0$ is unstable for some range of values $\beta > \alpha$.

Then the system has an asymptotically stable limit cycle over a range $\beta > \alpha$ (supercritical/soft bifurcation) OR an unstable limit cycle over some range $\beta < \alpha$. (subcritical/hard bifurcation).
Near $\beta = \alpha$ the frequency of oscillation will be approx. $\omega/2\pi$, and the oscillation emerges with infinitesimal amplitude sufficiently close to α.
What do we gain from this?

Example of application of Hopf bifurcation theorem (HBT)

e.g. van der Pol equations.

$$\frac{\mathrm{d}x}{\mathrm{d}t} = y$$
$$\frac{\mathrm{d}y}{\mathrm{d}t} = -\omega^2 x + y(\beta - x^2)$$

Apply HBT to determine period of limit cycle.

Integrate and fire models

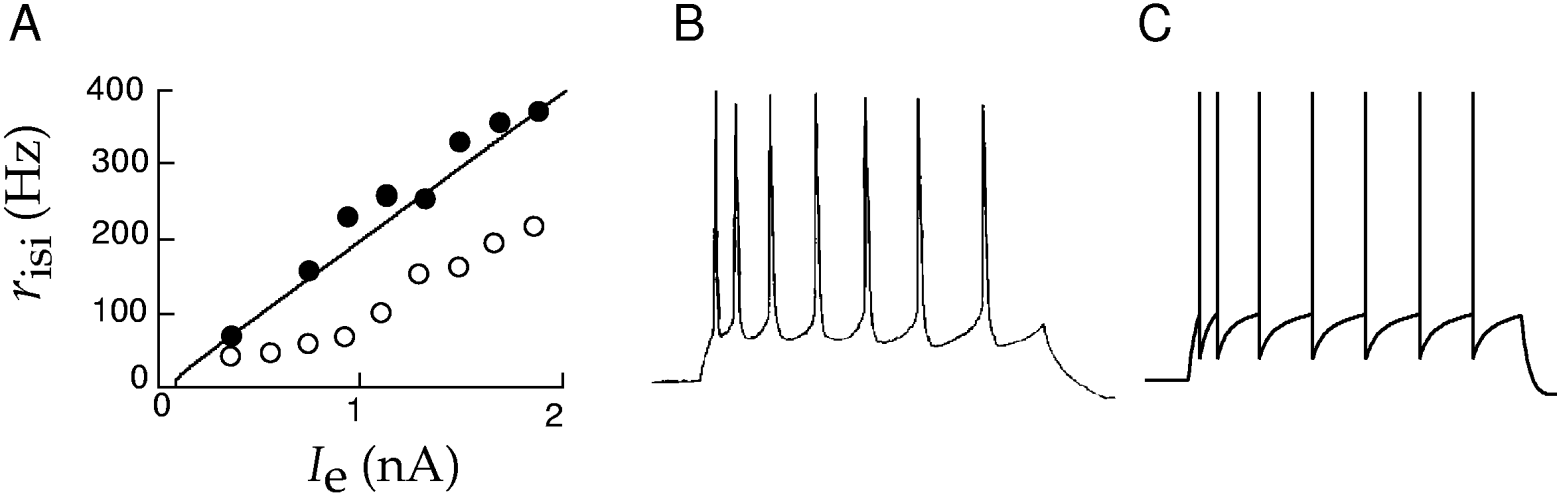
Integrate and fire. Generates time of spikes, but does not replicate spike shape; stick spike on top and then put $V = V_{\text{reset}}$ which is normally V_{rest}. *Passive integrate and fire* (no active channels):

$$c_m \frac{\mathrm{d}V}{\mathrm{d}t} = -g_L(V - E_{\mathrm{L}}) + I_e/A$$

Multiply both sides by r_m, recall $\tau_m = r_m c_m$:

$$\tau_m \frac{\mathrm{d}V}{\mathrm{d}t} = -(V - E_{\mathrm{L}}) + I_e R_m$$

Interspike interval (ISI) decays linearly with (large) I_e (TN eq 5.12, fig 5.6):



Spike-rate adaptation

Neurons show adaptation and refractoriness.
Add K channel to hyper-polarise neuron:

$$\tau_m \frac{\mathrm{d}V}{\mathrm{d}t} = -(V - E_\mathrm{L}) - r_m g_\mathrm{sra}(V - E_\mathrm{K}) + I_e R_m$$

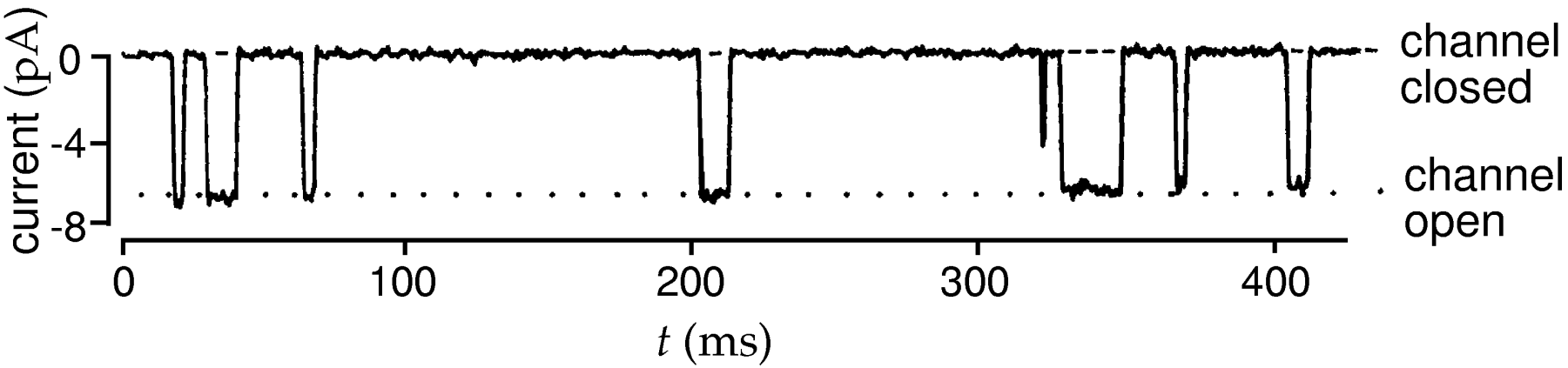
$$\text{decay:} \quad \tau_\mathrm{sra} \frac{\mathrm{d}g_\mathrm{sra}}{\mathrm{d}t} = -g_\mathrm{sra}$$

$$\text{when cell spikes:} \quad g_\mathrm{sra} \to g_\mathrm{sra} + \Delta g$$

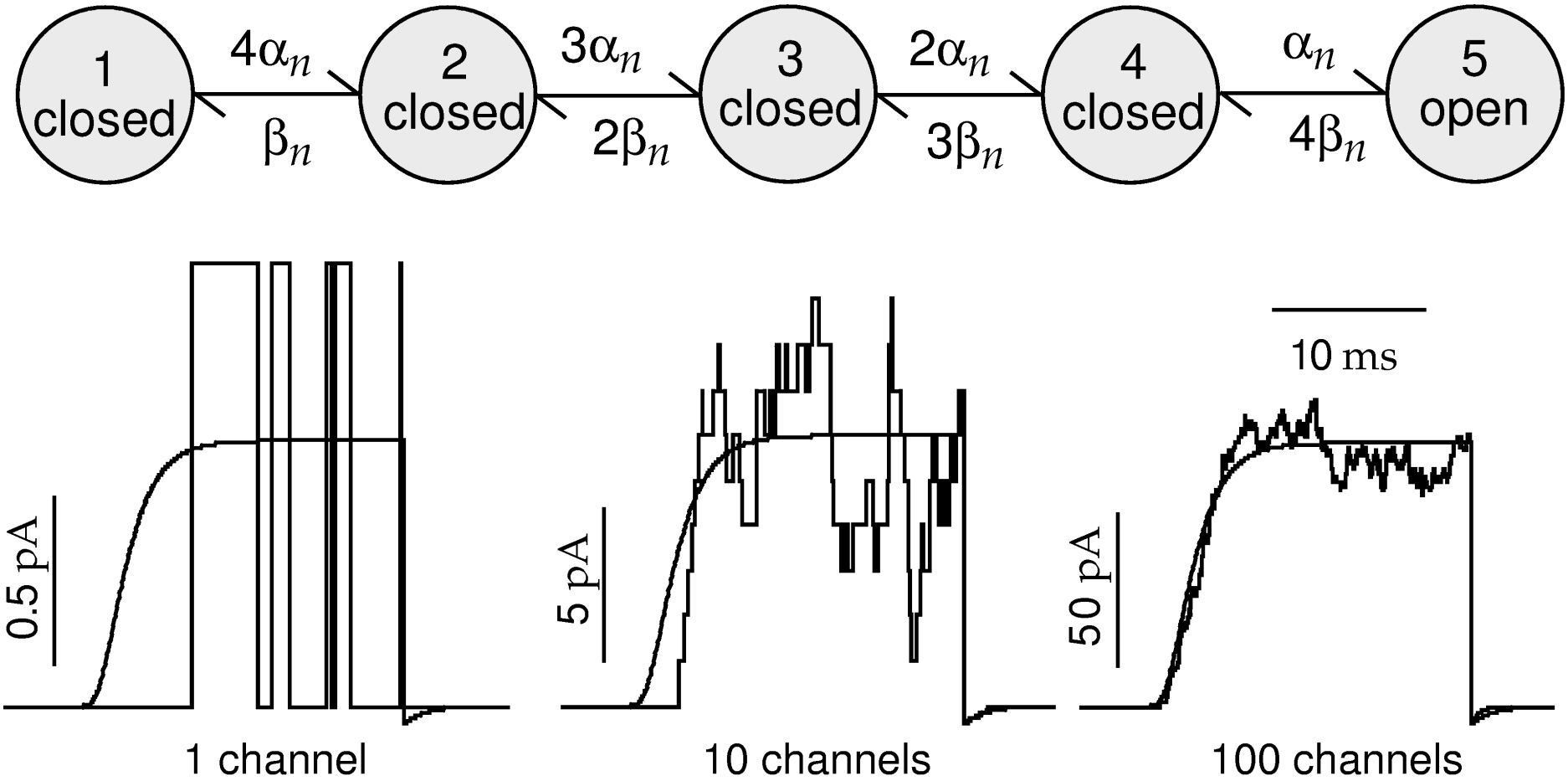
Refractoriness can be included e.g. by rigidly inhibiting spike for period after AP or by raising AP threshold. Many ways to get similar behaviour.

Individual channels

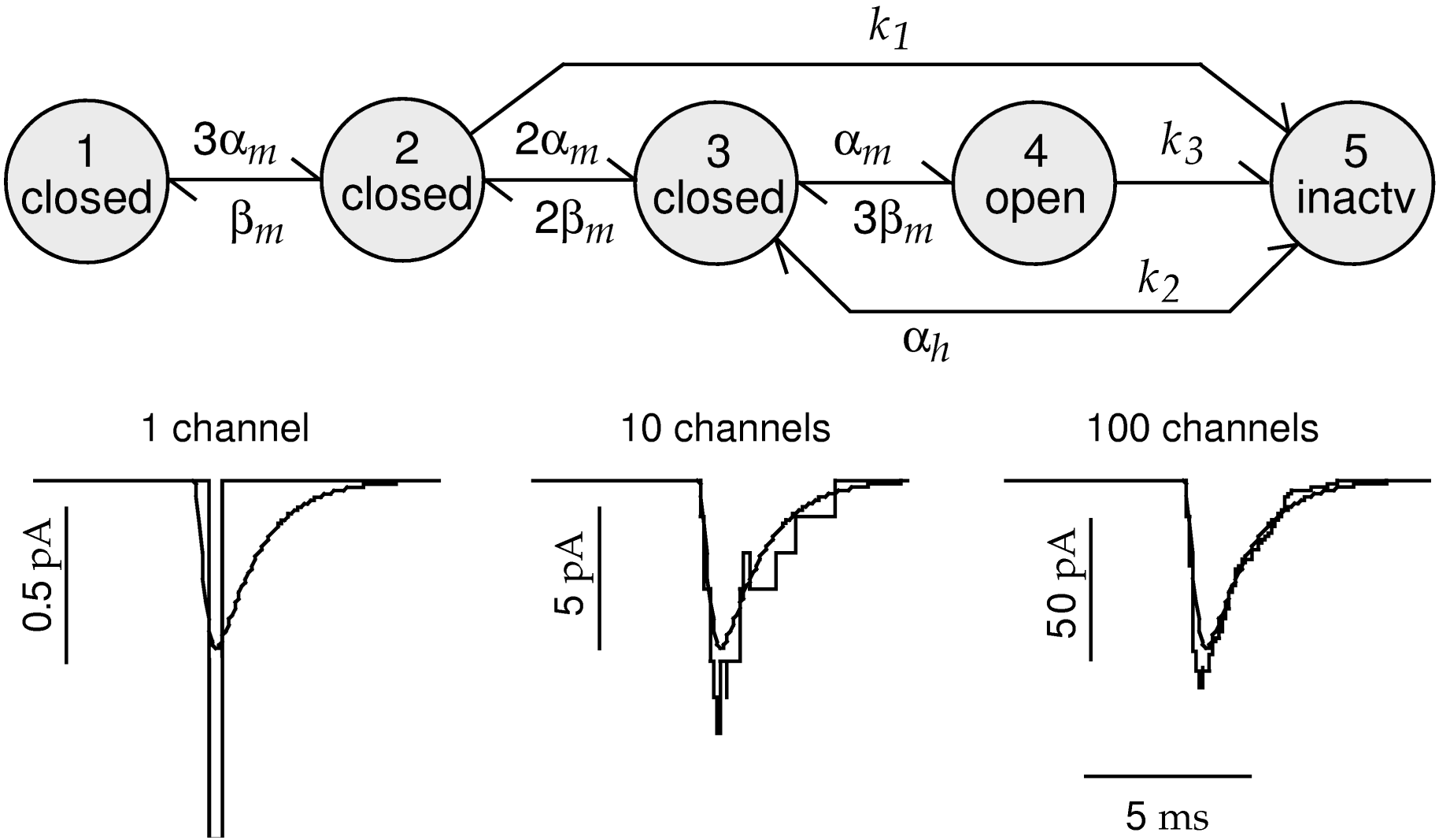
Individual channels are stochastic: open at random times for variable duration (AChR in response to ACh; TN fig 5.7).



K^+channel (TN fig 5.12)



Na^+channel (TN fig 5.13)



Modelling synaptic inputs

$$\tau_m \frac{\mathrm{d}V}{\mathrm{d}t} = -(V - E_L) - r_m \bar{g_s} P_{\mathrm{rel}} P_{\mathrm{s}} (V - E_s) + R_m I_e$$

P_{rel}: Stochastic release of vesicles.

P_{s}: postsynaptic conductance.

E_s: reversal potential of synapse ($+ve$ for excitatory synapse and $-ve$ for inhibitory synapse).

Postsynaptic conductances

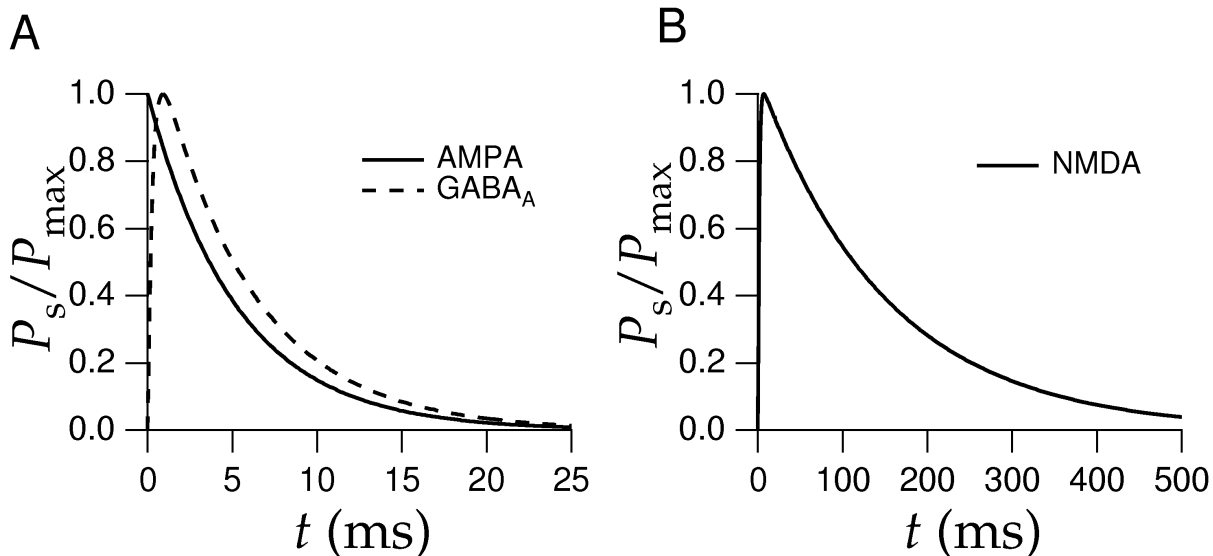
Postsynaptic conductances have an open probability that is increased in response to a presynaptic AP, and otherwise follows either (1) an exponential [AMPA], (2) difference of exponential ($\tau_1 > \tau_2$) [GABA, NMDA] or (3) alpha function:

upon AP at time t=0: $P_s \to P_s + P_{\max}(1 - P_s)$

$$(1) \quad \tau_s \frac{\mathrm{d}P_s}{\mathrm{d}t} = -P_s$$

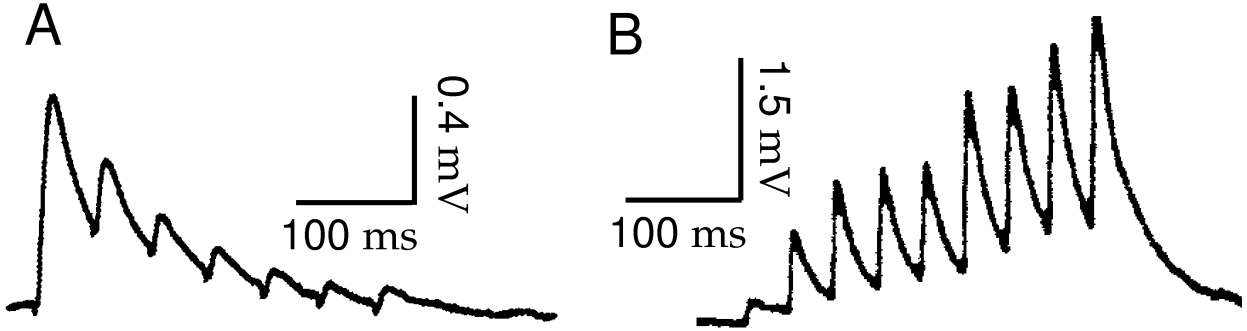
$$(2) \quad P_s = P_{\max} B(\exp(-t/\tau_1) - \exp(-t/\tau_2))$$

$$(3) \quad P_s = P_{\max}(t/\tau_s)\exp(1 - t/\tau_s)$$



Presynaptic release probability

Repeated presynaptic stimulation can elicit either facilitation or depression of a synapse. (TN Fig 5.17: rat pyramidal cells from somatosensory cortex.)



Presynaptic release is stochastic. In absence of AP:

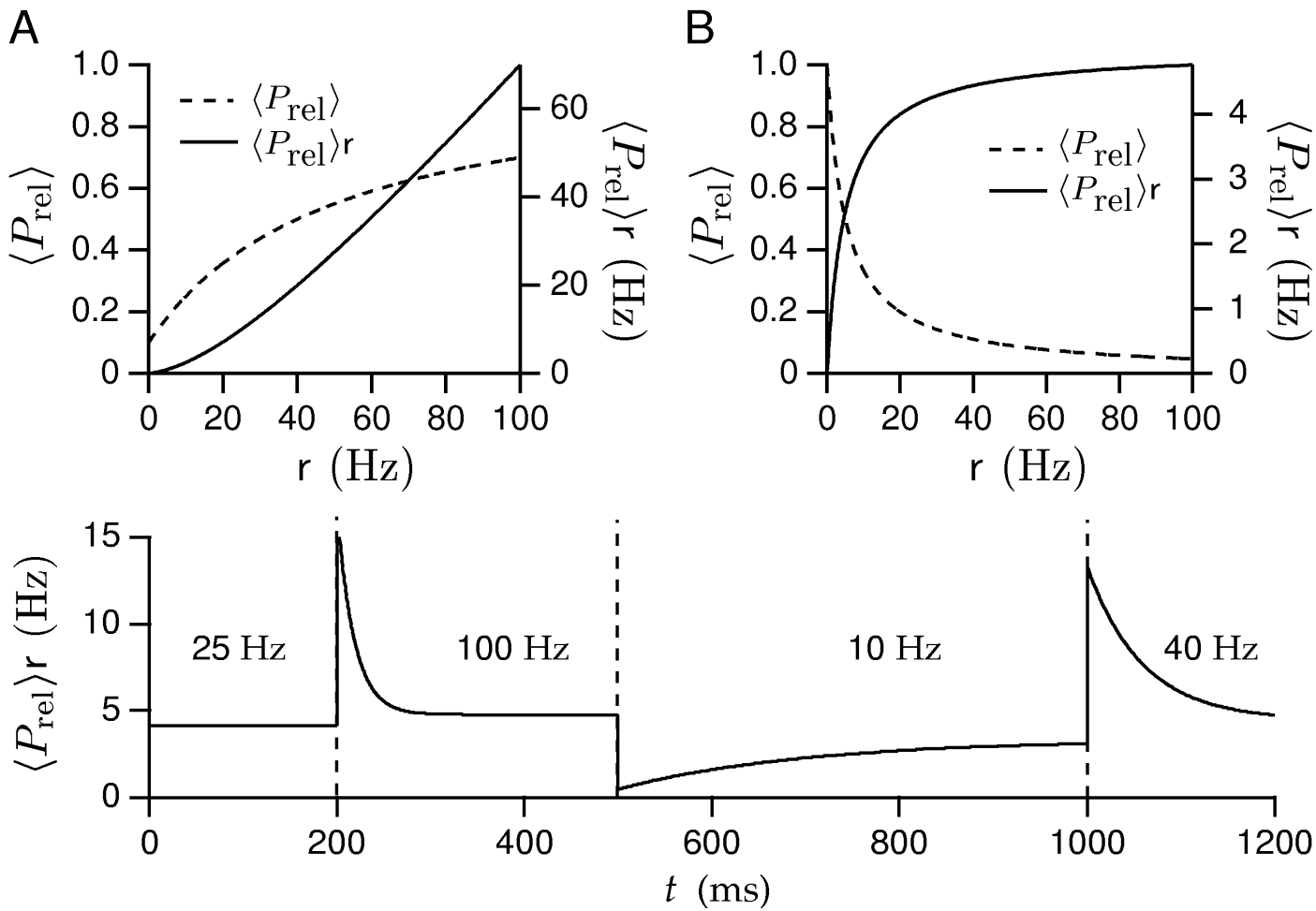
$$\tau_p \frac{\mathrm{d}P_{\mathrm{rel}}}{\mathrm{d}t} = P_0 - P_{\mathrm{rel}}$$

Upon presynaptic AP, we do one of:

$$P_{\mathrm{rel}} \to P_{\mathrm{rel}} + f_F(1 - P_{\mathrm{rel}})$$
$$P_{\mathrm{rel}} \to f_D P_{\mathrm{rel}}$$

Effects of P_{rel} upon rate of transmission

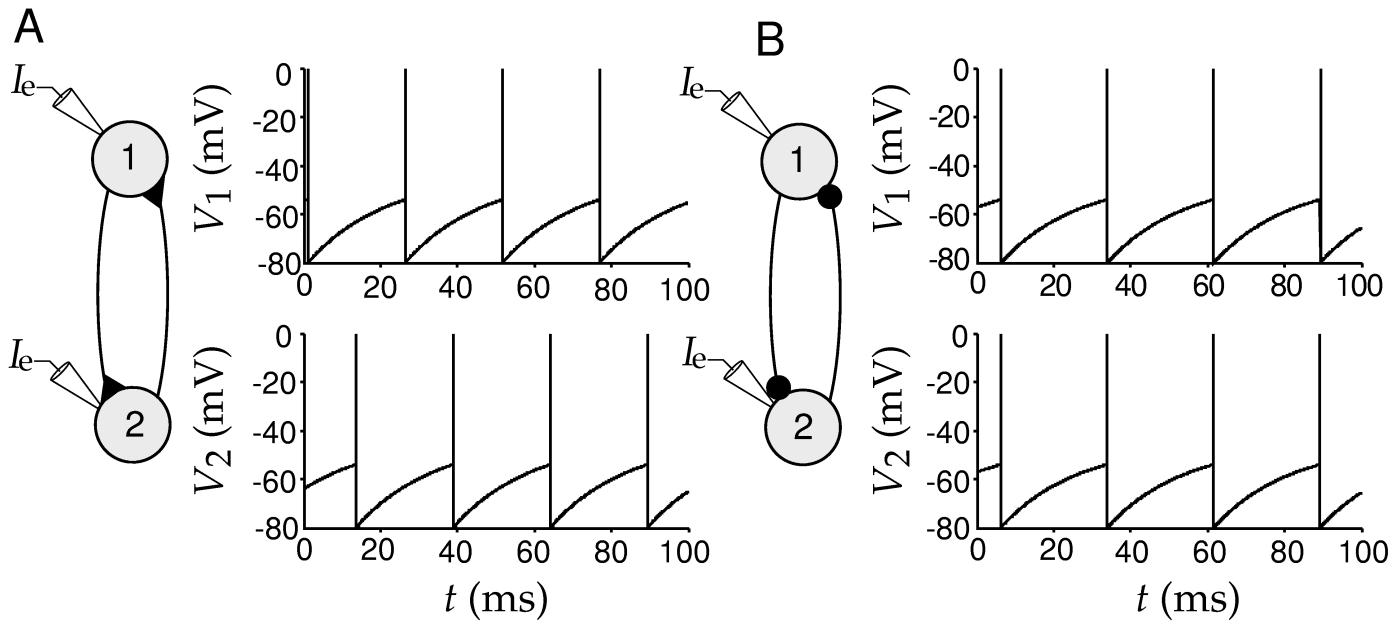
Assume Poisson spike train of rate r we can derive (TN eqn 5.37–5.42; fig 5.18, 5.19) analytical forms for $\langle P_{\text{rel}} \rangle$.



Synapses in I&F neurons

$$\tau_m \frac{\mathrm{d}V}{\mathrm{d}t} = -(V - E_\mathrm{L}) - r_m \overline{g_s} P_\mathrm{rel} P_s (V - E_s) + I_e R_m$$

Synapse type given by E_s (-80 mV for inhibitory, 0 mV for excitatory). Common assumption: excitation causes synchrony. Does this happen with long enough ($\tau_s = 10$ ms) synapses? (TN fig 5.20):



A: Excitatory synapses (▲). B: Inhibitory synapses (•).

Summary

- Ionic basis of action potential
- Simplifications to I&F models.
- Modelling channels stochastically.
- Handling pre- and post-synaptic factors.

- Main reading: TN Chapter 5, Hodgkin & Huxley (1952).