COMS30127/COMSM2127 Computational Neuroscience

Lecture 19: Ion channels (j)

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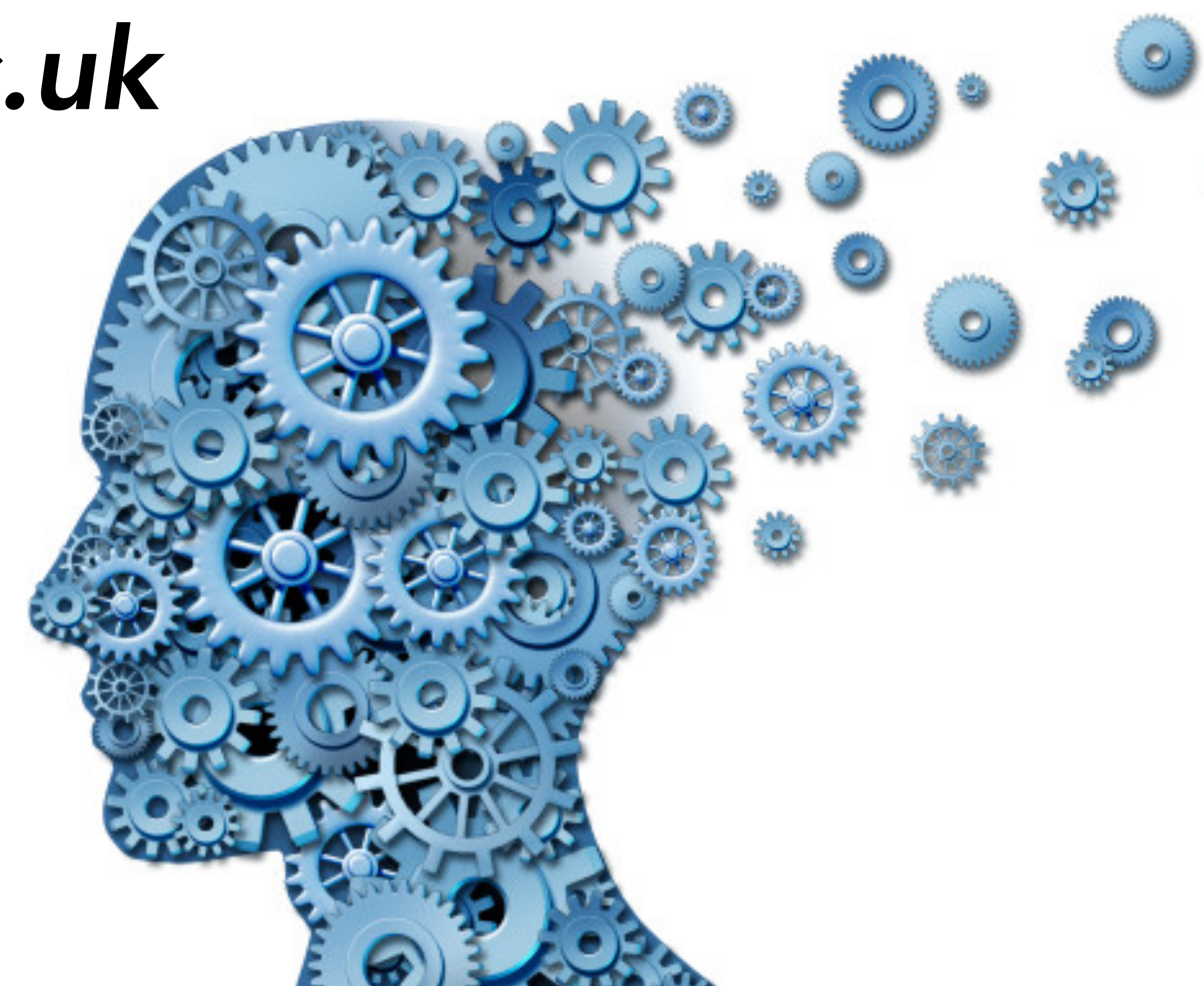
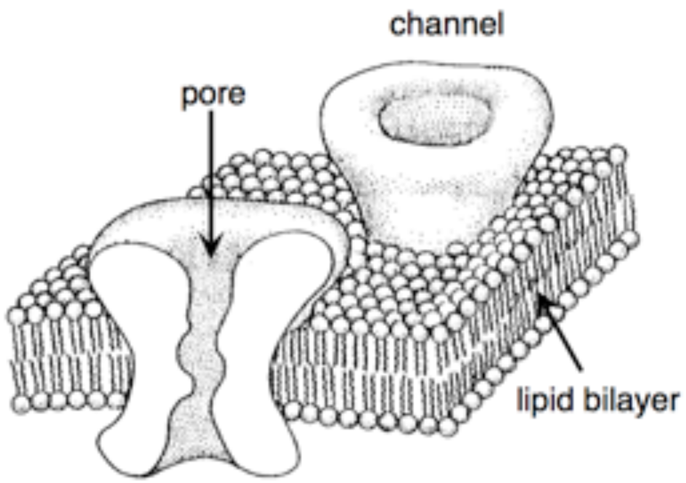


What we will cover today

- What are ion channels and what do they do?
- The different types of ion channels.
- Modelling ion channels.
- How ion channels make the neuron's input-output function nonlinear.
- Ion channels as an intrinsic source of noise in the brain.

What are ion channels?



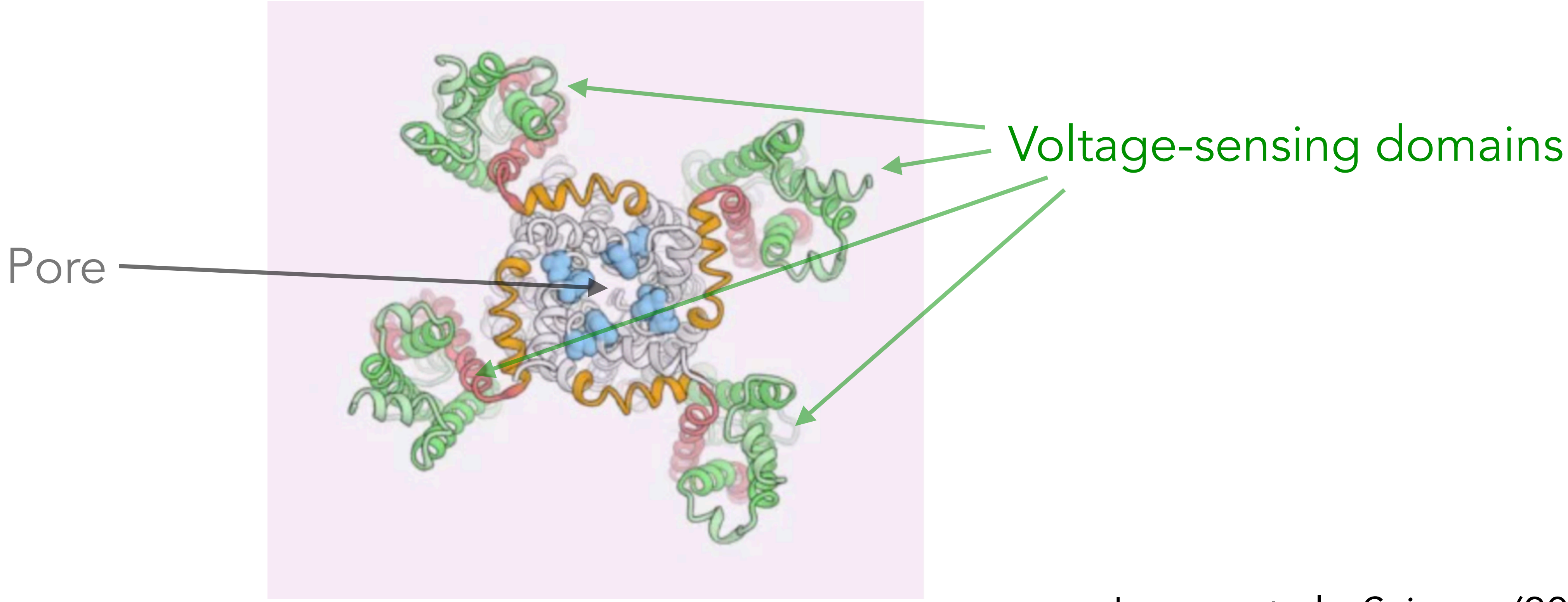
Hille (1992)

- Ion channels are ion-permeable pores in the lipid membrane of cells.
- A single neuron typically has hundreds of thousands to millions of ion channels embedded in its membrane.
- They open and close in response to stimuli (voltage, neurotransmitters, intracellular chemicals, pH, mechanical forces, temperature…), passing ions like Na^+, K^+, Ca^{2+}, Cl^-.
- Their currents mediate electrical signalling in the nervous system.
- The conductance of single ion channels vary between ~0.1 and 100 picoSiemens. For most channels it's around 10 pS.
- The flux through a single open channel can be millions of ions per second.

What are ion channels?

- Voltage-gated ion channels typically have a pore domain made up of four identical, or similar, channel subunits arranged in a ring. The ion pore is made along the axis where they meet.
- The channel also has secondary voltage-sensing domains, that deform in response to changes in the transmembrane voltage.
  These drag the pore-domain components to switch the channel open or closed.

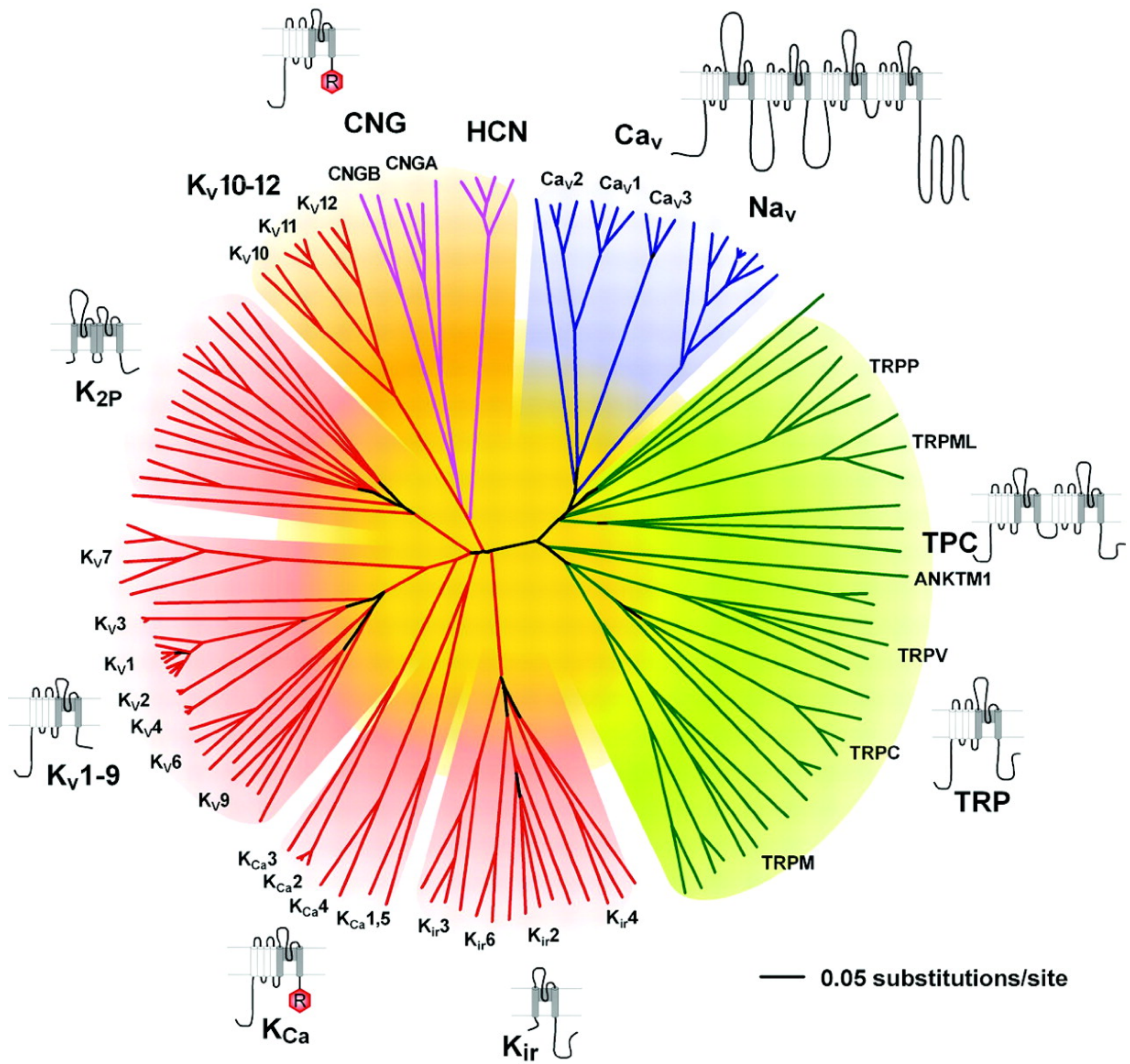
Bottom-up view of a potassium channel (from inside the cell)



Jensen et al., *Science* (2012)

Ion channel types

The ion channel zoo



Yu et al., *Pharm Rev* (2005)

Ion channel types

- Sodium (Na^+) channels mediate inward currents that depolarise the voltage.
  - Fast gating and activated by depolarisation (positive feedback).
  - Responsible for upswing of the action potential, and boosting subthreshold inputs in dendrites.
  - Targets for some anaesthetics (e.g. lidocaine, pufferfish venom)
- Potassium (K^+) channels mediate outward currents that hyperpolarise the voltage.
  - Can be fast or slow gating, activated by depolarisation (negative feedback).
  - Voltage-independent K^+ channels mediate the 'leak' current.
  - Very genetically diverse (around 50 types in mammals).
- Calcium (Ca^{2+}) channels, like sodium, mediate inward currents that depolarise the voltage.
  - Fast gating, but not as strongly expressed as sodium so have weaker effect on the voltage.
  - Responsible for some forms of dendritic spikes.
  - Generate intracellular calcium signals that the cell uses to monitor its electrical activity.
- Other channels include
  - Chloride (Cl^-) channels: involved in setting resting voltage.
  - HCN channels: mixed sodium/potassium permeability, active at resting voltage, inactivated by depolarisation (negative feedback), heavily expressed in dendrites).

Modelling ion channels

Modelling ion channels

- In most neuroscience applications we don’t care about all the molecular details of the ion channel, we just want a simple model that captures their dynamics.
- Usually this involves state-based modelling.
- We assume that each channel can be in one of a small number of of discrete states. The channel can transition between states, with transition rates that depend on the cell’s voltage.

Modelling ion channels

Consider a 2-state ion channel model with transitions between the closed s_0 and open s_1 states, with transition rates α and β:

$$s_o \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} s_1$$

If we imagine a large population of such channels, we could think of s_1 as representing the proportion of the population in the open state.
Then we can write down a differential equation to describe its dynamics:

$$\frac{ds_1(t)}{dt} = \alpha s_o(t) - \beta s_1(t)$$

The steady state value s_∞ is found by setting $ds_1/dt = 0$: $s_\infty = \dfrac{\alpha}{\alpha + \beta}$

Then we can rewrite the right hand side of the dynamics equations as

$$\frac{ds_1(t)}{dt} = \frac{s_\infty - s_1(t)}{\tau}$$

Where we have introduced the time constant $\tau = \dfrac{1}{\alpha + \beta}$

Modelling ion channels

- The previous slide showed a very simple 2-state channel example. Most real channels are too complicated to describe so compactly, so their models often have many more states.
- The voltage dependence is built into these channel models by making the the transitions rate (α and β) functions of voltage.
- You will go through a famous example of the Hodgkin-Huxley squid axon model in the next lecture.

The neuron’s input-output function

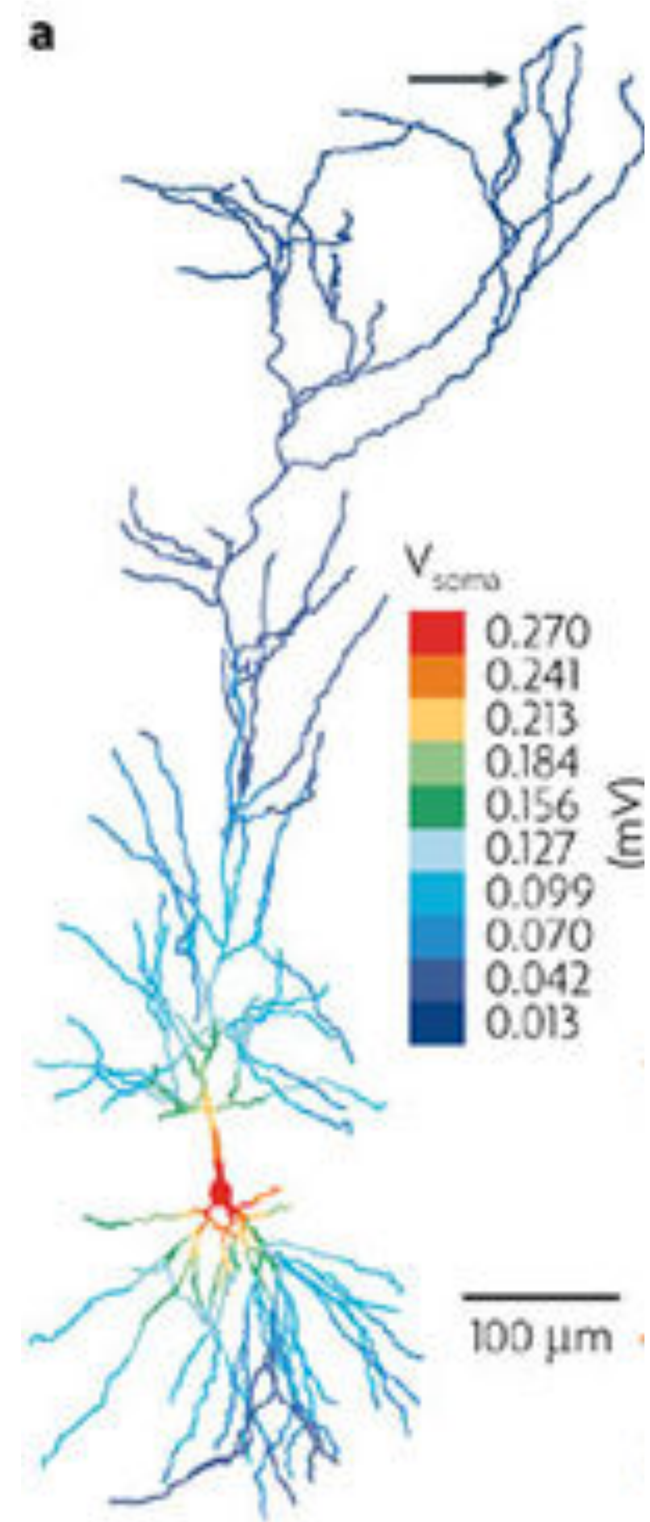
a.k.a. synaptic integration

Non-linear synaptic integration

- Neurons receive multiple temporal patterns of spike trains as input, and produce a single spike train as output.
- "Point" neuron models (like the integrate-and-fire) assume that the soma performs a weighted linear sum of the synaptic currents.
- However, real neurons differ from this idealisation in two key aspects:
  1. Neurons have dendrites, which implies a spatial layout of synaptic inputs.
  2. Dendrites have voltage-dependent (active) ion channels which makes synaptic integration non-linear.

Synaptic location matters

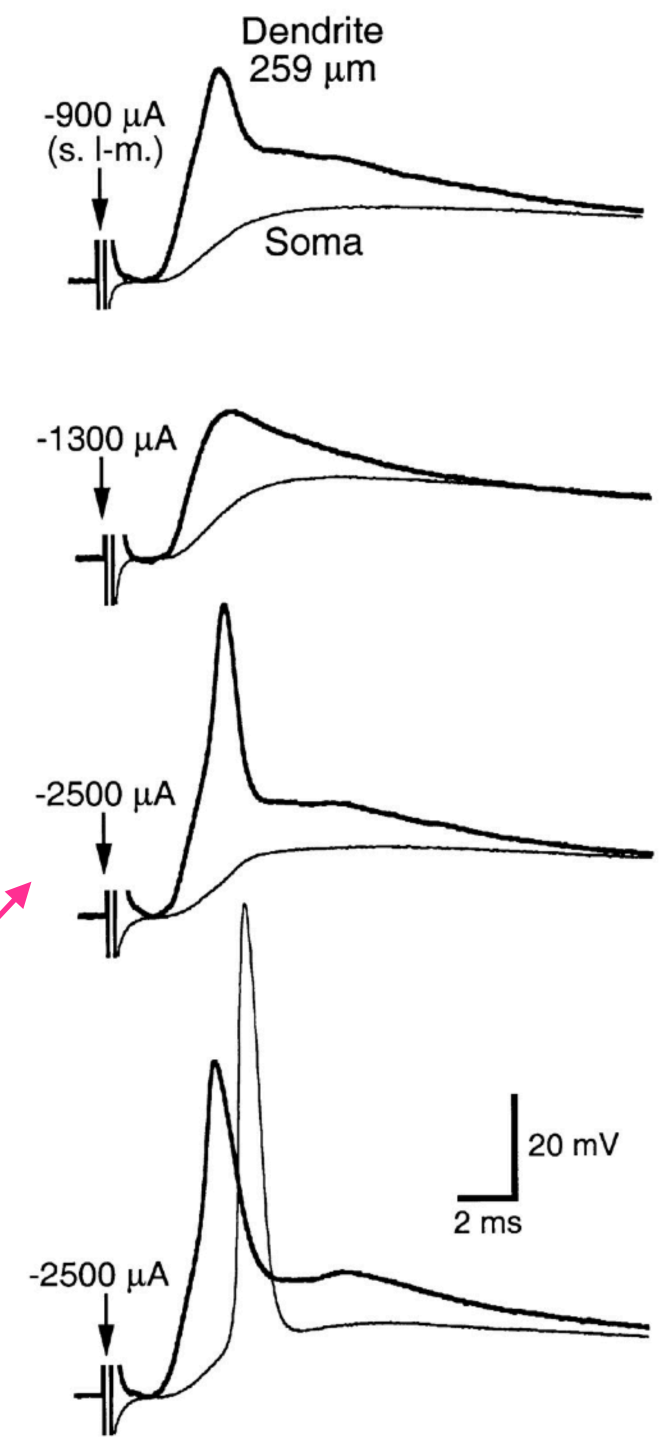
- The figure on the right is a trace of the dendritic tree of a CA1 pyramidal cell from a rat.
- The colour indicates the amplitude of the voltage response (EPSP) at the soma, when the synapse is placed at the corresponding location on the dendritic tree.
- Without any “boosting”, a synapse would give a smaller somatic response if it was located at a distal dendritic site.
- However it turns out that voltage-dependent ion channels in dendrites can boost synaptic inputs to amplify their effect at the soma.



Spruston, *Nat Rev Neurosci* (2008)

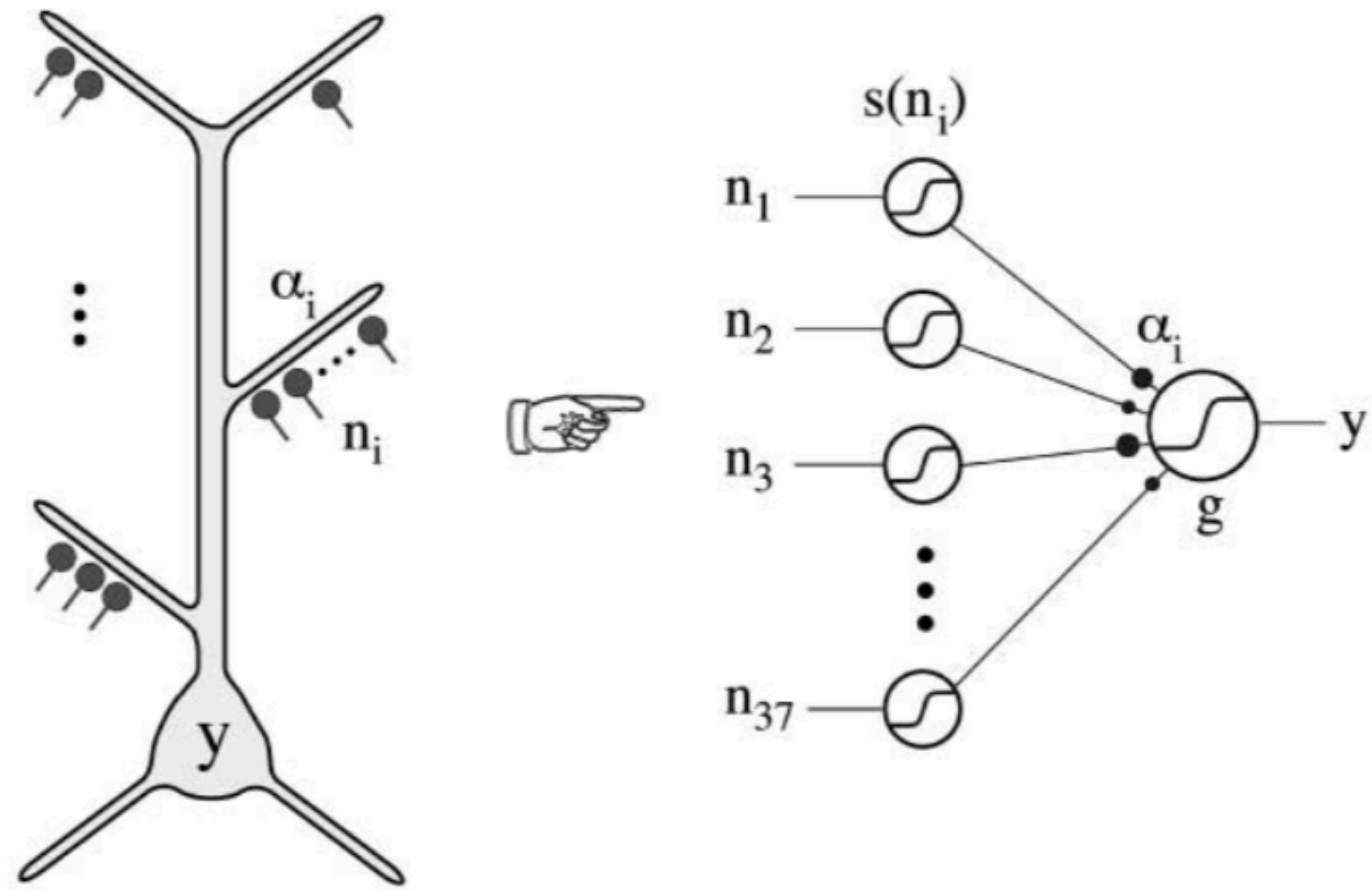
Dendritic spikes

- Some neurons have enough voltage-gated ion channels in their dendrites to enable purely dendritically-generated action potentials.
- These dendritic spikes tend to be weaker and less all-or-none that axonal action potentials
(note variable dendritic amplitudes in each plot on right).
- A single dendritic spike is not always sufficient to trigger an axonal spike.



Golding and Spruston, *Neuron* (1998)

The single neuron as two-layer neural network

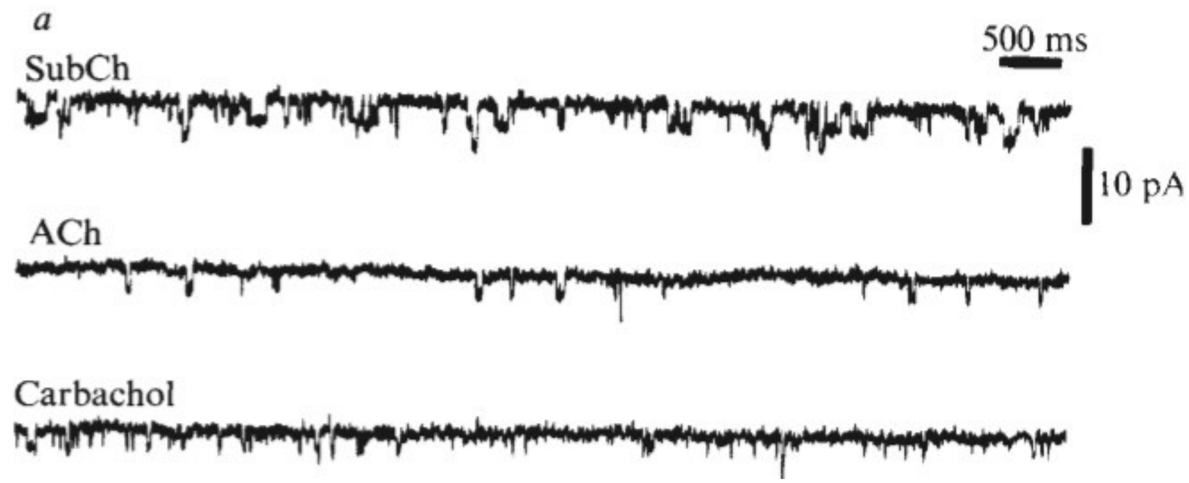


- The existence of dendritic spikes means we can almost think of a single pyramidal neuron as a multi-layer neural network. Each dendritic does a nonlinear operation on its inputs before passing the signal to the soma.
- Voltage-gated ion channels expand the brain's computational power.

Poirazi and Mel, *Neuron* (2003)

Stochasticity of ion channels

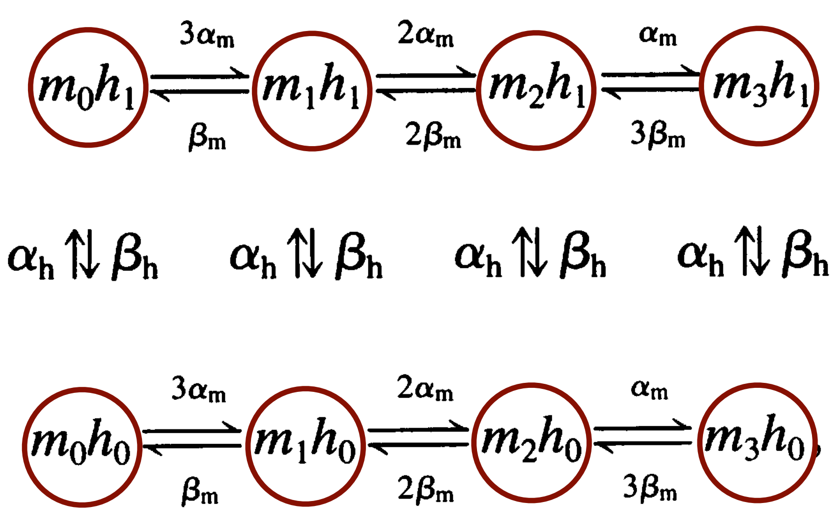
Ion channels are discrete and stochastic

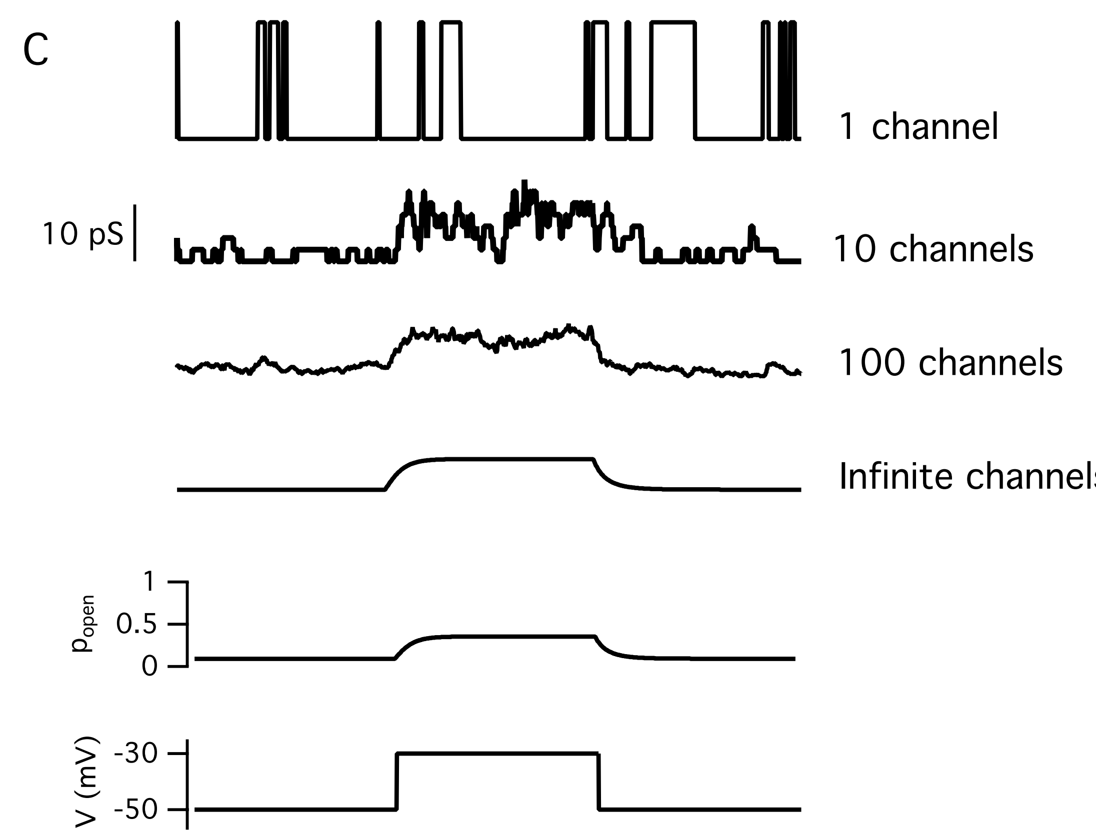


Neher & Sakmann, Nature (1976)

2-state: $C \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} O$

8-state:





O'Donnell & Nolan (2014)

Ion channel noise

- Ohm's law tells us that the open single-channel current i can be written as
$$i = \gamma(E_{rev} - V)$$
where γ is the single-channel conductance, E_{rev} the reversal potential, and V the membrane voltage.

- If we have N of these channels, the mean current through the population, for a constant voltage, is $\bar{I} = Nip$
where p is the steady-state open probability of the channel (fraction of time it is open).

- The standard deviation of the population current (i.e. "the noise") is given from the binomial distribution as
$$\sigma_I = i\sqrt{Np(1-p)}$$

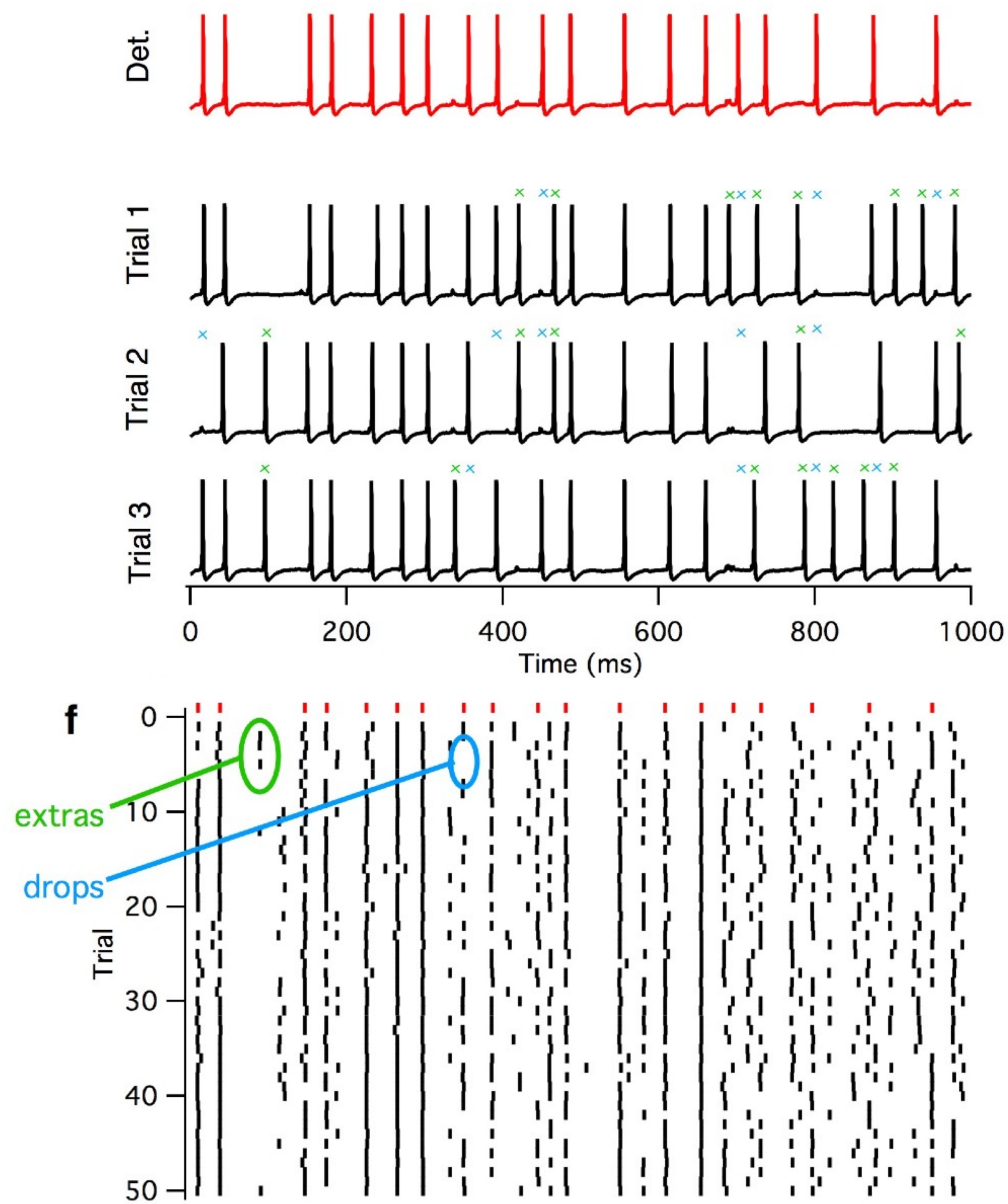
- The coefficient of variation (ratio of the standard deviation to the mean) is:
$$\mathrm{C.V.} = \frac{\sigma_I}{\bar{I}} = \sqrt{\frac{1-p}{Np}}$$

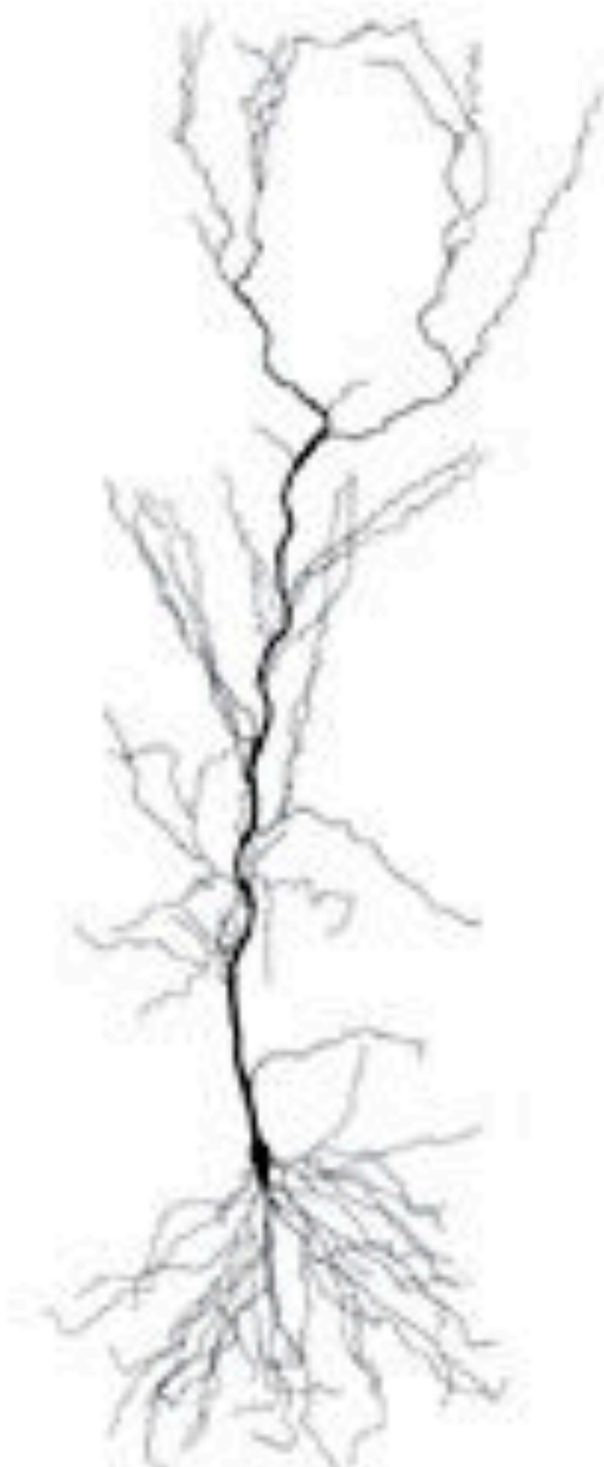
Ion channel noise makes the neuron's input-output function probabilistic

no noise

noise turned on

raster plot of many trials





Cannon, O'Donnell and Nolan, *PLoS Comput Biol* (2010)

Optional further reading

- Scholarpedia article by Hille: http://www.scholarpedia.org/article/Ion_channels

- Spruston 2008. "Pyramidal Neurons: Dendritic Structure and Synaptic Integration." *Nature Reviews Neuroscience* 9 (3): 206–21

- O'Donnell, and van Rossum, 2014. "Systematic Analysis of the Contributions of Stochastic Voltage Gated Channels to Neuronal Noise." Frontiers in Computational Neuroscience 8. Frontiers: 105