COMS30127: 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.

- How ion channels control the neuron's nonlinear input-output function.

- Ion channels as an intrinsic source of noise in the brain.

What are ion channels?

channel

pore

lipid bilayer

- 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.

Hille (1992)

- 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.
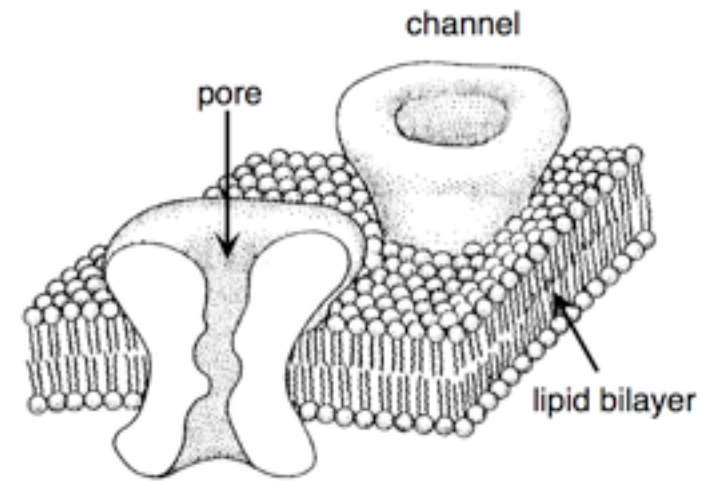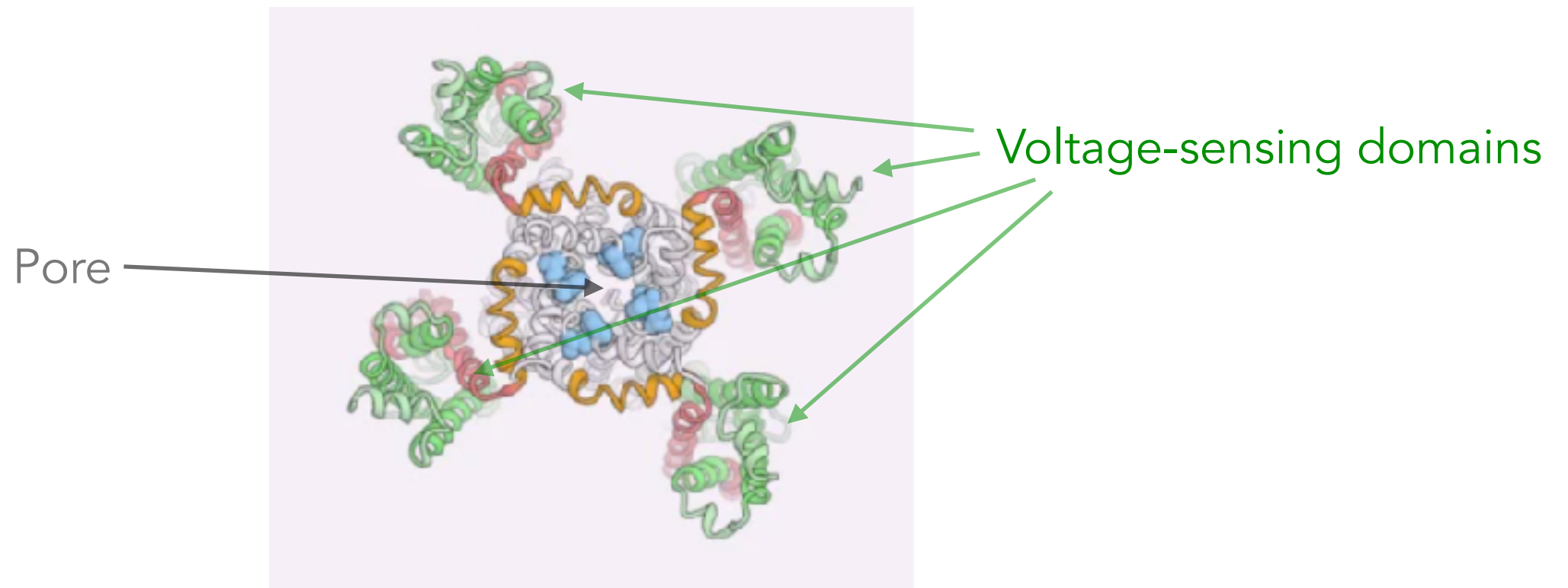
What are ion channels?

- 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)

Pore

Voltage-sensing domains

Jensen et al., *Science* (2012)

Ion channel types

The ion channel zoo

Yu et al., *Pharm Rev* (2005)
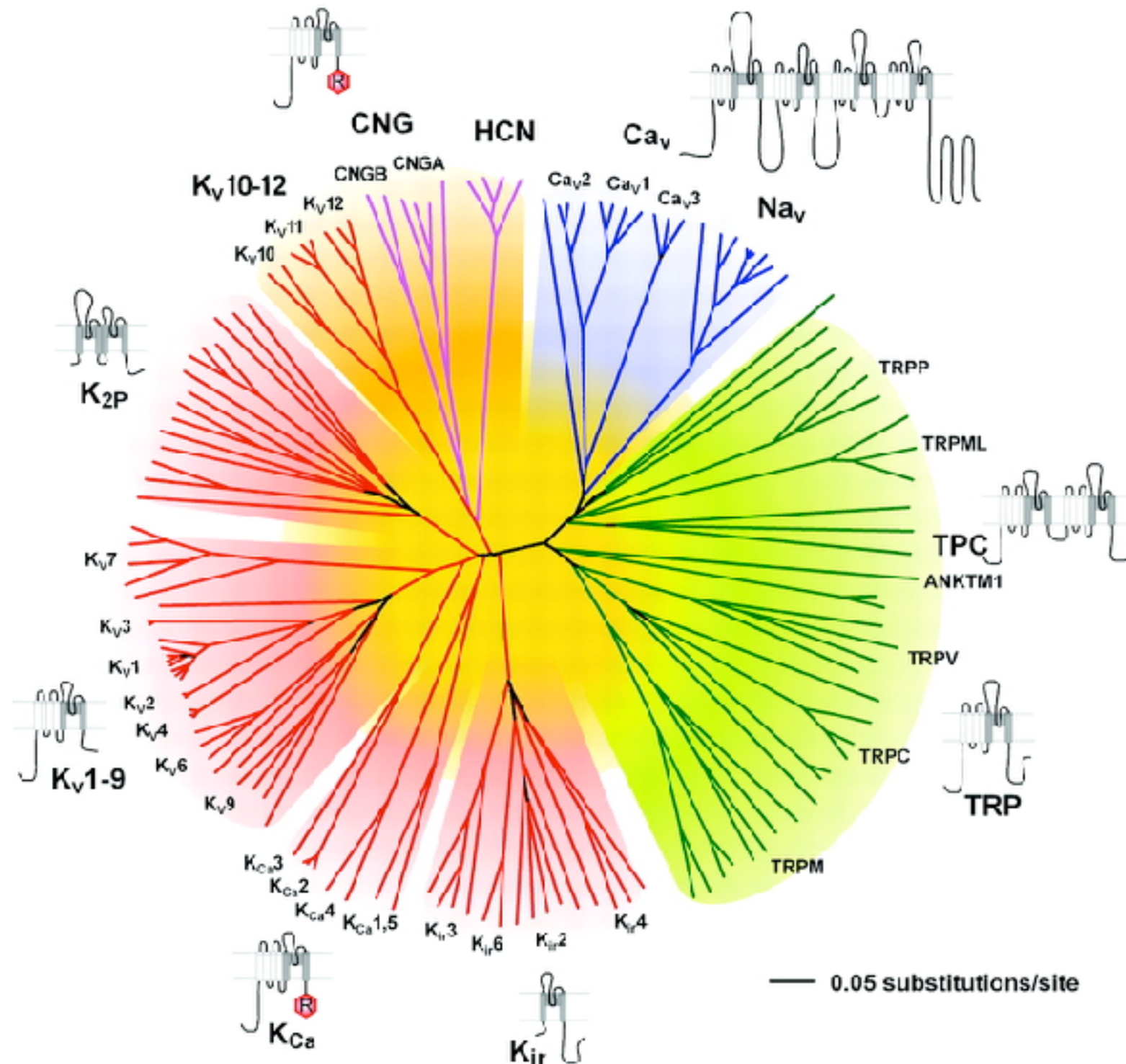
Ion channel types

- 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).

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 typically 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

- An otherwise identical synapse will give a smaller somatic response if it is located at a distal dendritic site (left figure).
This is true even for passive neurons.

- However, the local voltage change tends to be higher for distal synapses (right figure).
This is more likely to activate dendritic ion channels.

Spruston, *Nat Rev Neurosci* (2008)
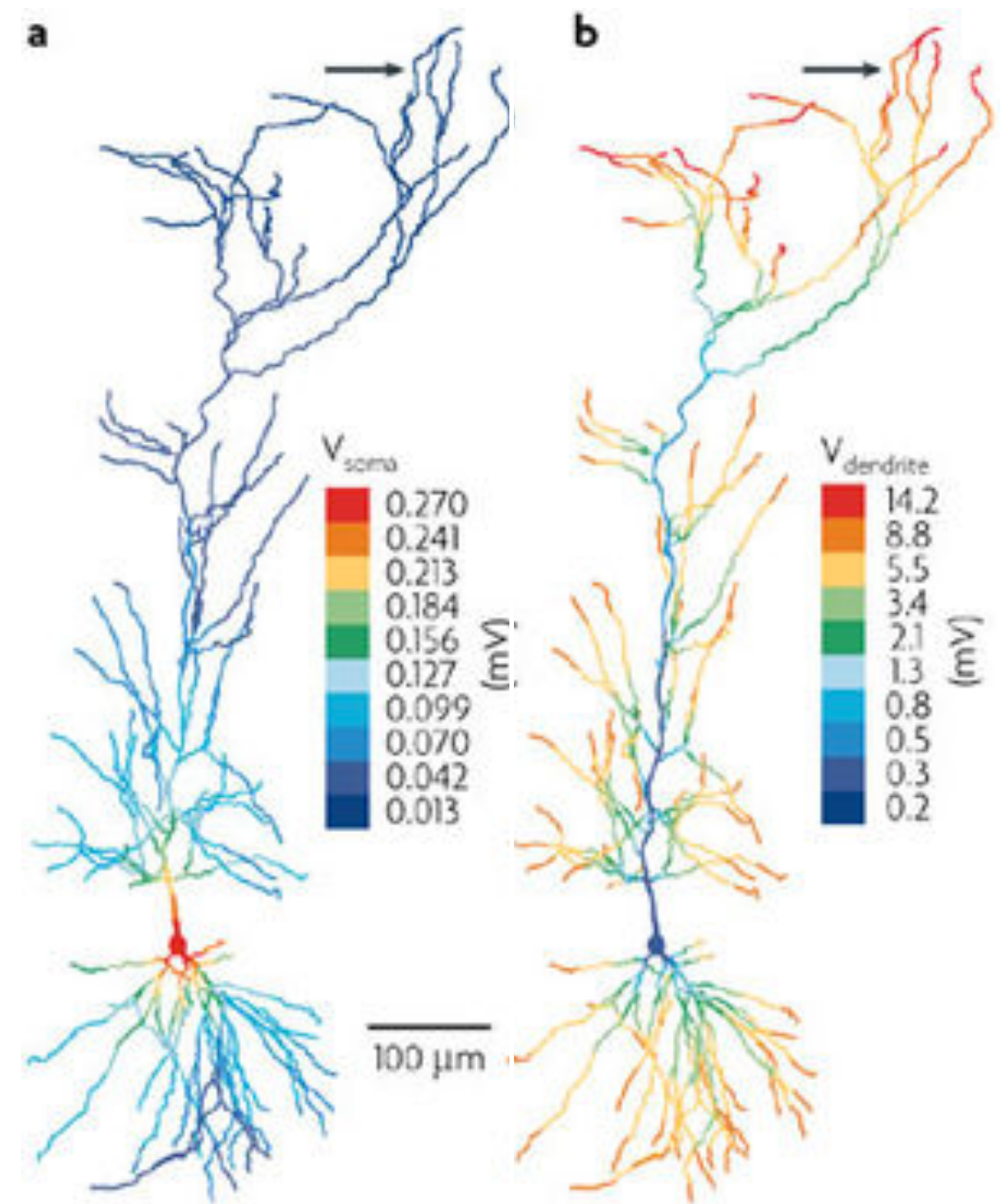
Dendritic spikes

- 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).

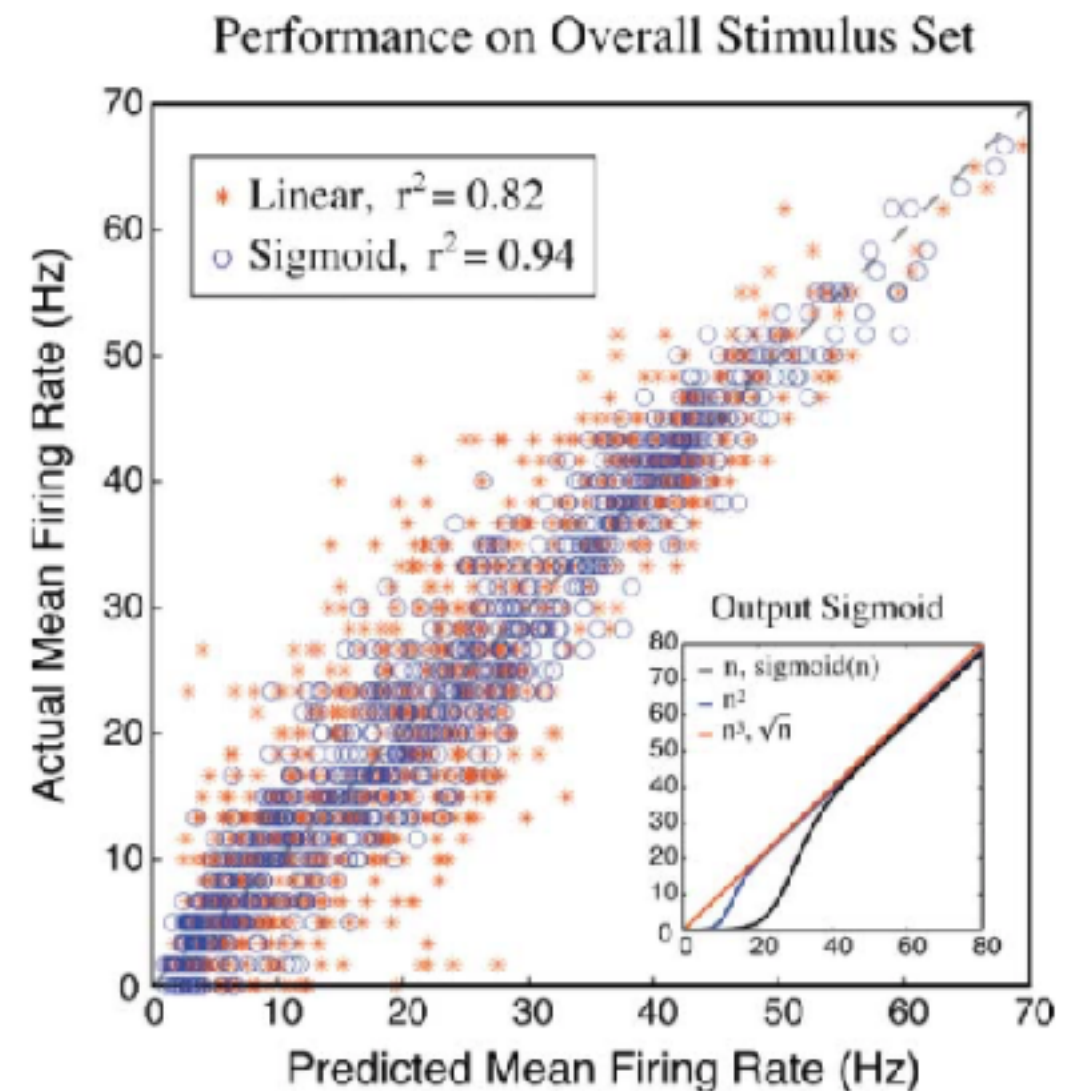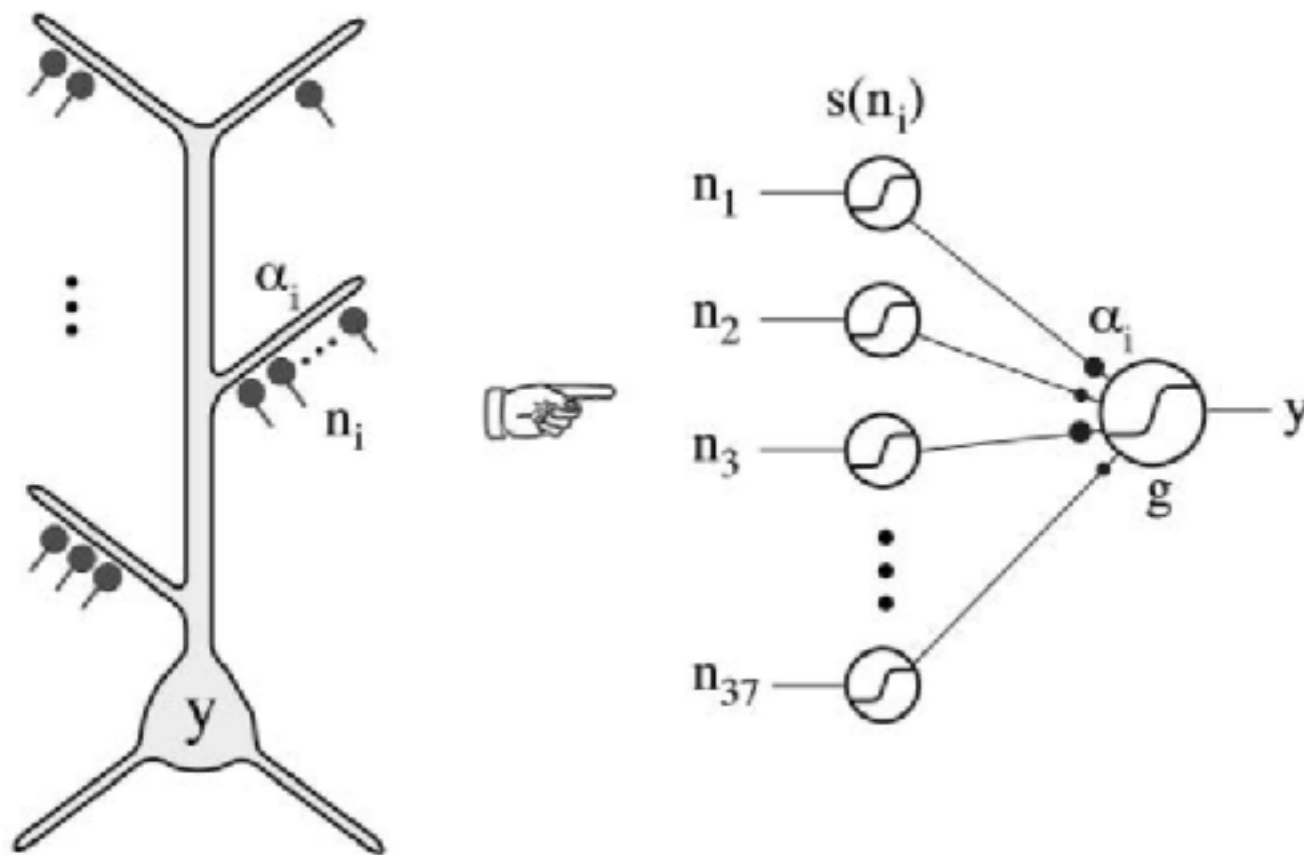- A single dendritic spike is not always sufficient to trigger an axonal spike.

Golding and Spruston, *Neuron* (1998)
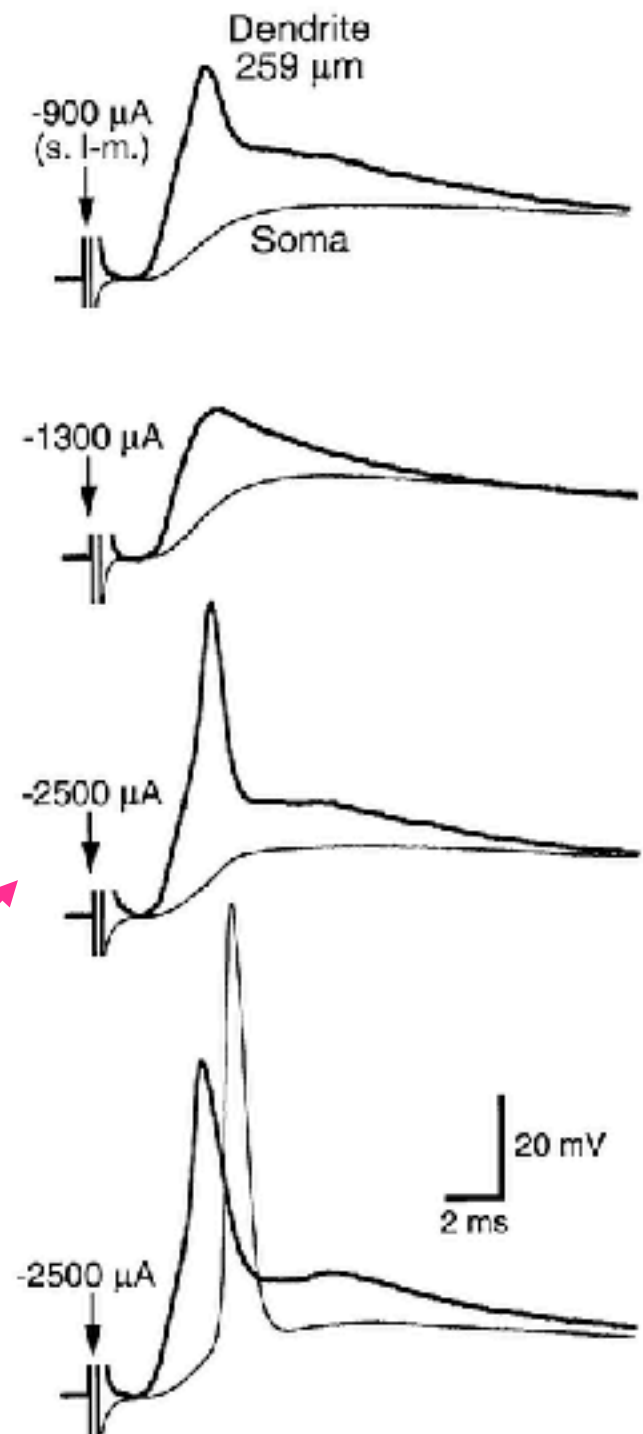
Co-incidence detection via active dendrites
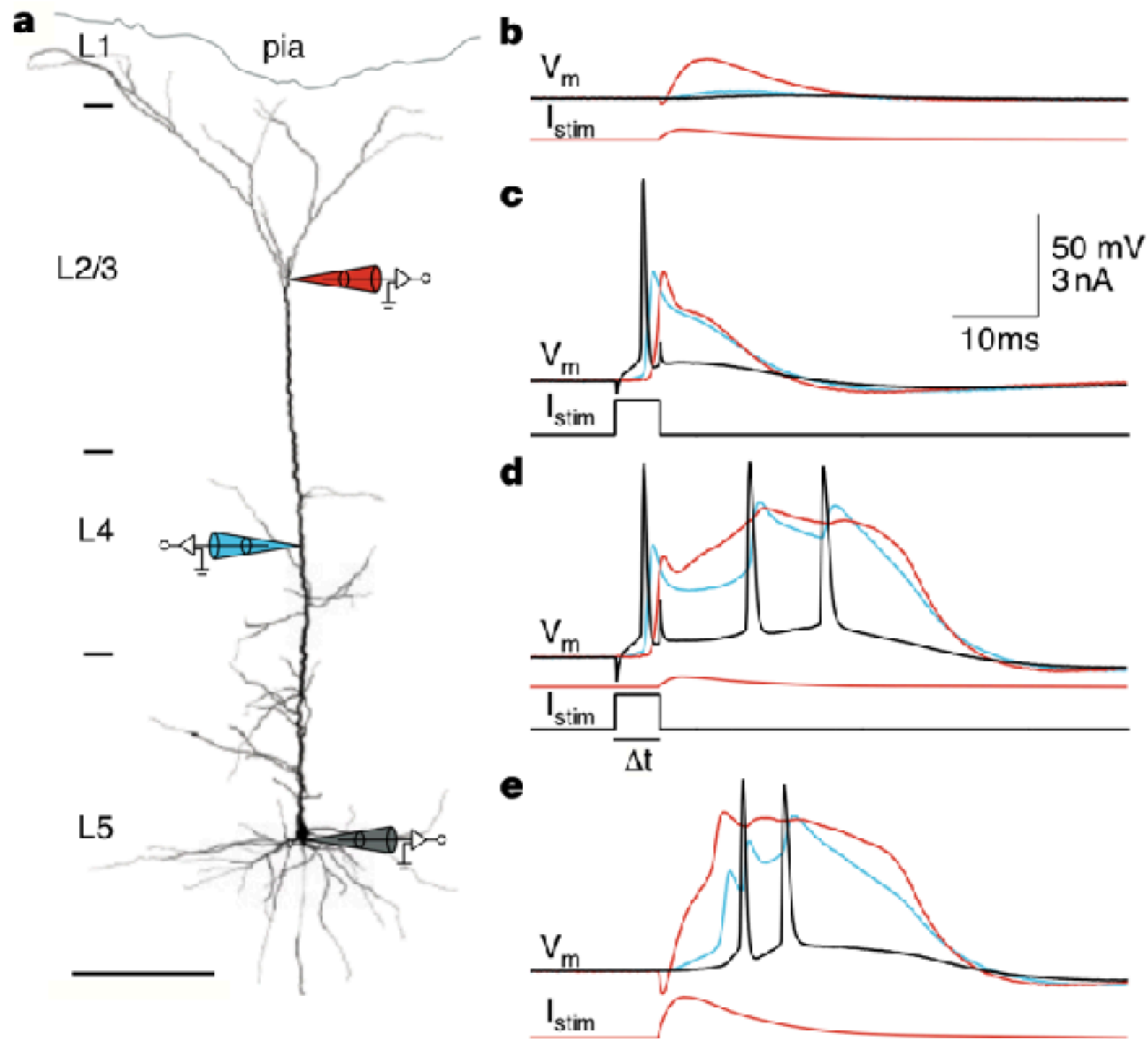
Weak distal stim alone

Somatic stim alone

Weak distal + somatic stim

Strong distal stim alone

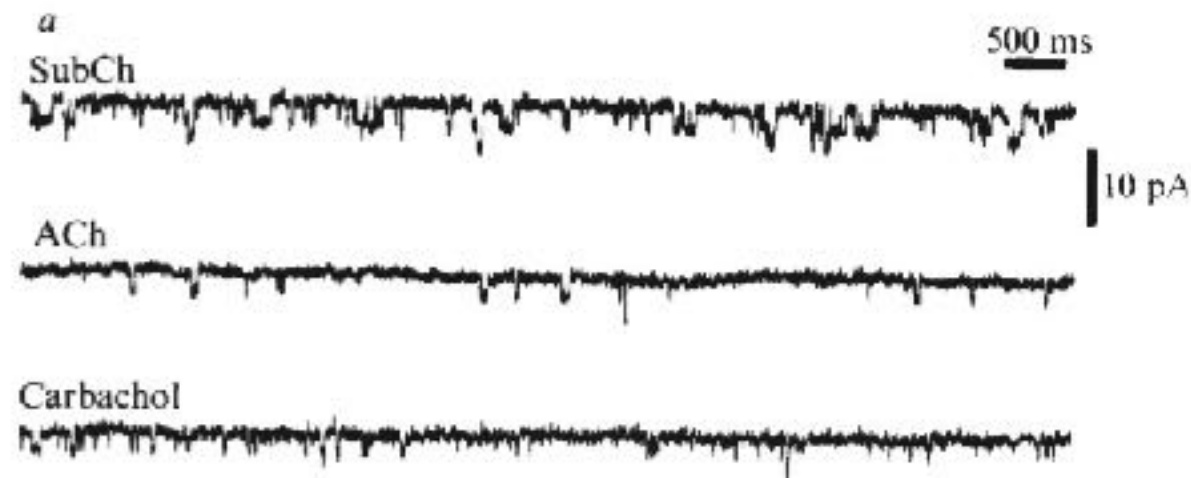Larkum, Zhu and Sakmann, *Nature* (1999)

The single neuron as two-layer neural network

Performance on Overall Stimulus Set
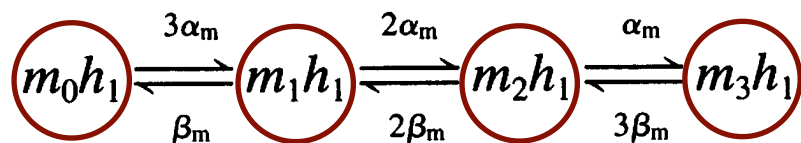
Poirazi and Mel, *Neuron* (2003)

Stochasticity of ion channels

Ion channels are discrete and stochastic

Neher & Sakmann, Nature (1976)

2-state:

$$C \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} O$$

$$m_0 h_1 \underset{\beta_m}{\overset{3\alpha_m}{\rightleftharpoons}} m_1 h_1 \underset{2\beta_m}{\overset{2\alpha_m}{\rightleftharpoons}} m_2 h_1 \underset{3\beta_m}{\overset{\alpha_m}{\rightleftharpoons}} m_3 h_1$$

8-state: $\quad \alpha_h \updownarrow \beta_h \quad\quad \alpha_h \updownarrow \beta_h \quad\quad \alpha_h \updownarrow \beta_h \quad\quad \alpha_h \updownarrow \beta_h$

$$m_0 h_0 \underset{\beta_m}{\overset{3\alpha_m}{\rightleftharpoons}} m_1 h_0 \underset{2\beta_m}{\overset{2\alpha_m}{\rightleftharpoons}} m_2 h_0 \underset{3\beta_m}{\overset{\alpha_m}{\rightleftharpoons}} m_3 h_0$$
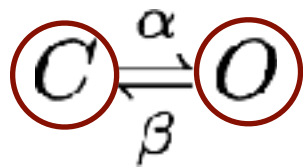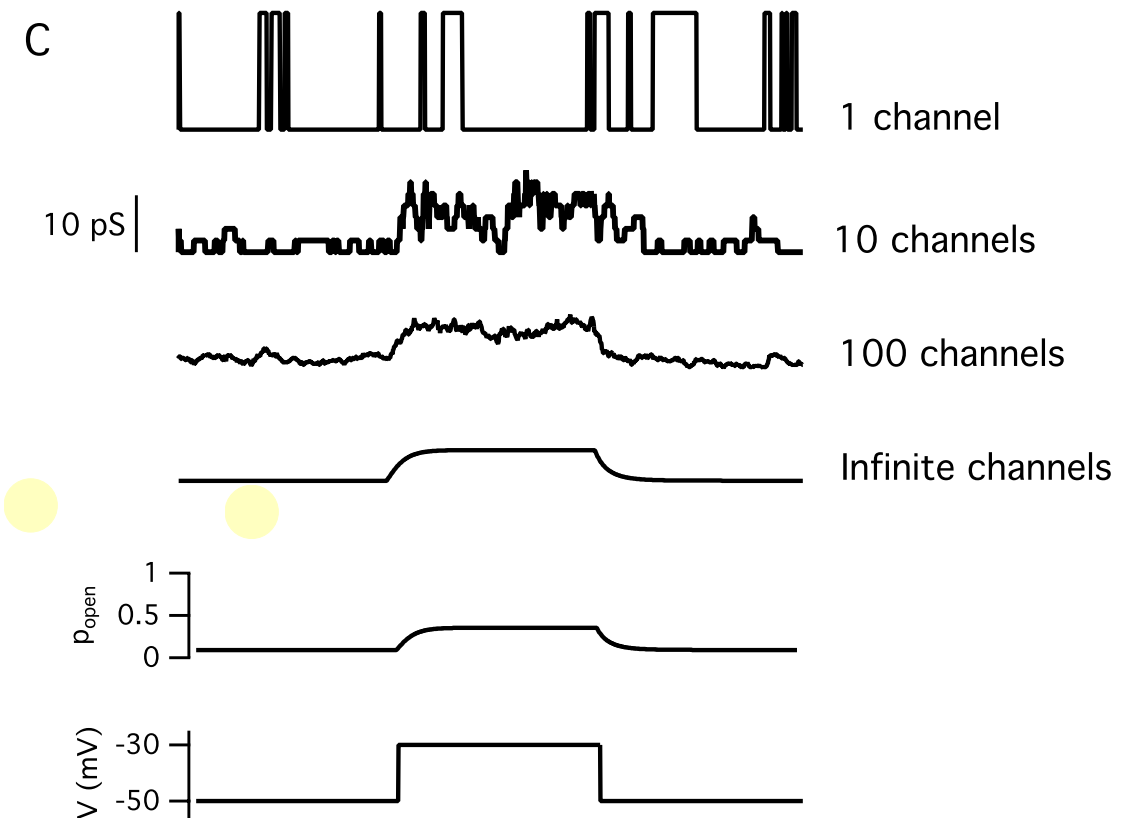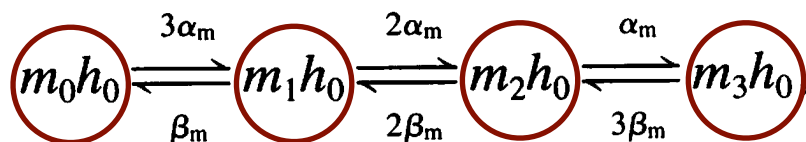

O'Donnell & Nolan (2014)

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 $\quad \bar{I} = Nip$

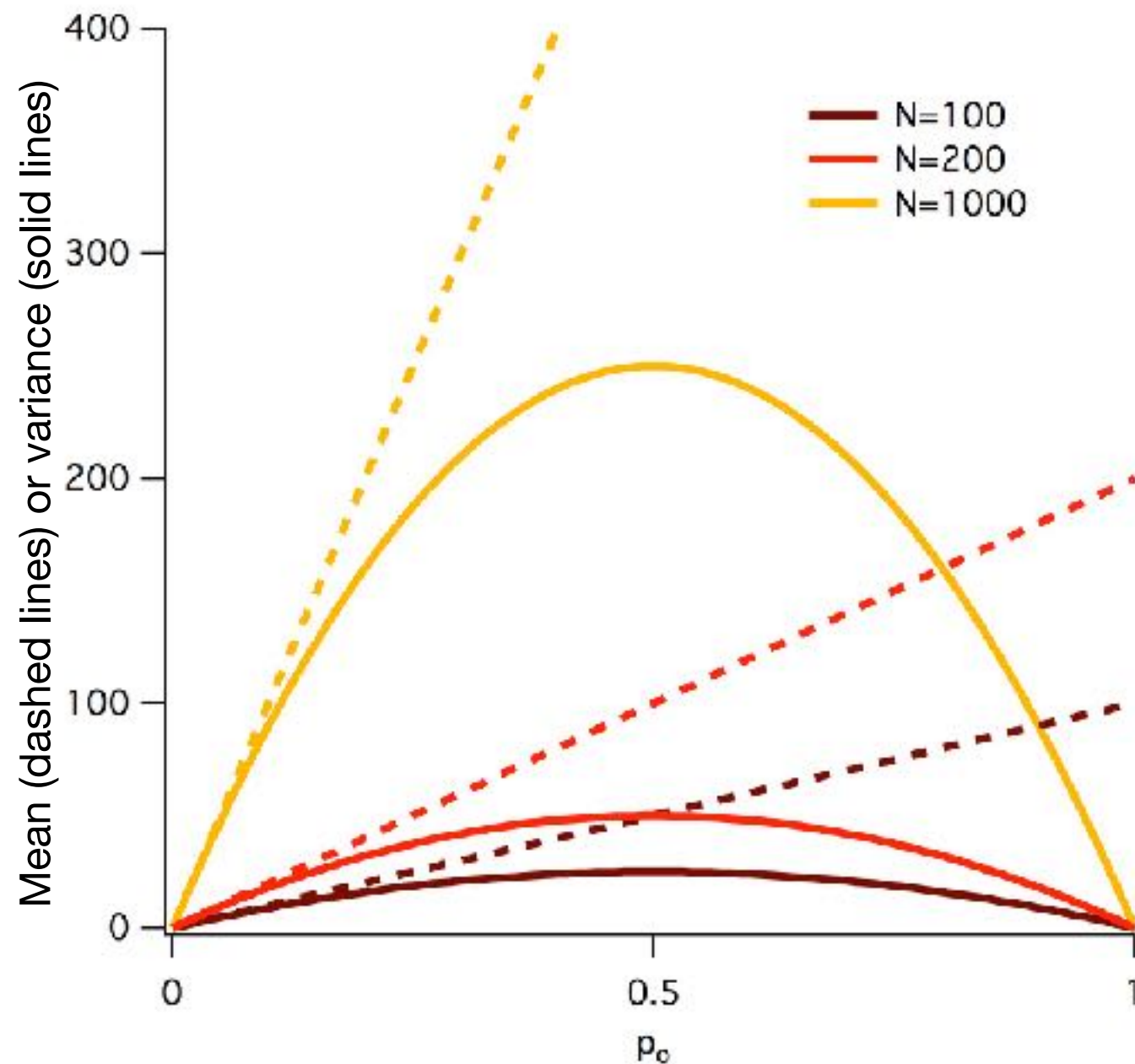 where p_∞ is the steady-state open probability of the channel (fraction of time it is open).

- The standard deviation of the population current (i.e. "the noise") is given from the binomial distribution as

$$\sigma_I = i\sqrt{Np(1-p)}$$

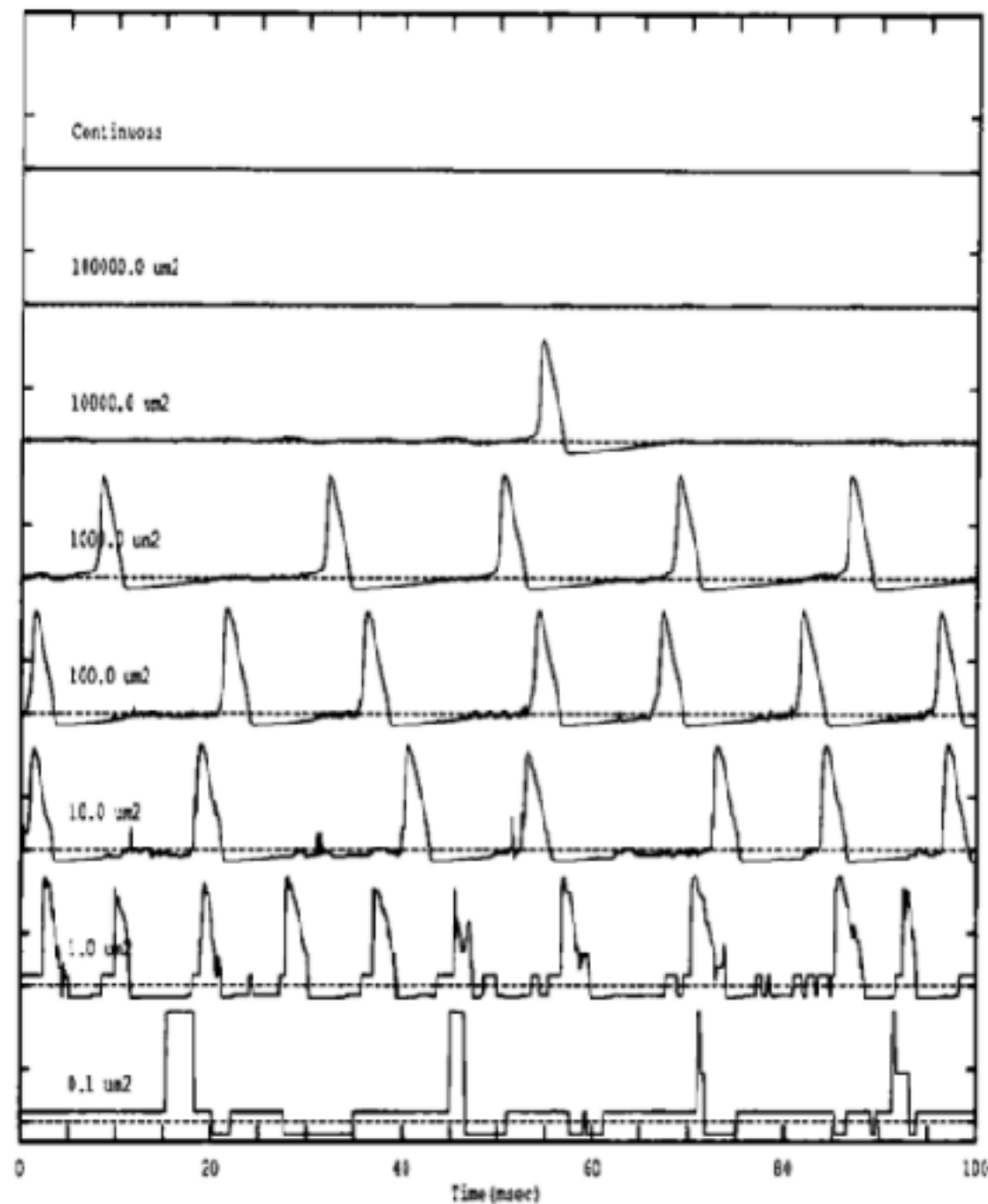- The coefficient of variation (ratio of the standard deviation to the mean) is:

$$\text{C.V.} = \frac{\sigma_I}{\bar{I}} = \sqrt{\frac{1-p}{Np}}$$
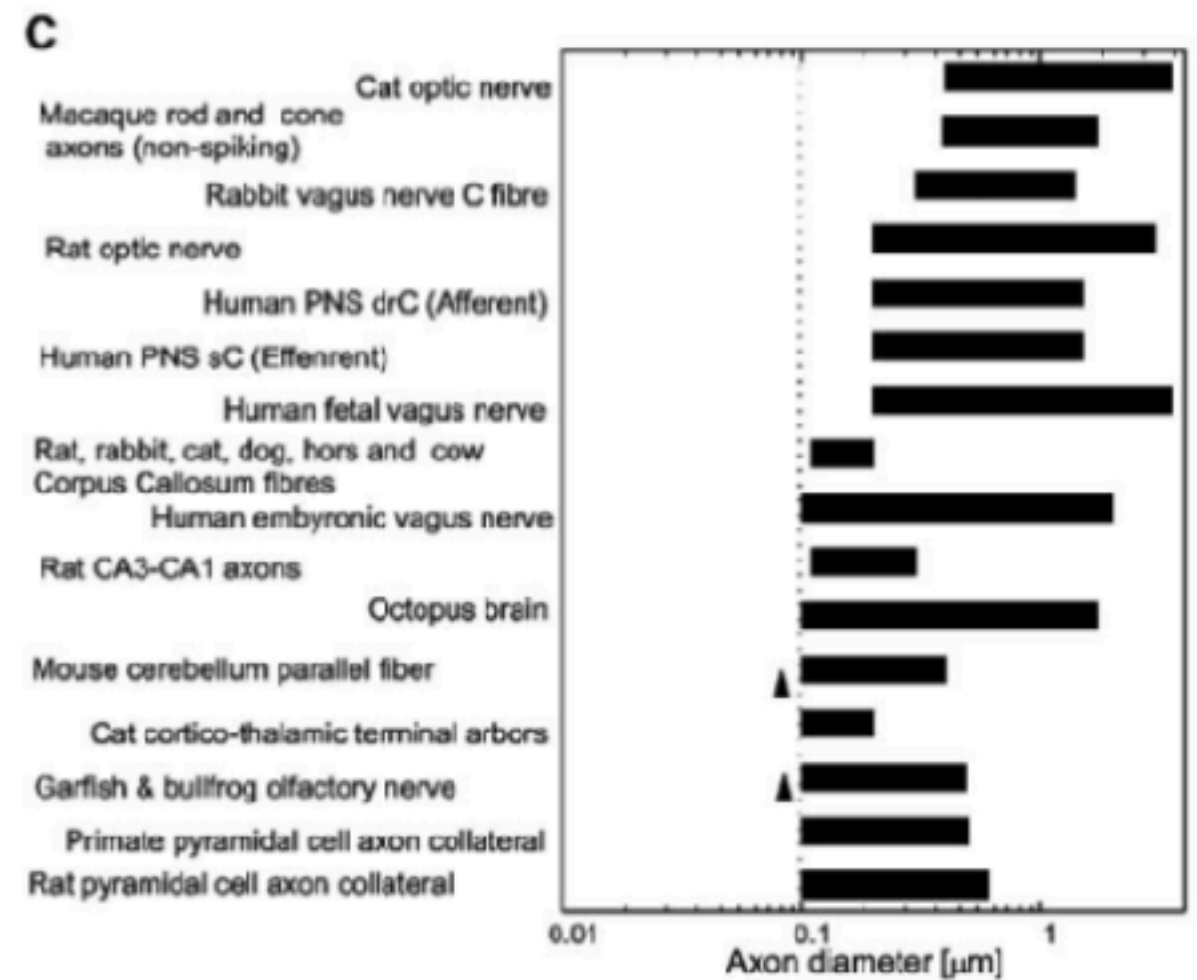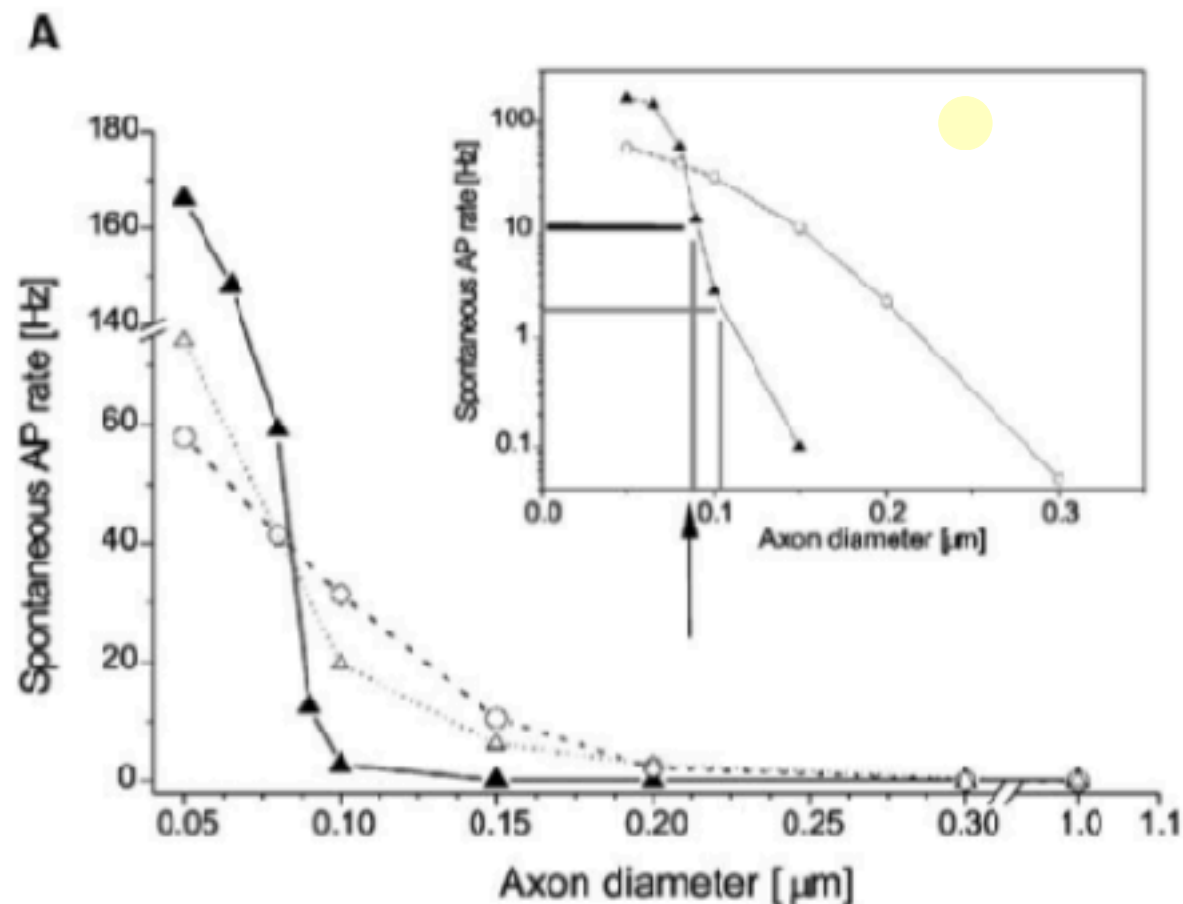
Ion channel noise

Mean current is proportional to open probability, but variance is parabolic in p, highest for $p=0.5$.
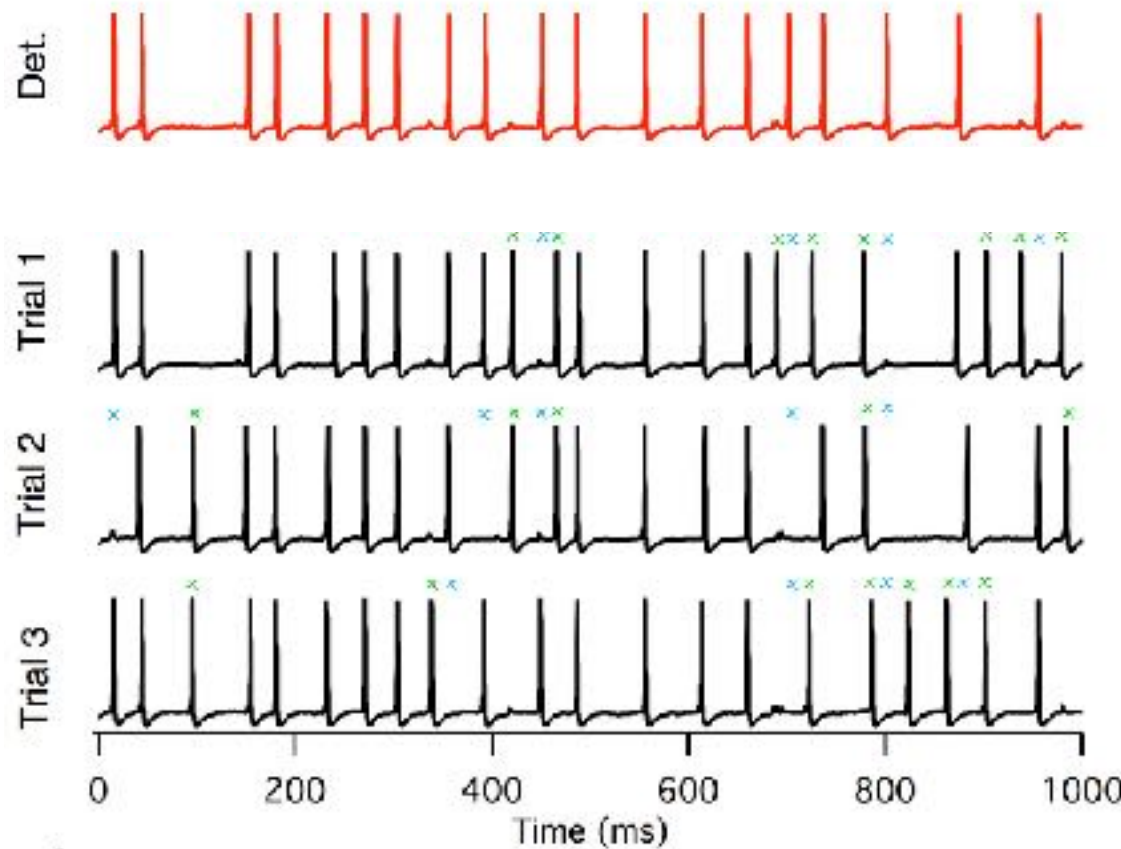
Spontaneous spikes from ion channel noise

Hodgkin-Huxley model with stochastic ion channels, vary the size of the cell membrane.

Strassberg & DeFelice, *Neural Comput* (1993)

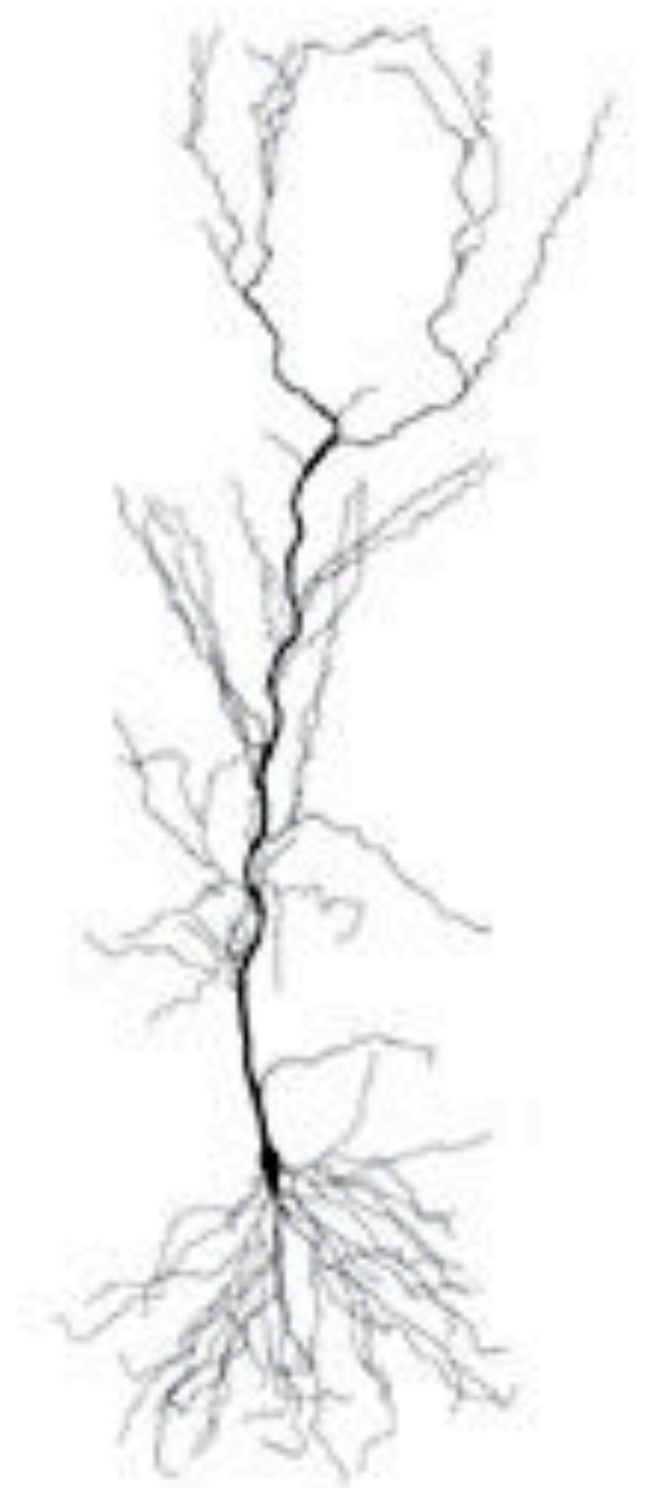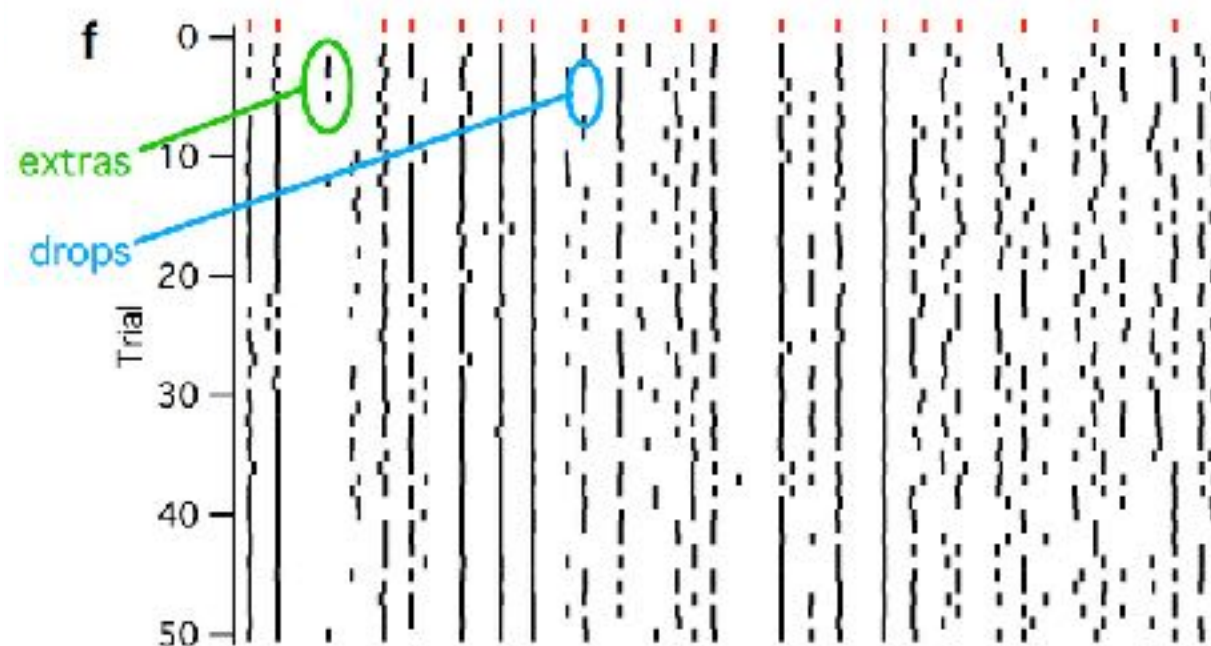# A lower limit on axon diameter due to ion channel noise

Faisal et al., *Curr Biol* (2005)

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)

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