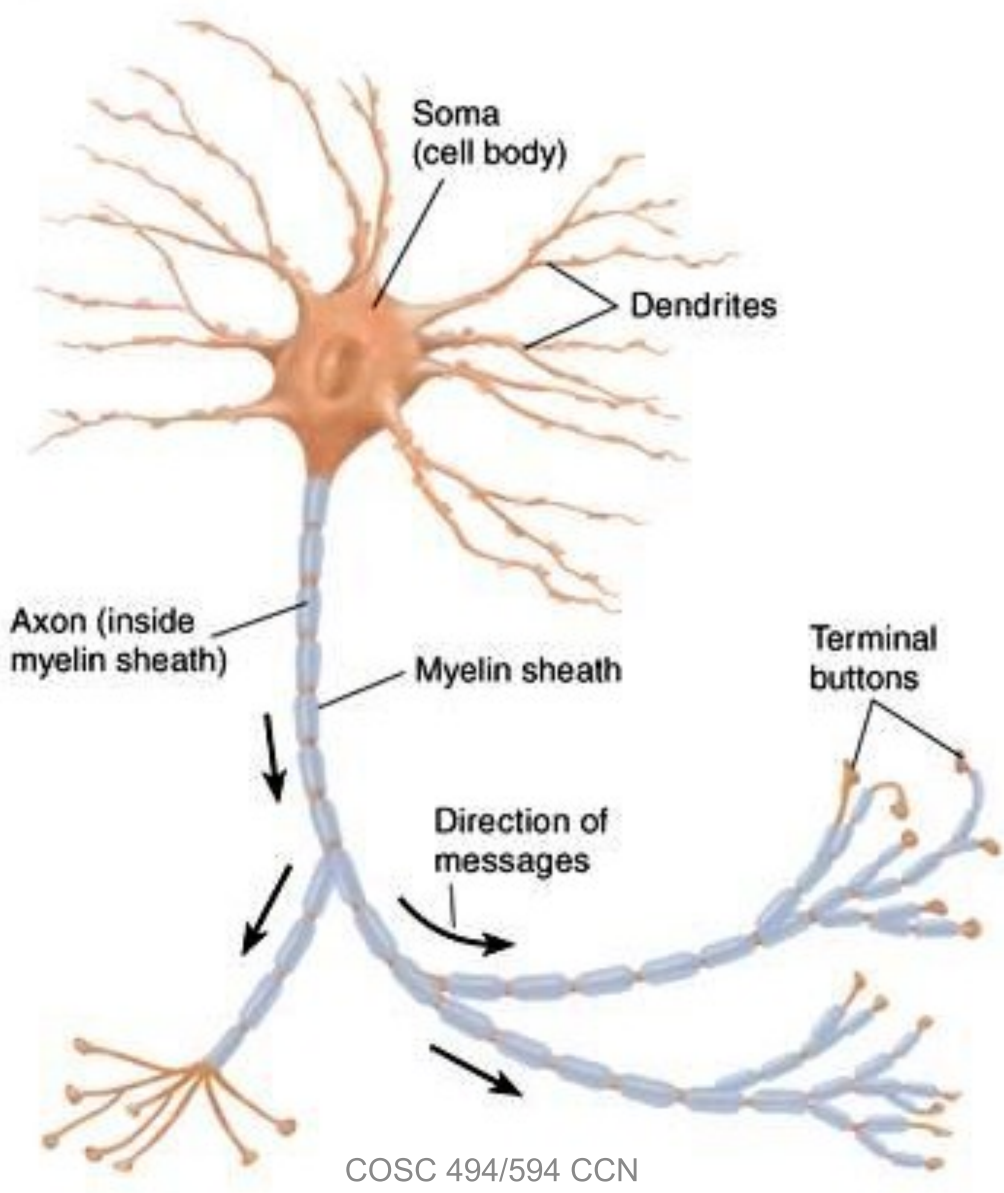
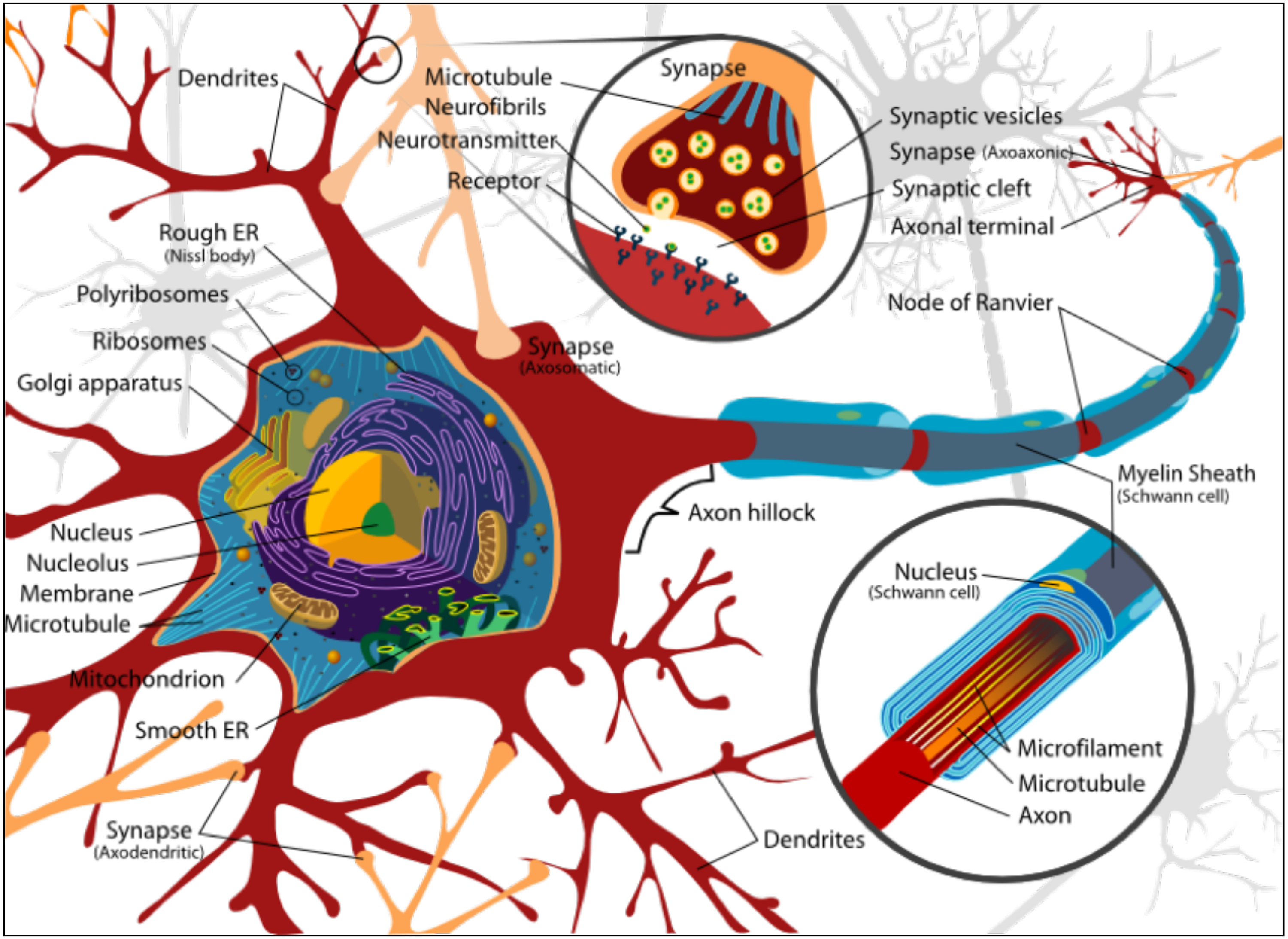
2. Neurons

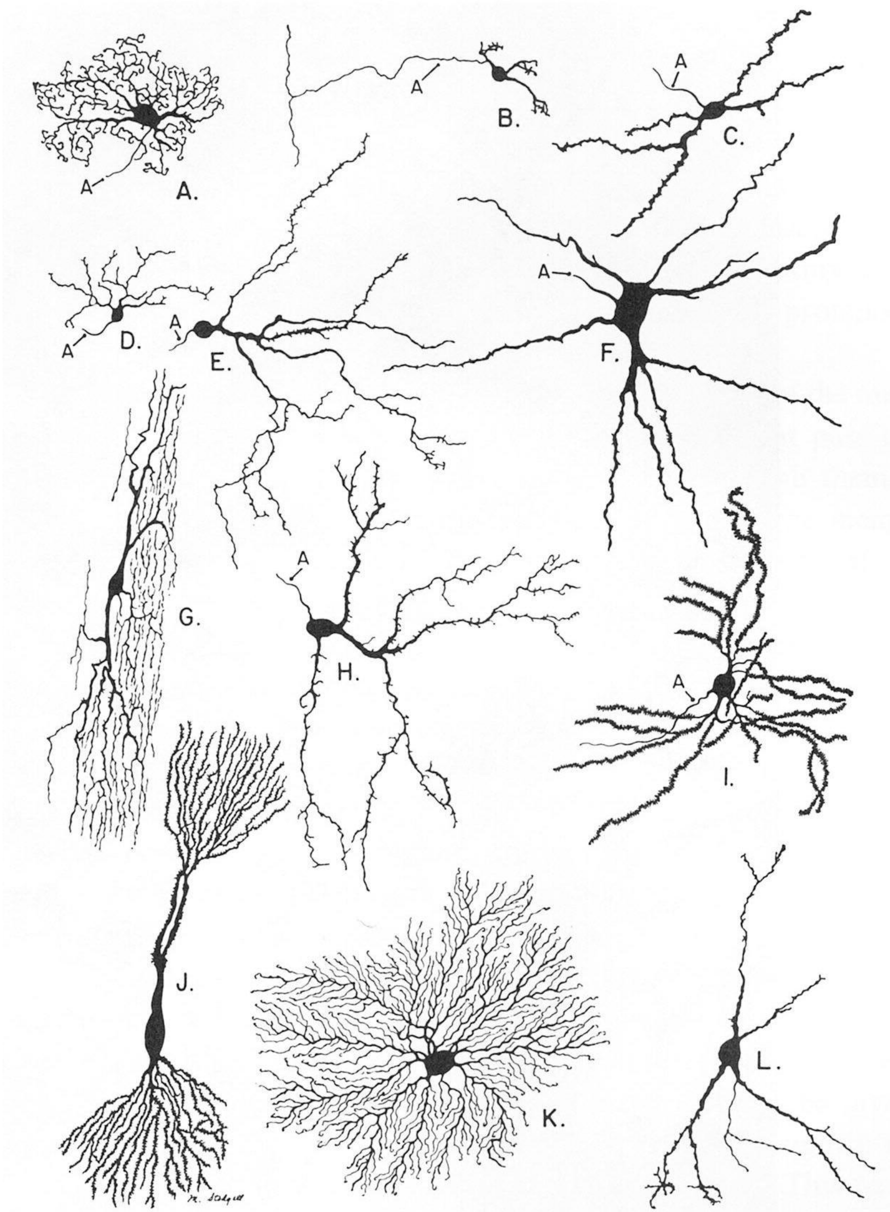
Typical Neuron



Typical Neuron



Dendritic Trees of Some Neurons



A. inferior olivary nucleus
B. granule cell of cerebellar cortex
C. small cell of reticular formation
D. small gelatinosa cell of spinal trigeminal nucleus
E. ovoid cell, nucleus of tractus solitarius
F. large cell of reticular formation
G. spindle-shaped cell, substantia gelatinosa of spinal chord
H. large cell of spinal trigeminal nucleus
I. putamen of lenticular nucleus
J. double pyramidal cell, Ammon's horn of hippocampal cortex
K. thalamic nucleus
L. globus pallidus of lenticular nucleus

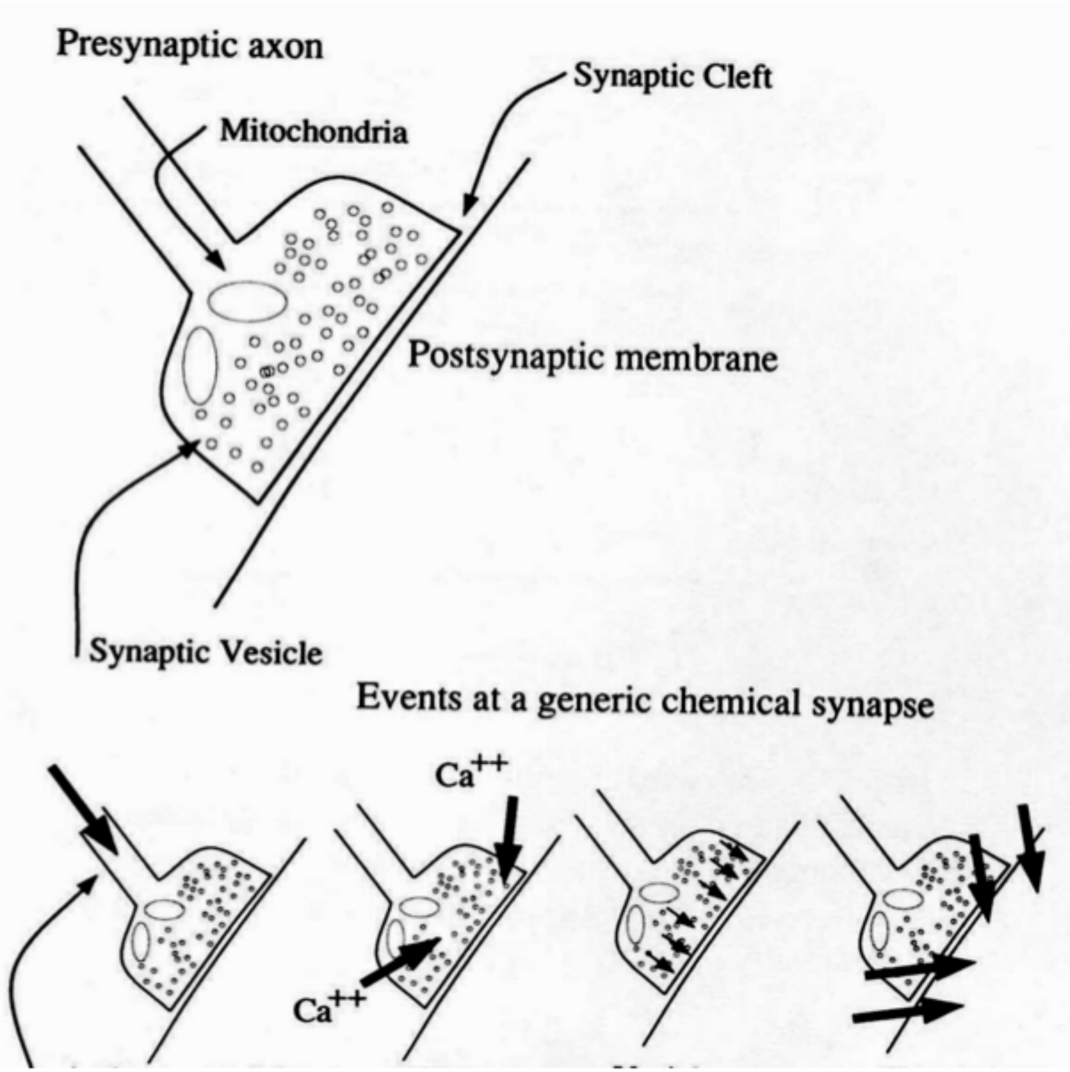
(fig. from Trues & Carpenter, 1964)

Synapses

Animation of synapses:

Hurd Studios Nicotine.flv

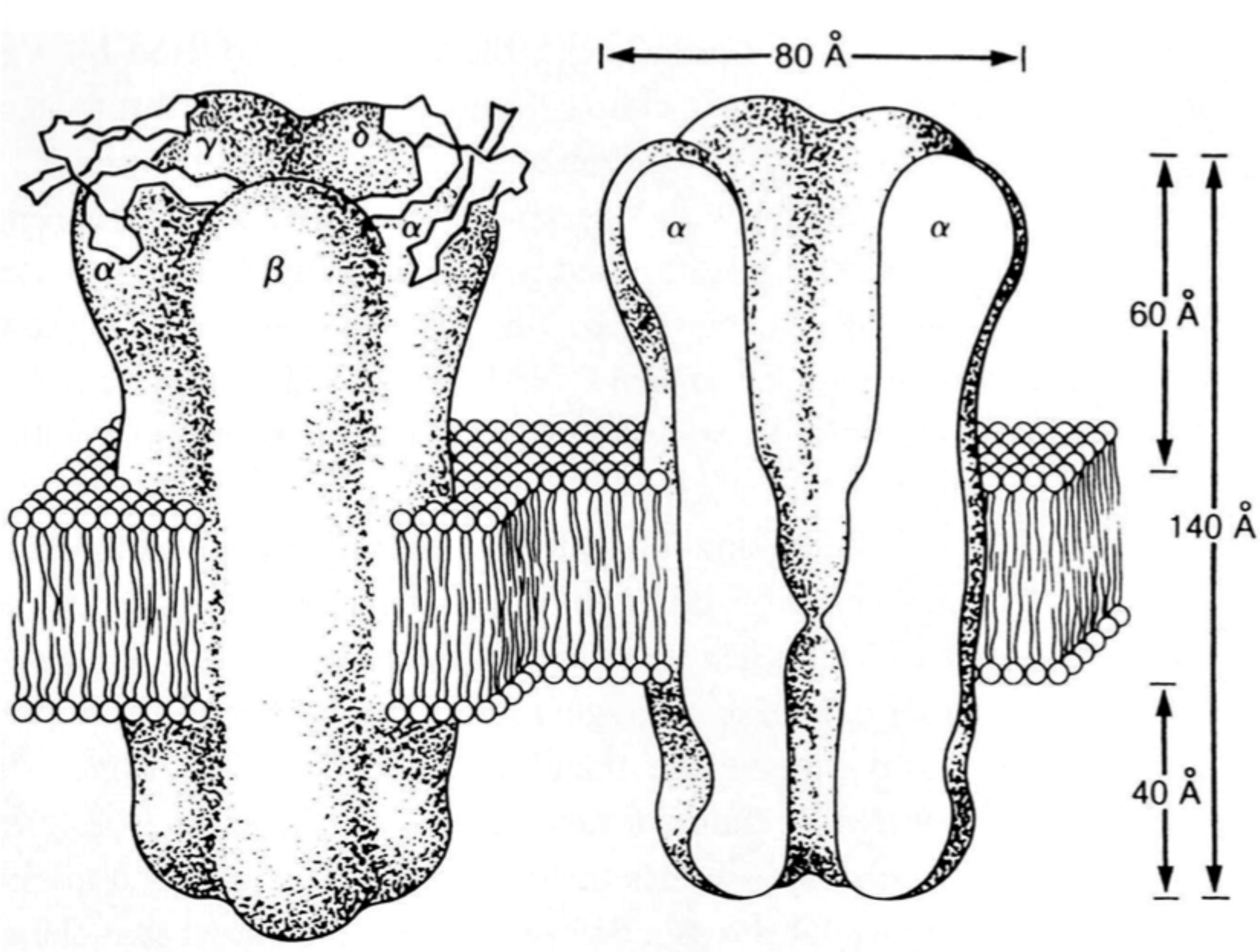
Chemical Synapse



1. Action potential arrives at synapse
2. Opens Ca ion channels and Ca^{++} ions enter cell
3. Vesicles move to membrane, release neurotransmitter
4. Transmitter crosses cleft, causes postsynaptic voltage change

(fig. from Anderson, *Intr. Neur. Nets*)

Typical Receptor



(fig. from Anderson, *Intr. Neur. Nets*)

Synapse with Receptors

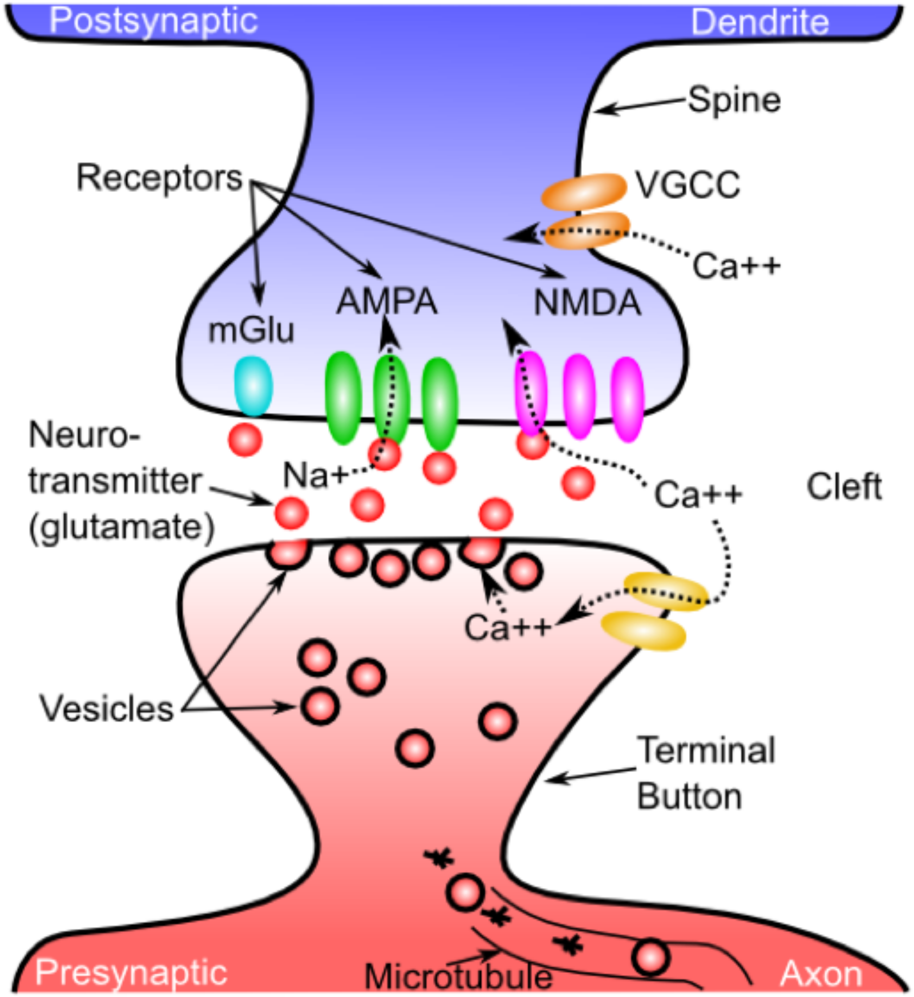


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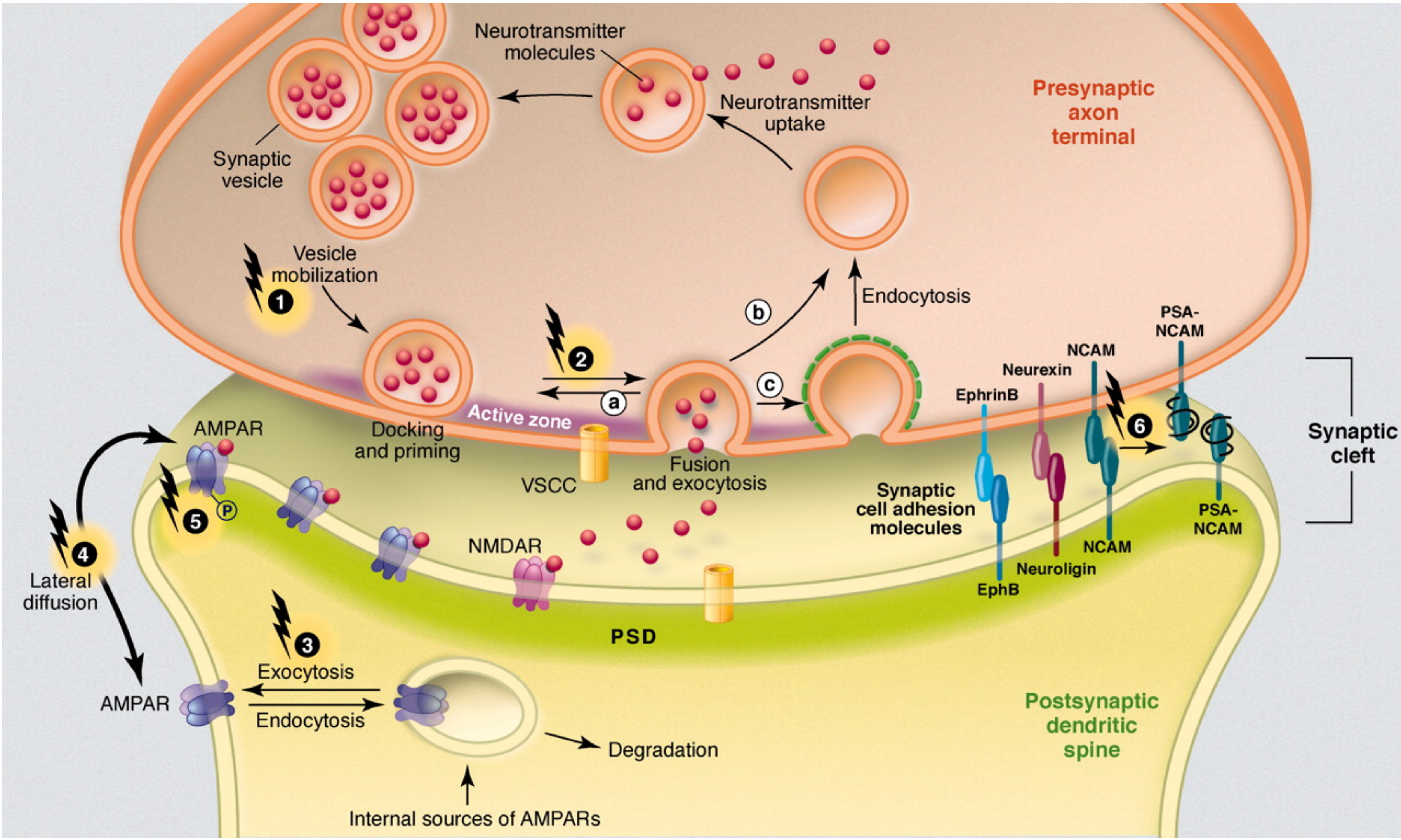
Fig. 3 Activity-dependent modulation of pre-, post-, and trans-synaptic components.



V M Ho et al. Science 2011;334:623-628

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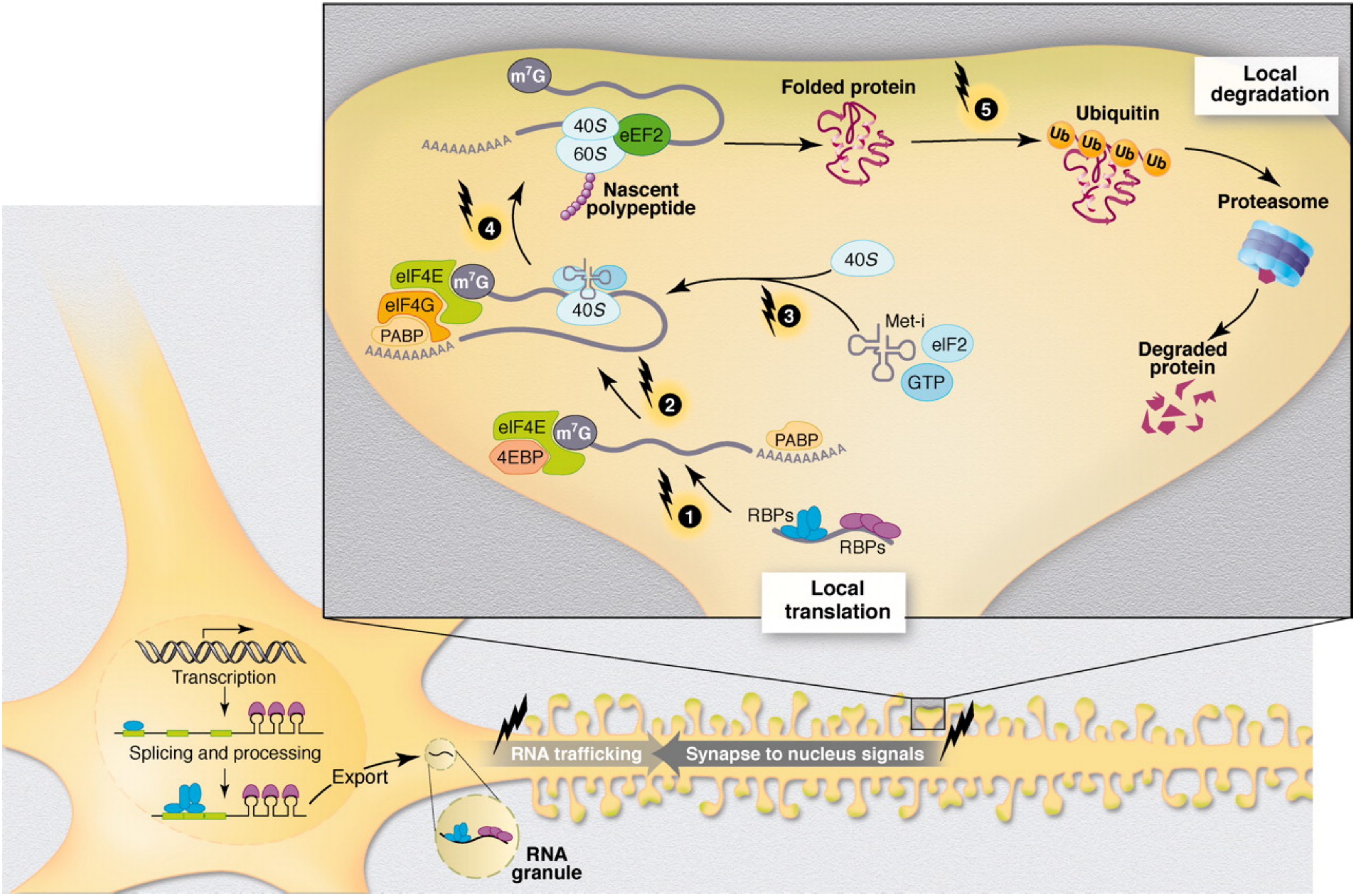
Fig. 4 Local regulation of the synaptic proteome.



V M Ho et al. Science 2011;334:623-628

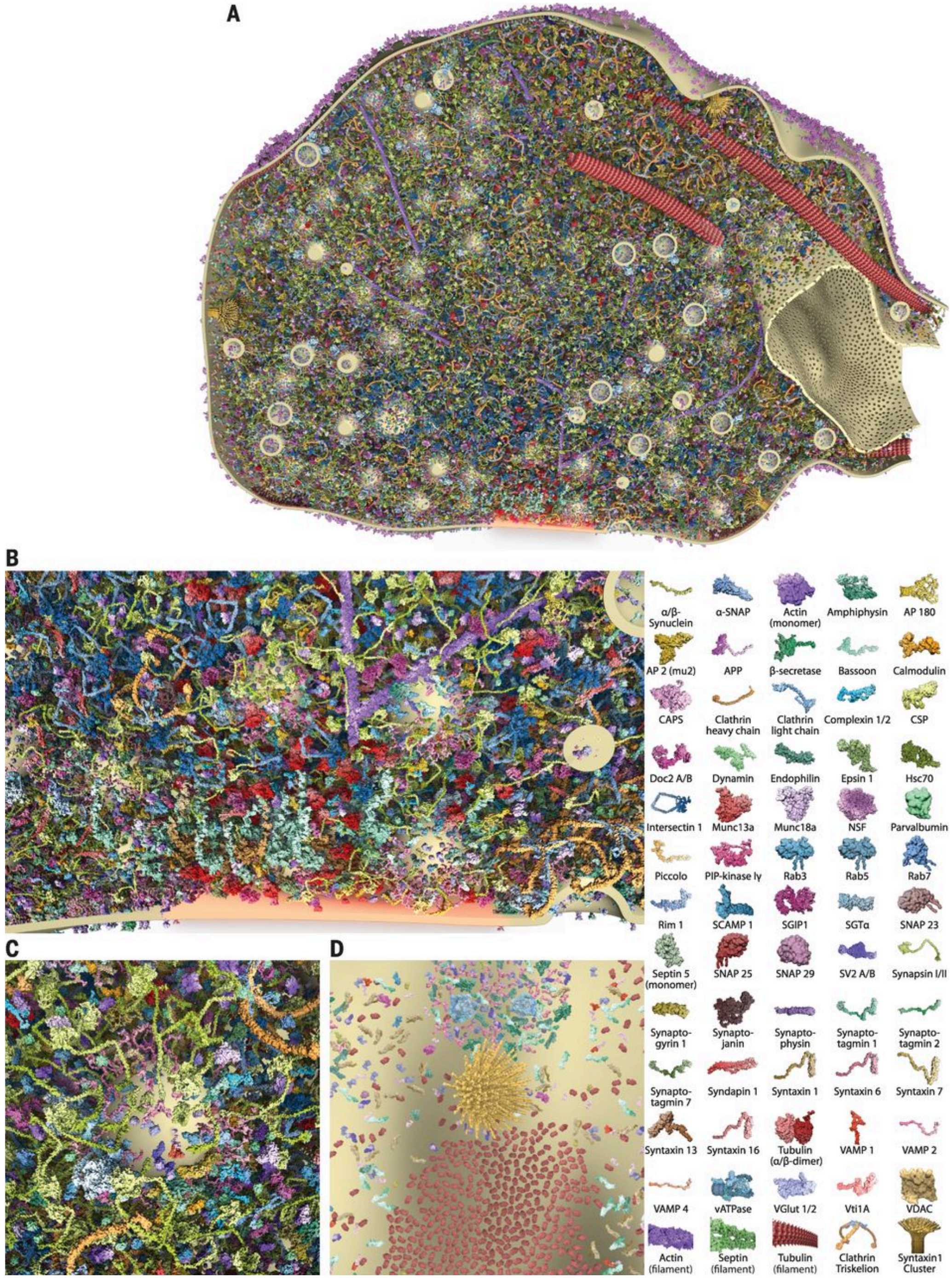


Fig. 3: A 3D model of synaptic architecture.

- A section through the synaptic bouton, indicating 60 proteins.
- High-zoom view of the active zone area.
- High-zoom view of one vesicle within the vesicle cluster.
- High-zoom view of a section of the plasma membrane in the vicinity of the active zone. Clusters of syntaxin (yellow) and SNAP 25 (red) are visible, as well as a recently fused synaptic vesicle (top). The graphical legend indicates the different proteins (right). Displayed synaptic vesicles have a diameter of 42 nm.

B G Wilhelm et al. Science 2014;344:1023-1028

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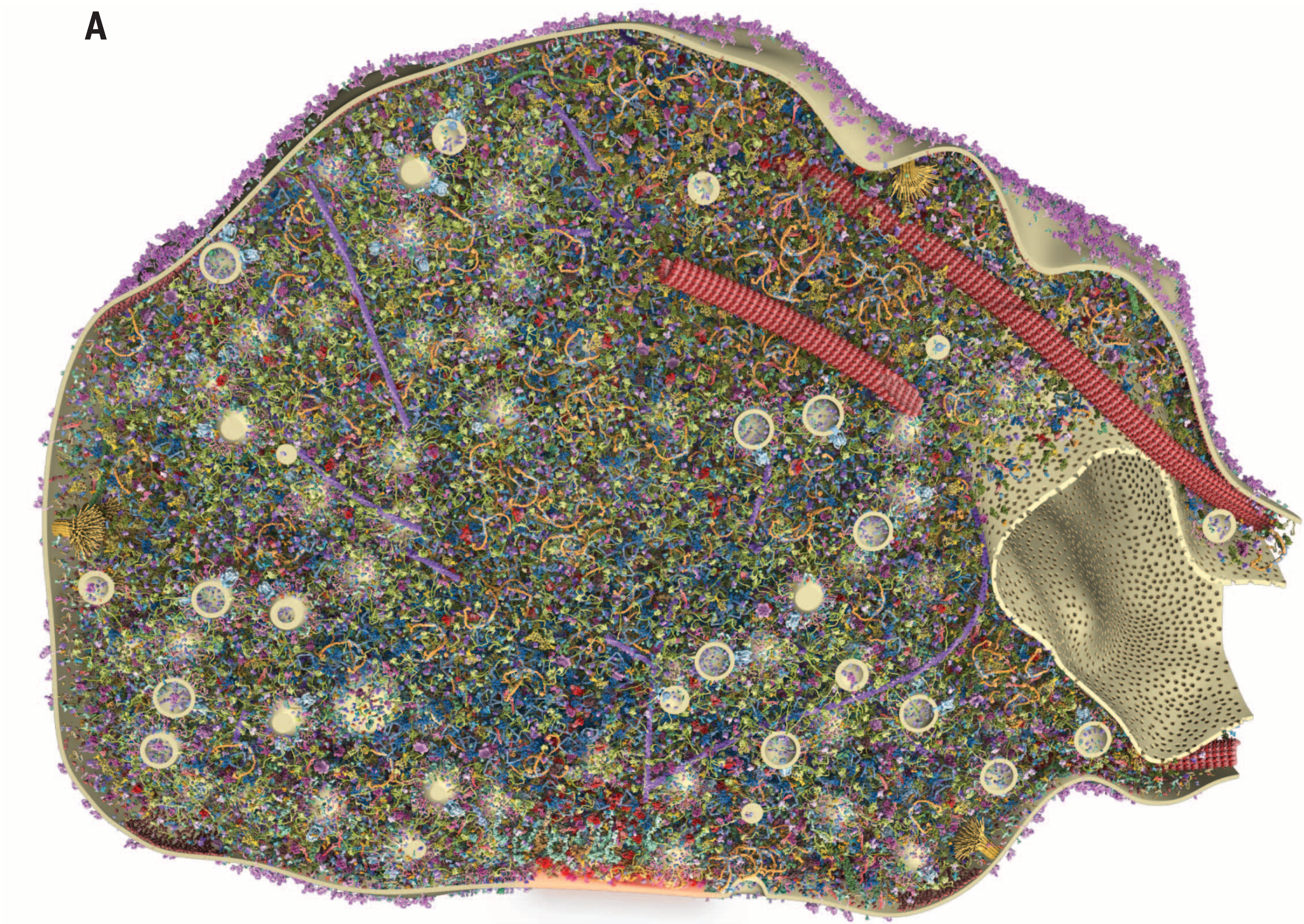
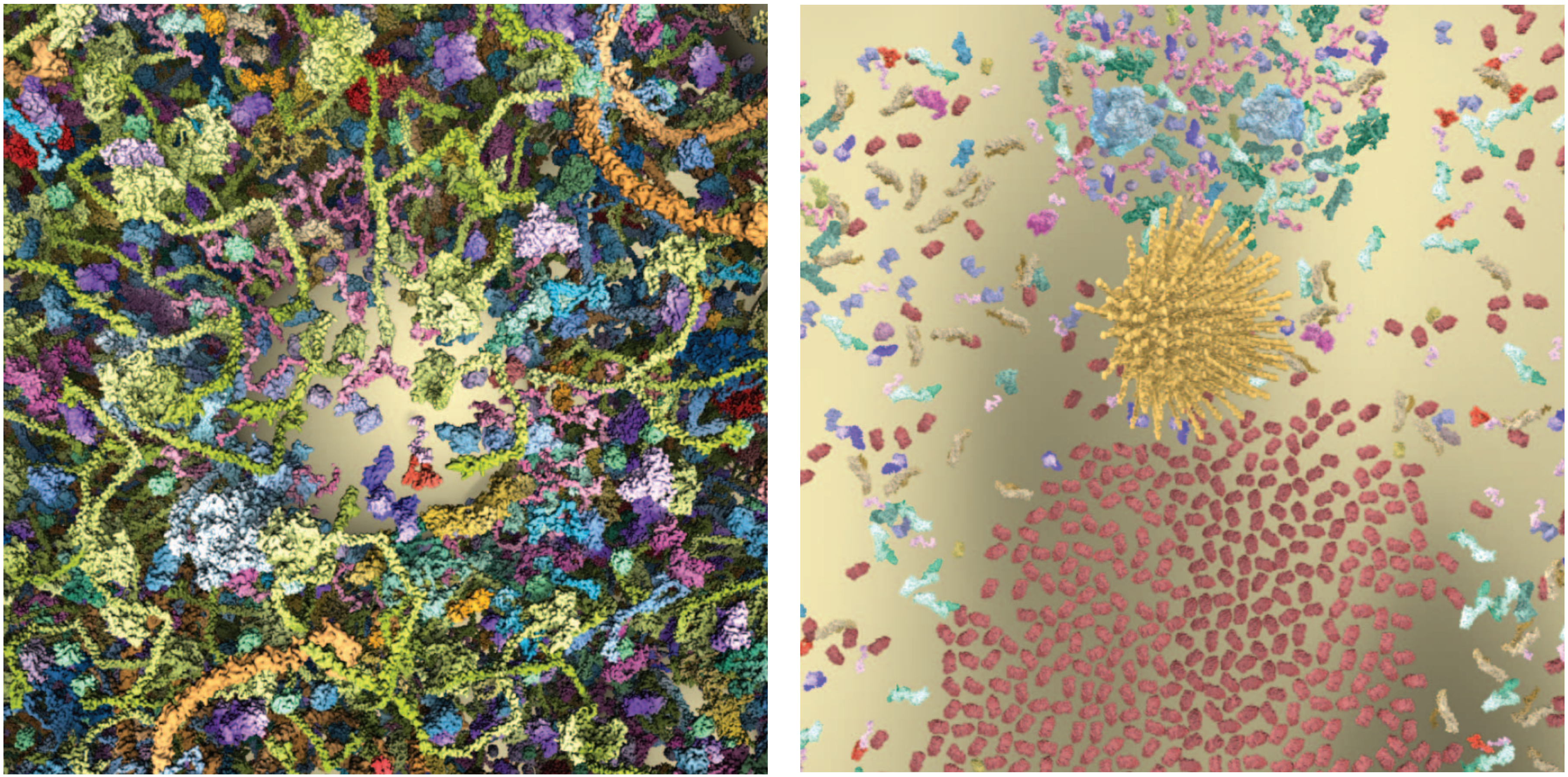
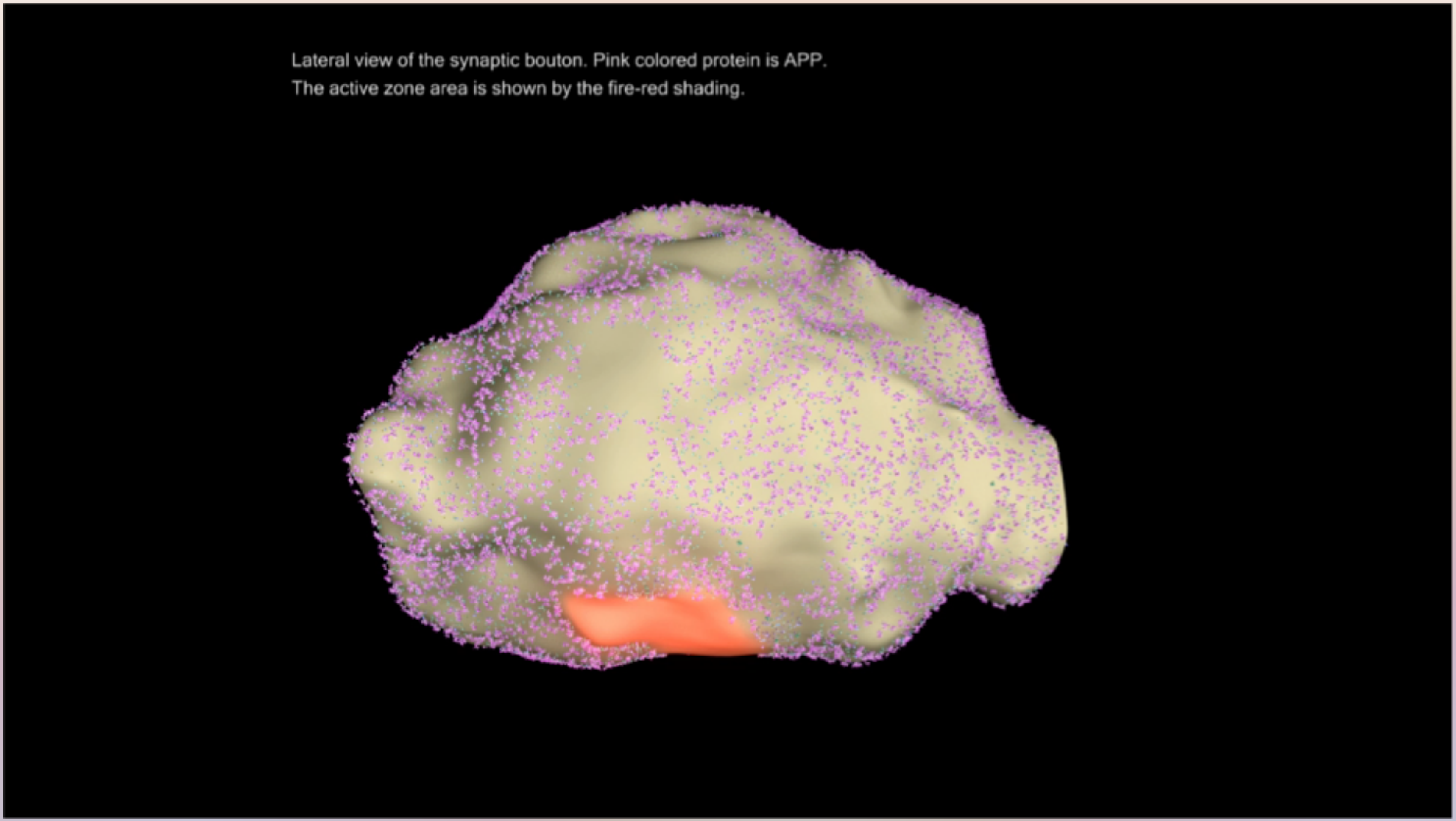

A

B

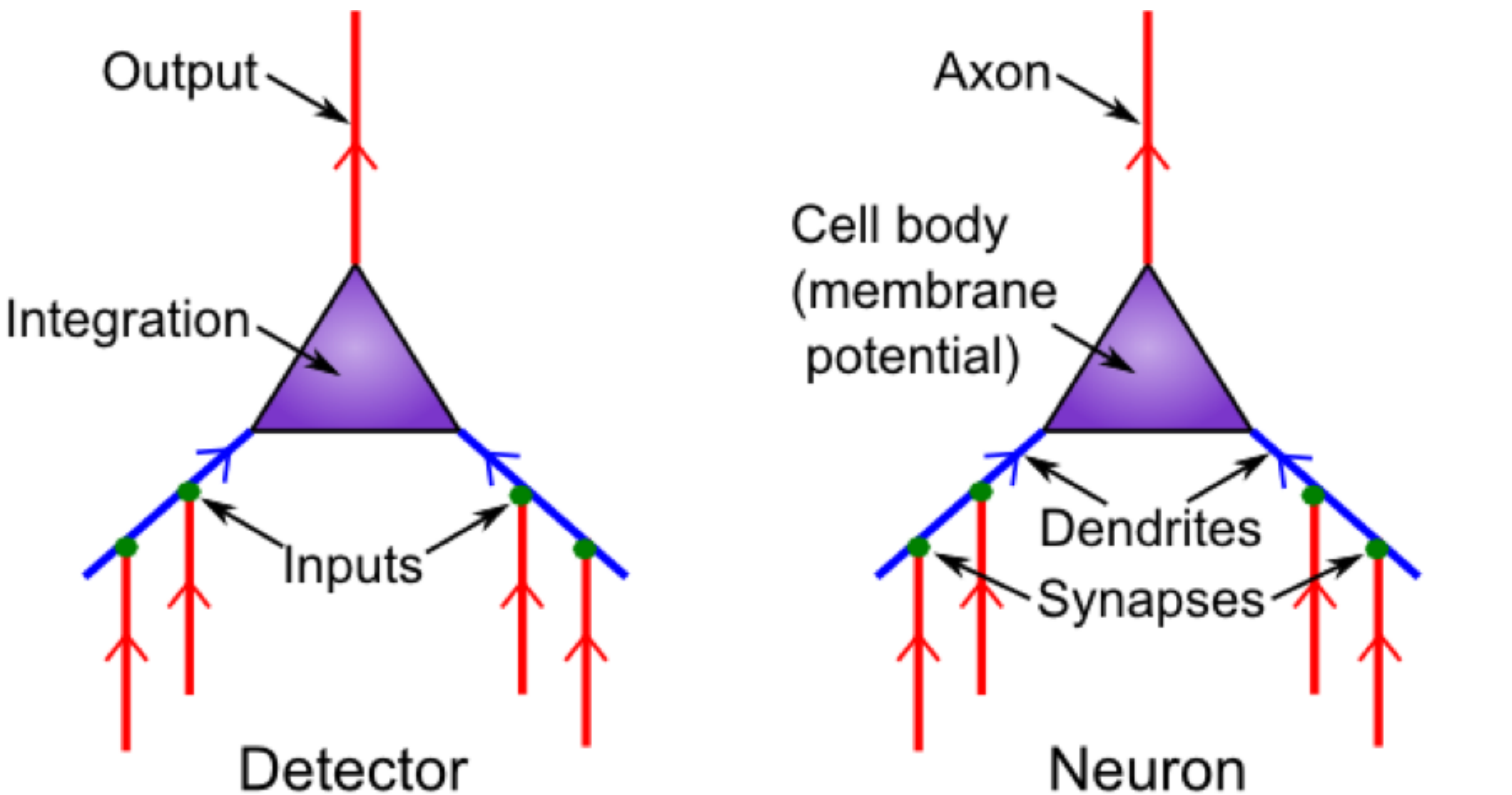
C D



Video of 3D Model



Detector Model



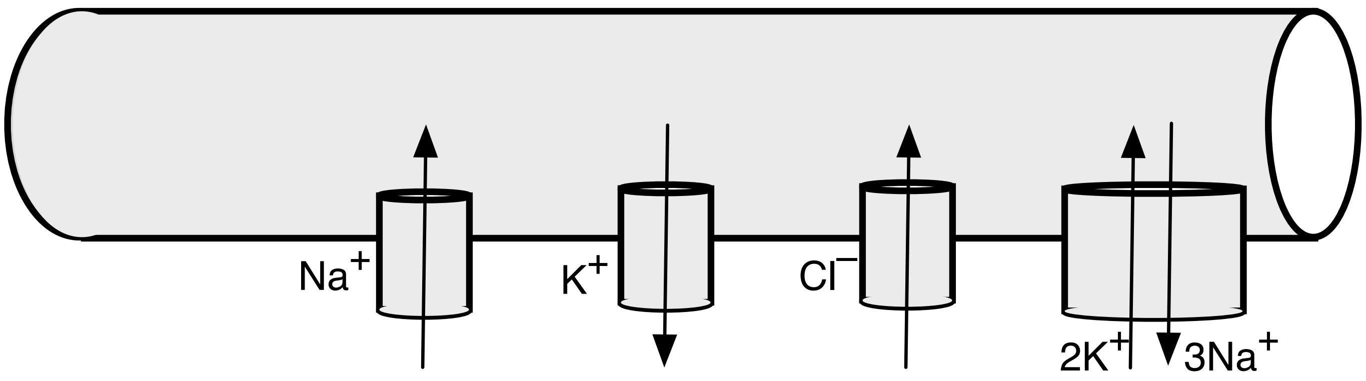
(slide from O'Reilly)

Overall Strategy

- Neurons are electrical systems, can be described using basic electrical equations.
- Use these equations to simulate on a computer.
- Need a fair bit of math to get a full working model (more here than most chapters), but you only really need to understand conceptually.

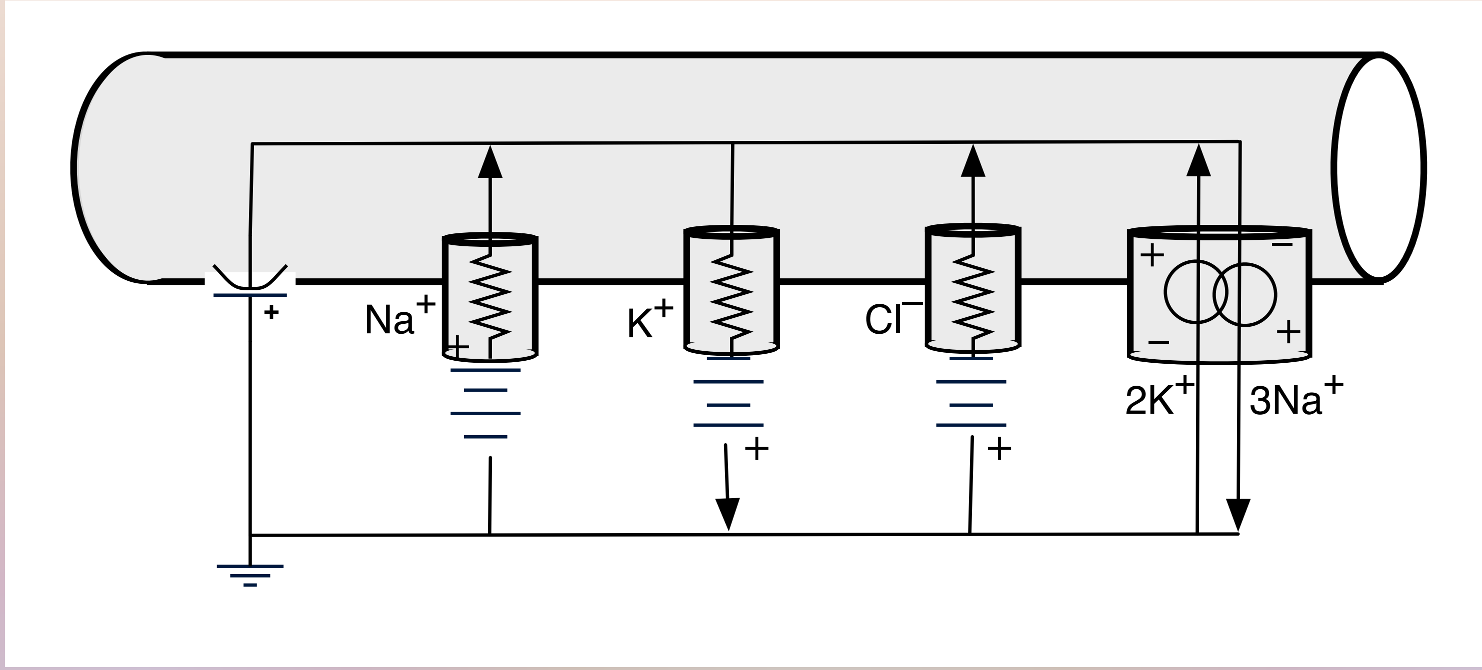
(slide from O'Reilly)

Membrane Potential: Channels



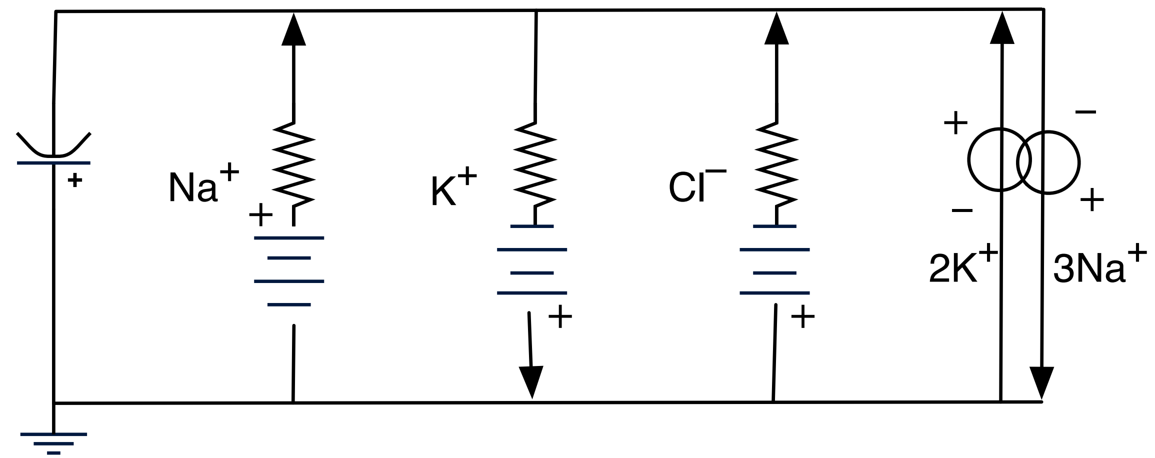
- Na-K pump ⇒ intracellular negative
- Na^+, K^+, Cl^- diffusing through their channels
- create potentials across channels

Membrane Potential: Channels & Equivalent Circuit



- Open channels define resistance to ion flow
- Membrane acts like insulator
- Ion pump charges membrane capacitance

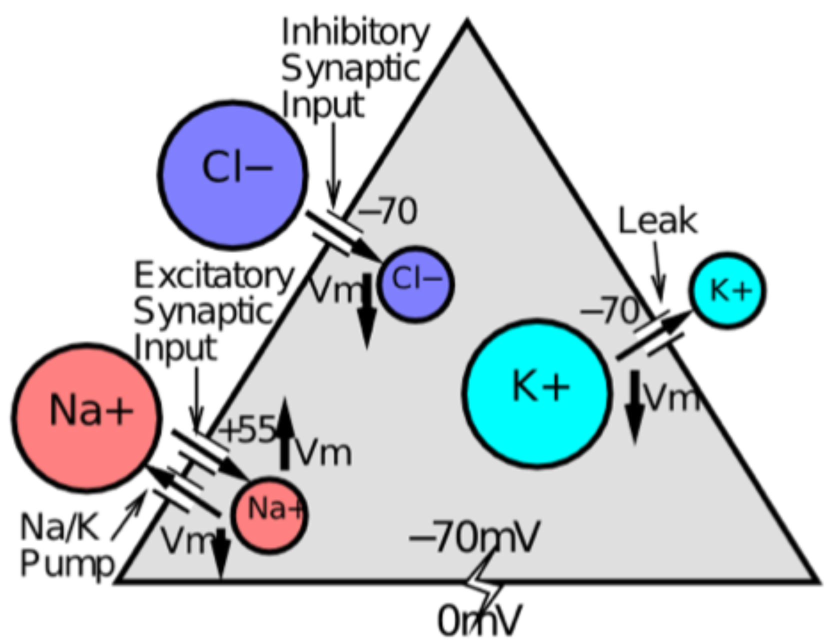
Membrane Potential: Equivalent Circuit



- Ion pump is constant
- Change in conductance of channels
- ⇒ change in membrane potential

Neurophysiology of Membrane

- Na-K pump pumps Na^+ out of the neuron and pumps a lesser amount of K^+ into the neuron
- Creates negative resting potential (–70 mV)
- Na^+ wants in (can't, due to closed channels)
- Cl^- is in balance (diffusion pushes in, electrical pushes out)
- K^+ is in balance (diffusion pushes out, electrical pushes in)



Ions Summary

- Excitatory synaptic input boosts the membrane potential by allowing Na^+ ions to enter the neuron (depolarization)
- Inhibitory synaptic input serves to counteract this increase in membrane potential by allowing Cl^- ions to enter the neuron
- The leak current (K^+ flowing out of the neuron through open channels) acts as a drag on the membrane potential. Functionally speaking, it makes it harder for excitatory input to increase the membrane potential.

(slide based on Frank)

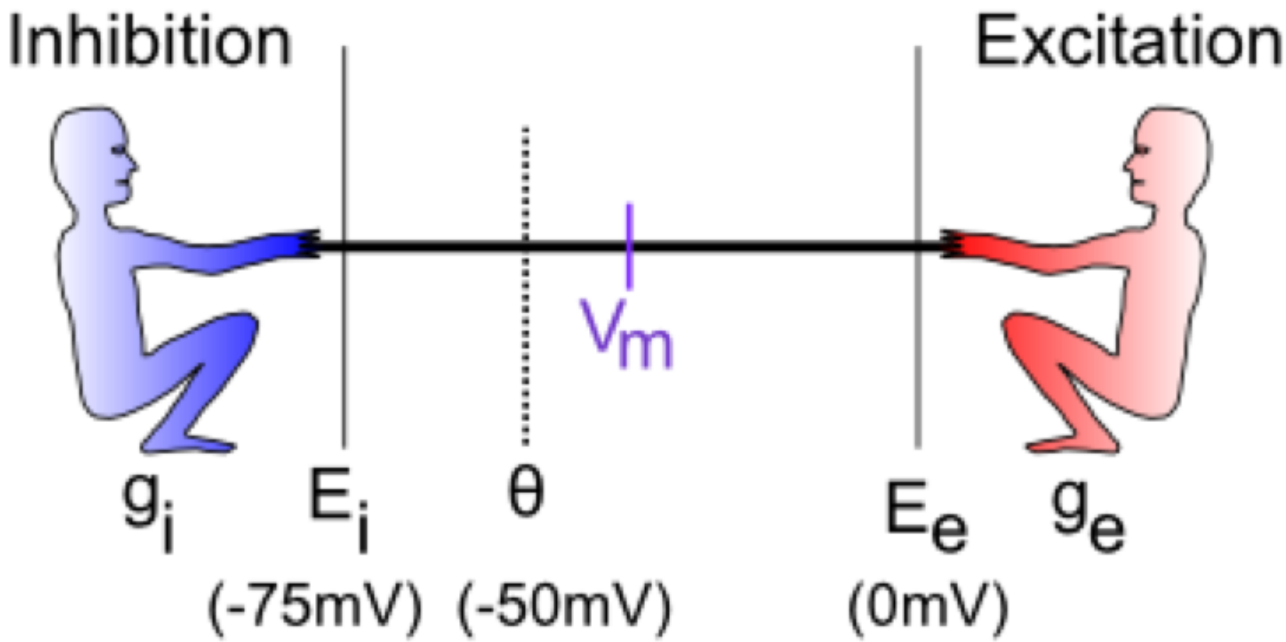
Input Signals

- Excitatory
  - about 85% of inputs
  - AMPA channels, opened by glutamate
- Inhibitory
  - about 15% of inputs
  - GABA channels, opened by GABA
  - produced by inhibitory interneurons
- Leakage
  - potassium channels
- Synaptic efficacy (weight) is net effect of:
  - presynaptic neuron to produce neurotransmitter
  - postsynaptic channels to bind it

Membrane Potential (Variables)

- g_e = excitatory conductance
- E_e = excitatory potential (~ 0 mV)
- g_i = inhibitory conductance
- E_i = inhibitory potential (–70 mV)
- g_l = leakage conductance
- E_l = leakage potential
- V_m = membrane potential
- θ = threshold

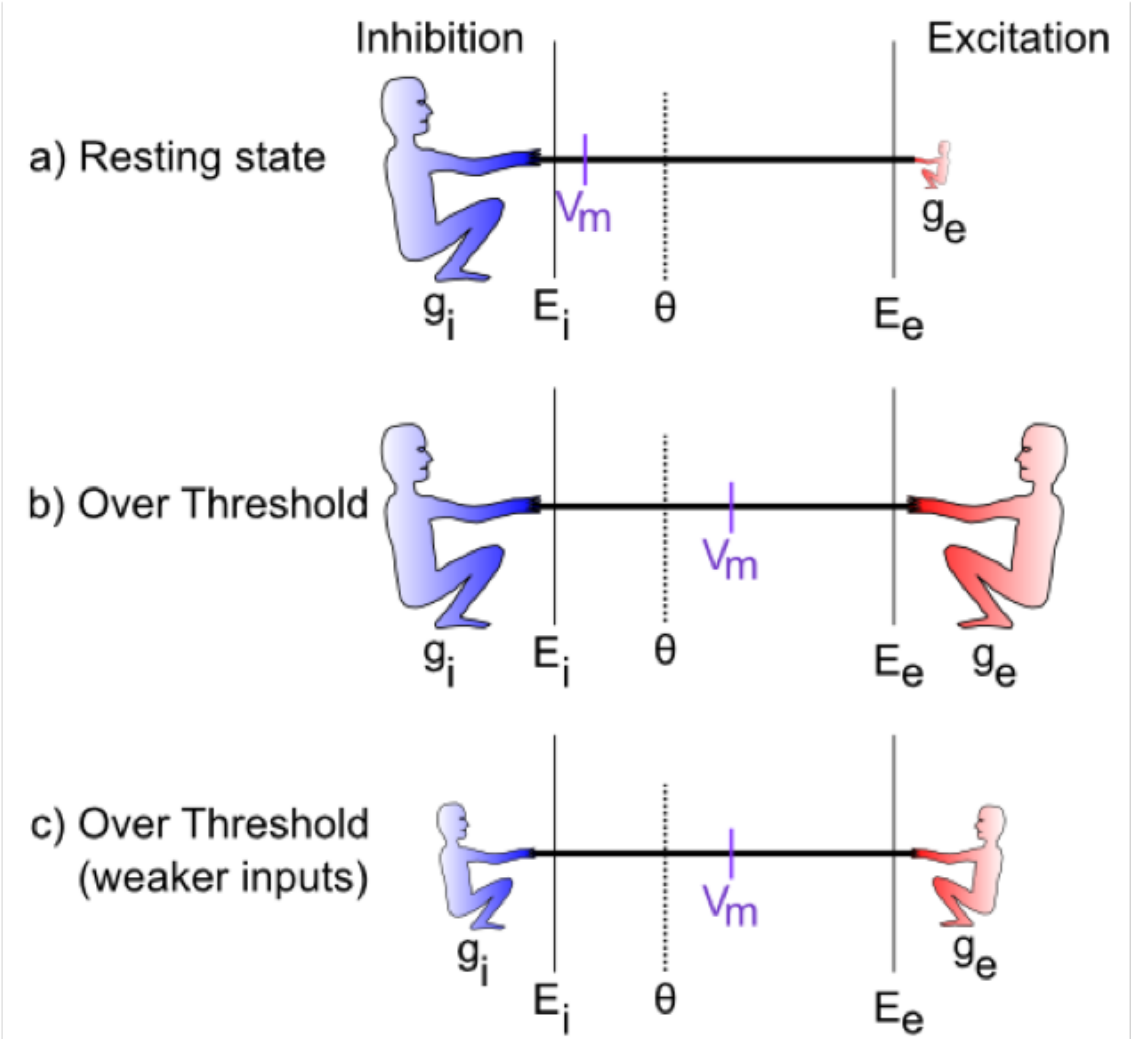
The Tug-of-War



How strongly each guy pulls: $I = g\ (E – V_m)$
g = how many input channels are open
E = driving potential (pull down for inhibition, up for excitation)
V_m = the "flag" – reflects net balance between two sides

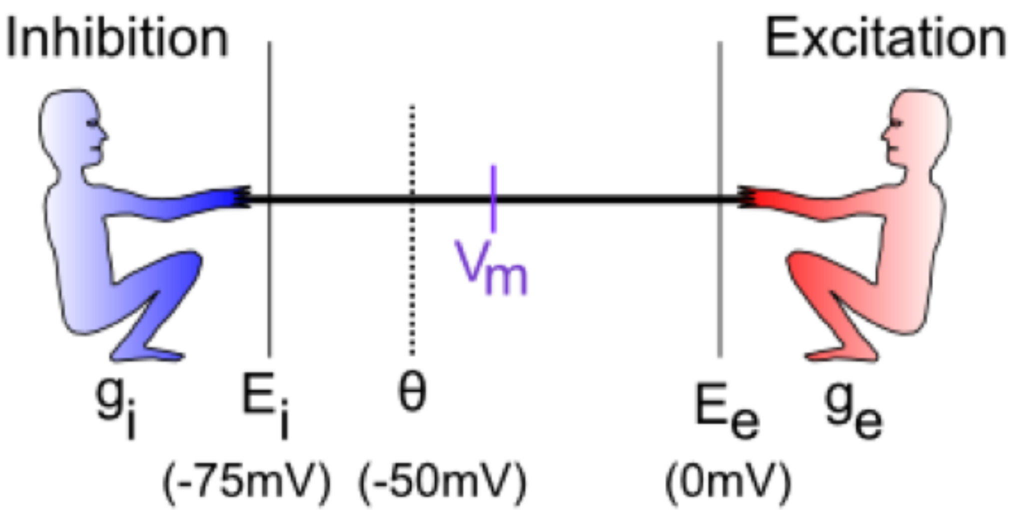
(slide from O'Reilly)

Relative Balance



(slide from O'Reilly)

Equations



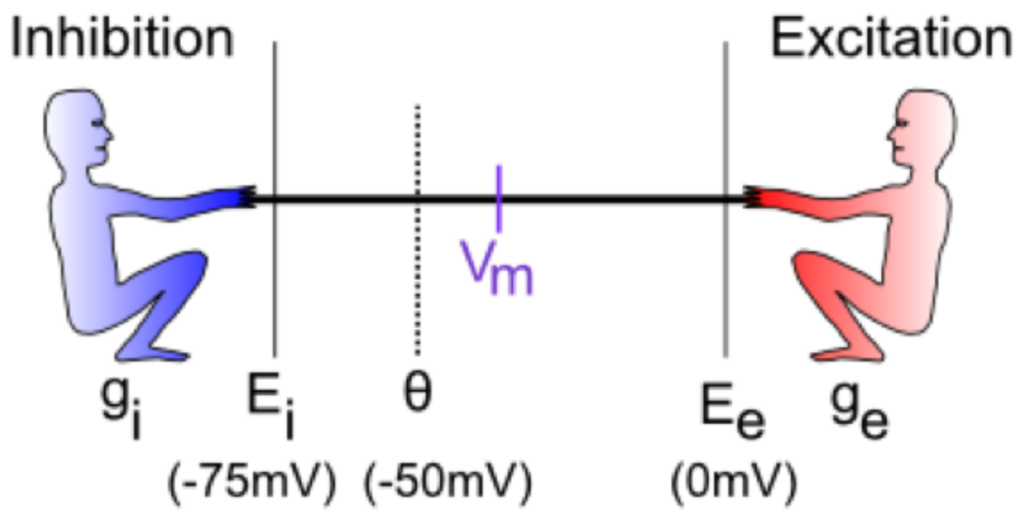
$$I_{net} = I_e + I_i + I_l = g_e\left(E_e - V_m\right) + g_i\left(E_i - V_m\right) + g_l\left(E_l - V_m\right)$$

$$V_m\left(t\right) = V_m\left(t-1\right) + dt_{vm} I_{net}$$

$$V_m(t) = V_m(t-1) + dt_{vm}\left[g_e(E_e - V_m) + g_i(E_i - V_m) + g_l(E_l - V_m)\right]$$

(slide from O'Reilly)

Equilibrium



$$V_m = \frac{g_e}{g_e + g_i + g_l} E_e + \frac{g_i}{g_e + g_i + g_l} E_i + \frac{g_l}{g_e + g_i + g_l} E_l$$

This is just the balance of forces

(slide from O'Reilly)

Input Conductances and Weights

- Just add them up (and take the average)

$$g_e(t) = \frac{1}{n} \sum_i x_i w_i$$

  - Key concept is *weight:* how much unit listens to given input
  - Weights determine what the neuron detects
  - Everything you know is encoded in your weights

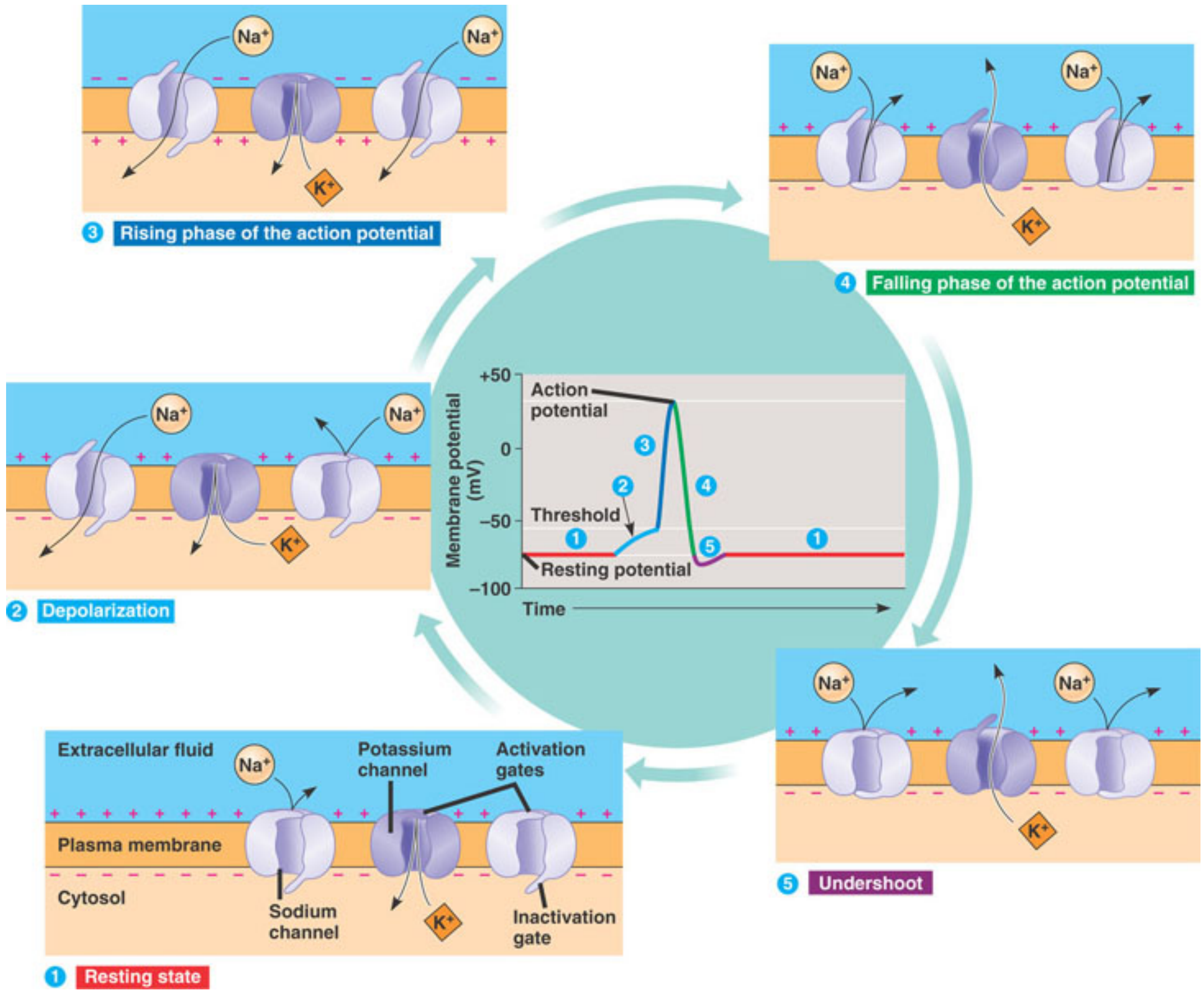
(slide from O'Reilly)

Generating Output

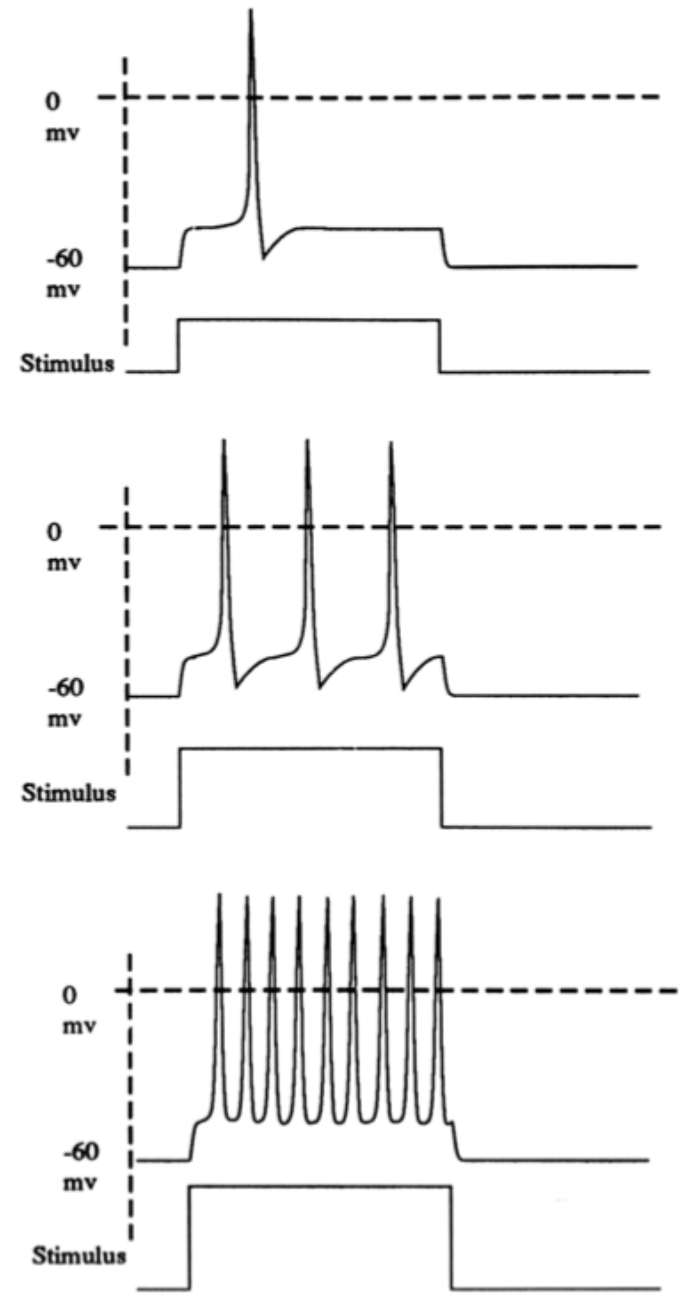
- If V_m gets over threshold, neuron fires a spike
- Spike resets membrane potential back to rest
- Has to climb back up to threshold to spike again

(slide from O'Reilly)

Action Potential Generation

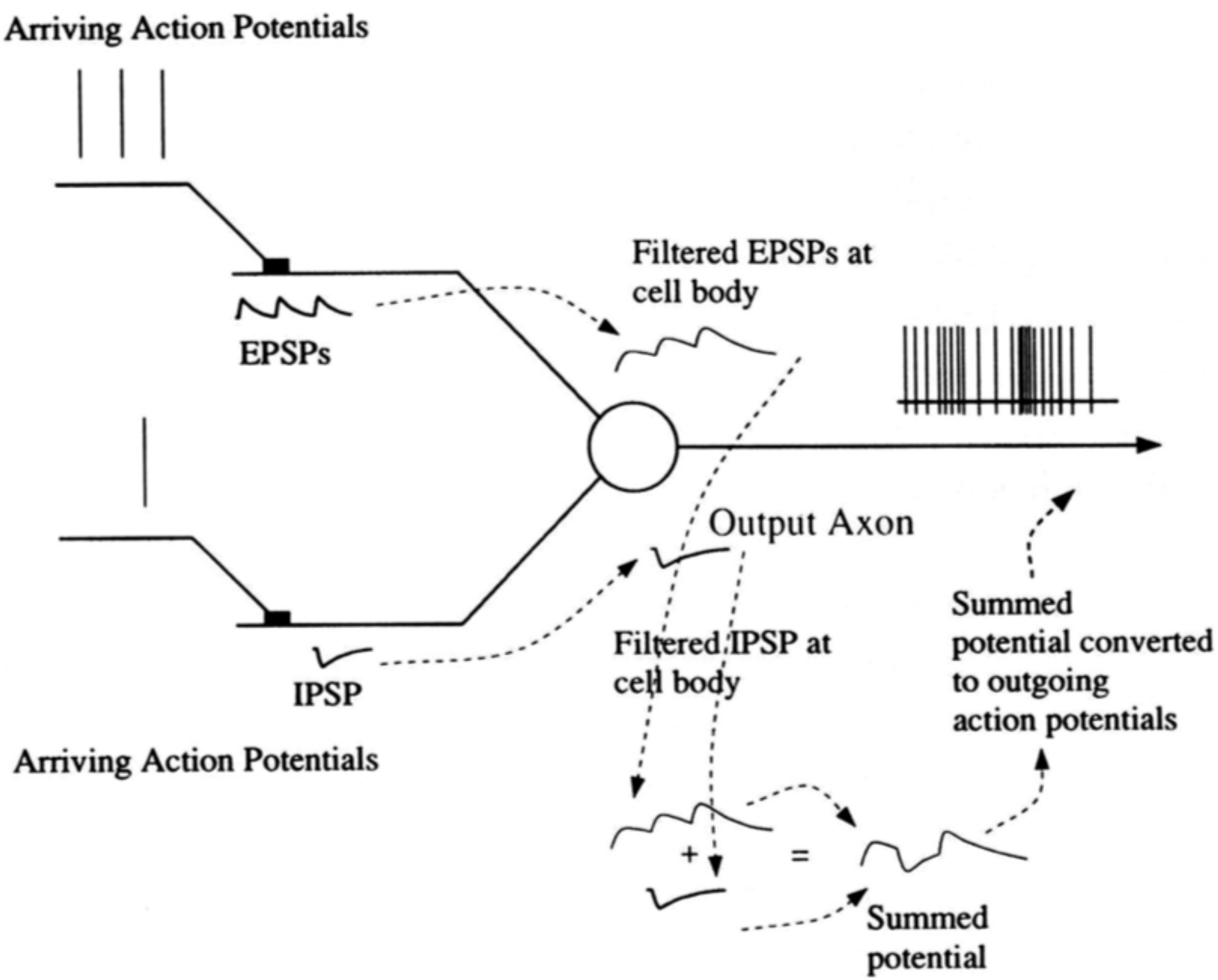


Frequency Coding



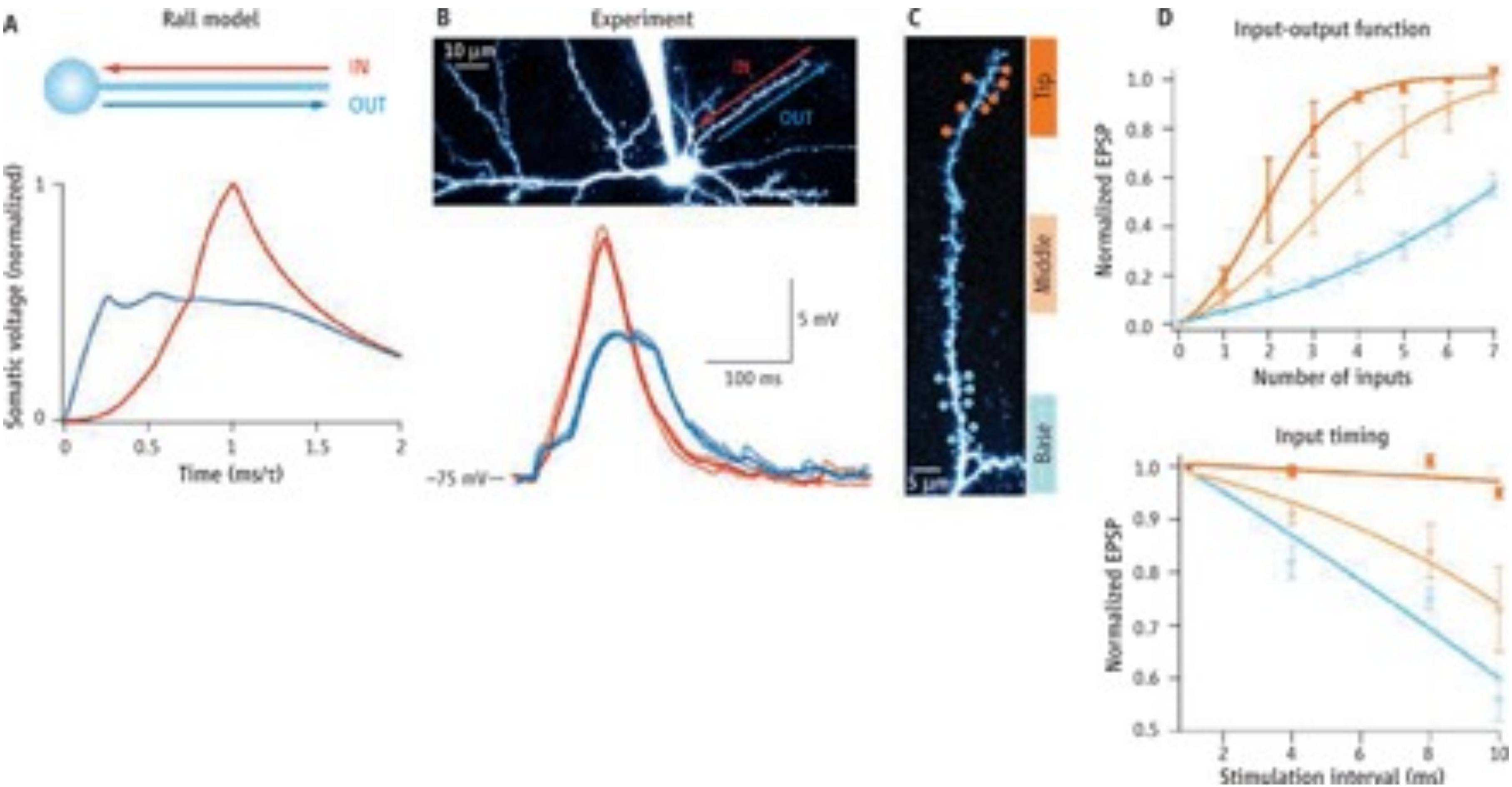
(fig. from Anderson, *Intr. Neur. Nets*)

Slow Potential Neuron



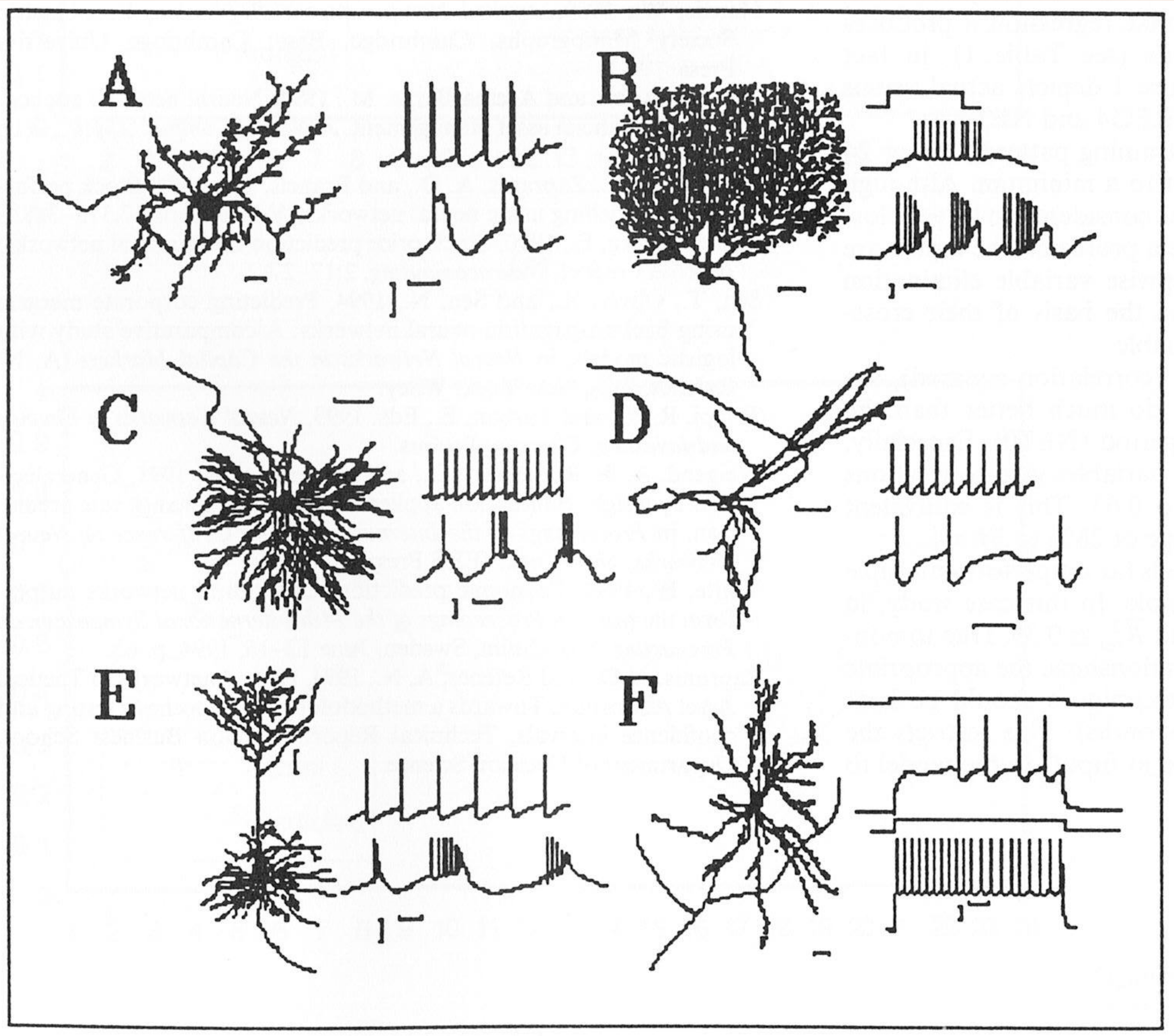
(fig. < Anderson, *Intr. Neur. Nets*)

Dendritic computation in pyramidal cells.



T Branco Science 2011;334:615-616

Variations in Spiking Behavior



Computational Formulation

Membrane Potential

$$\text{Currents: } I_x = g_x\left(E_x - V_m\right), \quad x = e,\ i,\ l$$

$$\text{Net current: } I_{\text{net}} = I_e + I_i + I_l$$

Change in membrane potential: $\dot{V}_m = C^{-1} I_{\text{net}}$ (C^{-1} is rate constant)

$$\dot{V}_m = C^{-1}[g_e(E_e - V_m) + g_i(E_i - V_m) + g_l(E_l - V_l)]$$

$$\text{Equilibrium } V_m = \frac{g_e E_e + g_i E_i + g_l E_l}{g_e + g_i + g_l}$$

Relative vs. Absolute Conductances

- Previously, g_x was absolute conductance (measured in nanosiemens)
- More convenient to represent as product $\bar{g}_x \, g_x(t)$
  - — where $\bar{g}_x$ is the absolute maximum conductance (all channels open)
  - — and $g_x(t)$ is the relative conductance at a given time, $0 \le g_x(t) \le 1$

$$V_m = \frac{\bar{g}_e g_e(t)}{\bar{g}_e g_e(t) + \bar{g}_i g_i(t) + \bar{g}_l} E_e + \frac{\bar{g}_i g_i(t)}{\bar{g}_e g_e(t) + \bar{g}_i g_i(t) + \bar{g}_l} E_i + \frac{\bar{g}_l}{\bar{g}_e g_e(t) + \bar{g}_i g_i(t) + \bar{g}_l} E_l$$

Discrete Spiking

if $Vm > \theta$ then
    $y := 1;$
    $Vm := Vm_r;$
else $y := 0;$

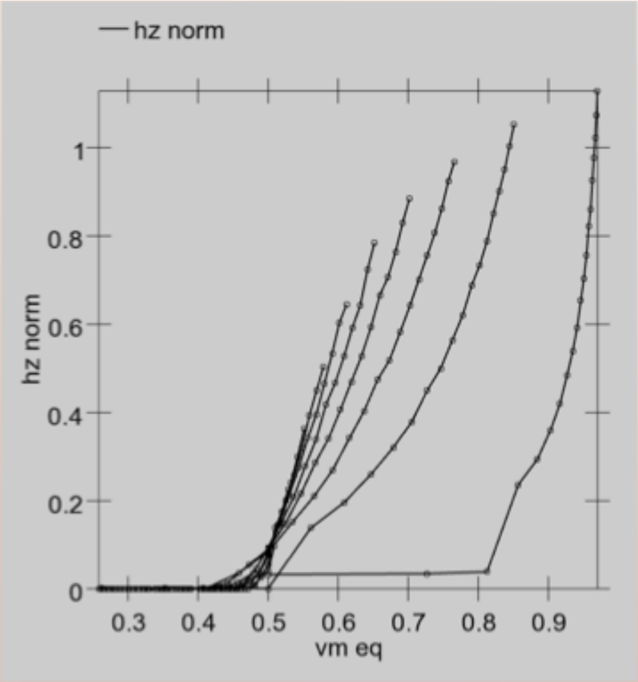
Rate Code Approximation

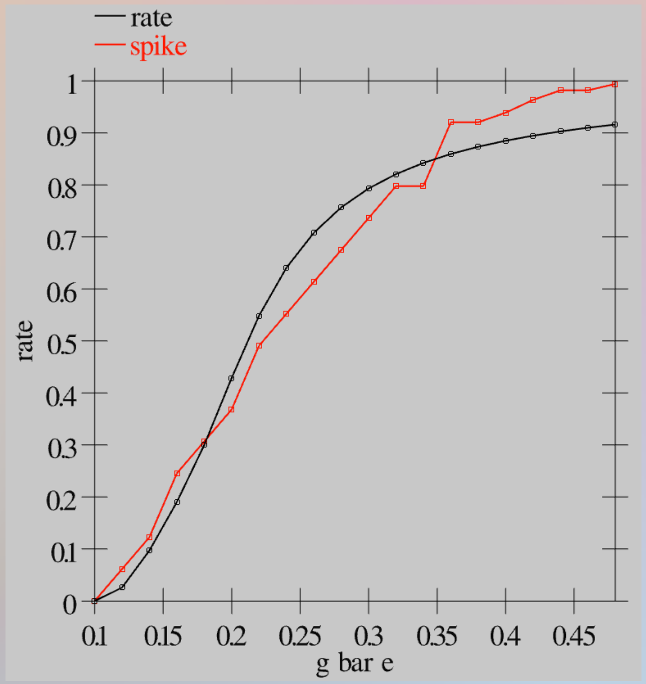
- Brain likes spikes, but rates are more convenient
  — Instantaneous and steady – smaller, faster models
  — But definitely lose several important things
  — Solution: do it both ways, and see the differences
- Goal: equation that makes good approximation of actual spiking rate for same sets of inputs

(slide based on O'Reilly)

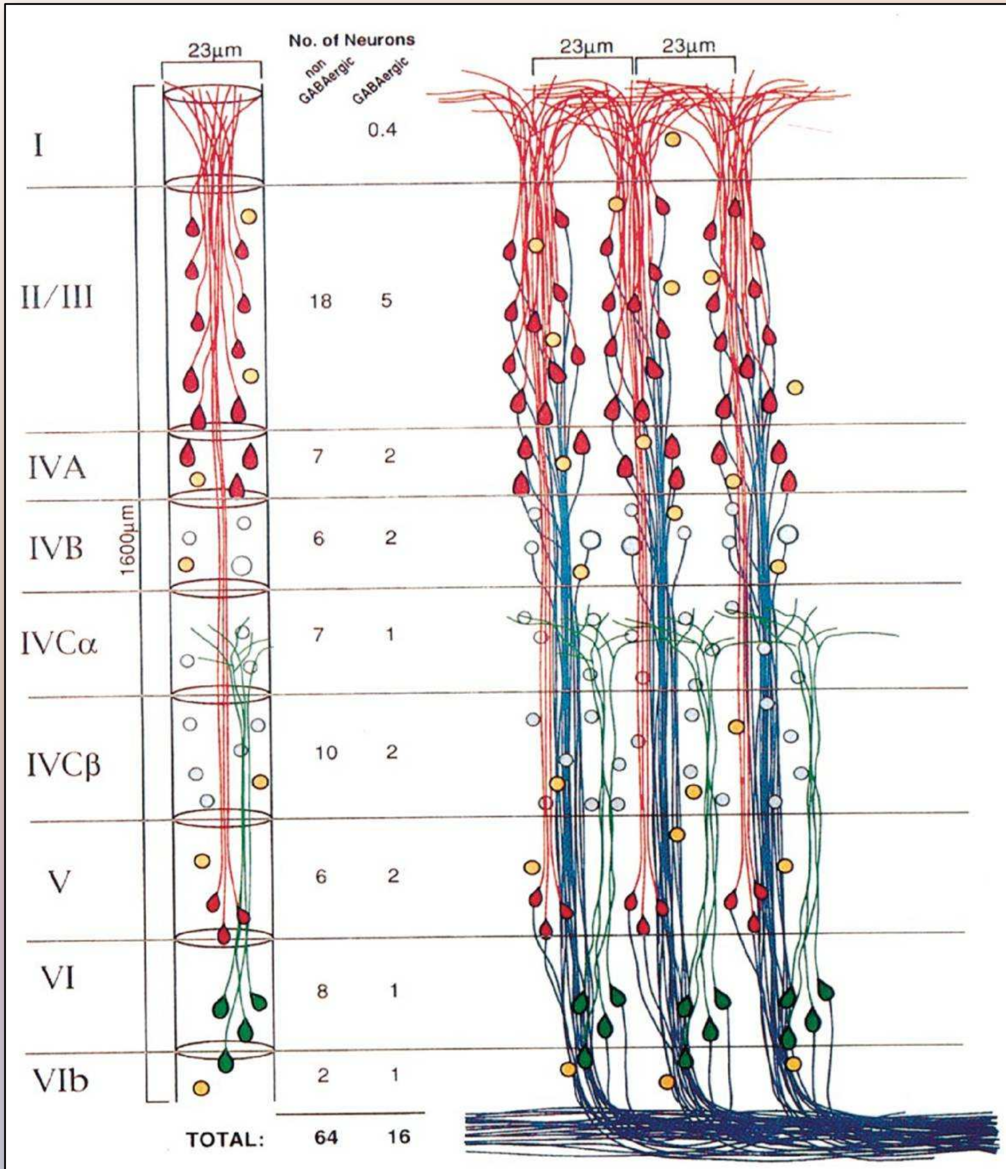
Rate Code Approximation

- Rate-coded (simulated) neurons:
  - short-time avg spike frequency ≈
  - avg behavior of minicolumn (~100 neurons) with similar inputs and output behavior
- Rate not predicted well by V_m
- Predicted better by g_e relative to a threshold value g_e^θ





Minicolumn



- Up to ~100 neurons
  - 75–80% pyramidal
  - 20–25% interneurons
- 20–50µ diameter
- Length: 0.8 (mouse) to 3mm (human)
- ~ 6×10^5 synapses
- 75–90% synapses outside minicolumn
- Interacts with 1.2×10^5 other minicolumns
- Mutually excitable
- Also called *microcolumn*

Intracortical Connections

- Dendrites extend 2–4 minicol. diameters
- Axons extend 5× (or even 30–40× minicol. diameter
- Periodic spacing of axon terminal clusters causes entrainment
- ~ 2×10^7 connections to macrocolumn

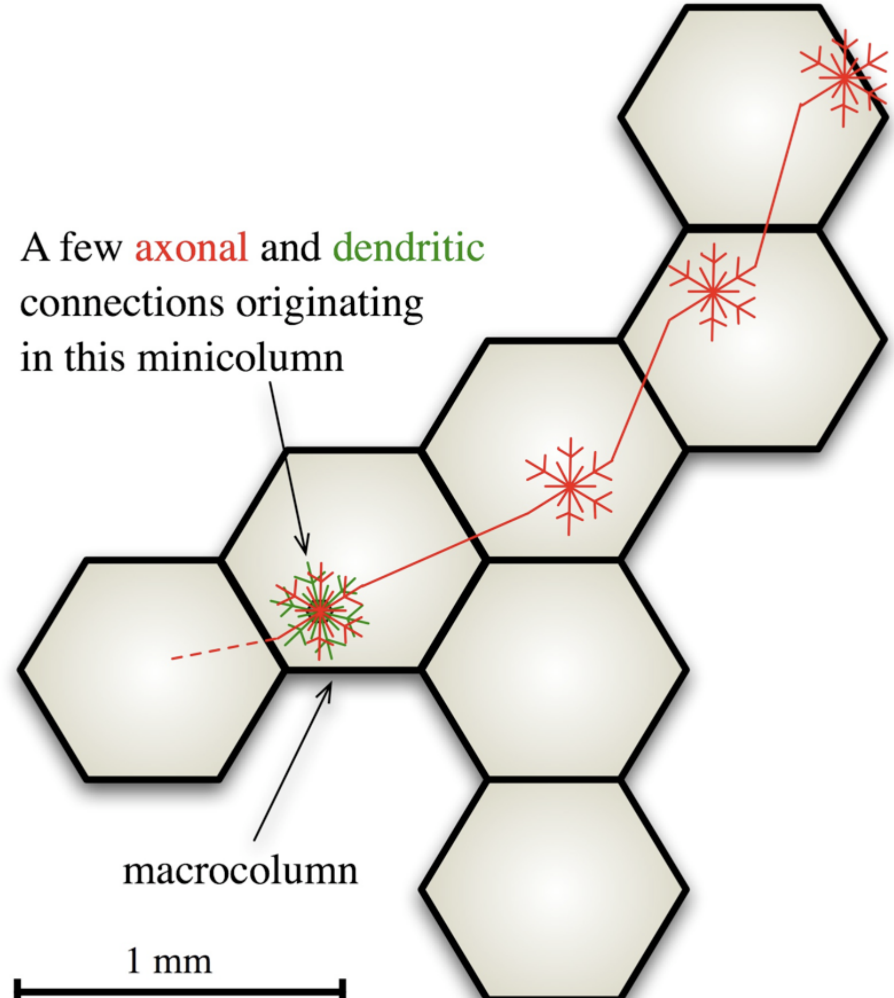
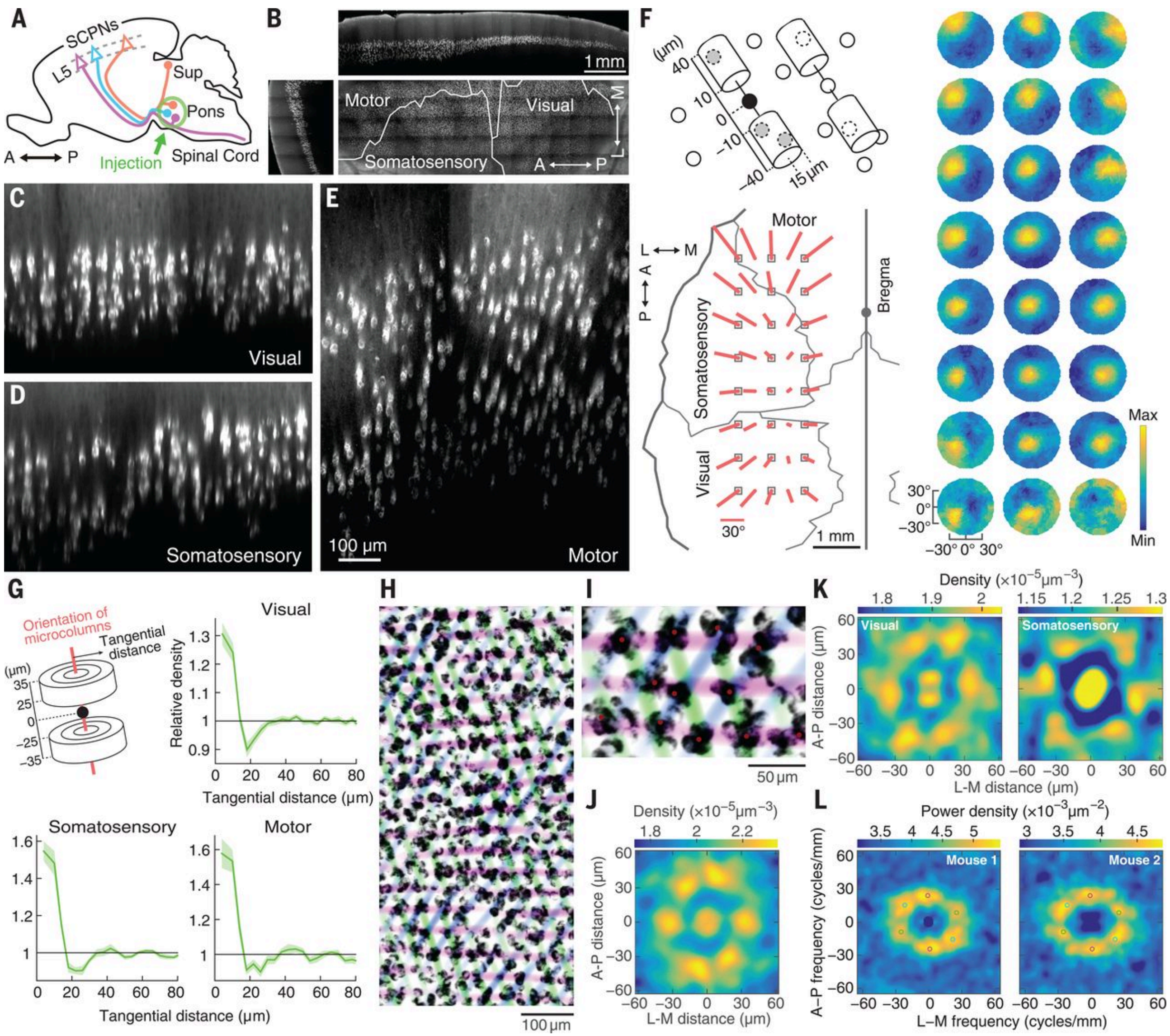


Fig. 1 Lattice organization of SCPN microcolumns.



Hisato Maruoka et al. Science 2017;358:610-615

Fig. 3 Synchronized activity in SCPN microcolumns.

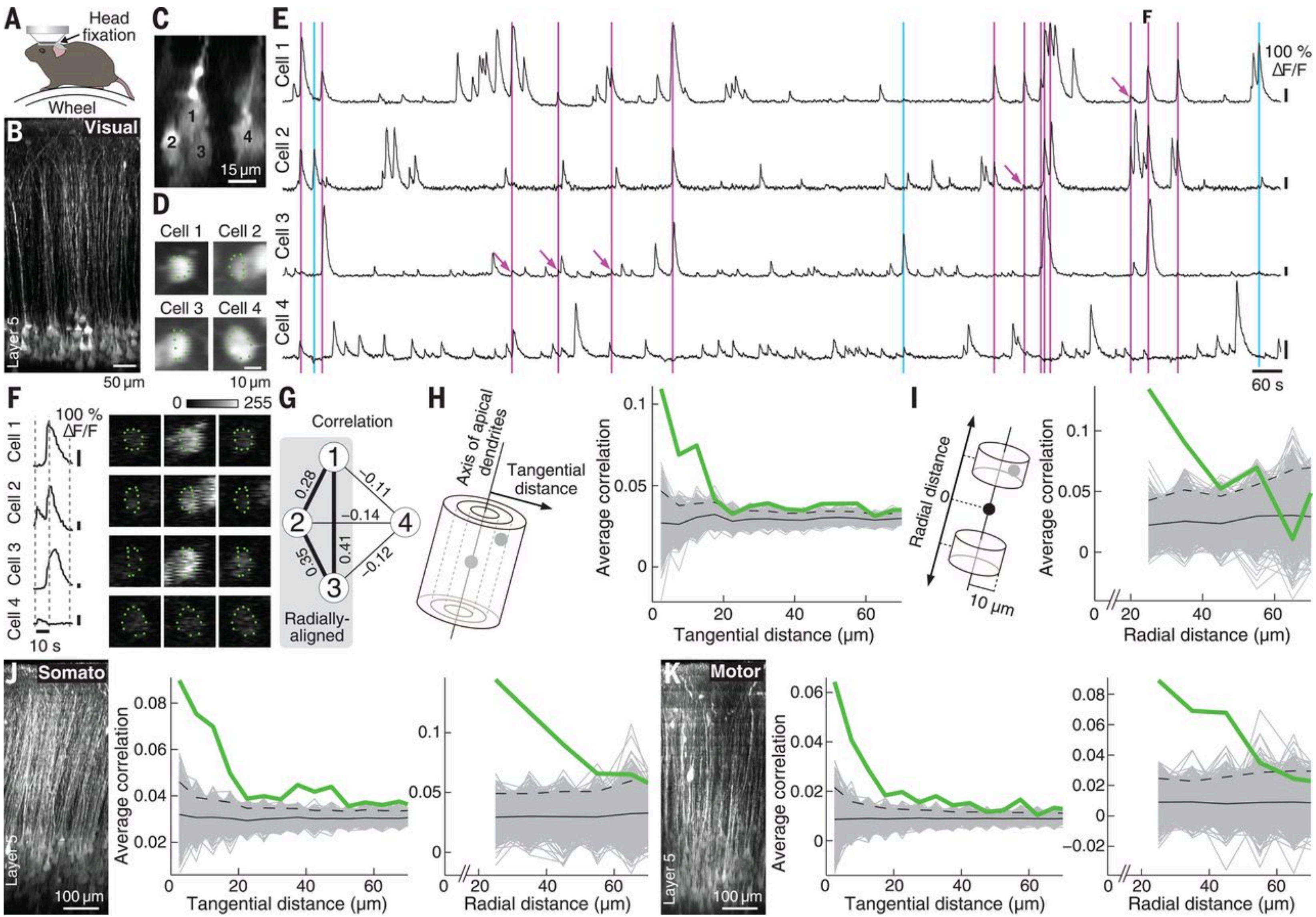


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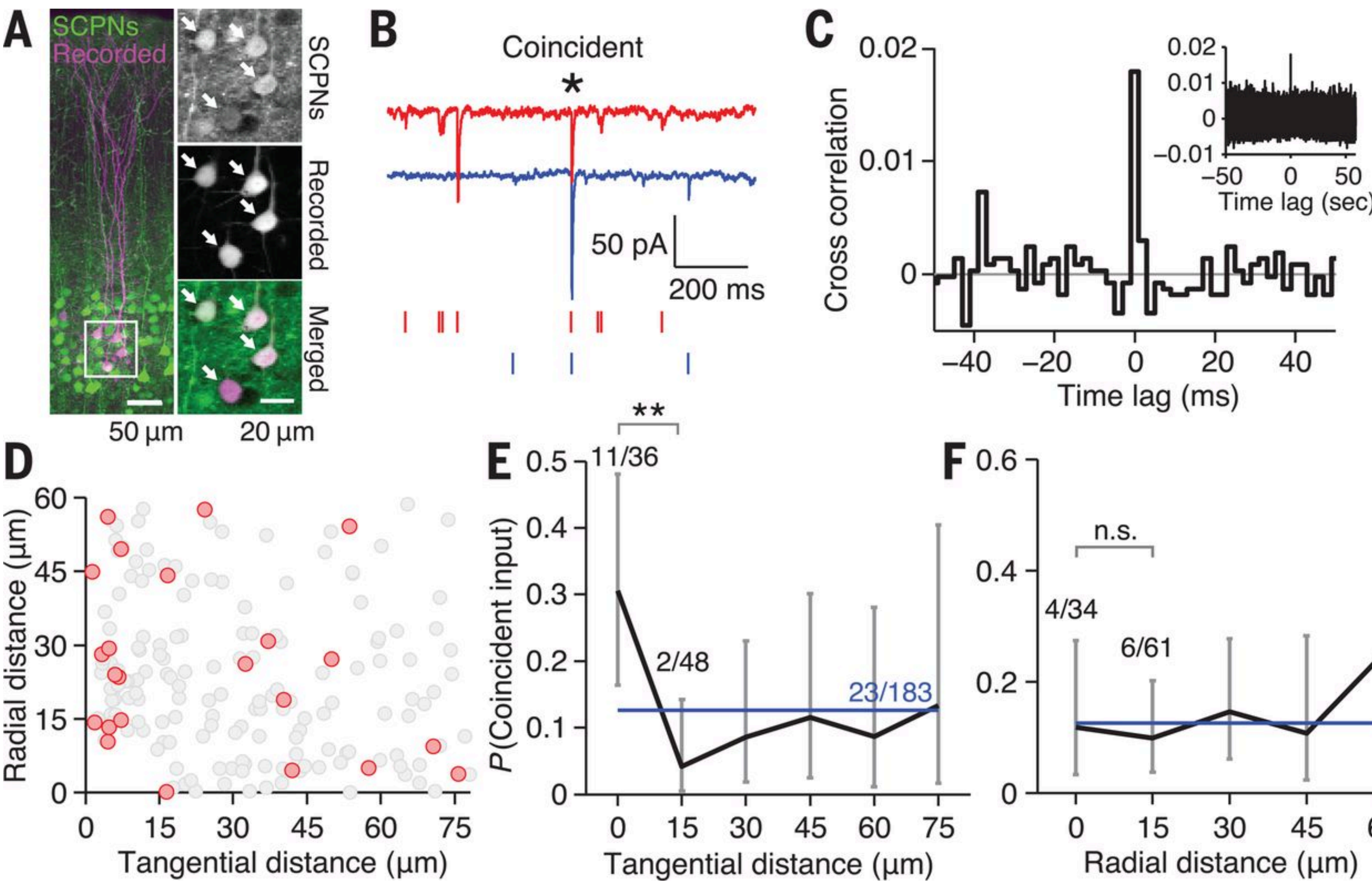
Fig. 5 Convergent strong inputs to SCPN microcolumns.



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Rate Code Approximation

- g_e^{θ} is the conductance when $V_m = \theta$
- Rate is a nonlinear function of relative conductance
- What is f?

$$\theta = \frac{g_e^{\theta} E_e + g_i E_i + g_l E_l}{g_e^{\theta} + g_i + g_l}$$

$$g_e^{\theta} = \frac{g_i \left(E_i - \theta\right) + g_l \left(E_l - \theta\right)}{\theta - E_e}$$

$$y = f\left(g_e - g_e^{\theta}\right)$$

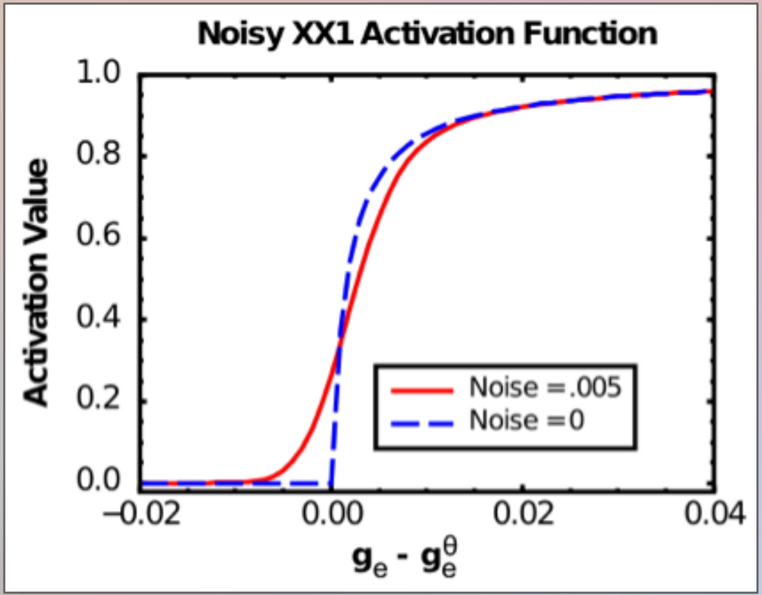
Activation Function

- Desired properties:
  - threshold (~0 below threshold)
  - saturation
  - smooth
- Smooth by convolution with Gaussian to account for noise
- Activity update:

$$y_{t+1} = y_t + C(y - y_t)$$

$$y = \frac{x}{x+1} \quad \text{where} \quad x = \eta\left[g_e - g_e^\theta\right]^+$$

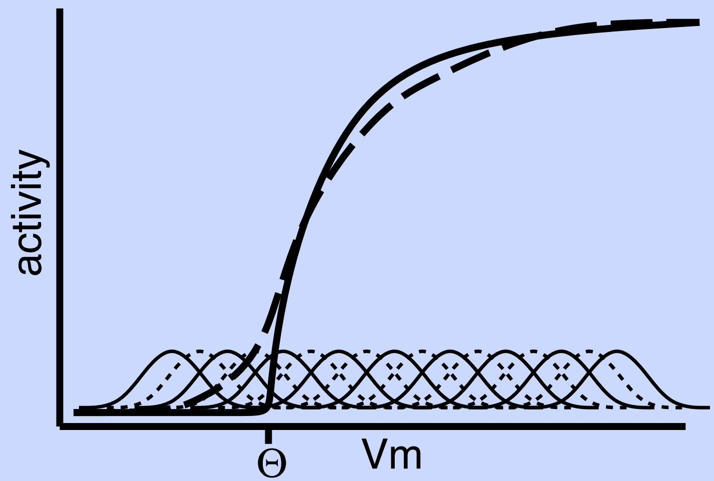
$$y = \frac{1}{1 + \frac{1}{\eta\left[g_e - g_e^\theta\right]^+}}$$

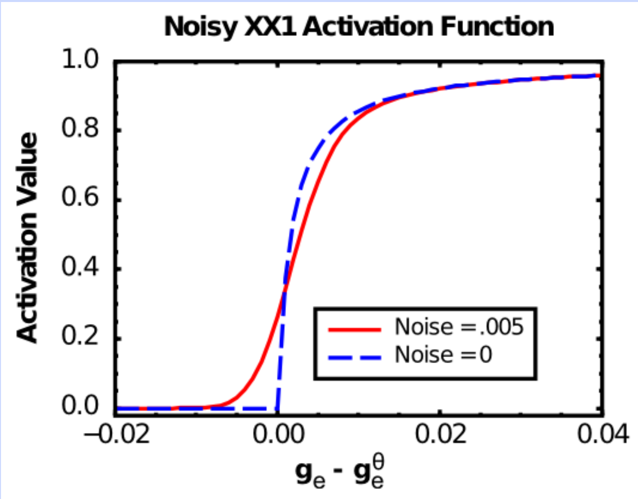


Gaussian Smoothing

X-over-X-plus-1 has a very sharp threshold

Smooth by *convolve* with noise (like "blurring" or "smoothing"):





$$y^*(x) = \int_{-\infty}^{\infty} \frac{1}{\sqrt{2\pi}\sigma} e^{-z^2/(2\sigma^2)} y(z-x)dz$$

(slide based on Frank)

Approximating Continuous Dynamics

- V_m changes gradually when input changes
- Firing rate $y(t)$ should also change gradually (subject to a time constant)
- Discrete-time update equation:

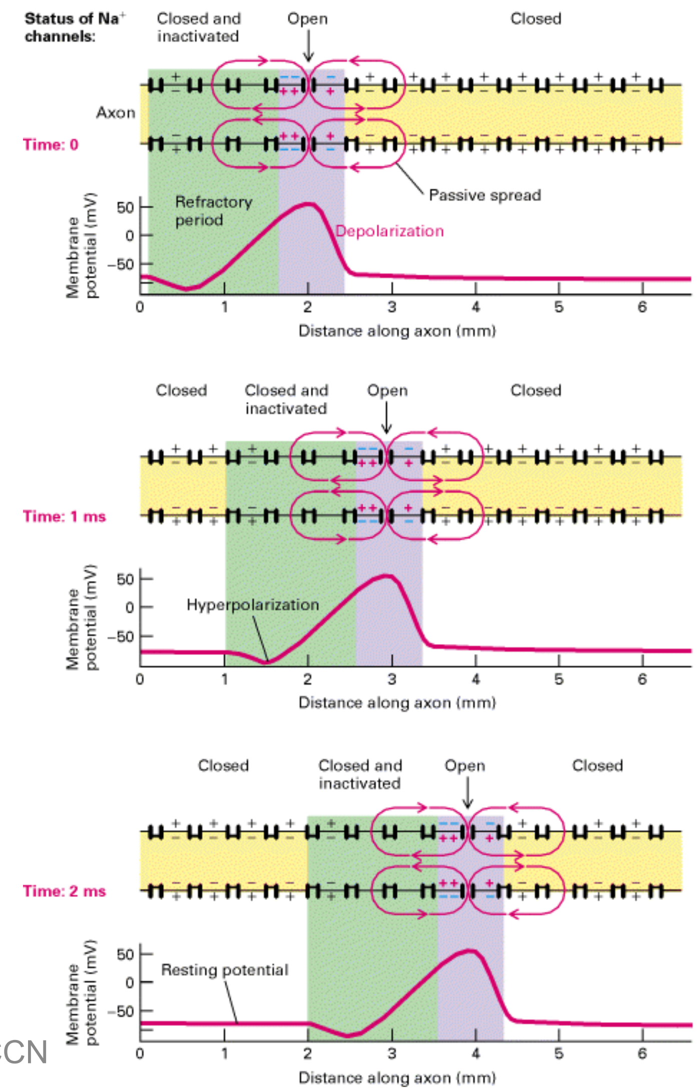
$$y(t) = y(t-1) + dt_{vm}\left(y^*(x) - y(t-1)\right)$$

emergent demonstration: Neuron

Supplementary: Mathematics of Action Potentials

Neural Impulse Propagation

$$
\begin{aligned}
C\frac{dv}{dt} &= I - g_{Na}m^3h(V - V_{Na}) - g_K n^4(V - V_K) - g_L(V - V_L) \\
\frac{dm}{dt} &= a_m(V)(1 - m) - b_m(V)m \\
\frac{dh}{dt} &= a_h(V)(1 - h) - b_h(V)h \\
\frac{dn}{dt} &= a_n(V)(1 - n) - b_n(V)n \\
a_m(V) &= .1(V + 40)/(1 - \exp(-(V + 40)/10)) \\
b_m(V) &= 4\exp(-(V + 65)/18) \\
a_h(V) &= .07\exp(-(V + 65)/20) \\
b_h(V) &= 1/(1 + \exp(-(V + 35)/10)) \\
a_n(V) &= .01(V + 55)/(1 - \exp(-(V + 55)/10)) \\
b_n(V) &= .125\exp(-(V + 65)/80)
\end{aligned}
$$



- ☝ Hodgkin-Huxley equations

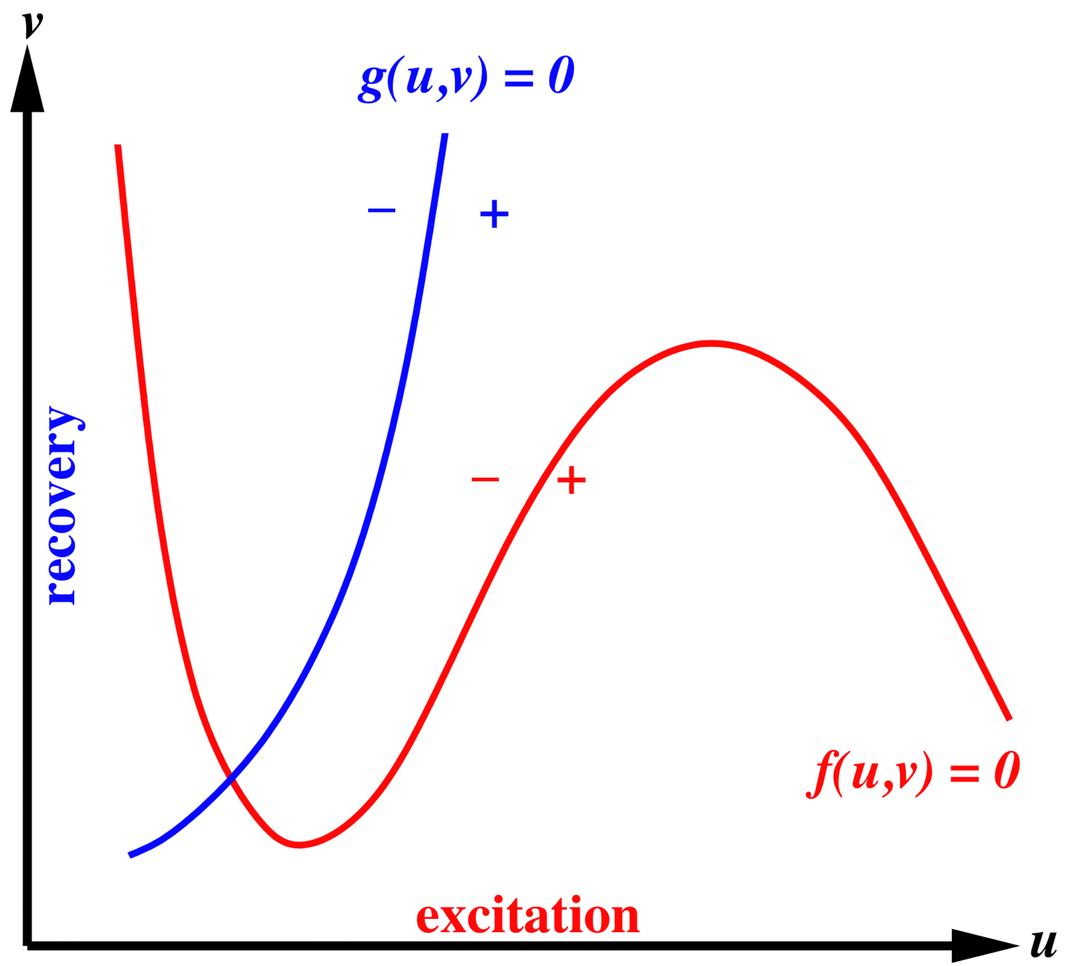
FitzHugh-Nagumo Model

- A simplified model of action potential generation in neurons
- The neuronal membrane is an excitable medium
- B is the input bias:

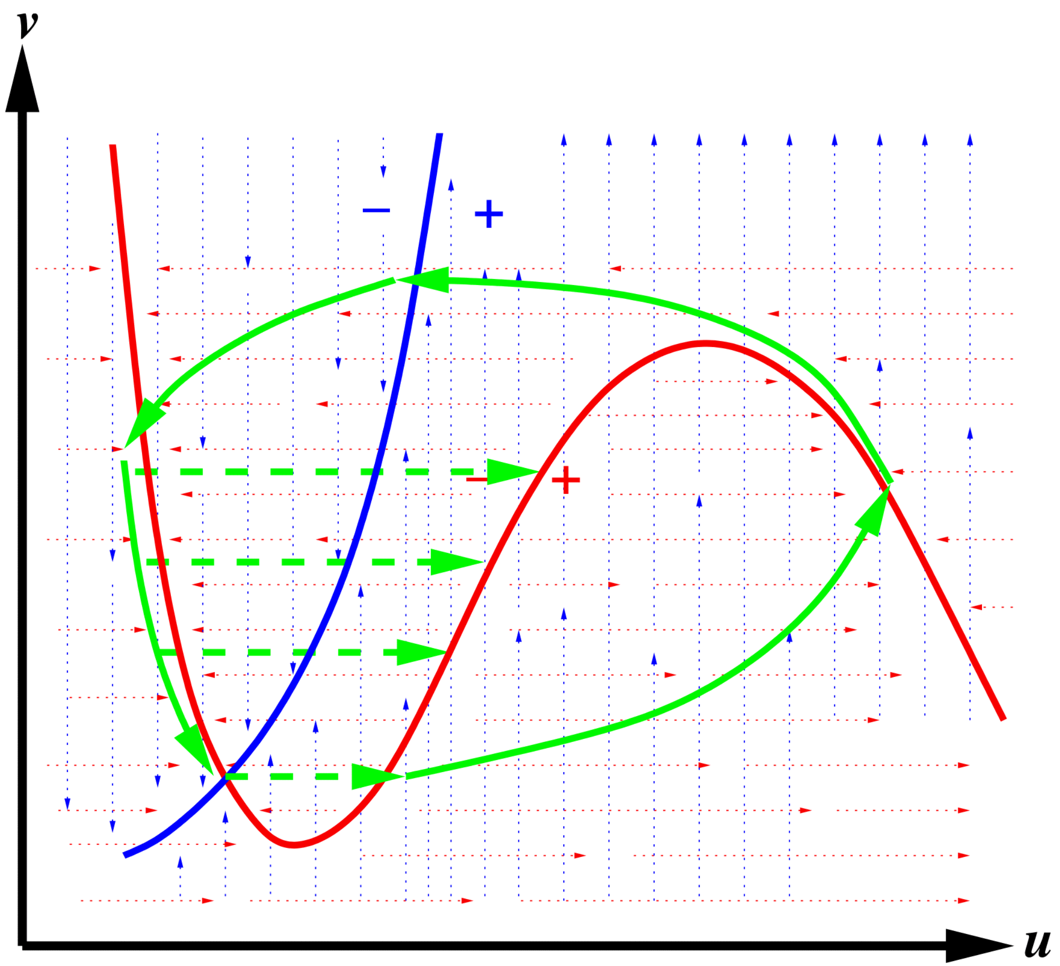
$$\dot{u} = u - \frac{u^3}{3} - v + B$$

$$\dot{v} = \varepsilon(b_0 + b_1 u - v)$$

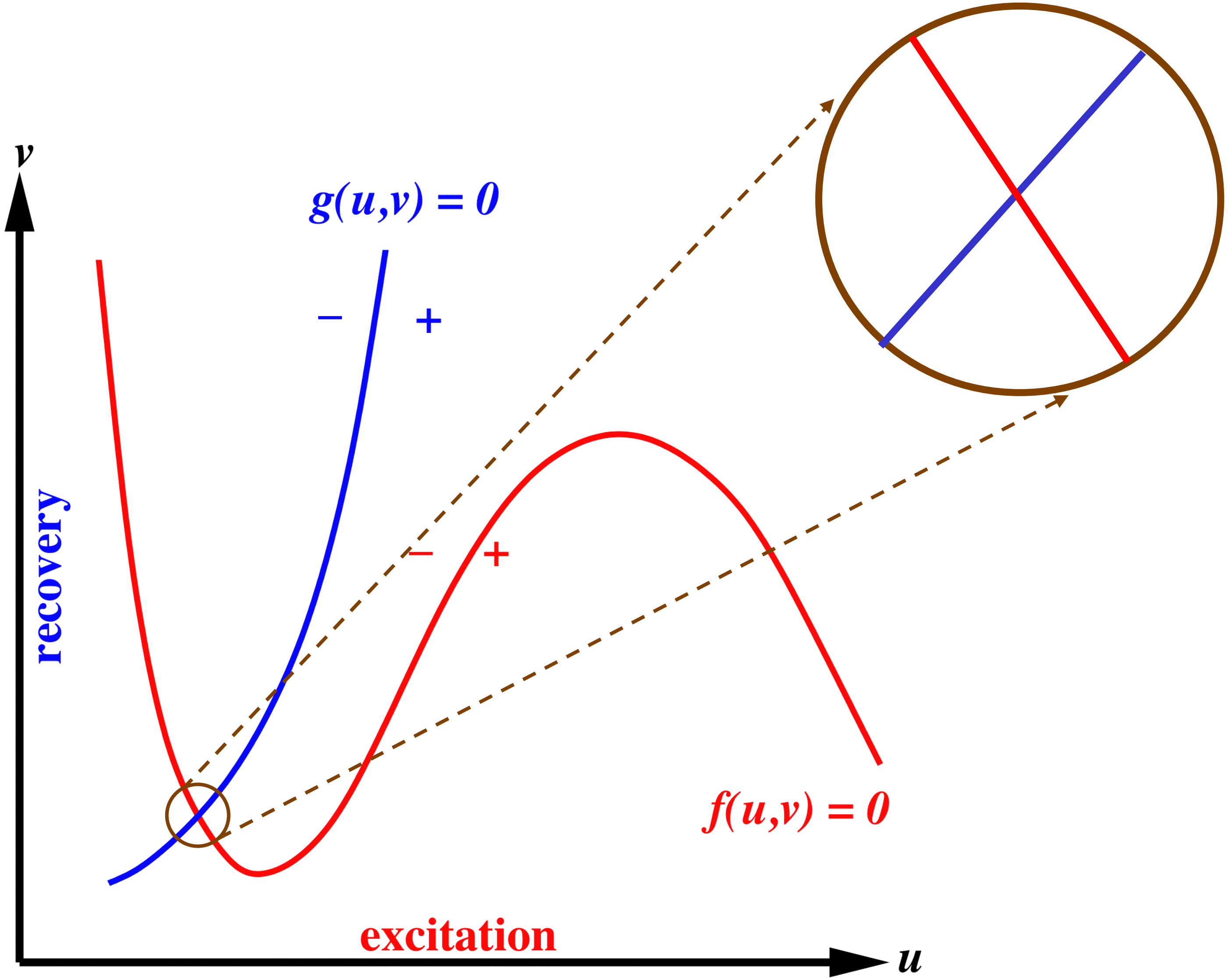
Nullclines



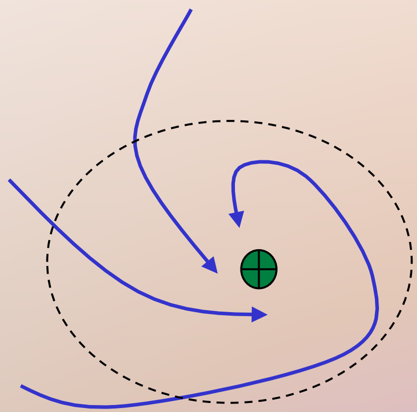
Elevated Thresholds During Recovery

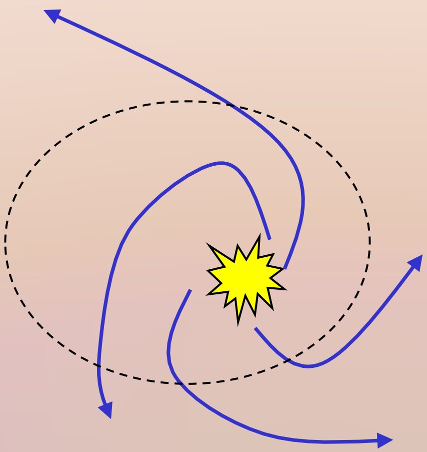


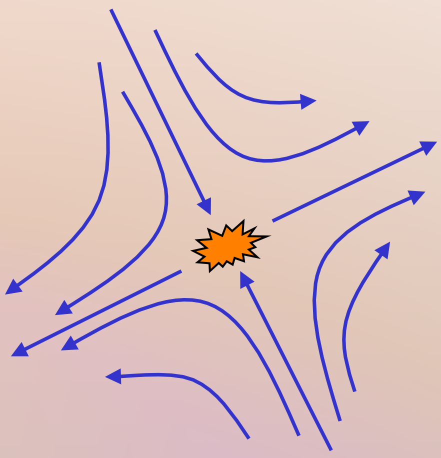
Local Linearization



Fixed Points & Eigenvalues

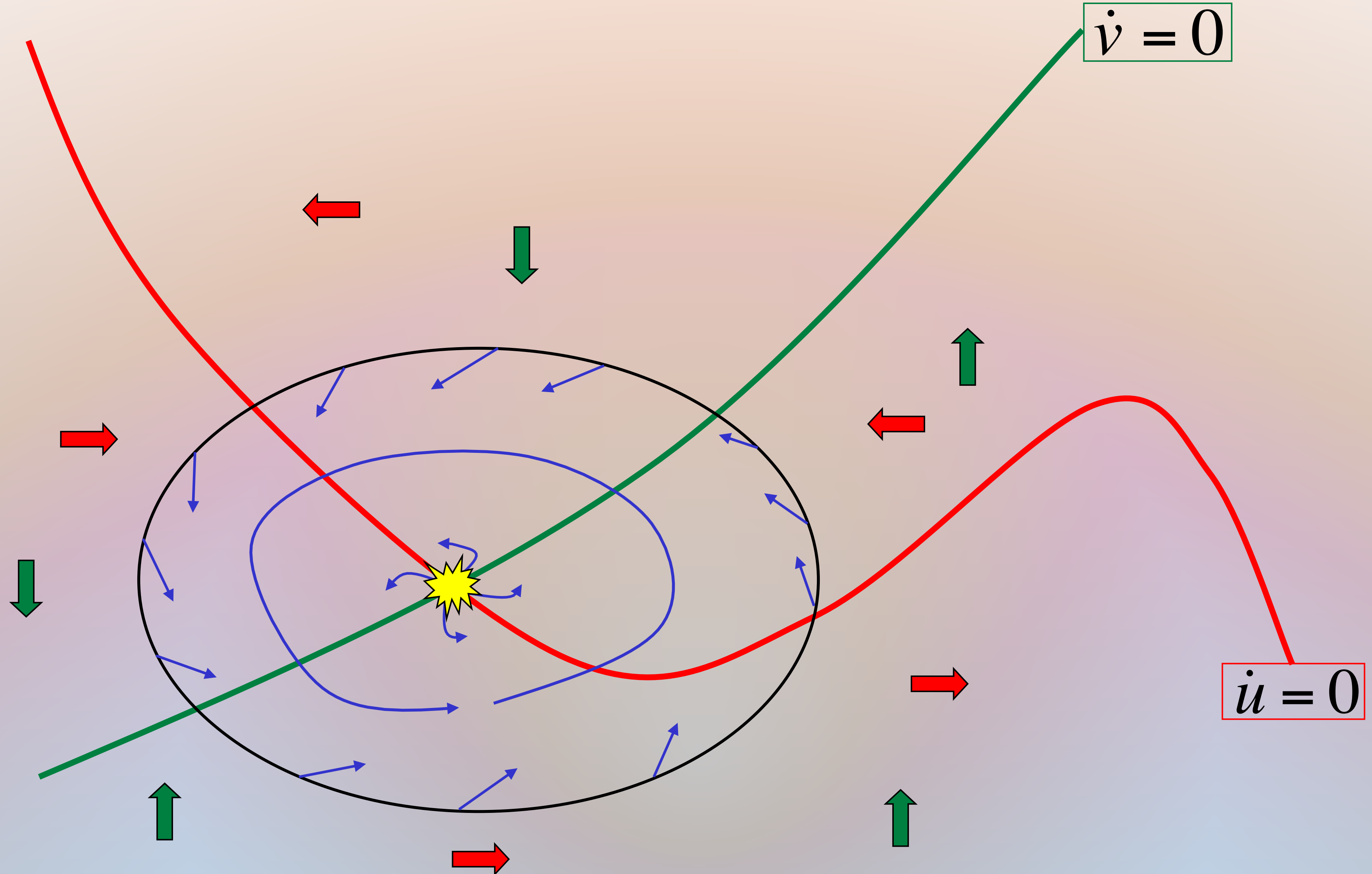






stable fixed point	**unstable fixed point**	**saddle point**
real parts of eigenvalues are negative	real parts of eigenvalues are positive	one positive real & one negative real eigenvalue

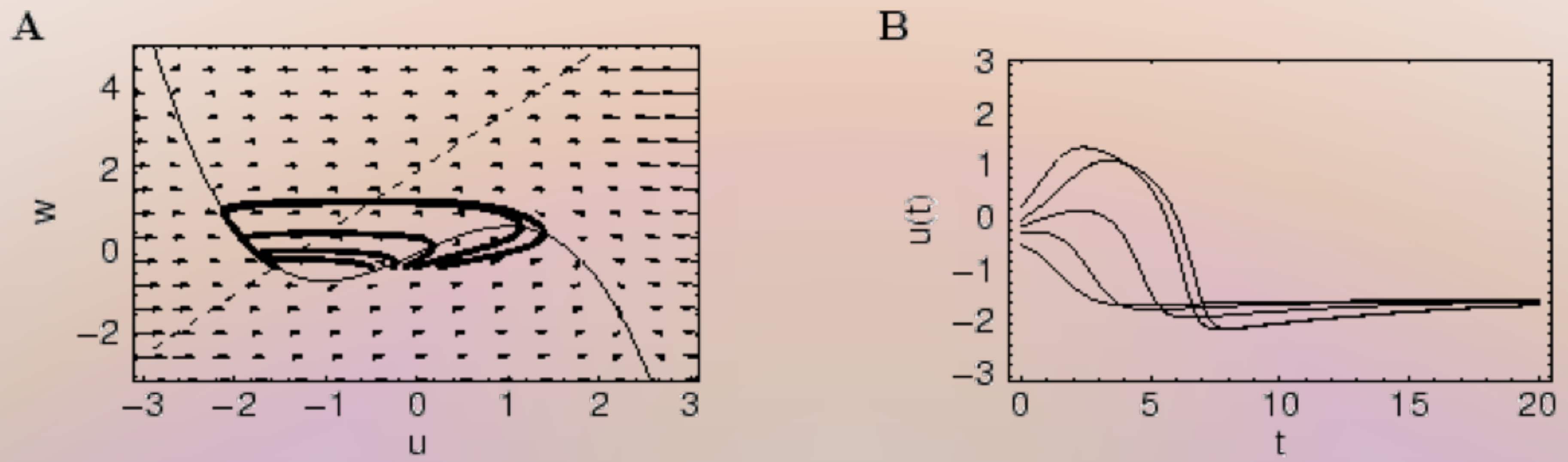
Poincaré-Bendixson Theorem



NetLogo Simulation of Excitable Medium in 2D Phase Space

(EM-Phase-Plane.nlogo)

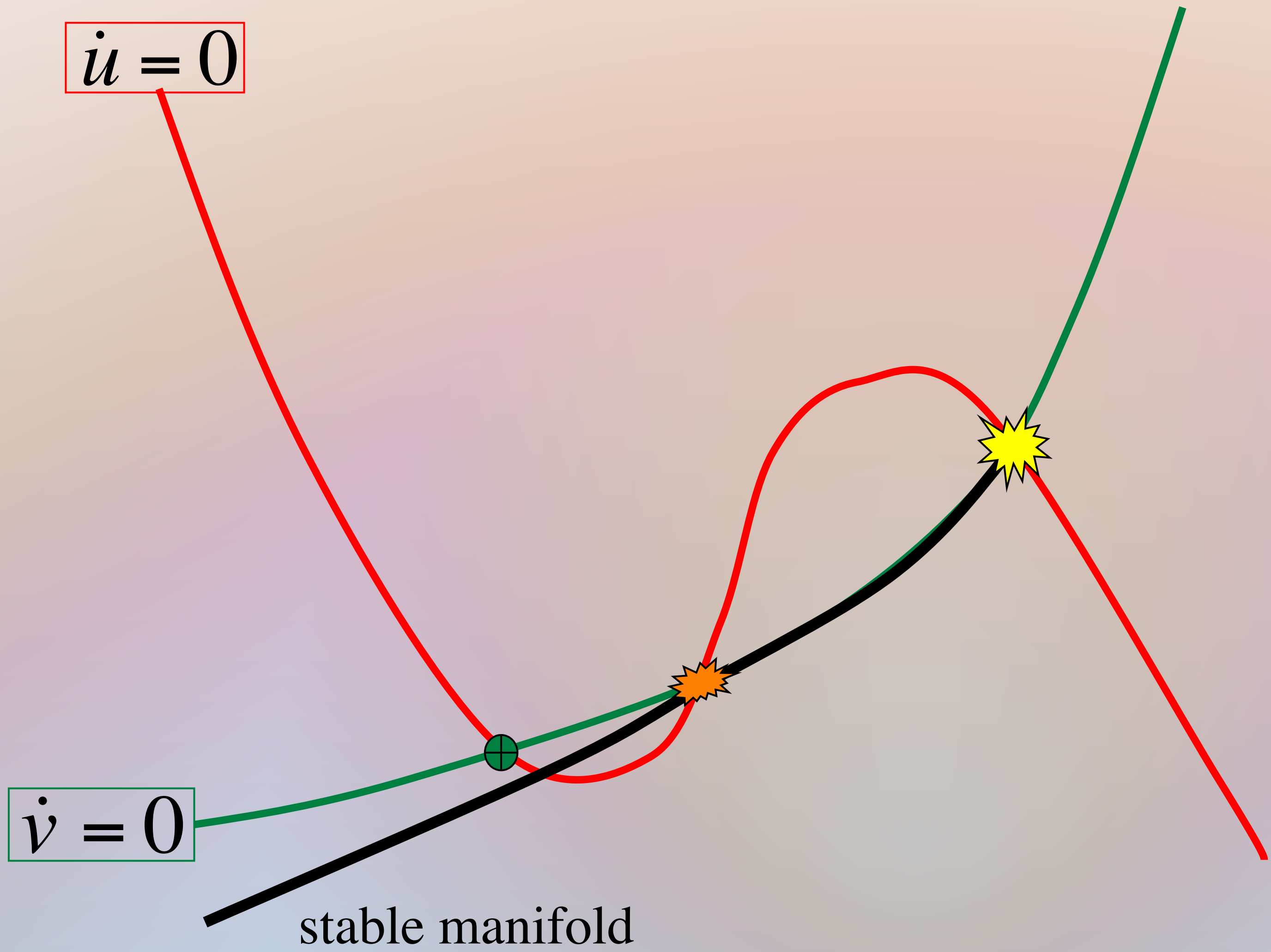
Type II Model



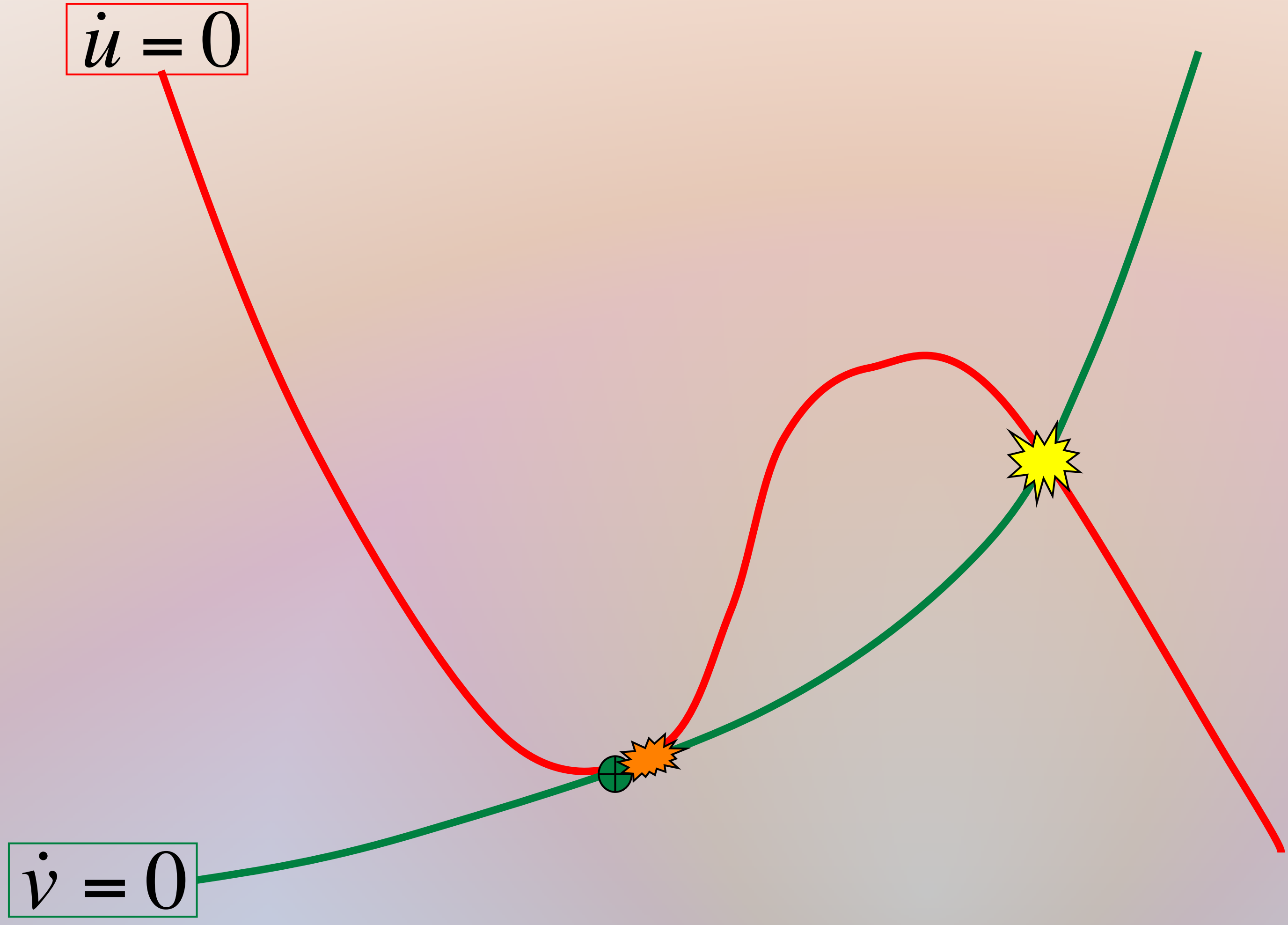
- Soft threshold with critical regime
- Bias can destabilize fixed point

(figs. < Gerstner & Kistler)

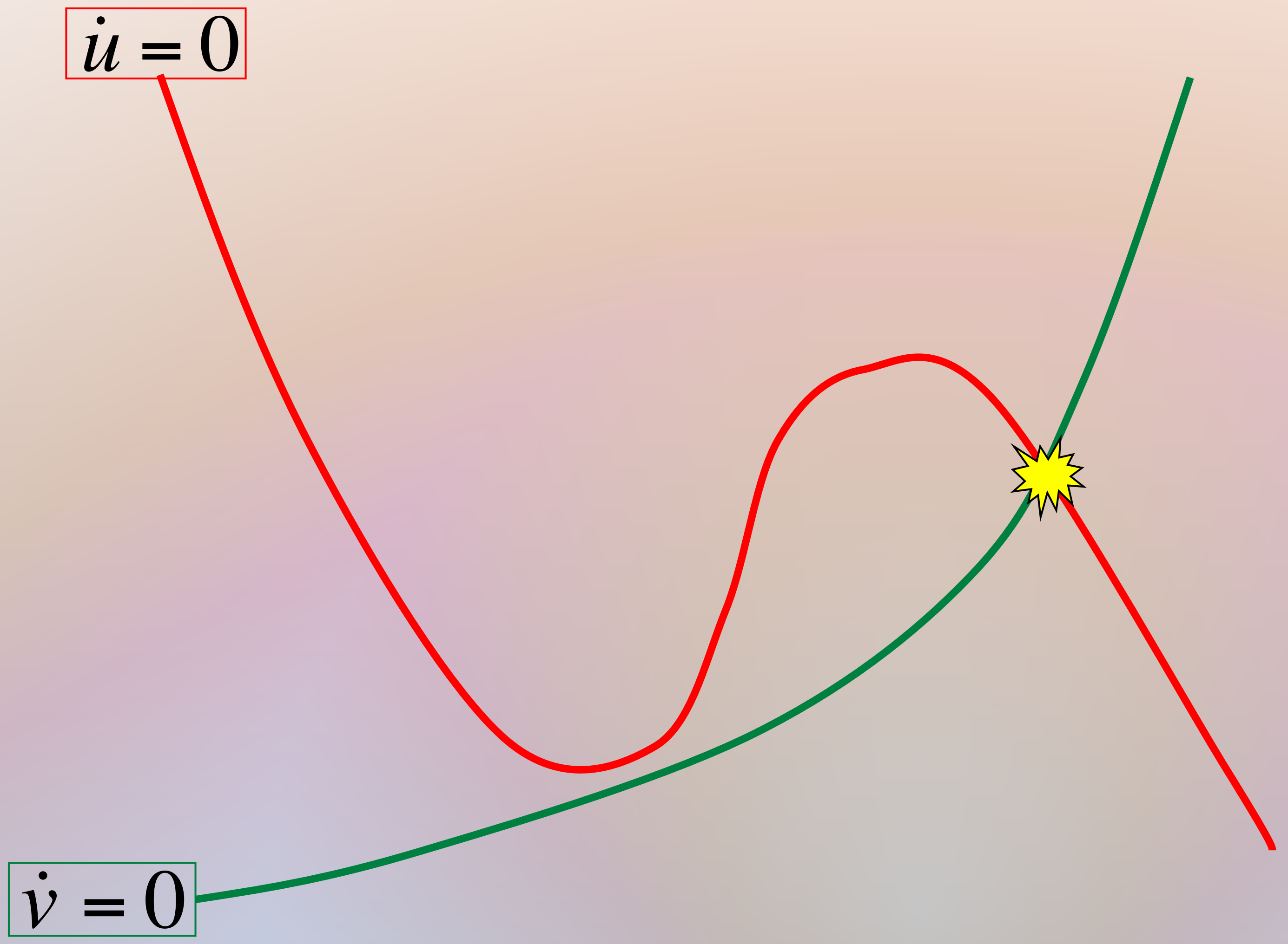
Type I Model



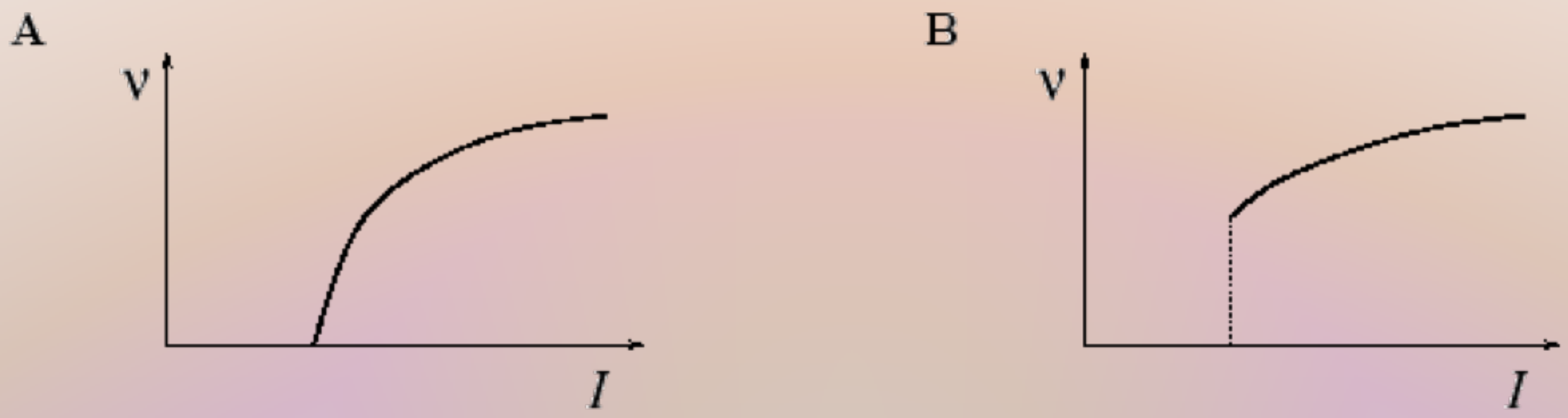
Type I Model (Elevated Bias)



Type I Model (Elevated Bias 2)



Type I vs. Type II



- Continuous vs. threshold behavior of frequency
- Slow-spiking vs. fast-spiking neurons

fig. < Gerstner & Kistler