INT3007: Systems Biology

Week 5

Modelling neural coding

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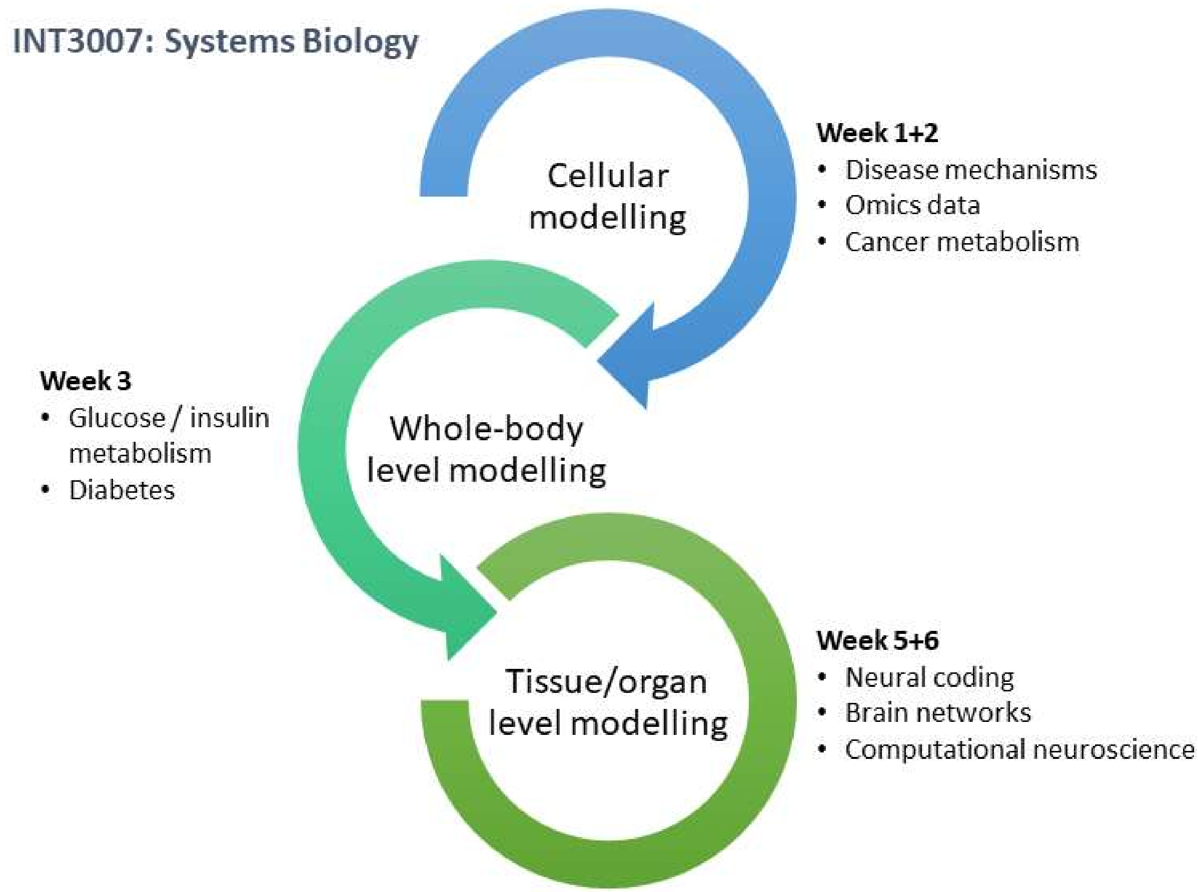
Modeling the brain



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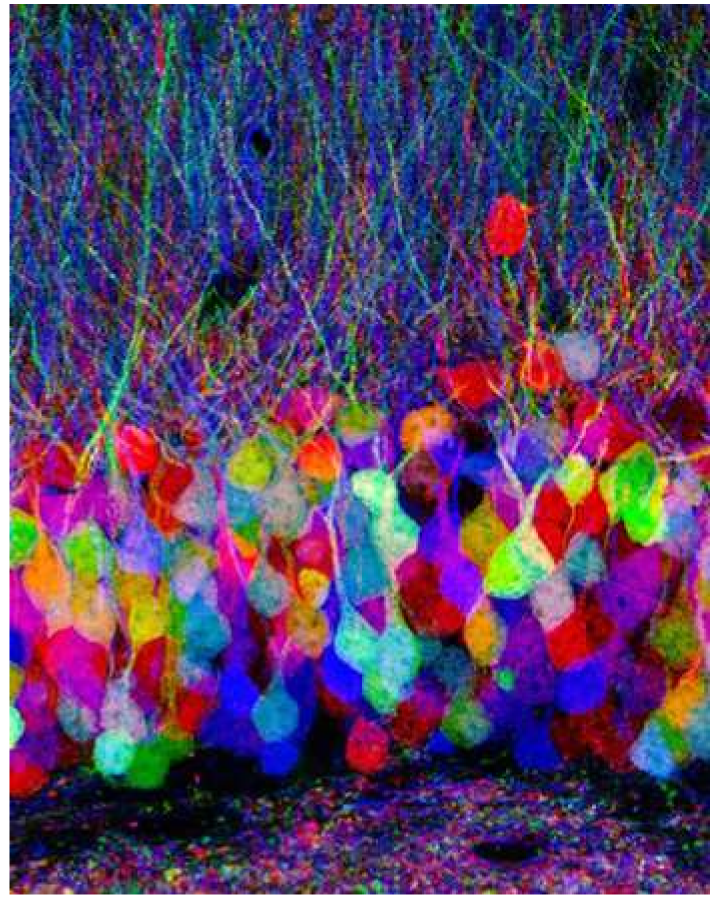
Overview

- **The brain as an organ to model**
  - Challenges
  - Current approaches
- **Single neuron models**
  - Hodgkin-Huxley model
  - Integrate-and-fire model
  - Compartmental modeling
- **Population level modeling**
  - Neural encoding
  - Wilson-Cowan model of the auditory cortex
- **Multiscale modeling**



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Why model the brain

- To **emulate**:

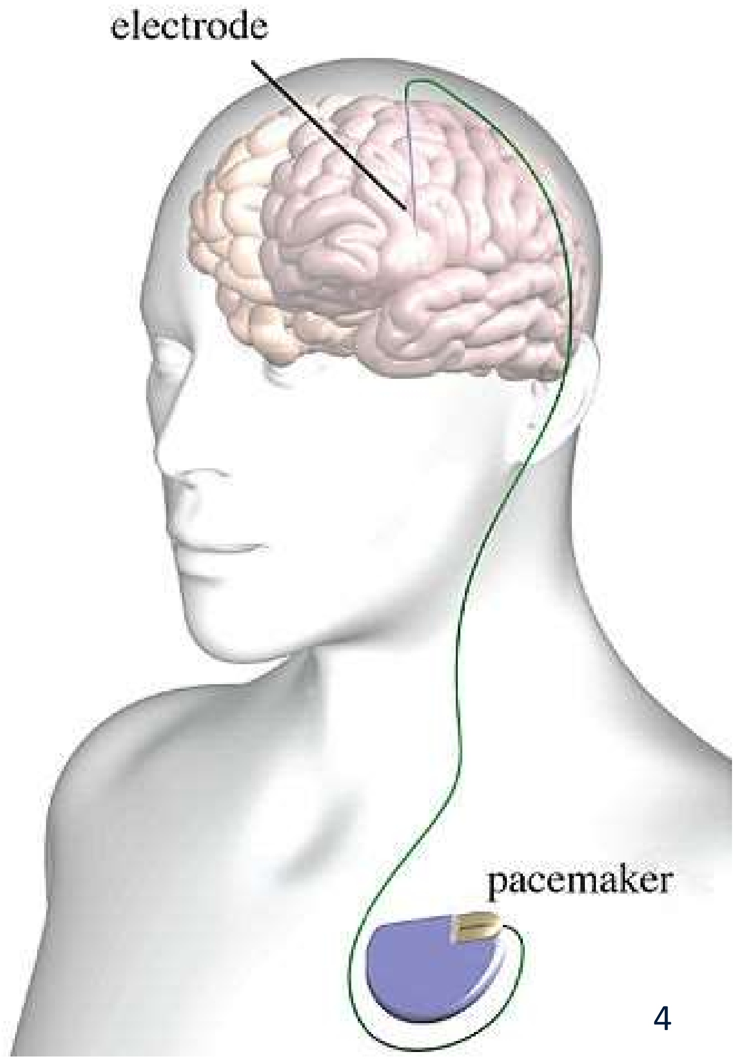
  new algorithms (e.g. deep learning)

- To **heal**:

  new therapies (e.g. deep brain stimulation)

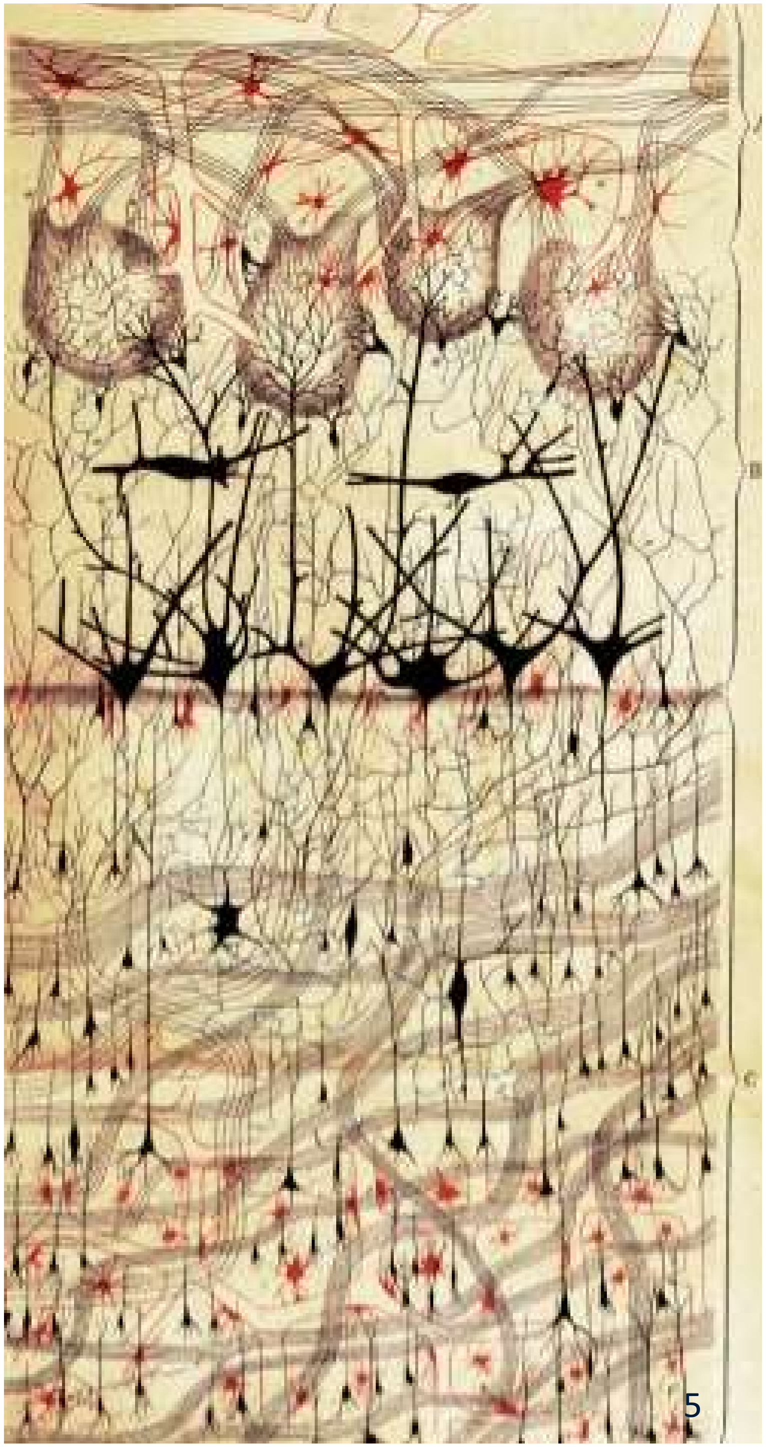
- To **understand**:

  new knowledge (e.g. learning)



The challenge

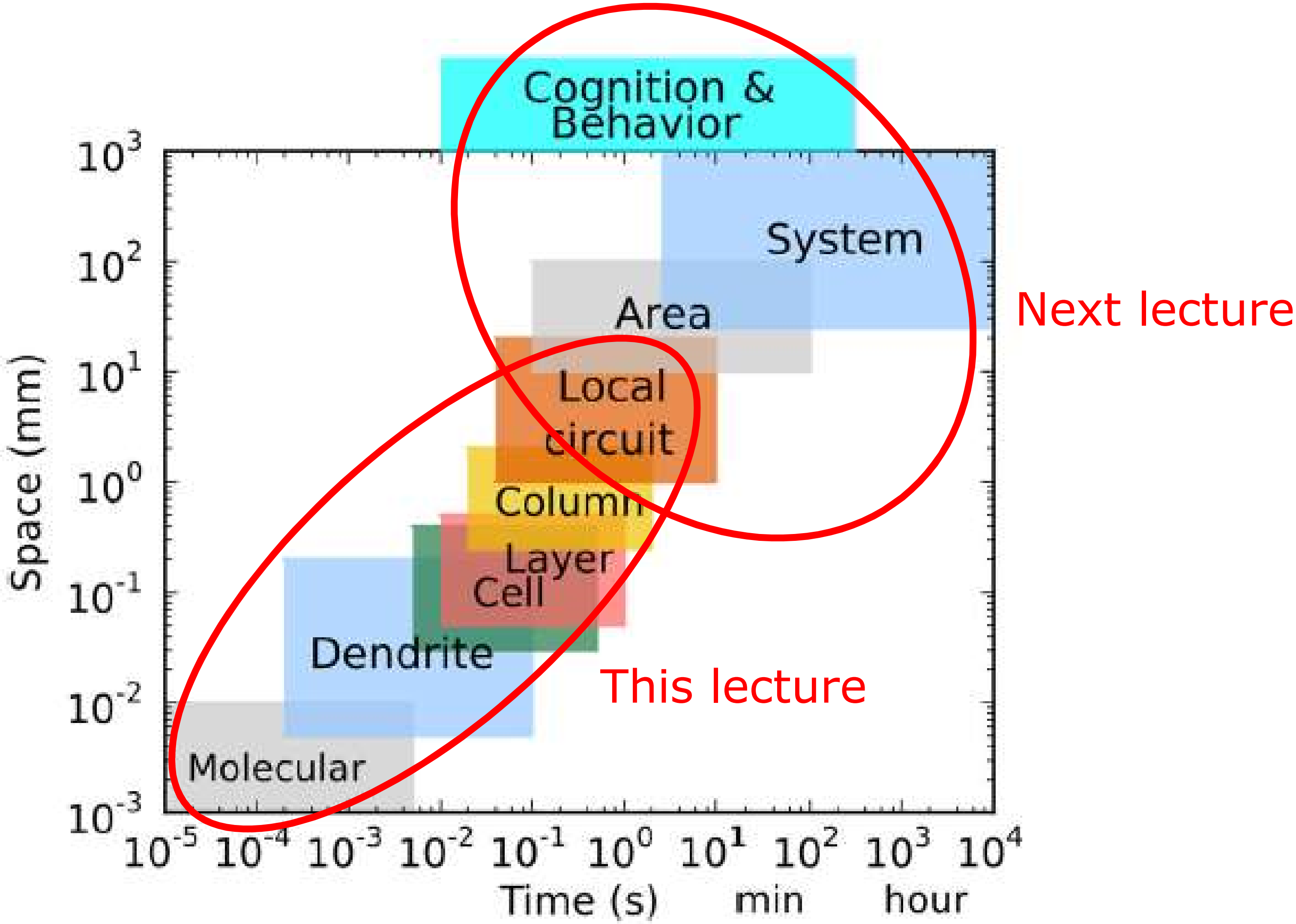
- The human brain is made of ~86 billion neurons
- Each neuron is connected to ~10,000 other neurons
- 1 mm^3 of cortex contains ~1 billion connections



Modeling the brain

Scales:

- Macro
- Meso
- Micro



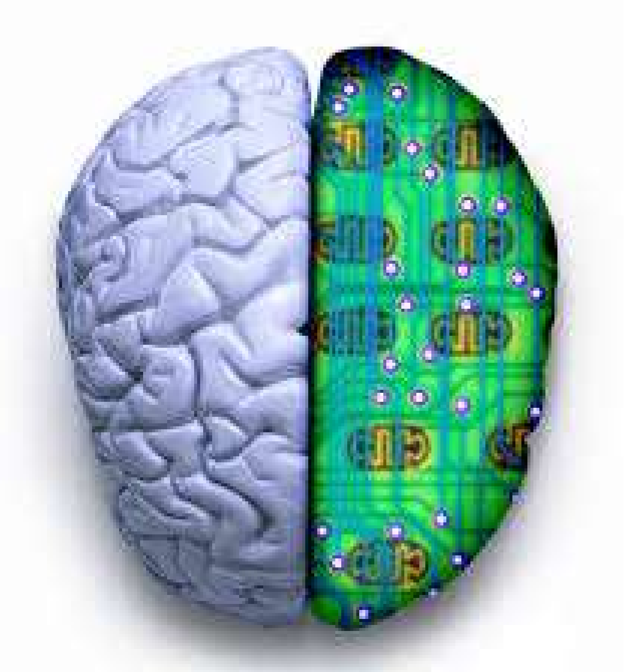
Systems Biology of Neuroscience

Neuroscience application has lagged behind

Due to specific challenges:

- Complexity of the research subject
- Traditions in existing field of computational neuroscience
- Lack of (human) data

Now catching up!



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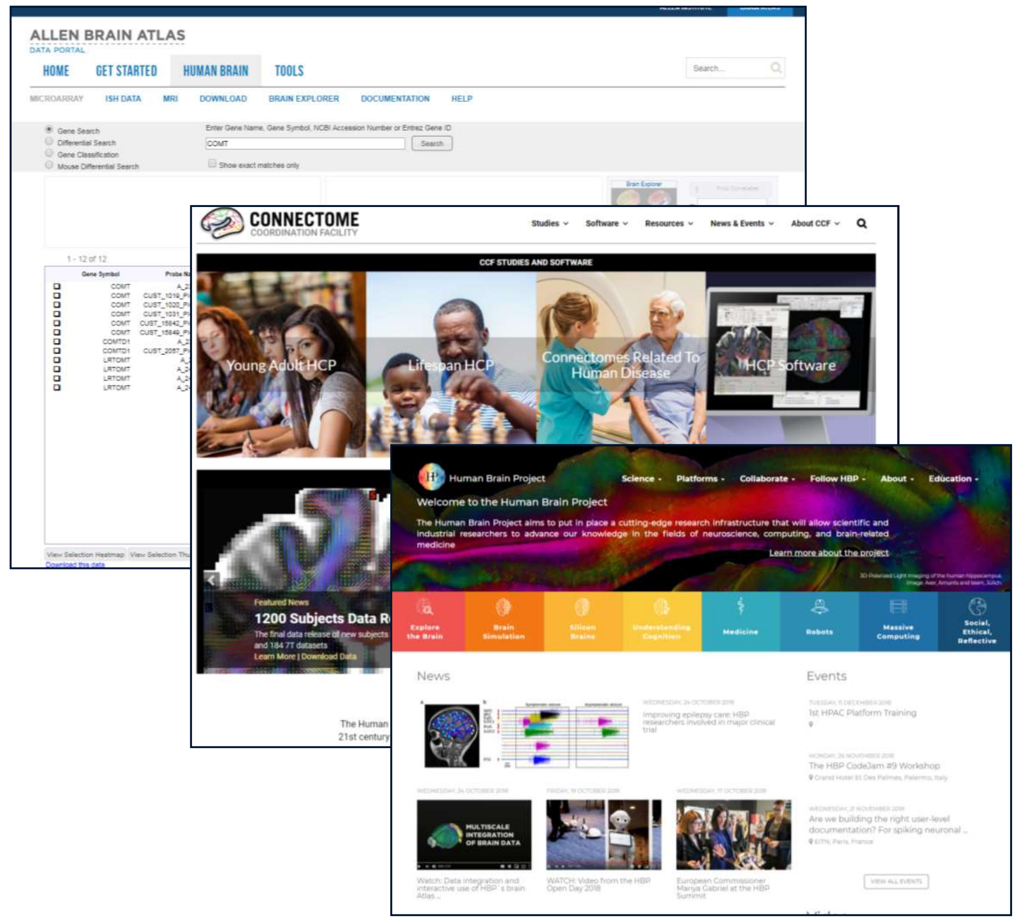
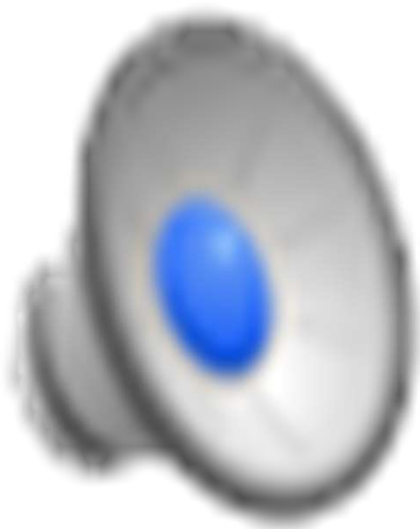
Current approaches

- Blue Brain project
- Human Brain Project
- Human Connectome project
- **Allen Brain Atlas**
- BrainSpan
- ENIGMA



Allen Brain Atlas



https://www.ted.com/talks/allan_jones_a_map_of_the_brain

TEDtalk Allan Jones
President and Chief Executive Officer of the Allen Institute

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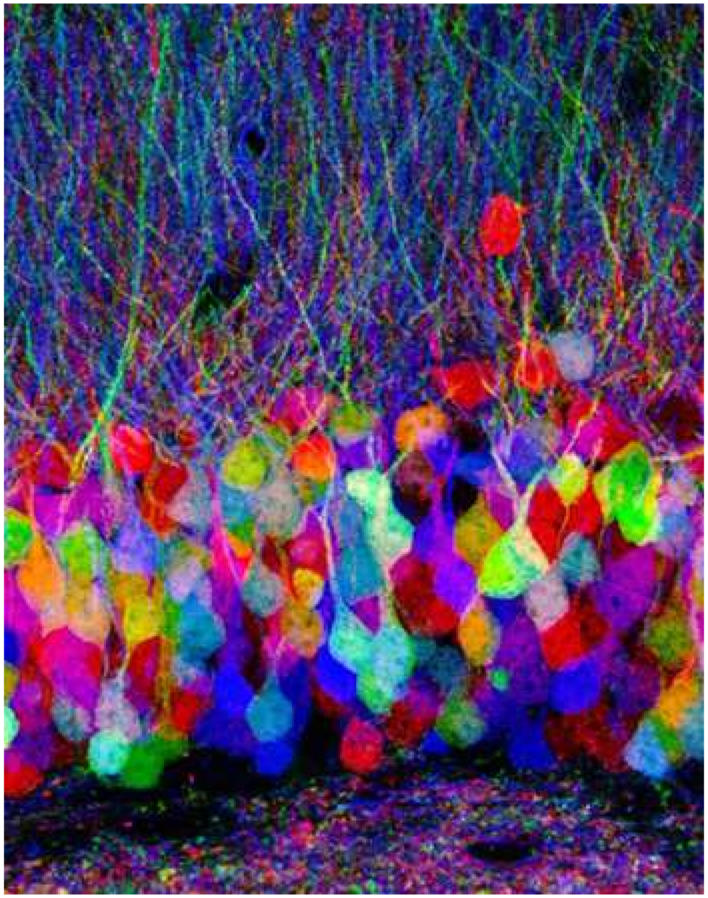

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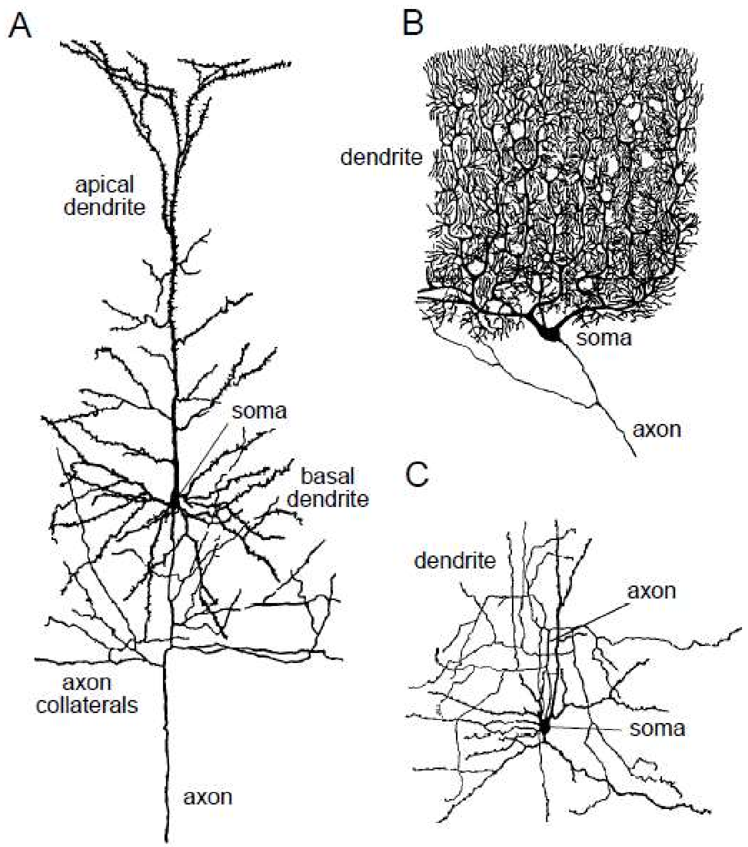
Single neuron: morphology

Neurons are highly specialized for:

- Generating electrical signals in response to input
- Transmitting that signal to other cells

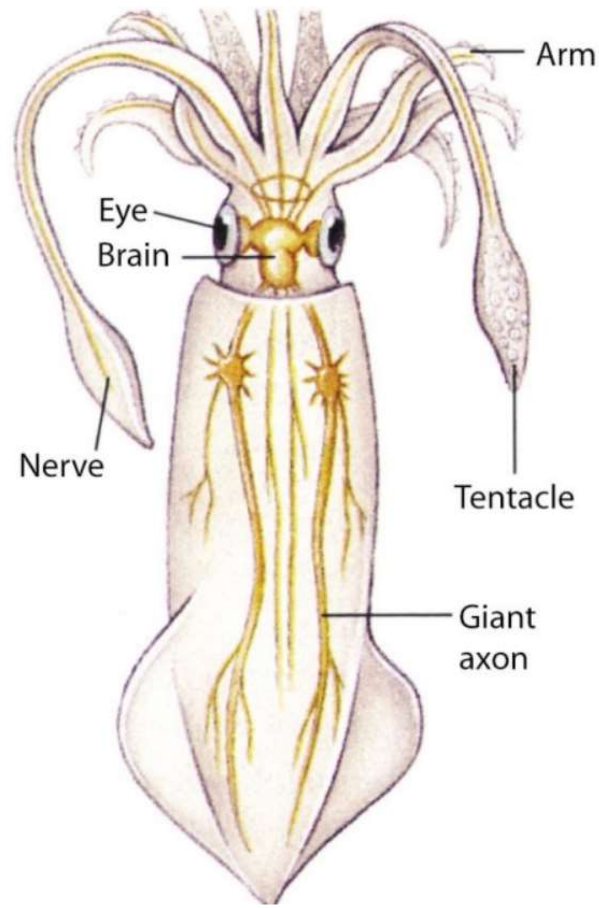
Dendrites allows neuron to receive input

Axon carries output to other cells



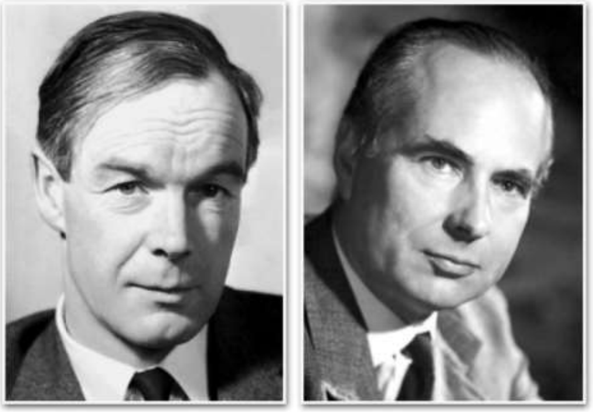
The squid giant axon

In 1952, Alan Hodgkin and Andrew Huxley described the ionic mechanisms underlying the initiation and propagation of action potentials in the squid giant axon



The squid giant axon

- Breakthrough voltage-clamp experiments
- A detailed mathematical model of action potential initiation and propagation
- Published in 1952
- Nobel prize in 1963



A.L Hodgkin A. Huxley

Important, because:

- Start of the field of computational neuroscience
- Can be used to model ion channels, different types of synapes
- Reference model for the derivation of simplified neuron models

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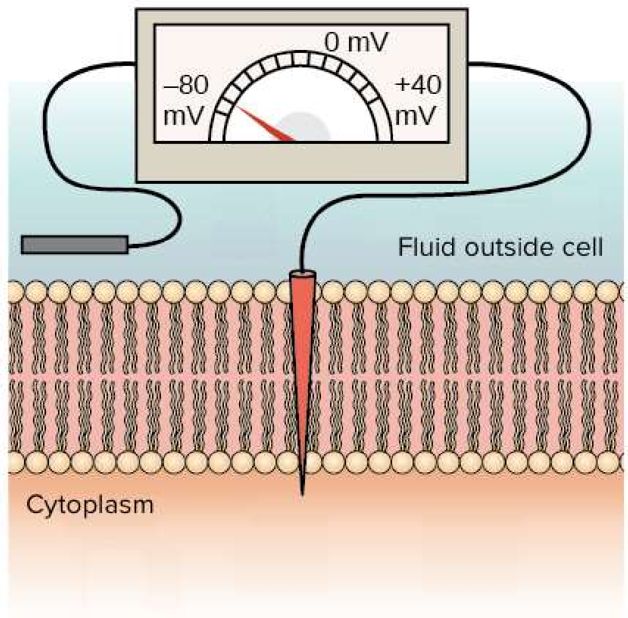
The squid giant axon

https://www.youtube.com/watch?v=CXCGqwdtJ78

Single neuron: the membrane potential and ion channels

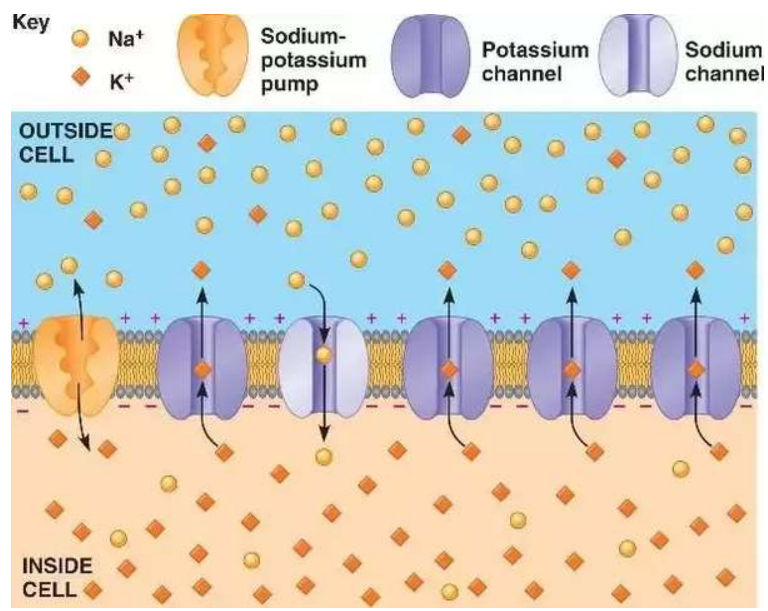
- Resting potential: potential inside neuron compared to extracellular medium ~-70 mV
- High concentration of potassium (K^+) inside neuron
- High concentration of sodium (Na^+) outside neuron



Single neuron: the membrane potential and ion channels

- Resting potential: potential inside neuron compared to extracellular medium ~70 mV
- High concentration of potassium (K^+) inside neuron
- High concentration of sodium (Na^+) outside neuron

- Membrane-spanning ion channels:
  - Mostly sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), and chloride (Cl^-)
  - Channels open and close to control the flow of ions across the cell membrane



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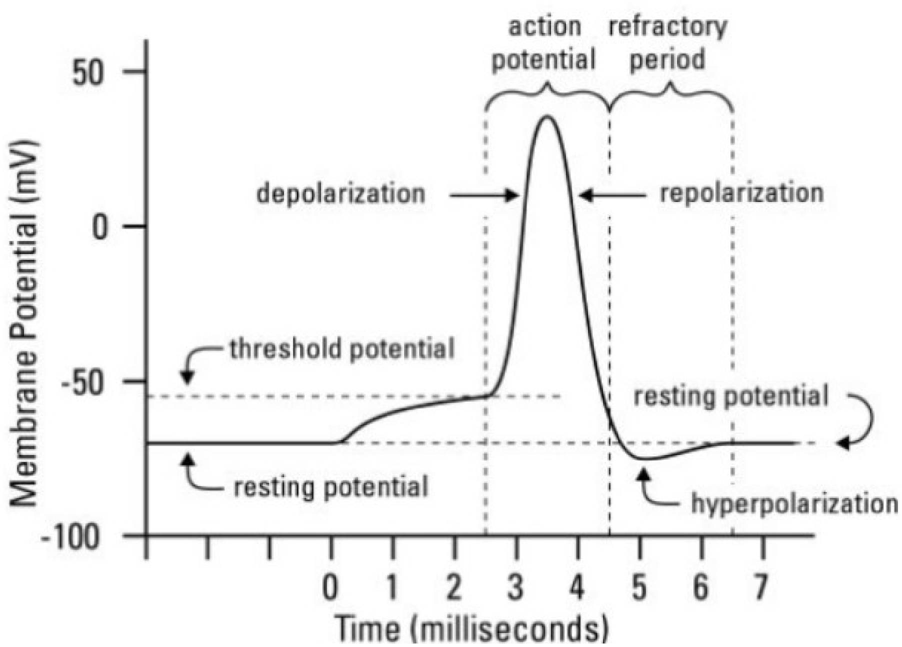
Action potential

Action potential (spike) = short-lasting event in which the electrical membrane potential of a cell rapidly rises and falls, following a consistent trajectory



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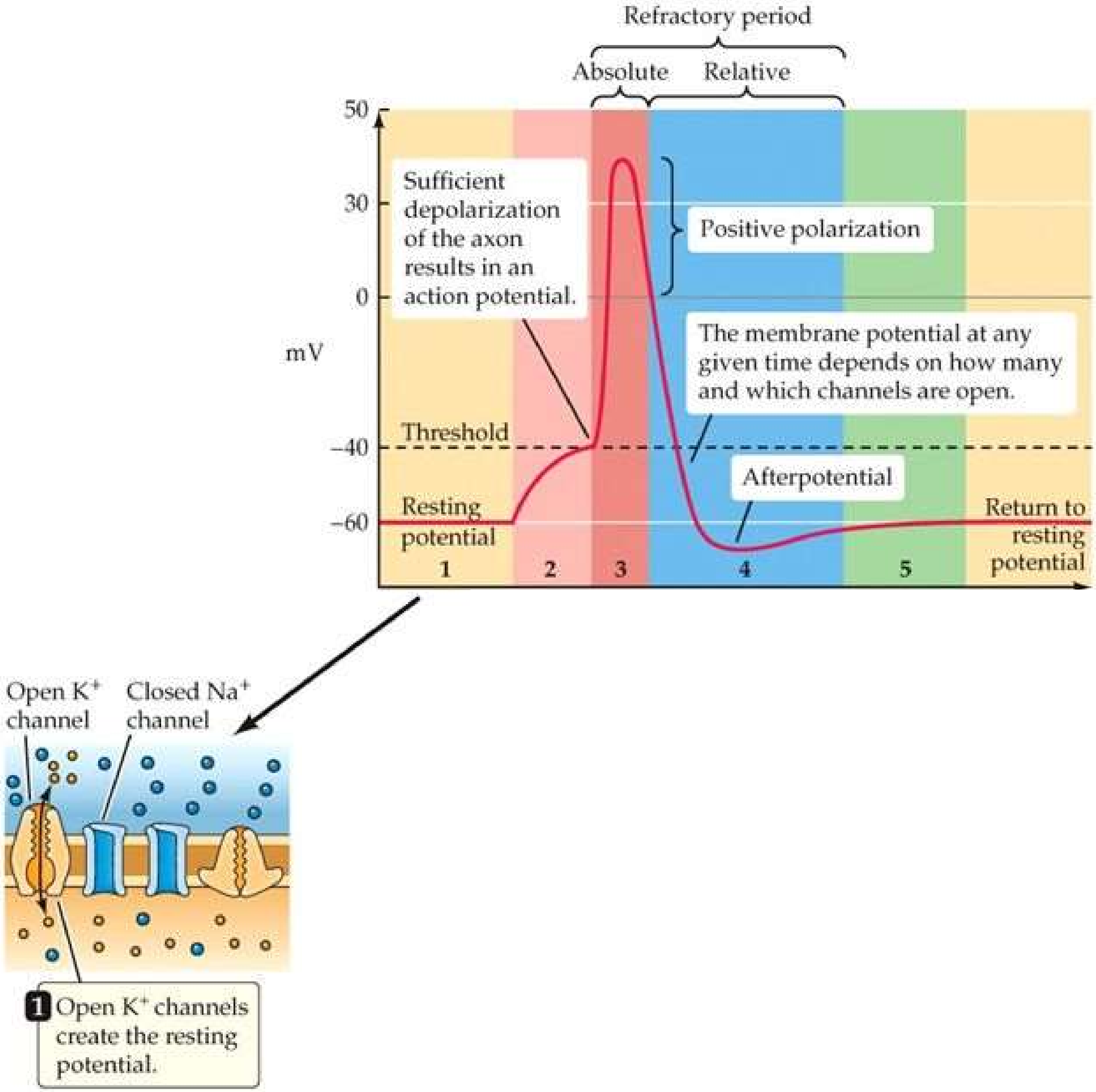
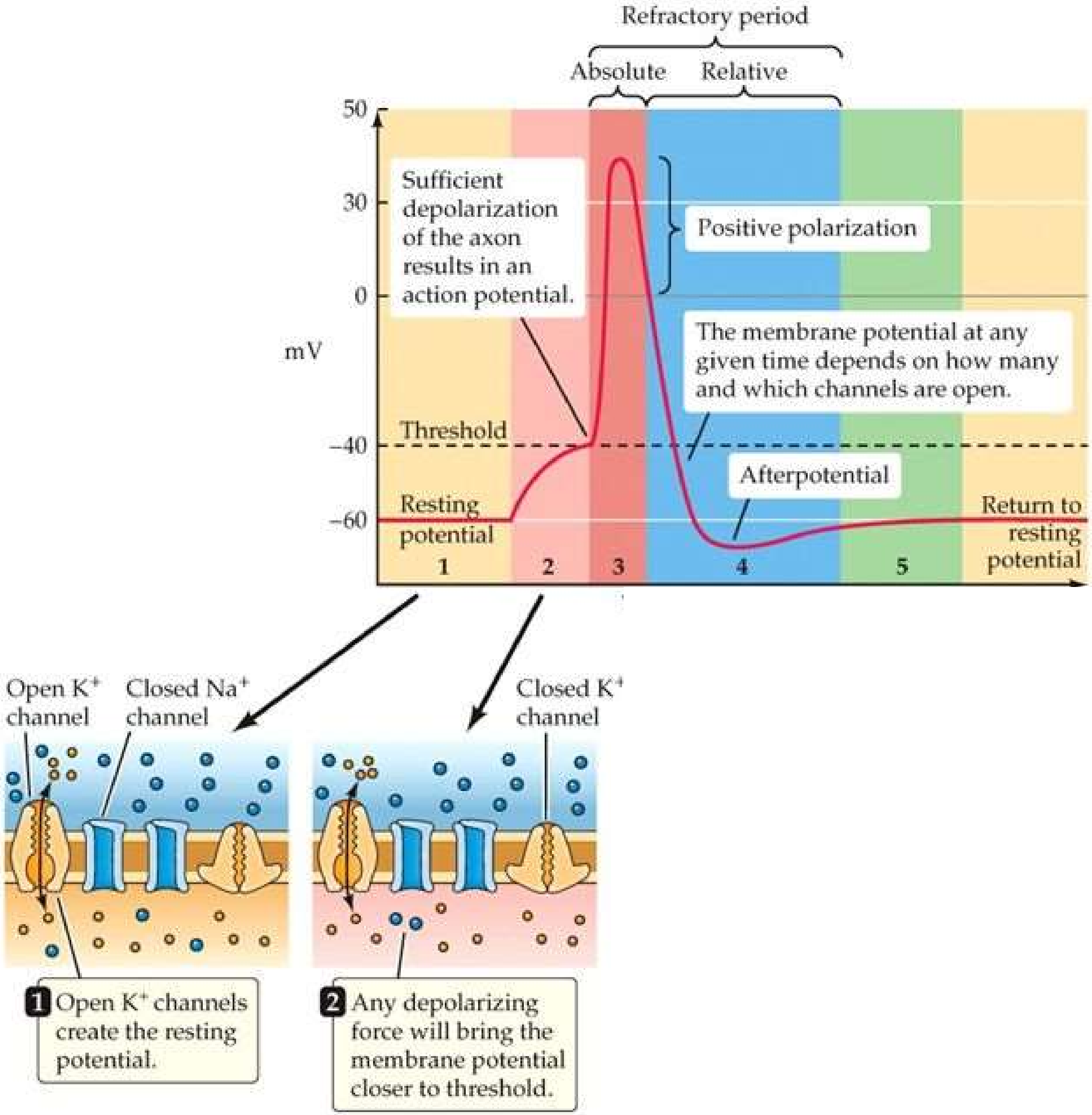

Refractory period
Absolute
Relative
50
30
0
mV
-40
-60
Sufficient depolarization of the axon results in an action potential.
Positive polarization
The membrane potential at any given time depends on how many and which channels are open.
Threshold
Afterpotential
Resting potential
Return to resting potential
1
2
3
4
5
Open K^+ channel
Closed Na^+ channel
1 Open K^+ channels create the resting potential.



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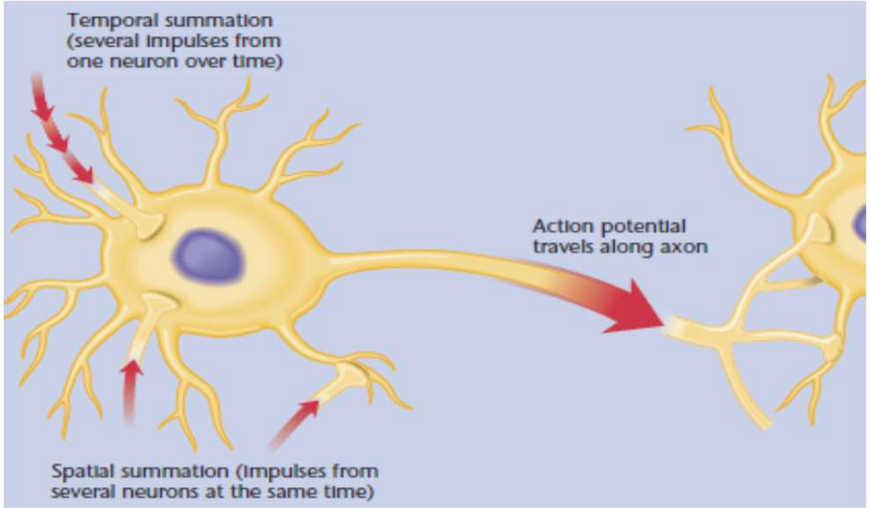
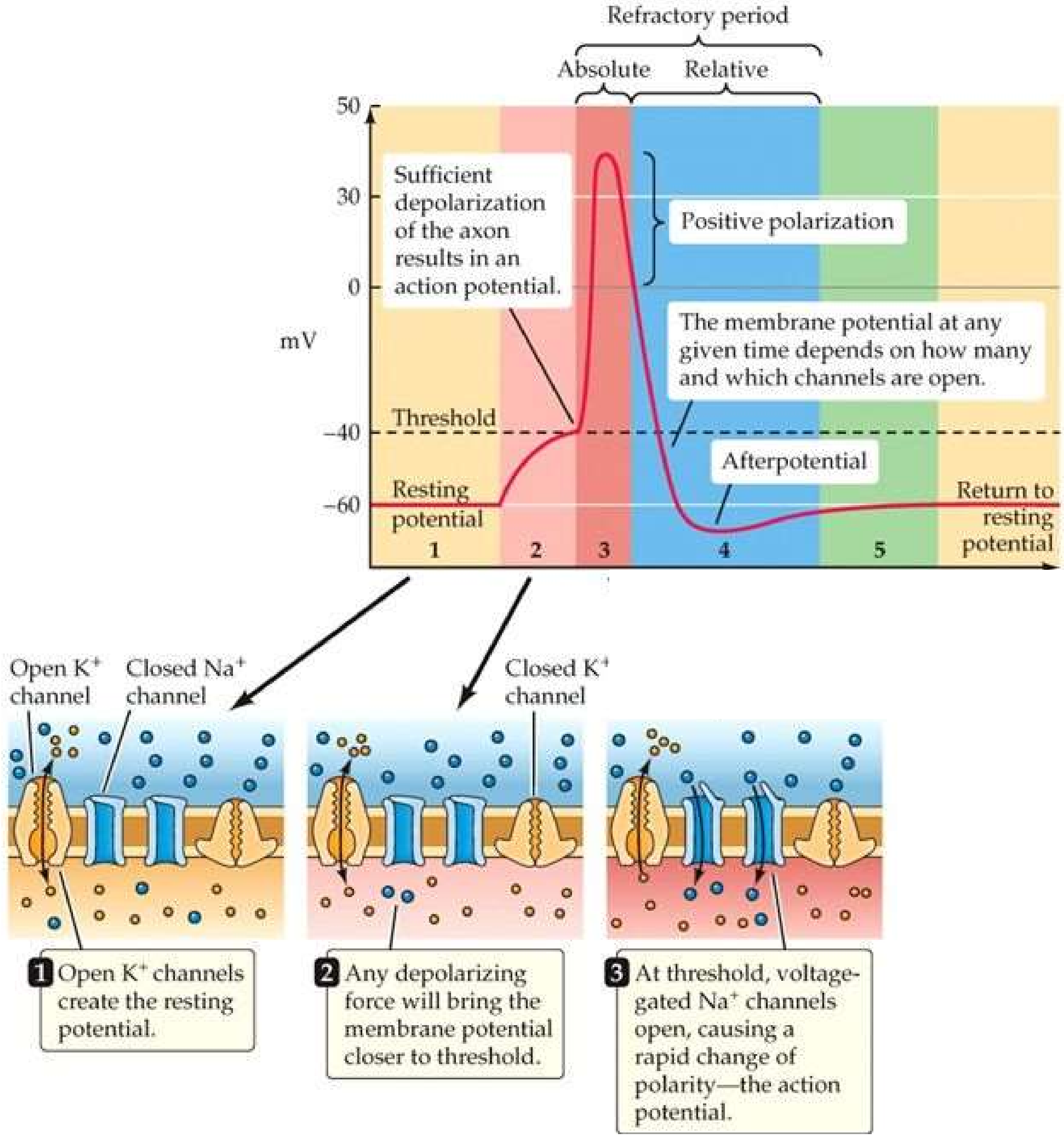
Open K+ channel
Closed Na+ channel
Closed K+ channel
1 Open K+ channels create the resting potential.
2 Any depolarizing force will bring the membrane potential closer to threshold.

Excitatory and inhibitory potentials

- Neurotransmitter binds to (ligand-gated) ion-channels:
  - Sodium (Na^+) channels: excitatory post-synaptic potential (EPSP)
  - Potassium (K^+)/Chloride (Cl^-) channels: inhibitory post-synaptic potential (IPSP)
- PSPs are graded potentials



- Summation at axon hillock:
  - **Passive** conductance of PSPs from dendrites through soma to axon hillock
  - Axon hillock:
    if $\sum EPSP - \sum IPSP >$ threshold, then generation of **Action Potential**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Open K+ channel
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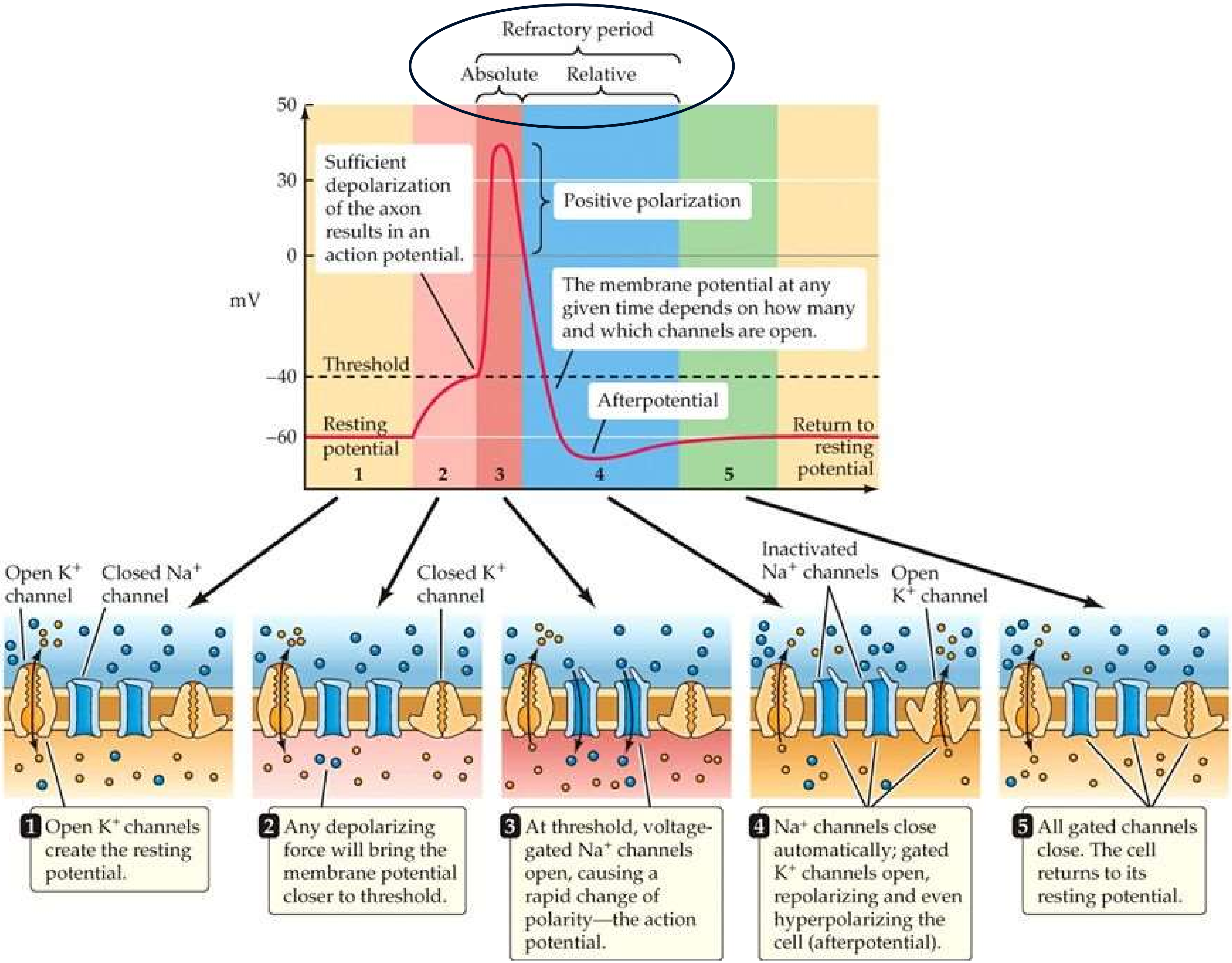
Closed K+ channel
1 Open K+ channels create the resting potential.
2 Any depolarizing force will bring the membrane potential closer to threshold.
3 At threshold, voltage-gated Na+ channels open, causing a rapid change of polarity—the action potential.



Refractory period
Absolute
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50
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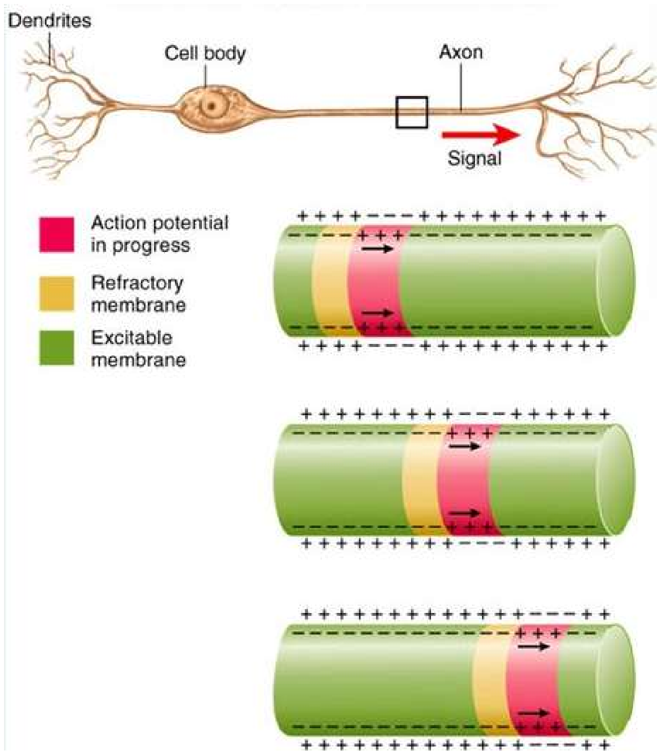
Sufficient depolarization of the axon results in an action potential.
Positive polarization
The membrane potential at any given time depends on how many and which channels are open.
Threshold
Afterpotential
Resting potential
Return to resting potential
1
2
3
4
5
Open K+ channel
Closed Na+ channel
Closed K+ channel
Inactivated Na+ channels
Open K+ channel
1 Open K+ channels create the resting potential.
2 Any depolarizing force will bring the membrane potential closer to threshold.
3 At threshold, voltage-gated Na+ channels open, causing a rapid change of polarity—the action potential.
4 Na+ channels close automatically; gated K+ channels open, repolarizing and even hyperpolarizing the cell (afterpotential).
5 All gated channels close. The cell returns to its resting potential.

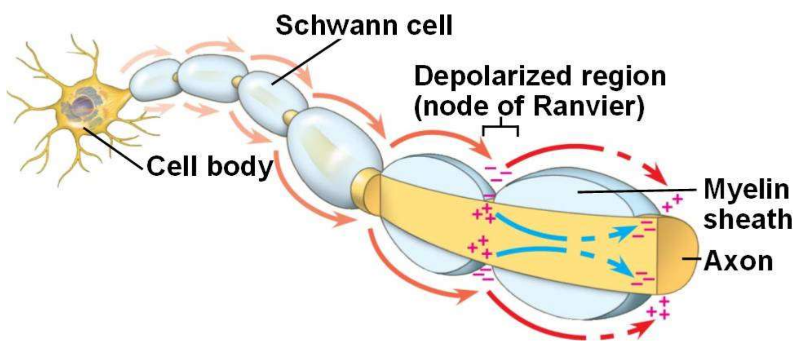
Action potential

For a summary, watch:
https://www.youtube.com/watch?v=iBDXOt_uHTQ

Conducting action potentials

- Subthreshold potentials severely attenuate over distance of ~1mm
- Action potentials can propagate over large distances:
    - Myelination: Saltatory conduction





Conducting action potentials

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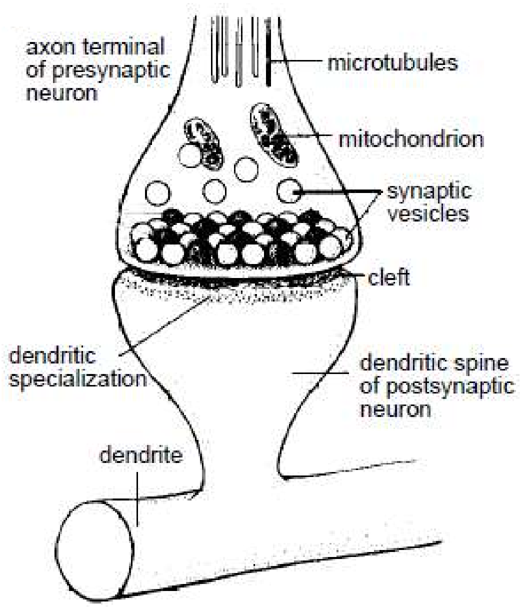
  - Terminate at the synapse → Ca^{2+} influx leads to neurotransmitter release



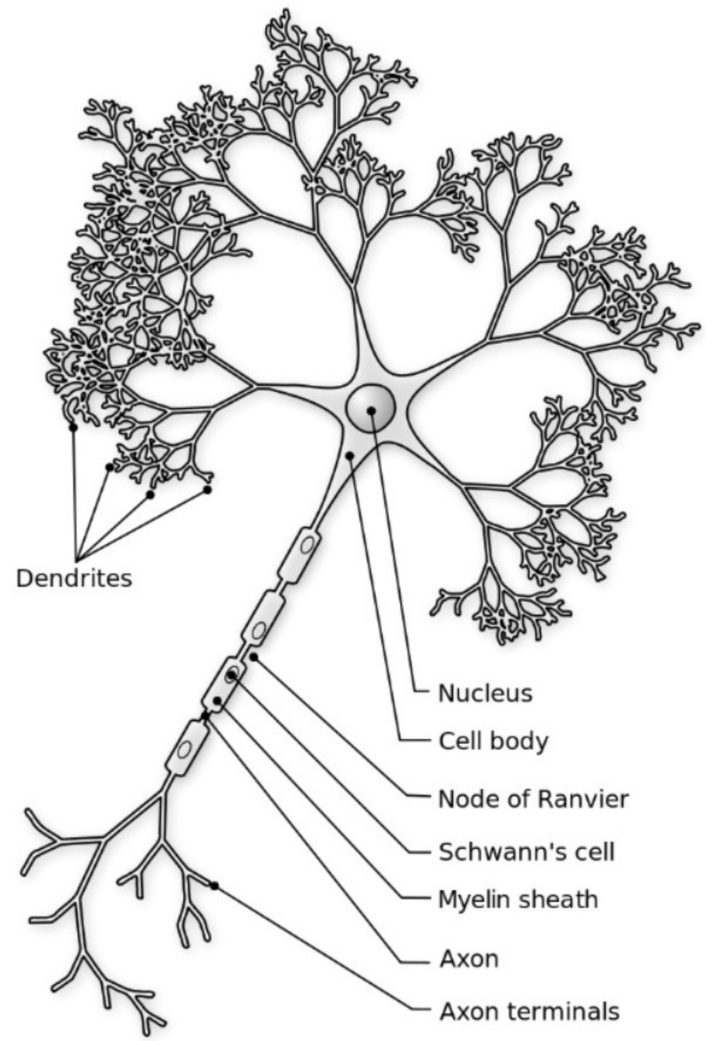
Conducting action potentials

- Subthreshold potentials severely attenuate over distance of ~1mm
- Action potentials can propagate over large distances:
  - Myelination: Saltatory conduction
  - Terminate at the synapse → Ca^{2+} influx leads to neurotransmitter release
  - Neurotransmitters open ion-channels on postsynapse:
    - Excitatory effect (EPSP): depolarization
    - Inhibitory effect (IPSP): hyperpolarization

Single neuron models

How do we simulate the behavior of a single neuron in a computer?

“Make it as simple as possible, but not simpler”



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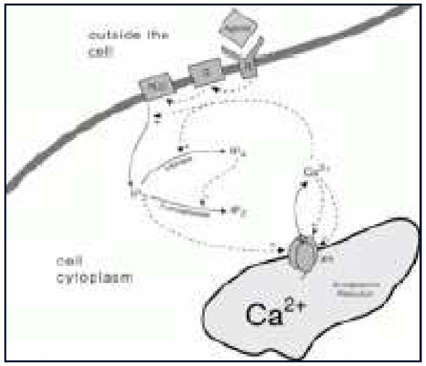
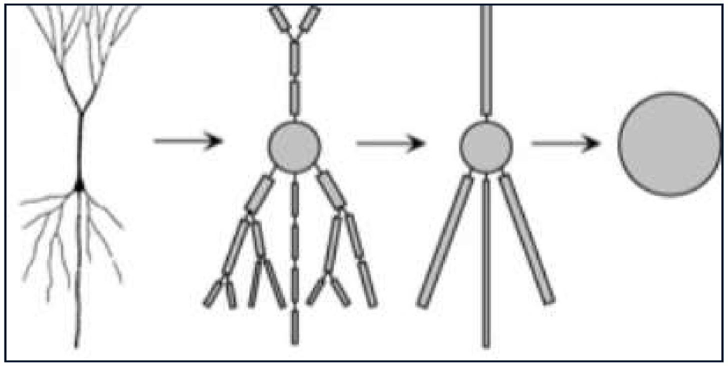
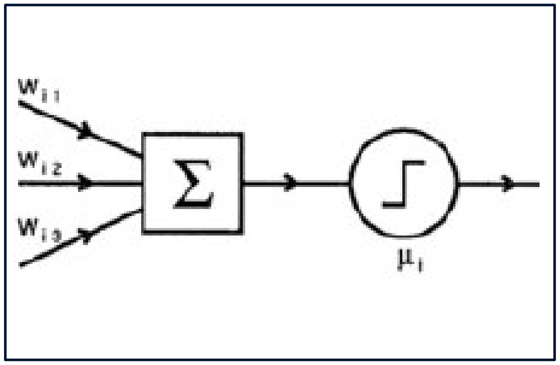
Appropriate level of model complexity

Biological detail

High ⟷ Low







Molecular

Electrical

Computational

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The Hodgkin & Huxley model (1952)

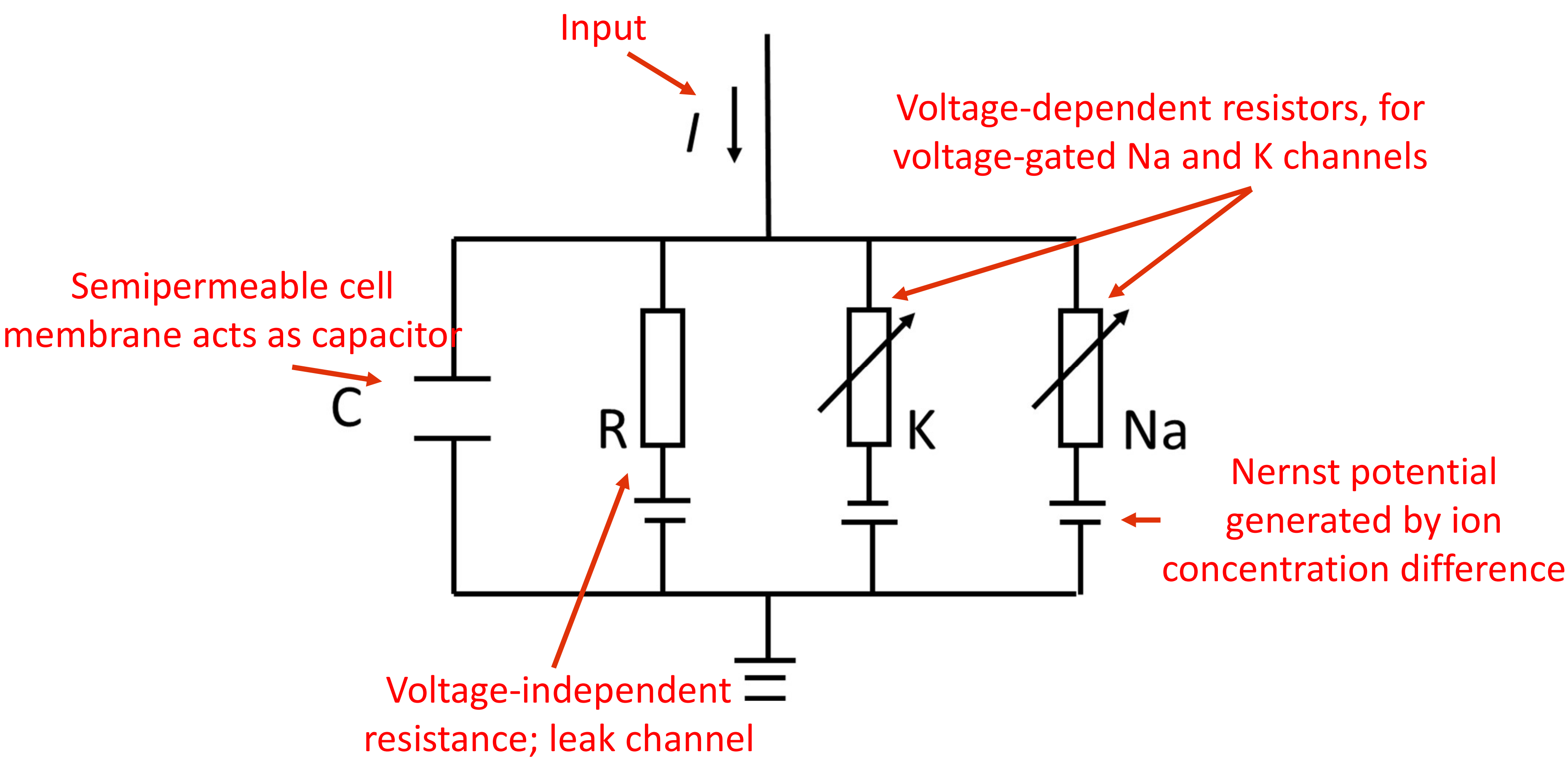
Four differential equations, describing the ionic basis of the action potential

Three components of ionic current:

1. Sodium current I_{NA}
2. Potassium current I_K
3. small leakage current I_L (consisting mostly of cloride ions)

$$\boxed{C\frac{\mathrm{d}V}{\mathrm{d}t} = -g_{\mathrm{K}}n^4(V - E_{\mathrm{K}}) - g_{\mathrm{Na}}m^3h(V - E_{\mathrm{Na}}) - g_{\mathrm{L}}(V - E_{\mathrm{L}}) + I(t)}$$

The Hodgkin & Huxley model (1952)



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The Hodgkin & Huxley model (1952)

Membrane capacitance (constant)

Sum of ionic currents that pass through membrane

$$C\frac{\mathrm{d}V}{\mathrm{d}t} = \underbrace{-g_{\mathrm{K}}n^4(V - E_{\mathrm{K}}) - g_{\mathrm{Na}}m^3h(V - E_{\mathrm{Na}}) - g_{\mathrm{L}}(V - E_{\mathrm{L}})}_{\text{Sum of ionic currents that pass through membrane}} + I(t)$$

Change in membrane potential over time

The Hodgkin & Huxley model (1952)

$$\boxed{C\frac{\mathrm{d}V}{\mathrm{d}t} \quad = \quad -g_{\mathrm{K}}n^4(V-E_{\mathrm{K}})-g_{\mathrm{Na}}m^3h(V-E_{\mathrm{Na}})-g_{\mathrm{L}}(V-E_{\mathrm{L}})+I(t)}$$

Max conductance when channels are open
(Empirically determined)

Reversal potentials
(Empirically determined)

The Hodgkin & Huxley model (1952)

$$C\frac{\mathrm{d}V}{\mathrm{d}t} = -g_{\mathrm{K}}n^4(V-E_{\mathrm{K}}) - g_{\mathrm{Na}}m^3h(V-E_{\mathrm{Na}}) - g_{\mathrm{L}}(V-E_{\mathrm{L}}) + I(t)$$

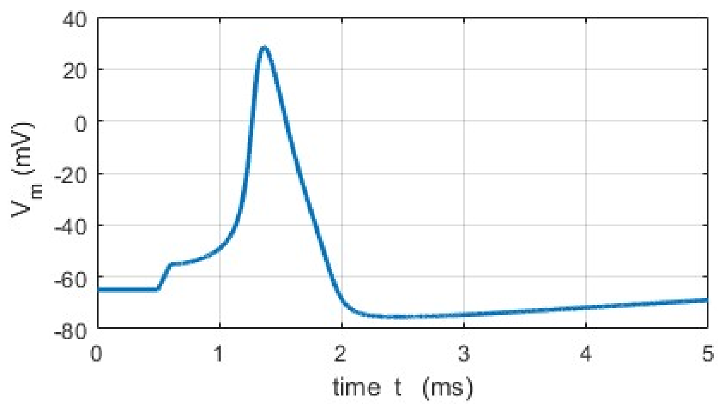
m, h, n:

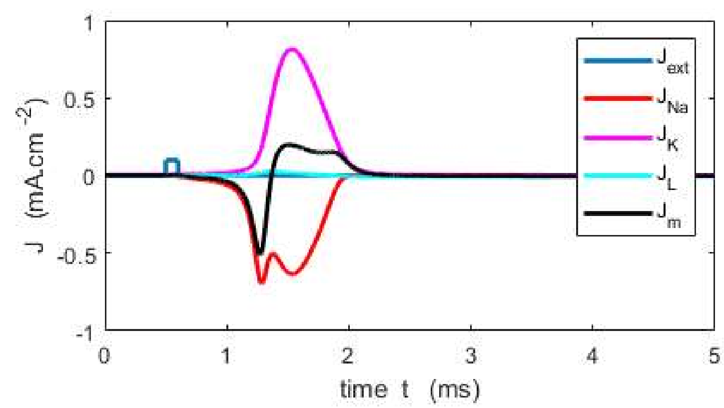
- Gating variables that describe the probability that a channel is open
- Evolve according to differential equations
- Empirical functions to fit the data from the squid axon

$$\tau_{\mathrm{n}}(V)\frac{\mathrm{d}n}{\mathrm{d}t} = -[n - n_0(V)]$$
$$\tau_{\mathrm{m}}(V)\frac{\mathrm{d}m}{\mathrm{d}t} = -[m - m_0(V)]$$
$$\tau_{\mathrm{h}}(V)\frac{\mathrm{d}h}{\mathrm{d}t} = -[h - h_0(V)]$$

Hodgkin-Huxley (HH) model

- Calculate currents, conductances and voltages throughout nerve cells of all types
- We will test a HH model implemented in Matlab during the skills training





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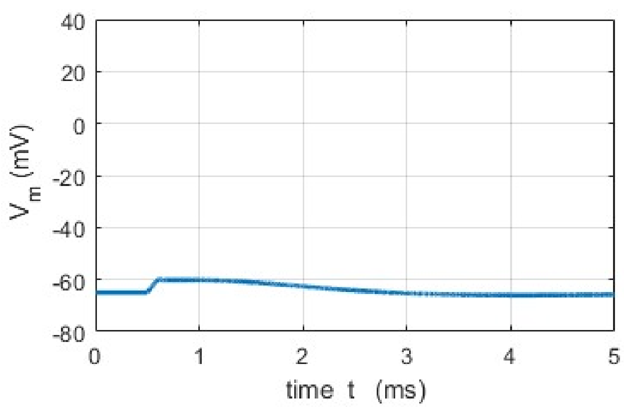
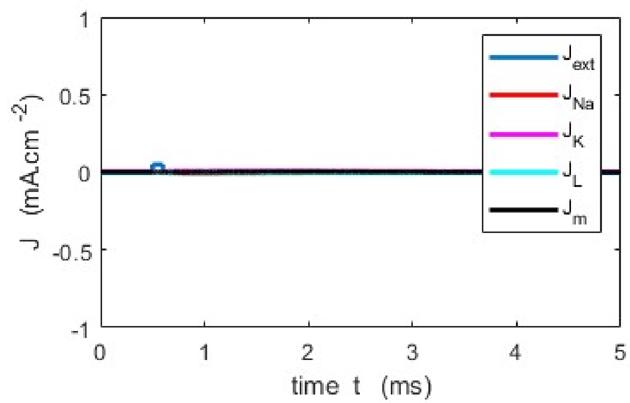
Hodgkin-Huxley (HH) model

What happens if we vary the strength of stimulation?

- Shape/amplitude of the action potential

Near threshold
↓
Weak
↓
Strong





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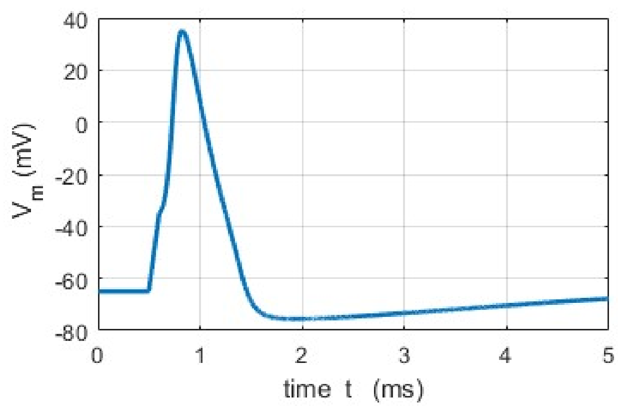
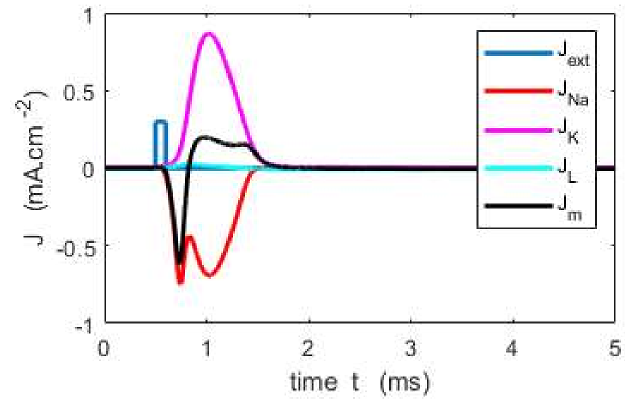




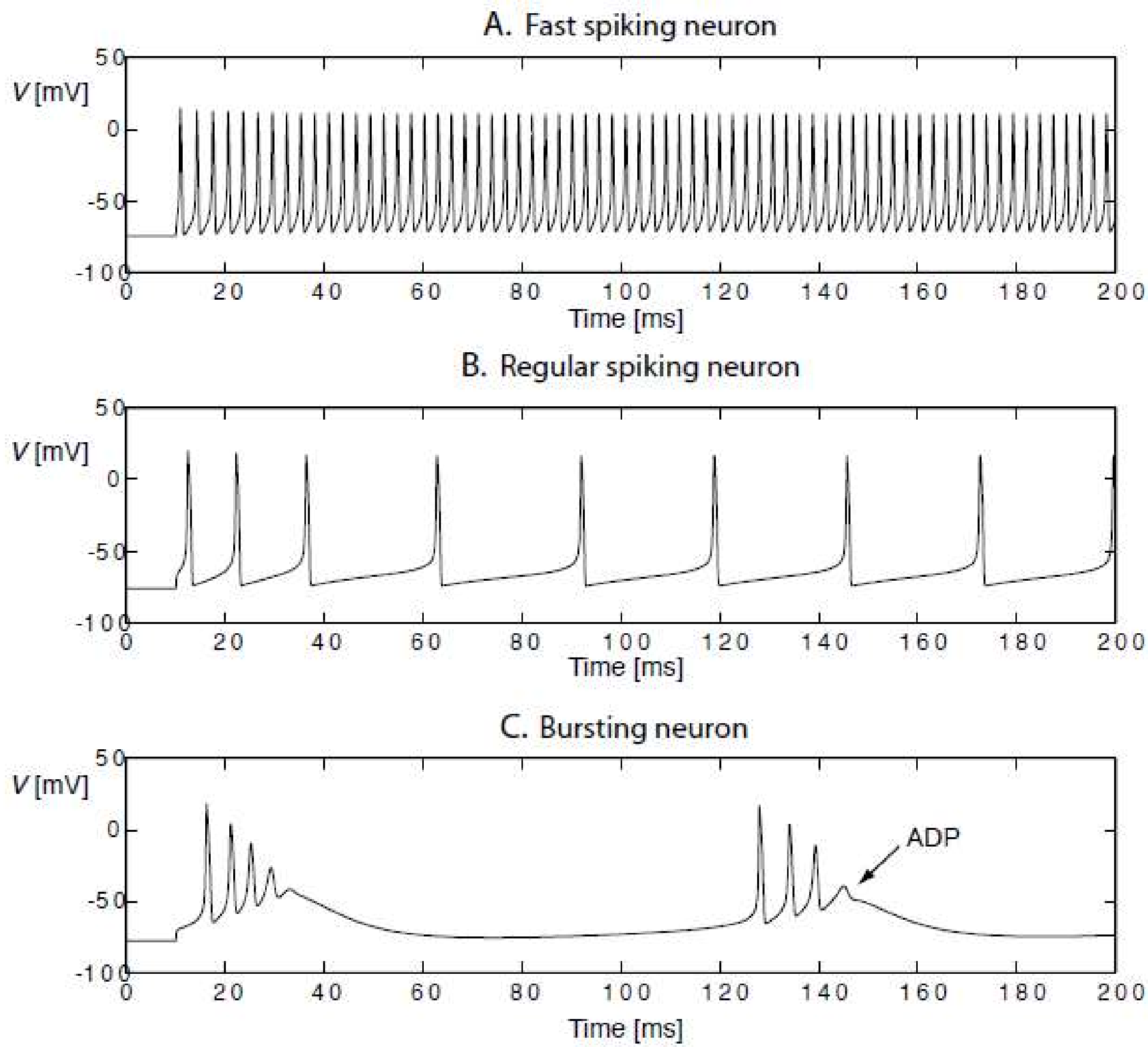
Hodgkin-Huxley (HH) adaptation by Wilson

Simplified HH model and added two cation channels:

- Graded-influx cation channel
- Slow depolarizing current

Captures more complex behavior:

- adaptation/fatigue
- long-lasting after-depolarizing potential of bursting neurons



Simpler models

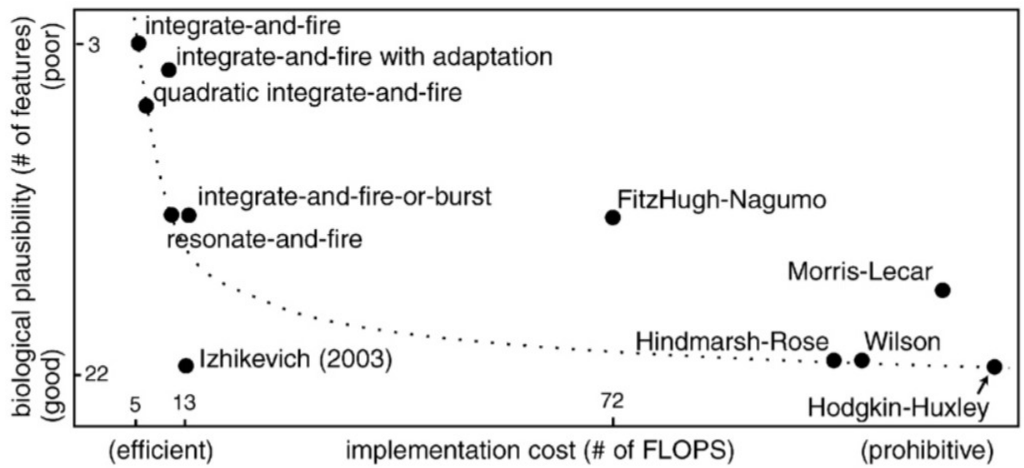
Conductance-based models

Hodgkin-Huxley model

Threshold-based models

For studying neural coding, memory, and network dynamic

For example: integrate-and-fire neurons



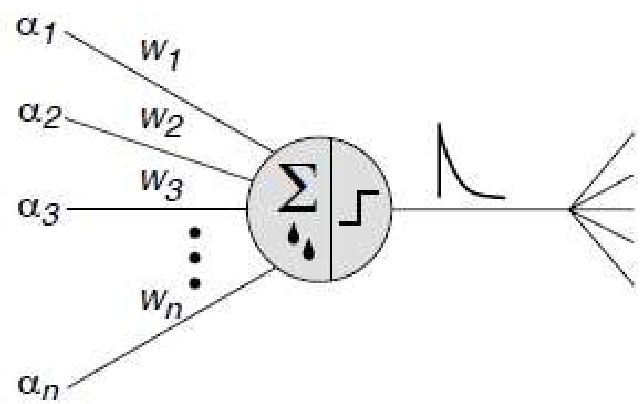
Integrate-and-fire (IF) neurons

Simplification may be:

- necessary to make computations with a large number of neuron possible
- advantageous to highlight the minimal features necessary to enable certain emergent properties in the network

IF neurons consist of:

- Subthreshold leaky-integrator dynamic
- Firing threshold
- Reset mechanism



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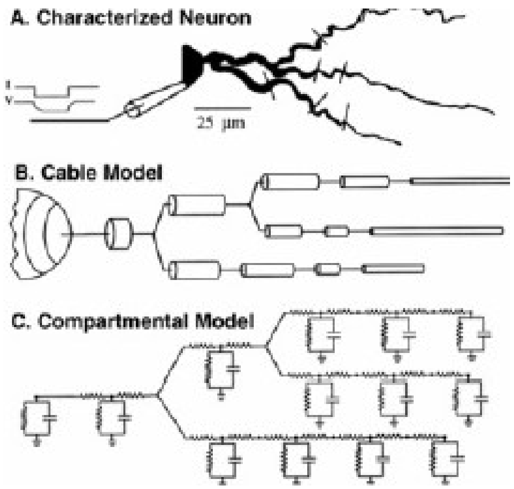
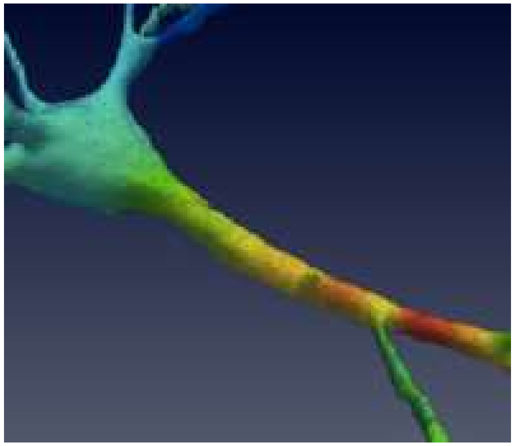
More detailed model

Multi-compartment models (compartmental modeling)

- Takes physical shape of neuron into account
- Used for detailed simulations of one or few neurons
- Divide a neuron in compartments (with distinct electrical properties) and connect the equivalent circuits
- Allows fine study of morphological, pharmacological, or electrical effects

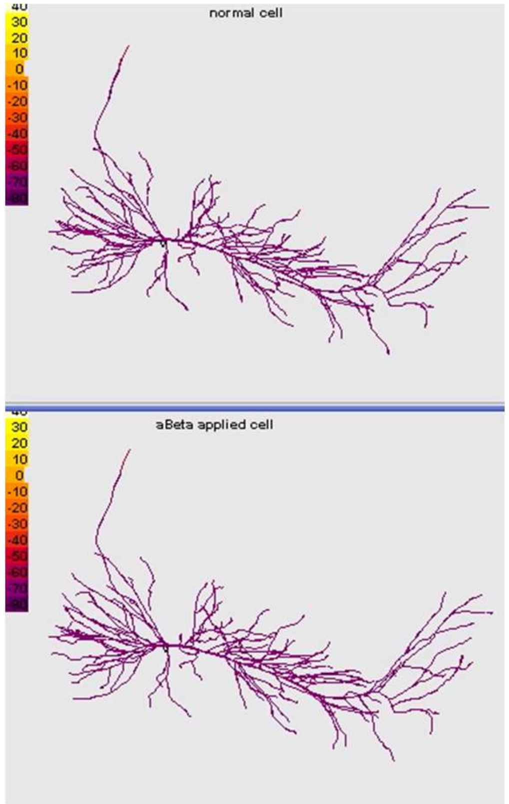


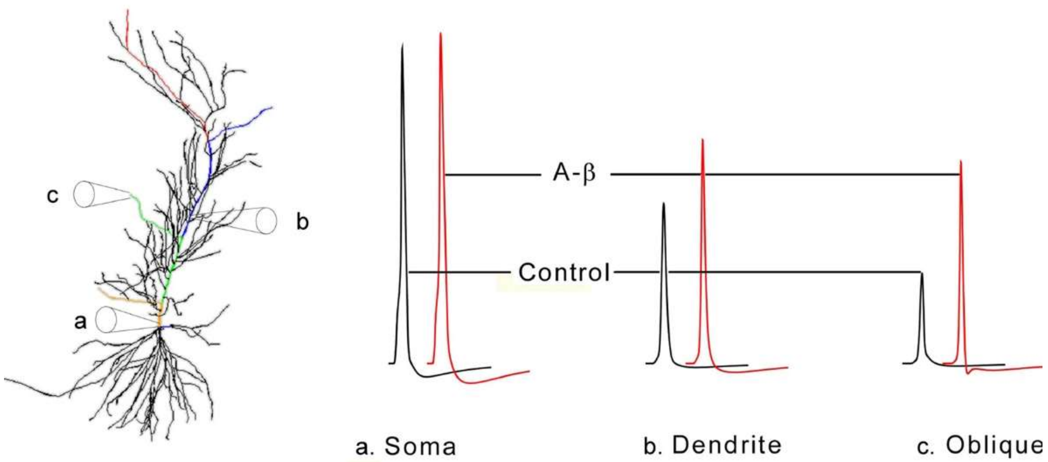


Compartmental modeling

Alzheimer's Disease:
- aβ blocked K^+ channels → dendritic hyperexcitability
- Causes enhanced back-propagating action potentials (bAPs)
- bAPs are critical for information processing/ memory storage

- Model hippocampal CA1 pyramidal neuron
- Model can explore any part of the dendritic tree that might be affected
- Fine oblique branches of the apical dendritic tree are especially vulnerable to increased excitability





Morse et al., (2010) Front Neural Circuits

Overview

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  - Challenges
  - Current approaches
- **Single neuron models**
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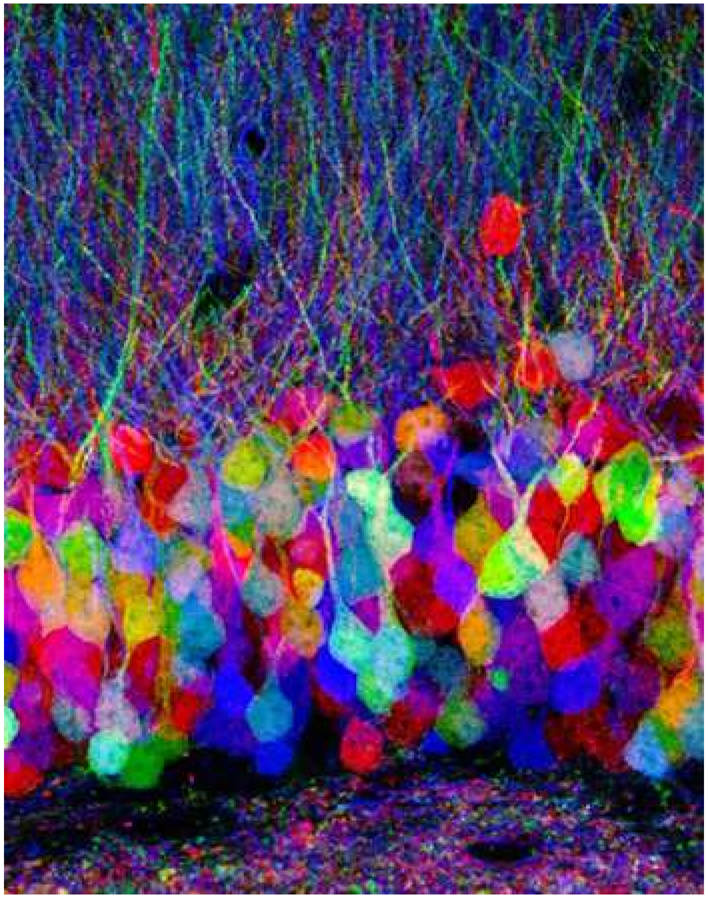
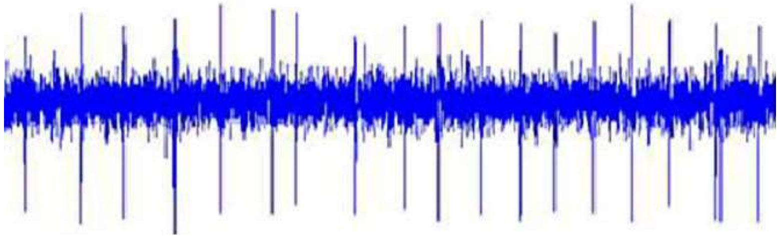
  - Neural encoding
  - Wilson-Cowan model of the auditory cortex
- **Multiscale modeling**

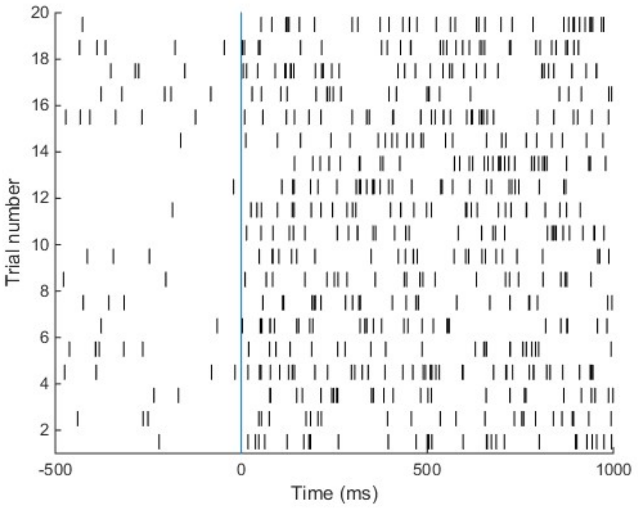


Recording from the brain: electrophysiology

Recorded activity (extracellular)



Raster plot



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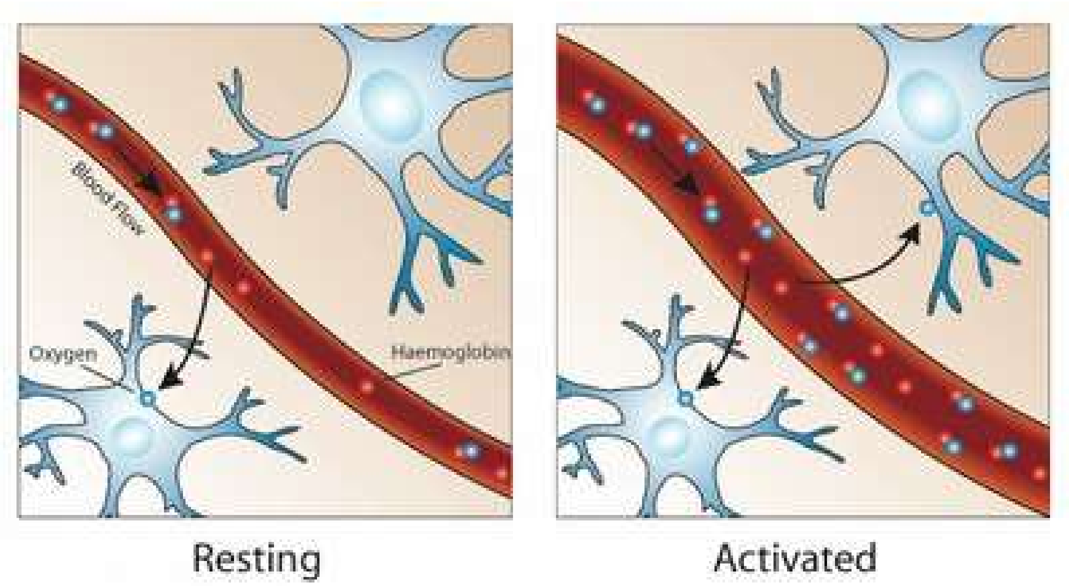
Recording from the brain: fMRI

Recording from the brain: fMRI

Functional Magnetic Resonance Imaging (fMRI)

- Blood oxygenation level dependent signal
- neurovascular coupling still not well understood (next lecture)



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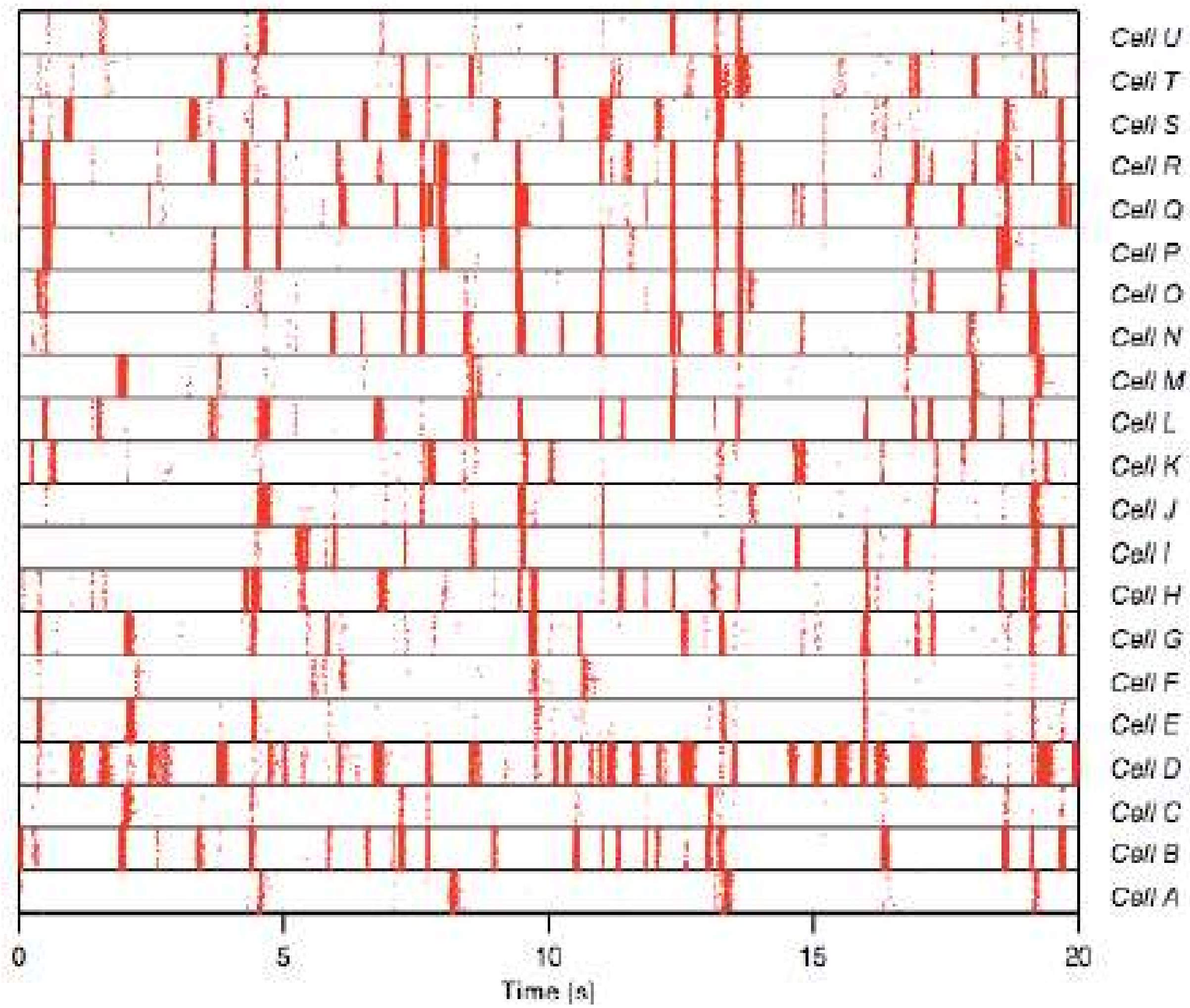
What is the neural code?



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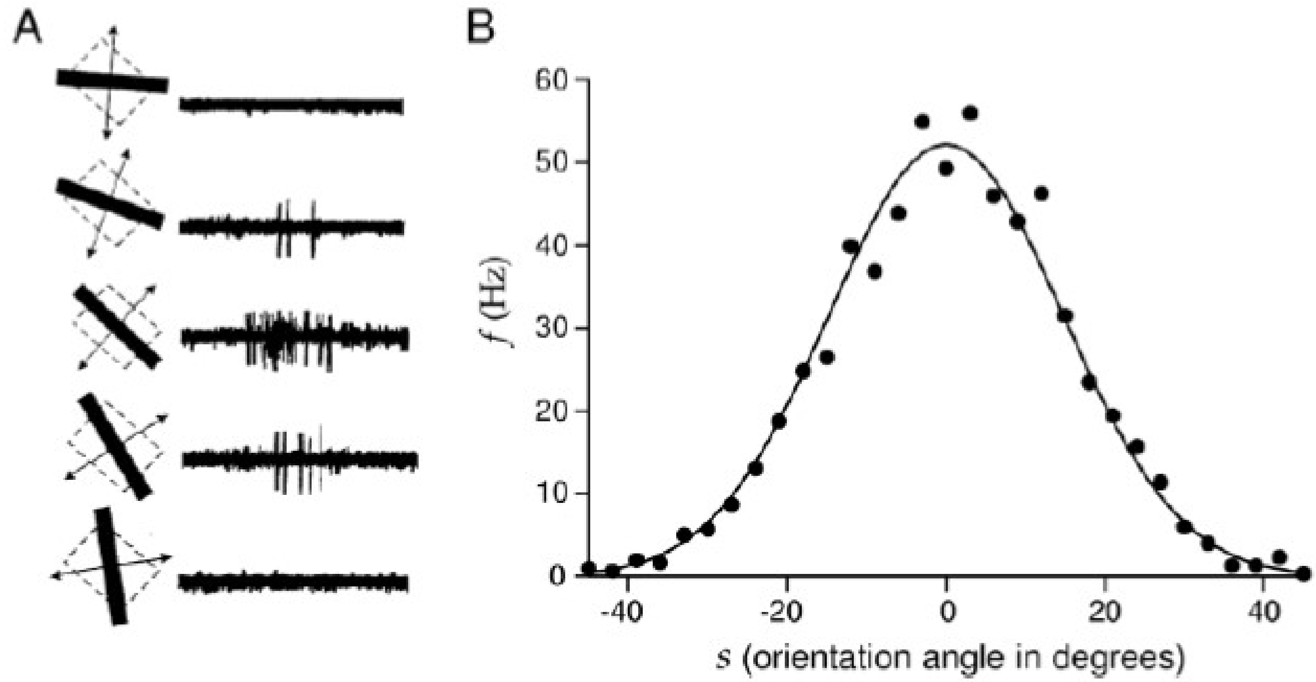
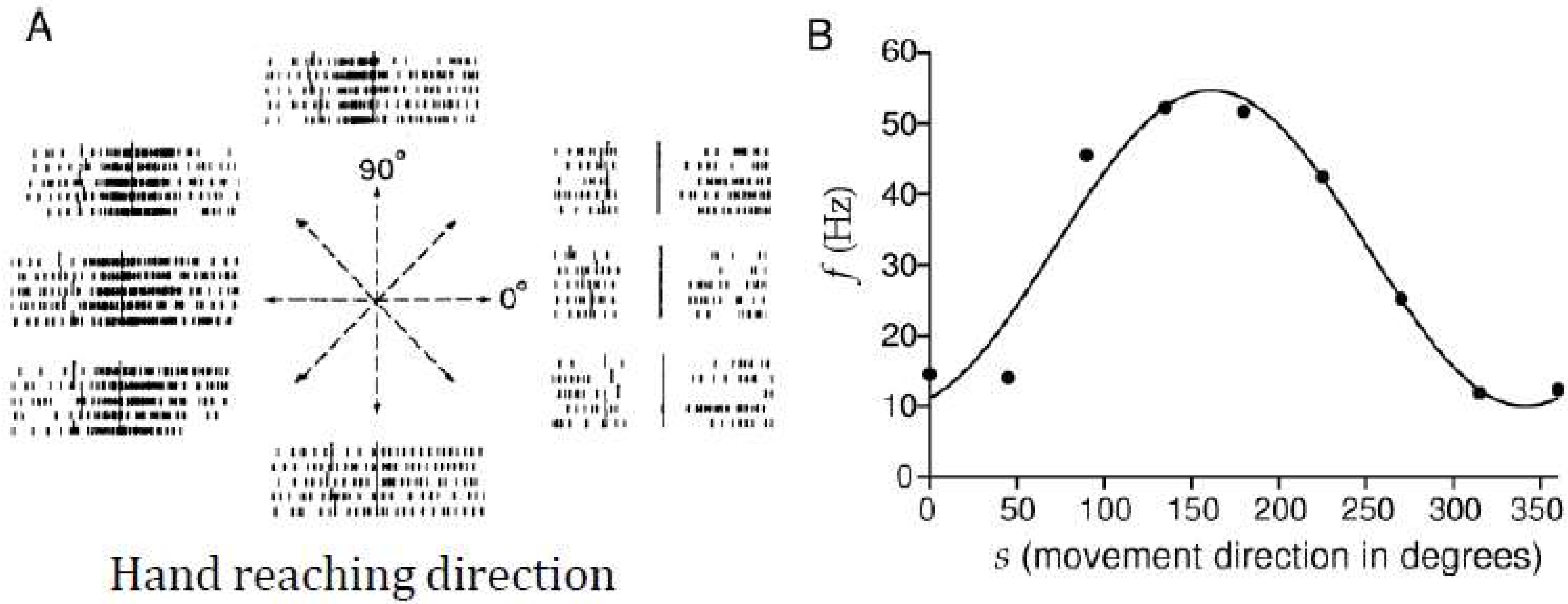
Tuning curves



Tuning curve of a cortical primary visual cortex (V1) neuron

Tuning curves



Tuning curve of a motor cortical neuron

Population coding

Neural spikes are noisy

Neurophysiological recordings/ fMRI: average data from many trials to see correlate behavior

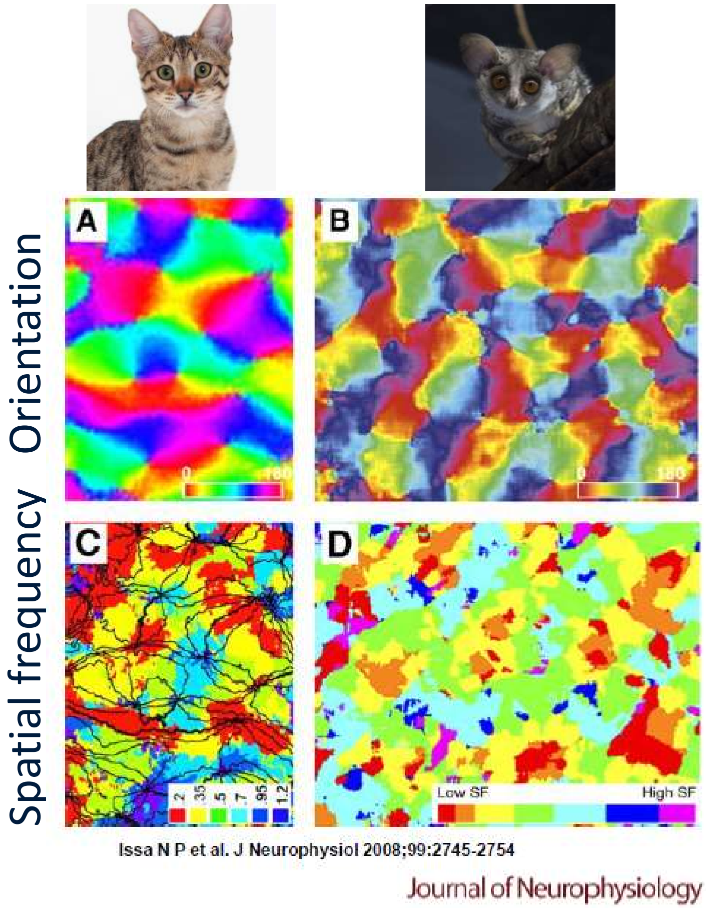
PROBLEM: the brain does not have many trials!
SOLUTION: Population coding

→ The temporal average of single neurons measured in repeated physiological experiments approximates the neuro-computationally relevant average population activity of neurons
→ Divide population into subpopulations of same type, with similar response properties

Population coding

Neurons are organized in populations with similar properties

Describe the mean activity of a neural population, rather than the spiking of individual neurons



Feature selectivity in V1

Population equations

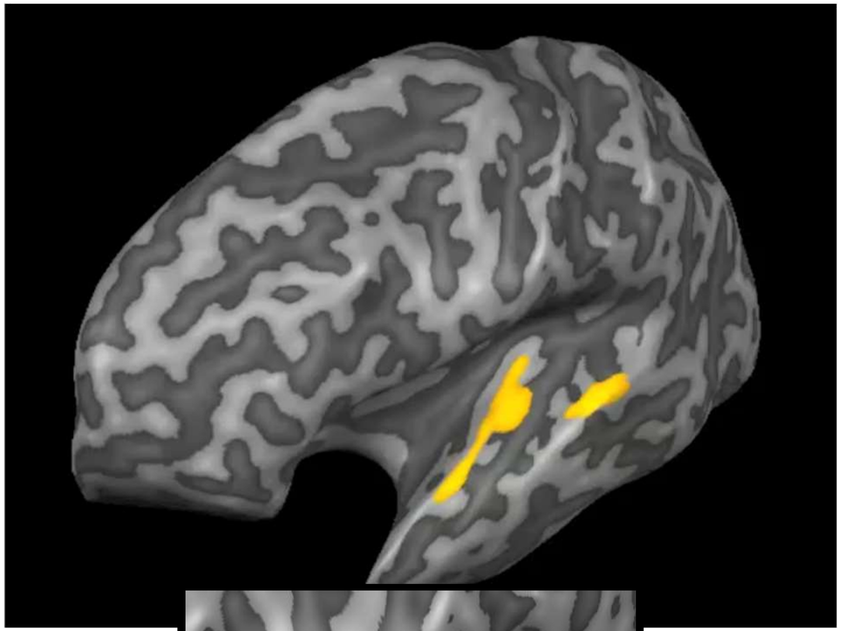
Neurons are organized in populations with similar properties

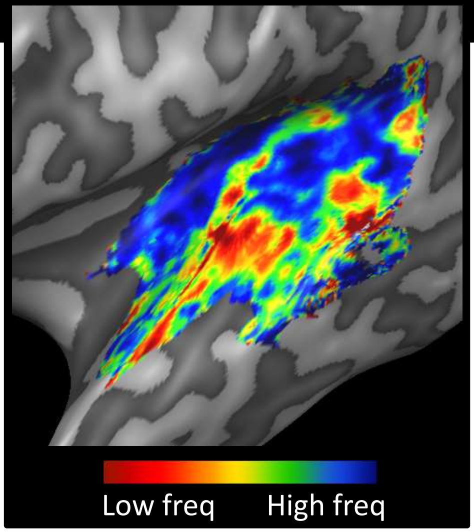
Auditory system: sound frequency

Population equations

Neurons are organized in populations with similar properties

Auditory system: sound frequency





Wilson Cowan Cortical Model (WCCM)

Wilson Cowan Cortical Model

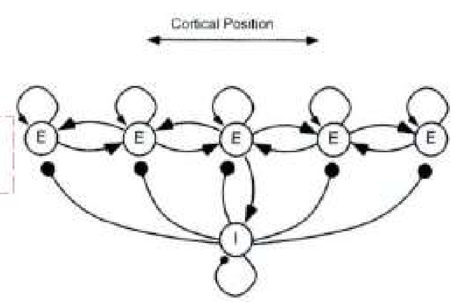
firing rate model

simple, non-linear & dynamic

"...all nervous processes of any complexity are dependent upon the interaction of excitatory and inhibitory cells."

output: spike frequency / proportion of cells active per unit time / temporal dynamics of aggregate

anatomical assumptions



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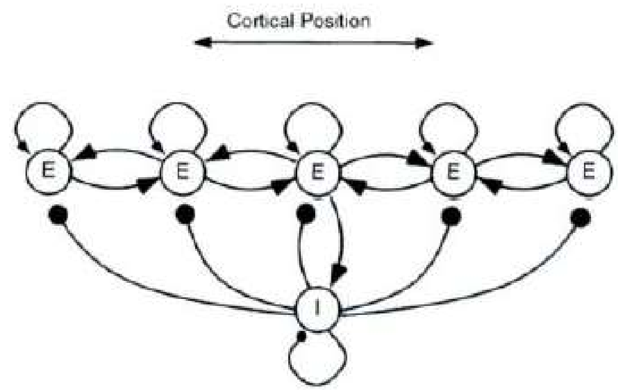
Wilson & Cowan (1972)

Wilson Cowan Cortical Model (WCCM)

$$\tau \frac{dE(x)}{dt} = -E(x) + S_E\left(\sum_x w_{EE} E(x) - \sum_x w_{IE} I(x) + P(x)\right)$$

$$\tau \frac{dI(x)}{dt} = -I(x) + S_I\left(\sum_x w_{EI} E(x) - \sum_x w_{II} I(x) + Q(x)\right)$$



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Wilson & Cowan (1972)

Wilson Cowan Cortical Model (WCCM)

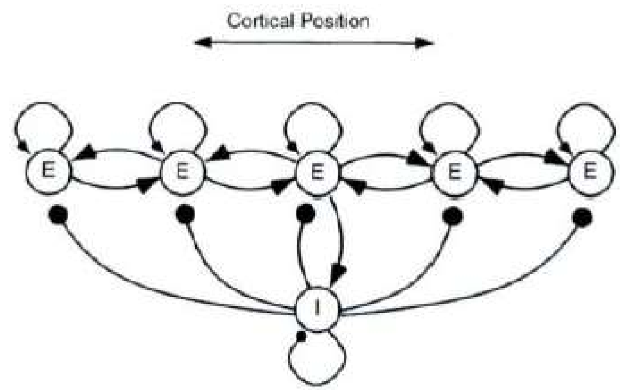
excitatory firing rate at position x

rate of change of activity

$$\tau \frac{dE(x)}{dt} = -E(x) + S_E\left(\sum_x w_{EE}\, E(x) - \sum_x w_{IE}\, I(x) + P(x)\right)$$

time constant

afferent input



describes neural spike rate

$$S(P) = \frac{V_m\, P^2}{\theta^2 + P^2}$$

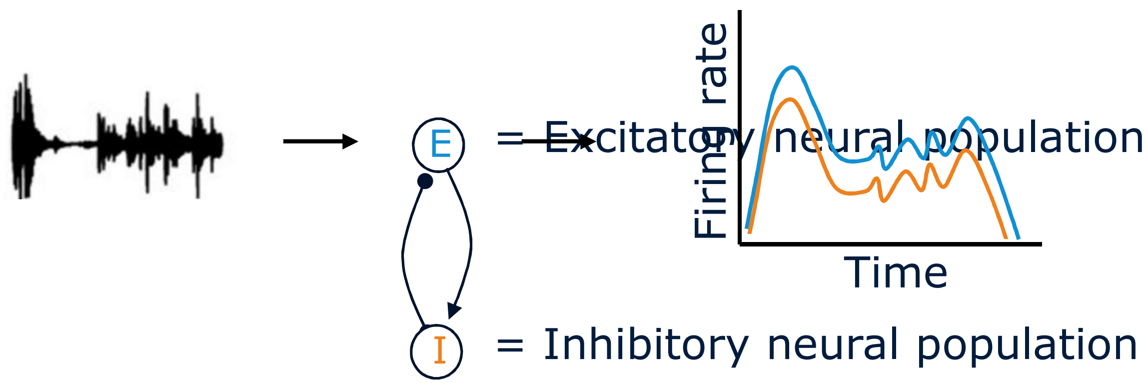
θ: semi-saturation constants

connectivity function $w_{ij}(x - x') = b_{ij} \exp\left(-|x - x'|/\sigma_{ij}\right)$

bij: maximum synaptic strength
σij: space constant controlling the spread of connectivity
i,j = E,I

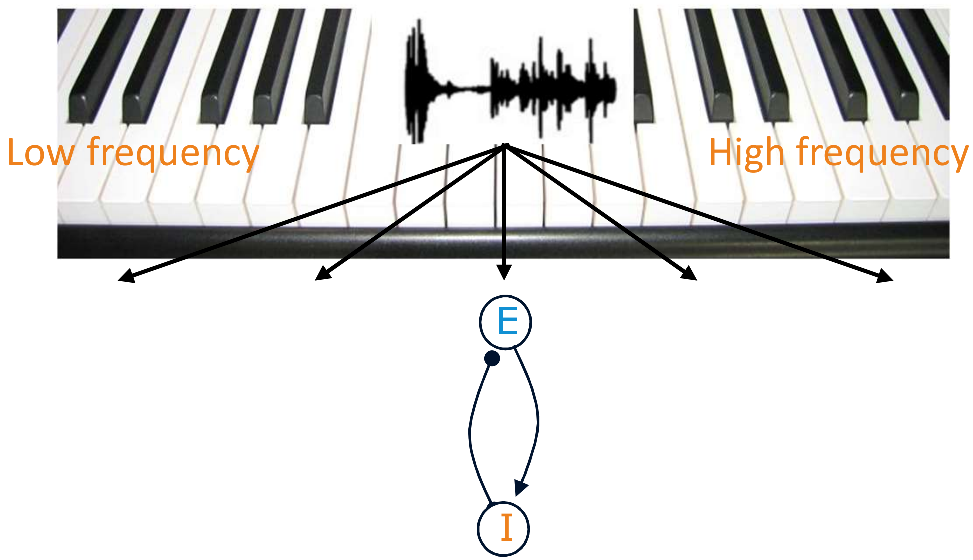
Wilson & Cowan (1972)

WCCM of auditory cortex



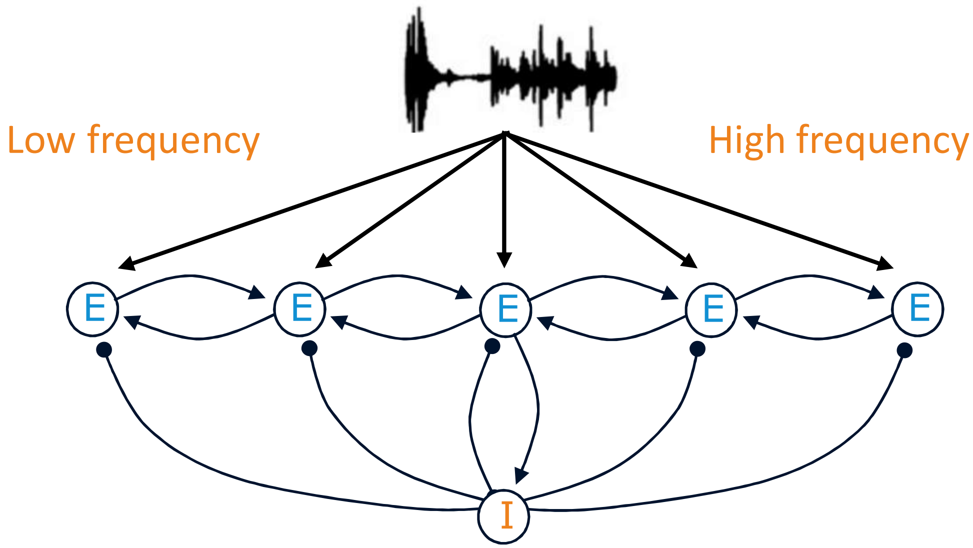
Zulfiqar et al., 2020

WCCM of auditory cortex



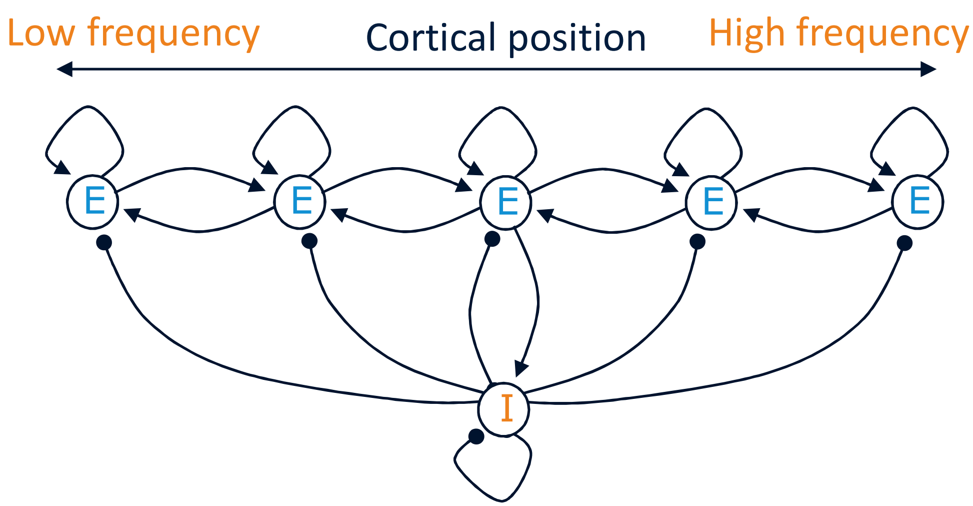
Zulfiqar et al., 2020

WCCM of auditory cortex



Zulfiqar et al., 2020

WCCM of auditory cortex

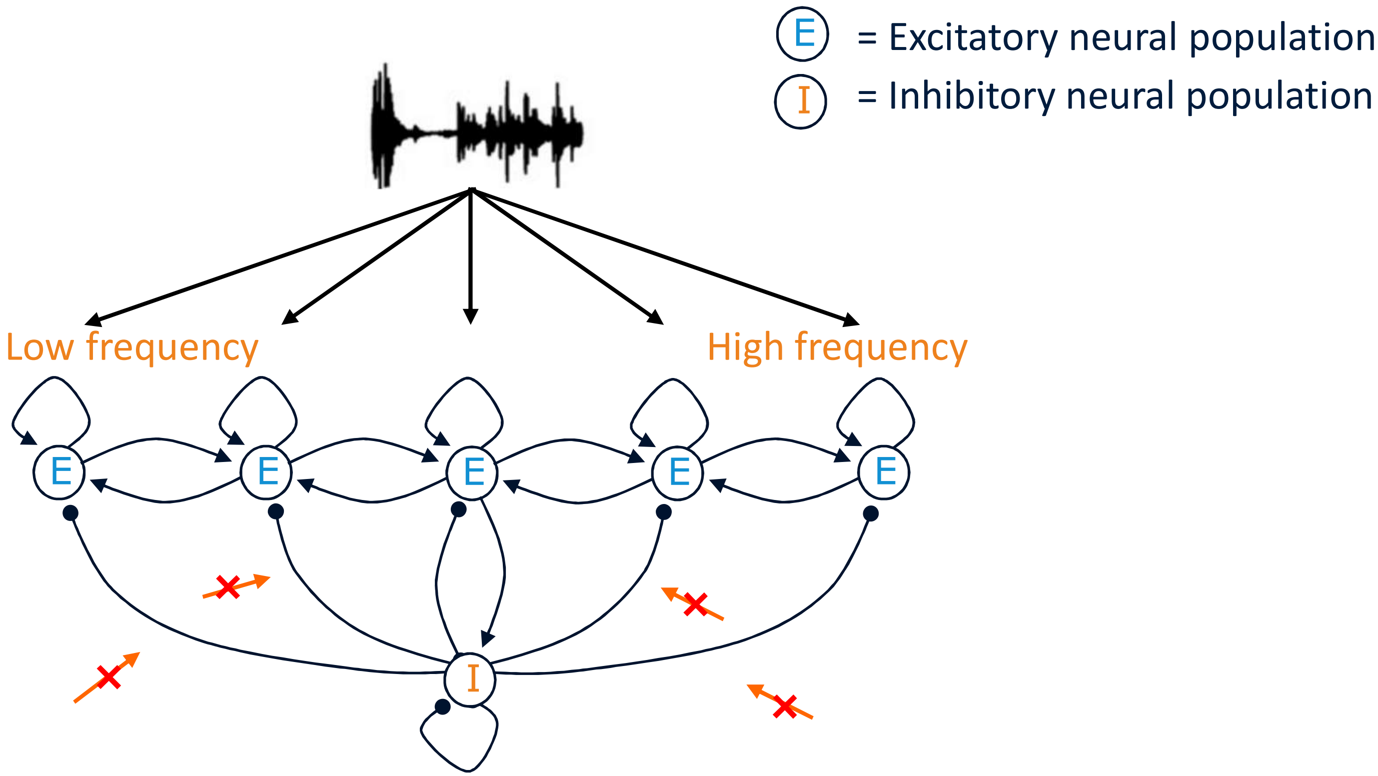


Zulfiqar et al., 2020

WCCM of auditory cortex

Zulfiqar et al., 2020

WCCM of auditory cortex



- Study auditory attention: how are irrelevant sounds filtered out?
- Study the mechanism underlying tinnitus

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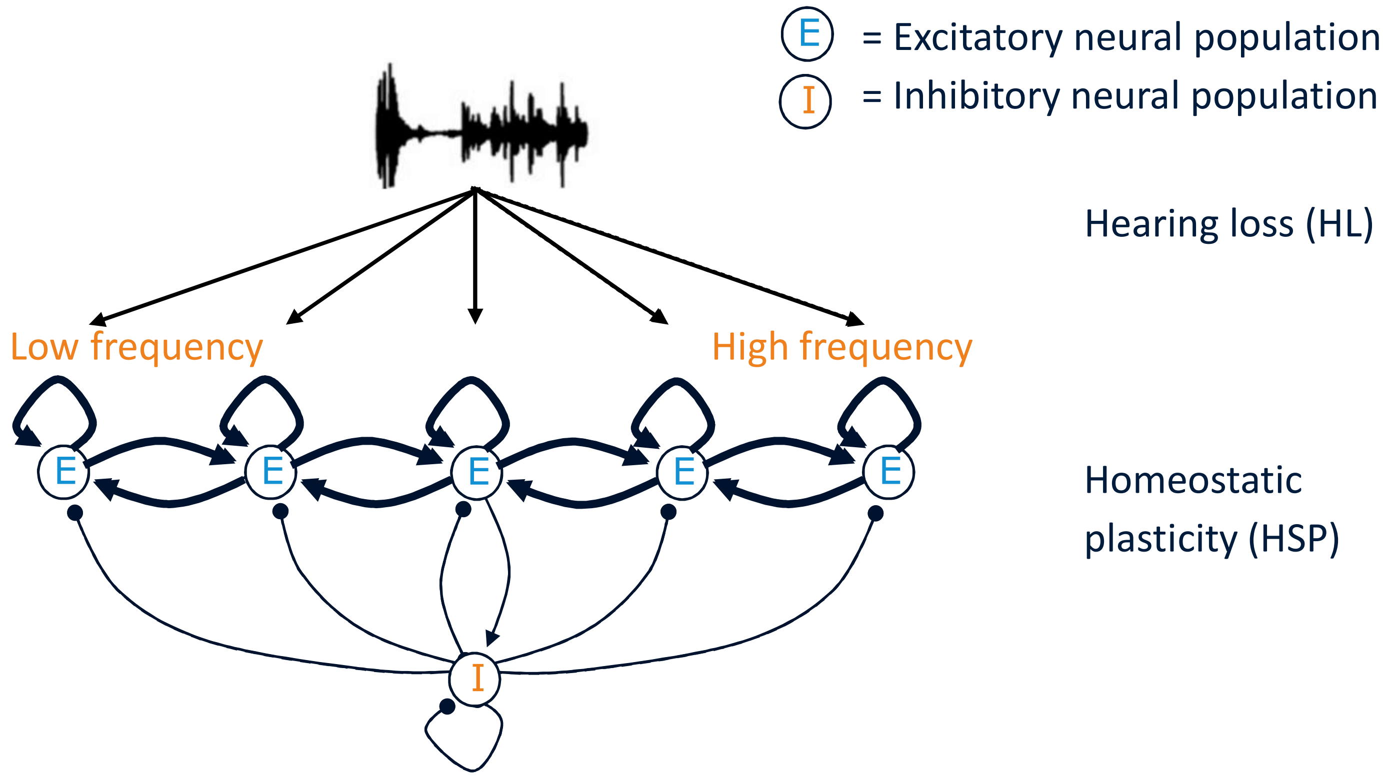
Zulfiqar et al., 2020

Model of homeostatic plasticity following hearing loss



Homeostatic plasticity (HSP)

- Compensate for decreased neural activity due to hearing loss
- Increase excitability and weaken inhibitory transmission

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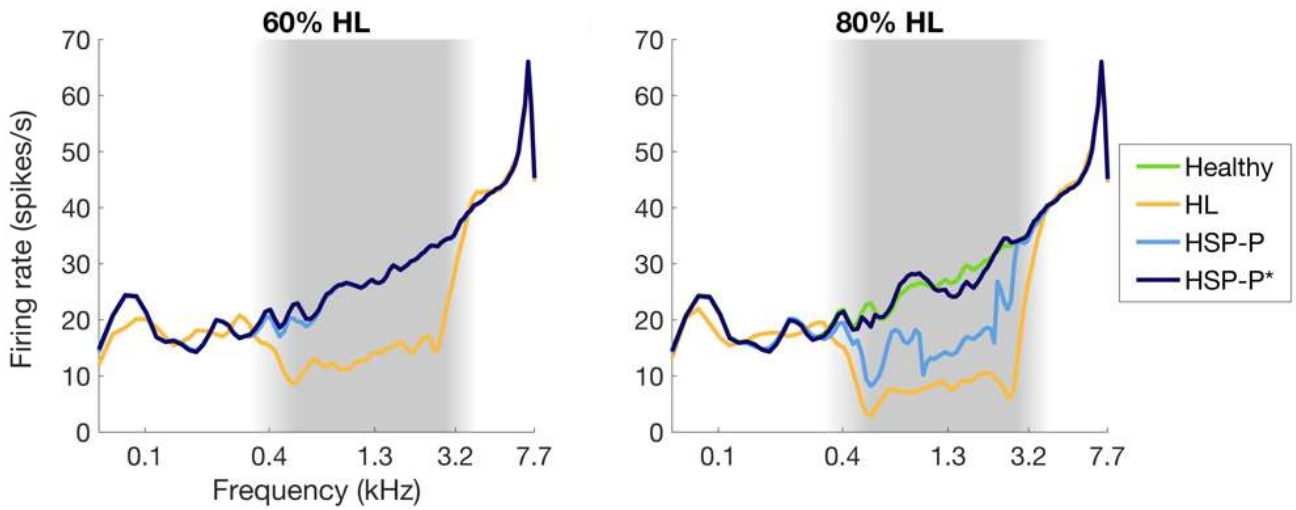
Schultheiβ et al., submitted

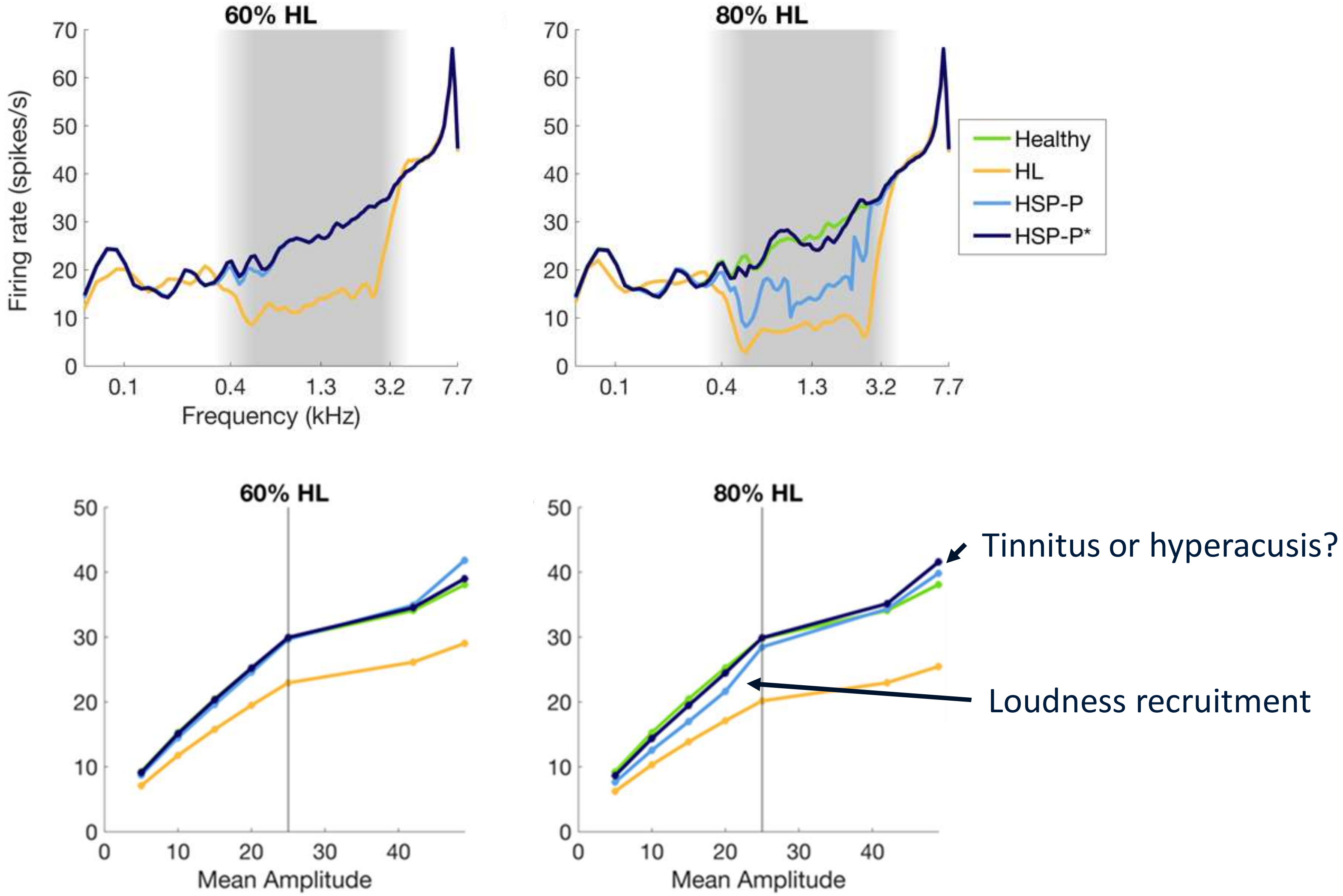
Model of homeostatic plasticity following hearing loss



Up to moderate levels of hearing loss, homeostatic plasticity (HSP) can compensate for the input reduction

Schultheiβ et al., submitted

Model of homeostatic plasticity following hearing loss

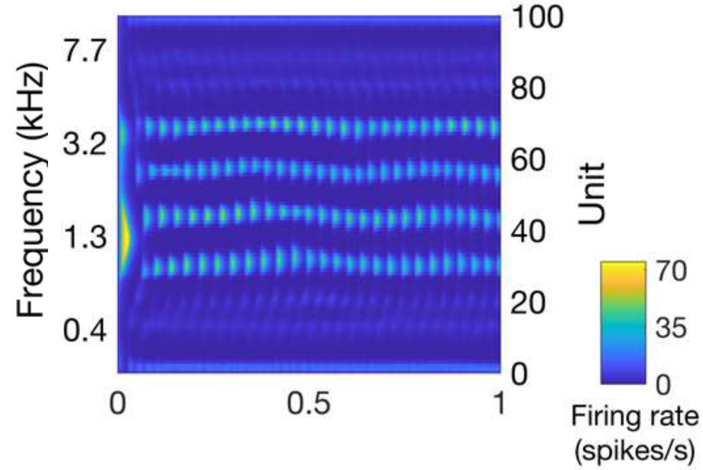


Schultheiβ et al., submitted

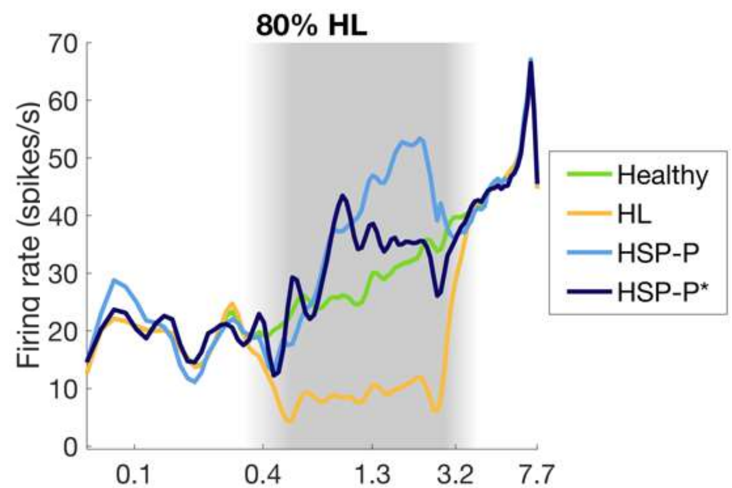
Model of homeostatic plasticity following hearing loss

After adding neural noise to the model:

Evidence of model instability
Spatiotemporal oscillations



Increased sound driven responses



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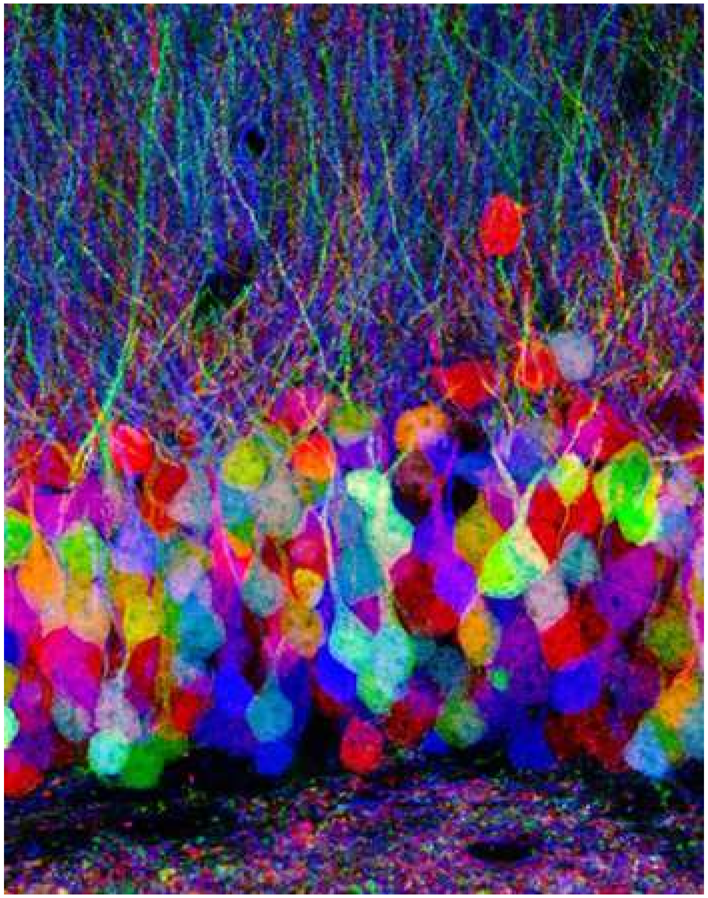
Schultheiβ et al., submitted

Overview

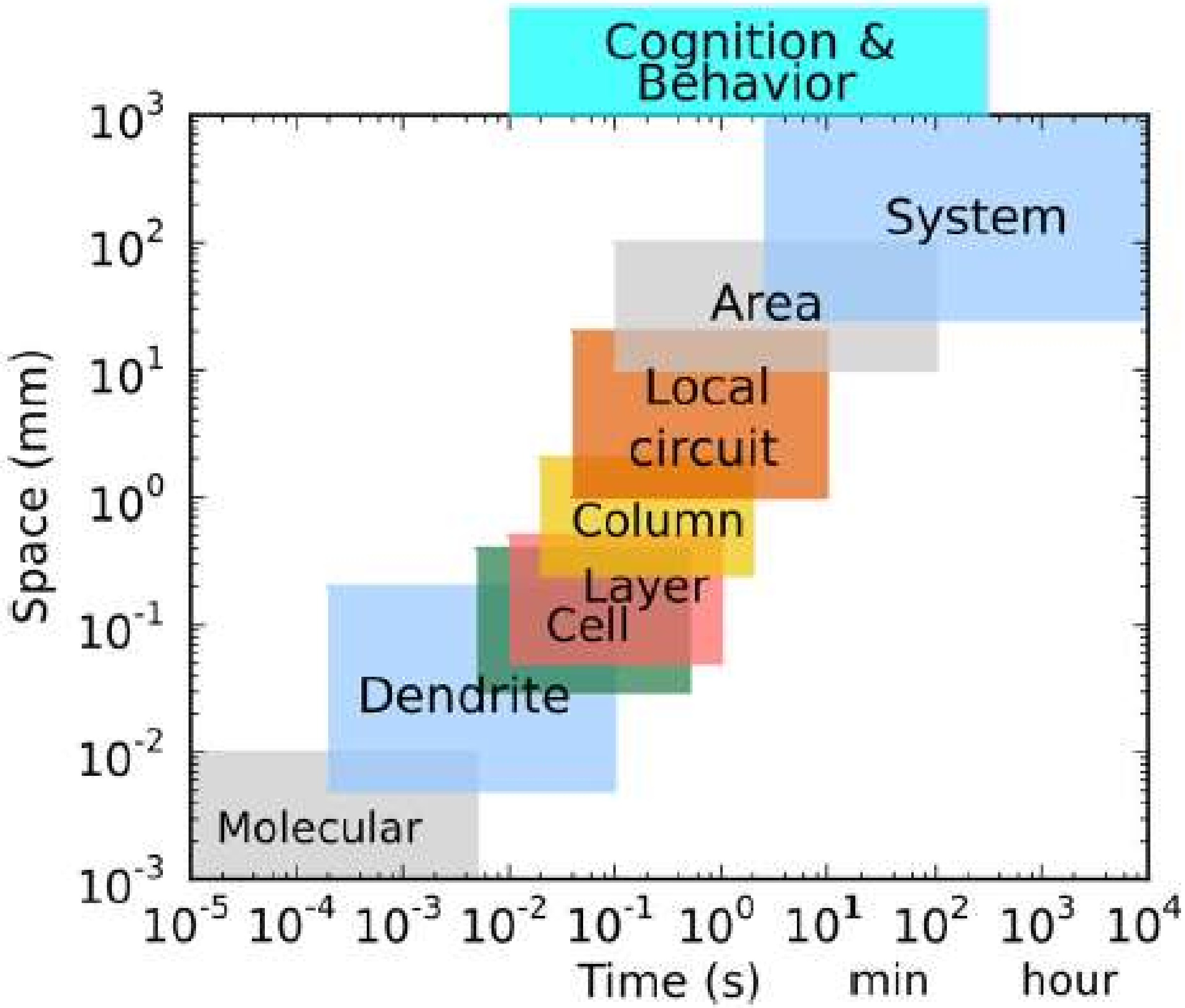
- **The brain as an organ to model**
  - Challenges
  - Current approaches
- **Single neuron models**
  - Hodgkin-Huxley model
  - Integrate-and-fire model
  - Compartmental modeling
- **Population level modeling**
  - Neural encoding
  - Wilson-Cowan model of the auditory cortex
- **Multiscale modeling**



Modeling the brain

Scales:

- Macro
- Meso
- Micro



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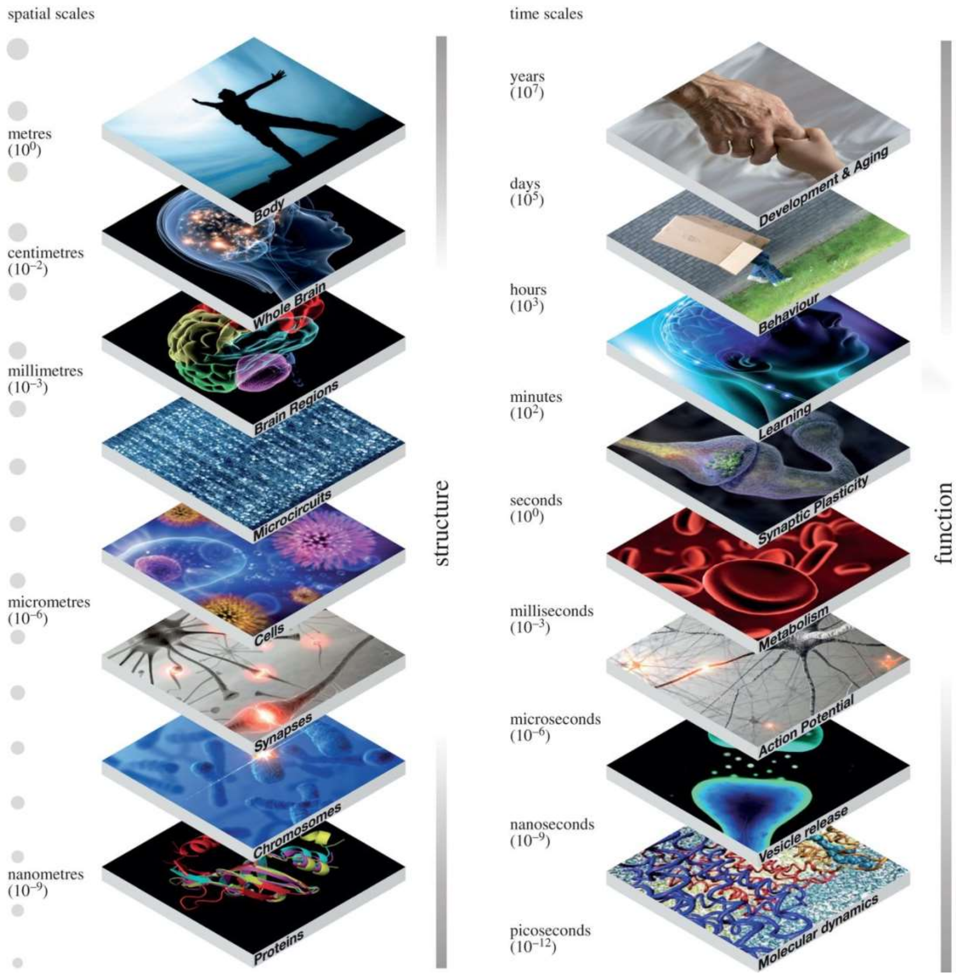
Multiscale modeling



Needed due to limited computational power

Model is **multiscale** if:

- Modeled object spans multiple time/space scales
- Parts of the model run with different scales
- These model parts influence each other

Can be extremely challenging!