HERTIE INSTITUTE FOR AI IN BRAIN HEALTH

Simulation and Inference in Neuroscience

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GEMEINNÜTZIGE Hertie Stiftung

Lecture 1

What is Hertie AI?

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- Institute at the Medical School of the University of Tübingen
- Research at the interface between AI and clinical neuroscience
- Funded by the Chartiable Hertie Foundation
- Two departments:
    - Data Science
    - Machine Learning

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www.hertie.ai

Models in science

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Making models is part of the scientific method

Models capture some aspect of reality

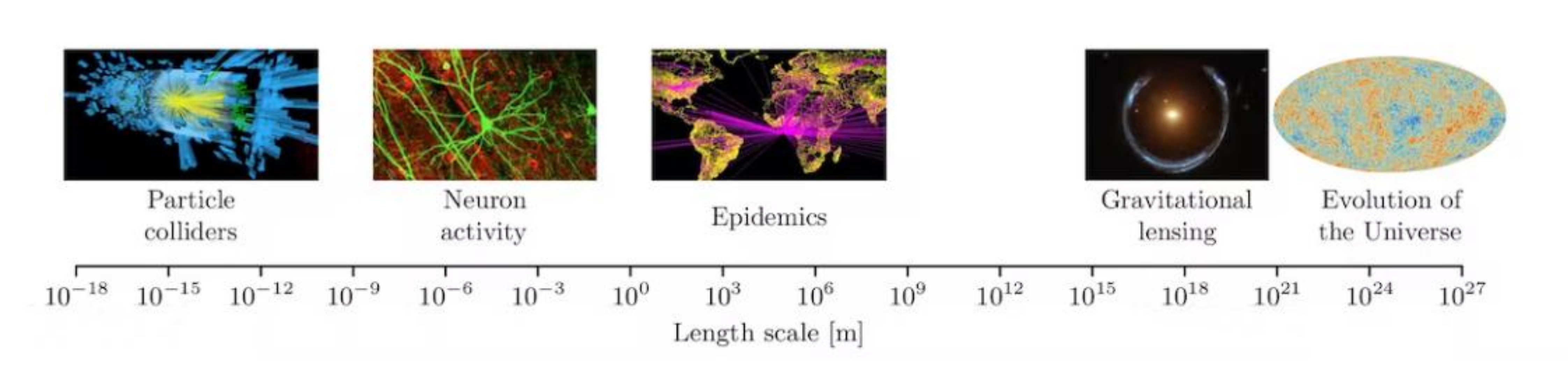
Models are testable and make predictions

- Didactic models
- Idealized models

- Phenomenological models
- Computational models
- Living models

https://plato.stanford.edu/entries/models-science/

Models in science



DNA double helix

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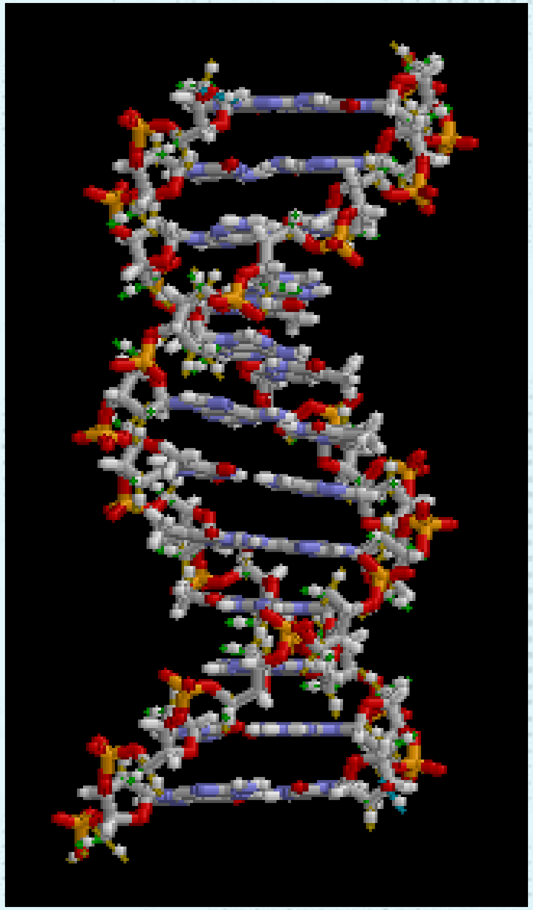
Physical model

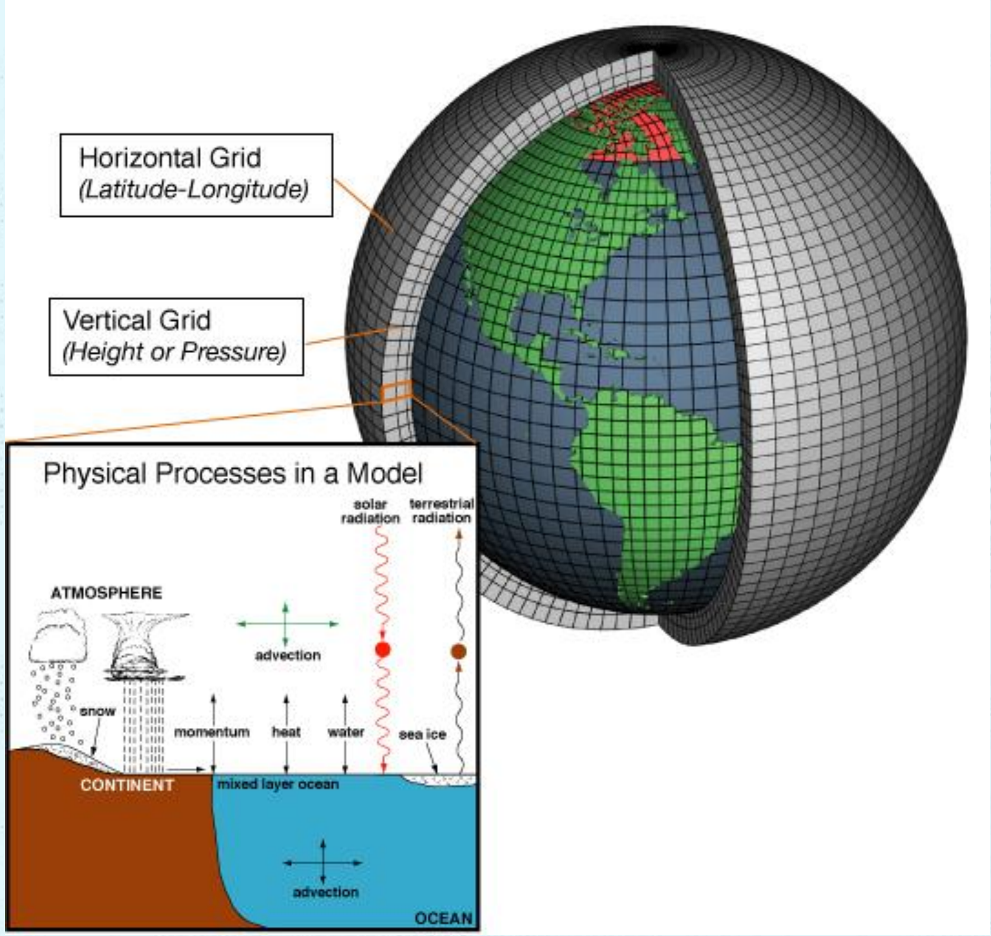
Explains previous data, e.g. X-ray diffraction images

Makes predictions about function of enzymes, consequences of mutations and ...



Climate model

- Describes physical processes: material in each cell and how energy moves around
- Based on our knowledge of physics and chemistry
- Consists of equations
- Can be simulated, i.e. computed in a computer

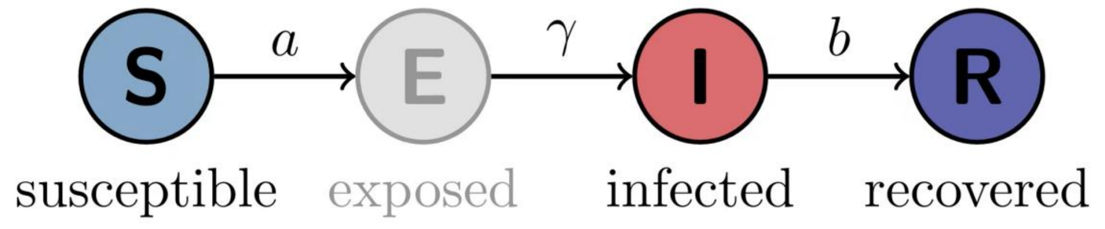


Simulation in science

Equations define explicit model

- Ordinary differential equations
- Partial differential equations
- Stochastic differential equations
- …

If there is no analytic solution, use numerical integration to solve the equation

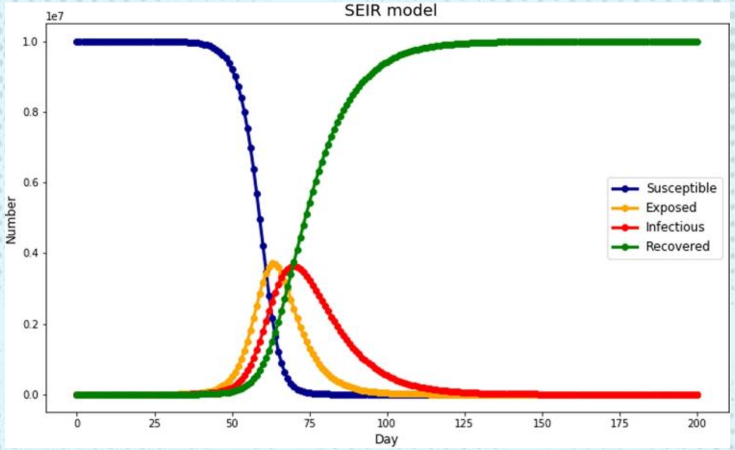


$$\frac{dS}{dt} = -aSI$$

$$\frac{dE}{dt} = aSI - \gamma E$$

$$\frac{dI}{dt} = \gamma E - bI$$

$$\frac{dR}{dt} = bI$$



Simulation vs. statistical models

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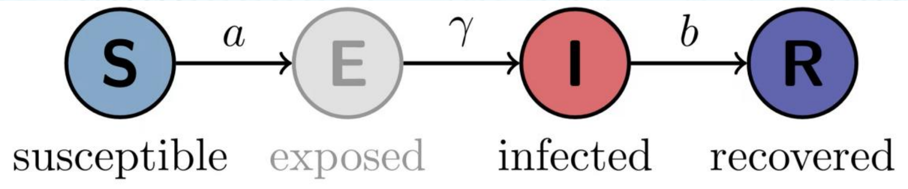
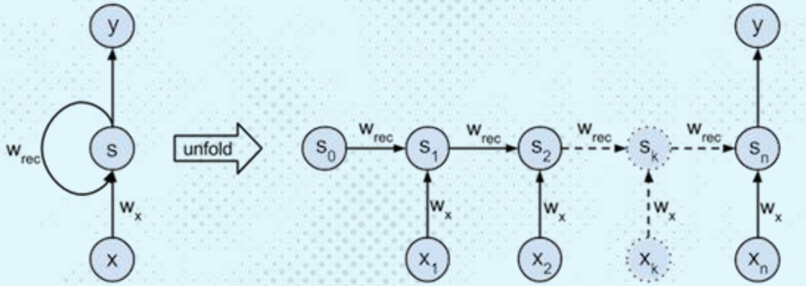
ODE-based SIR model

- ODE, limited modeling repertoire
- Use rate constant for modeling kinetics
- Few interpretable parameters
- Expresses knowledge about world



Recurrent Neural Network model

- RNN, flexible approximator
- Specific architecture to fit temporal correlations in data
- Many opaque parameters
- Model hard to interpret
- Data hungry
- Unclear extrapolation



Simulation and inference?

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- From parameters to measurements:
  simulation - *forward problem*
- From measurements to parameters:
  parameter estimation - *inverse problem*

  - Classical modeling (hand-tuning, experiments)
  - Point estimates via optimization
  - Parameter estimates with uncertainty

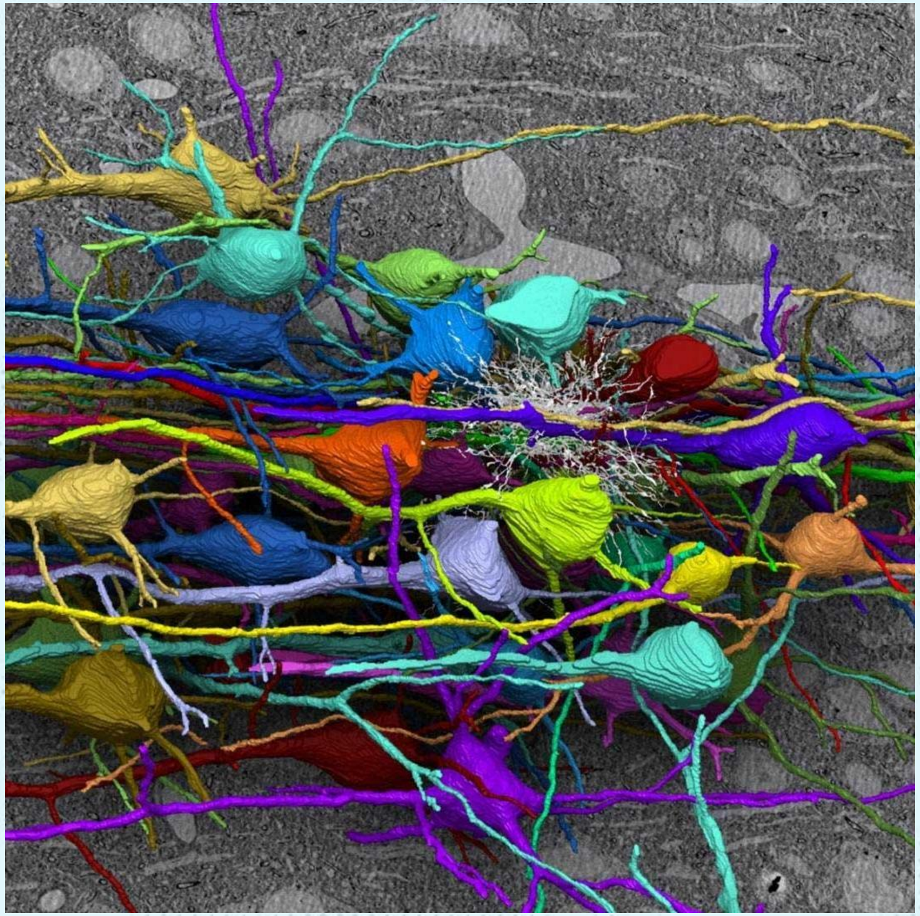
- Modern ML techniques for this will be the content of week 2 and 3!

Overview of the course

- Week 1:
  - Neuroscience basics
  - Mechanistic models in neuroscience
  - Implementing and simulating models
- Week 2:
  - Bayesian parameter inference
  - Simulation-based inference (SBI) basics
  - Implementing examples to get experience with SBI
- Week 3:
  - Advanced SBI techniques
  - Mini-project

Why neuroscience?

- Understanding to organ that allows us to do science is fun
- Neurological diseases are a major burden on society (dementia, multiple sclerosis, ...)
- There is amazing data!



Zeiss

What does neuroscience do?

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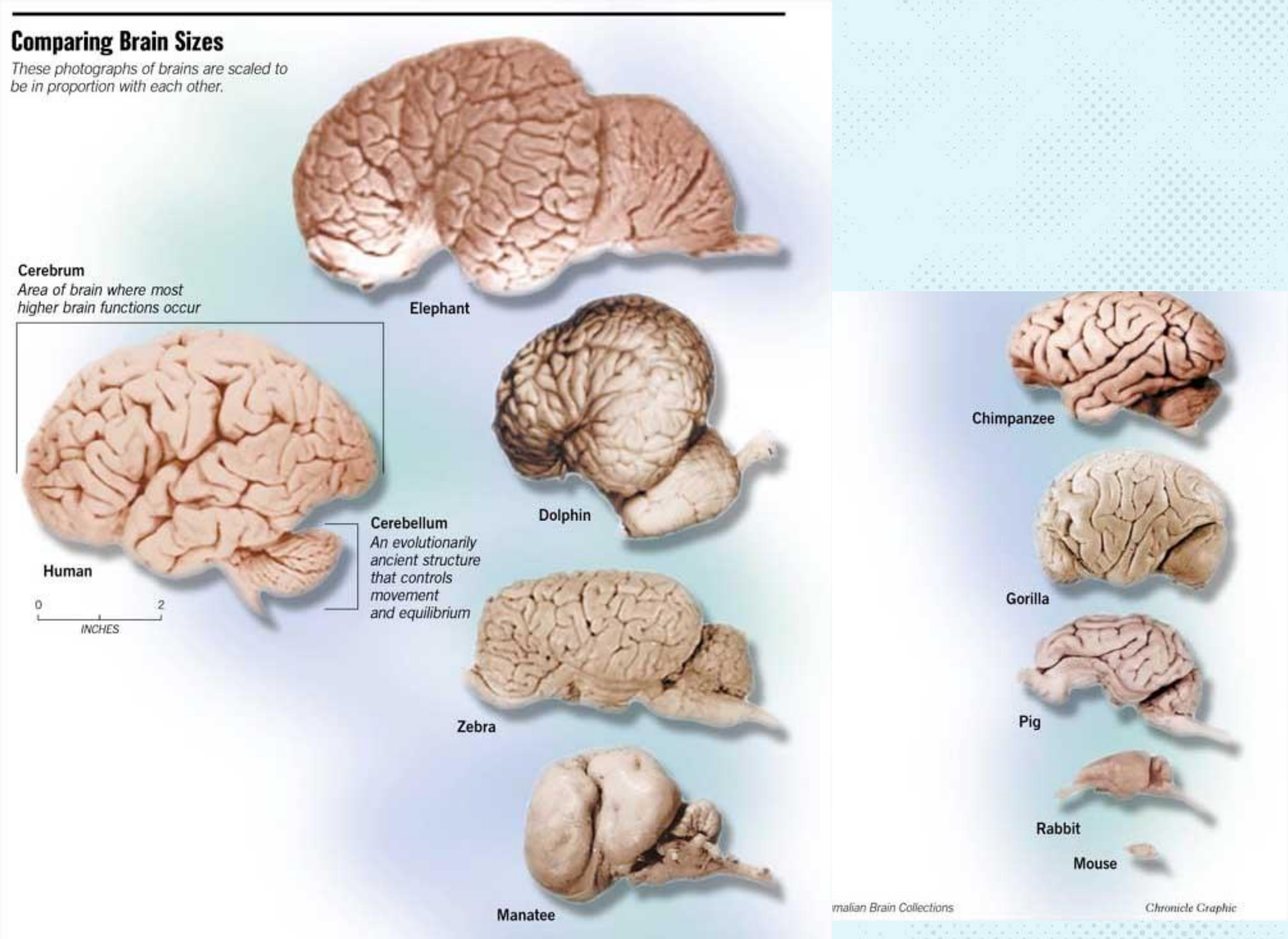
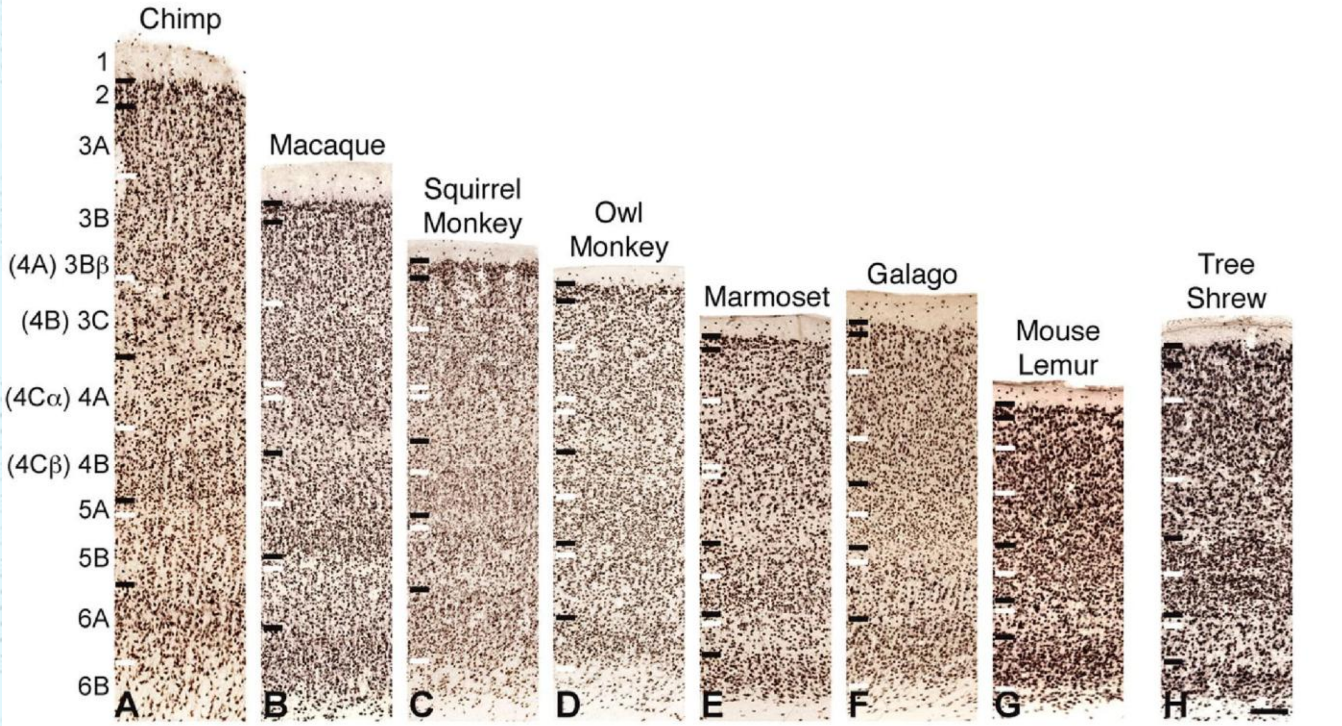
- Understand brain function on different levels – from psychological to cellular or even subcellular
- Figure out mechanisms of how the healthy brain works and how it changes in disease
- Test a hypothesis
    - ➢Measure neuronal activity
    - ➢Make mathematical models of neuronal activity

Mammalian brains



Layers of neurons



Balaram & Kaas 2014 Front Neuroanat

Different layers, different cells

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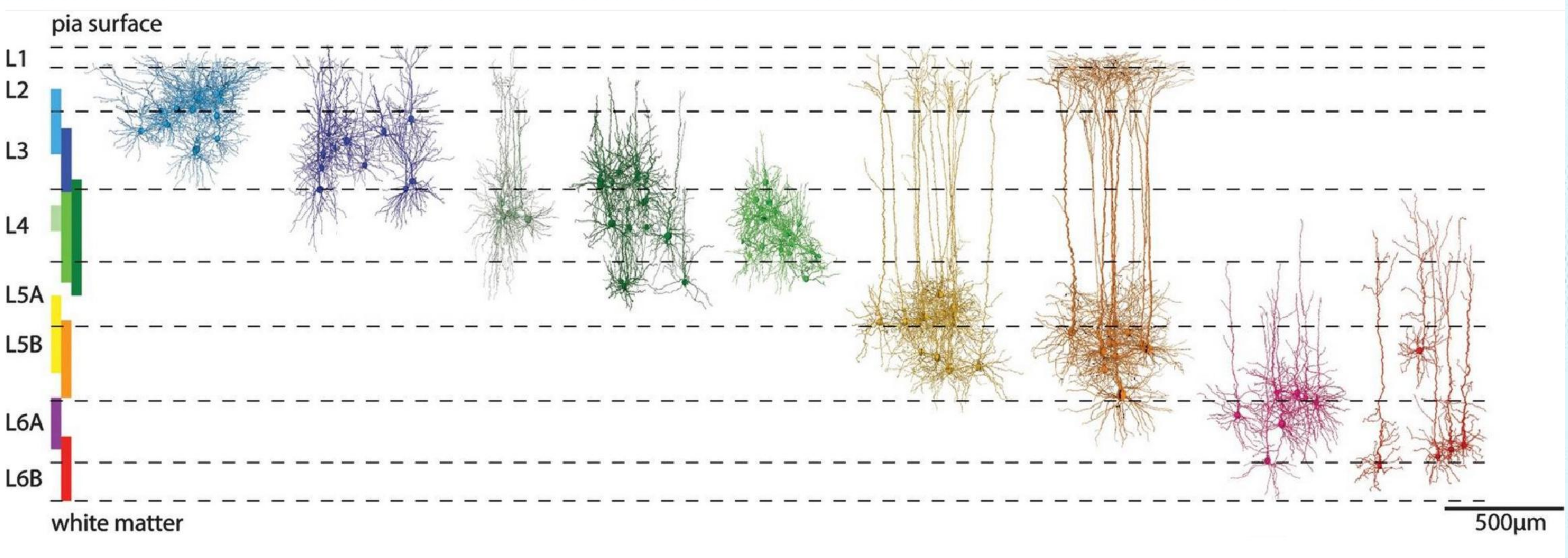

Oberlaender et al. 2012

A prototypical neuron

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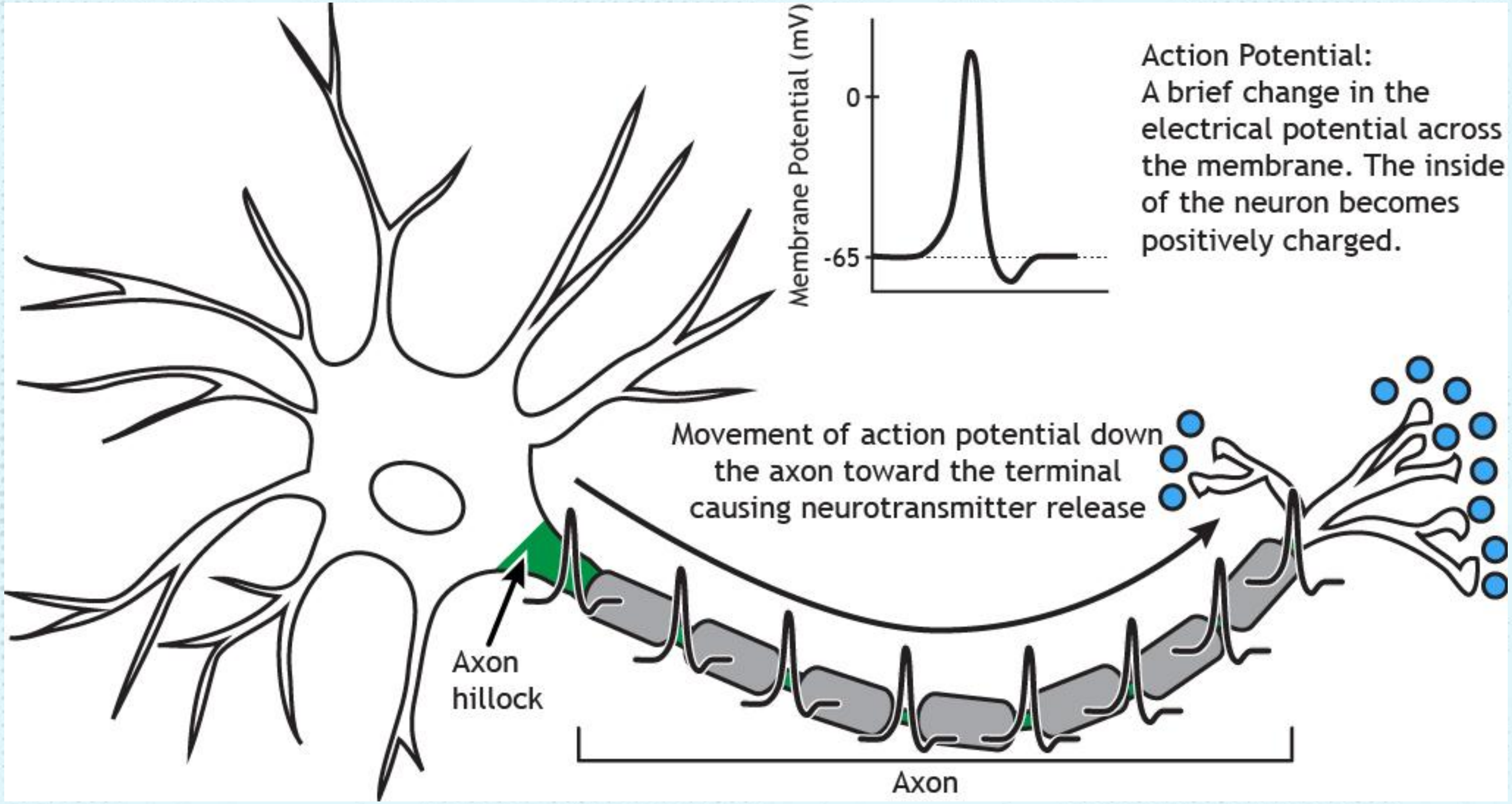

Neural recording techniques

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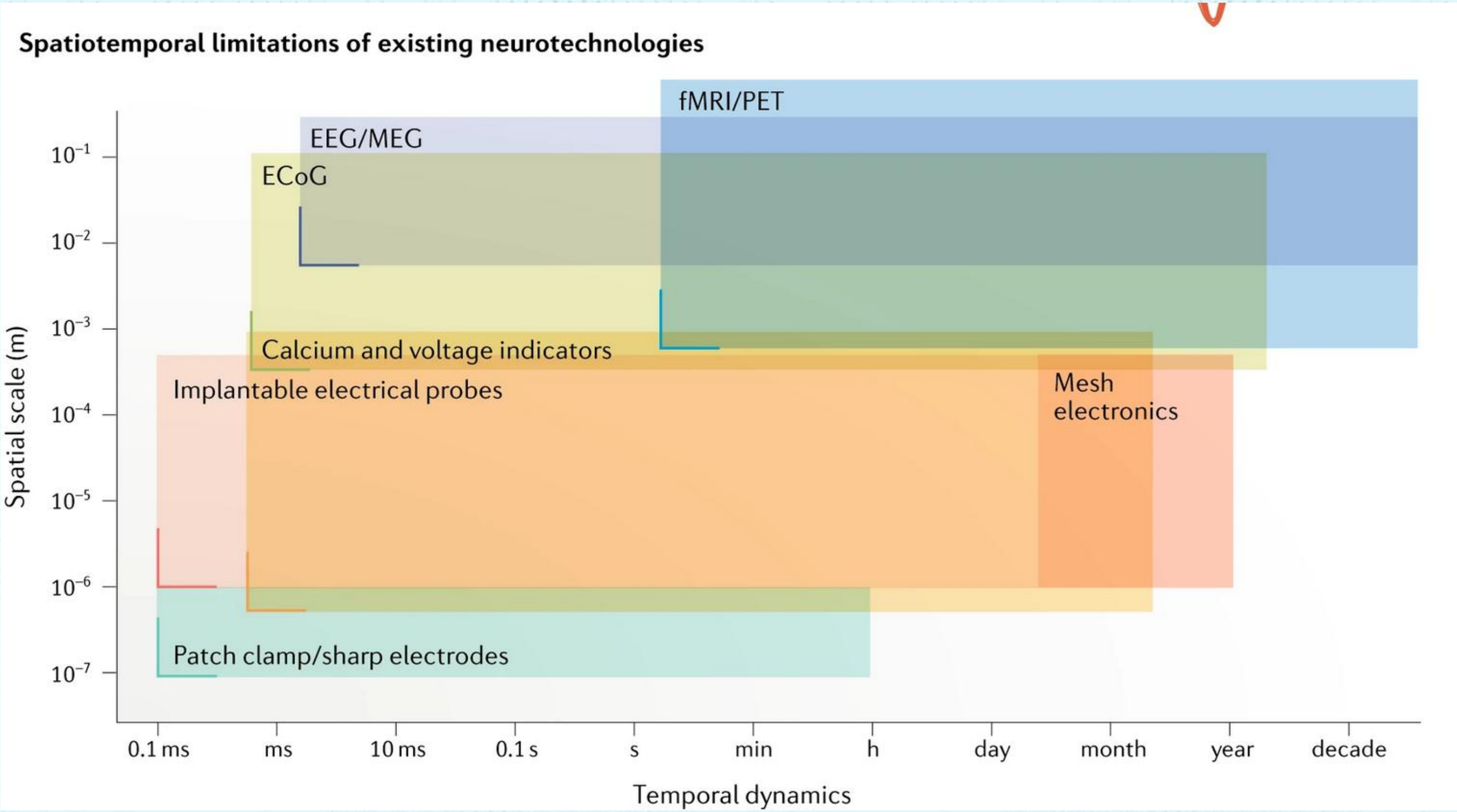
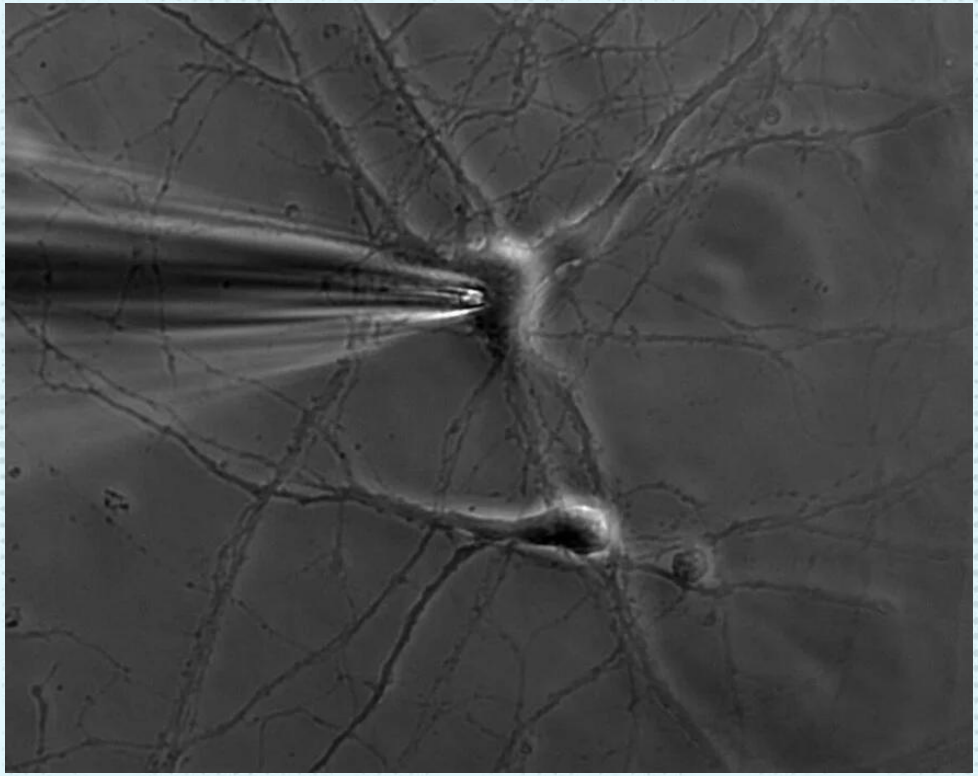
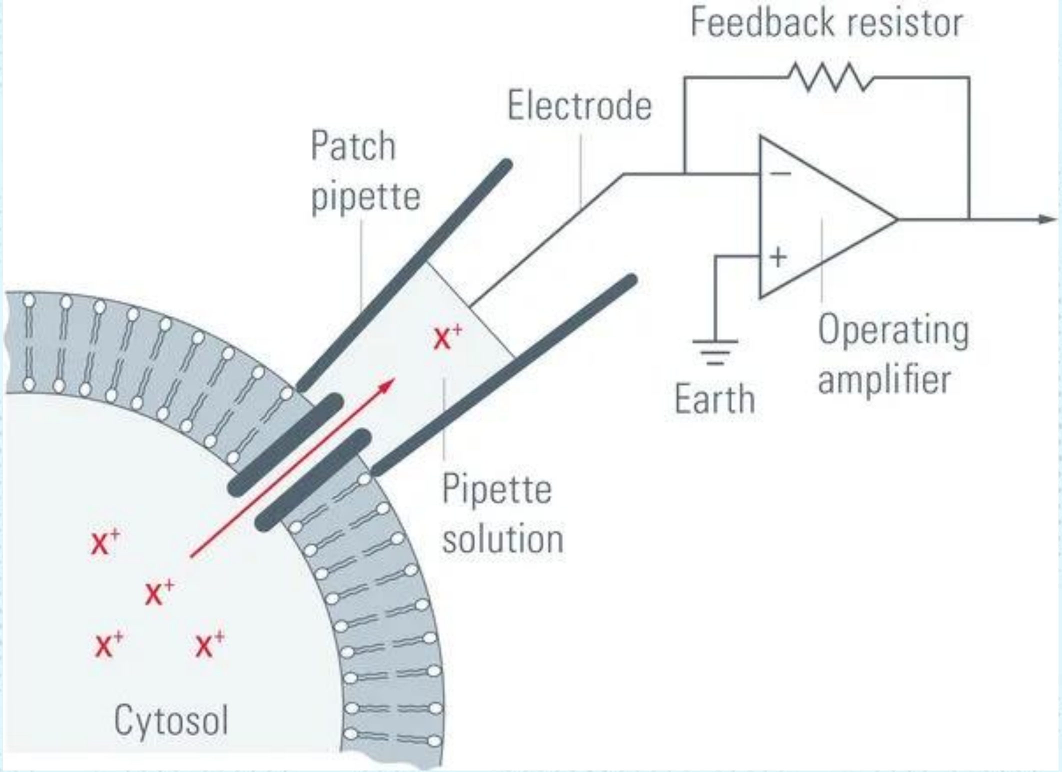


Patch-clamp electrophysiology





Leica

Electrical properties of neurons

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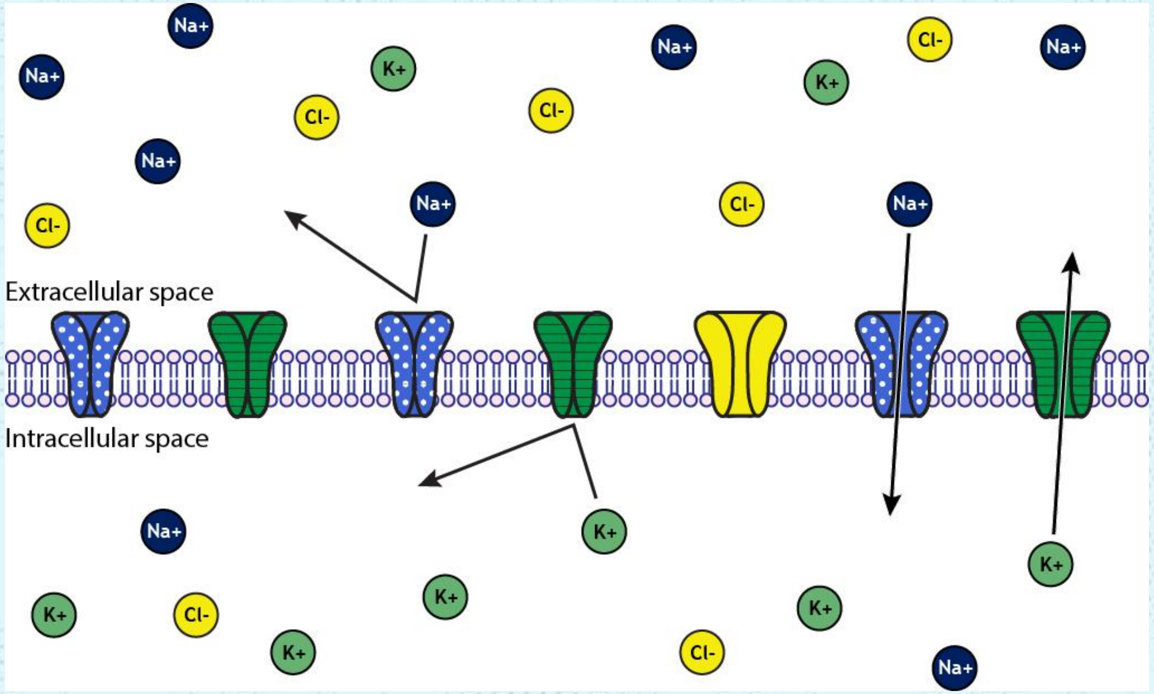
- Lipid bilayer acts as capacitor separating charges
- Ion channels with pores allow certain ions to pass often depending on voltage or ligands
- Ion pumps maintain ion gradient
- Membrane potential V_T outside is defined to be 0
- V_T is between -90 and +50 mV



Intracellular resistance

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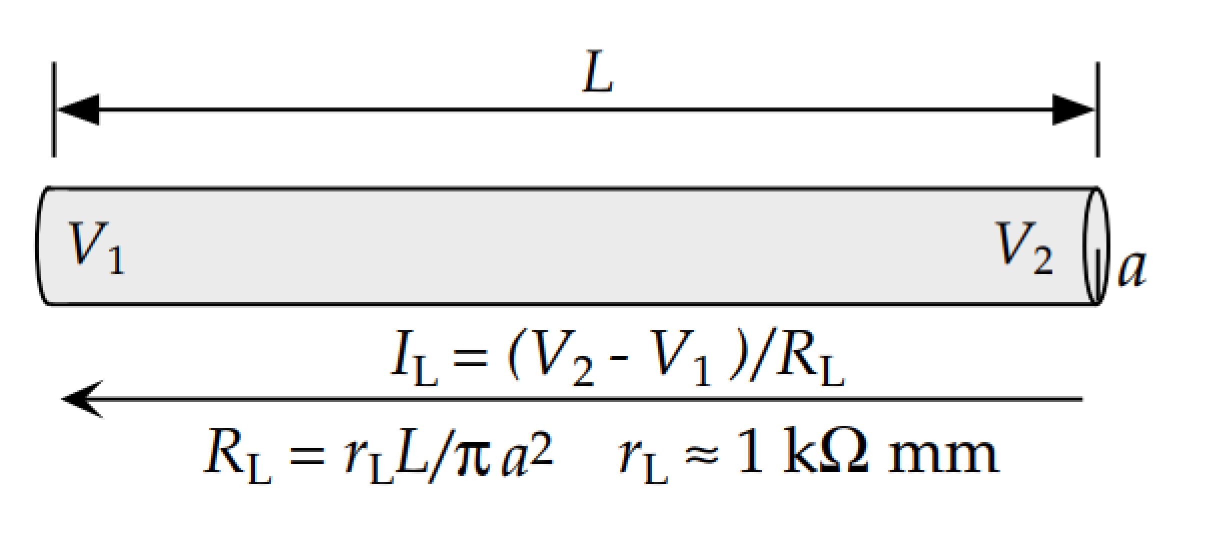
- Membrane potential can vary across dendrite / axons

  → ions flow inside the cell against resistance of intracellular medium

- Resistance: ~L
  ~1/a²



Dayan & Abbott, 2001

Membrane capacitance & resistance

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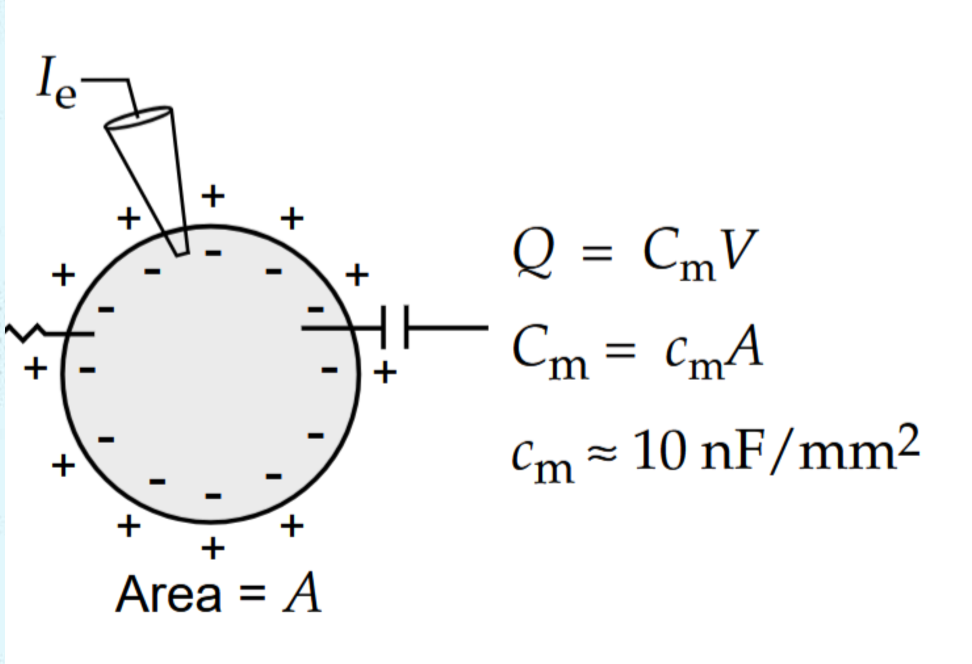
- Electrotonically compact neuron: Single compartment

- How much current is required to change the membrane potential?

$$C_m \frac{dV}{dt} = \frac{dQ}{dt}$$



Dayan & Abbott, 2001

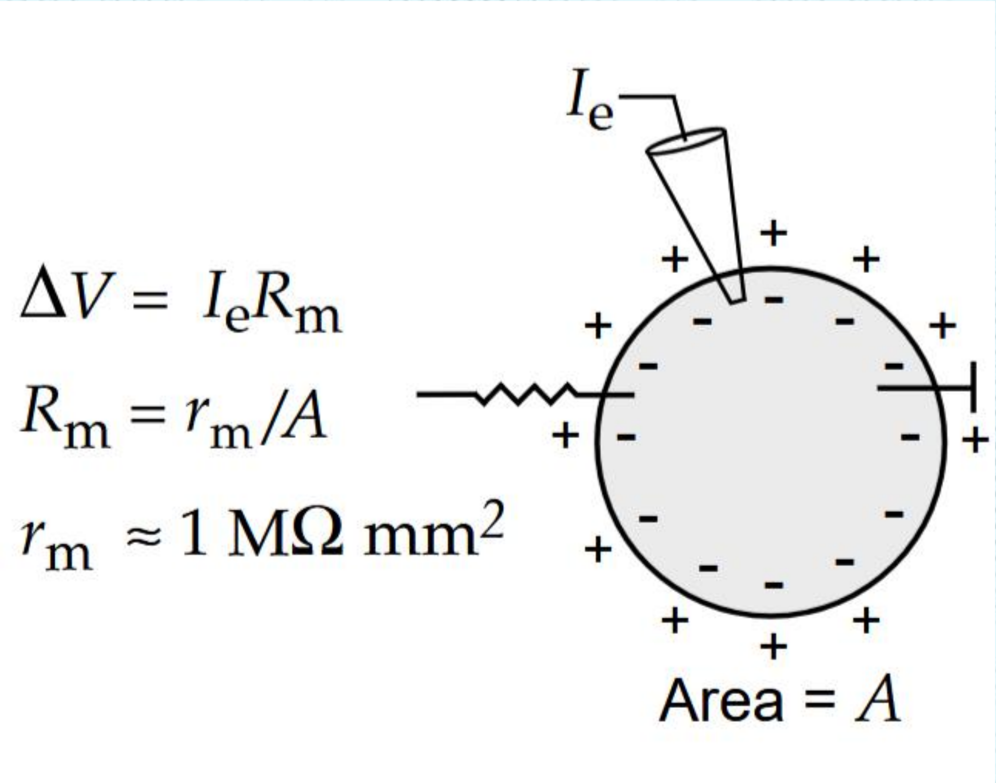
Membrane capacitance & resistance

- How much current is required to keep the membrane potential at a level different than its resting value?

- Determined by membrane resistance

- Membrane time constant:

$$\tau_m = r_m c_m$$



Dayan & Abbott, 2001

Equilibrium potential

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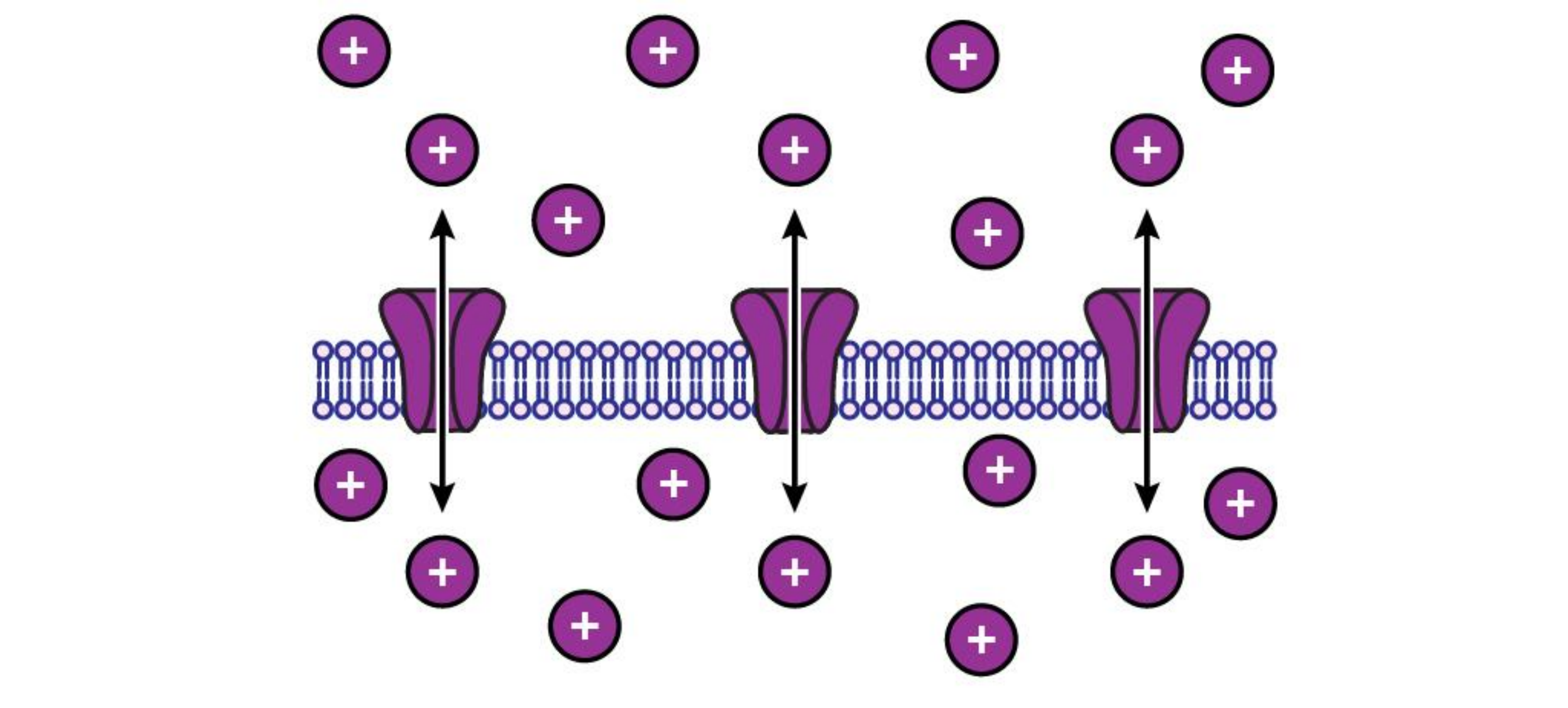
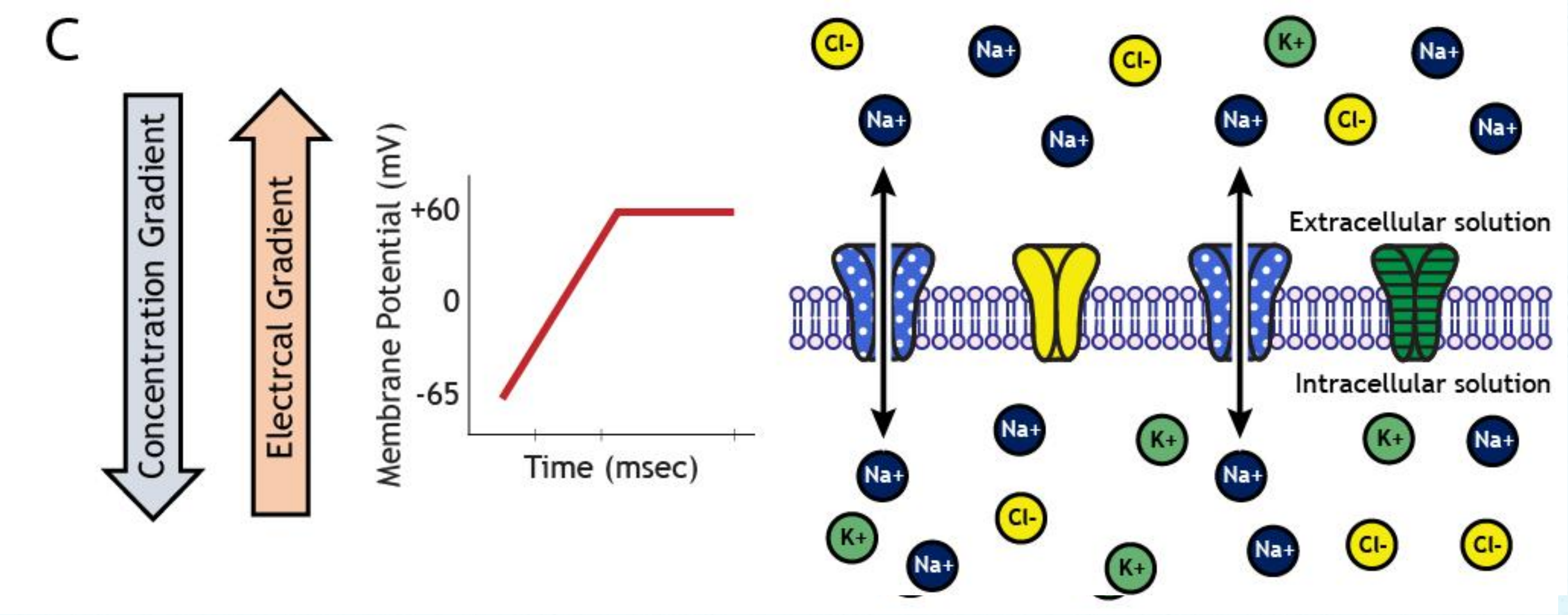


Equilibrium potential of Sodium



Equilibrium potentials

- Nernst equation:

$$E = \frac{V_T}{z} \ln\left(\frac{[\text{outside}]}{[\text{inside}]}\right)$$

- $E_{Na} = +50\, mV$
- $E_K = -70\, mV$

- V > E: positive current will flow outward
- V < E: positive current will flow inward

- What is the effect of Na-channels?
- What of K-channels?

Resting potential

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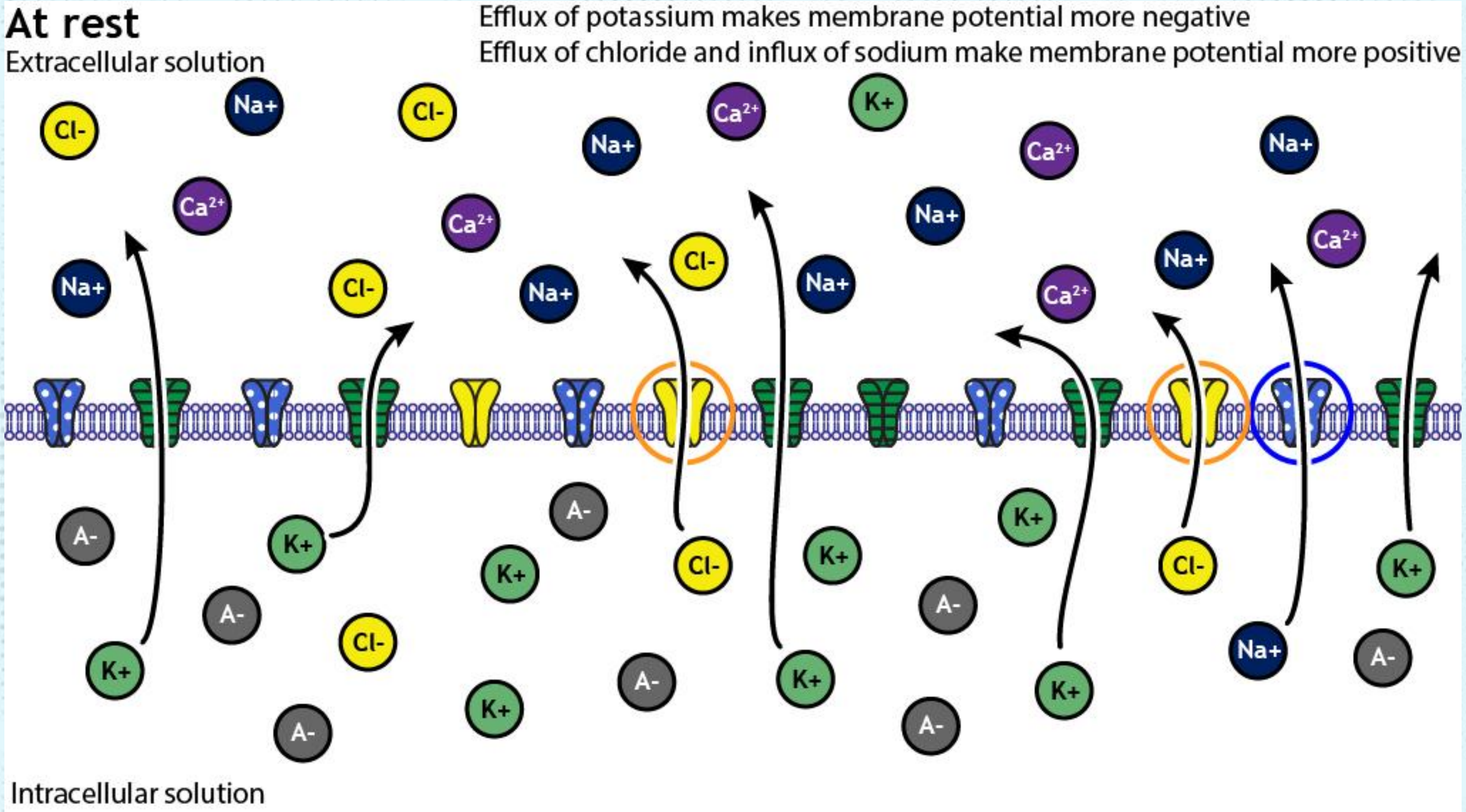

Membrane current

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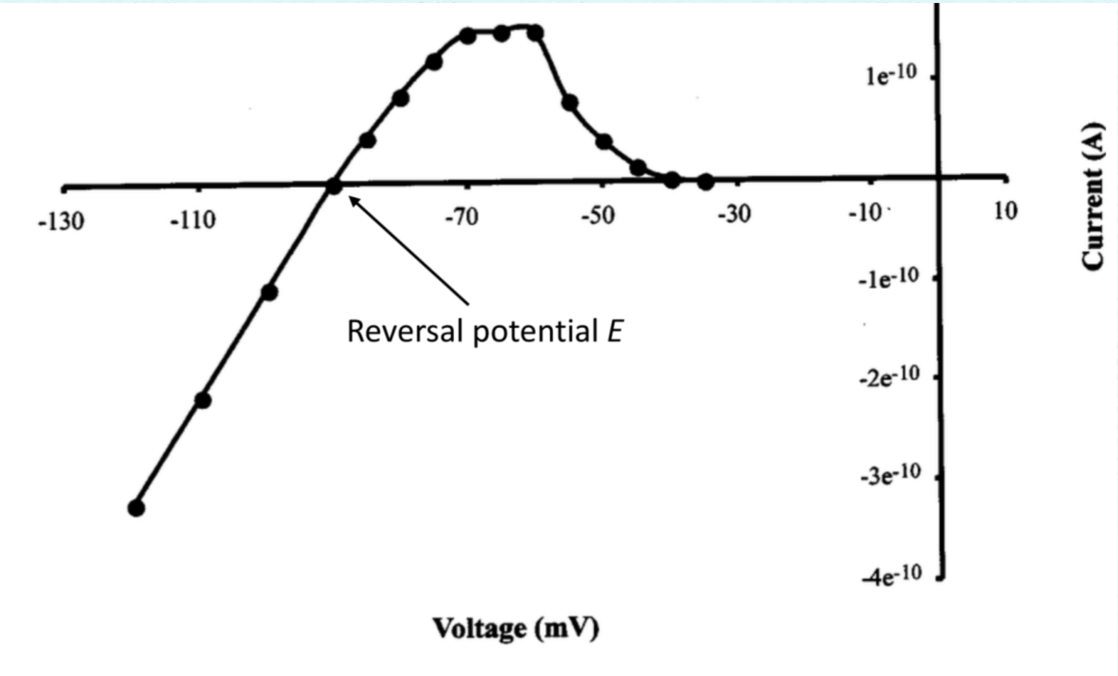
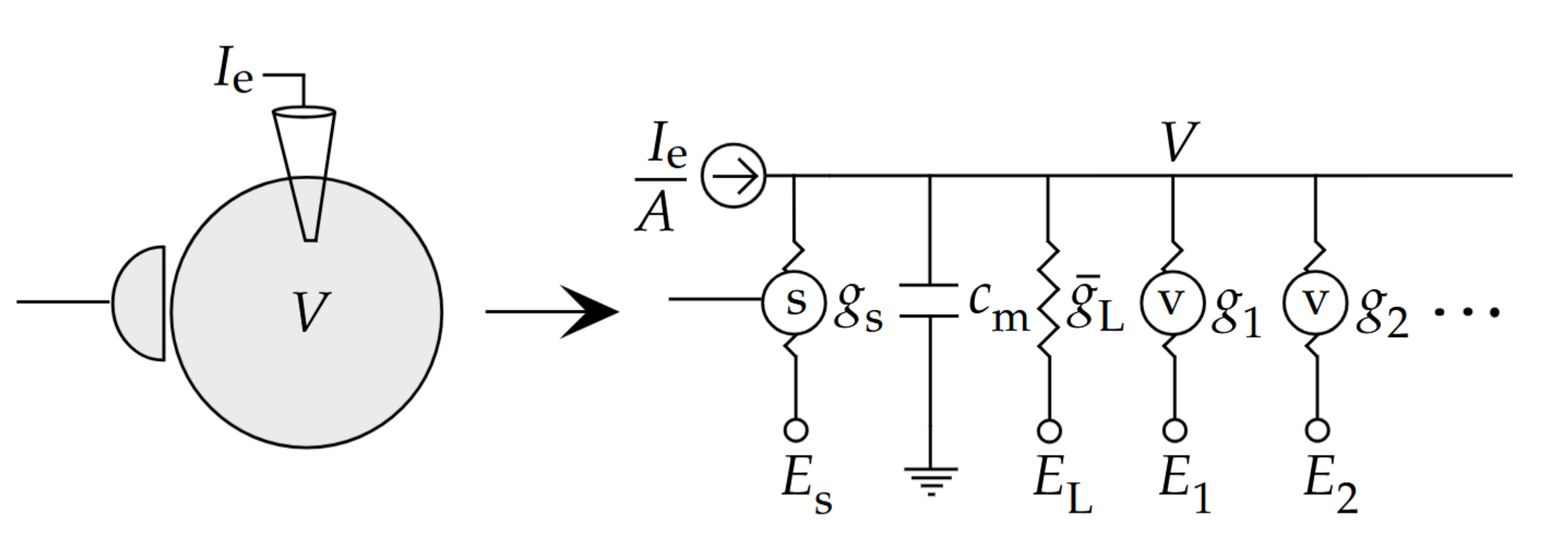
- Total flow of ions across the membrane

$$i_m = \sum_i g_i (V - E_i)$$



- g_i conductance, may change over time!
- g_l "leak", summarizes ion-pumps, passive channels....

Equivalent circuit model of a single compartment neuron

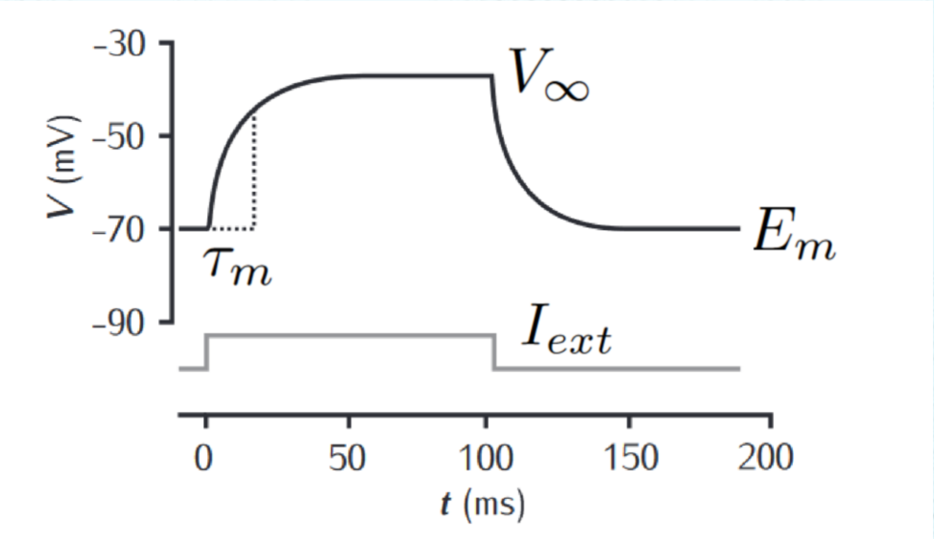


$$c_m \frac{dV}{dt} = -i_m + \frac{I_e}{A}.$$

Dayan & Abbott, 2001

Passive neuron model

$$c_m \frac{dV}{dt} = -i_m + \frac{I_e}{A}.$$

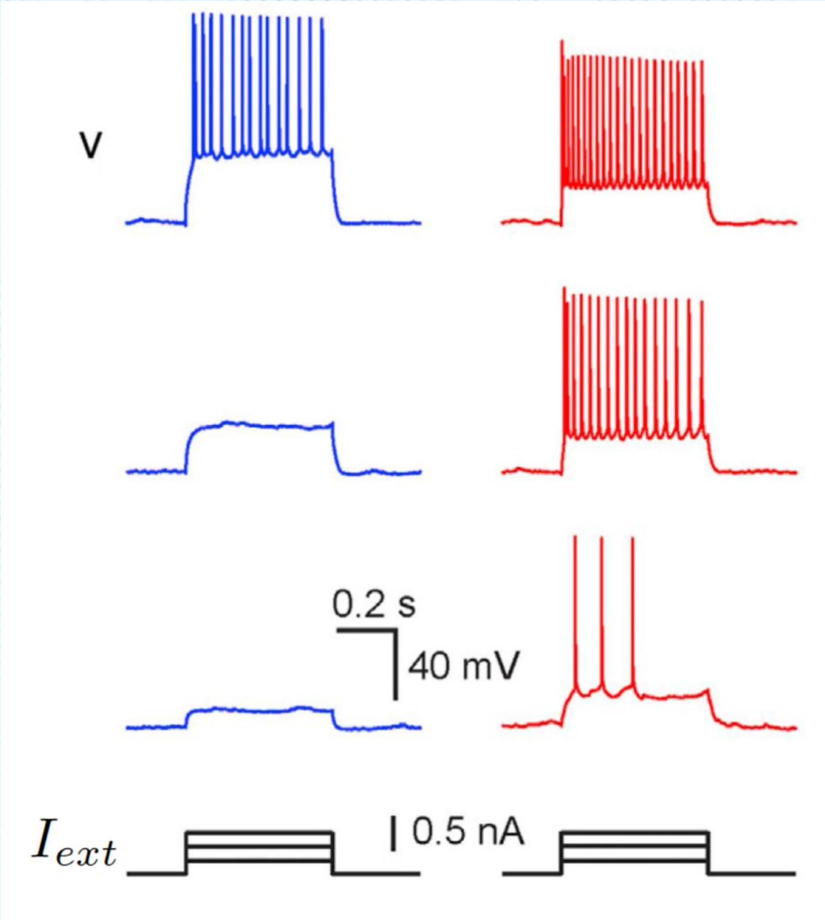


Angus Chadwick

$$V(t) - E_m = \boxed{e^{-t/\tau_m}(V(0) - E_m)} + \boxed{\frac{1}{g_m \tau_m}\int_0^t e^{-(t-t')/\tau_m} I_{ext}(t')dt'}$$

Decay of initial membrane potential towards resting potential

Low-pass filter of external current input (also called a "leaky integrator")



Angus Chadwick