

Electrochemistry of synapses and dendritic spines

Thibault LAGACHE

Biological Image Analysis Unit
INSTITUT PASTEUR

Advanced Biology Course in
Computational Neuroscience

Thibault.lagache@pasteur.fr

Outline

- Cell membrane potential
- Propagating the membrane potential in dendrites: Cable theory
- The peculiar geometry of dendritic spines
- Indirect estimation of spine neck resistance
- Electro-diffusion modeling of ions and potential dynamics in spines
- Inferring physical parameters from direct nanopipettes recordings

Outline

- Cell membrane potential
- Propagating the membrane potential in dendrites: Cable theory
- The peculiar geometry of dendritic spines
- Indirect estimation of spine neck resistance
- Electro-diffusion modeling of ions and potential dynamics in spines
- Inferring physical parameters from direct nanopipettes recordings

Ion compartmentalization at cell membrane

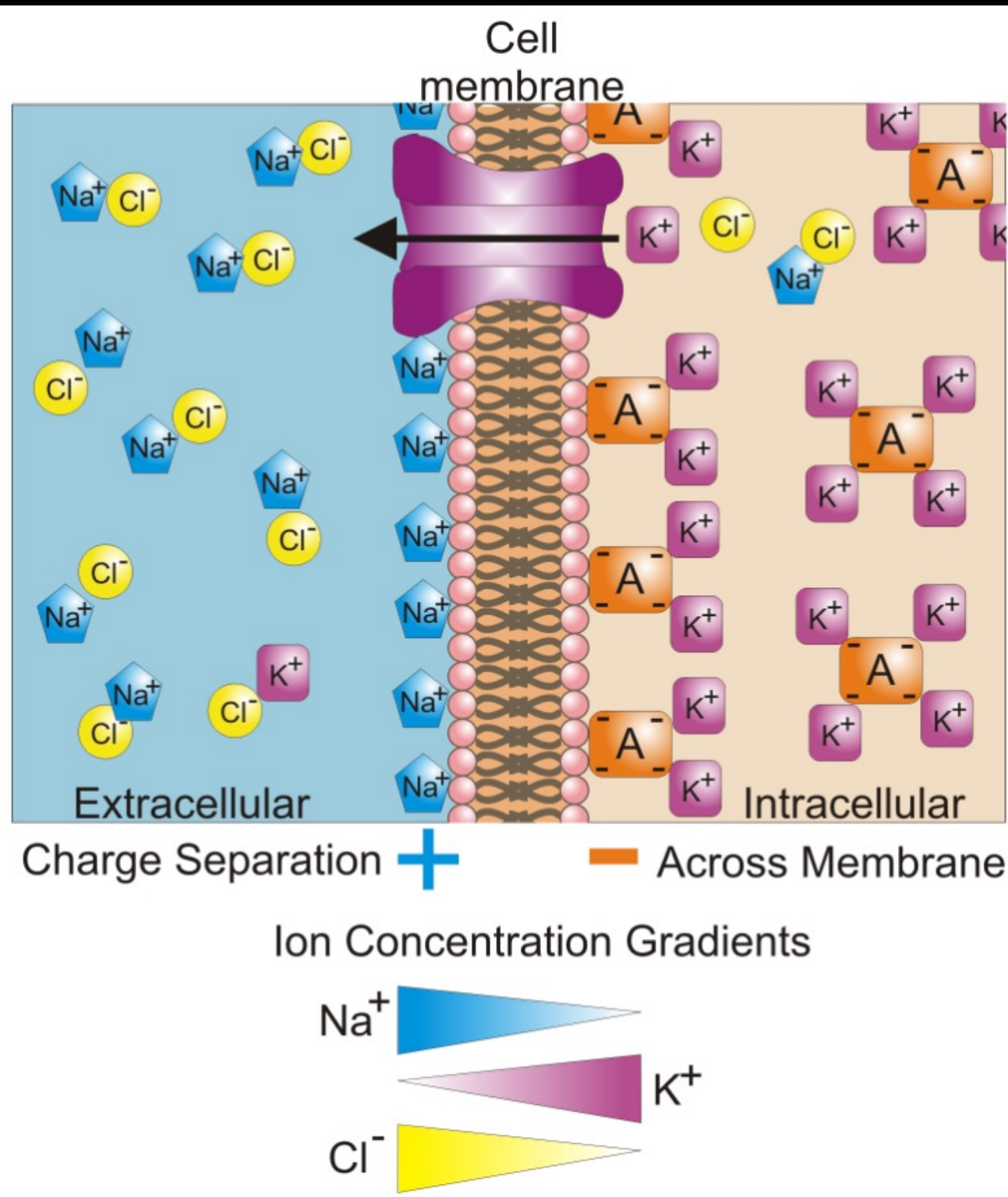


Table 11-1 Comparison of Ion Concentrations Inside and Outside a Typical Mammalian Cell

Component	Intracellular Concentration (mM)	Extracellular Concentration (mM)
Cations		
Na ⁺	5–15	145
K ⁺	140	5
Mg ²⁺	0.5	1–2
Ca ²⁺	10 ⁻⁴	1–2
H ⁺	7 × 10 ⁻⁵ (10 ^{-7.2} M or pH 7.2)	4 × 10 ⁻⁵ (10 ^{-7.4} M or pH 7.4)
Anions*		
Cl ⁻	5–15	110

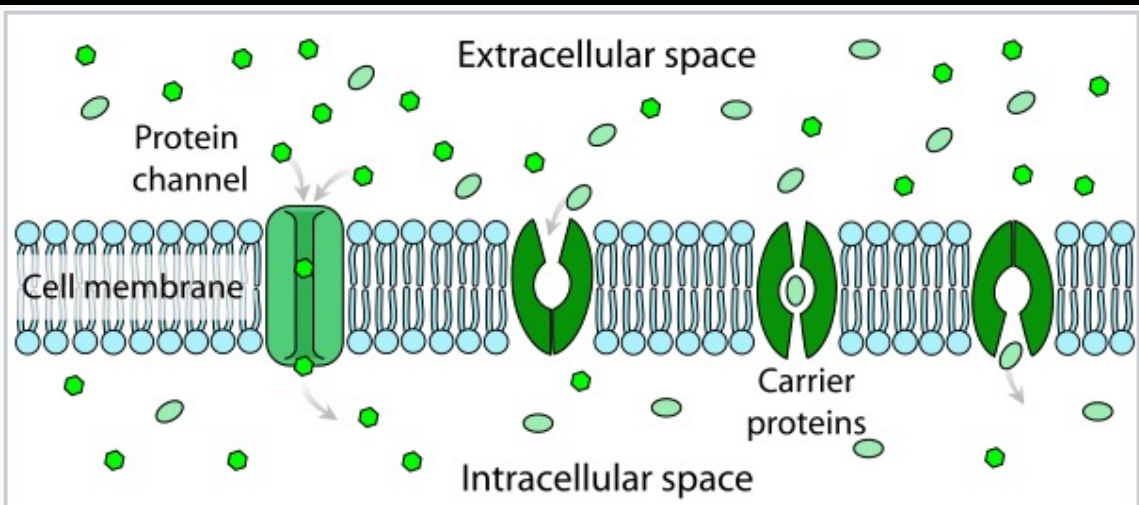
*The cell must contain equal quantities of + and – charges (that is, be electrically neutral). Thus, in addition to Cl⁻, the cell contains many other anions not listed in this table; in fact, most cellular constituents are negatively charged (HCO₃⁻, PO₄³⁻, proteins, nucleic acids, metabolites carrying phosphate and carboxyl groups, etc.). The concentrations of Ca²⁺ and Mg²⁺ given are for the free ions. There is a total of about 20 mM Mg²⁺ and 1–2 mM Ca²⁺ in cells, but this is mostly bound to proteins and other substances and, in the case of Ca²⁺, stored within various organelles.

Membrane potential

Cell membrane = lipid bilayer with proteins and ions channels

2 Roles:

- **Capacitor**: Accumulation of positively and negatively charged ions across the membrane create an electric field
- **Resistor** with limited permeability to ions. Permeability is increased by channels, ion pumps...



Membrane potential counter-balances the diffusion gradients of ions

The Nernst-Planck equation

Ion motion is driven by concentration gradient & electric field

$$J = -D\nabla c + \frac{DnF}{RT} cE$$

Across a lipid bilayer (thickness L) and a single ion species A

$$j_A = -D_A \left(\frac{d[A]}{dz} - \frac{n_A F}{RT} \frac{E_{m,A}}{L} [A] \right)$$

Reversal (membrane) potential for a single ion species A

Reversal potential counter-balances ion diffusion through the membrane

$$j_A = 0 \rightarrow \frac{d[A]}{dz} = \frac{n_A F E_{m,A}}{RT} [A]$$

$$\rightarrow \int_{in}^{out} \frac{d[A]}{[A]} = \frac{n_A F}{RT} E_{m,A} \rightarrow E_{m,A} = \frac{RT}{n_A F} \ln \left(\frac{[A]_{out}}{[A]_{in}} \right)$$

Goldman–Hodgkin–Katz equation for membrane potential

Reversal potential for multiple (monovalent) ion species

$$\sum_A n_A j_A = 0$$

$$E_m = \frac{RT}{F} \ln \left(\frac{\sum_{A^+} P_{A_i^+} [A_i^+]_{out} + \sum_{A^-} P_{A_i^-} [A_i^-]_{in}}{\sum_{A^+} P_{A_i^+} [A_i^+]_{in} + \sum_{A^-} P_{A_i^-} [A_i^-]_{out}} \right)$$

with $P_A = \frac{D_A}{L}$, the ion permeability

Component	Intracellular Concentration (mM)	Extracellular Concentration (mM)
Cations		
Na ⁺	5–15	145
K ⁺	140	5
Mg ²⁺	0.5	1–2
Ca ²⁺	10 ^{−4}	1–2
H ⁺	7 × 10 ^{−5} (10 ^{−7.2} M or pH 7.2)	4 × 10 ^{−5} (10 ^{−7.4} M or pH 7.4)
Anions*		
Cl [−]	5–15	110

Neuron resting potential



$$E_m \approx -70 \text{ mV}$$

Outline

- Cell membrane potential
- Propagating the membrane potential in dendrites: Cable theory
- The peculiar geometry of dendritic spines
- Indirect estimation of spine neck resistance
- Electro-diffusion modeling of ions and potential dynamics in spines
- Inferring physical parameters from direct nanopipettes recordings

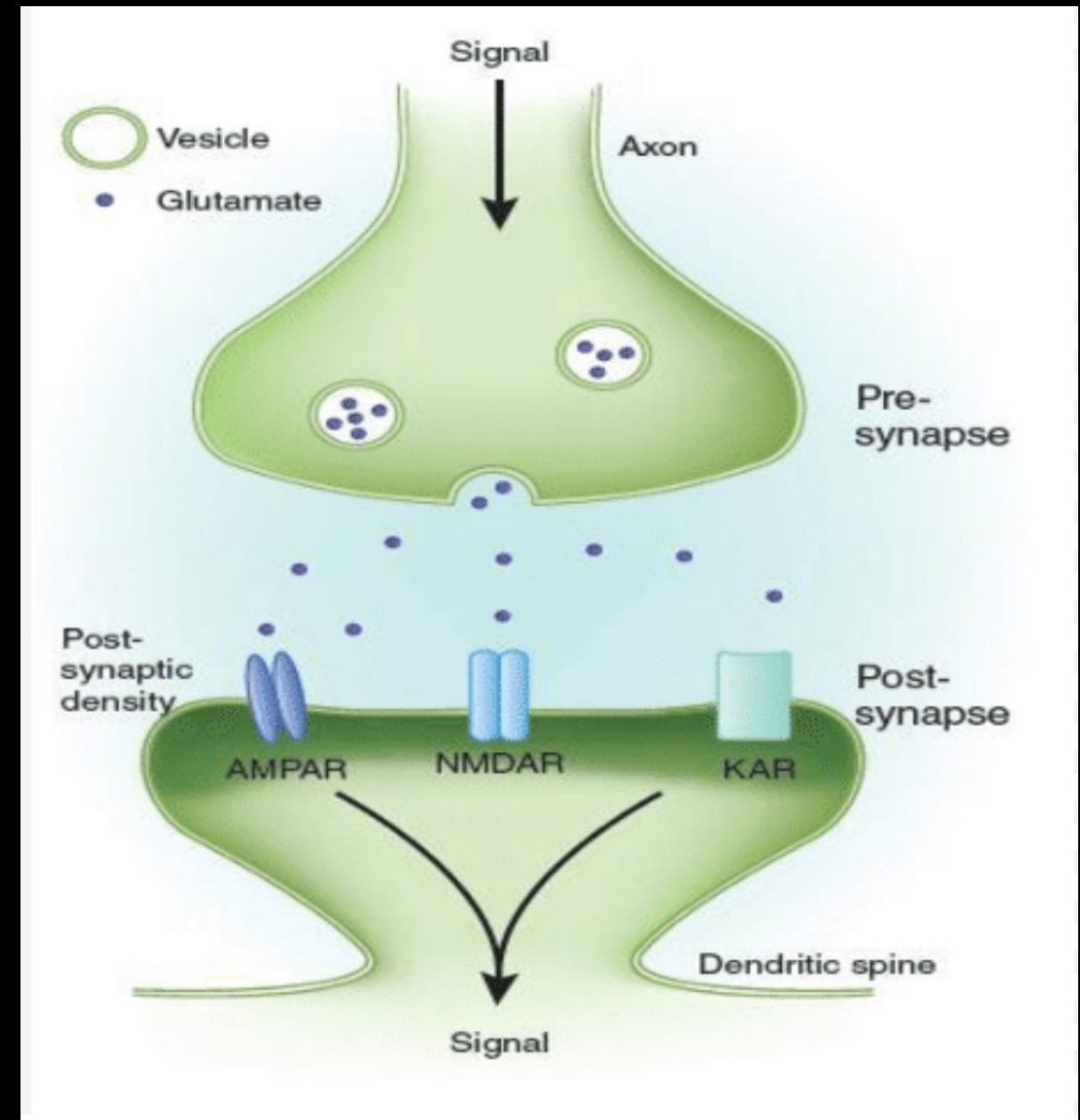
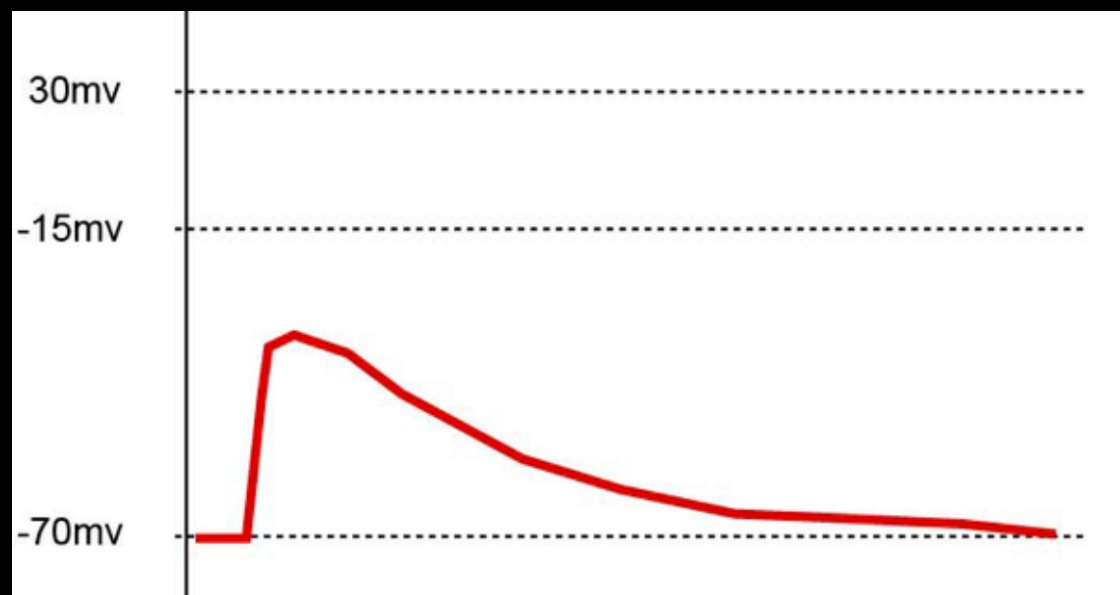
Excitatory synapses in central nervous system

Main neurotransmitter: Glutamate

Main receptors: AMPAR, NMDAR, KAR

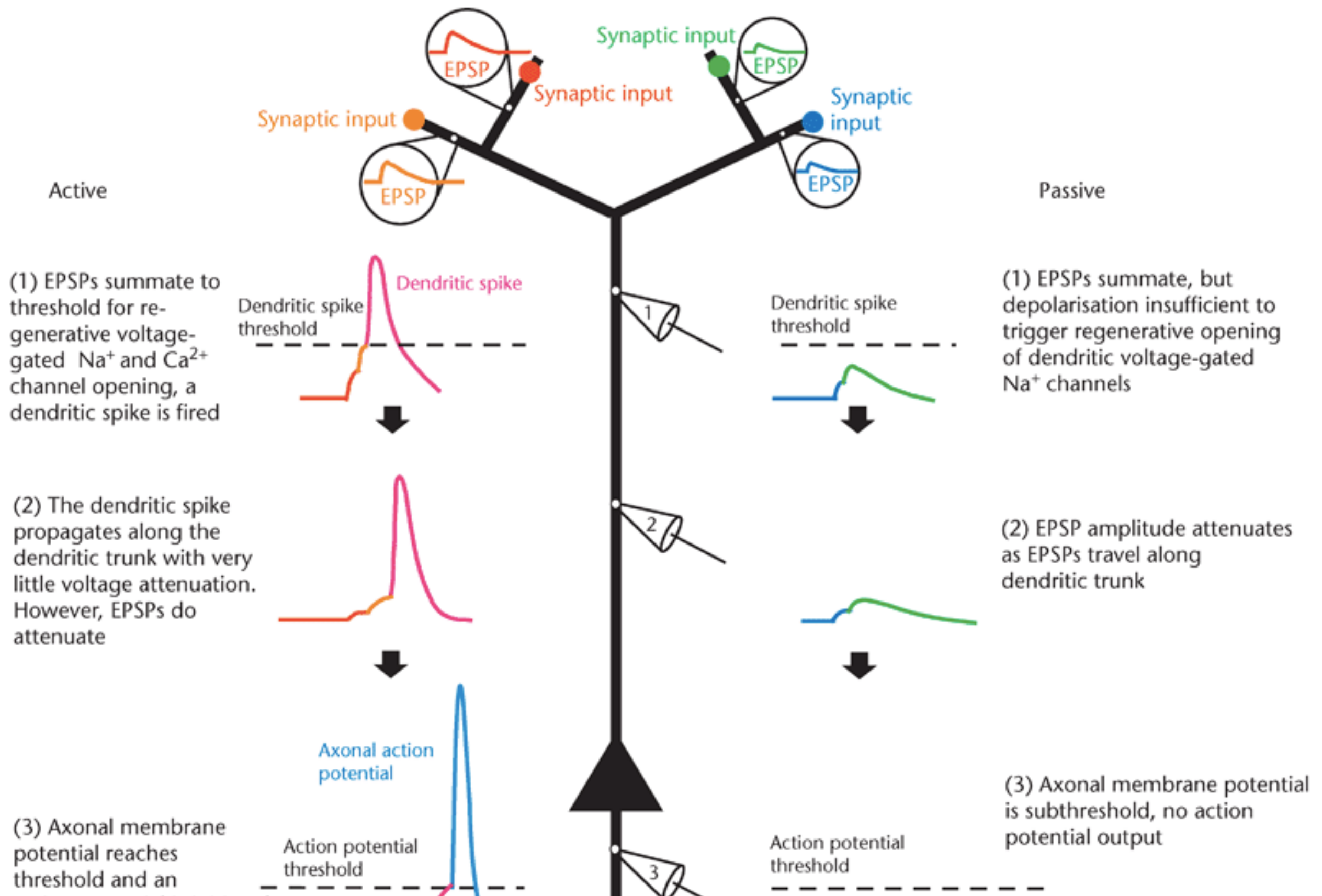
Receptors are permeable to cations (Na^+ and Ca^{2+} principally)

Trigger membrane depolarization

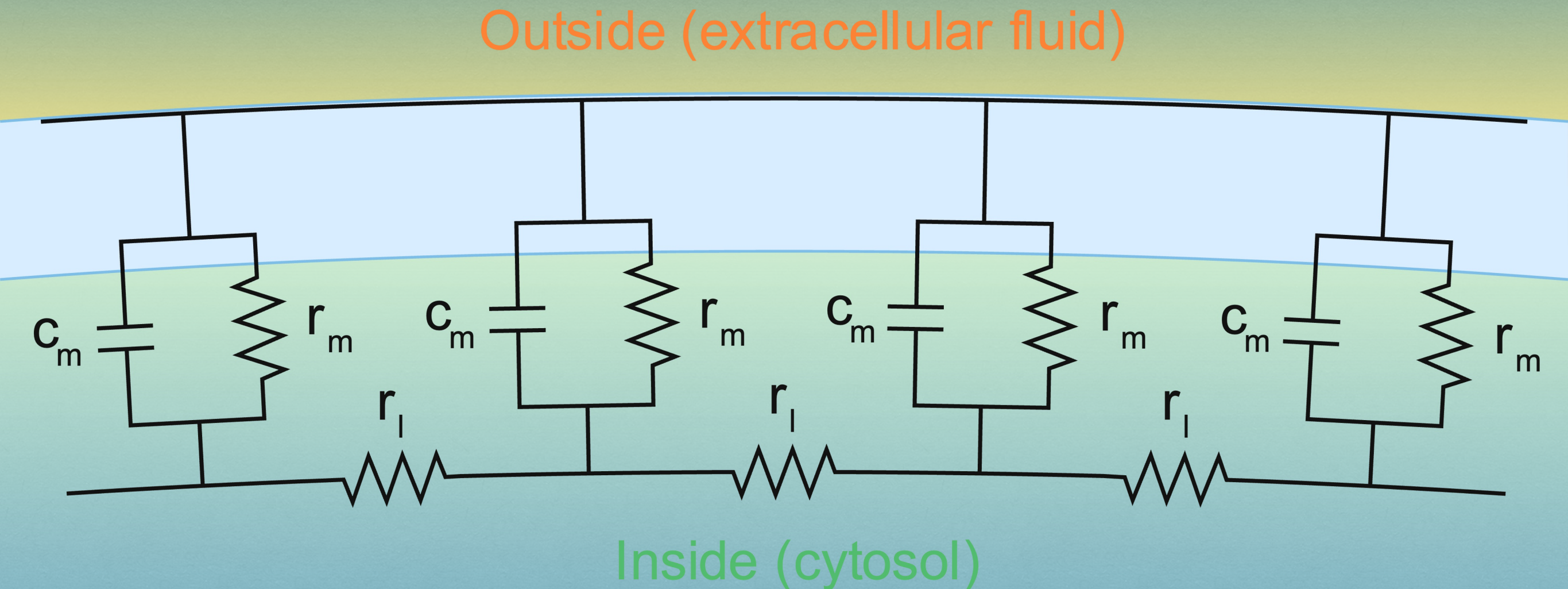


Excitatory post-synaptic potential (EPSP)

Propagation of EPSPs along dendrites and action potential generation



Modeling passive propagation with Cable Theory



—||— Capacitance

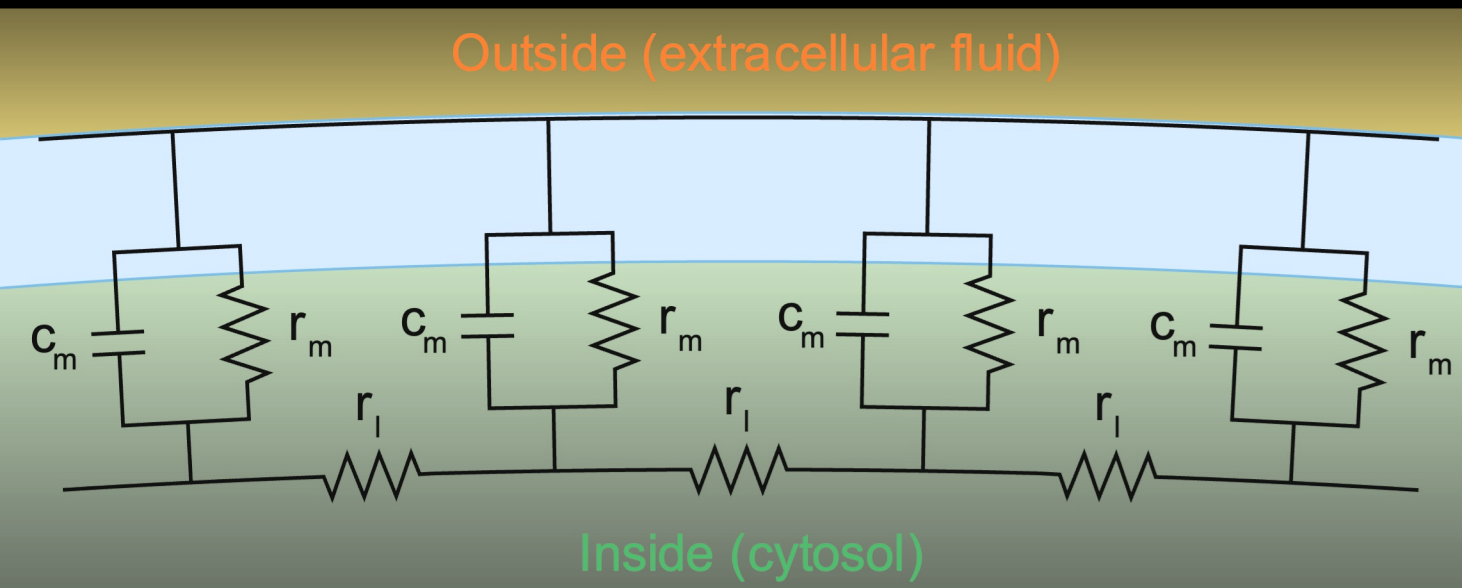
—— Resistance

r_m : Membrane resistance

r_i : Longitudinal resistance

C_m : Capacitance due to electrostatic forces

Deriving the voltage propagation



Voltage propagation

$$\frac{\partial V(x, t)}{\partial x} = -i_l r_l$$



Per unit length, radius of dendrite = a

$$r_m = \frac{R_m}{2\pi a}, c_m = C_m 2\pi a, r_l = \frac{\rho_l}{\pi a^2}$$

Longitudinal i_l and membrane i_m (leak + capacitor) currents

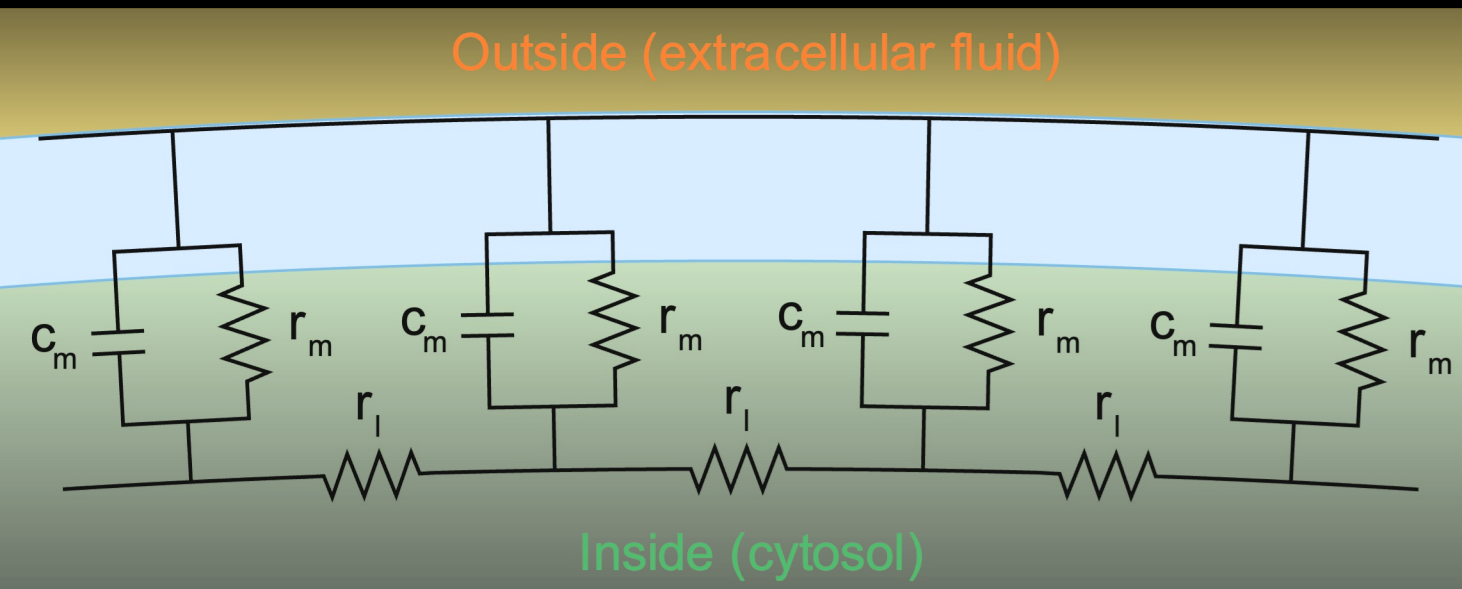
$$\frac{\partial i_l}{\partial x} = -i_m, \text{ and } i_m = \frac{V}{r_m} + c_m \frac{\partial V}{\partial x}$$

$$\frac{1}{r_l} \frac{\partial^2 V}{\partial x^2} = c_m \frac{\partial V}{\partial x} + \frac{V}{r_m}$$

Koch C. *Biological cybernetics* 50, 15-33 (1984).

Segev I, Rall W. *Trends in neurosciences* 21, 453-460 (1998).

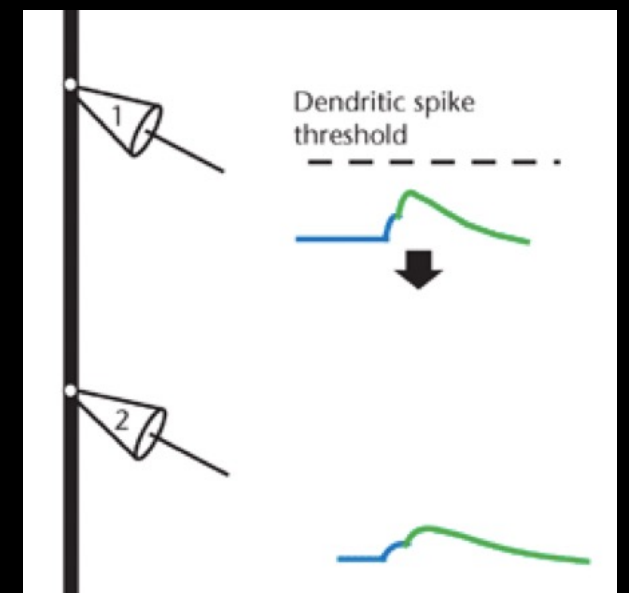
Voltage attenuation along dendrite



$$\frac{1}{r_l} \frac{\partial^2 V}{\partial x^2} = c_m \frac{\partial V}{\partial x} + \frac{V}{r_m} \quad c_m \ll 1, \lambda = \sqrt{\frac{r_m}{r_l}}$$

Exponential decay
(steady state)

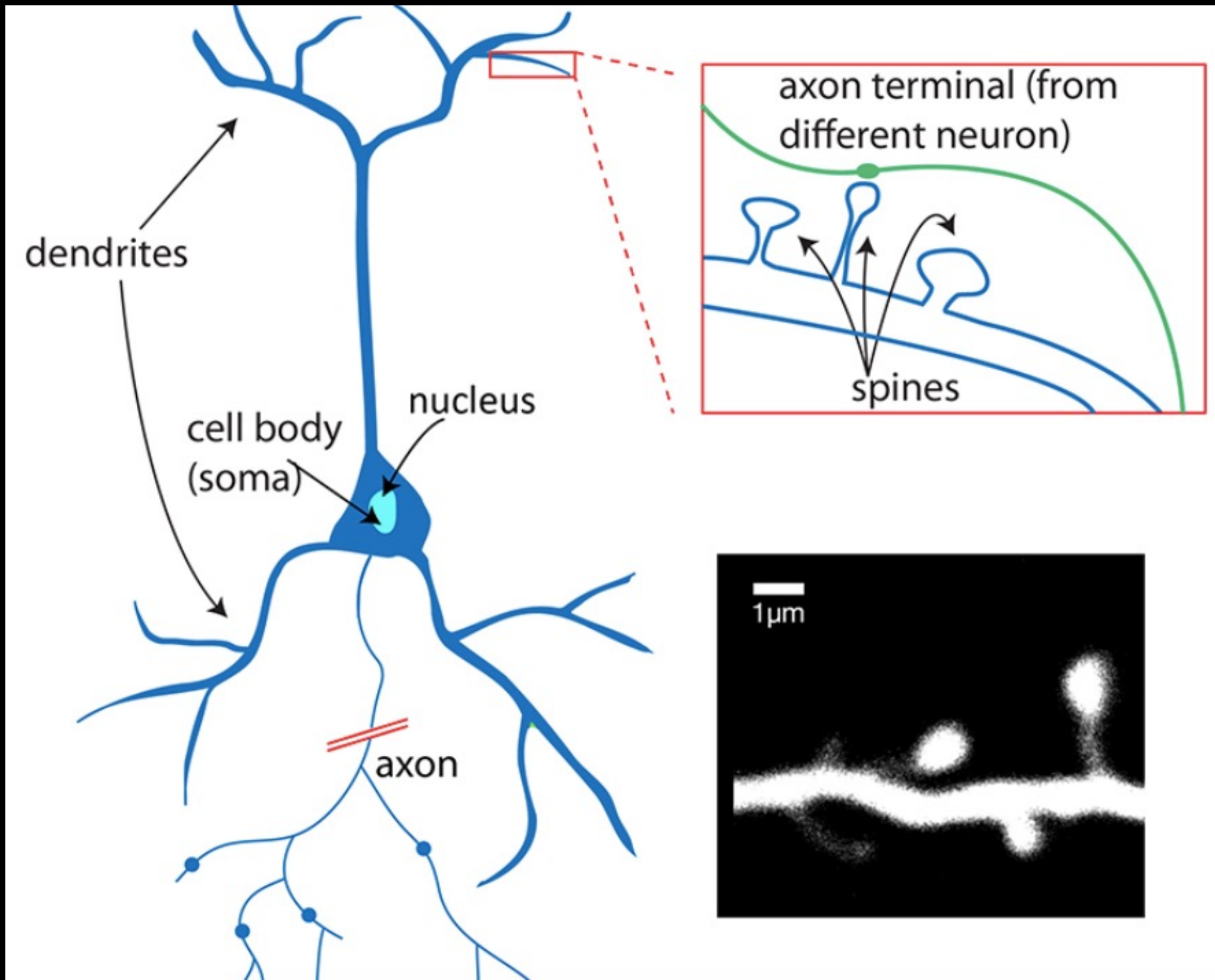
$$V(x, \infty) = V(x = 0, \infty) e^{-\frac{x}{\lambda}}$$



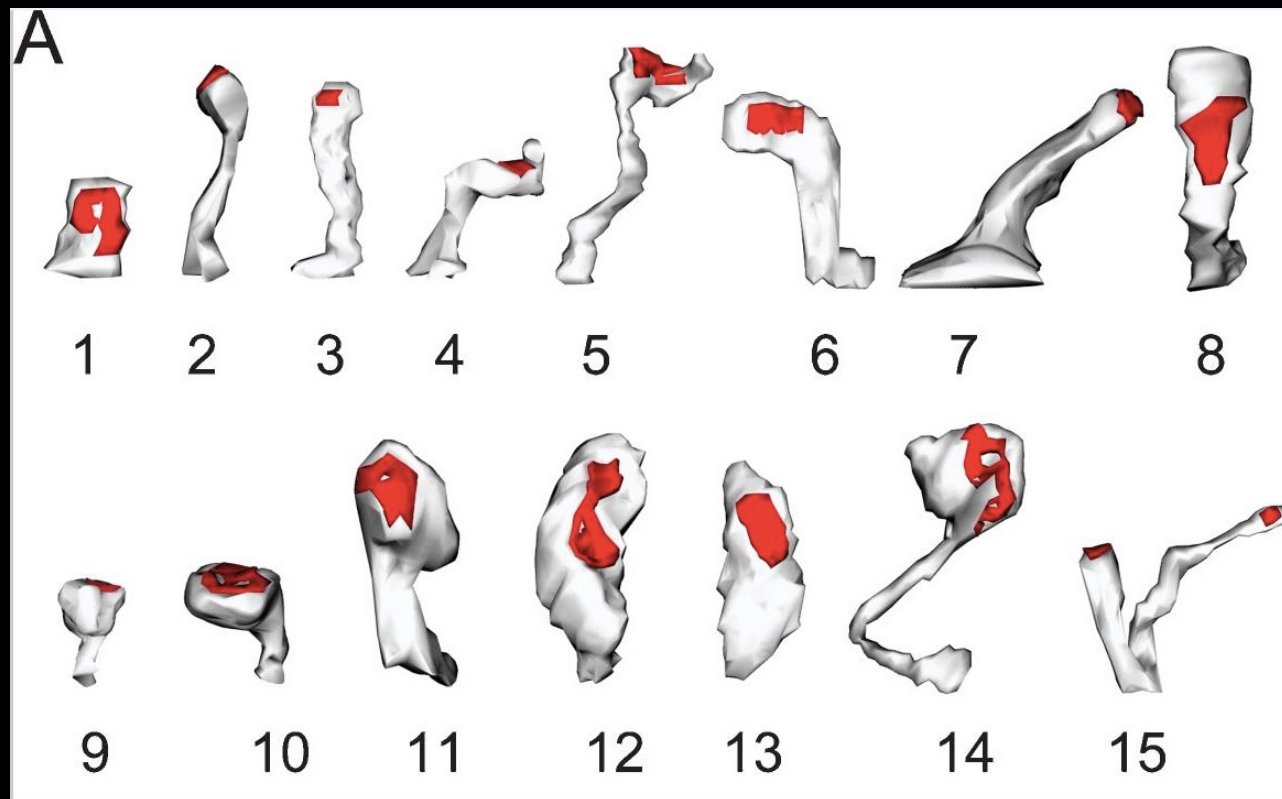
Outline

- Cell membrane potential
- Propagating the membrane potential in dendrites: Cable theory
- The peculiar geometry of dendritic spines
- Indirect estimation of spine neck resistance
- Electro-diffusion modeling of ions and potential dynamics in spines
- Inferring physical parameters from direct nanopipettes recordings

Dendritic spines are the primary sites of excitatory synaptic integration

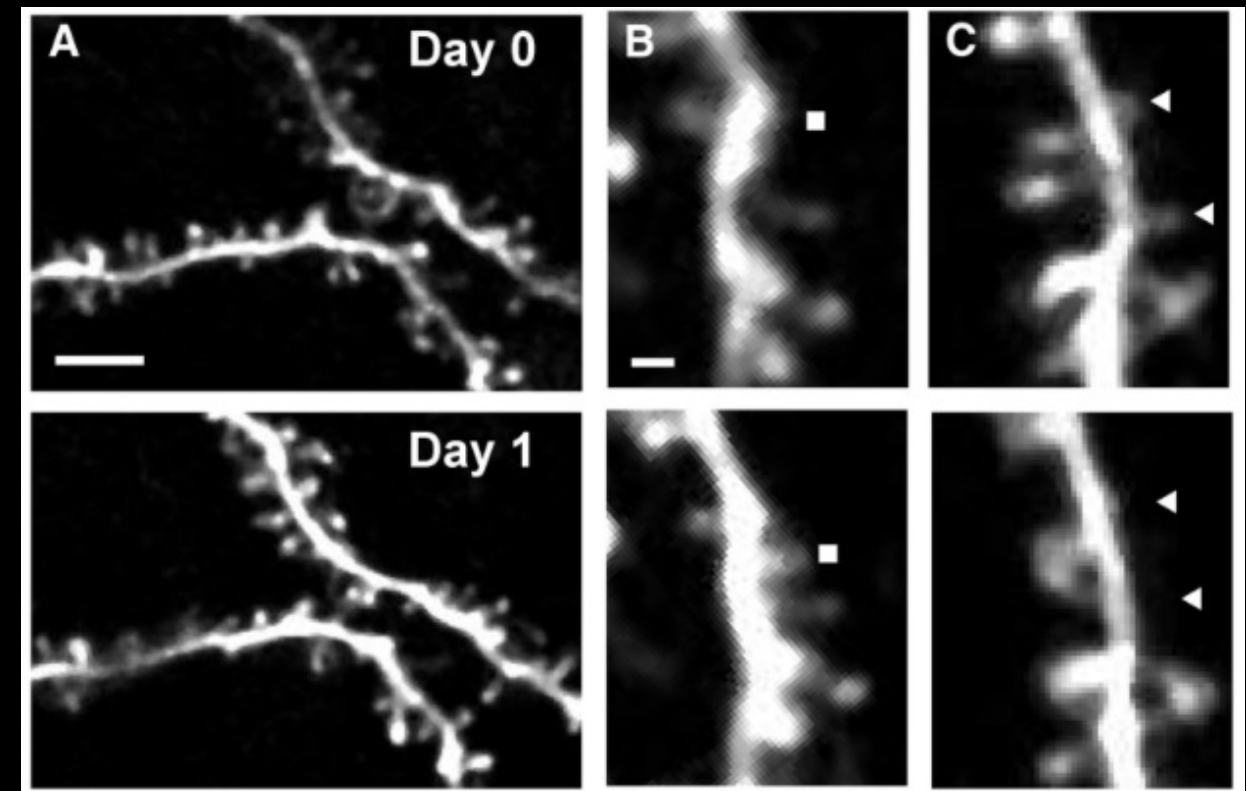


Important diversity and dynamic shapes



Diversity of shapes

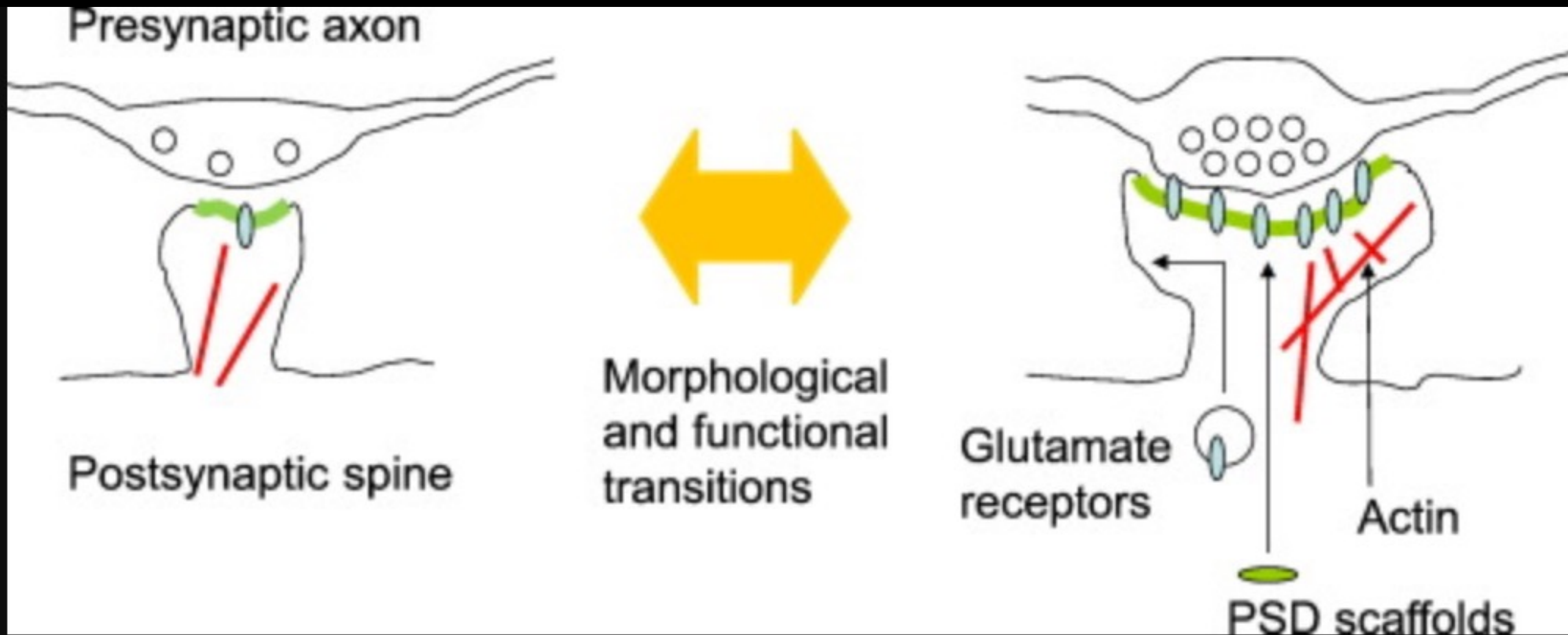
Arellano et al. Front. Neuro. 2017



Dynamic shape

Sadakane et al. eNeuro. 2015

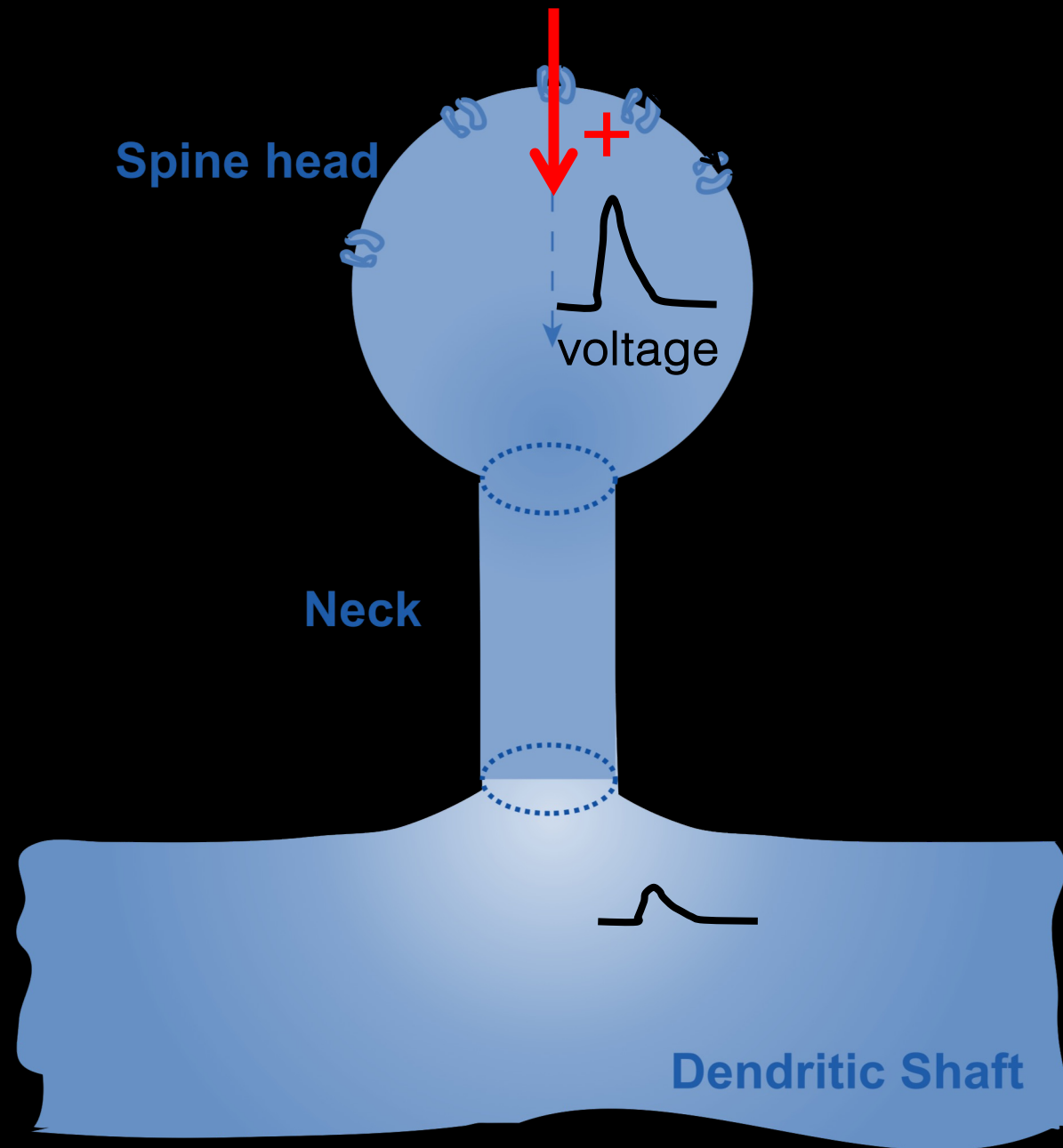
Encoding memory through morphological changes



Saman Ebrahimi, Shigeo Okabe,
Structural dynamics of dendritic spines: Molecular composition, geometry and functional regulation,
Biochimica et Biophysica Acta (BBA) - Biomembranes, Volume 1838, Issue 10, 2014, Pages 2391-2398,

Question ?

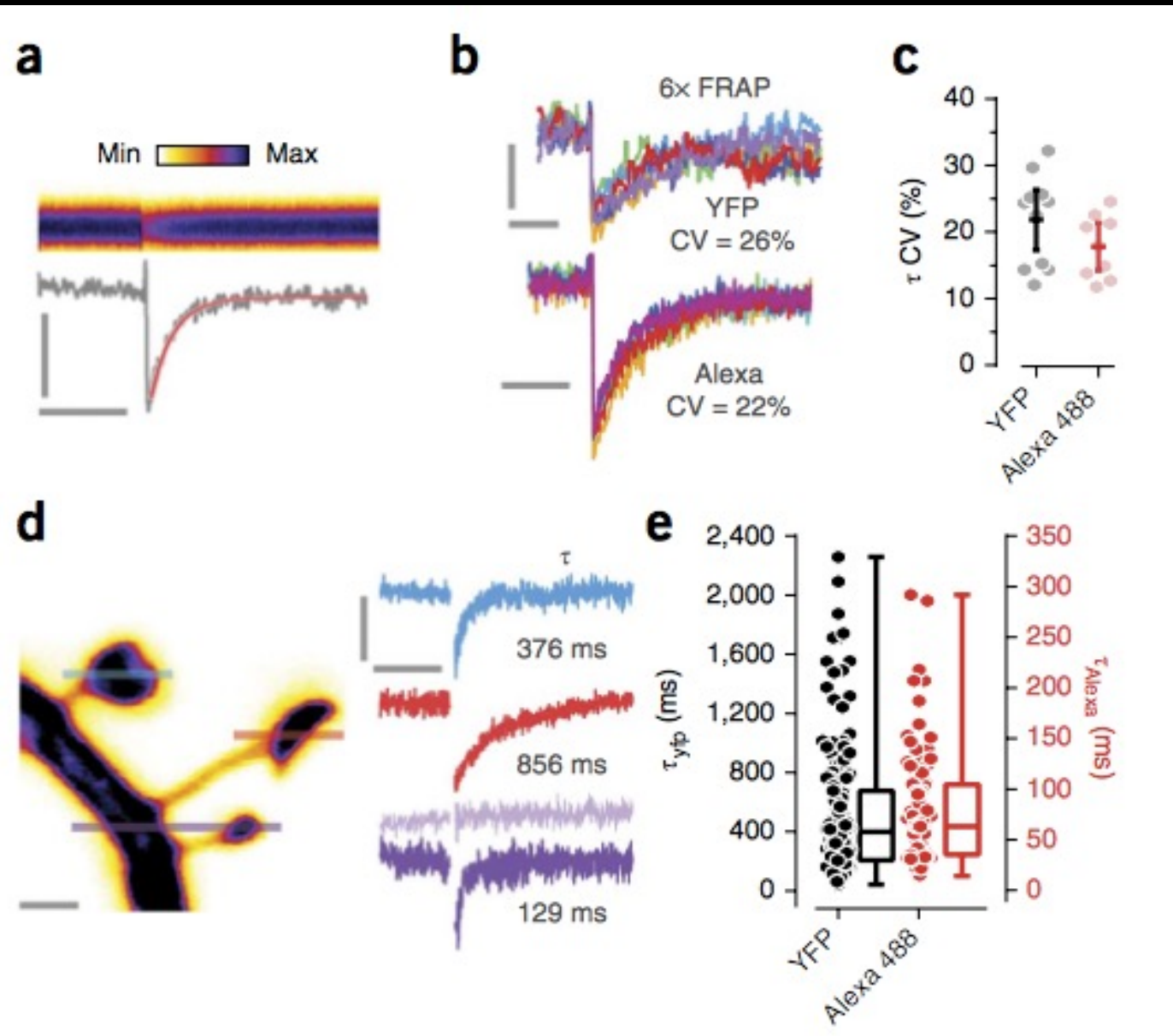
How does spine geometry shape synaptic input ?



Outline

- Cell membrane potential
- Propagating the membrane potential in dendrites: Cable theory
- The peculiar geometry of dendritic spines
- Indirect estimation of spine neck resistance
- Electro-diffusion modeling of ions and potential dynamics in spines
- Inferring physical parameters from direct nanopipettes recordings

Biochemical compartmentalization (=restriction of molecular diffusion) in spines is well established



$$\tau_{escape} = D^{-1} \left(\frac{Vol_{head}}{4r_{neck}} + \frac{L_{neck}^2}{2} + \frac{Vol_{head}L_{neck}}{\pi r_{neck}^2} \right)$$

Escape time ~ 0.1-1 s

Experimental: Svoboda et al, Science 1996

Theoretical: Holcman- Schuss, J. Math. Neuro. 2011

FRAP experiments with YFP/Alexa

Tonnesen et al, Nature Neuroscience 3014

Estimating the neck resistance from escape time

$$\tau_{escape} = D^{-1} \left(\frac{Vol_{head}}{4r_{neck}} + \frac{L_{neck}^2}{2} + \frac{Vol_{head}L_{neck}}{\pi r_{neck}^2} \right).$$

Leading term

Neck resistance (Cable theory) $R_{neck} \approx \frac{L_{neck}\rho_c}{\pi r_{neck}^2}$

$$R_{neck} \approx \frac{D\rho_c}{Vol_{head}} \tau_{escape}$$

Estimating the neck resistance from escape time

$$\tau_{escape} = D^{-1} \left(\frac{Vol_{head}}{4r_{neck}} + \frac{L_{neck}^2}{2} + \frac{Vol_{head}L_{neck}}{\pi r_{neck}^2} \right).$$

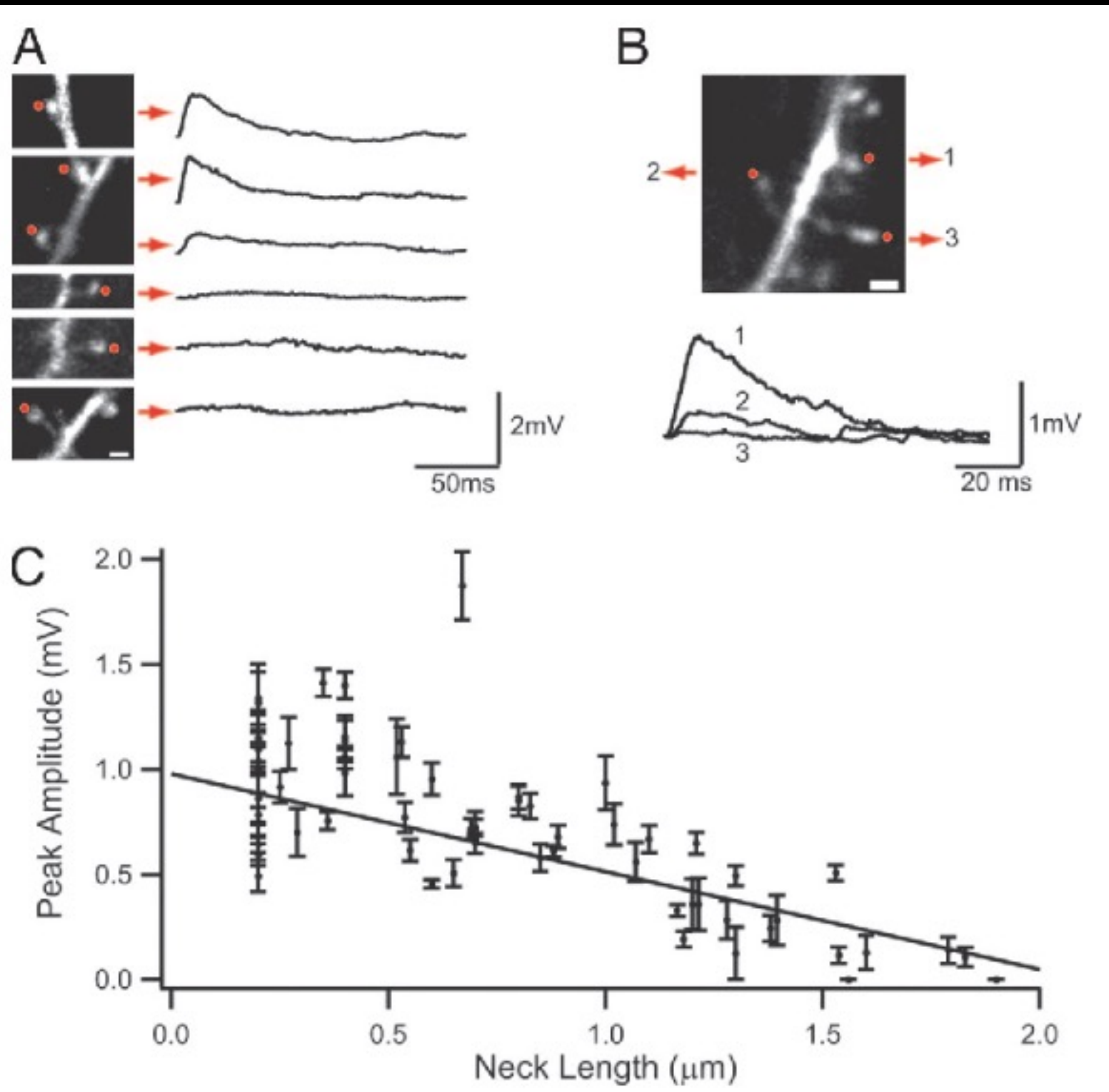
Leading term

Neck resistance (Cable theory) $R_{neck} \approx \frac{L_{neck}\rho_c}{\pi r_{neck}^2}$

*Difficult to
estimate...*

$$R_{neck} \approx \frac{D\rho_c}{Vol_{head}} \tau_{escape}$$

Resistance of the neck scales with neck length

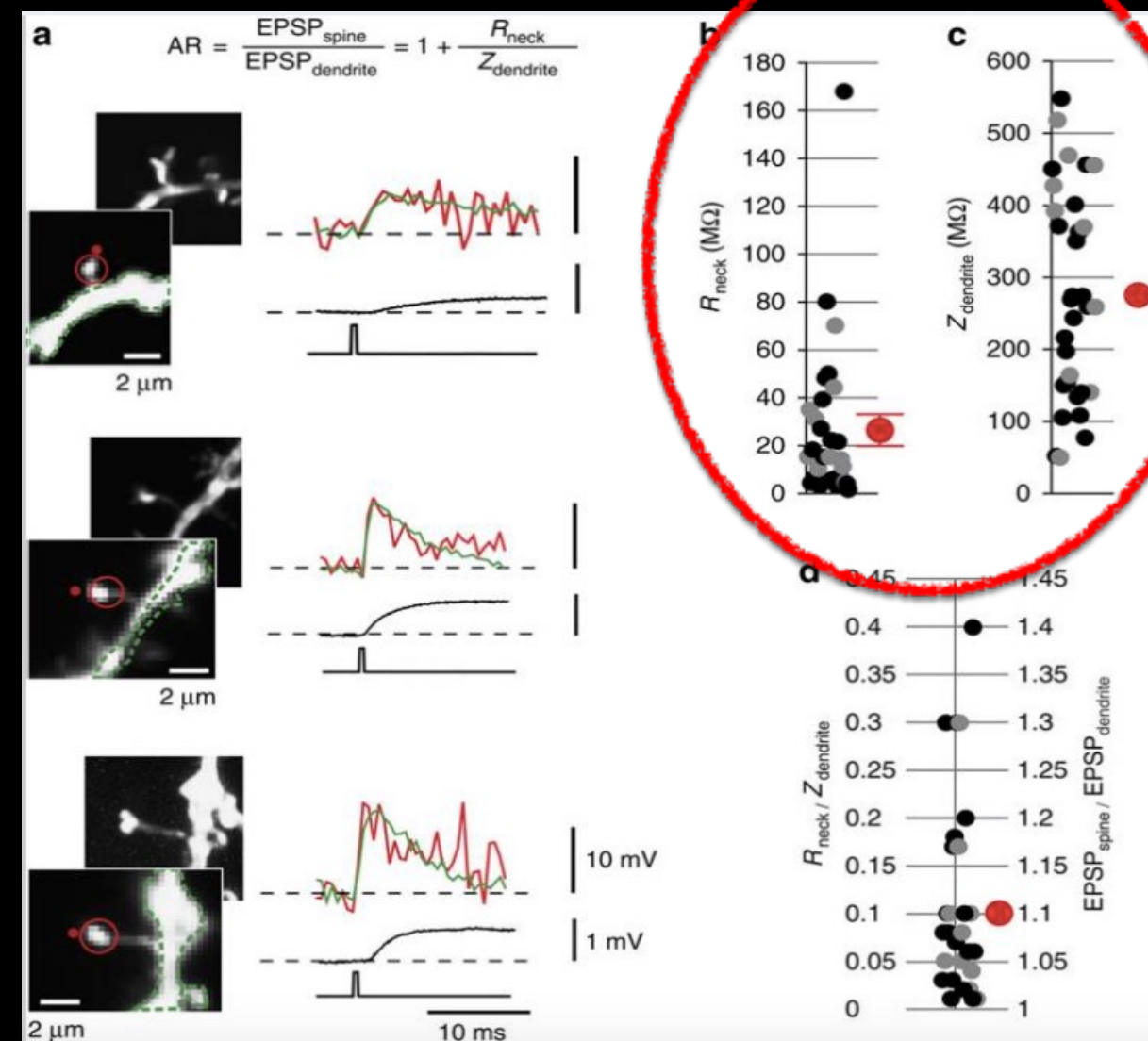
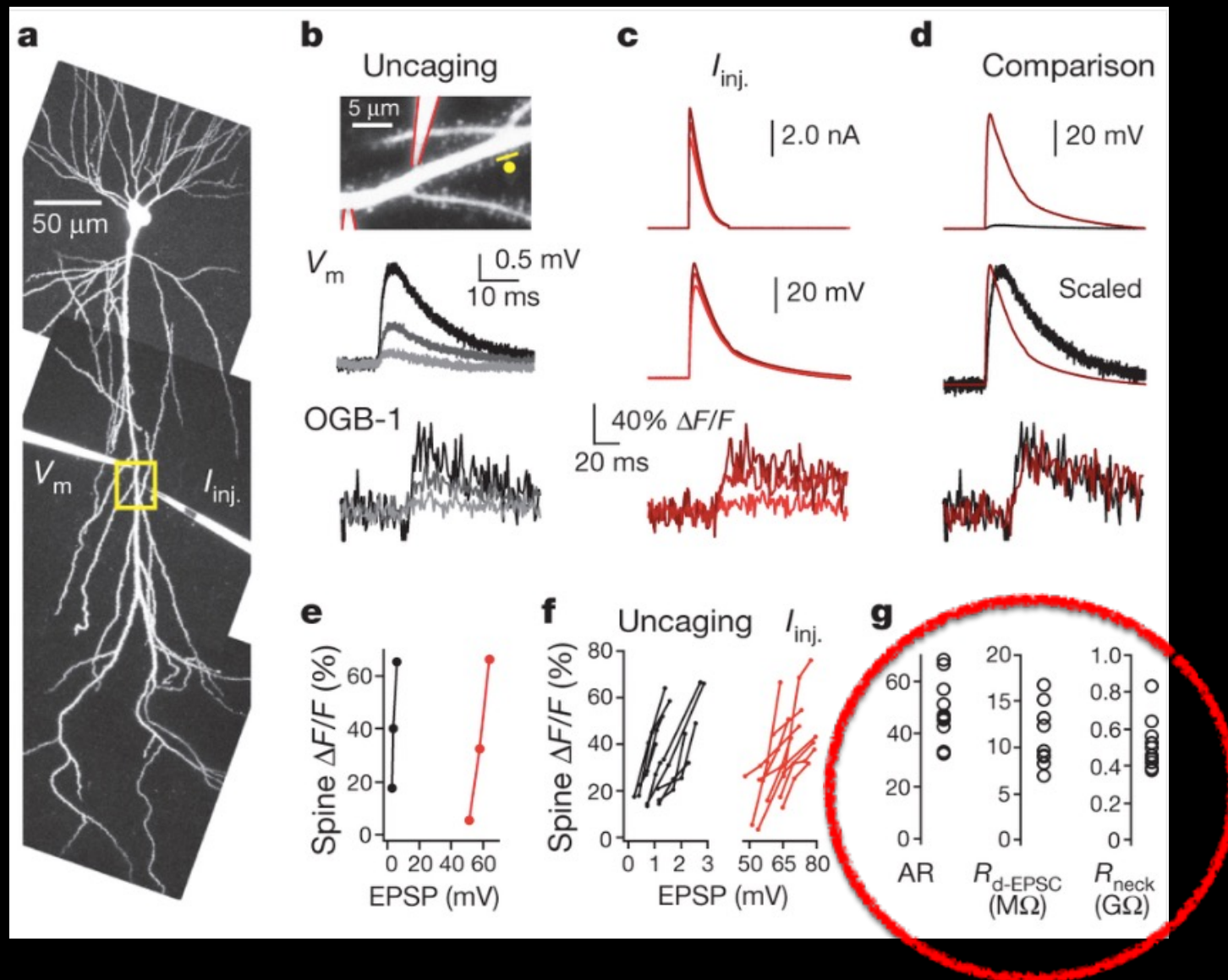


Somatic EPSPs after glutamate uncaging at different dendritic spines

Electrical compartmentalization of spines is actually controversial !

Yes: Neck resistance is high

No: Neck resistance is low



Harnett MT, Makara JK, Spruston N, Kath WL, Magee JC. Synaptic amplification by dendritic spines enhances input cooperativity. *Nature*. 2012

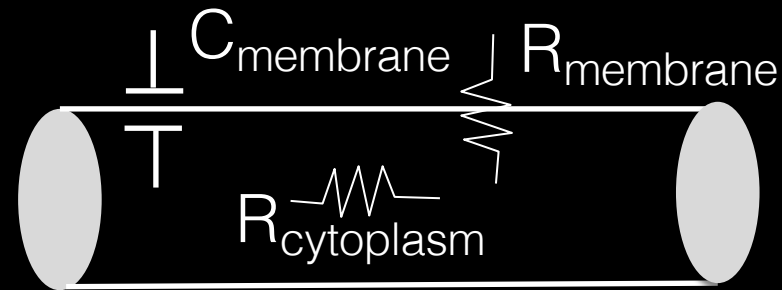
Popovic, M. A., Carnevale, N., Rozsa, B., & Zecevic, D. (2015). Electrical behaviour of dendritic spines as revealed by voltage imaging. *Nature communications*, 6(1), 8436.

Reasons of the controversy

- Tiny spines -> direct measurement is difficult
- Voltage imaging noisy and slow -> difficult data interpretation
- Different experimental conditions (in vivo, slices, in vitro) -> different spines' shapes, different dendritic impedance...

Need for a robust theoretical framework to constrain experimental observations

Standard cable theory is insufficient



Spine head ~ ball with (small) neck junction $\neq$ cylinder

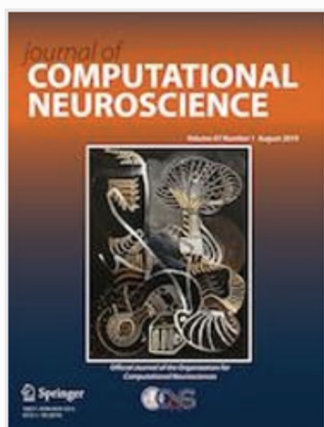
Neglects changes in ion concentration (diffusion flux in Nernst-Planck equation) ... that can be significant in spine nanodomain

Joined dynamics of ions and potential ?

Outline

- Cell membrane potential
- Propagating the membrane potential in dendrites: Cable theory
- The peculiar geometry of dendritic spines
- Indirect estimation of spine neck resistance
- Electro-diffusion modeling of ions and potential dynamics in spines
- Inferring physical parameters from direct nanopipettes recordings

Outline



[Journal of Computational Neuroscience](#)

August 2019, Volume 47, [Issue 1](#), pp 77–89 | [Cite as](#)

Electrodiffusion models of synaptic potentials in dendritic spines

Authors

[Authors and affiliations](#)

Thibault Lagache , Krishna Jayant, Rafael Yuste

Article

First Online: 13 August 2019

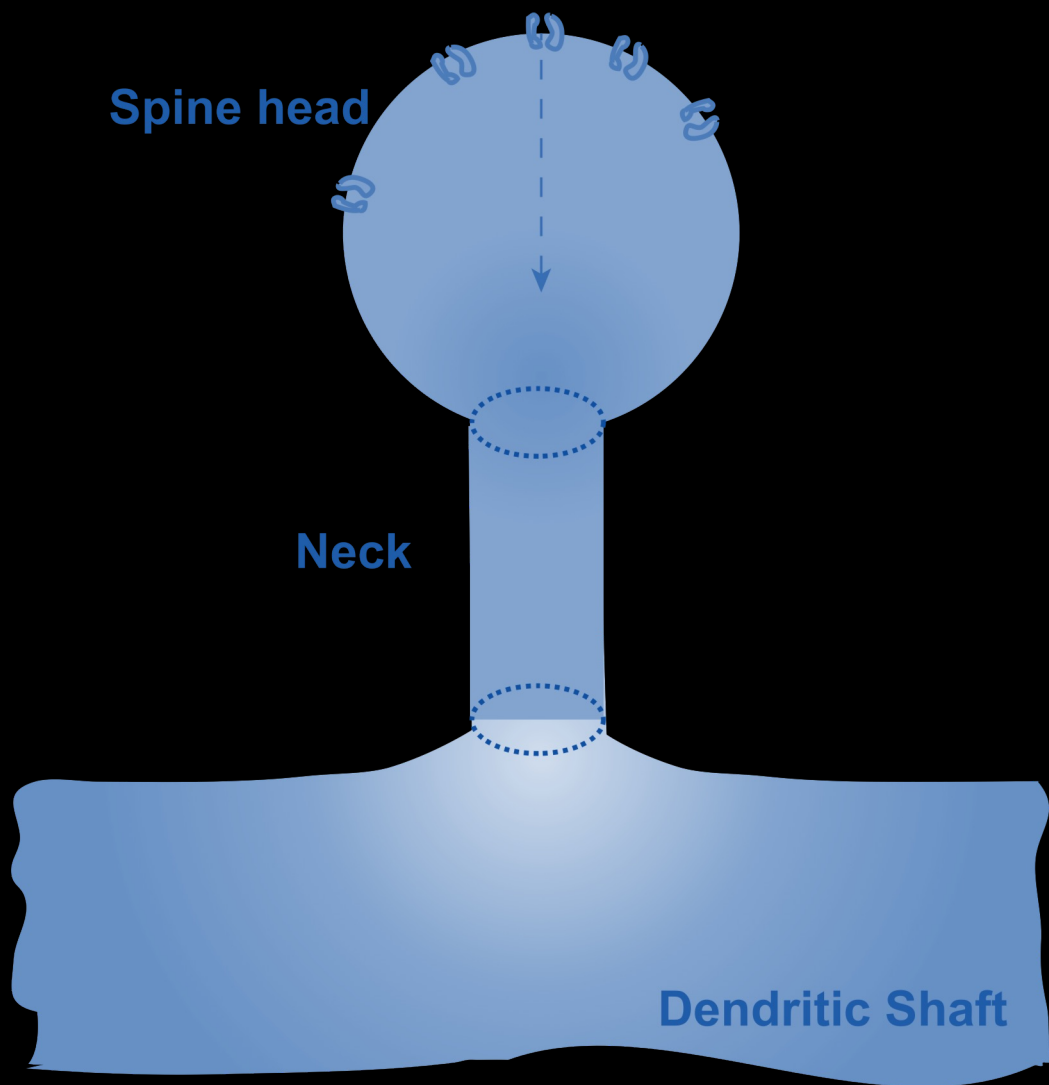
6

Shares

94

Downloads

Electro-diffusion equations



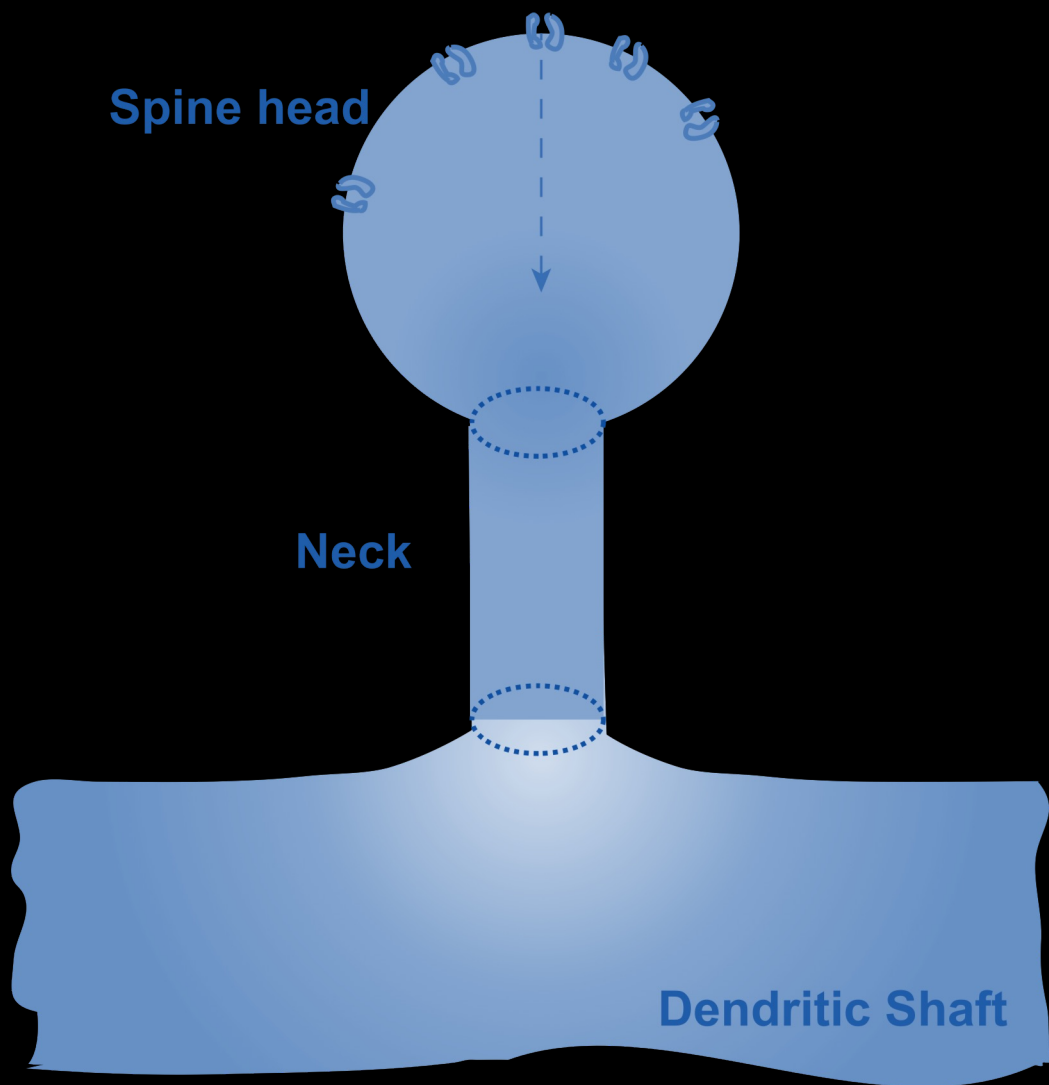
Poisson: Potential is related to local differences between positive and negative concentrations

$$\Delta\Phi(\mathbf{x}, t) = -\frac{e}{\epsilon_c} (c^+(\mathbf{x}, t) - c^-(\mathbf{x}, t))$$

Nernst-Planck = Fick's law (diffusion between concentration gradient) + Action of electric field on ions (potential gradient)

$$\frac{\partial c(\mathbf{x}, t)}{\partial t} = D \nabla \cdot \left[\overset{\text{Diffusion}}{\nabla \cdot c} + \overset{\text{Electric field}}{\frac{ze}{kT} c \nabla \cdot \Phi} \right] (\mathbf{x}, t)$$

Electro-diffusion equations



Poisson: Potential is related to local differences between positive and negative concentrations

$$\Delta\Phi(\mathbf{x}, t) = -\frac{e}{\epsilon_c} (c^+(\mathbf{x}, t) - c^-(\mathbf{x}, t))$$

Nernst-Planck = Fick's law (diffusion between concentration gradient) + Action of electric field on ions (potential gradient)

$$\frac{\partial c(\mathbf{x}, t)}{\partial t} = D \nabla \cdot \left[\overset{\text{Diffusion}}{\nabla \cdot c} + \overset{\text{Electric field}}{\frac{ze}{kT} c \nabla \cdot \Phi} \right] (\mathbf{x}, t)$$

No analytical solution. Require numerical solutions

➔ Simple mathematical framework is needed (pen&paper equations)

Analysis of PNP equations inside the spine head

Spine head is a capacitor !

$$\Phi_{head}(t) = \frac{n^+(t) - n^-(t)}{s_h C_m}$$

Analysis of PNP equations inside the spine head

Spine head is a capacitor !

Difference between the number of charges $\sim 10^4$
 $\ll$ Total number of charge in the head $\sim 10^7$

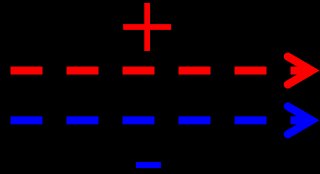
$$\Phi_{head}(t) = \frac{n^+(t) - n^-(t)}{s_h C_m}$$

(Surface of head membrane) x (Unit surface capacitance) $\ll 1$

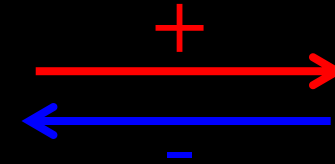
Fluxes of ions through the spine neck

Diffusion and electrical-field contributions

Ion motion = **Diffusion** (concentration gradient) and **Electrical field** (potential gradient)



Same direction
Net current = 0



Opposite direction

$$J_+(t) = J_{diff}(t) + \frac{I(t)}{2}$$

$$J_-(t) = J_{diff}(t) - \frac{I(t)}{2}$$

Head

$$\Phi_{head}(t) > \Phi_0$$

$$c_{head}(t) > c_0$$

Neck

Dendrite

$$c_{dendrite}(t) \approx c_0$$

$$\Phi_{dendrite}(t) \approx \Phi_0 \approx -60 \text{ mV}$$

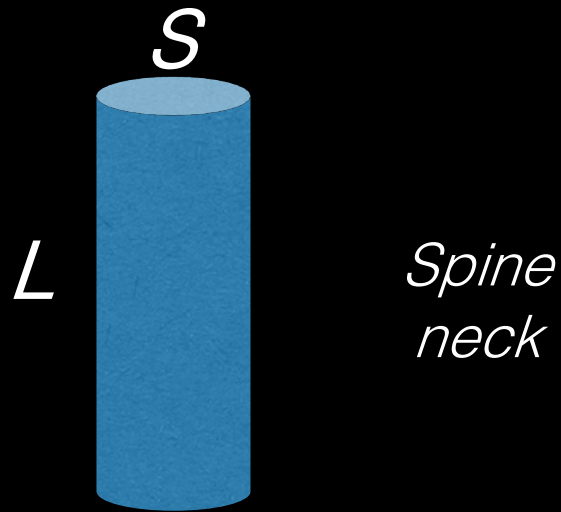
Mathematical estimation of fluxes

After 1D simplification of equations & Asymptotic expansion of solutions...

Kosińska I et al. Physical Review E 77, 031131 (2008).

$$J_{diff}(t) = \frac{DS}{L} (c_{head}(t) - c_0) \longleftrightarrow \tau_{escape} = \frac{v_h L}{SD}$$

Used to fit FRAP experiments (Svoboda et al, Science 1996)
Diffusion theory (Holcman- Schuss, J. Math. Neuro. 2011)



$$I(t) = \frac{LkT}{2eSD (c_{head}(t) - c_0)} \log \left(\frac{c_{head}(t)}{c_0} \right) (\Phi_{head}(t) - \Phi_0)$$

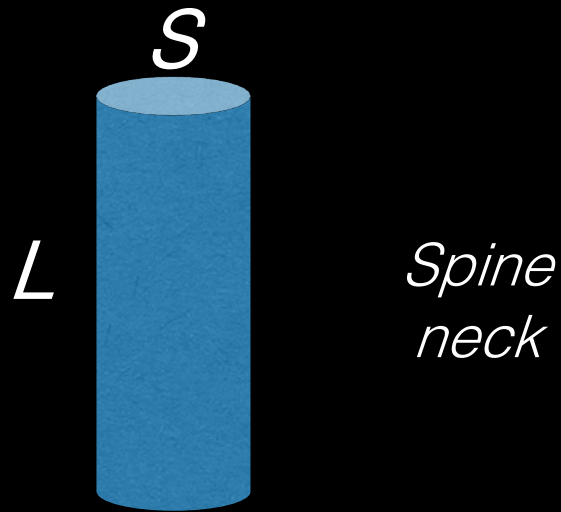
Mathematical estimation of fluxes

After 1D simplification of equations & Asymptotic expansion of solutions...

Kosińska I et al. Physical Review E 77, 031131 (2008).

$$J_{diff}(t) = \frac{DS}{L} (c_{head}(t) - c_0) \longleftrightarrow \tau_{escape} = \frac{v_h L}{SD}$$

Used to fit FRAP experiments (Svoboda et al, Science 1996)
Diffusion theory (Holcman- Schuss, J. Math. Neuro. 2011)

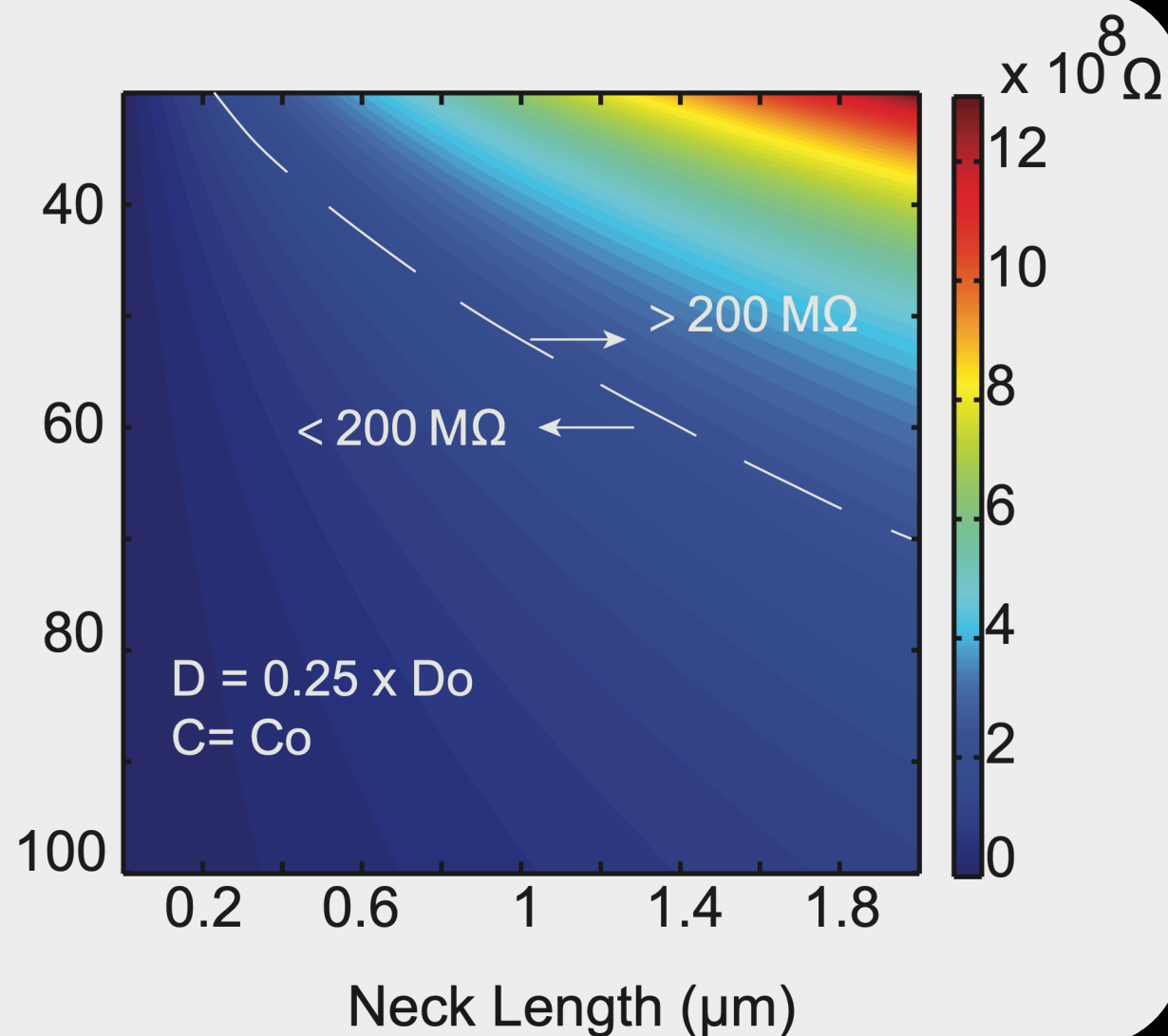


$$I(t) = \frac{LkT}{2eSD (c_{head}(t) - c_0)} \log \left(\frac{c_{head}(t)}{c_0} \right) (\Phi_{head}(t) - \Phi_0)$$

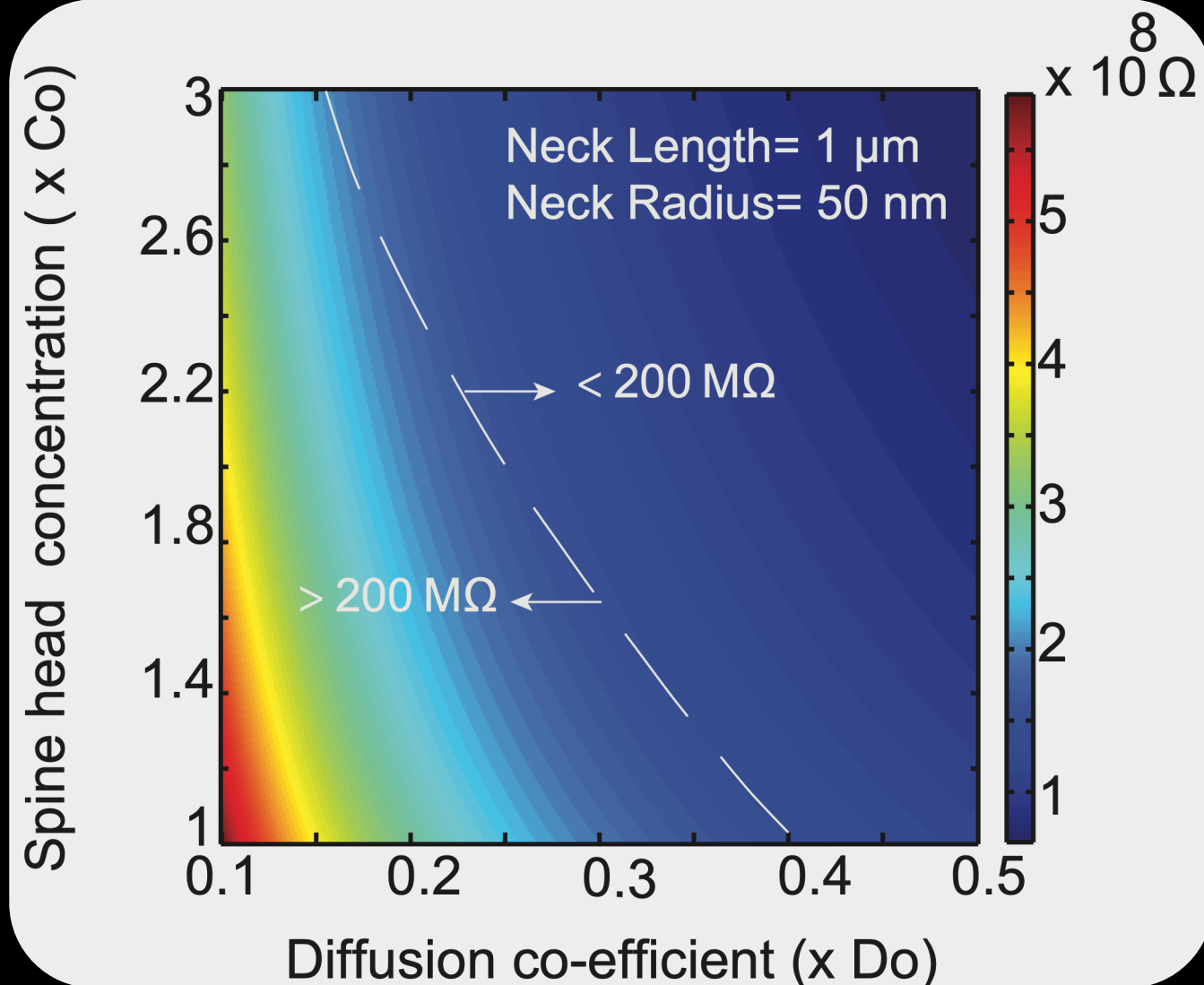
Neck resistance depends on head concentration !

The high variability of neck resistance

Neck geometry



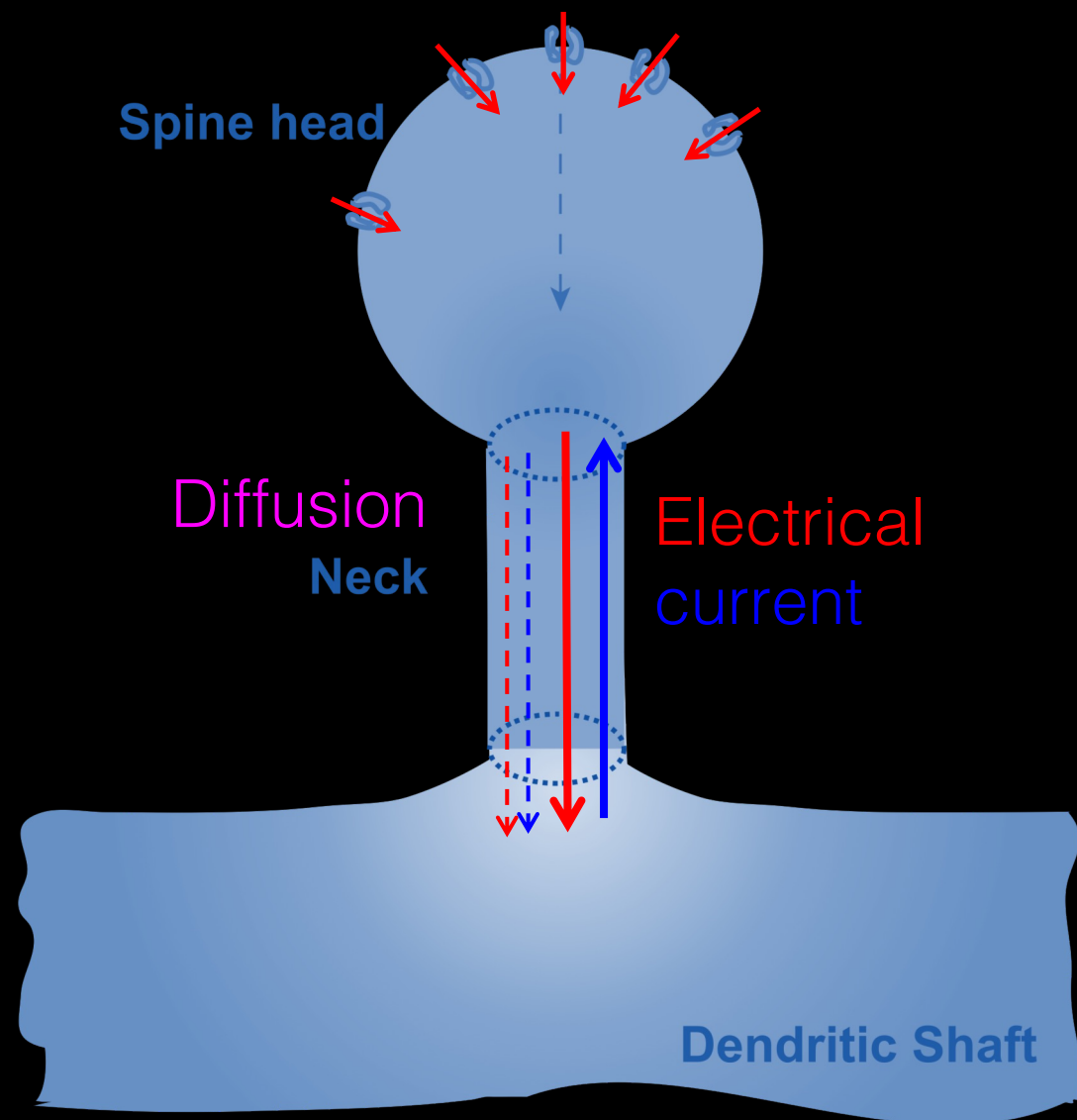
Diffusion



Electrical potential & ion concentration is a
fast & slow system of coupled equations

Coupled kinetics of concentration and potential inside the spine head

Synaptic entry (AMPA..)



Coupled kinetics of concentration and potential inside the spine head

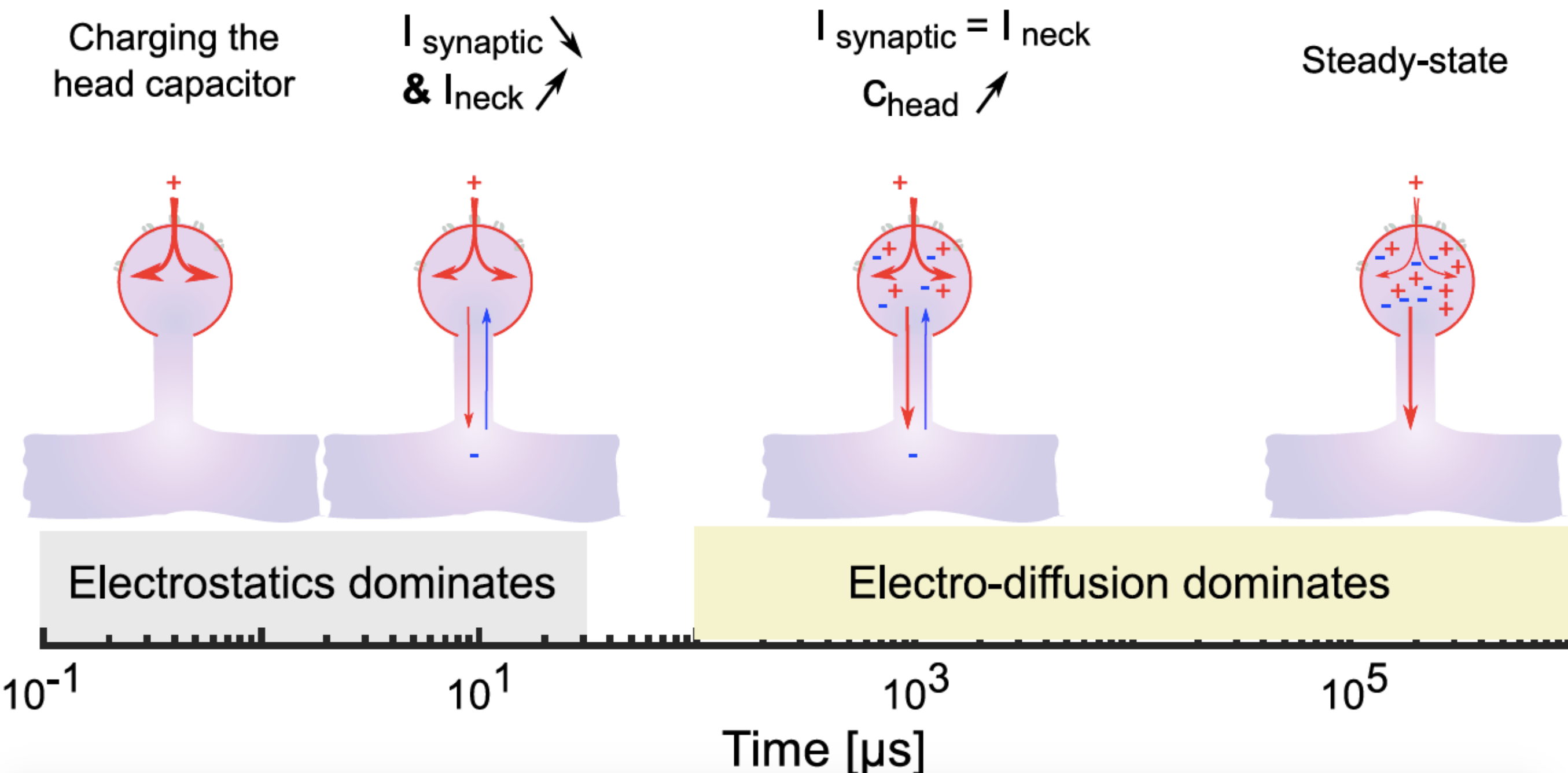
Fast electrostatics (charging head capacitor) $\sim 1\text{-}100\ \mu\text{s}$

$$s_h c_m \frac{d\Phi_{head}(t)}{dt} = \underbrace{-g^+(t) (\Phi_{head}(t) - \Phi_{reversal}(c_{head}(t)))}_{I_{AMPA}(t)} - \underbrace{\frac{\Phi_{Head}(t) - \Phi_0}{R_{neck}(c_{head}(t))}}_{I_{neck}(t)}$$

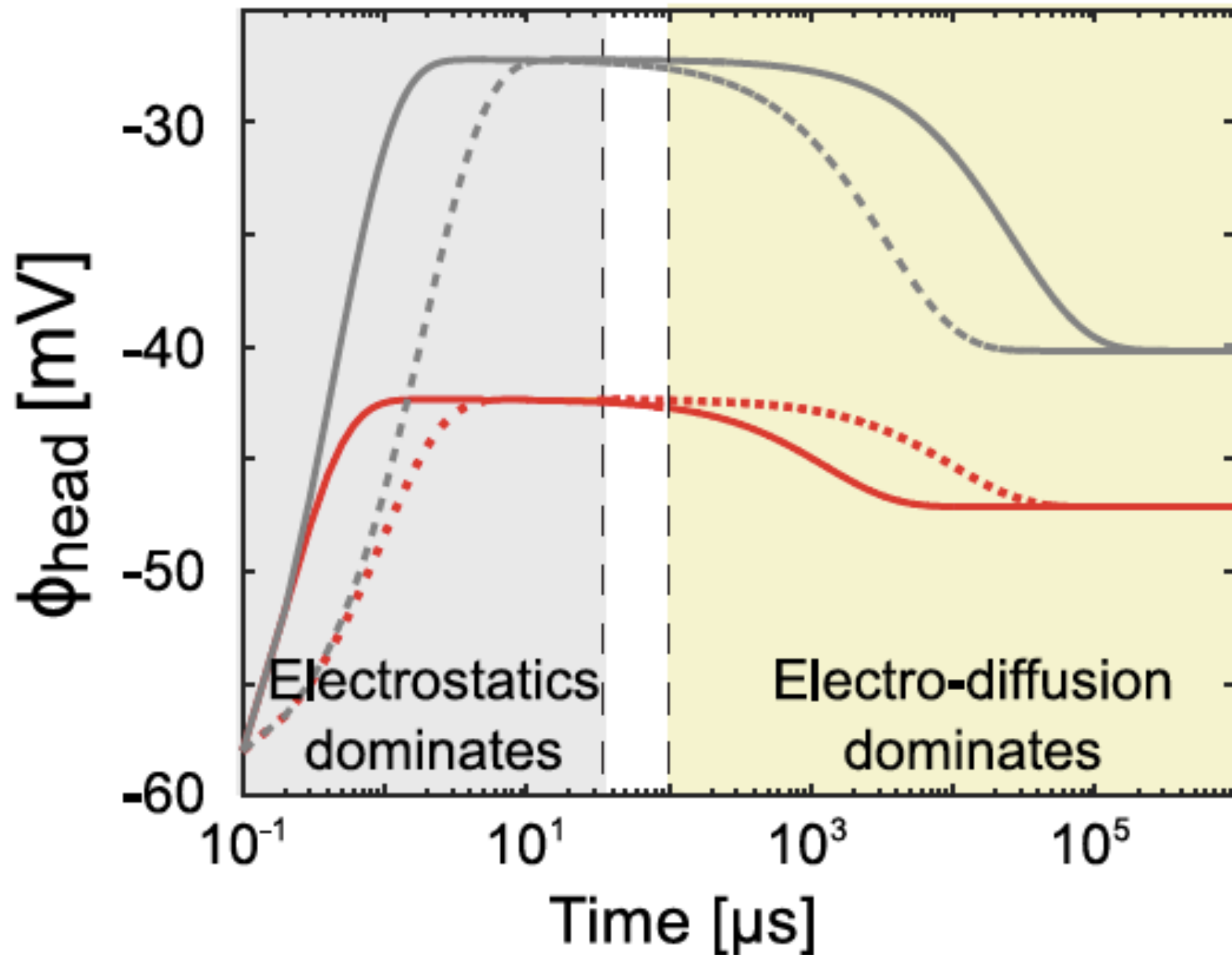
Slow concentration increase $\sim 1 - 1,000\ \text{ms}$

$$v_h \frac{dc_{head}(t)}{dt} = \underbrace{-\frac{1}{2}g^+(t) (\Phi_{head}(t) - \Phi_{reversal}(c_{head}(t)))}_{I_{AMPA}(t)/2} - \underbrace{\frac{D\pi r_{neck}^2}{L_{neck}} (c_{head}(t) - c_0)}_{J_{diff}(t)}$$

Electrostatics & Electro-diffusion for sustained synaptic current



Current & Resistance decrease lead to potential drop



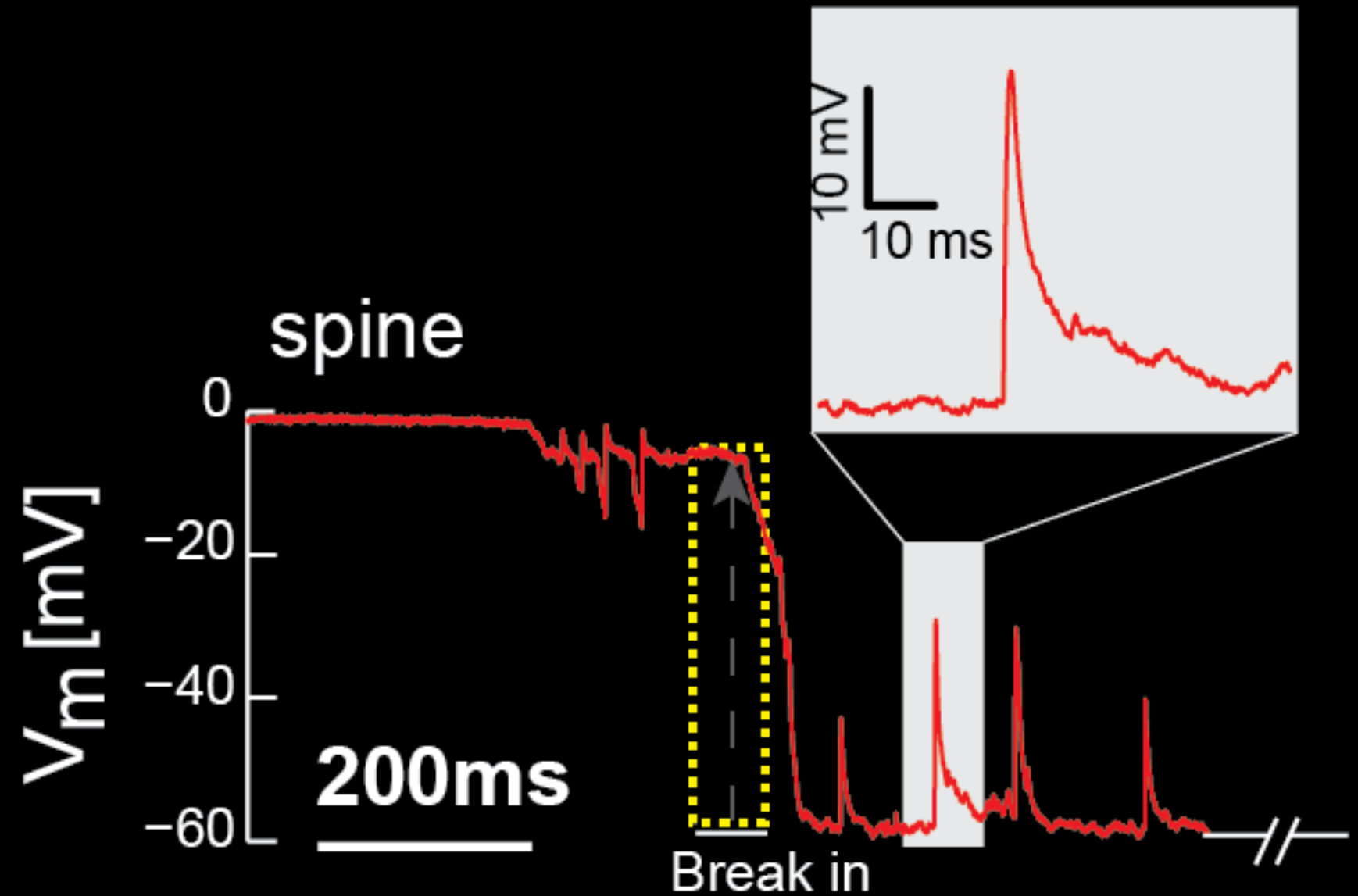
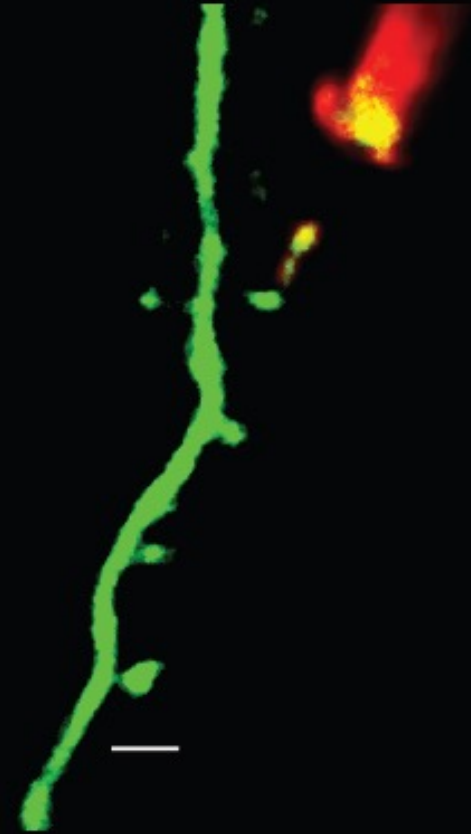
Outline

- Cell membrane potential
- Propagating the membrane potential in dendrites: Cable theory
- The peculiar geometry of dendritic spines
- Indirect estimation of spine neck resistance
- Electro-diffusion modeling of ions and potential dynamics in spines
- Inferring physical parameters from direct nanopipettes recordings

What can we learn and predict from electrical
recordings inside the spine ?

Nanopipette recording inside spines

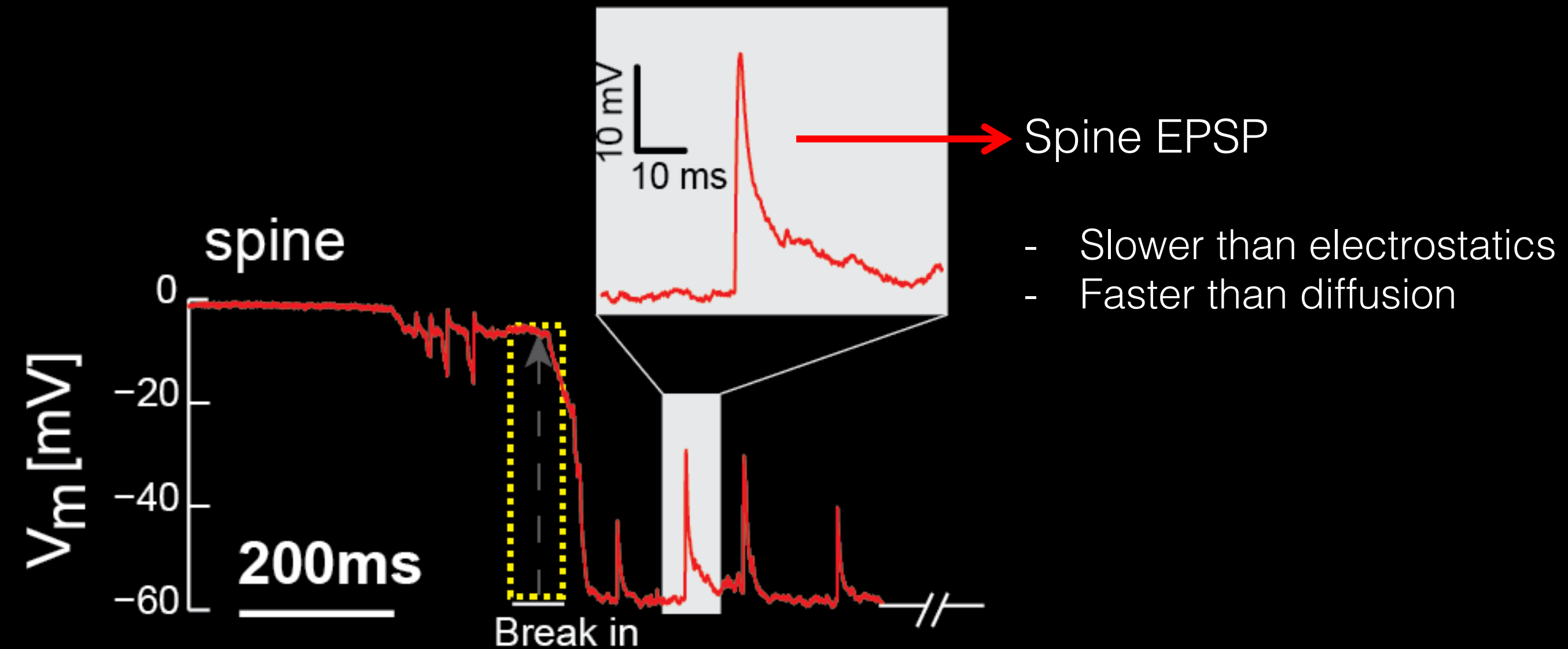
Nano-electrode



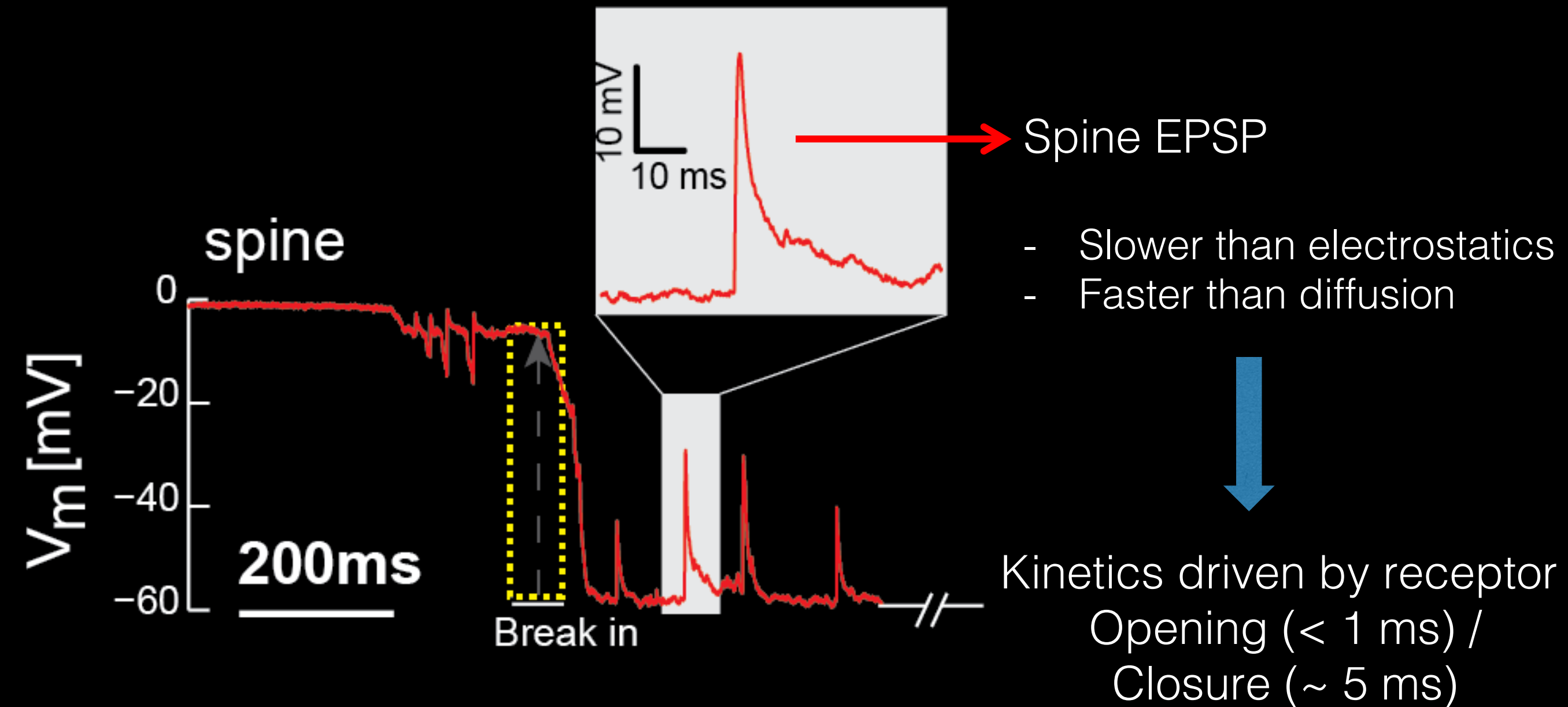
First report of direct voltage measurements in the spine

Jayant et al,
Nature Nano 2017

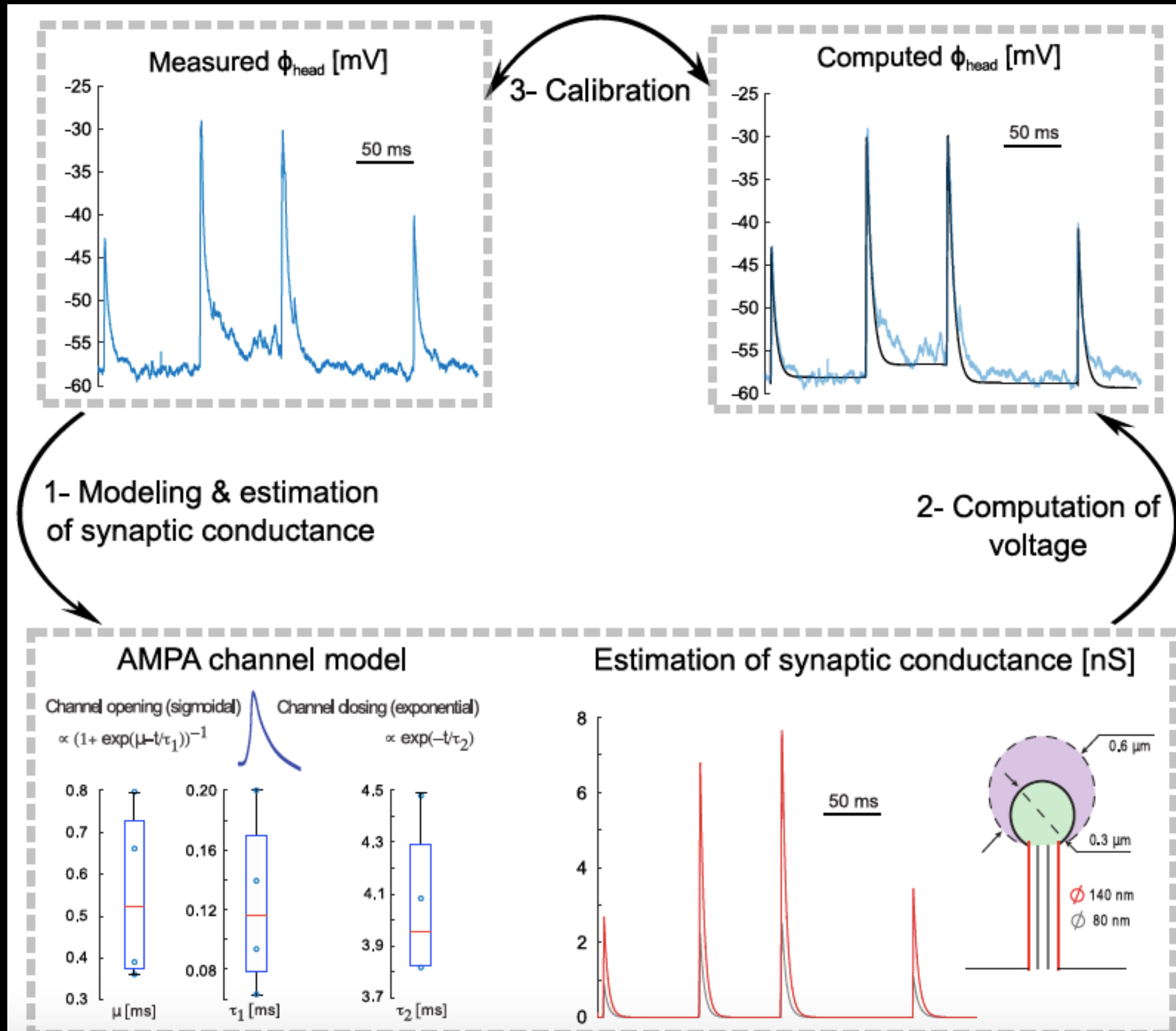
Direct voltage recordings inside dendritic spines



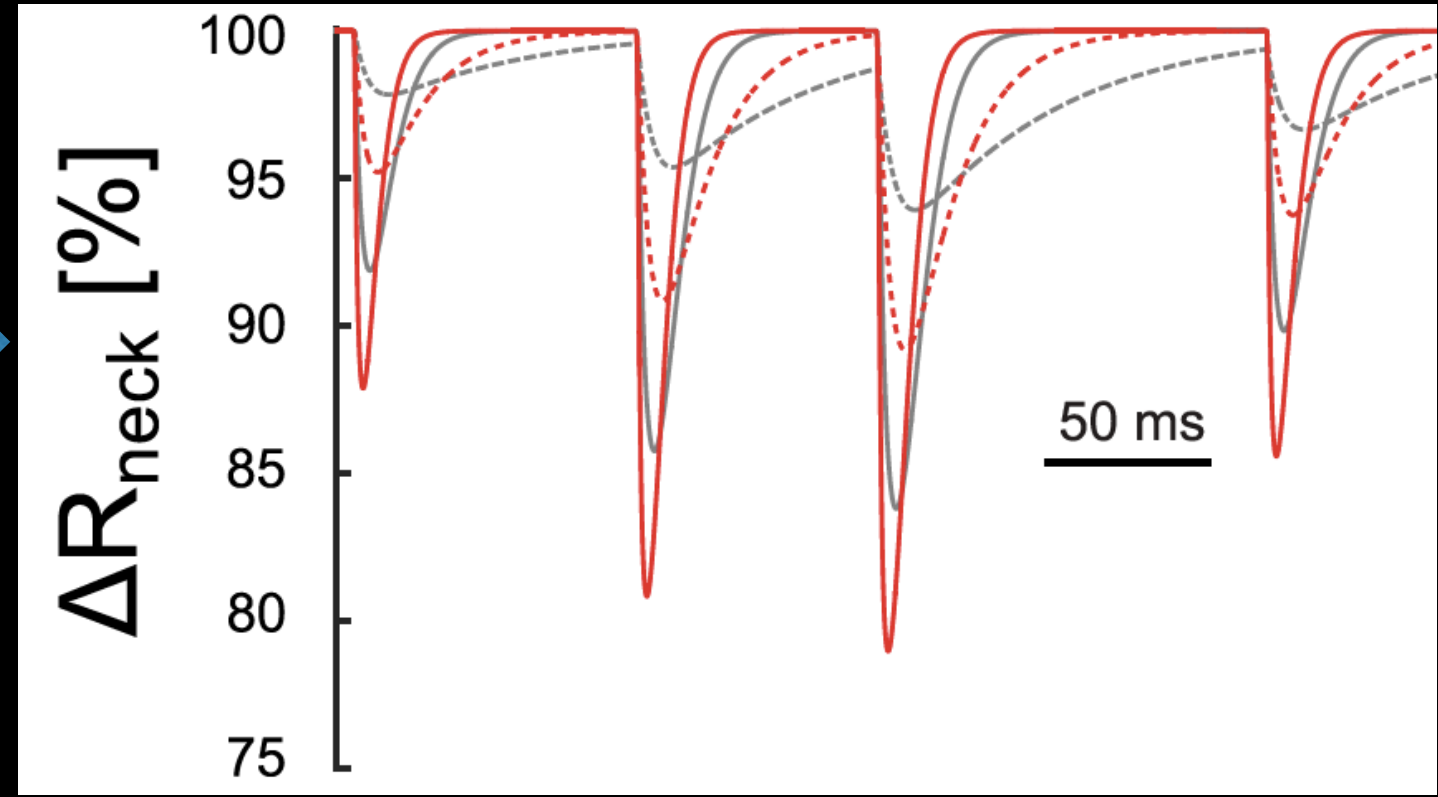
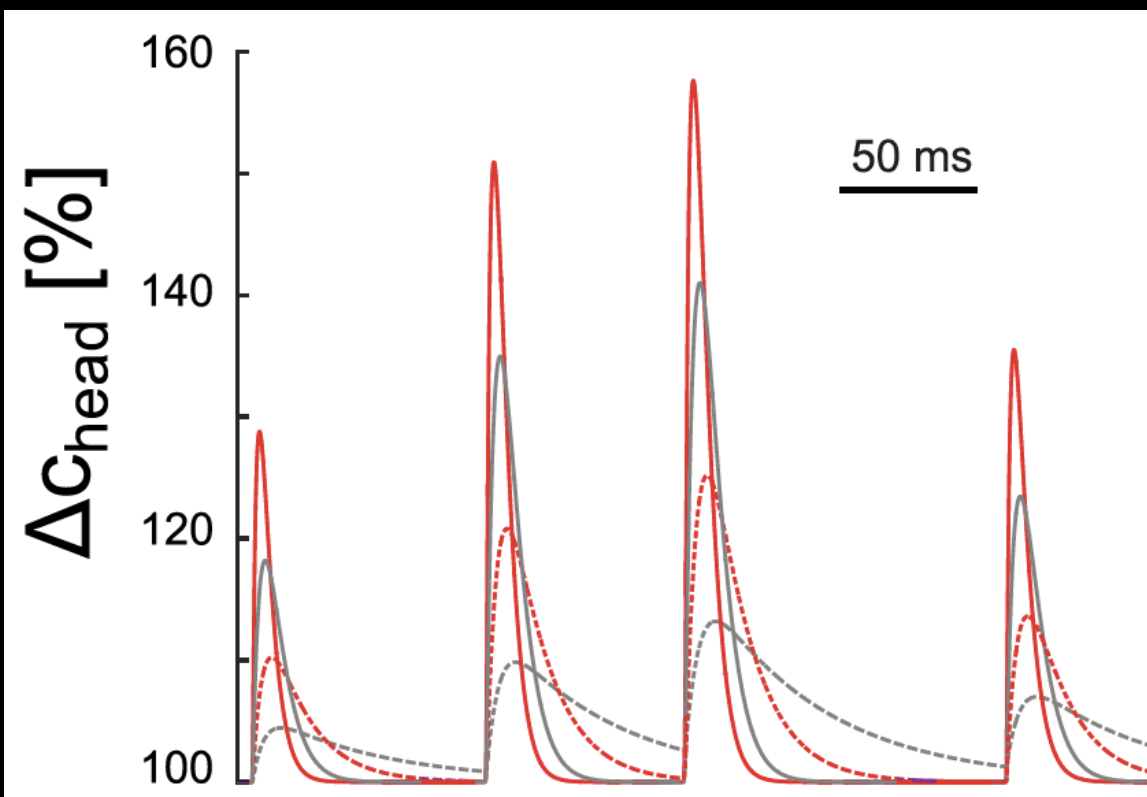
Direct voltage recordings inside dendritic spines



Fitting synaptic conductances to recorded potentials

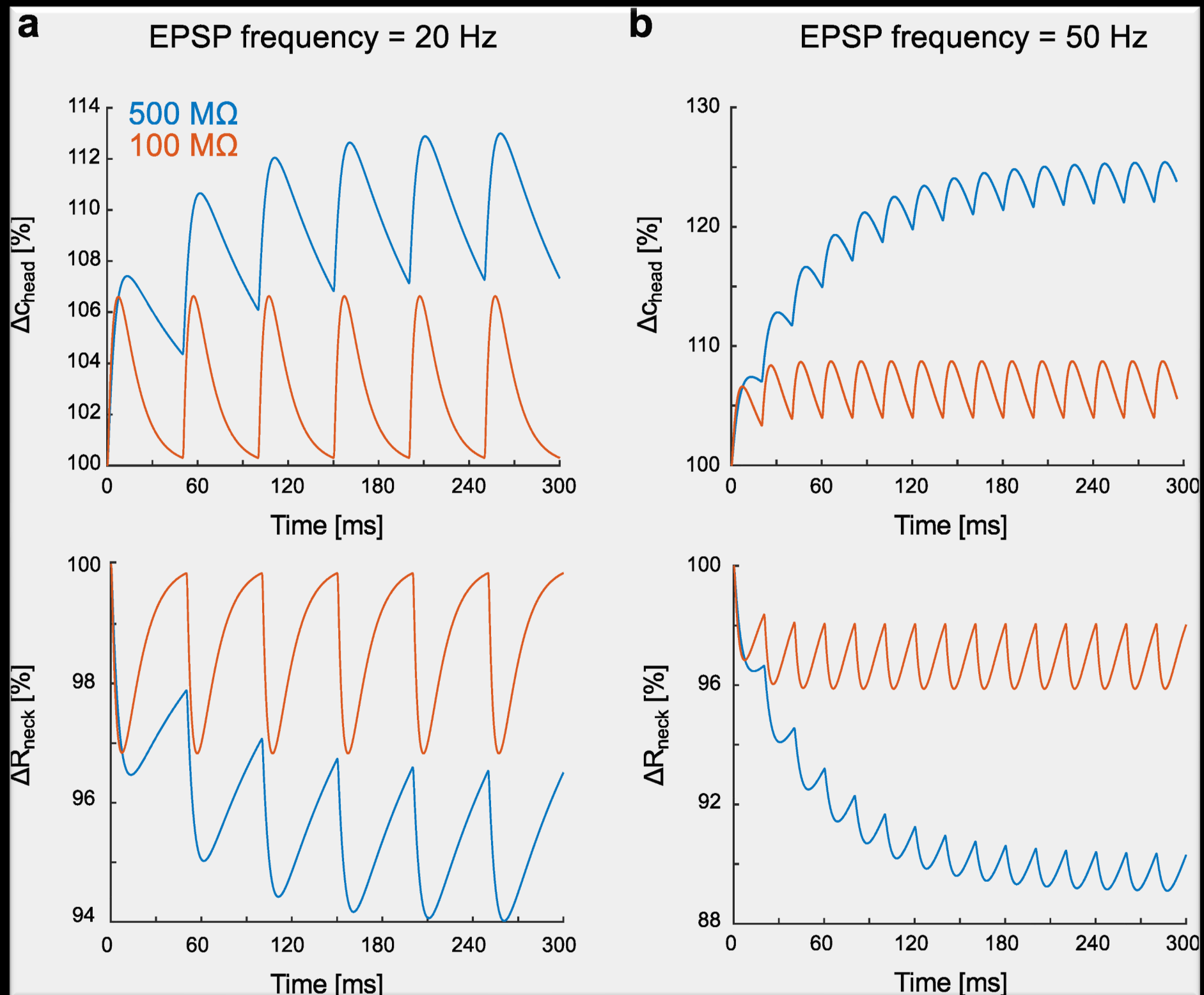


Predicting concentration changes during spontaneous EPSPs



Change in concentration induce dynamic neck resistance

Repeated stimulations and short-term potentiation



Decreased resistance and enhanced connectivity

Conclusion

- Voltage signaling is driven by ion dynamics
- Electro-diffusion equations can model the interplay between ion and voltage dynamics
- Spine geometry is very variable and changing; Geometry shapes the filtering of EPSPs do the parent dendrite
- Ion concentration varies and influences the electrical potential in spines

Take-home message

Nanodomains are ubiquitous in neurobiology (synapses, neuron-glia communication, thin dendrites...) and require the careful derivation of the physical laws that govern the constrained and non-linear dynamics of ions