Integrating rule-based models with compartmental models of neurons

David Sterratt, Oksana Sorokina, Douglas Armstrong

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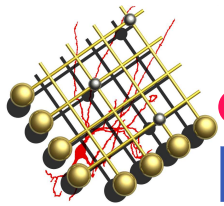


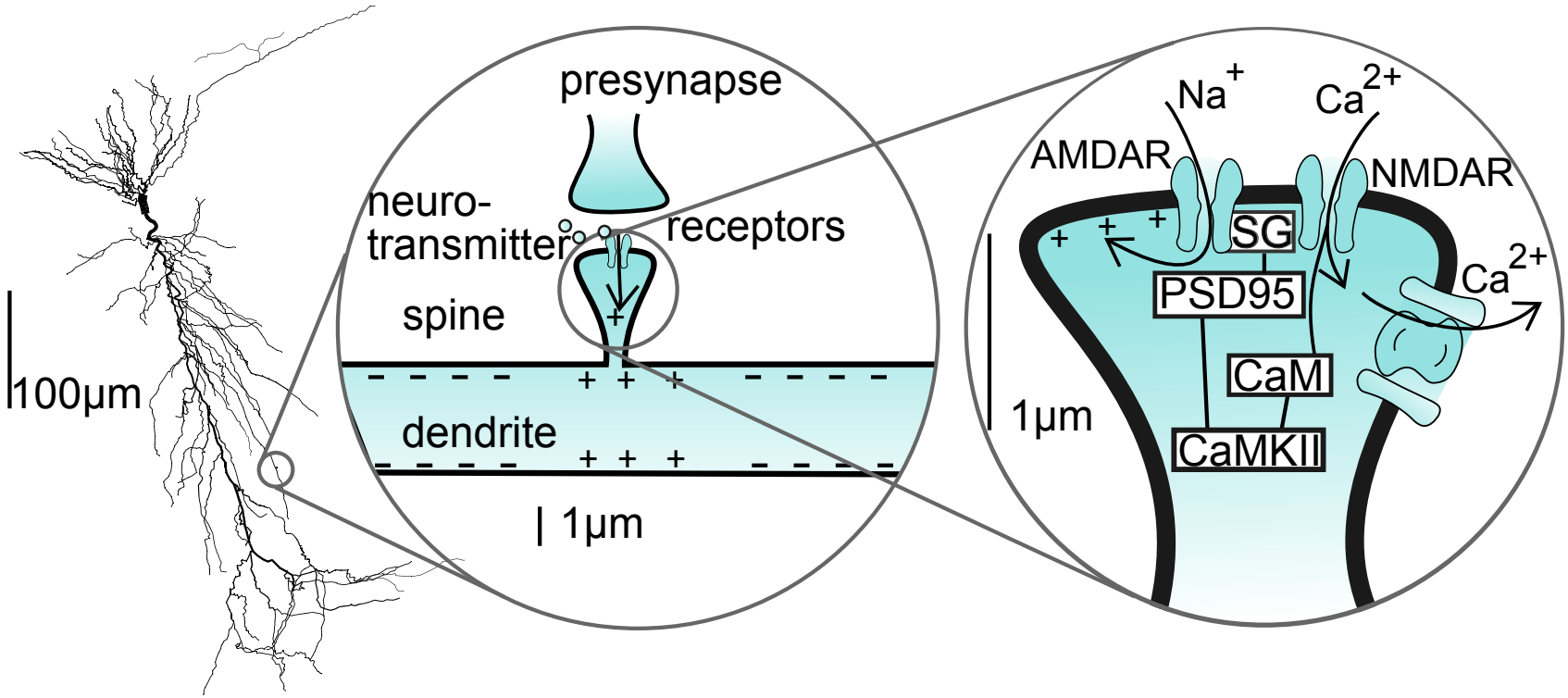
School of informatics

THE UNIVERSITY OF EDINBURGH

EUROSPIN, SynSys and Human Brain Projects.

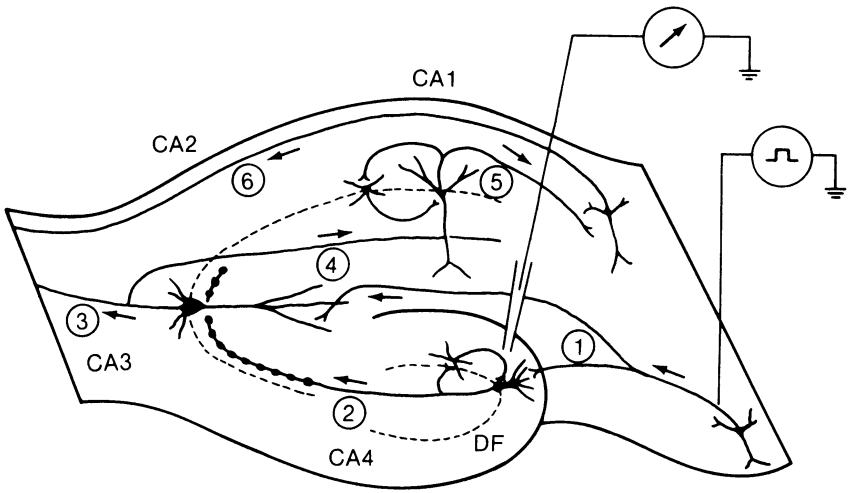
With thanks to Anatoly Sorokin, The NEURON developers, Jean Krivine, Vincent Danos & al.

Motivation 1: Understanding the basis of synaptic plasticity

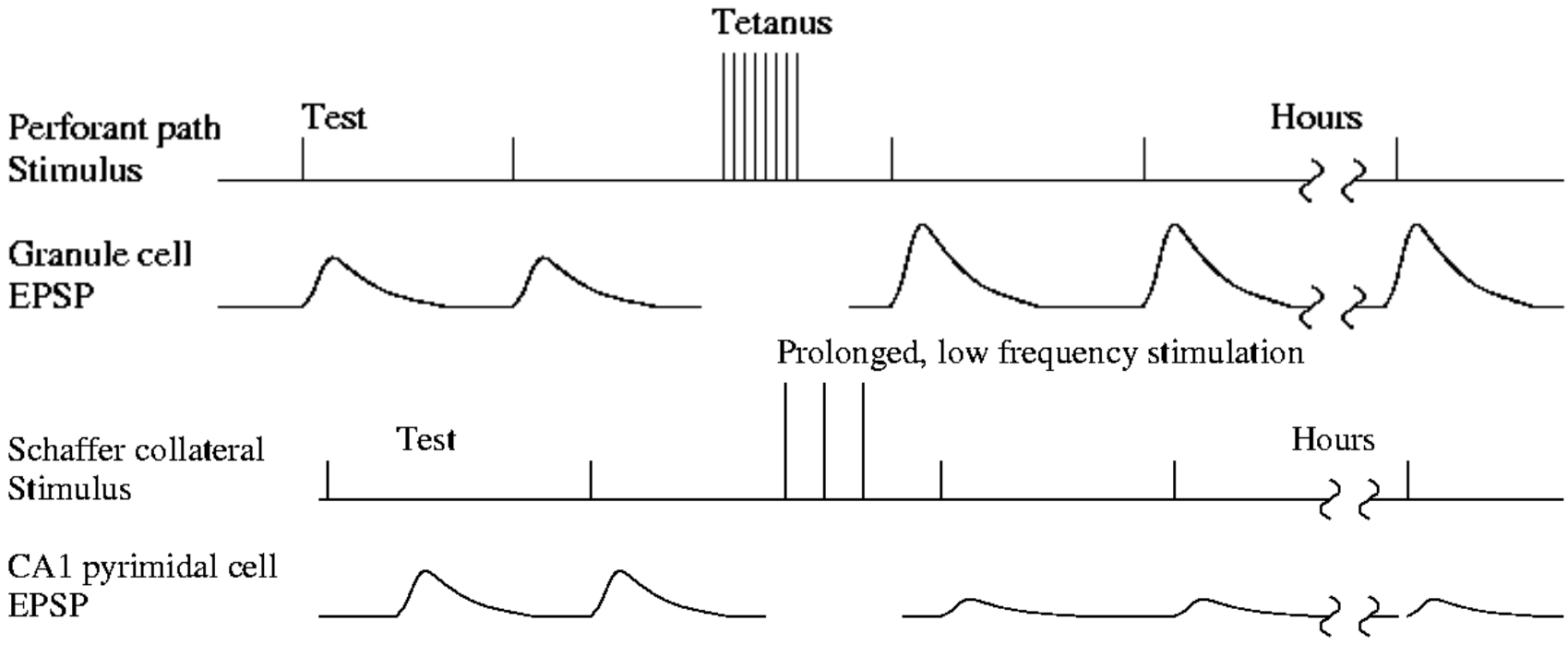


- Synapses crucial for development of functional brains and encoding semantic and episodic memories
- Patterns of pre- and postsynaptic activity on a time scale of milliseconds lead to long-lasting changes in synaptic strength

Long term potentiation & long term depression



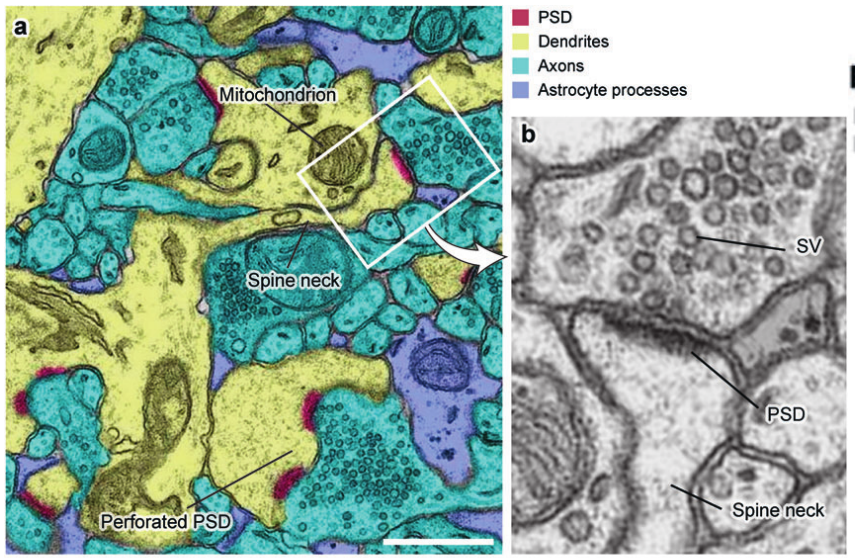
- Bliss and Lømo (1973)
- Electrical activity (ms) leads to change in AMPAR receptors in membrane that lasts for days

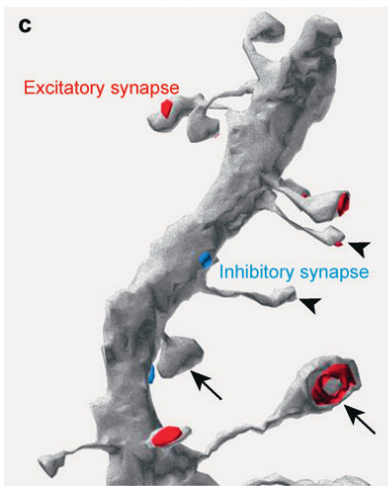


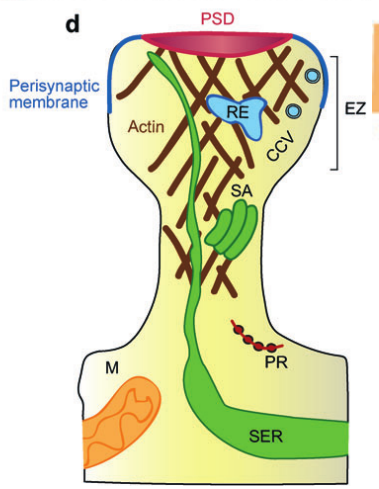
Motivation 2: synaptic plasticity in disease

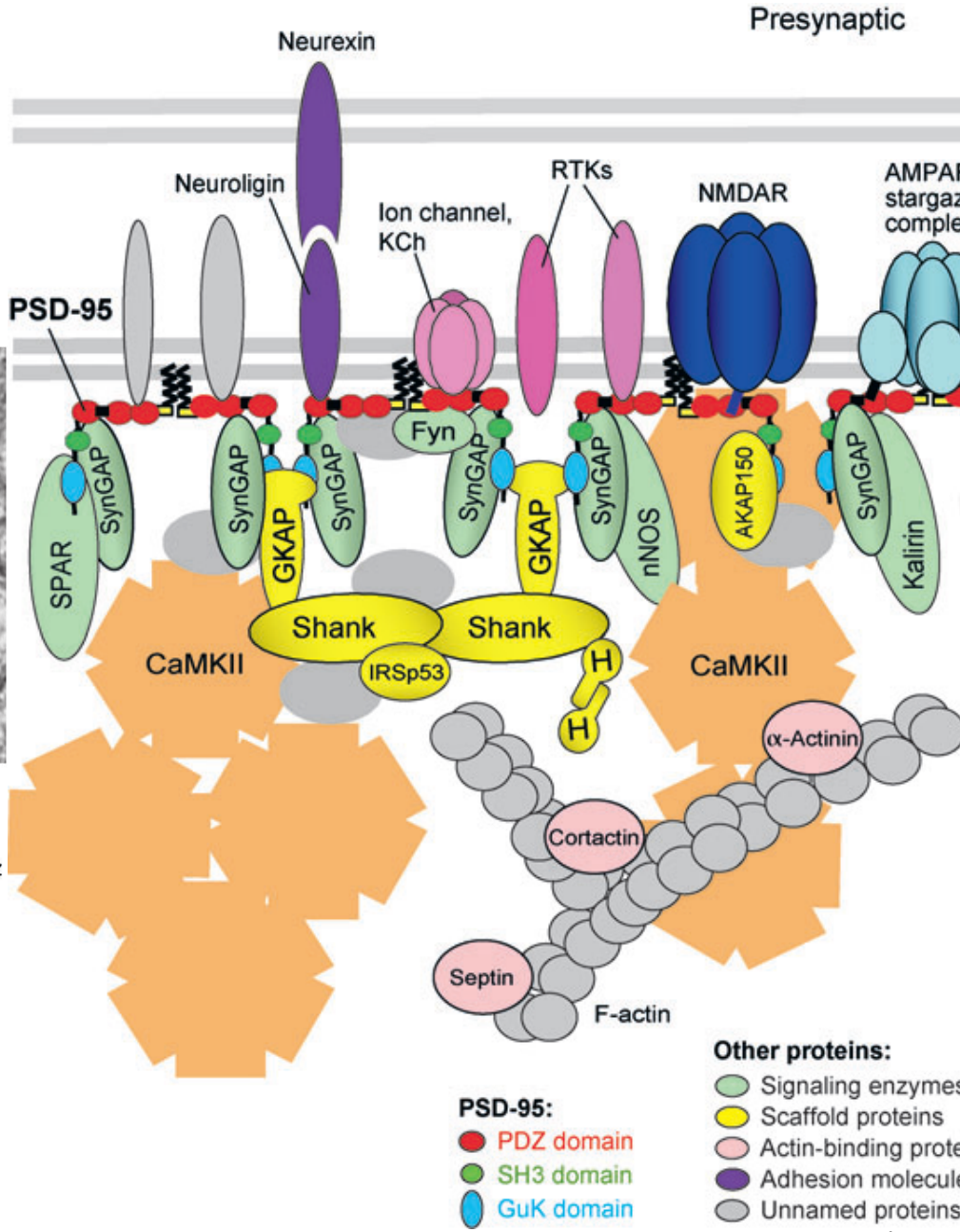
- Models of LTP and LTD based on signalling cascades Ca->CaM->CaMKII etc exist...
- ... But other synaptic proteins are involved in many brain diseases (schizophrenia, depression) (Pocklington et al., 2006)
- Why does this go wrong?
- There is a feedback loop: neural activity → synaptic changes → neural activity

The postsynaptic density (PSD)



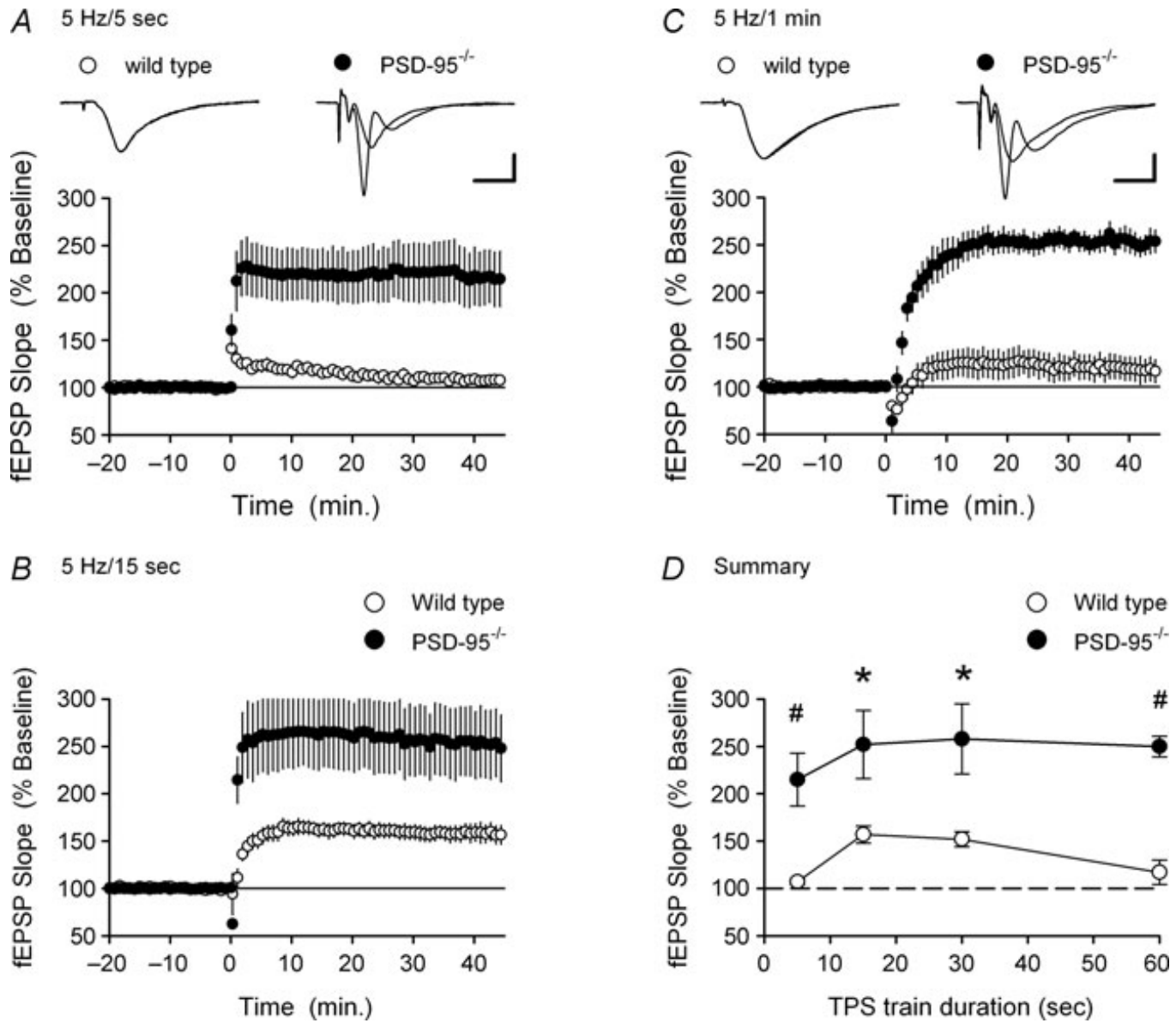






[Sheng and Hoogenraad (2007)

Mutations in PSD proteins affect synaptic plasticity

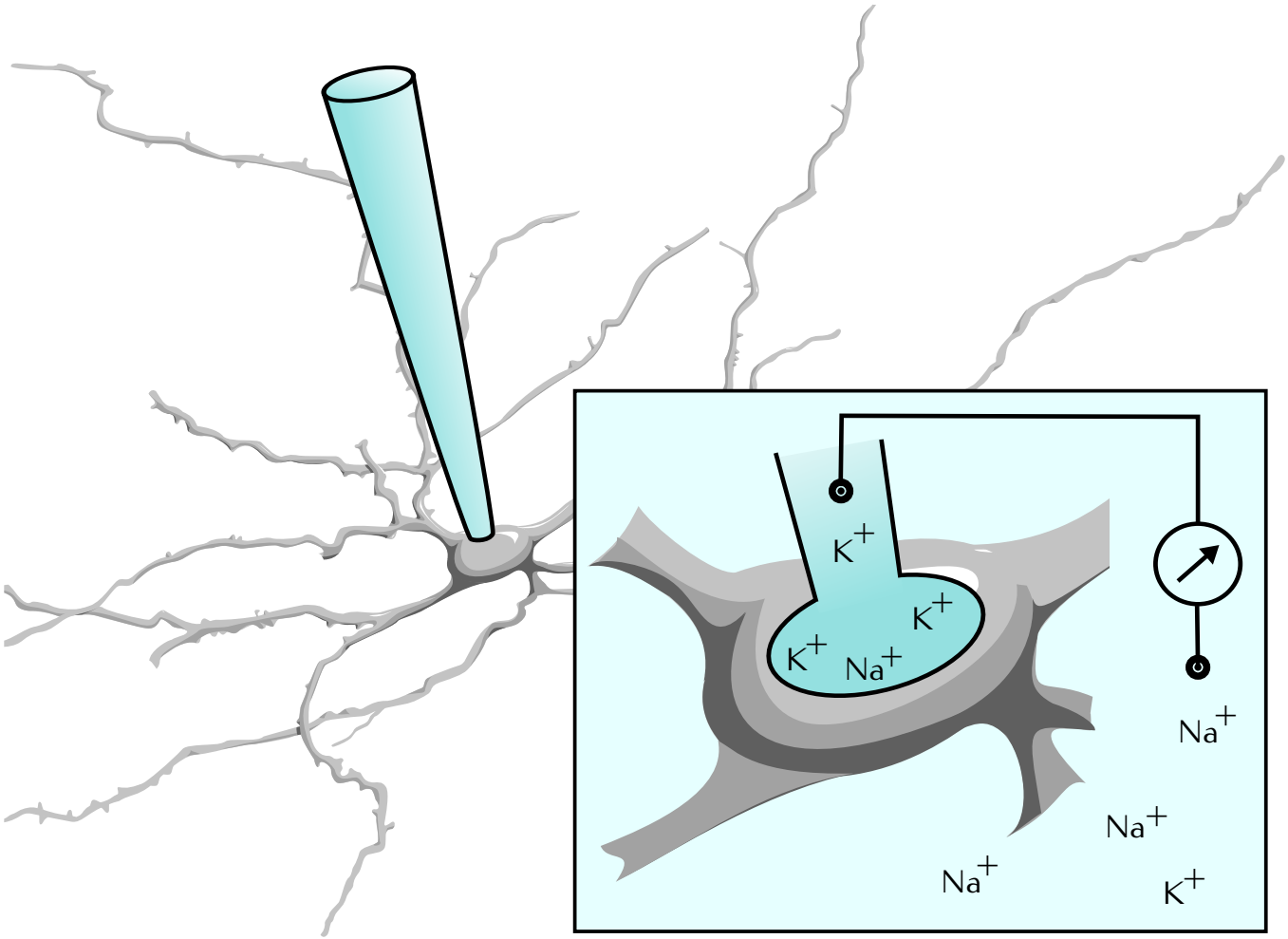


Carlisle et al. (2008)

Outline

Outline

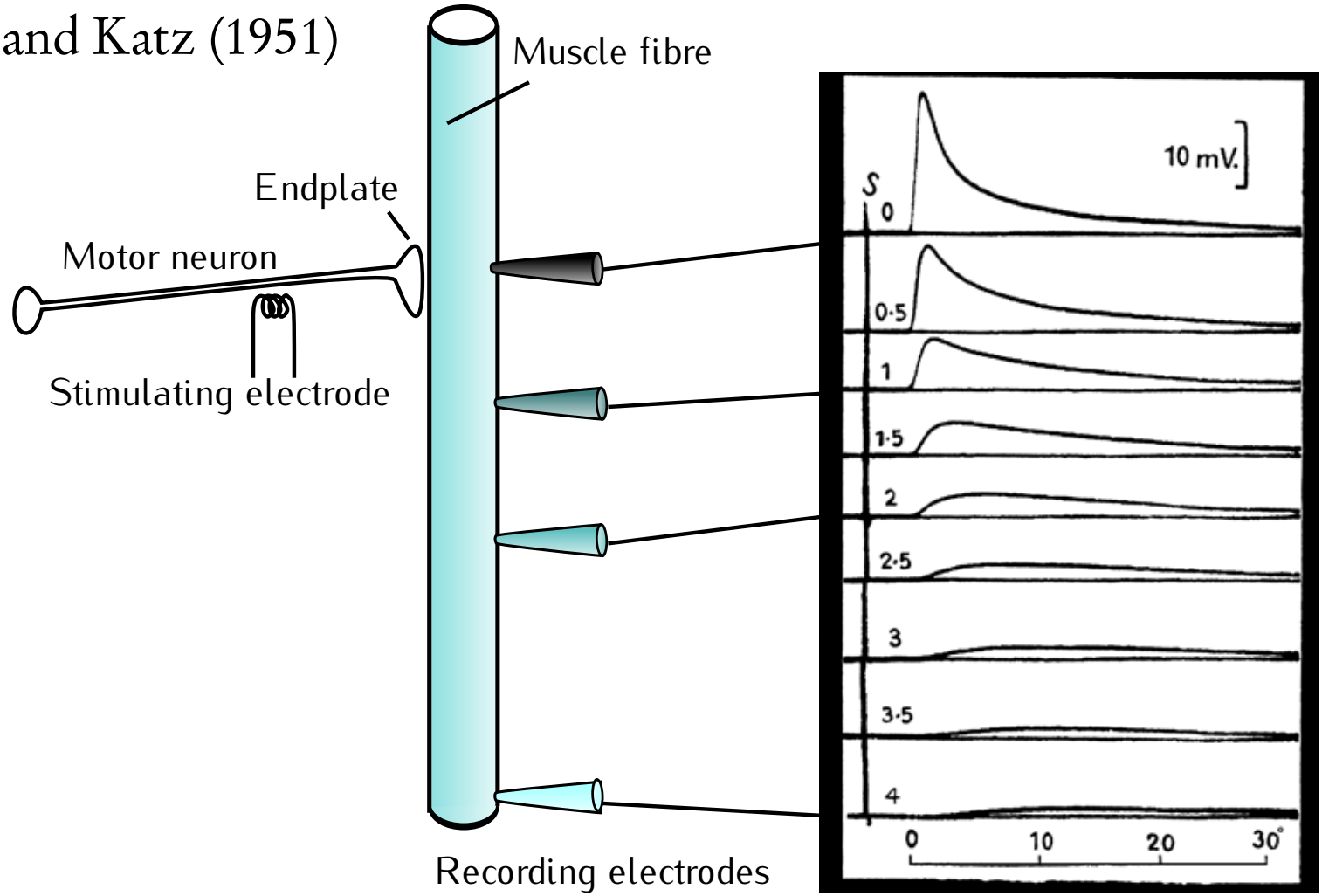
Neuron as electrical device: The resting membrane potential



- Intracellular space (**cytoplasm**), extracellular space
- **membrane potential** typically about −65 mV

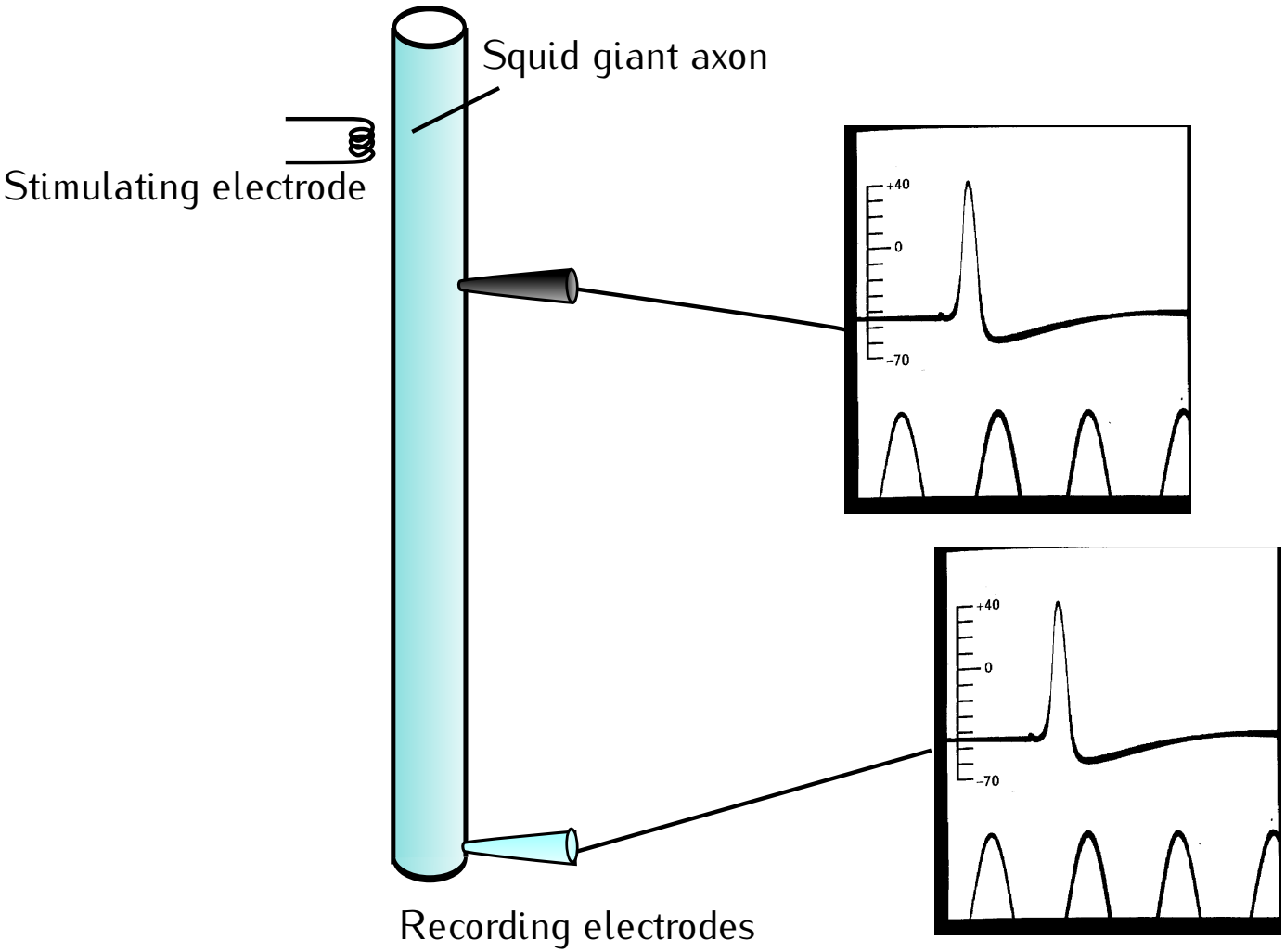
Intracellular recordings of endplate potentials

Fatt and Katz (1951)



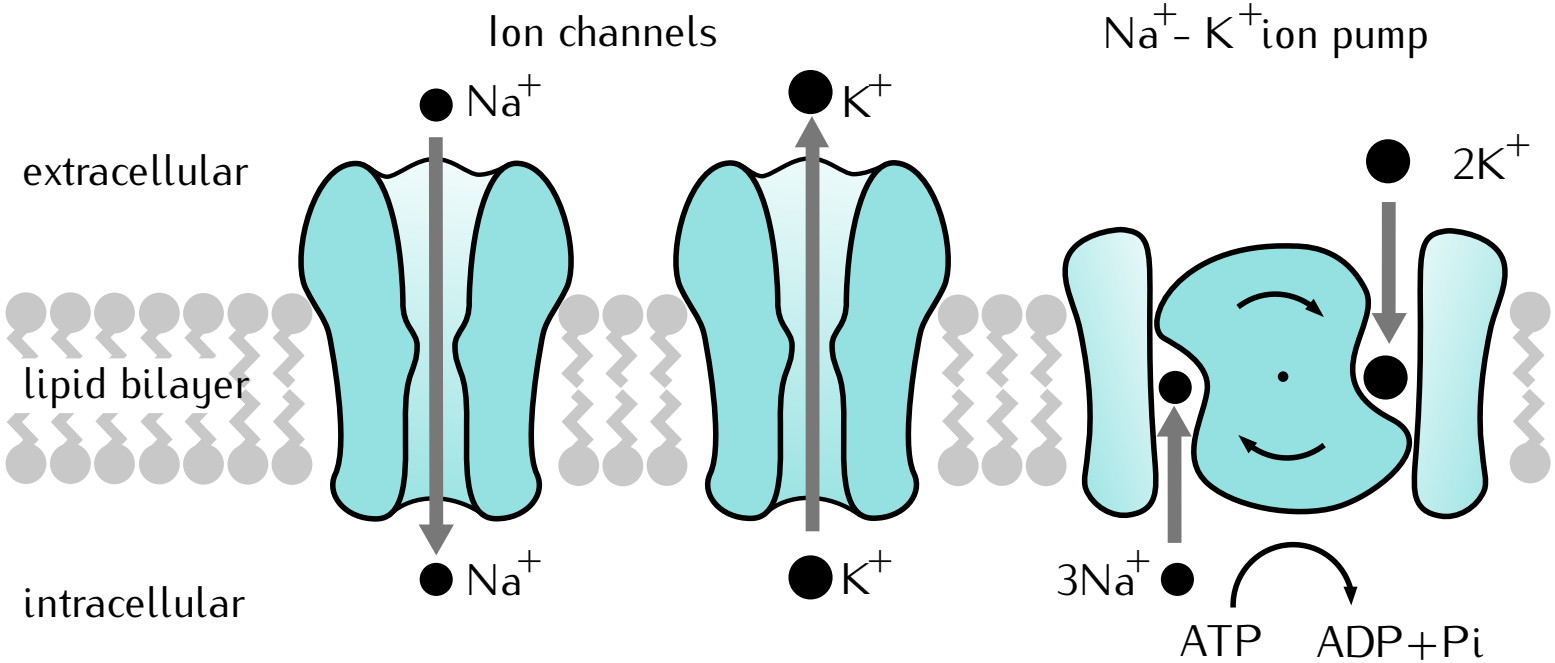
- Propagation is **passive**: it decays with distance
- Excitatory postsynaptic potentials (EPSPs) in motor neurons (Coombs et al., 1956)

Action potentials (Hodgkin and Huxley, 1939)



- Propagation is **active**: the amplitude of the action potential does not decay with distance

The neuronal membrane

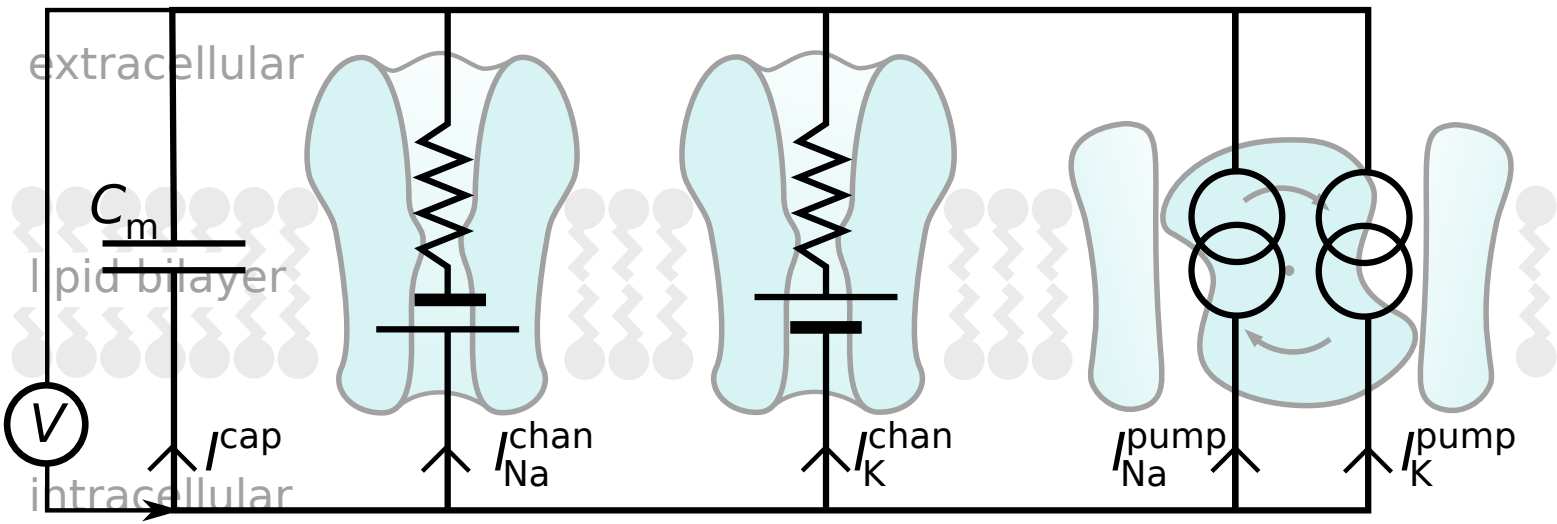


Impermeable

Permeable

Transporting
2 K^+ in 3 Na^+ out

The equivalent electrical circuit of a patch of membrane.



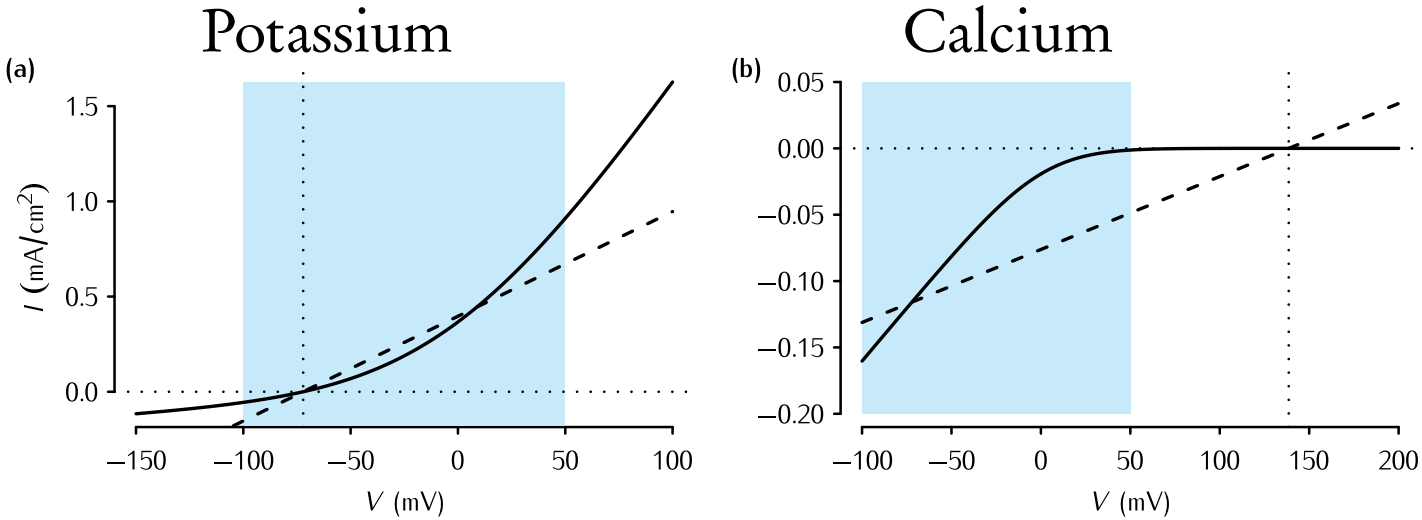
- Lipid bilayer modelled by a capacitor + Kirchoff's first law $\Rightarrow$

$$I^{\text{cap}} = C_{\text{m}} \frac{\mathrm{d}V}{\mathrm{d}t} = -I^{\text{chan}}_{\text{Na}} - I^{\text{chan}}_{\text{K}} - I^{\text{pump}}_{\text{Na}} - I^{\text{pump}}_{\text{K}}$$

- In neurons pump currents often ignored due to small size

Channel current

- Goldman-Hodgkin-Katz theory:



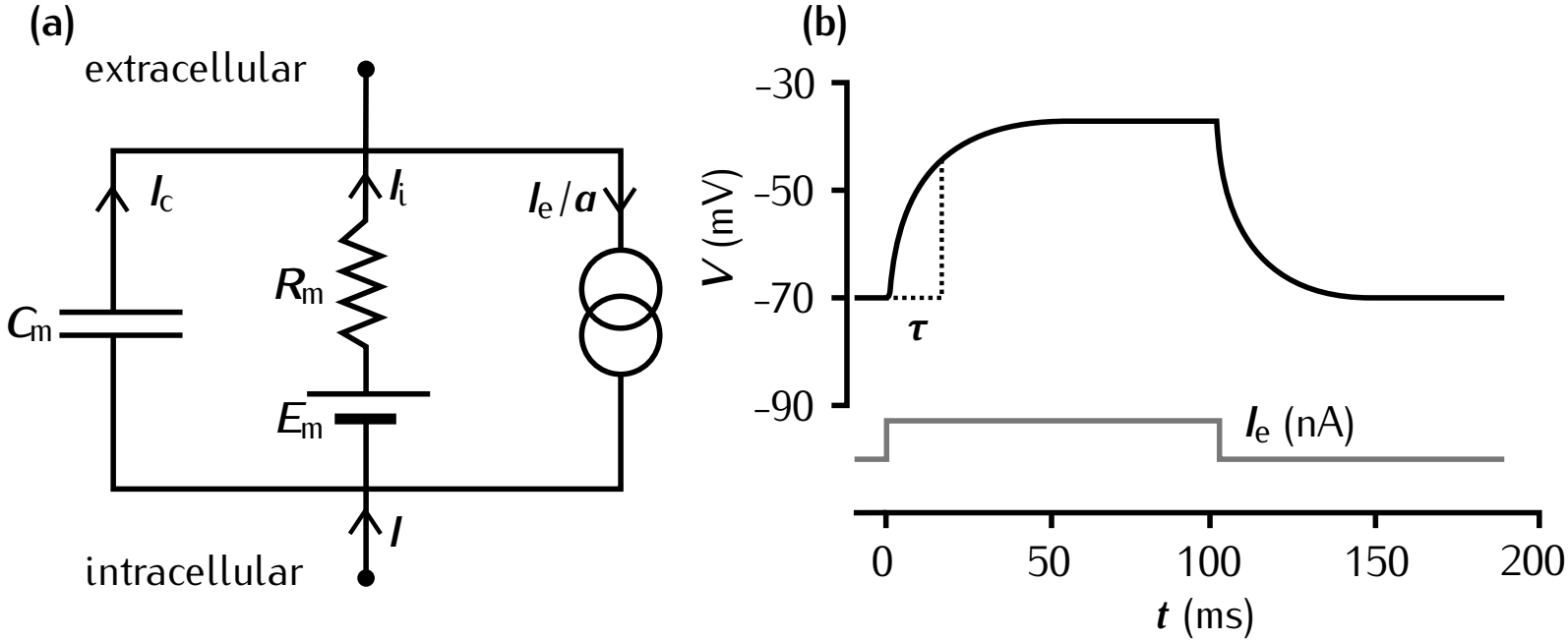
- In general, current carried by species S depends on the membrane potential V and the intra- and extracellular concentrations of S:

$$I_S^{\text{chan}} = g_S f_S(V, [S]_i, [S]_e)$$

- In biological range, reasonable to approximate curve for K^+ with a straight line intersecting the voltage axis at E_K

$$I_K = g_K(V - E_K)$$

Passive patch of membrane



- **Membrane time constant** is product of membrane resistance and capacitance:

$$\tau = R_m C_m$$

Hodgkin & Huxley's big insight

$$g_{\mathrm{K}} = \bar{g}_{\mathrm{K}} n^4 \quad \text{and} \quad g_{\mathrm{Na}} = \bar{g}_{\mathrm{Na}} m^3 h$$

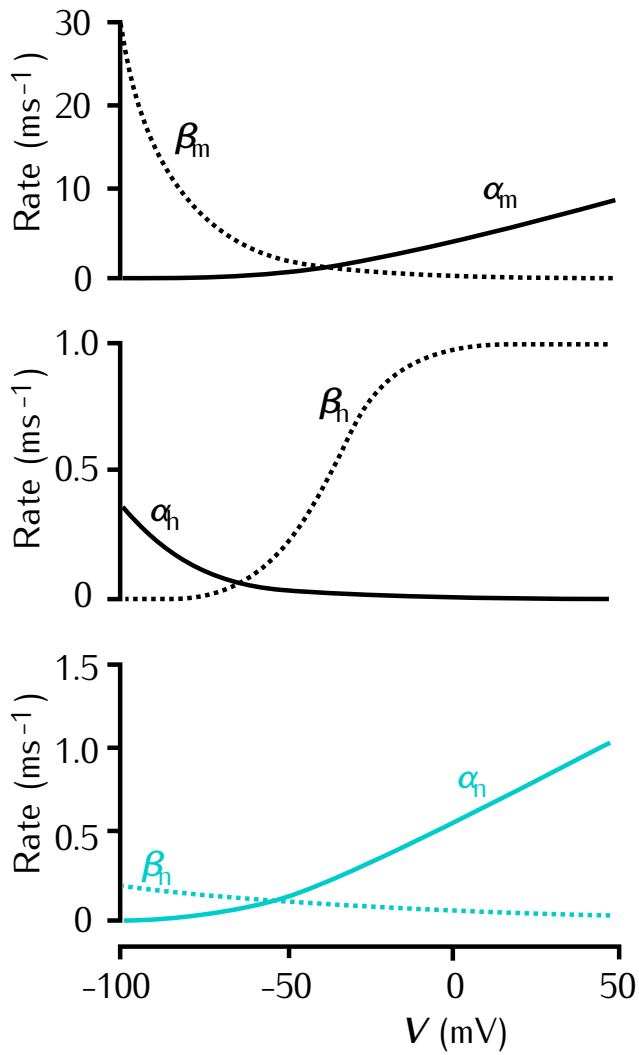
e.g. Potassium activation gating variable

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_{\mathrm{n}}(1-n) - \beta_{\mathrm{n}} n$$

OR express the HH potassium n^4 variable as Markov system:

$$\mathrm{C}_1 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{C}_2 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{C}_3 \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \mathrm{C}_4 \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} \mathrm{O}$$

$$g_{\mathrm{K}} = \bar{g}_{\mathrm{K}} O$$



Example of pump

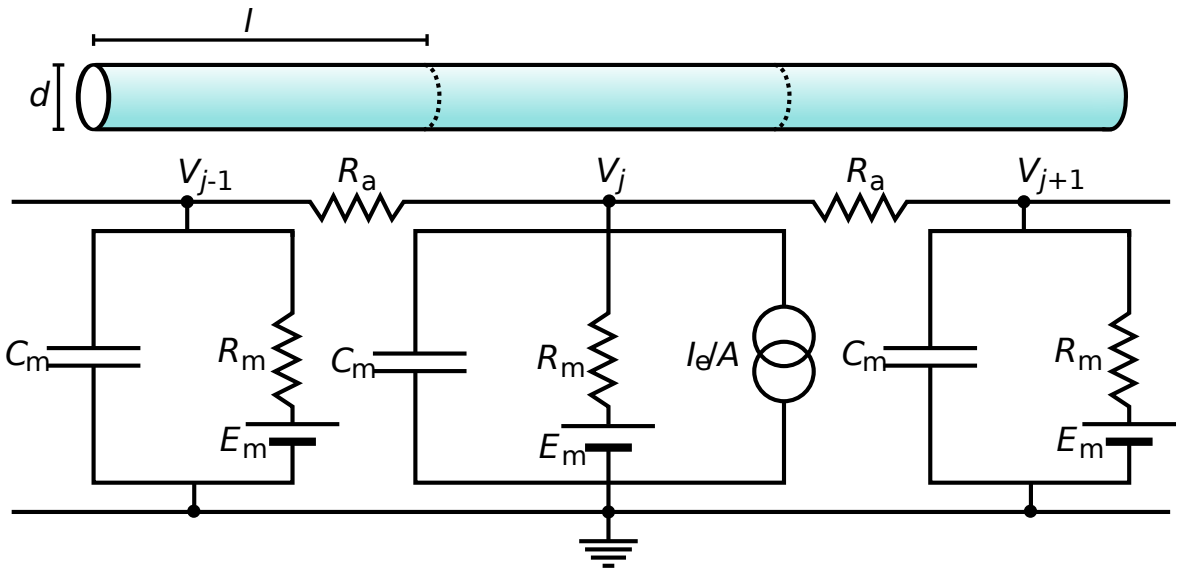
$$\text{Ca binding:} \quad \mathrm{P} + \mathrm{Ca} \xrightarrow{k_1} \mathrm{P} \cdot \mathrm{Ca}$$

$$\text{Ca release:} \quad \mathrm{P} \cdot \mathrm{Ca} \xrightarrow{k_2} \mathrm{P}$$

- Here $I_{\mathrm{Ca}}^{\mathrm{pump}} = k_2[\mathrm{P} \cdot \mathrm{Ca}]2Fv/a$

A length of passive neurite

- To deal extended neurites, where voltage may vary down length, split into multiple isopotential **compartments**
- A **compartmental model** with N compartments, each representing length l of neurite of diameter d



R_a is the **axial resistivity**

- New version of the membrane equation for each compartment

$$C_m \frac{dV_j}{dt} = \frac{E_m - V_j}{R_m} + \frac{V_{j+1} - V_j}{4R_a l^2} + \frac{V_{j-1} - V_j}{4R_a l^2} + \frac{I_{e,j}}{\pi dl}$$

Summary of system

$$C_i \frac{\mathrm{d}V_i}{\mathrm{d}t} = \sum_{j \in \mathcal{N}i} \frac{d_{ij}(V_j - V_i)}{4R_\mathrm{a} l_{ij}^2} - \sum_S \left(I_{S,i}^{\mathrm{chan}} + I_{S,i}^{\mathrm{pump}} \right) + I_{\mathrm{e},i}$$

I_e is a forcing input (e.g. current injection), which does not depend on other state variables.

$$I_{S,i}^{\mathrm{chan}} = \sum_j \bar{g}_{S,j,i} O_{ij} f_{S,i}(V_i, [S]_i, [S]_\mathrm{e})$$

O_{ij} are number of channels in compartment i in state j, determined by Markov schemes, which can be simulated as ODEs.

$$\frac{\mathrm{d}[S]_i}{\mathrm{d}t} = -\frac{a_i}{z_S F v_i} (I_{S,i}^{\mathrm{chan}} + I_{S,i}^{\mathrm{pump}}) + \sum_r J_{S,r,i}$$

$J_{S,r,i}$ are fluxes into intracellular reactions r, determined by ODEs.

Solution of ODEs, e.g. with implicit Euler

- Gather all state variables into vector $\vec{x}$, and express RHS as function of states $\vec{G}$ and forcing inputs $\vec{b}$
- Derivative evaluated at $t + \Delta t$, the end of the time step:

$$\frac{\vec{x}(t+\Delta t) - \vec{x}(t)}{\Delta t} = \vec{G}(\vec{x}(t+\Delta t)) + \vec{b}(t+\Delta t)$$

- Taylor expand RHS in Δt and rearrange:

$$\vec{x}(t+\Delta t) = \vec{x}(t) + \left(I - \frac{\partial \vec{G}}{\partial \vec{x}}\Delta t\right)^{-1} \left(\vec{G}(\vec{x}(t)) + \vec{b}(t)\right)\Delta t$$

where $\partial \vec{G}/\partial \vec{x}$ is the Jacobian matrix at time t

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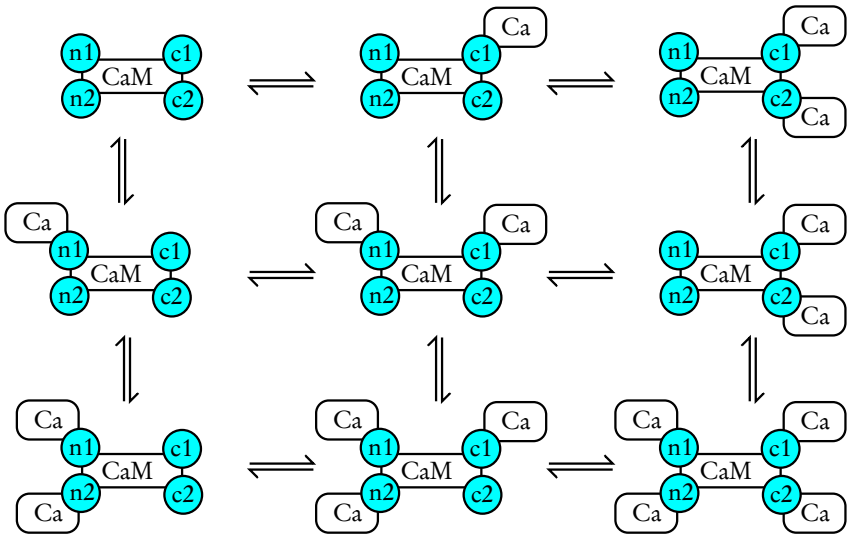
Motivating example: Calmodulin-calcium binding



- Cooperative binding to C & N lobes of calmodulin; C & N lobes independent
- **Reaction-based** stochastic simulation algorithm would need **24 unidirectional reactions** for **9 separate species**

- **Rule-based** expression of binding to C lobe, in terms of agents, binding sites and links:

```
ca(b), CaM(c1,   c2)  <=>  ca(b!1), CaM(c1!1,c2)
ca(b), CaM(c1!_,c2)  <=>  ca(b!1), CaM(c1!_,c2!1)
```

- Full definition of `CaM` agent is

```
CaM(c1, c2, n1, n2, ck, h)
```

"Don't care, don't write"

Kappa equivalent

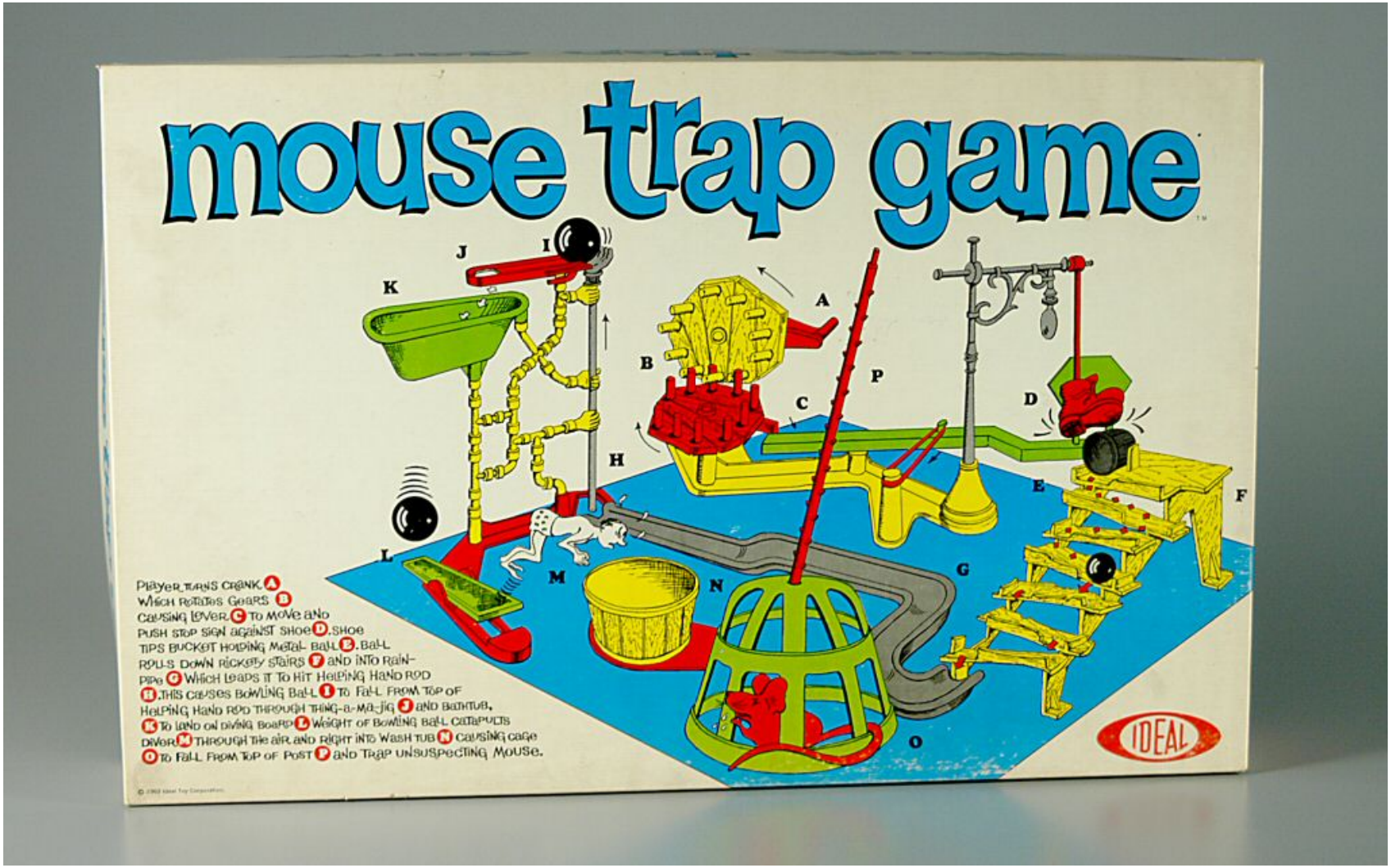
- Thus equivalent model in the **rule-based Kappa language** requires **8 unidirectional rules** to describe the behaviour of **2 agents** with **binding sites**
- **Rule-based solvers**, e.g. KaSim (Danos et al., 2007) or SpatialKappa (Sorokina et al., 2013), use variant of the Gillespie algorithm, but with rules rather than reactions.
- States can also be defined:

```
%Agent:  A(l~u~p)
A(l~u) <-> A(l~p)
```

- Deal with complexity: only keep track of complexes that actually exist at any time point in a simulation, not all possible complexes that could arise. E.g. EGFR with 9 phosphorylation sites $\Rightarrow 2^9 = 512$ possible states

Outline

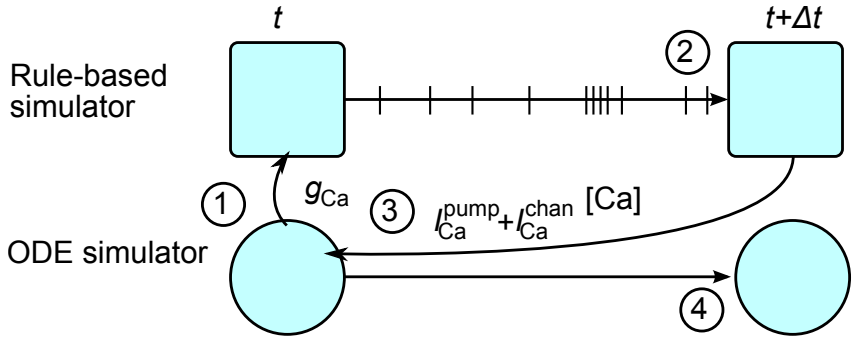
Approach: simulator integration



To integrate rule-based and compartmental simulators, assume that there are:

- variables which exist only in the electrical simulator (e.g.

Update algorithm



1. Pass relevant continuous variables (e.g. Ca channel conductance or current) to the rule-based simulator
2. Run the rule-based solver from t to $t+\Delta t$, creating bridge species S_i in compartment i due to channel current $I_{S,i}^{\text{chan}}$
3. Compute the net change ΔS_i^{tot} in the total number of each bridging species S (including in any complexes) over the time step and convert back to a current density $I_{S,i}^{\text{chan}}+I_{S,i}^{\text{pump}}$. To ensure consistency between membrane potential and ionic concentrations, set the corresponding element of $\vec{b}(t)$ equal to $-(1/C_i)\sum_S(I_{S,i}^{\text{chan}}+I_{S,i}^{\text{pump}})$
4. Update the continuous variables using a standard numerical integration method.

Summary of system 23

$$C_i \frac{\mathrm{d}V_i}{\mathrm{d}t} = \sum_{j \in \mathcal{N} i} \frac{d_{ij}(V_j - V_i)}{4 R_\mathrm{a} l_{ij}^2} - \sum_S \left(I_{S,i}^\mathrm{chan} + I_{S,i}^\mathrm{pump} \right) + I_{\mathrm{e},i}$$

I_e is a forcing input (e.g. current injection), which does not depend on other state variables.

$$I_{S,i}^\mathrm{chan} = \sum_j \bar{g}_{S,j,i} O_{ij} f_{S,i}(V_i, [S]_i, [S]_\mathrm{e})$$

I_e and $I_{S,i}^\mathrm{chan} + I_{S,i}^\mathrm{pump}$ are forcing inputs which do not depend directly on other state variables. Channel current replaced by creation rule:

$$\frac{\sum_j \bar{g}_{S,j,i} O_{ij} f_{S,i}(V_i, [S]_i, [S]_\mathrm{e}) \cdot N_\mathrm{A} a_i / z_S F}{\longrightarrow \texttt{S(b)}}$$

$$I_{S,i}^\mathrm{chan} + I_{S,i}^\mathrm{pump} = -\Delta S_i^\mathrm{tot} / \Delta t \cdot z_S F / a_i N_\mathrm{A}$$

O_{ij} are number of channels in compartment i in state j, determined by Markov schemes, which can be simulated as ODEs. O_{ij} are number of channels in compartment i in state j, computed within

Outline

Validation simulations: simple calcium pump

Kappa fragment `caPump.ka`:

```
# Concentration of one agent in the volume in mM
% var: 'ac' 1E18/('NA' * 'vol')
## Rules
'Bind'      ca(x), P(x)      -> ca(x!1),P(x!1) @ 'k1'*'ac'
'Release'   ca(x!1),P(x!1)   -> P(x)           @ 'k2'
## Observations
% obs: 'ca'    ca(x)            # Free Ca
% obs: 'P-Ca'  ca(x!1), P(x!1)  # Bound Ca-P
% obs: 'P'     P(x)             # Free P
```

Validation simulations: simple calcium pump

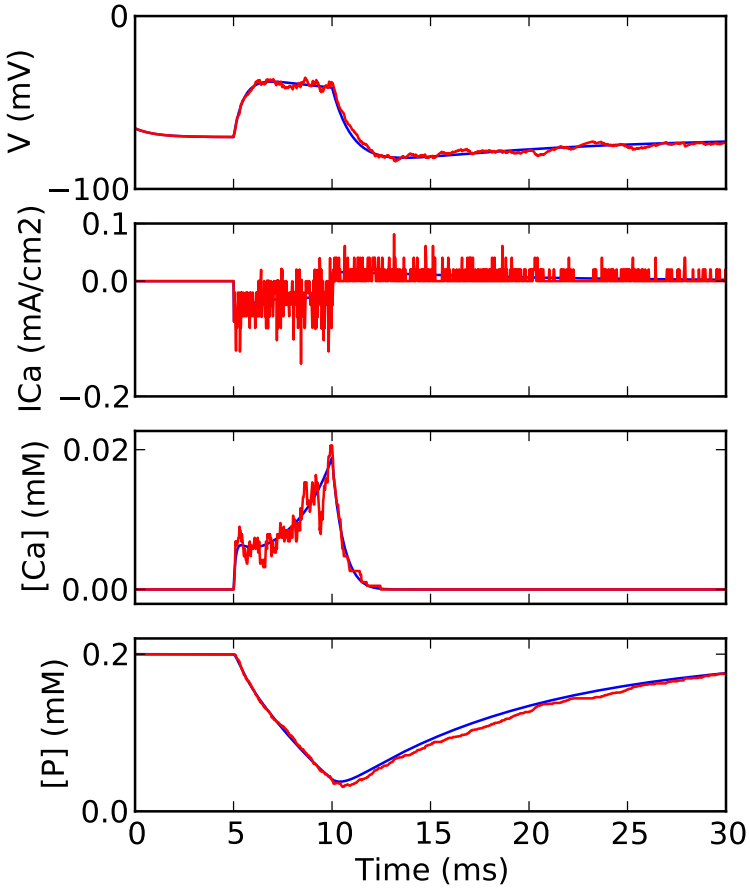
NEURON python fragment:

```
from neuron import *
import KappaNEURON
sh = h.Section()
r = rxd.Region([sh], nrn_region='i')
## Define the species, the ca ion (already built-in to NEURON)
## and the pump molecule. These names must correspond to the
## agent names in the Kappa file.
ca = rxd.Species(r, name='ca', charge=2, initial=0.0)
P  = rxd.Species(r, name='P',  charge=0, initial=0.2)
## Create the link between the Kappa model and the species
## just defined
kappa = KappaNEURON.Kappa(membrane_species=[ca], species=[P],
                          kappa_file="caPump.ka", regions=r)
run(30)
```

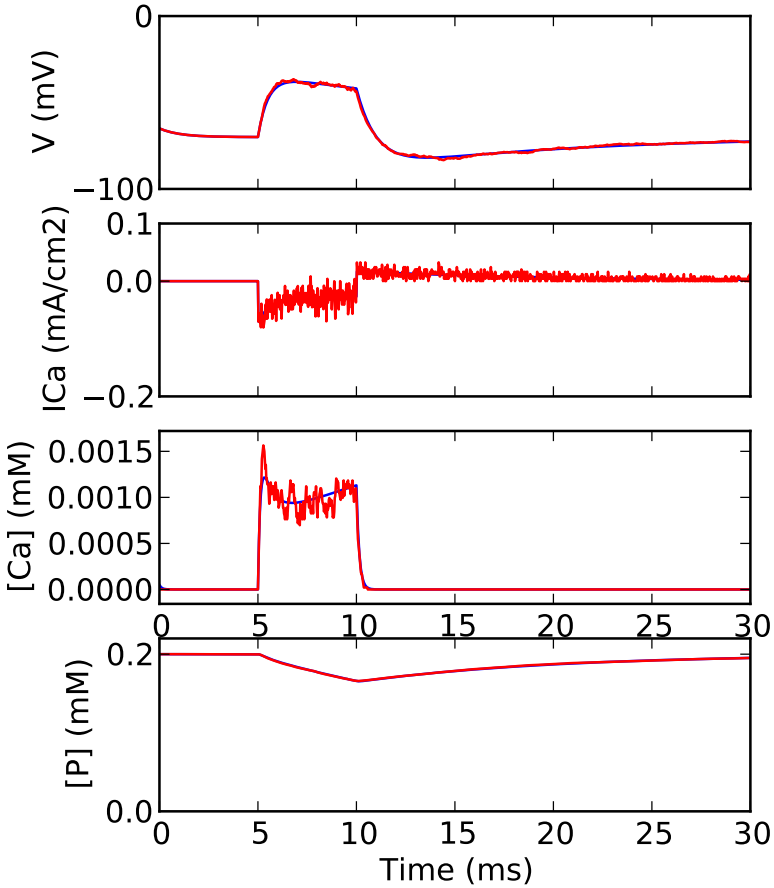
Validation results

Single compartment, Ca influx and pumping, stochastic Kappa and deterministic ODE simulation

Diameter 0.2μm

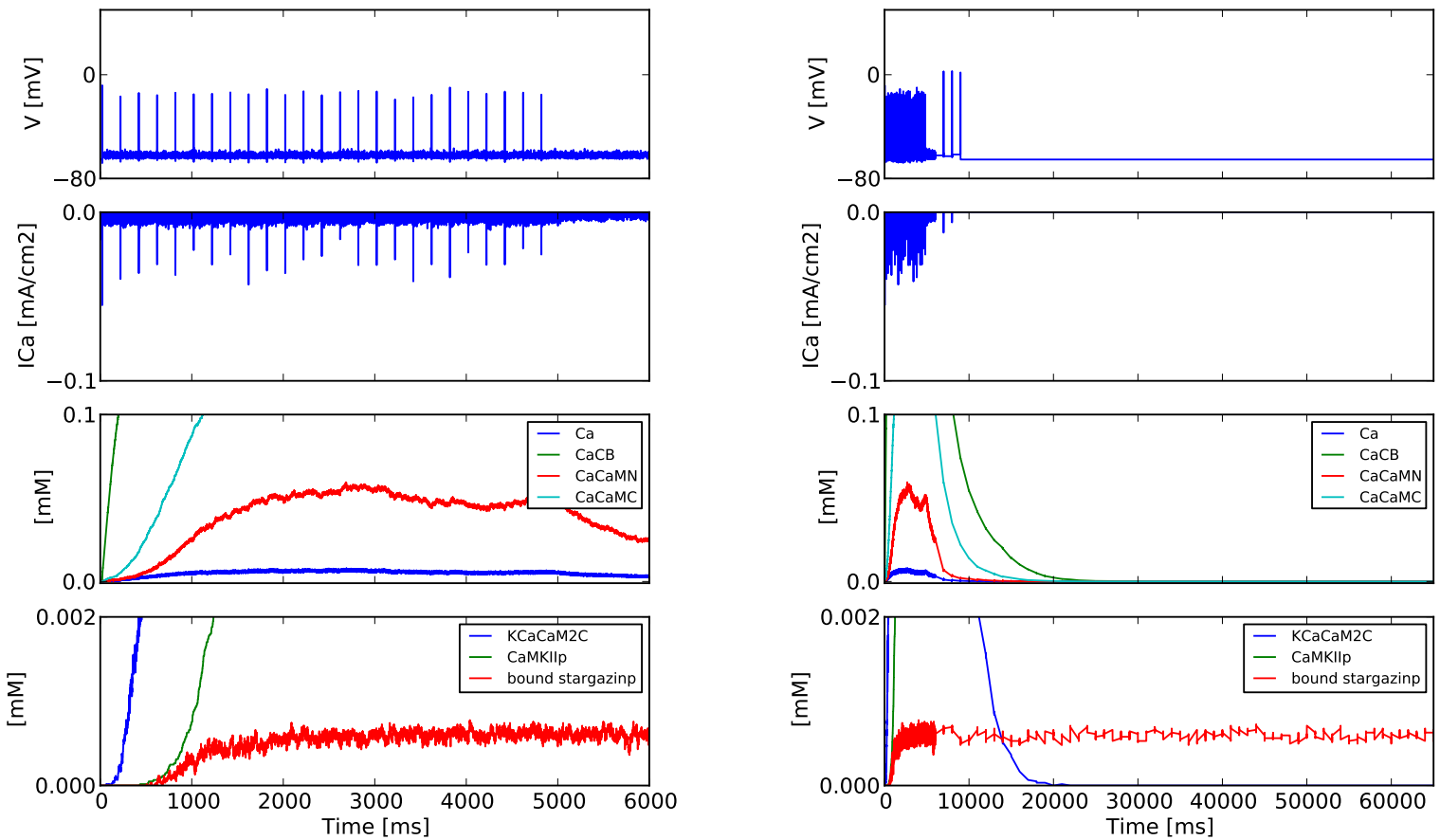


Diameter 1.0μm



Demonstration simulations

- Incorporates data-driven model of proteome (Sorokina et al., 2011) and detailed models of Ca-CaM-CaMKII cascade
- Involves phosphorylated-CAMKII dependent binding of PSD95, stargazin and GluR
- NMDAR channel state controlled by rule-based simulator



Discussion

- Method is similar to integration of electrical & biochemical models introduced by Mattioni and Le Novère (2013)
  - Rule-based simulator here
  - Also calcium is accounted for in the biochemical simulation rather than in the electrical simulation; this can model competition for calcium
- Algorithm still needs more debugging
  - Perhaps outwith the NEURON framework
- System almost ready to be applied!
- The curse of parameters?
- Efficiency needs to be improved; however interprocess communication does not seem to be much of a problem.

Carlisle, H. J., Fink, A. E., Grant, S. G., and O'Dell, T. J. (2008). Opposing effects of PSD-93 and PSD-95 on long-term potentiation and spike timing-dependent plasticity. *Journal of Physiology*, 586(Pt 24):5885–5900.

Coombs, J. S., Curtis, D. R., and Eccles, J. C. (1956). Time courses of motoneuronal responses. *Nature*, 178:1049–1050.

Danos, V., Feret, J., Fontana, W., and Krivine, J. (2007). Scalable simulation of cellular signaling networks. In Shao, Z., editor, *Programming Languages and Systems*, volume 4807 of *Lecture Notes in Computer Science*, chapter 10, pages 139–157. Springer, Berlin, Heidelberg.

Fatt, P. and Katz, B. (1951). An analysis of the end-plate potential recorded with an intra-cellular electrode. *Journal of Physiology*, 115:320–370.

Hodgkin, A. and Huxley, A. (1939). Action potentials recorded from inside a nerve fibre. *Nature*, 144:710–711.

Mattioni, M. and Le Novère, N. (2013). Integration of biochemical and electrical Signaling-Multiscale model of the medium spiny neuron of the striatum. *PLoS ONE*, 8(7):e66811.

Pocklington, A. J., Cumiskey, M., Armstrong, J. D., and Grant, S. G. N. (2006). The proteomes of neurotransmitter receptor complexes form modular networks with distributed functionality underlying plasticity and behaviour. *Molecular Systems Biology*, 2(1).

Sheng, M. and Hoogenraad, C. C. (2007). The postsynaptic architecture of excitatory synapses: a more quantitative view. *Annual Review of Biochemistry*, 76:823–847.

Sorokina, O., Sorokin, A., and Armstrong, J. D. (2011). Towards a quantitative model of the post-synaptic proteome. *Molecular Biosystems*, 7:2813–2823.

Sorokina, O., Sorokin, A., Armstrong, J. D., and Danos, V. (2013). A simulator for spatially extended kappa models. *Bioinformatics*, pages 3105–3106.