Neuron electrophysiology: From biology to modeling

Simula summer school

25.6.2019

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Outline

- Part I: Neuron biology in brief
- Part II: Fundamentals of multicompartmental neuron modeling
- Part III: Modeling with NEURON software: Examples

Part I: Neuron biology in brief

Neuron electrophysiology

- Many shared features with cardiac cell electrophysiology
  - Expression of ion-channel encoding genes that allow electrogenesis
  - Cell hyperpolarization mediated by voltage-gated K^+ currents
  - Ca^{2+} an Na^+ currents contribute to depolarization
  - Communication with neighboring cells through gap junctions (electrical synapses)
- Many different features too
  - Action potentials in neurons are sharper than in cardiac cells, lasting typically 0.4-1.5 ms
  - Neurons express genes that
    - regulate the neurite growth and branching (e.g. neurotrophins and actin pathway-interacting genes)
    - contribute to synaptogenesis and encode synaptic ion channels

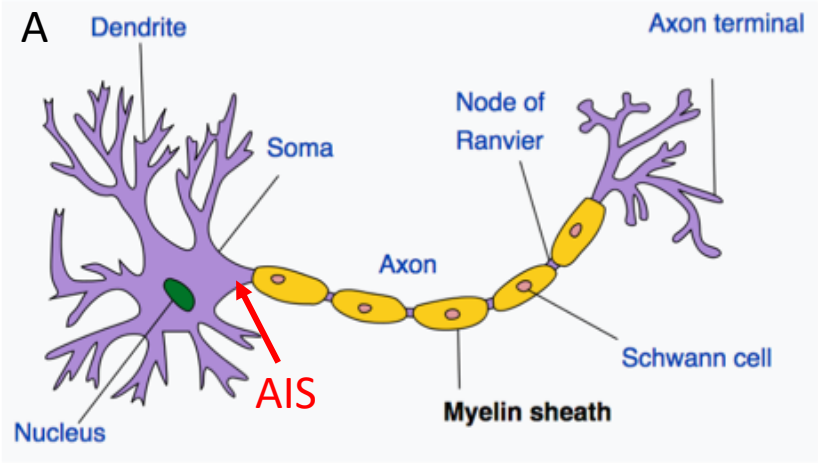
[Felfly, H., Xue, J., Zambon, A. C., Muotri, A., Zhou, D., & Haddad, G. G. (2011). Identification of a neuronal gene expression signature: Role of cell-cycle arrest in murine neuronal differentiation in vitro. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*.]
[Bullock, T., & Horridge, G. A. (1965). Structure and function in the nervous systems of invertebrates.]

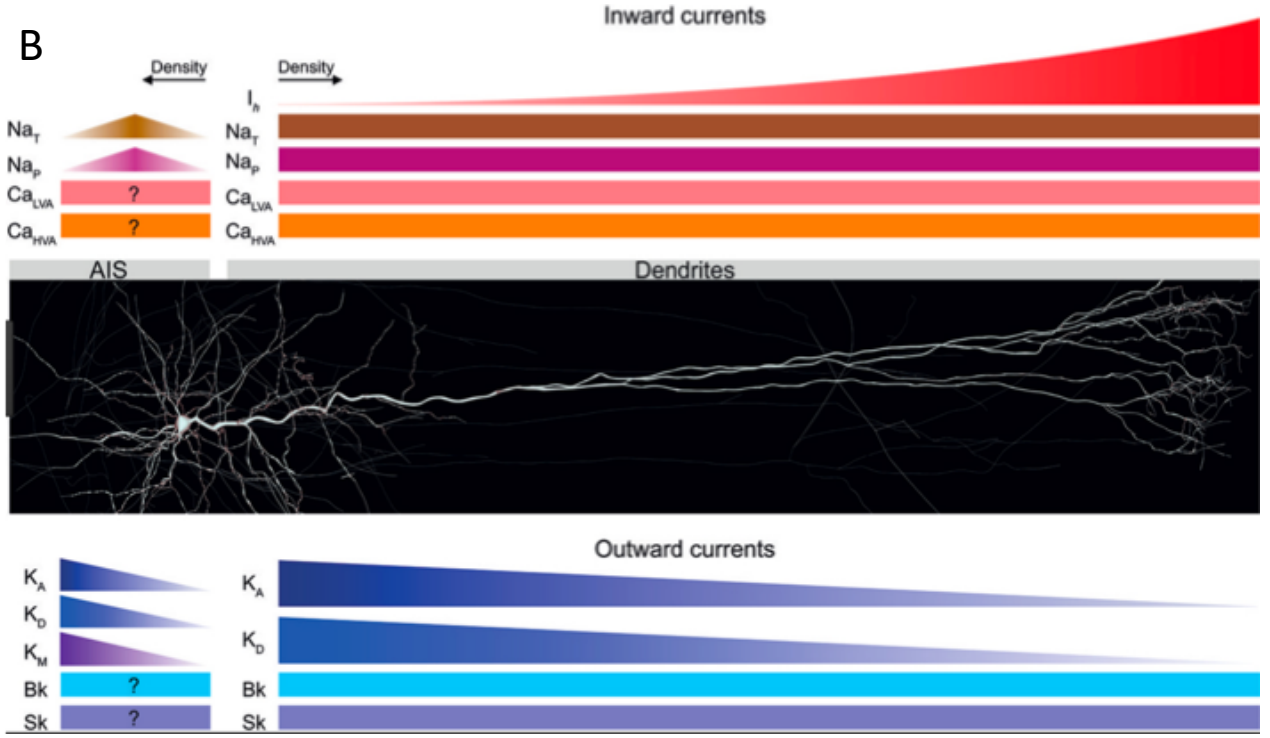
Neuron electrophysiology

- Other distinct features
  - Instead of sarcoplasmic reticulum (SR), neurons have endoplasmic reticulum (ER)
  - Neuromodulators (messenger molecules released from neurons) such as dopamine, serotonin, norepinephrine, acetylcholine and histamine have an important role in regulating the neuron activity
  - Chemical synapses and synaptic plasticity
  - Non-uniform expression of ion channels across the cell morphology
    - Also synaptic inputs can be differentially localized

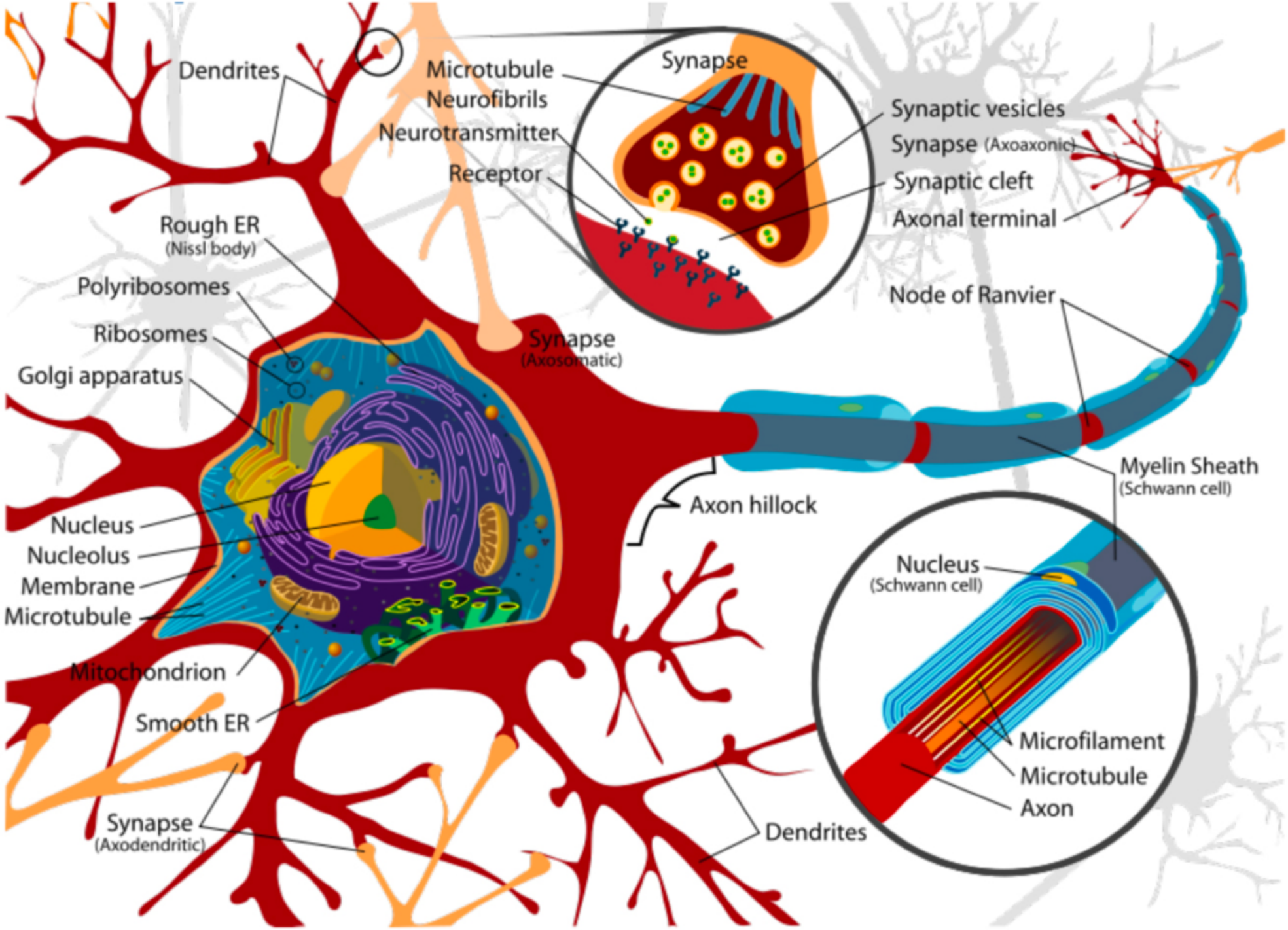
Ion channel distribution

- Ion channels localized to specific parts of the neuron
- Action potentials are typically generated in the axon initial segment (AIS)
  - Characterized by high density of Na^+ and K^+ channels

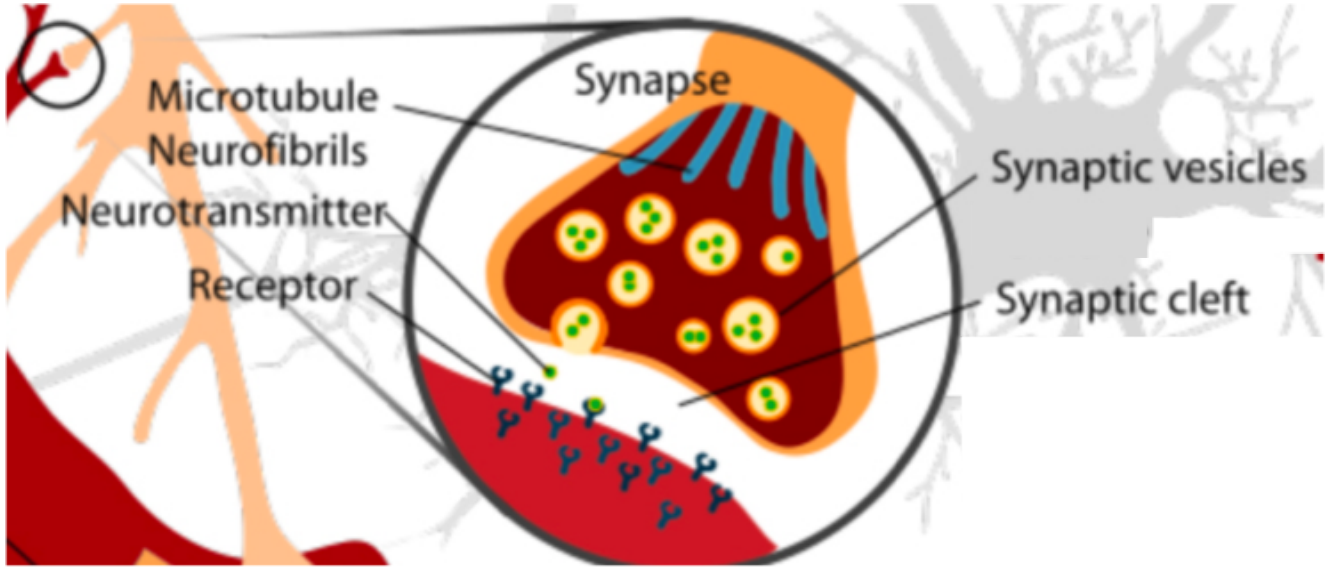




[Ramaswamy, S., & Markram, H. (2015). Anatomy and physiology of the thick-tufted layer 5 pyramidal neuron. *Frontiers in cellular neuroscience*, *9*, 233.]

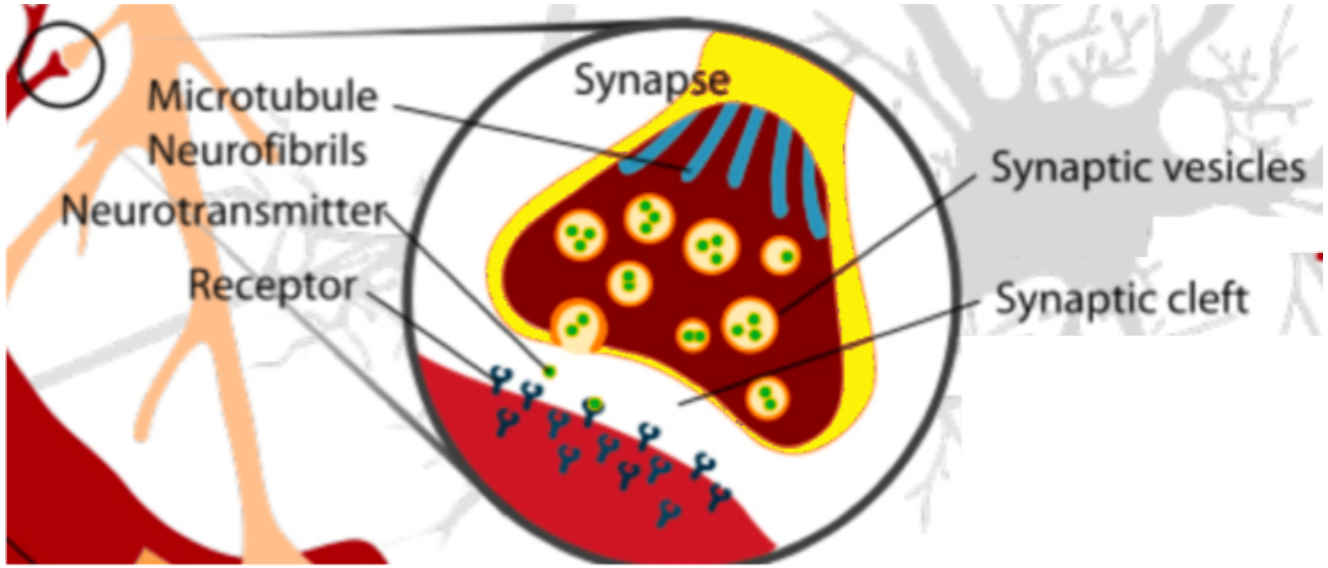

Dendrites
Microtubule
Neurofibrils
Neurotransmitter
Receptor
Synapse
Synaptic vesicles
Synapse (Axoaxonic)
Synaptic cleft
Axonal terminal
Rough ER
(Nissl body)
Polyribosomes
Ribosomes
Golgi apparatus
Synapse
(Axosomatic)
Node of Ranvier
Myelin Sheath
(Schwann cell)
Axon hillock
Nucleus
Nucleolus
Membrane
Microtubule
Mitochondrion
Smooth ER
Synapse
(Axodendritic)
Nucleus
(Schwann cell)
Microfilament
Microtubule
Axon
Dendrites

Chemical synapse function

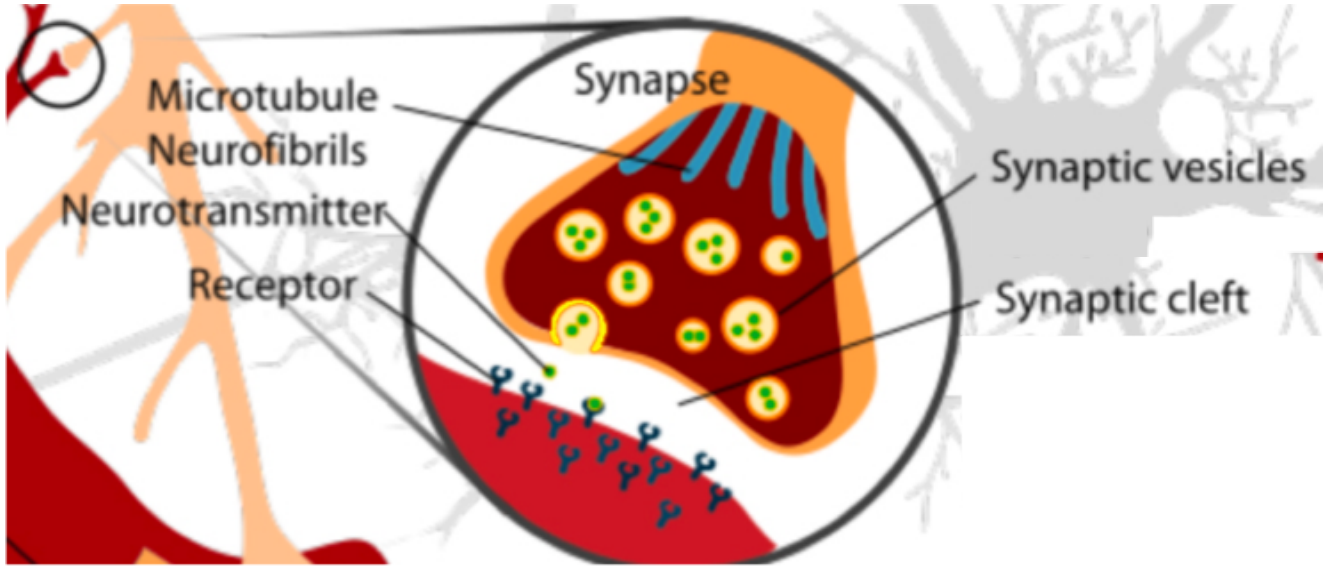


Chemical synapse function

- 1) Activation of the presynaptic axon



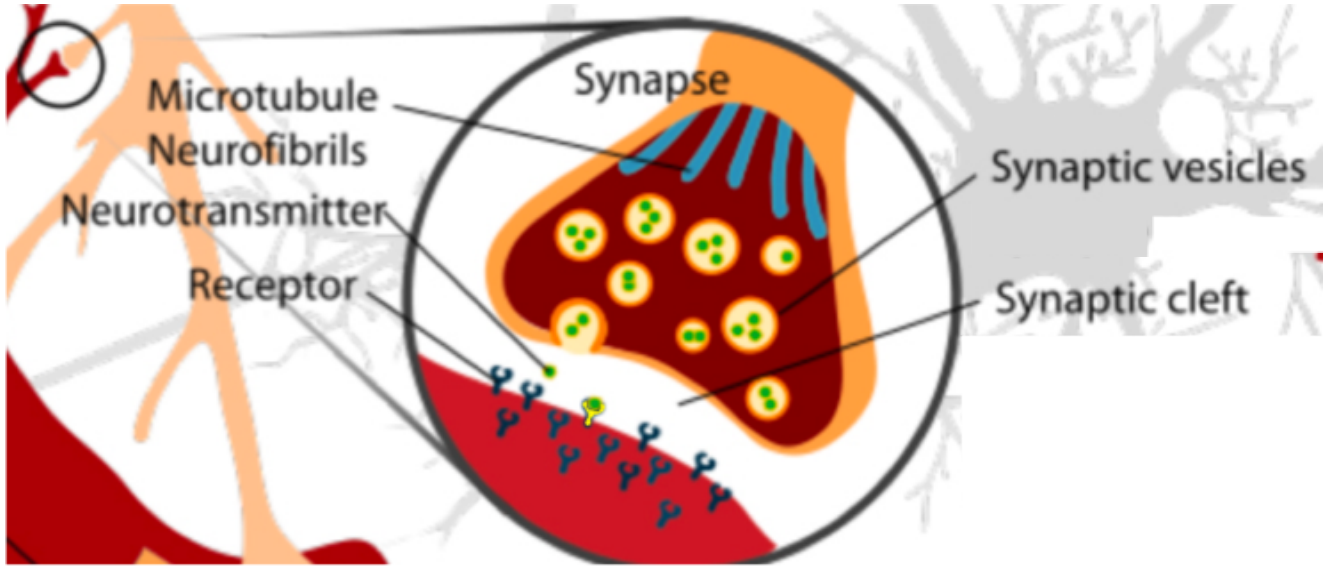
Chemical synapse function



- 1) Activation of the presynaptic axon
- 2) Fusion of neurotrans-mitter containing vesicles

  into the membrane and release of the neurotransmitters

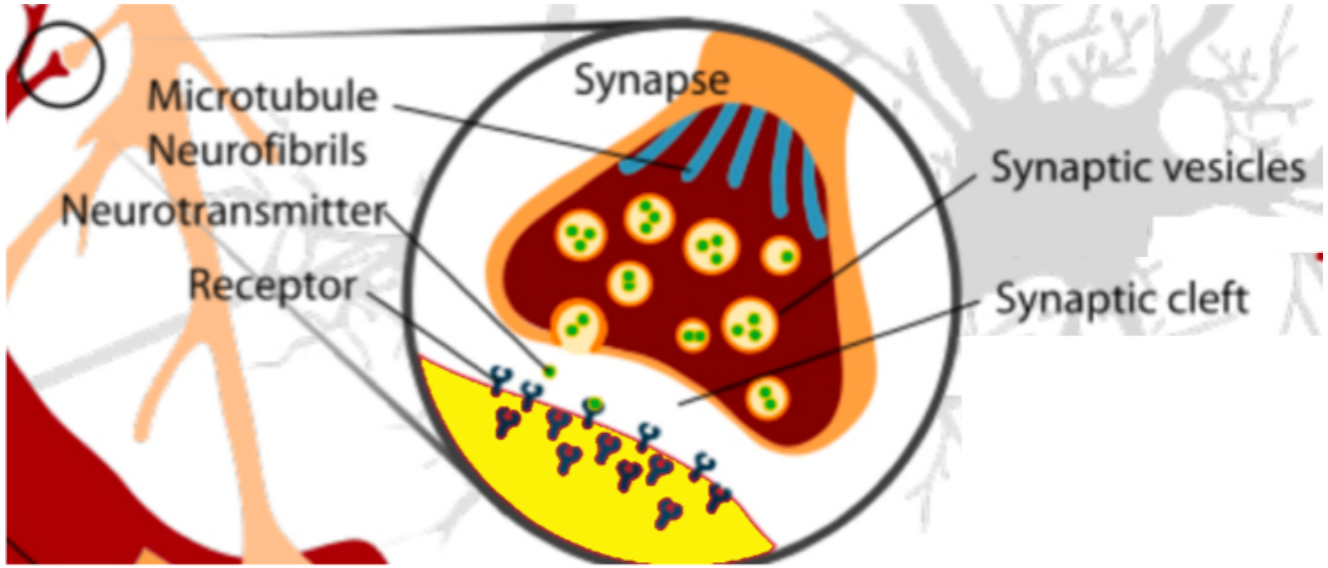
Chemical synapse function



- 1) Activation of the presynaptic axon
- 2) Fusion of neurotrans-mitter containing vesicles

  into the membrane and release of the neurotransmitters
- 3) Neurotransmitter binding and opening of the post-synaptic ion channels
  - Excitatory transmission: Glutamate binds to AMPA, NMDA or kainate receptors
  - Inhibitory transmission: GABA binds to GABA receptors

Chemical synapse function



- 1) Activation of the presynaptic axon
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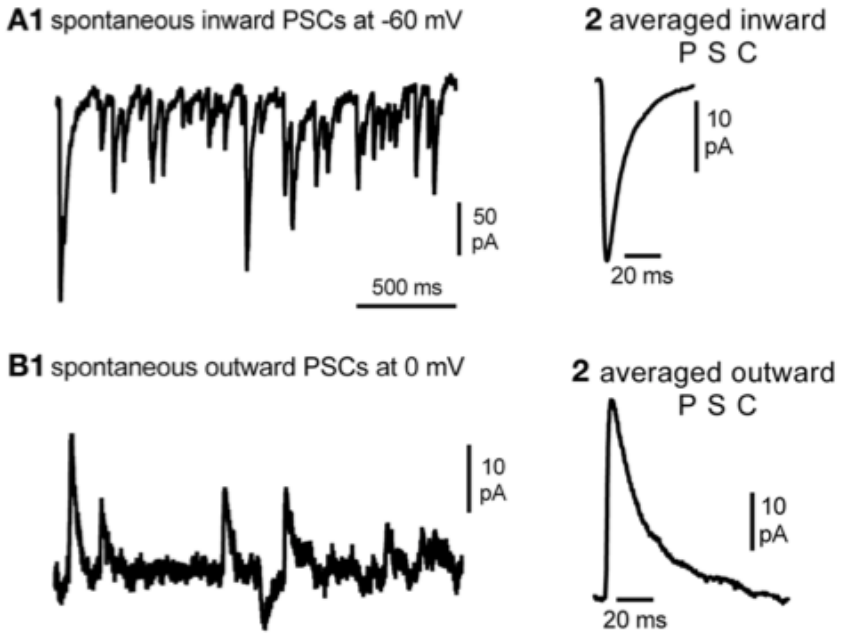
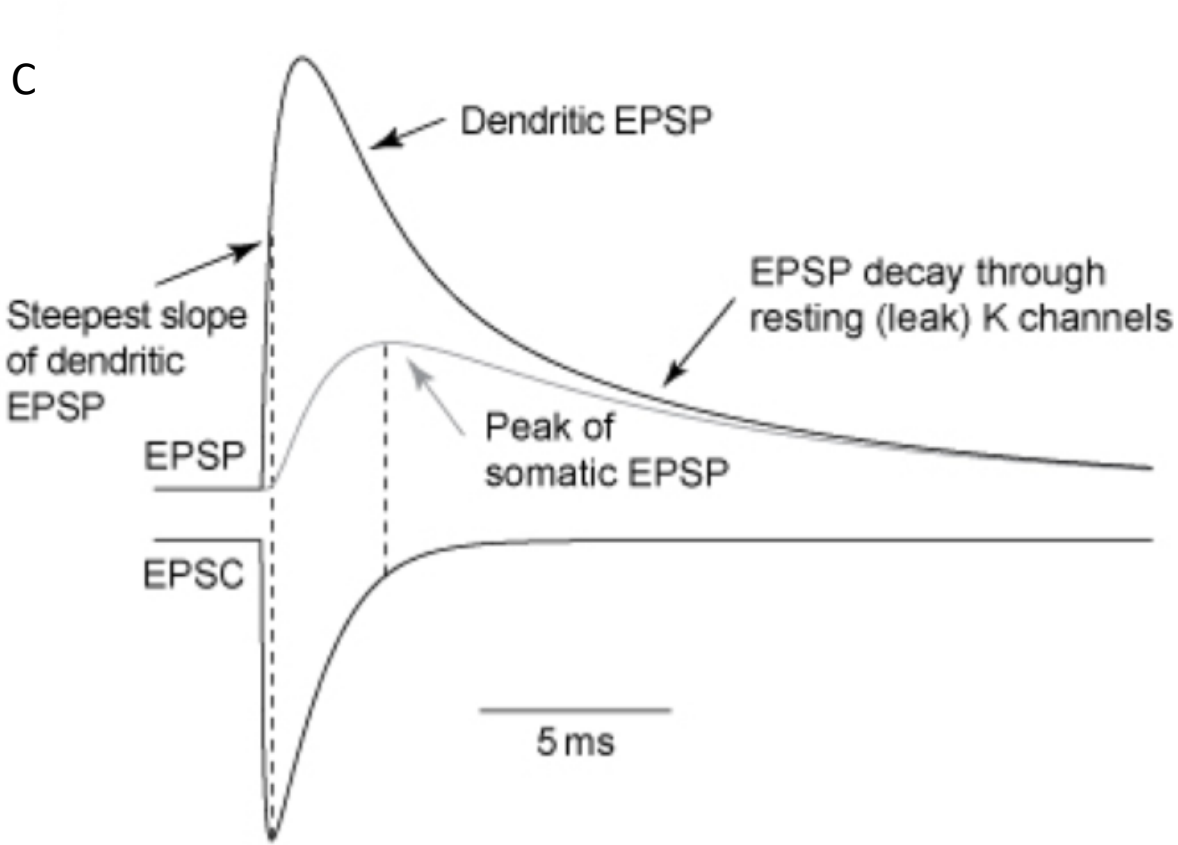
  into the membrane and release of the neurotransmitters
- 3) Neurotransmitter binding and opening of the post-synaptic ion channels
  - Excitatory transmission: Glutamate binds to AMPA, NMDA or kainate receptors
  - Inhibitory transmission: GABA binds to GABA receptors
- 4) Depolarization of the post-synaptic membrane

Synaptic currents



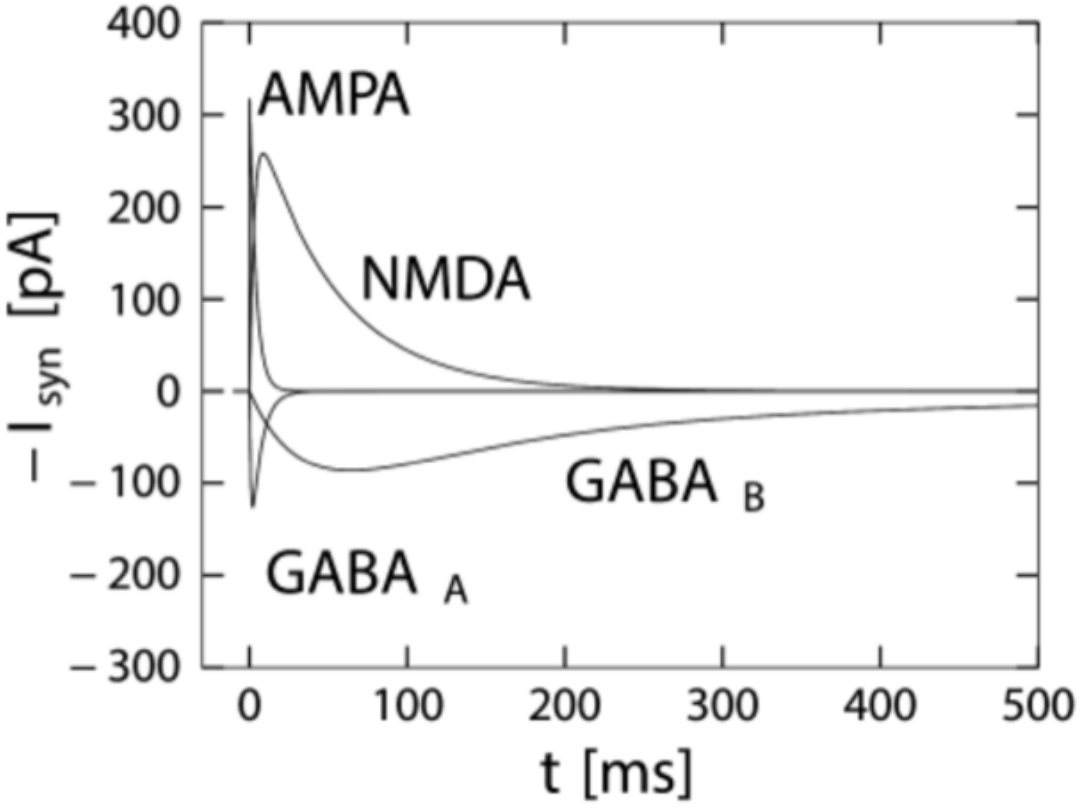
[Fogarty, M. J., Hammond, L. A., Kanjhan, R., Bellingham, M. C., & Noakes, P. G. (2013). A method for the three-dimensional reconstruction of Neurobiotin™-filled neurons and the location of their synaptic inputs. *Frontiers in neural circuits*, *7*, 153.]



[Spruston, N., Häusser, M., & Stuart, G. (2012). Information processing in dendrites and spines. In: Squire, L., Berg, D., Bloom, F. E., Du Lac, S., Ghosh, A., & Spitzer, N. C. (Eds.). (2012). *Fundamental neuroscience*. Academic Press.]

Synaptic currents

- AMPA and NMDA are agonists that mimic effects of neurotransmitter glutamate
- GABA is a neurotransmitter itself
- AMPA and NMDA receptors: Ca^{2+} and other cationic currents
- GABA: Cl^-
- AMPA and $GABA_A$-mediated currents are fast, while NMDA and $GABA_B$-mediated currents are much slower



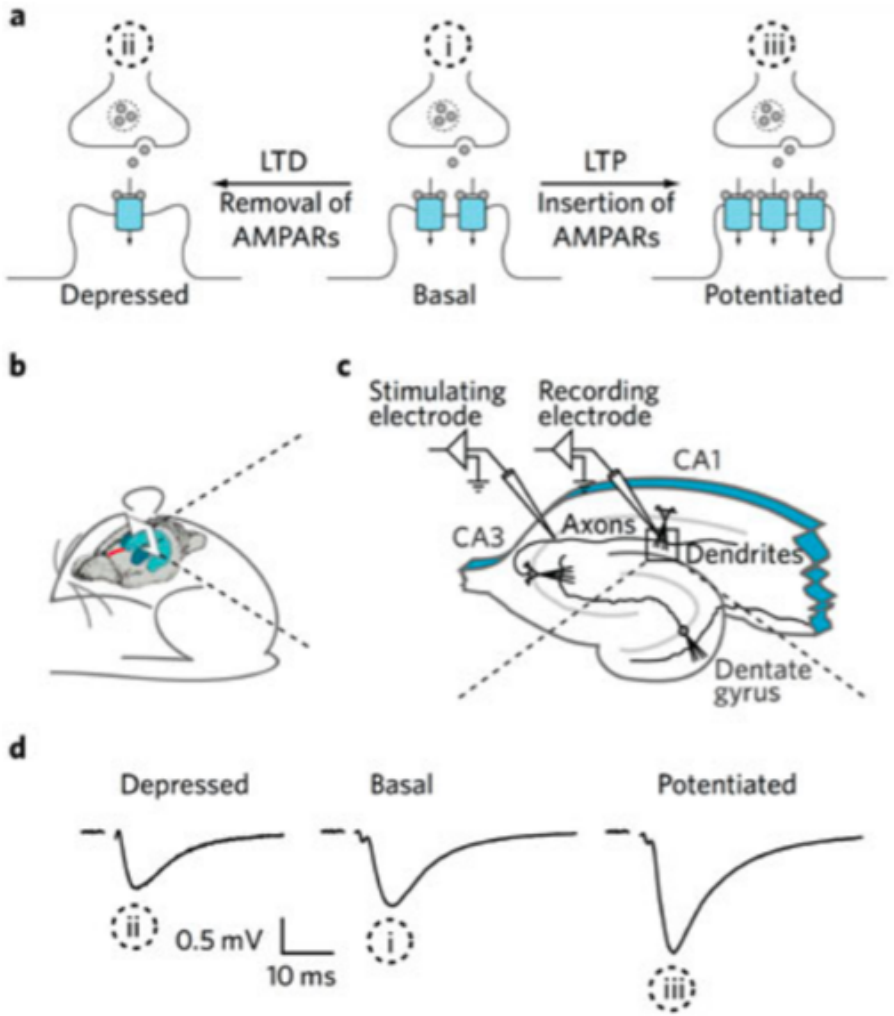
[Gerstner, W., Kistler, W. M., Naud, R., & Paninski, L. (2014). *Neuronal dynamics: From single neurons to networks and models of cognition*. Cambridge University Press.]

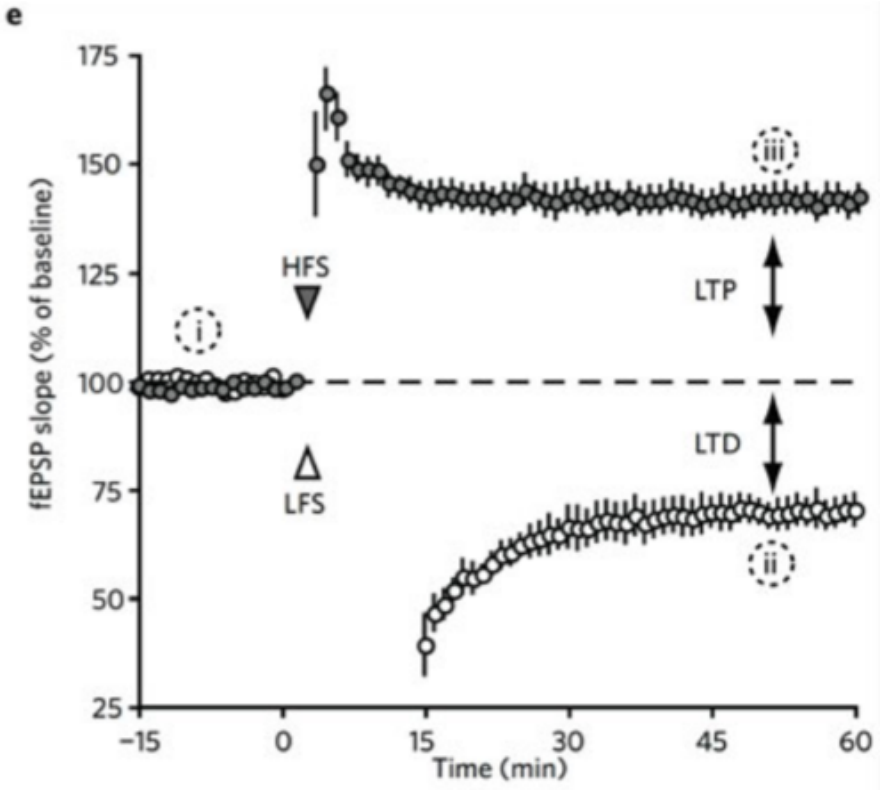
Synaptic plasticity

- Strengthening or weakening the input of a synapse
- Required for memory and learning
- Different time scales
  - Short-term plasticity (< 1s)
    - Enhanced fusion (short-term facilitation) or depletion (short-term depression) of the synaptic vesicles in the pre-synaptic terminal
  - Early long-term plasticity (< 1h)
    - Phosphorylation and trafficking of synaptic receptors
  - Late long-term plasticity ($\lesssim$ 1d)
    - Transcription and protein synthesis
- May lead to structural changes in the synapse, i.e. change in size or complete removal of the synapse

[Woolfrey, K. M., & Srivastava, D. P. (2016). Control of dendritic spine morphological and functional plasticity by small GTPases. *Neural plasticity*, *2016*.
Piochon, C., Kano, M., & Hansel, C. (2016). LTD-like molecular pathways in developmental synaptic pruning. *Nature neuroscience*, *19*(10), 1299-1310.]

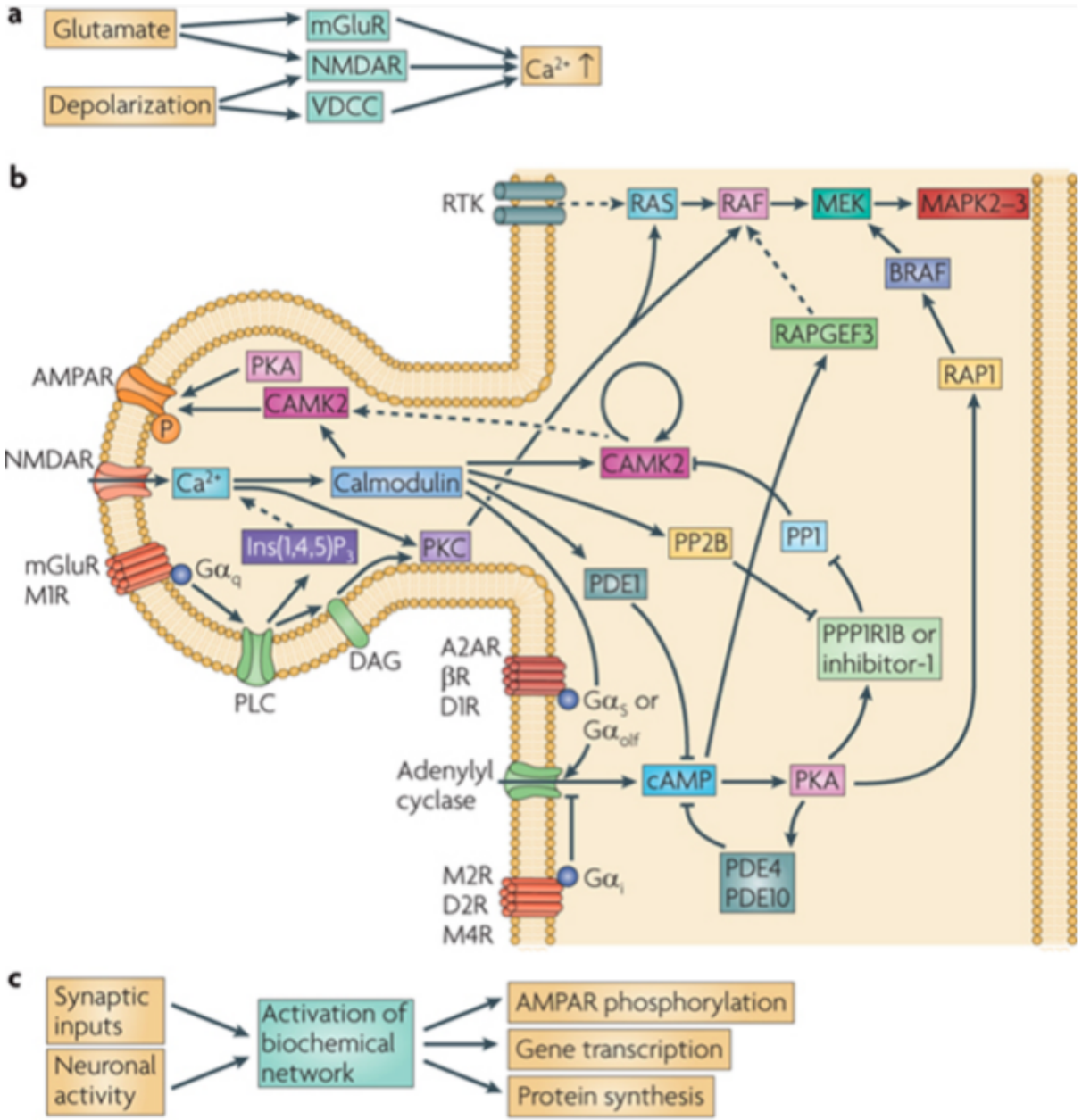
Long-term synaptic plasticity





[Fleming, J. J., & England, P. M. (2010). AMPA receptors and synaptic plasticity: a chemist's perspective. *Nature chemical biology*, *6*(2), 89-97.]

Long-term synaptic plasticity: cellular mechanisms



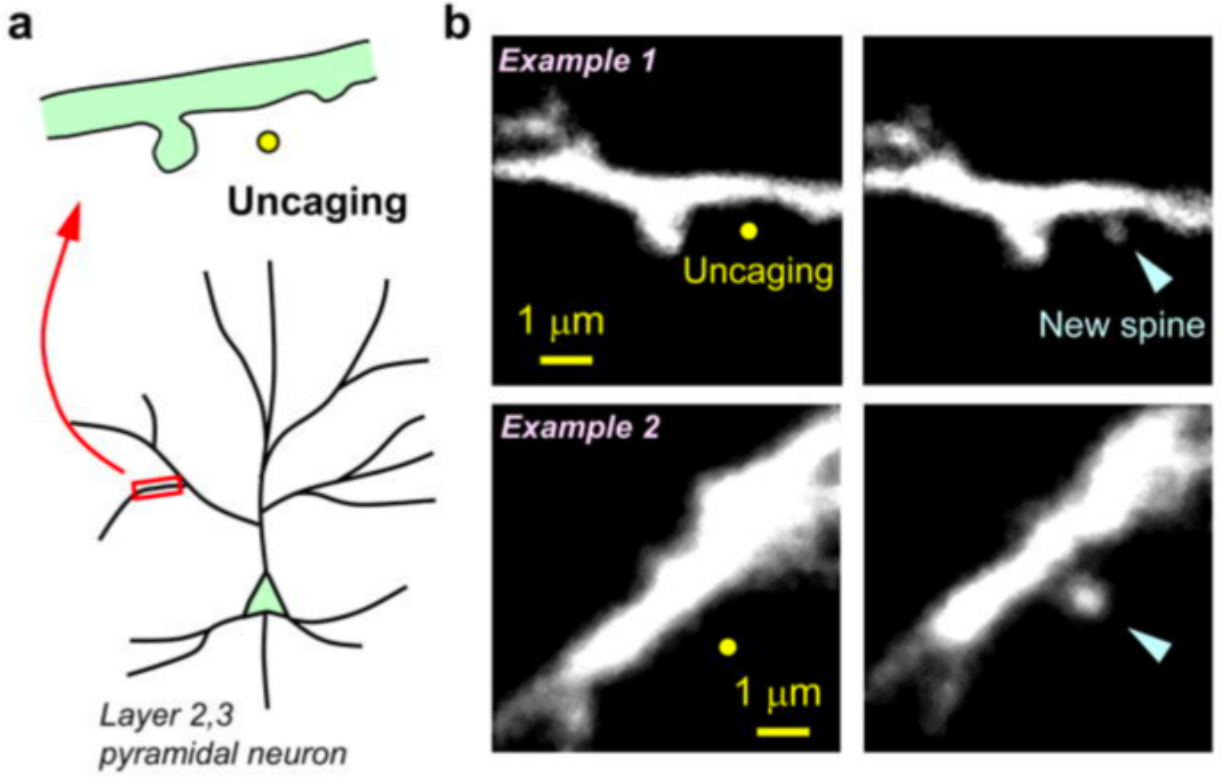
[Kotaleski, J. H., & Blackwell, K. T. (2010). Modelling the molecular mechanisms of synaptic plasticity using systems biology approaches. *Nature Reviews Neuroscience*, *11*(4), 239-251.]

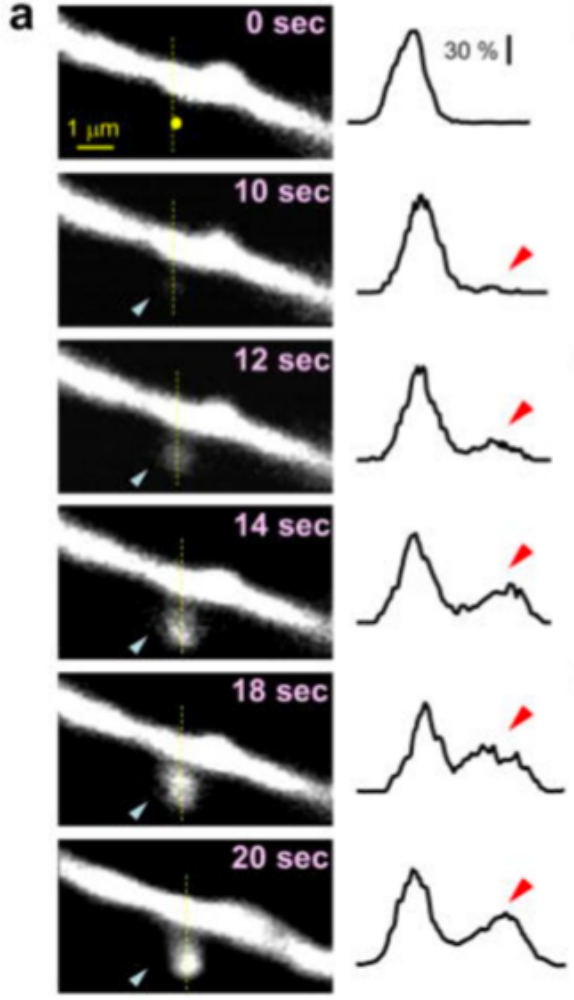
Other types of brain plasticity

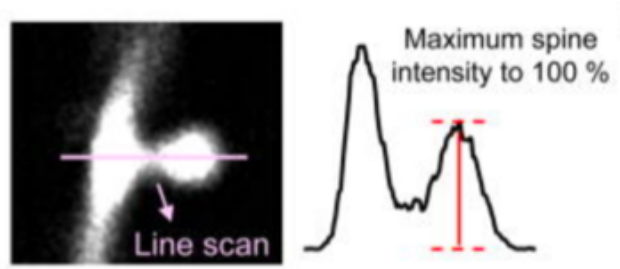
- Structural plasticity
  - Growth and retraction of neurites
  - Formation and pruning of synapses
- Adult neurogenesis
  - Formation of new neurons in dentate gyrus (in hippocampus)
- Homeostatic plasticity
  - Cellular and synaptic mechanisms that alter the excitability in case the neuron is firing too frequently or too seldom
- Trafficking of other (non-synaptic) ion channels to different locations in the neuron
- Perineuronal nets

[Kimpinski, K., Campenot, R. B., & Mearow, K. (1997). Effects of the neurotrophins nerve growth factor, neurotrophin-3, and brain-derived neurotrophic factor (BDNF) on neurite growth from adult sensory neurons in compartmented cultures. *Journal of neurobiology*, *33*(4), 395-410.]
[Eriksson, P. S., Perfilieva, E., Björk-Eriksson, T., Alborn, A. M., Nordborg, C., Peterson, D. A., & Gage, F. H. (1998). Neurogenesis in the adult human hippocampus. *Nature medicine*, *4*(11), 1313-1317.]
[Turrigiano, G. G., & Nelson, S. B. (2004). Homeostatic plasticity in the developing nervous system. *Nature Reviews Neuroscience*, *5*(2), 97-107.]

Example: Growth of synaptic spine by glutamate exposure







[Kwon, H. B., & Sabatini, B. L. (2011). Glutamate induces de novo growth of functional spines in developing cortex. *Nature*, *474*(7349), 100-104.]
[Richards, D. A., Mateos, J. M., Hugel, S., de Paola, V., Caroni, P., Gähwiler, B. H., & McKinney, R. A. (2005). Glutamate induces the rapid formation of spine head protrusions in hippocampal slice cultures. *Proceedings of the National Academy of Sciences*, *102*(17), 6166-6171.]

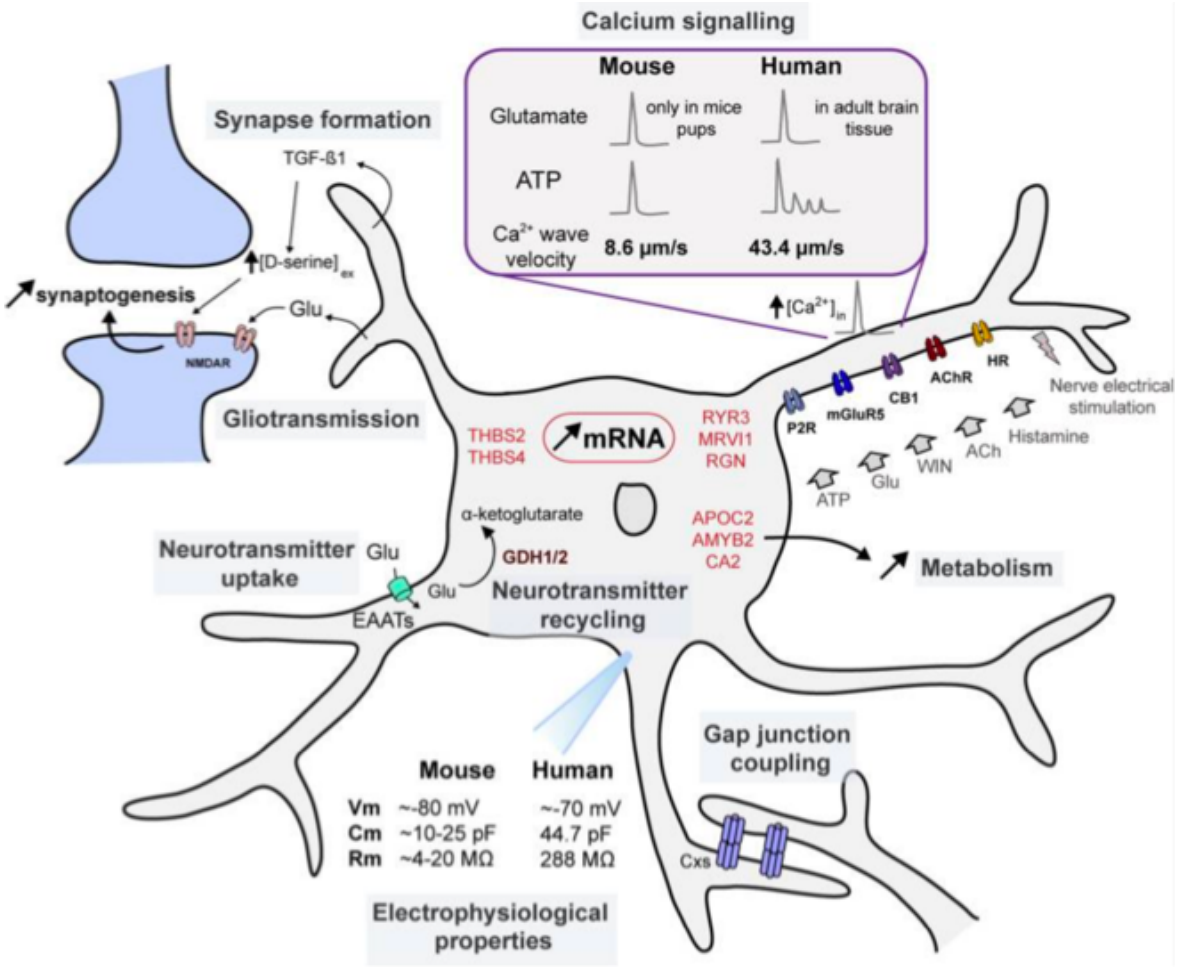
Glial cells: short introduction

- As many as neurons in the human brain (85 billion)
- Historical view: “nerve glue”
- Types of glia
  - Astrocytes
  - Microglia
  - Oligodendrocytes
  - NG2 glia (progenitors of oligodendrocytes)

Jäkel S, Dimou L. Glial Cells and Their Function in the Adult Brain: A Journey through the History of Their Ablation. *Front Cell Neurosci*. 2017;11:24. Published 2017 Feb 13. doi:10.3389/fncel.2017.00024

Astrocyte functions

- Glutamate uptake and metabolism
- GABA uptake less established
- Ca^{2+} signaling
- K^{+} homeostasis
- Tripartite synapse
  - "Gliotransmission" as a result of Ca^{2+} activation



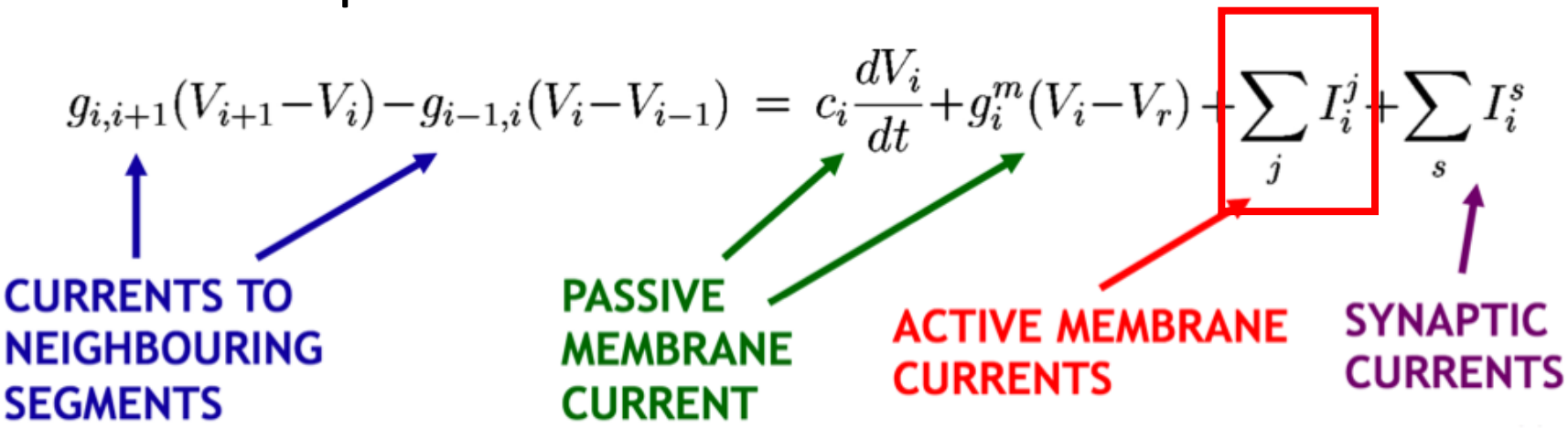
Olsen ML, Khakh BS, Skatchkov SN, Zhou M, Lee CJ, Rouach N. New Insights on Astrocyte Ion Channels: Critical for Homeostasis and Neuron-Glia Signaling. *J Neurosci*. 2015;35(41):13827–13835. doi:10.1523/JNEUROSCI.2603-15.2015

Vasile F, Dossi E, Rouach N. Human astrocytes: structure and functions in the healthy brain. *Brain Struct Funct*. 2017;222(5):2017–2029. doi:10.1007/s00429-017-1383-5

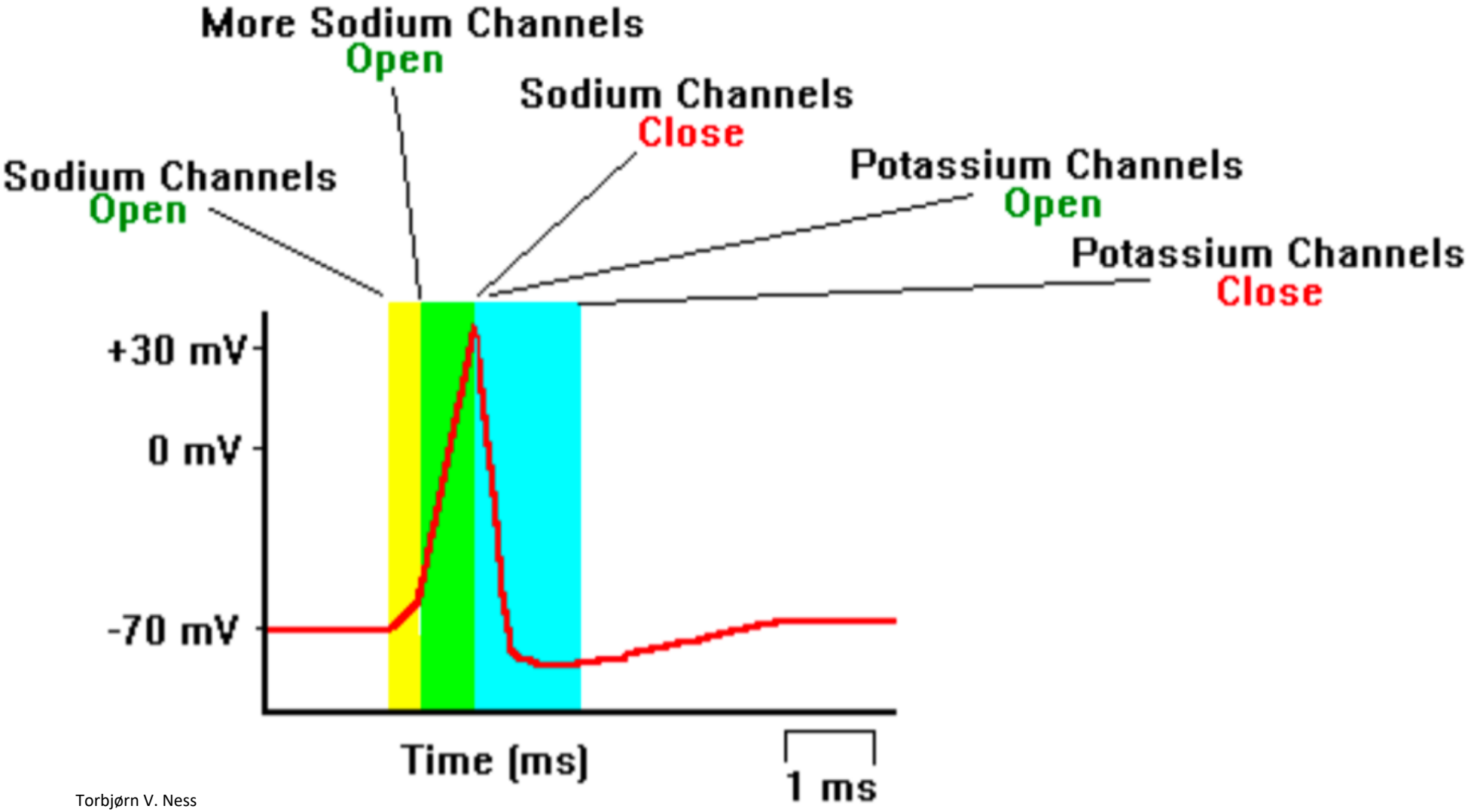
Part II: Fundamentals of multicompartmental neuron modeling

Modeling the membrane potential dynamics

- Current balance equation

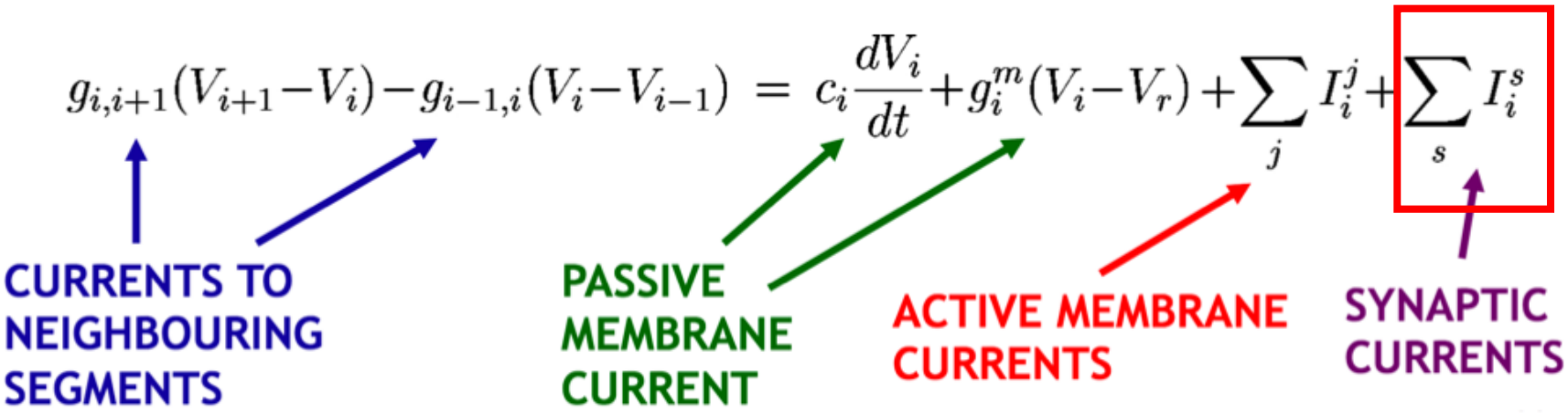


Neuronal action potential



Modeling the membrane potential dynamics

- Current balance equation



Modeling synaptic currents

$$I_{\text{syn}}(t) = g_{\text{syn}}(t)\ \left(u(t) - E_{\text{syn}}\right)$$

Synaptic current

Synaptic conductance

Membrane potential

Reversal potential

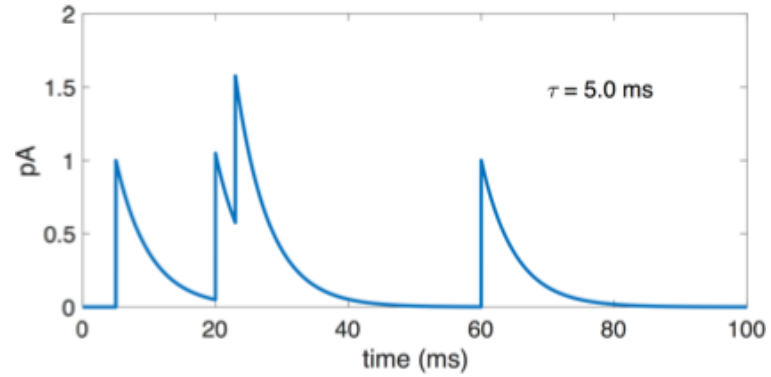
$$g_{\text{syn}}(t) = \sum_f \bar{g}_{\text{syn}}\, e^{-\left(t-t^{(f)}\right)/\tau}\, \Theta\left(t - t^{(f)}\right)$$

Maximal conductance

Decay constant

Heaviside function

Time of presynaptic spike



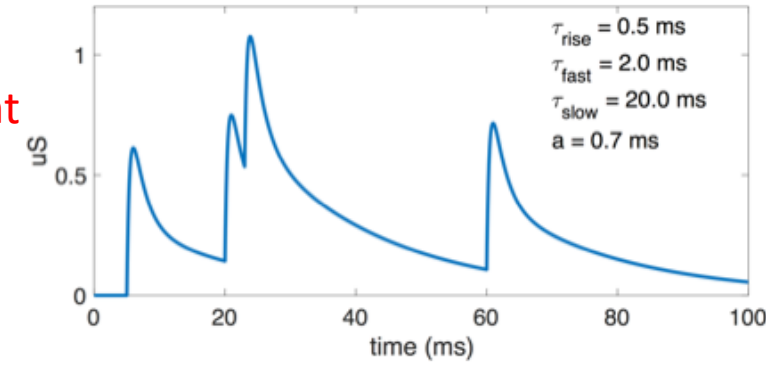
$$g_{\text{syn}}(t) = \sum_f \bar{g}_{\text{syn}}\ \left[1 - e^{-\left(t-t^{(f)}\right)/\tau_{\text{rise}}}\right]\ \left[a\, e^{-\left(t-t^{(f)}\right)/\tau_{\text{fast}}} + (1-a)\, e^{-\left(t-t^{(f)}\right)/\tau_{\text{slow}}}\right] \Theta\left(t - t^{(f)}\right)$$

Rise time constant

Proportion of fast current

Fast decay constant

Slow decay constant



[Gerstner, W., Kistler, W. M., Naud, R., & Paninski, L. (2014). *Neuronal dynamics: From single neurons to networks and models of cognition*. Cambridge University Press.]

Modeling the membrane potential dynamics

- Current balance equation

$$g_{i,i+1}(V_{i+1}-V_i)-g_{i-1,i}(V_i-V_{i-1}) = c_i\frac{dV_i}{dt}+g_i^m(V_i-V_r)+\sum_j I_i^j+\sum_s I_i^s$$

CURRENTS TO NEIGHBOURING SEGMENTS

PASSIVE MEMBRANE CURRENT

ACTIVE MEMBRANE CURRENTS

SYNAPTIC CURRENTS

$$\frac{1}{2\pi a}\frac{\partial}{\partial x}\left(\frac{\pi a^2}{R_a}\frac{\partial V}{\partial x}\right) = C_m\frac{\partial V}{\partial t}+I_{HH}$$

[Hines (1984): Efficient computation of branched nerve equations. Int. J. Bio-Medical Computing 15: 69-76]

Solution method in the NEURON simulator

$$\frac{\mathrm{d}y}{\mathrm{d}t} = f(t, y)$$

$$y_{k+1} = y_k + hf(t_{k+1}, y_{k+1})$$

- Default integration method: Backward Euler
- Hines (1984): Efficient computation of branched nerve equations. Int. J. Bio-Medical Computing 15: 69-76

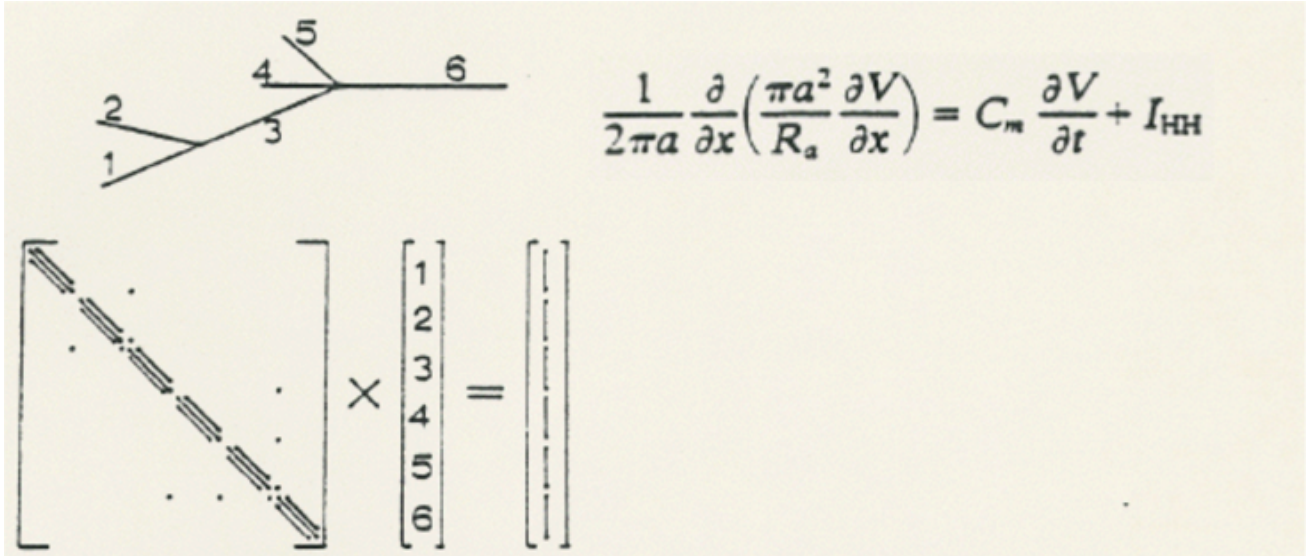


Fig. 1. An example of a branched cable and the form of its finite difference matrix equation. The position of the branches in the matrix equation is reflected in the membrane voltage vector, V_i. Most of the equations for a branch form a tridiagonal system but connected branches can generate non-zero far off diagonal elements.

- Tree-like dependence of solved parameters from each other

➡ Efficient Gaussian elimination

Part III: Modeling with NEURON software: Examples

NEURON: What is it?

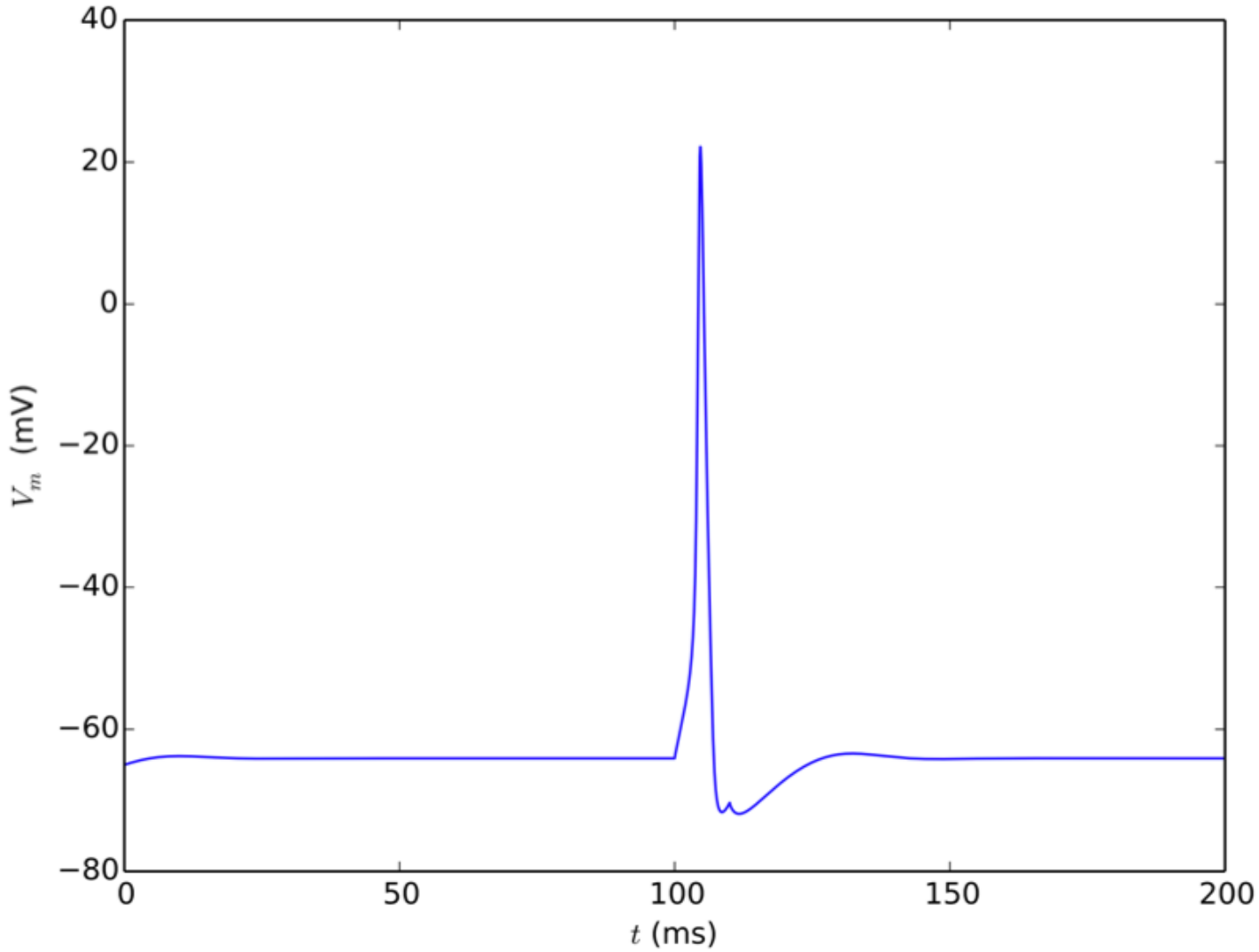
- A simulation environment for neuron modelling
- Based on an interpreted hoc language
- Efficient for simulating the cable equation in branching geometries
- Membrane mechanisms described using NMODL language, which allows the extension of
  - Stimulating currents
  - Ion channels
  - Synapses
- Supports use of reconstructed neuron morphologies

HOC language: Short tutorial

- The binary *nrniv* opens the hoc interpreter
- Things to do before running the simulation
  - Define the neuron morphology / morphologies and create the neuron(s)
  - Insert the membrane mechanisms and define the model parameters for each section
  - Define the numbers of segments, the time step size and the simulation end time
  - Introduce the stimuli
  - Define which model variables will be recorded
  - Initialize the variables
- Things to do after running the simulation
  - Save the recorded data into file

HOC language: Short tutorial

```
load_file("stdlib.hoc")
load_file("stdrun.hoc")

objref cvode
cvode = new CVode()
cvode.active(0)

create soma, dend[3]

connect dend[0](0), soma(1)
connect dend[1](0), soma(1)
connect dend[2](0), dend[0](1)

access soma

dend[0] insert pas
dend[1] insert pas
dend[2] insert pas
soma insert hh
soma {Ra = 100 cm = 1 diam = 10 L = 20}
dend[0] {Ra = 100 cm = 1 diam = 5 L = 200 e_pas = -54.3 g_pas = 0.00003}
dend[1] {Ra = 100 cm = 1 diam = 2 L = 100 e_pas = -54.3 g_pas = 0.00003}
dend[2] {Ra = 100 cm = 1 diam = 2 L = 160 e_pas = -54.3 g_pas = 0.00003}
forall nseg = 5dt = 0.025
tstop = 200

objref stim, Vrec

soma stim = new IClamp(0.5)
stim.del = 100
stim.dur = 10
stim.amp = 0.075

Vrec = new Vector()
Vrec.record(&v(0.5),dt)

init()
run()
objref myFile
myFile = new File()
myFile.wopen("run.dat")
for i=0,tstop/dt-1 {
  myFile.printf("%g %g\n", dt*i, Vrec.x(i))
}
myFile.close()
```



HOC language: Short tutorial

```
load_file("stdlib.hoc")
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cvode.active(0)

create soma, dend[3]

connect dend[0](0), soma(1)
connect dend[1](0), soma(1)
connect dend[2](0), dend[0](1)

access soma
```

Load standard hoc functions that may be useful

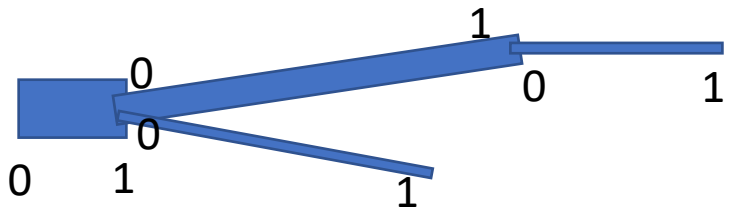
Define an object cvode

Initialize a variable time step integrator

But for now, use fixed time step method

Create four segments called soma, dend[0], dend[1] and dend[2]

Connect 0-ends of dend[0] and dend[1] to the 1-end of soma, and 0-end of dend[2] to 1-end of dend[0]



Set soma as the “reference” section

HOC language: Short tutorial

```
dend[0] insert pas
dend[1] insert pas
dend[2] insert pas
soma insert hh
soma {Ra = 100 cm = 1 diam = 10 L = 20}
dend[0] {Ra = 100 cm = 1 diam = 5 L = 100 e_pas = -54.3 g_pas = 0.00003}
dend[1] {Ra = 100 cm = 1 diam = 2 L = 50 e_pas = -54.3 g_pas = 0.00003}
dend[2] {Ra = 100 cm = 1 diam = 2 L = 80 e_pas = -54.3 g_pas = 0.00003}
forall nseg = 5
dt = 0.025
tstop = 200

objref stim, Vrec

soma stim = new IClamp(0.5)
stim.del = 100
stim.dur = 10
stim.amp = 0.12

Vrec = new Vector()
Vrec.record(&v(0.5),dt)
```

Insert passive membrane mechanism to all sections

Insert Hodgkin-Huxley currents (including leak) to soma section

Define the lengths and thicknesses and passive membrane parameters of each section

Define the number of compartments in each section

Define the time step size (only when cvode.active(0)), in milliseconds

Define the simulation end time in milliseconds

Define two objects, one for stimulus and one for recordings

Initialize object stim to be a current clamp stimulus

Set the delay (onset time) and duration of the current clamp in milliseconds and the amplitude in nanoamps

Initialize object Vrec to be a vector

Set Vrec to record membrane potential at the middle of soma

HOC language: Short tutorial

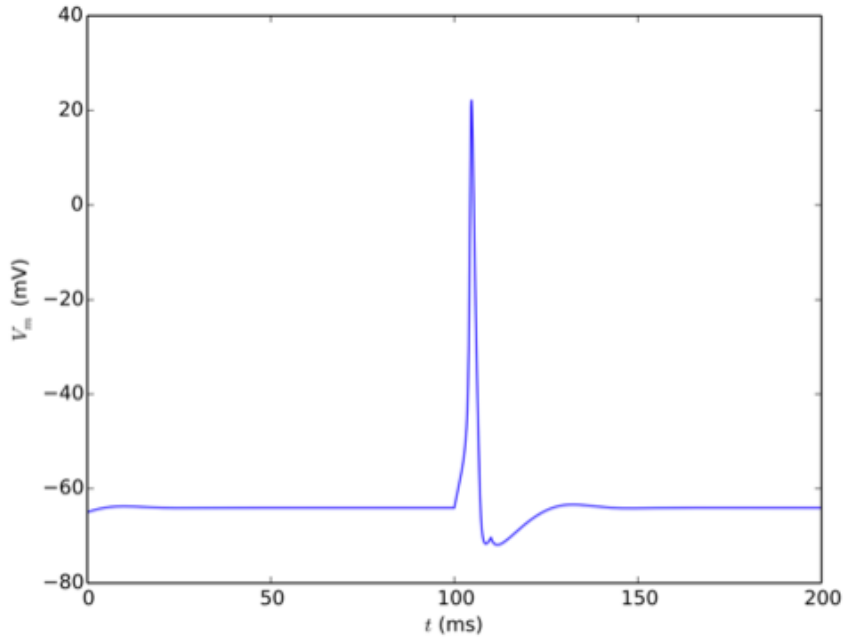
```
init()
run()

objref myFile
myFile = new File()
myFile.wopen("run.dat")
for i=0,tstop/dt-1 {
  myFile.printf("%g %g\n", dt*i, Vrec.x(i))
}
myFile.close()
```

Initialize all state variables to their initial values

Run the simulation

Save the simulation output (time, V) in a file “run.dat”



HOC language: Short tutorial

- Useful commands
  - psection(): show all mechanisms of the selected section
  - topology(): show all compartments and how they are connected

```
bash-3.2$ nrniv
NEURON -- VERSION 7.5 (1515:79f6026b82d7) 2017-02-09
Duke, Yale, and the BlueBrain Project -- Copyright 1984-2016
See http://neuron.yale.edu/neuron/credits

oc>load_file("myneuron.hoc")
        1
        1
        0
        1
        1
        0
        1
oc>soma psection()
soma { nseg=5  L=20  Ra=100
        /*location 0 attached to cell 0*/
        /* First segment only */
        insert hh { gnabar_hh=0.12 gkbar_hh=0.036 gl_hh=0.0003 el_hh=-54.3}
        insert na_ion { ena=50}
        insert k_ion { ek=-77}
        insert capacitance { cm=1}
        insert morphology { diam=10}
}
oc>topology()

|-----|       soma(0-1)
        `----|       dend[0](0-1)
              `----|       dend[2](0-1)
        `----|       dend[1](0-1)

        1
oc>
```

HOC language with Python interface

```
from neuron import h
h('<hoc command>')
```

If NEURON is installed with a Python interface, the hoc interpreter can be loaded in a Python script

```
Vrec = numpy.array(h.Vrec)
```

Any command in hoc language can then be run through Python

There exist built-in commands in Python for the hoc interpreter, e.g., for loading a hoc vector as a numpy array

NMODL language: Very short tutorial

- Mechanism files (.mod) can be compiled with the binary *nrnivmodl*
- NMODL code distributed to blocks:
  - NEURON: define the interface with NEURON
  - PARAMETER: define the model parameters
  - STATE: define the solved state variables
  - ASSIGNED: define other variables that will be handled by the mechanism
  - DERIVATIVE: define the differential equation for the state variables
  - BREAKPOINT: calculate the current terms based on the state variables
  - INITIAL: initialize the state variables

NMODL example: I_h channel

- https://senselab.med.yale.edu/modeldb/showModel.cshtml?model=139653&file=/L5bPCmodelsEH/mod/Ih.mod

$$I = \bar{g} m^{N_m} (E - V) \qquad \frac{dm}{dt} = \frac{m - m_\infty}{\tau_m}$$

$$\alpha_m = -\frac{1}{\tau_{\mathrm{ma}}} \cdot \frac{V_{\mathrm{offma}} - V}{\exp(-\frac{V_{\mathrm{offma}} - V}{V_{\mathrm{sloma}}}) - 1}$$

$$\beta_m = \frac{1}{\tau_{\mathrm{mb}}} \exp(-\frac{V_{\mathrm{offmb}} - V}{V_{\mathrm{slomb}}})$$

$$m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m}$$

$$\tau_m = \frac{1}{\alpha_m + \beta_m}$$

```
NEURON  {
        SUFFIX Ih
        NONSPECIFIC_CURRENT ihcn
        RANGE gIhbar, gIh, ihcn
}

UNITS   {
        (S) = (siemens)
        (mV) = (millivolt)
        (mA) = (milliamp)
}

PARAMETER       {
        gIhbar = 0.00001 (S/cm2)
        ehcn =  -45.0 (mV)
}

ASSIGNED        {
        v       (mV)
        ihcn    (mA/cm2)
        gIh     (S/cm2)
        mInf
        mTau
        mAlpha
        mBeta
}

STATE   {
        m
}

BREAKPOINT      {
        SOLVE states METHOD cnexp
        gIh = gIhbar*m
        ihcn = gIh*(v-ehcn)
}

DERIVATIVE states       {
        rates()
        m' = (mInf-m)/mTau
}

INITIAL{
        rates()
        m = mInf
}

PROCEDURE rates(){
        UNITSOFF
        if(v == -154.9){
            v = v + 0.0001
        }
                mAlpha =  0.001*6.43*(v+154.9)/(exp((v+154.9)/11.9)-1)
                mBeta  =  0.001*193*exp(v/33.1)
                mInf = mAlpha/(mAlpha + mBeta)
                mTau = 1/(mAlpha + mBeta)
        UNITSON
}
```

NMODL example: I_h channel (Hay et al. 2011)

```
NEURON  {
        SUFFIX Ih
        NONSPECIFIC_CURRENT ihcn
        RANGE gIhbar, gIh, ihcn
}

UNITS   {
        (S) = (siemens)
        (mV) = (millivolt)
        (mA) = (milliamp)
}

PARAMETER       {
        gIhbar = 0.00001 (S/cm2)
        ehcn =  -45.0 (mV)
}

ASSIGNED        {
        v       (mV)
        ihcn    (mA/cm2)
        gIh     (S/cm2)
        mInf
        mTau
        mAlpha
        mBeta
}
```

Name of the mechanism

Name of the current

Variables that may be recorded in the hoc code

Units used

Model parameters and their default values

Variables that are in dependence with the state variables of the STATE block

NMODL example: I_h channel (Hay et al. 2011)

```
STATE   {
        m
}

BREAKPOINT      {
        SOLVE states METHOD cnexp
        gIh = gIhbar*m
        ihcn = gIh*(v-ehcn)
}

DERIVATIVE states       {
        rates()
        m' = (mInf-m)/mTau
}

INITIAL{
        rates()
        m = mInf
}

PROCEDURE rates(){
        UNITSOFF
        if(v == -154.9){
            v = v + 0.0001
        }
                mAlpha =  0.001*6.43*(v+154.9)/(exp((v+154.9)/11.9)-1)
                mBeta  =  0.001*193*exp(v/33.1)
                mInf = mAlpha/(mAlpha + mBeta)
                mTau = 1/(mAlpha + mBeta)
        UNITSON
}
```

The state variable

In the beginning of the BREAKPOINT block the program is told to solve the update the state variables using a solution method for linear ODEs

Update the RANGE variable gIh

Update the current term ihcn

Calculate mInf and mTau based on membrane potential v

Define the differential equation for m (linear w.r.t. m)

Initialize the variable m at a value which is stable if the membrane potential value is stable

Prevent an operation of dividing zero by zero

HH equations for the functions mInf(v) and mTau(v)