ENCODS 2023 · Workshop

Neuronal & Network computational models
· Practical part ·

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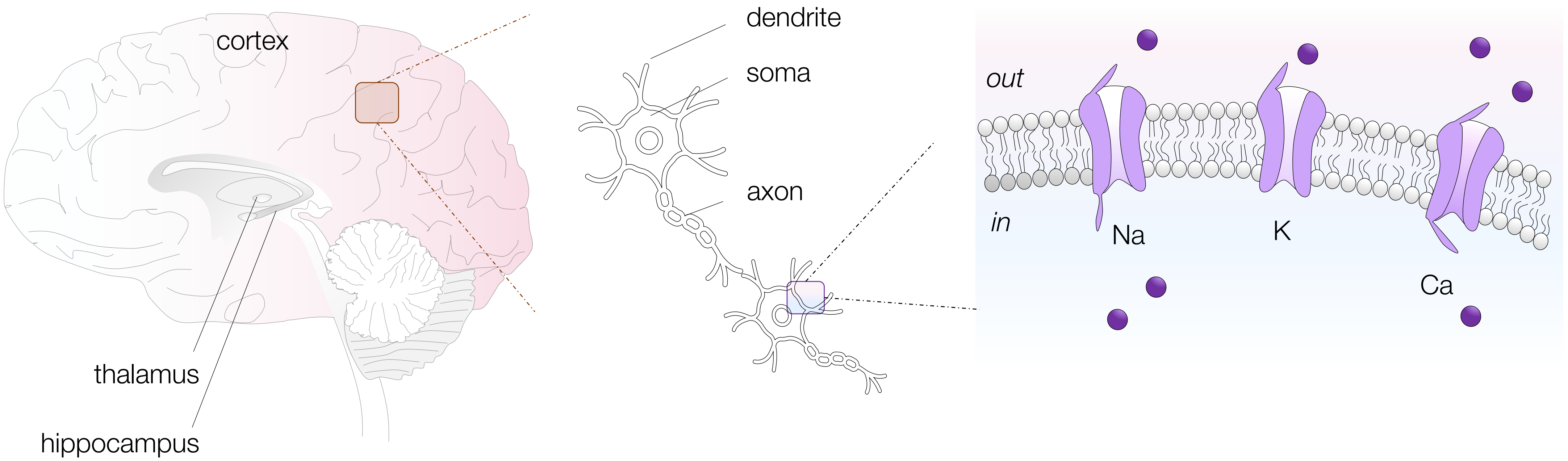
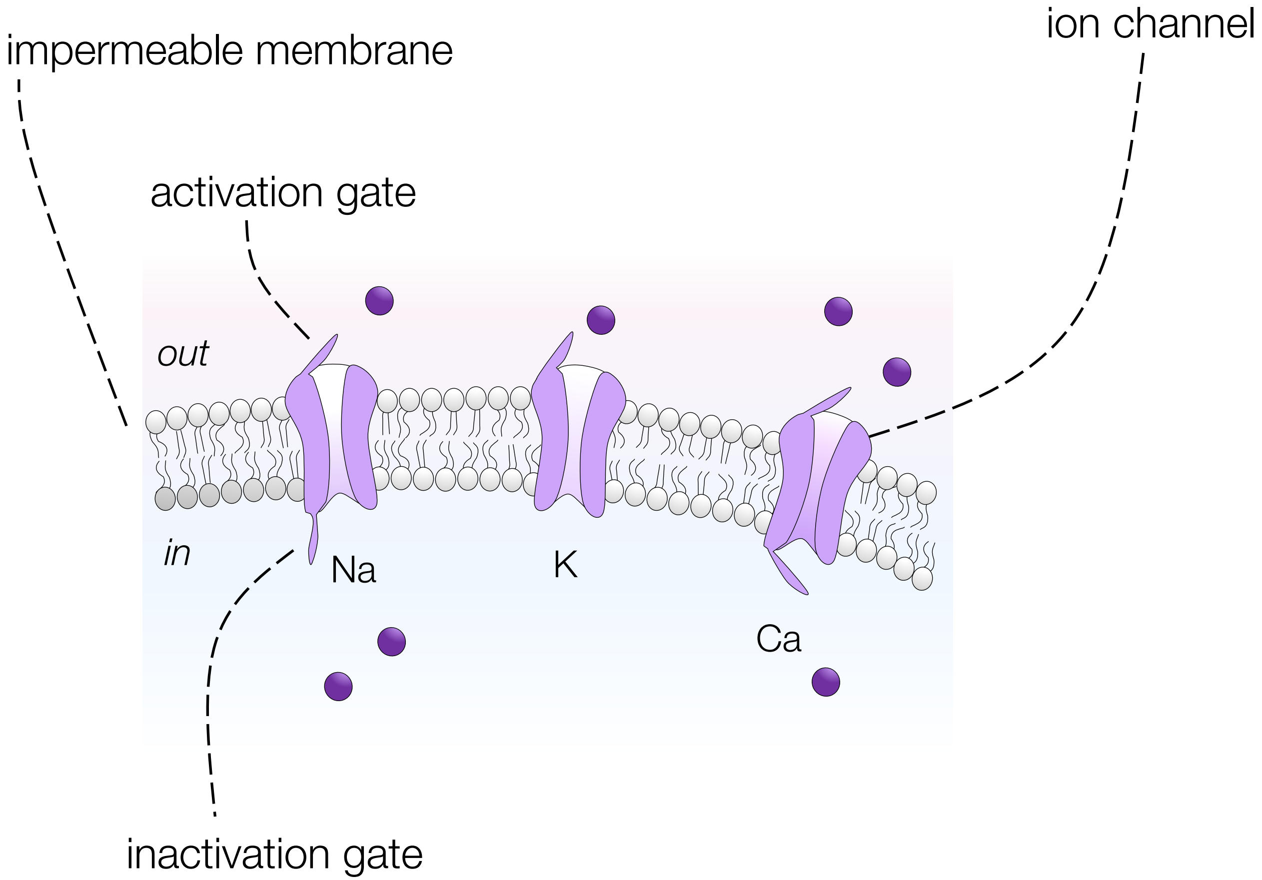
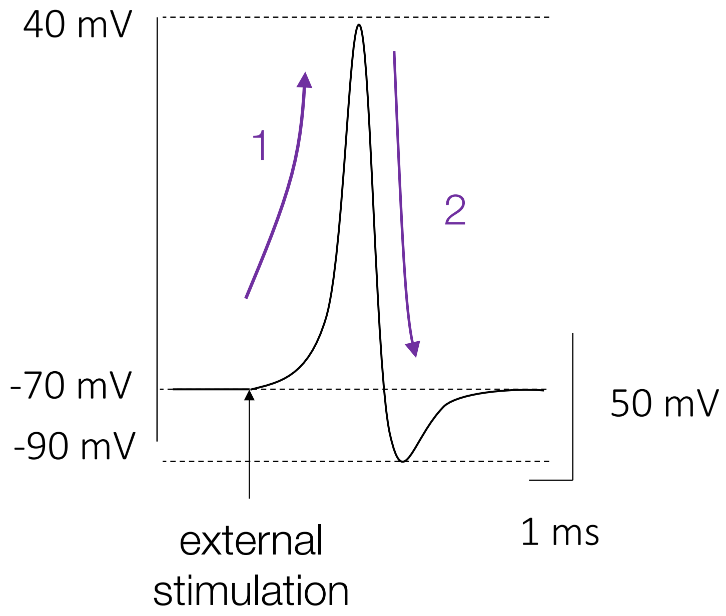
Zooming at the neuronal level



Action potential





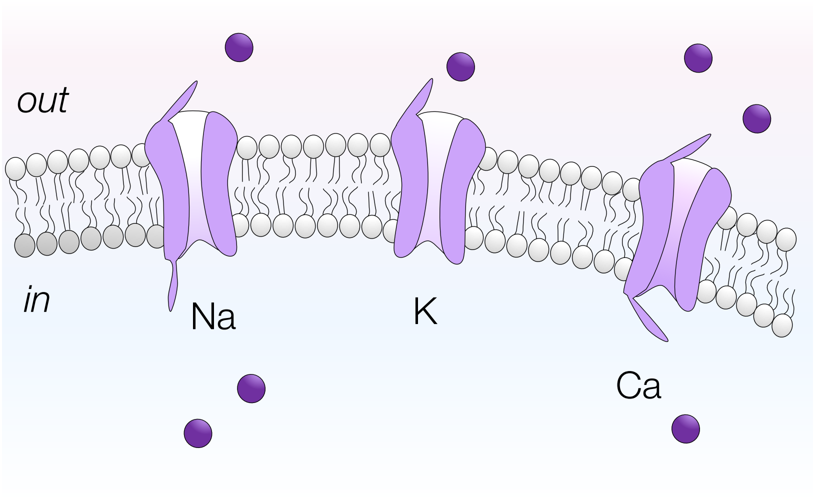
1 – Na rapidly flows inside the neuron: fast depolarization
2 – K starts to go out: slow hyperpolarization

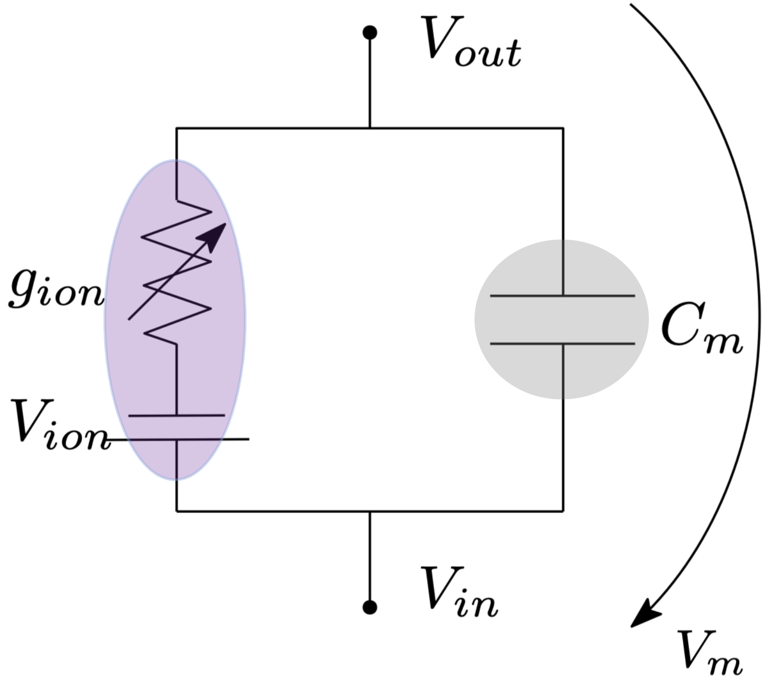
How to model an action potential ?

How to reproduce a patch clamp experiment ?

Hodgkin & Huxley model

Concept: from the neuron membrane to the conductance-based model





· The impermeable membrane acts as a capacitance.
It accumulates ion on both sides.

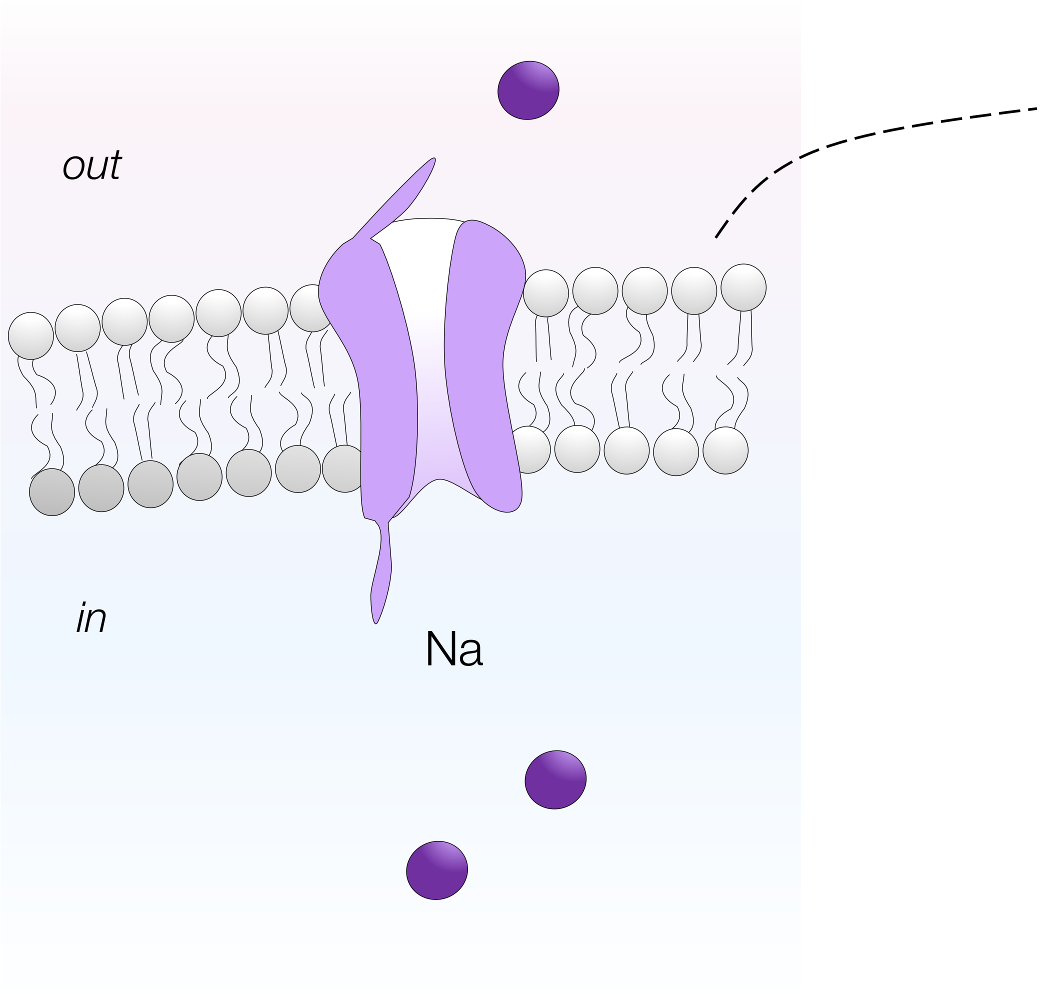
· The ion channels allow flow of ions across the membrane.
They correspond to resistance. The inverse of a resistance is a conductance.

$$V_m = V_{in} - V_{out}$$

membrane voltage

Hodgkin & Huxley model

Current through the membrane



The impermeable membrane causes a capacitance current I_C:

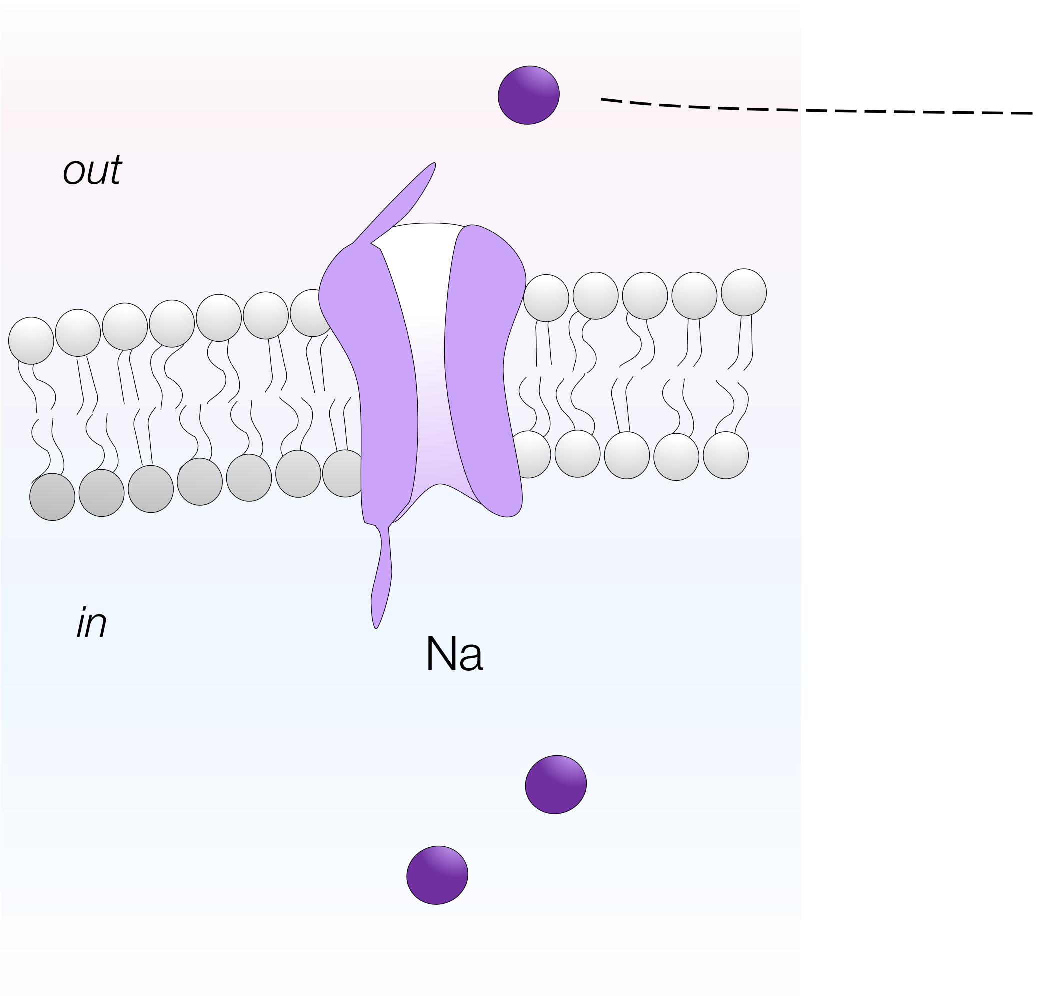
$$I_C = C \, dV_m/dt$$

C: membrane capacitance

dV_m/dt: the variation of the membrane voltage

Hodgkin & Huxley model

Current through the ion channel



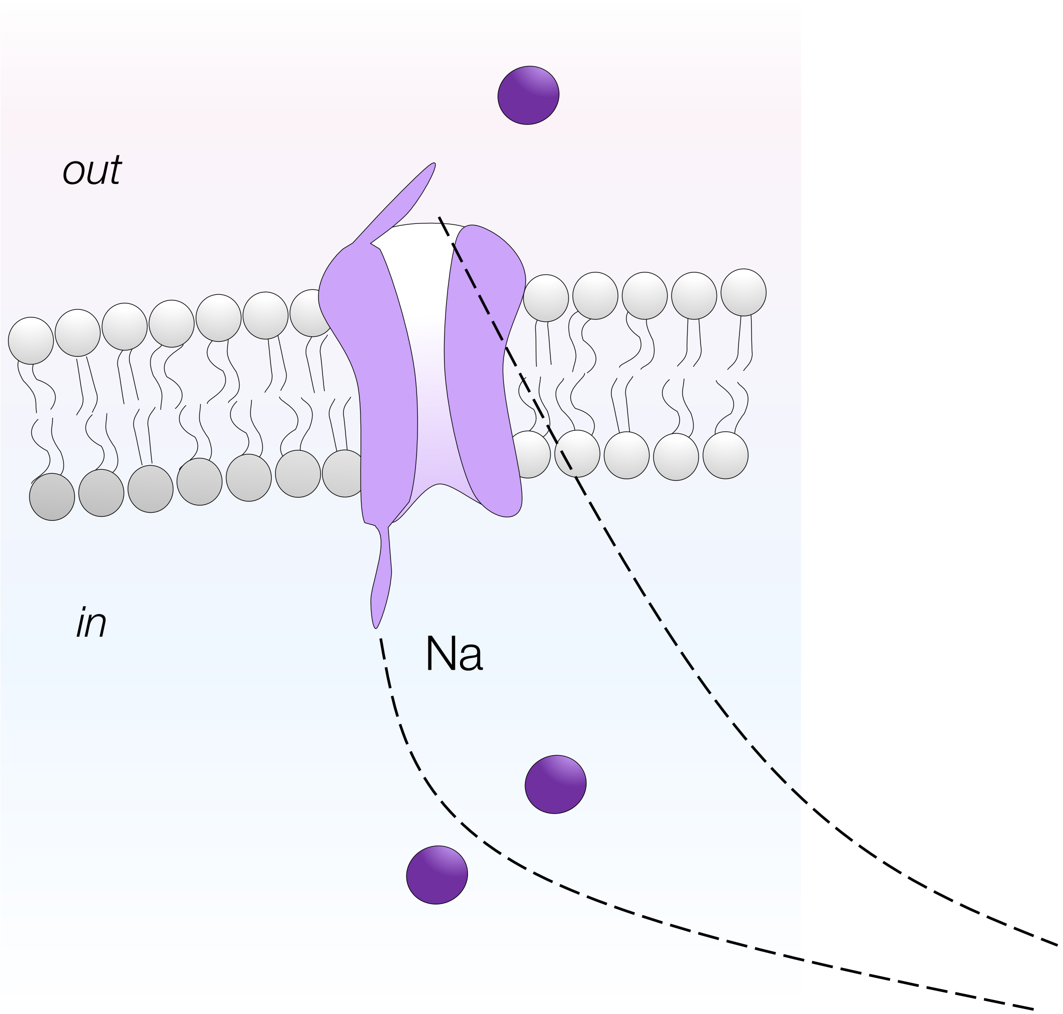
The sodium ions that flow through the membrane lead to a sodium current I_{Na}:

$$I_{Na} = \overline{g}_{Na} (V_m - E_{Na})$$

$\overline{g}_{Na}$: sodium conductance
V_m: membrane voltage
E_{Na}: sodium reversal potential

Hodgkin & Huxley model

Current through the ion channel



The sodium ions that flow through the membrane lead to a sodium current I_{Na}:

$$I_{Na} = \bar{g}_{Na} (V_m - E_{Na})$$

$\bar{g}_{Na}$: sodium conductance
V_m: membrane voltage
E_{Na}: sodium reversal potential

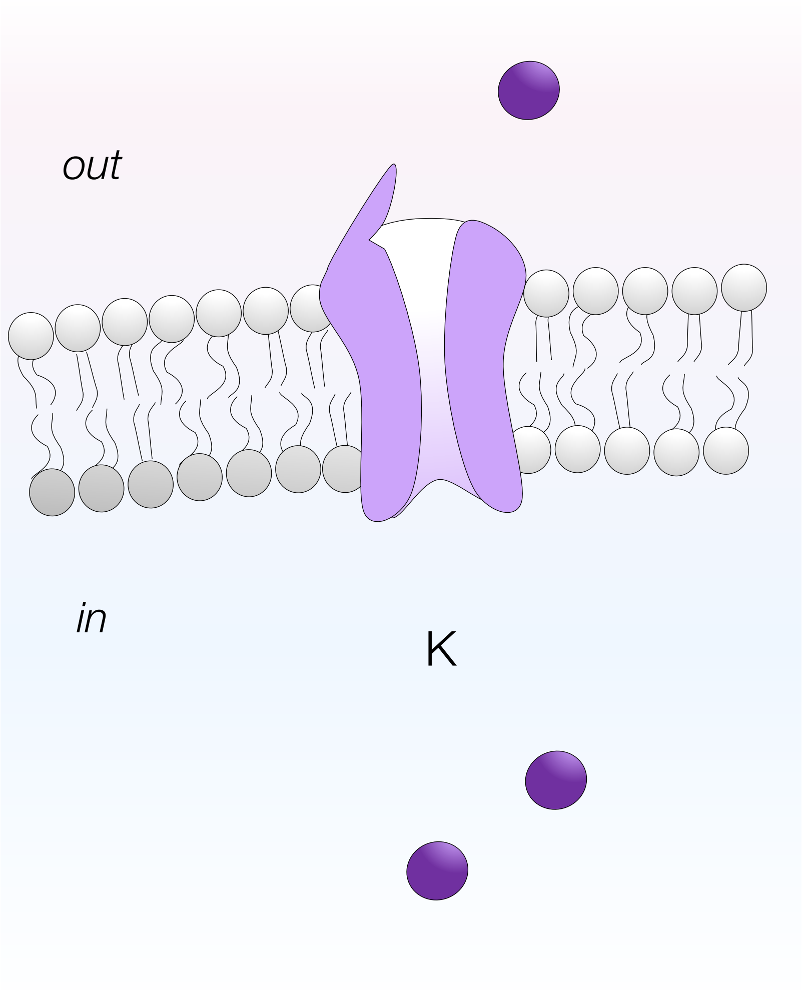
The ion channel opens and closes depending on the membrane voltage. It is modeled by a conductance that depends on the membrane voltage

$$\bar{g}_{Na} = g_{Na} m_{Na}^3 h_{Na}$$

g_{Na} : maximum sodium conductance
m_{Na} models the activation gate
h_{Na} models the inactivation gate

Hodgkin & Huxley model

Current through the ion channel



The potassium ions that flow through the membrane leads to a potassium current I_K:

$$I_K = \overline{g}_K (V_m - E_K)$$

$\overline{g}_K$: potassium conductance
V_m: membrane voltage
E_K: potassium reversal potential

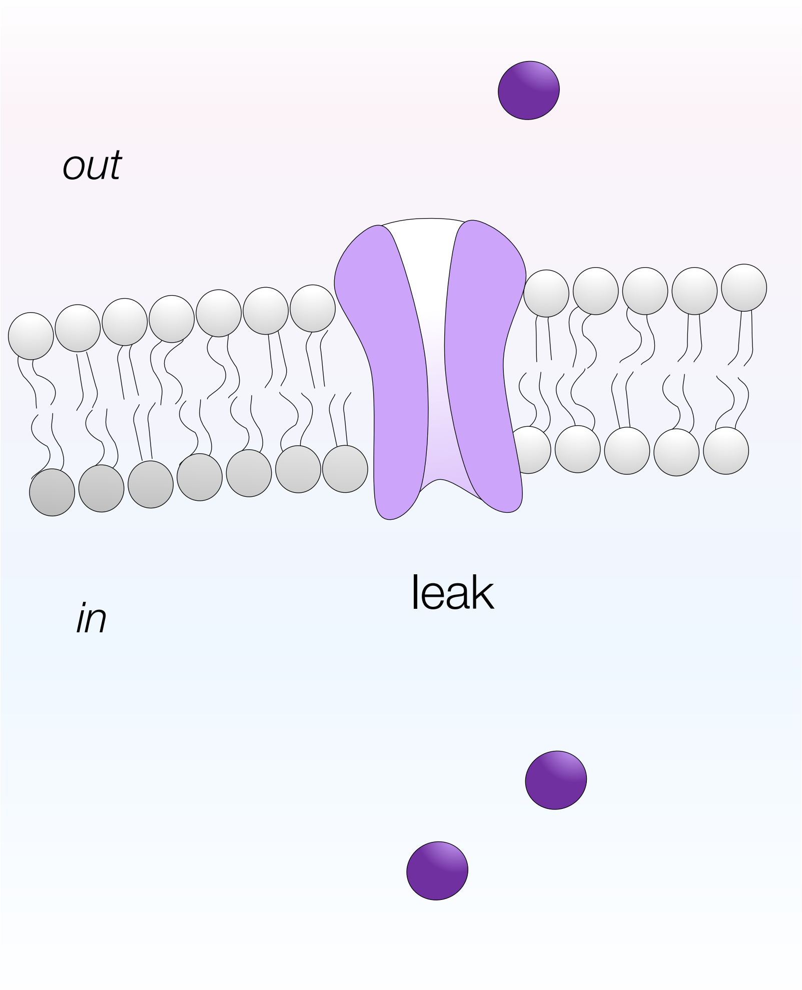
The ion channel opens and closes depending on the membrane voltage. It is modeled by a conductance that depends on the membrane voltage

$$\overline{g}_K = g_K m_K^4$$

g_K : maximum potassium conductance
m_K models the activation gate

Hodgkin & Huxley model

Current through the ion channel



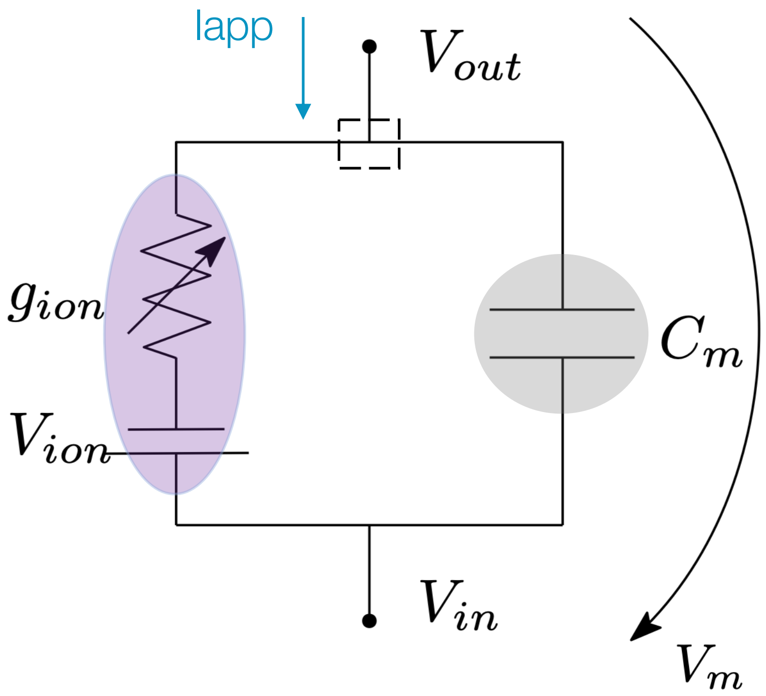
The membrane is not perfectly impermeable and leaks.

$$I_{leak} = g_{leak} (V_m - E_{leak})$$

g_K: leak conductance
V_m: membrane voltage
E_{leak}: leak reversal potential

Hodgkin & Huxley model

Equations



$$V_m = V_{in} - V_{out}$$

An electrical circuit can be studied via Kirchhoff's law:
The sum of the currents entering a node is equal to the sum of the currents going out the node.

$$I_{app} = I_C + \sum I_{ion}$$

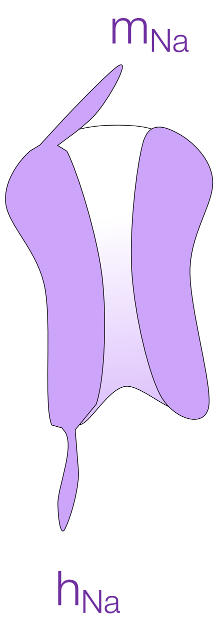
We replace the different terms in the equations:

$$C\ dV_m/dt = - \sum I_{ion} + I_{app}$$

$$C\ dV_m/dt = - (I_{Na} + I_K + I_{leak}) + I_{app}$$

Hodgkin & Huxley model

Equations

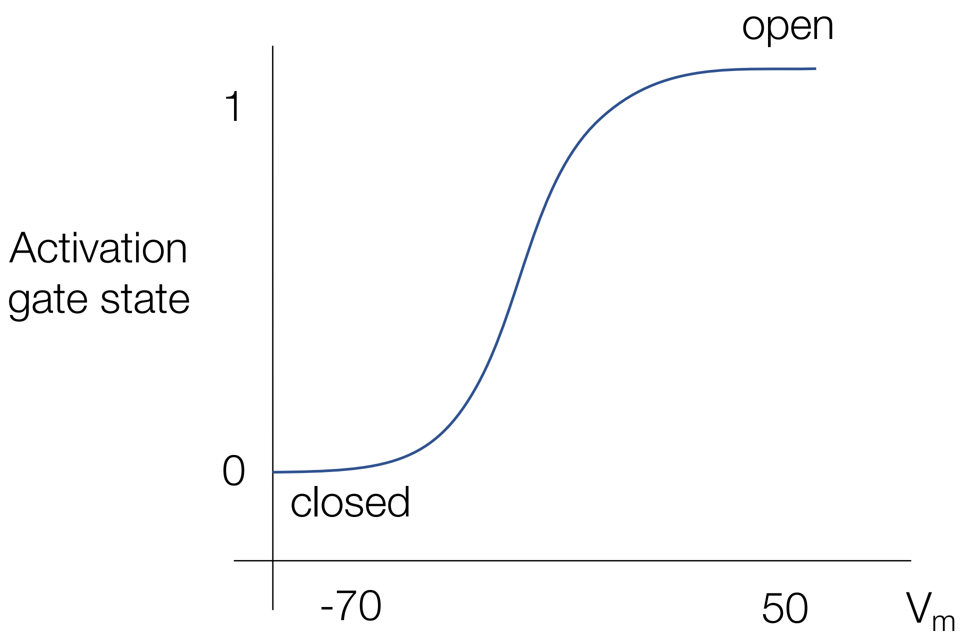


This variable models the dynamics of the activation gate.

$m_{Na}=1$: gate is open
$m_{Na}=0$: gate is closed

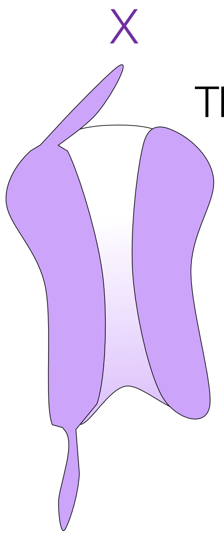
It depends on the membrane voltage V_m.

This variable models the dynamics of the inactivation gate



Hodgkin & Huxley model

Equations



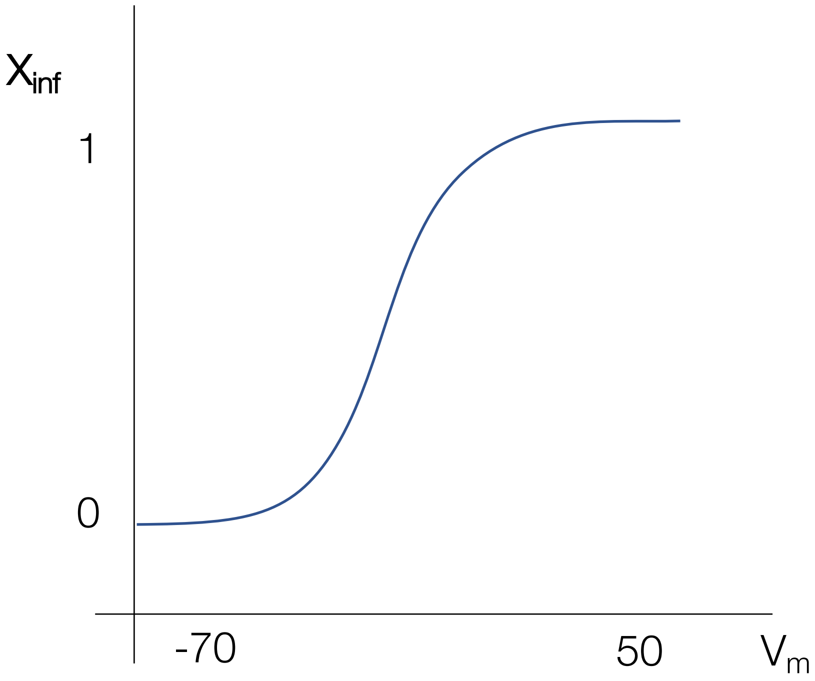
This variable models the dynamics of the activation gate.

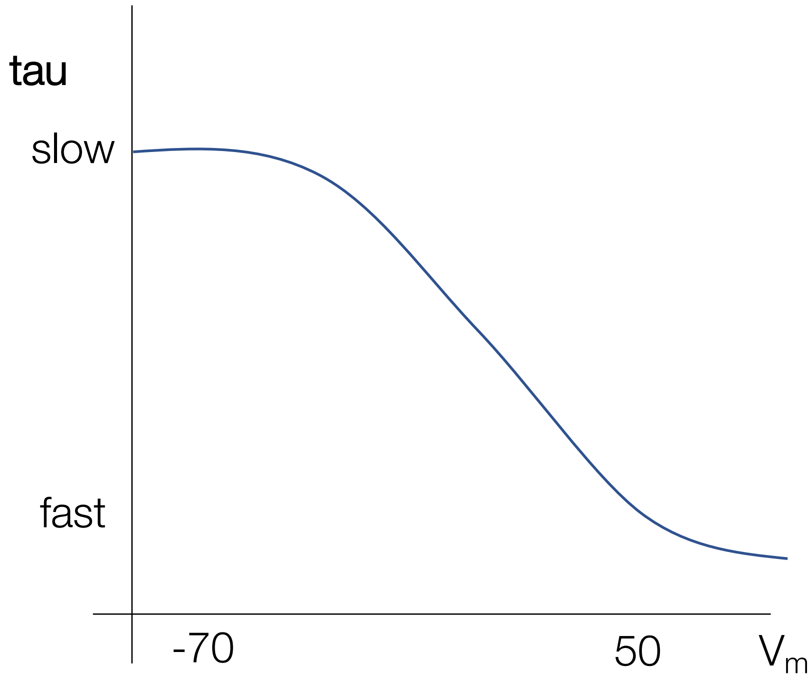
X = 1: gate is open
X = 0: gate is closed

In general, dynamics is governed by a differential equation
$\tau \, dX/dt = X_{inf} - X$

It is simply read as:
"the variable X converges towards its steady state X_{inf} with a time constant of tau"

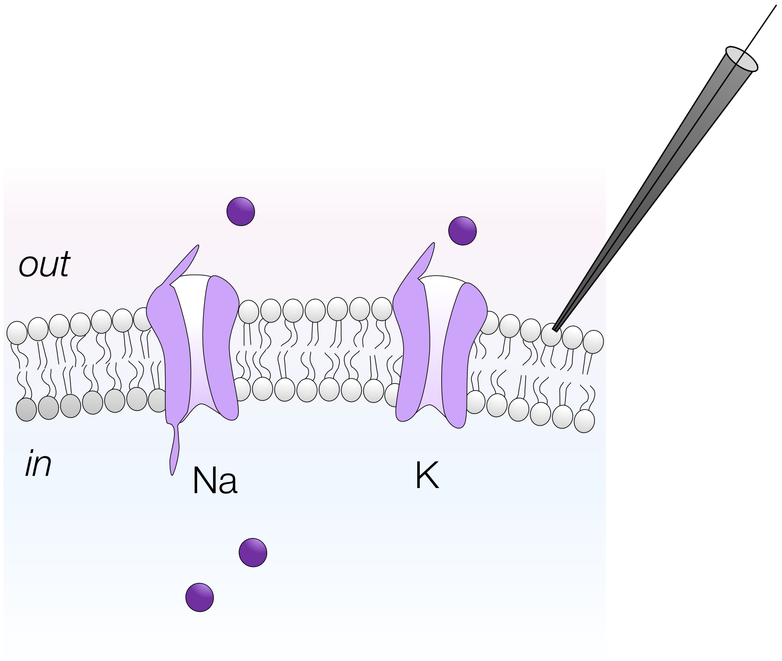
To model ion channel, the steady state and the time constant depend on the membrane voltage.

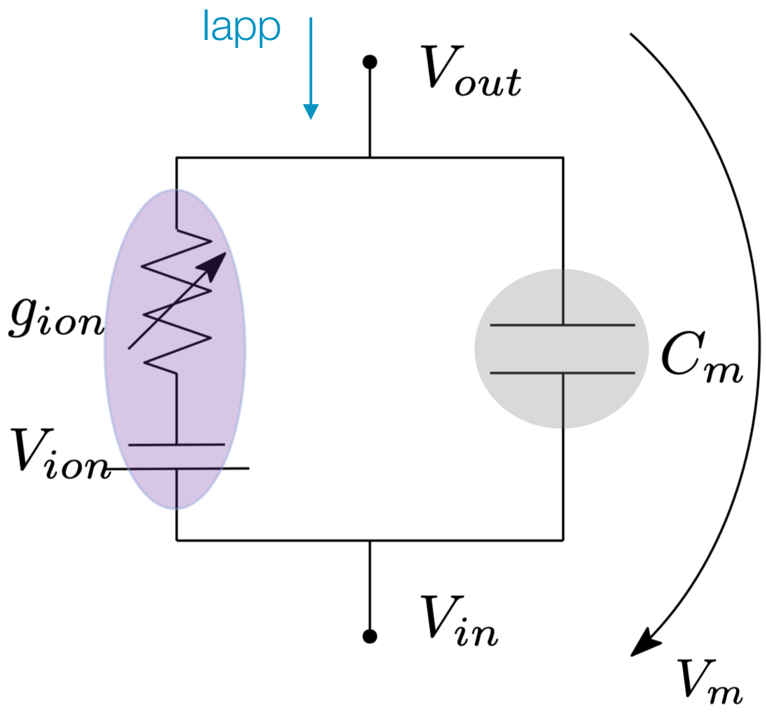




Hodgkin & Huxley model
Reproduce a current clamp experiment

When the neuron is patched
You can record the membrane voltage.





$$V_m = V_{in} - V_{out}$$

Let’s move to the notebook

Notebook

Step by step: let's simulate an action potential

Open the link urlis.net/HH_neuron
This is a **SHARED** code. Each modification done on this code affects the code of the other collaborators.
Do a copy on your computer. File > Save a copy in your Drive

Let's go through the code.

Run each cell one by one (from top to bottom)

Simulate a current-clamp experiment

Play with the parameters

WIFI

Network: ualg – conferencias
ID: encods23
Password: 62878832

Notebook

Step by step: let's simulate an action potential

$$C\, dV_m/dt = -\,(I_{Na} + I_K + I_{leak}) + I_{app}$$

$$C\, dV_m/dt = -\, g_{Na} m_{Na}^3\, h_{Na}\, (V_m - E_{Na}) \;-\; g_K m_K^4\, (V_m - E_K) \;-\; g_{leak}\, (V_m - E_{leak}).\,) + I_{app} + I_{appstep}$$

Differential equation written on a code to be solved by the Euler method
(or with solver like ode)
dV/dt = function
V(t+1) = V(t) + dt . function

```
# HH rule
V += (dt)*(1/C)*(-gNa*mNa**3*hNa*(V-VNa) -gK*mK**4*(V-VK) -gl*(V-Vl) +Iapp +Iappstep)
```

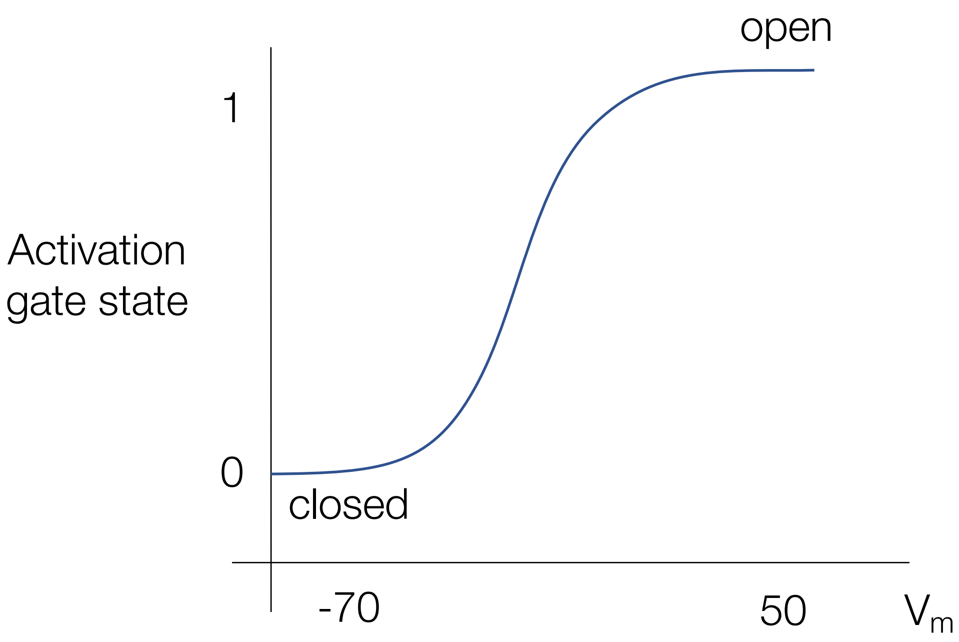
Current constantly applied to the neuron

Current step in addition to the applied current

Notebook

Step by step: let's simulate an action potential

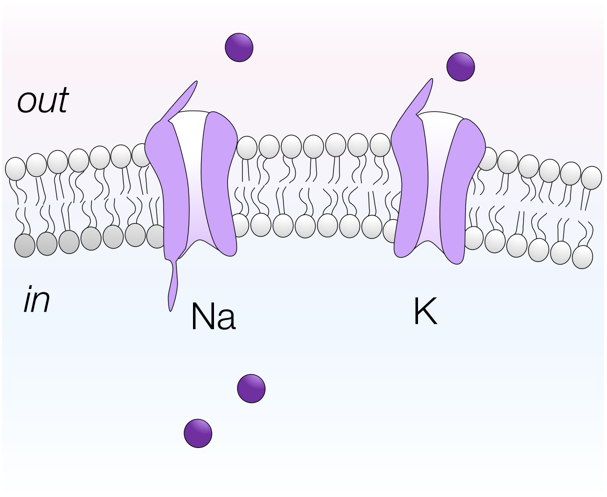
alpha and beta are used to describe the sigmoidal shape of the gating variables. They are fitted on the experimental data obtained by Hodgkin & Huxley




```python
def alpha_mNa(V):
    return -0.10*(V+35)/(np.exp(-(V+35)/10)-1)

def beta_mNa(V):
    return 4*np.exp(-(V+60)/18)

def alpha_hNa(V):
    return 0.07*np.exp(-(V+60)/20)

def beta_hNa(V):
    return 1/(1+np.exp(-(V+30)/10))

def alpha_mK(V):
    return (V+50)/(100*(1-np.exp(-(V+50)/10)))

def beta_mK(V):
    return 0.125*np.exp(-(V+60)/80)
```

Notebook

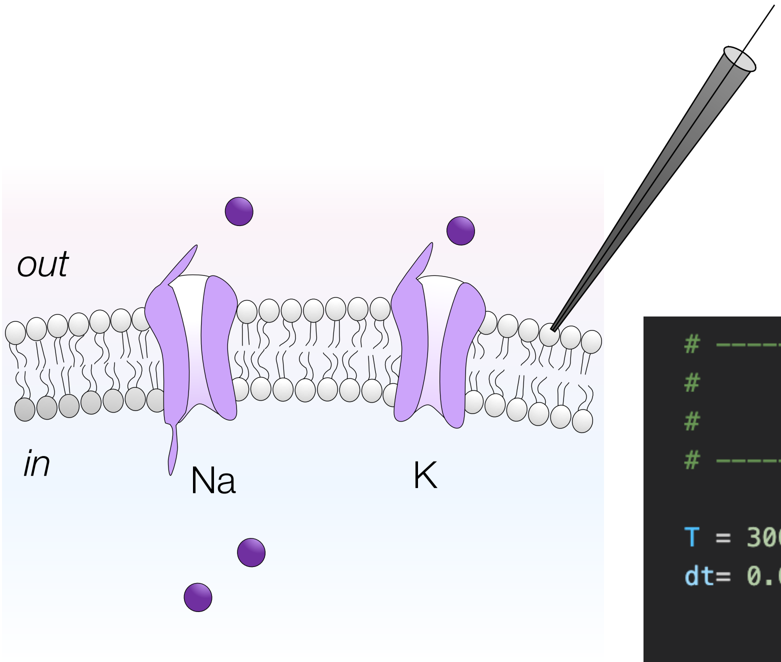
Step by step: let’s simulate an action potential




```
# --------------------------------------------------------------------------------
#                               Parameters of the neuron
# --------------------------------------------------------------------------------



C = 1                        # capacitance
VNa = 50                     # reserval potential of sodium channels
VK  = -77                    # reserval potential of potassium channels
Vl  = -49                    # reserval potential of leak channels

Erev = [VNa, VK, Vl, C]      # array to send all the reversal potentials in once

gNa = 120                    # conductance of sodium channels
gK  = 36                     # conductance of potassium channels
gl  = 0.3                    # conductance of leak channels

param_g = [gl, gNa, gK]      # array to send all the conductances in once
```

Notebook

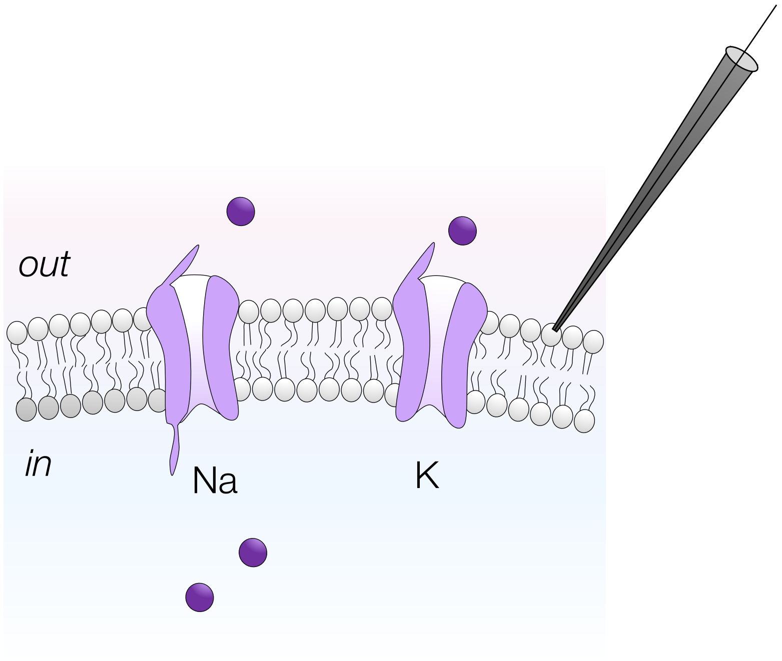
Step by step: let's simulate an action potential

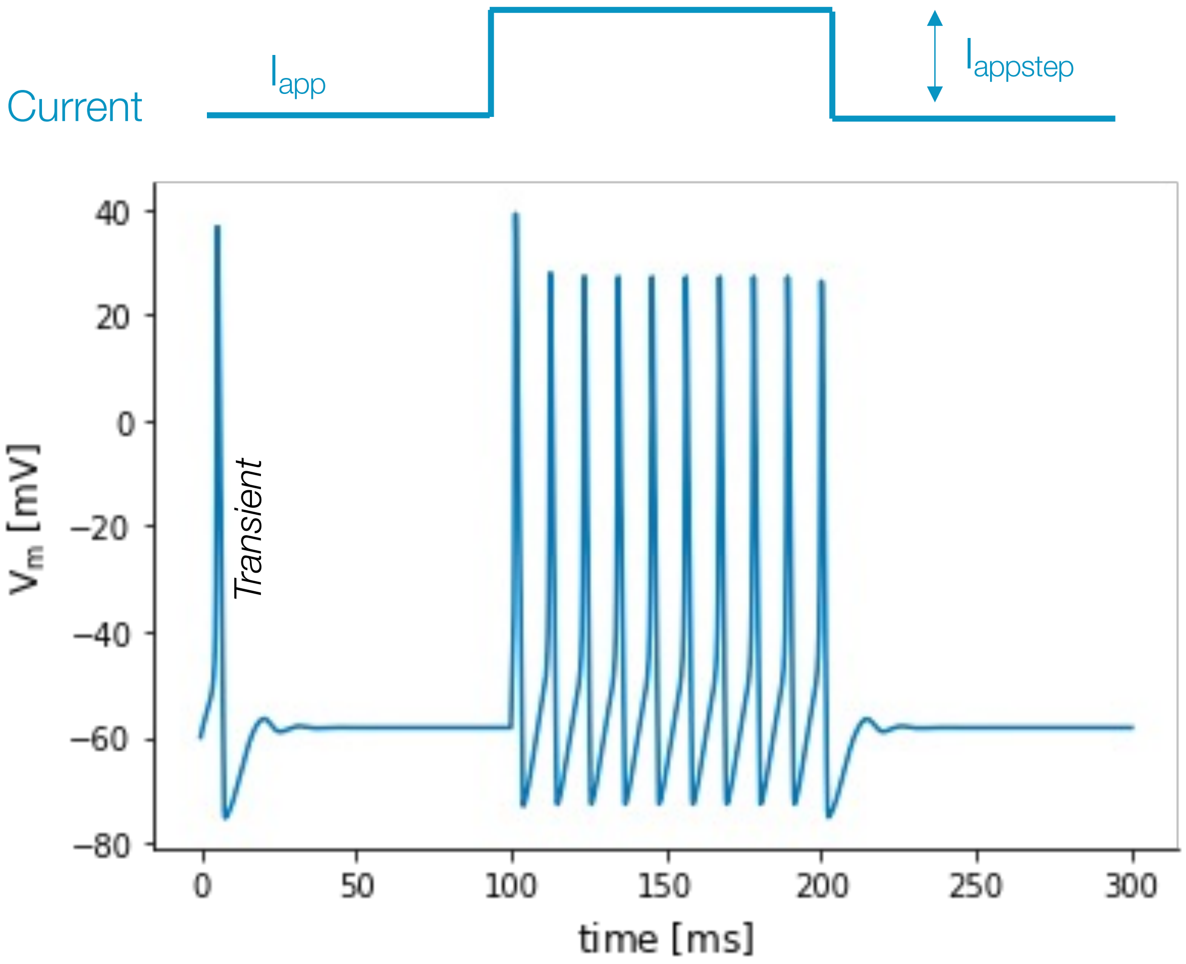



```
# ------------------------------------------------------------------------------
#                          Parameters chosen by the experimentalist
#                 Define the parameters used during a patch clamp recording
# ------------------------------------------------------------------------------

T = 300                       # [ms] Duration of the recording
dt= 0.01                      # Time step for numerical integration (Euler method)


T_dt = int(T/dt)              # array converting the duration into a numerical duration
t = np.arange(0.0, T, dt)     # array containing the timestep at which the membrane is updateing

Iapp = -10                    # current applied during the whole simulation
Istep = 20                    # increment of current in addition to the previous one used to drive a pulse
Tstep_init = 100              # instant when the pulses starts
Tstep_end = 200               # instant when the pulses stops
```

Notebook

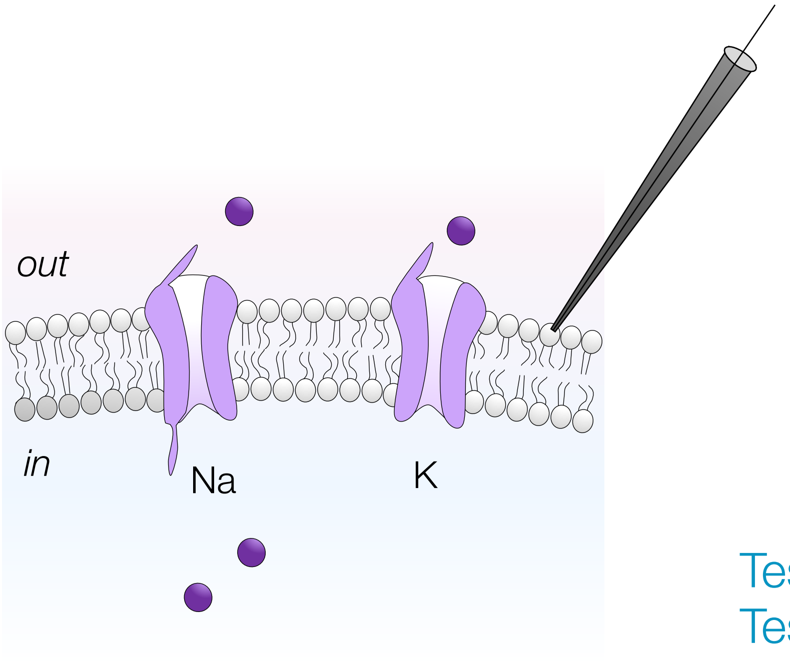
Step by step: let’s simulate an action potential during current clamp





Notebook

Step by step: let’s simulate an action potential during current clamp

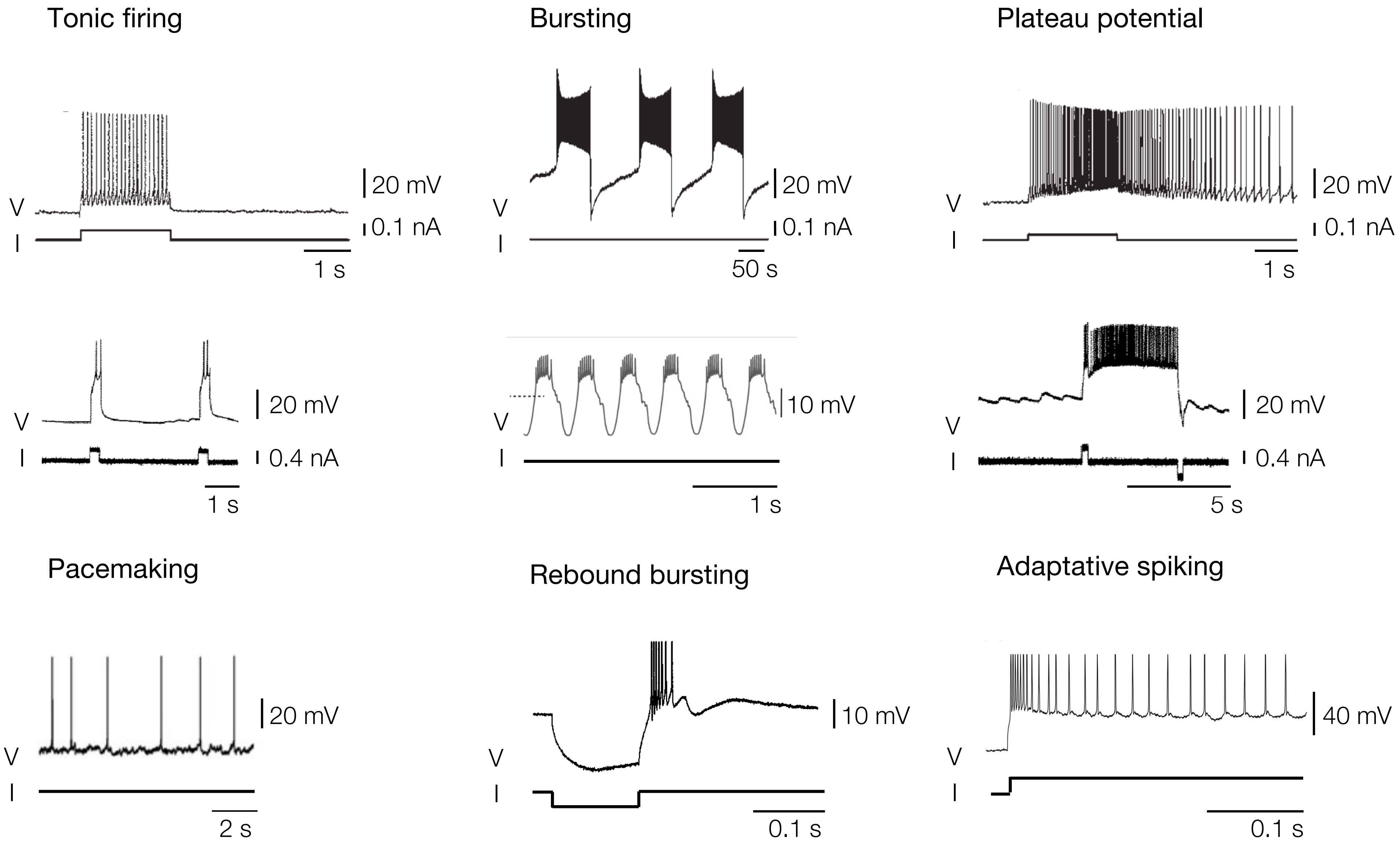


Your turn

Test 1: increase the firing frequency.
Test 2: mimic a TTX experiment where TTX is a sodium channel blockers.
Test 3: explore the impact of some parameters by your choice.

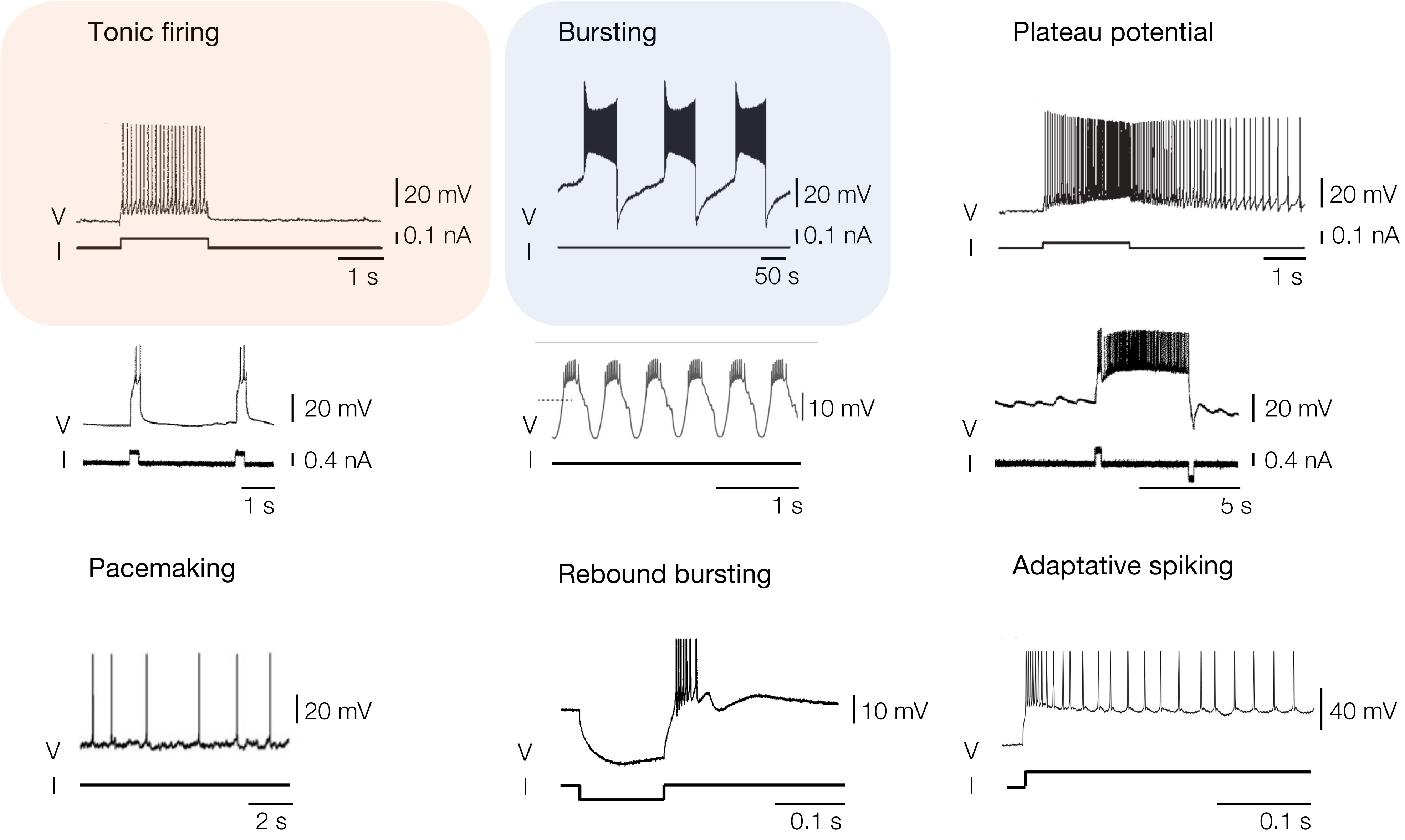
Move from HH model to more complicated models

Neurons have a rich variety of firing patterns



Move from HH model to more complicated models

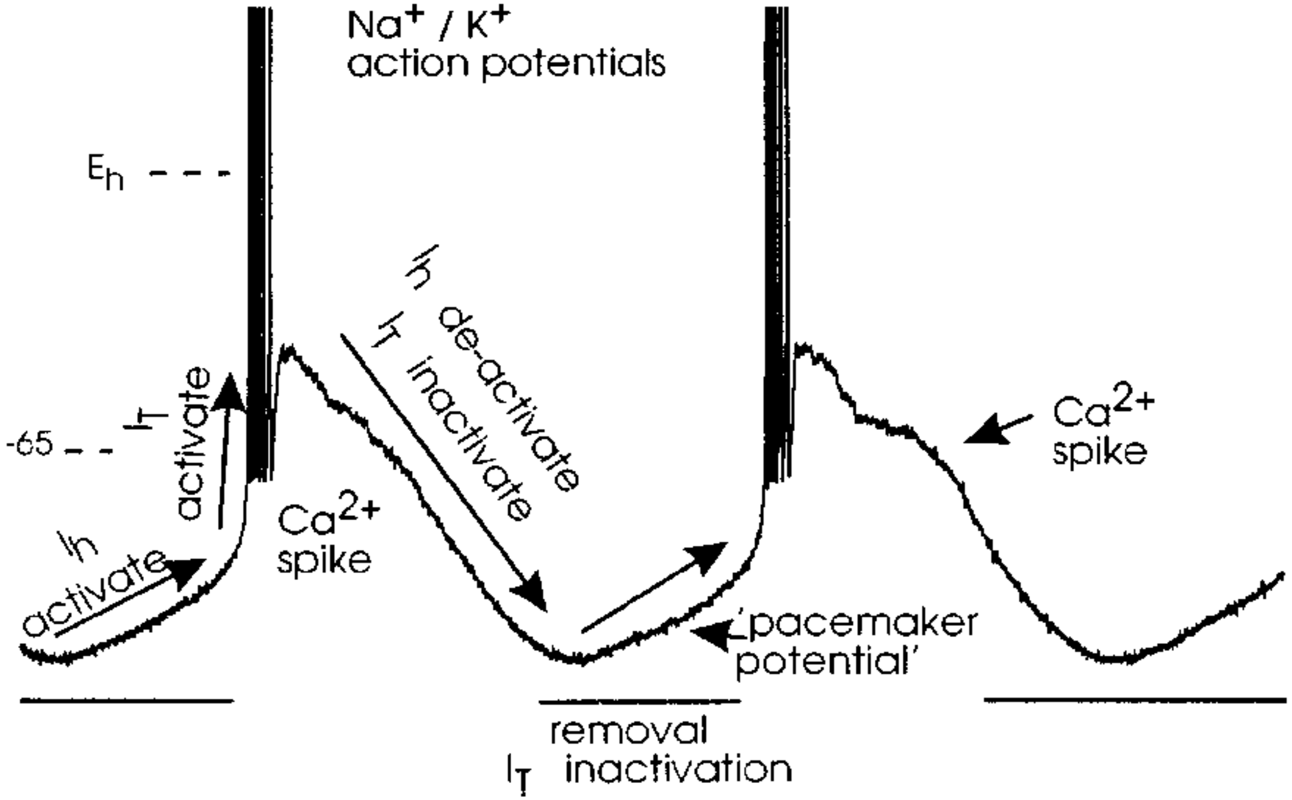
Neurons have a rich variety of firing patterns



[My thesis for references]

Move from HH model to more complicated models

Intrinsic burst generation



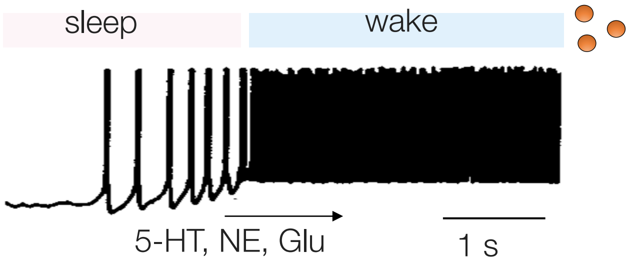
Just need to add more channels on the model with their own dynamics

[McCormick et al., 1997]

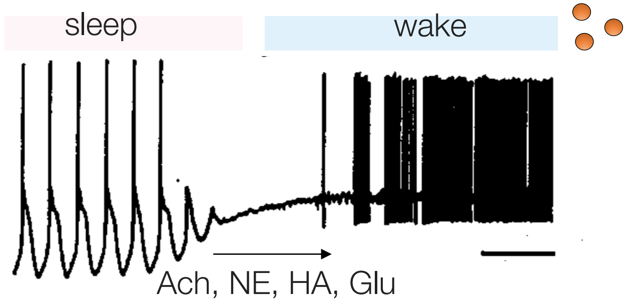
Move from HH model to more complicated models

Switches from tonic firing to bursting occur in a lot of types of neurons

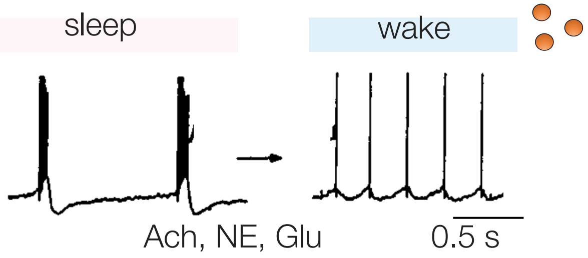
Thalamic reticular neuron



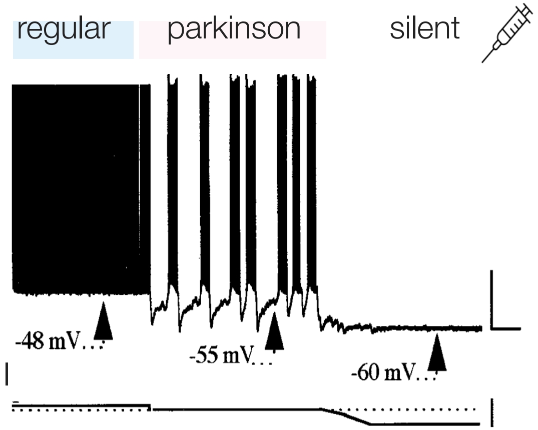
Thalamic relay neuron



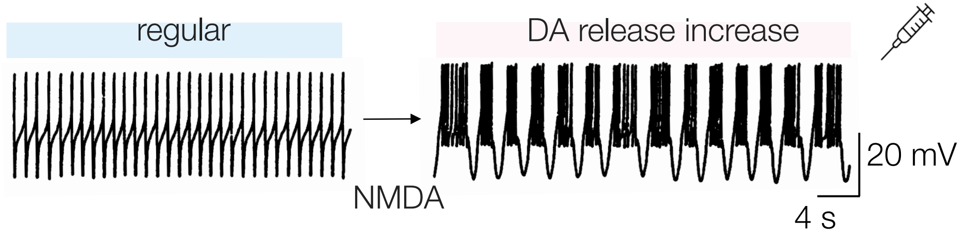
Cortical neuron



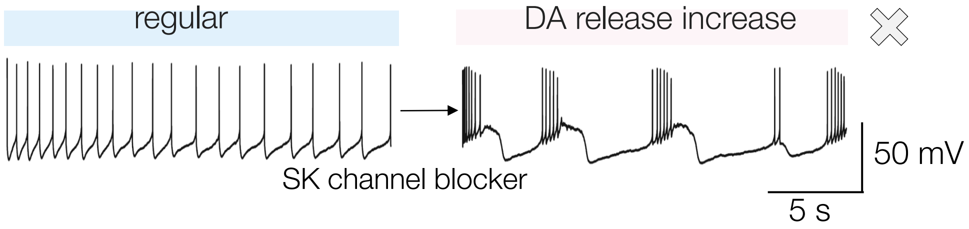
Subthalamic nucleus neuron



Dopaminergic neuron in the ventral tegmental area



Midbrain dopaminergic neuron (DA)



Notebook

Step by step: let’s simulate a neuron able to switch from tonic firing to burst

- Open the link mysl.nl/XZKy
  This is a **SHARED** code. Each modification done on this code affects the code of the other collaborators.
  Do a copy on your computer. File > Save a copy in Drive
- Let’s go through the code.
- Run each cell one by one (from top to bottom)
- Do some tests by yourself
- Study a thalamic neuron