CN510: Principles and Methods of Cognitive and Neural Modeling

Electrophysiology of Cell Membrane

Lecture 5

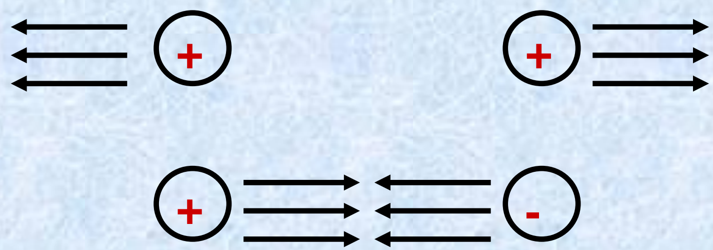
Instructor: Anatoli Gorchetchnikov <anatoli@bu.edu>

Elementary Circuit Theory: Electric Charge

Can think of an ion as a unit of charge + or –

Charges of opposite sign attract

Charges of the same sign repel

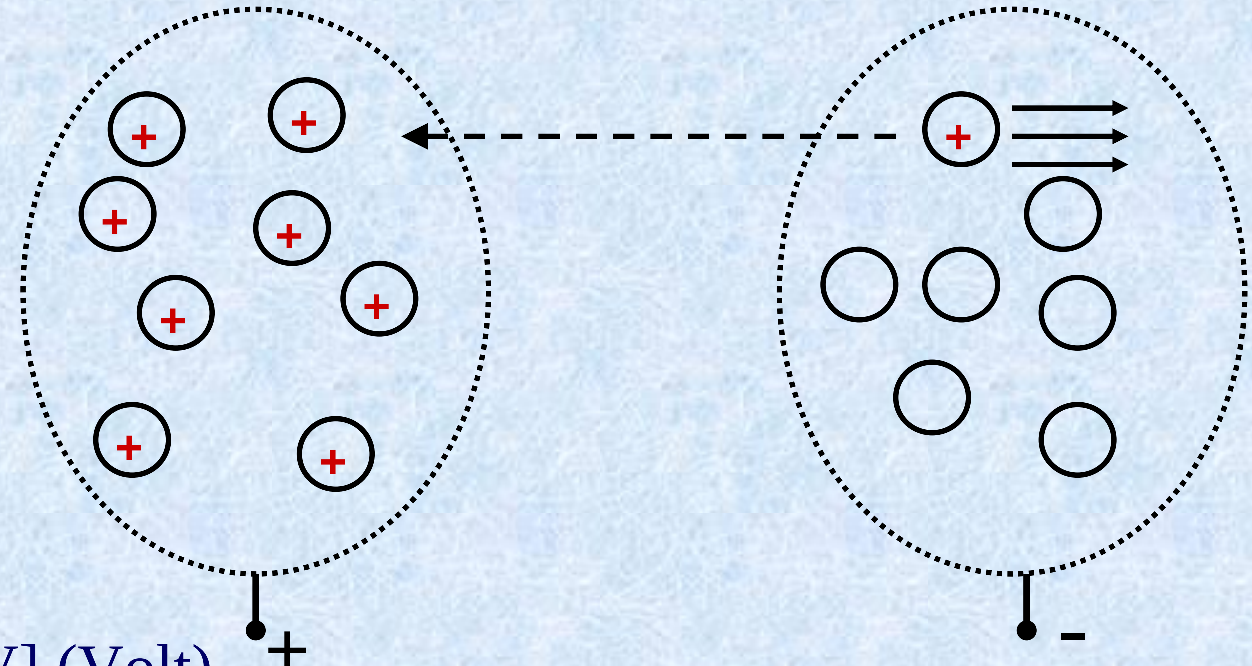


Units: [C] (Coulomb)

Notation: Q

Elementary Circuit Theory: Potential, Voltage

The potential difference across two points is the work that must be done to move a unit of charge from one point to another

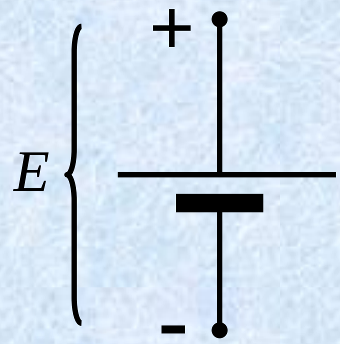


Units: [V] (Volt)

Notation: V

Elementary Circuit Theory: Voltage Source

Charge separation can be accomplished by a battery and is usually schematized as

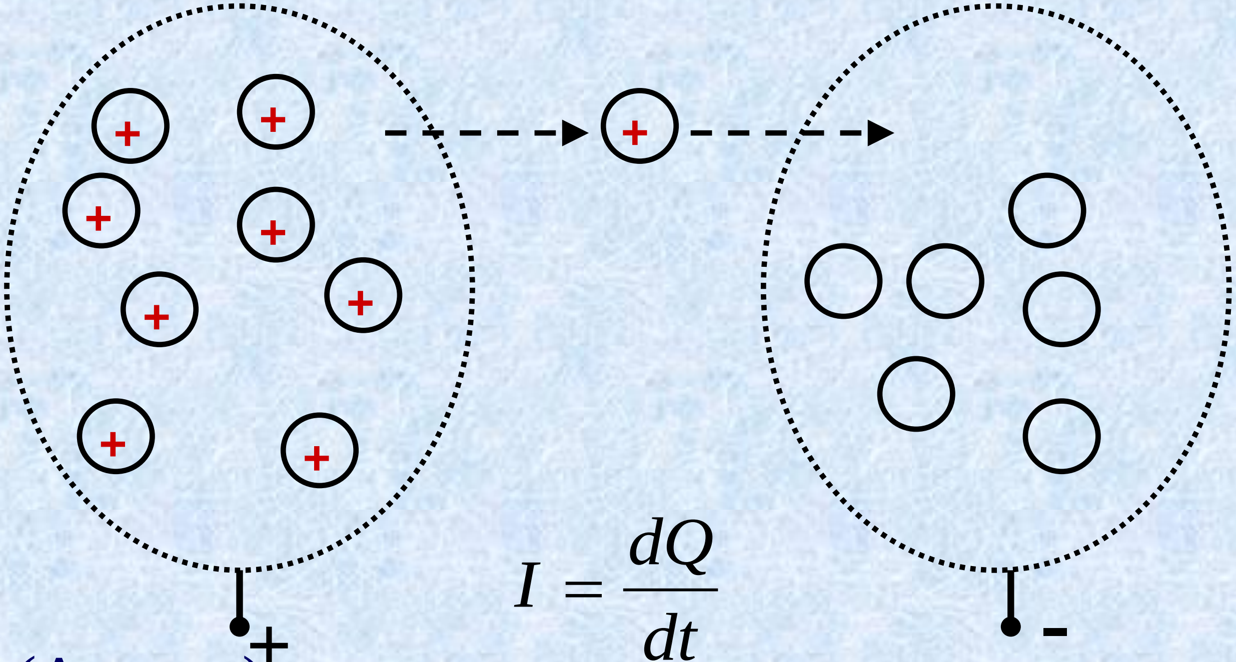


Voltage across the battery is assumed to be constant and is usually written as E

Elementary Circuit Theory: Current

Rate at which charge moves from one point to another

Number of positive ions leaving the cell per unit of time is the current leaving the cell



$$I = \frac{dQ}{dt}$$

Unit: [A] (Ampere)

Notation: I

Elementary Circuit Theory: Resistance, Conductance

Resistance is a measure of how a medium resists the flow of a current

Insulators have high resistance (porcelain, rubber, cell membrane)

Conductors have low resistance (metals, ionic solutions)

Ionic channels are gates in the cell membrane, the more gates are open the lower the resistance of the membrane

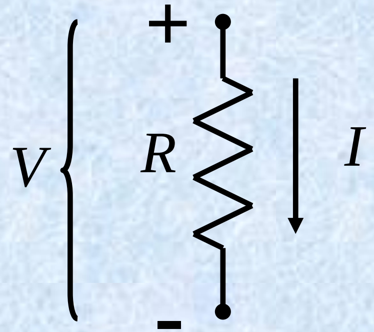
Conductance is the reciprocal of resistance $g=1/R$

Units: resistance [Ω] (Ohm); conductance [S] (Siemens)

Notation: resistance R; conductance g

Elementary Circuit Theory: Ohm's Law

Describes the relationship between voltage and current across a resistor



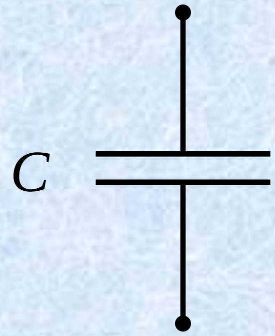
$$V = IR$$

If a neuron has a membrane with resistance R (conductance g), then the current across the membrane is

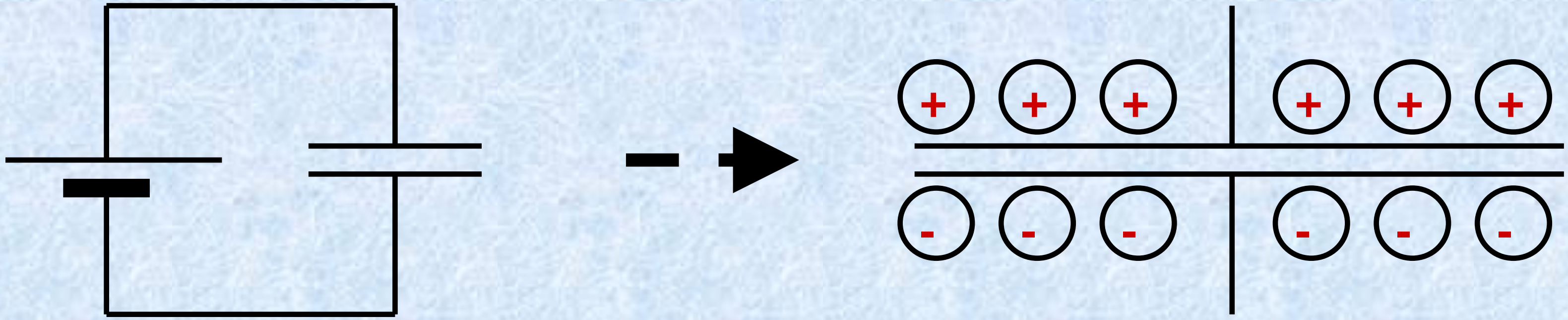
$$I = \frac{V}{R} = gV$$

Elementary Circuit Theory: Capacitor

A capacitor is a circuit element consisting of two conducting plates (i.e., effectively zero resistance within each plate) separated by insulating material (i.e., infinite resistance between plates).

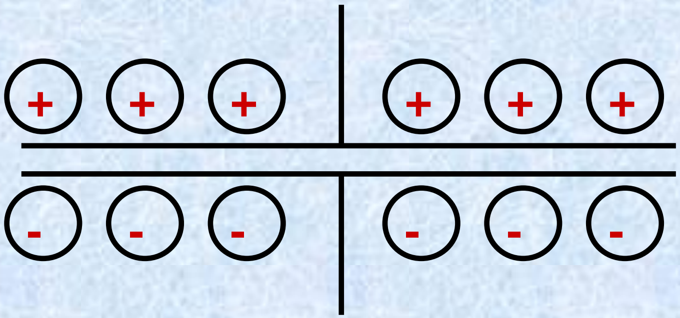


If a constant voltage is applied across a capacitor, opposite charges will collect on the two sides:



Elementary Circuit Theory: Capacitance

In a capacitor the amount of charge on each side is proportional to the voltage between sides



$$Q = CV$$

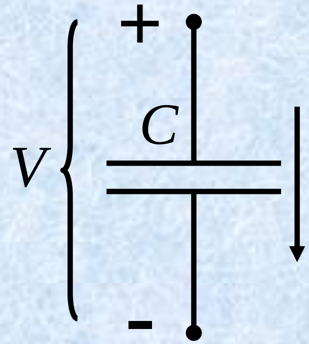
The coefficient *C* or capacitance is specific for a given capacitor, it is proportional to the area of the plates and inversely proportional to the distance between them

Units: [F] Farad

Notation: C

Current "across" the capacitor

Recall that $I = \frac{dQ}{dt}$ and since $Q = CV$

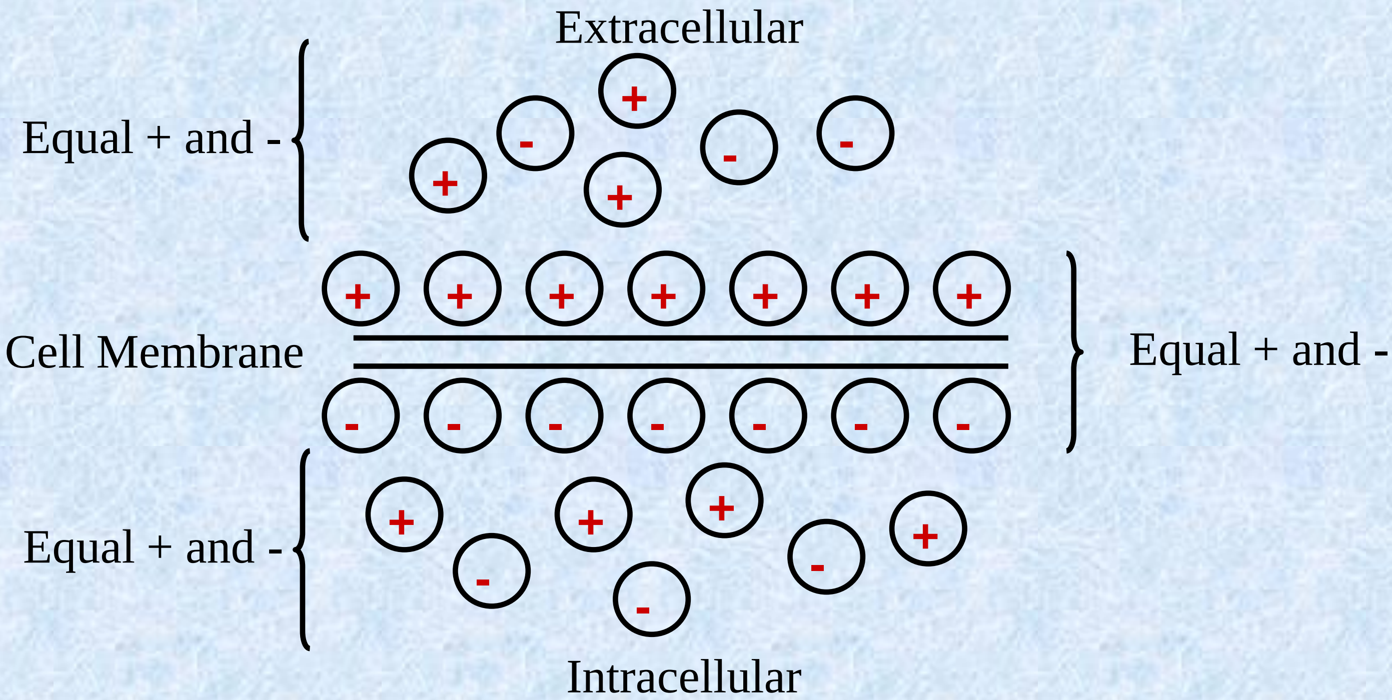


$$I = C\frac{dV}{dt}$$

Thus the larger the capacitance the smaller the voltage change will be inflicted by the same current

Since the capacitance is proportional to the area of the plates, large cells will require more current for the same voltage change

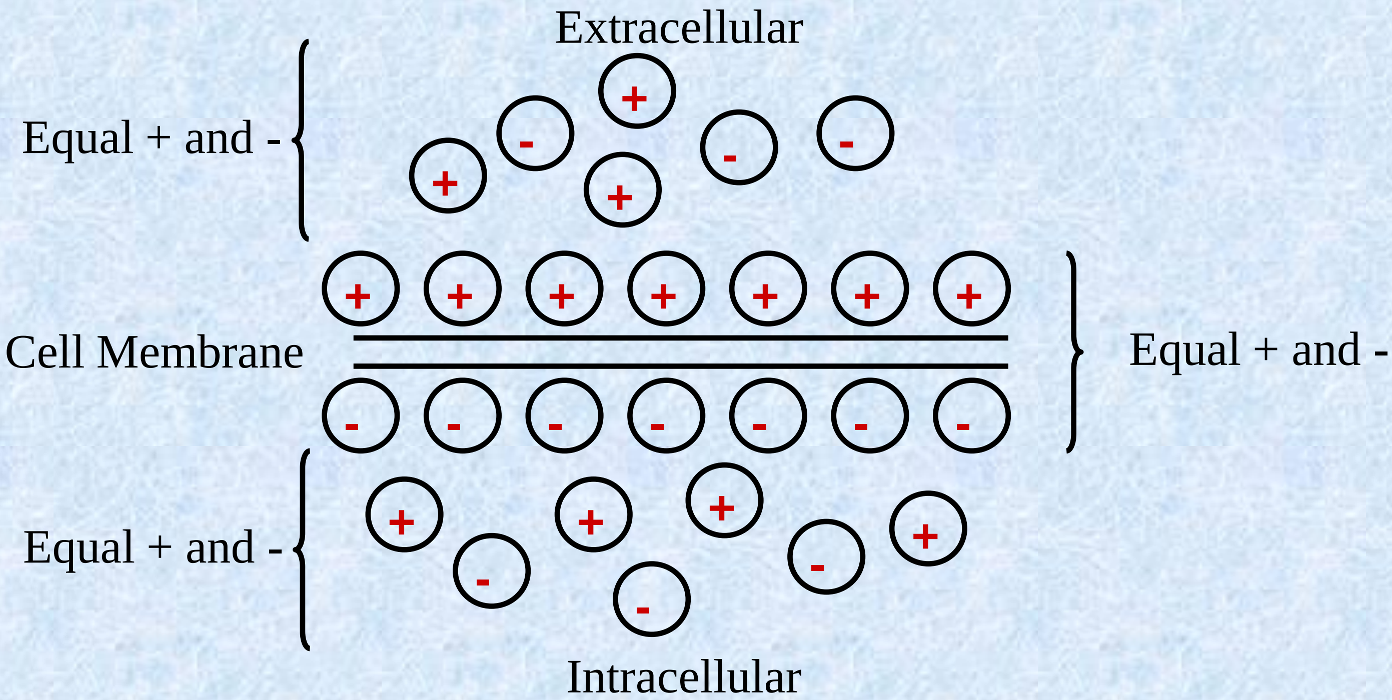
Neuro-terminology



Membrane potential: the voltage difference caused by charge separation across the membrane $V_m = V_{in} - V_{out}$

Resting membrane potential: membrane potential when there is no input to the cell

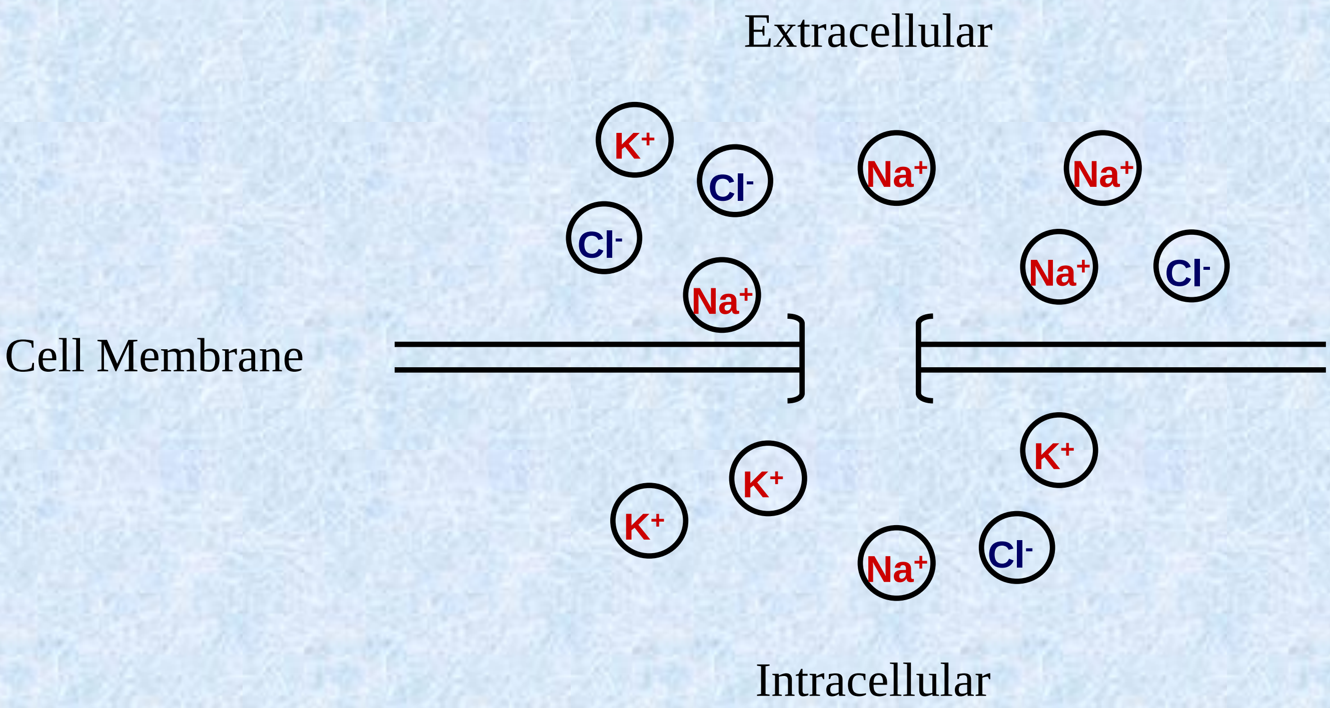
Neuro-terminology



Depolarization: increase in membrane potential due to influx of + ions in the cell (membrane becomes less polarized)

Hyperpolarization: decrease in membrane potential due to efflux of + ions from the cell (membrane becomes more polarized)

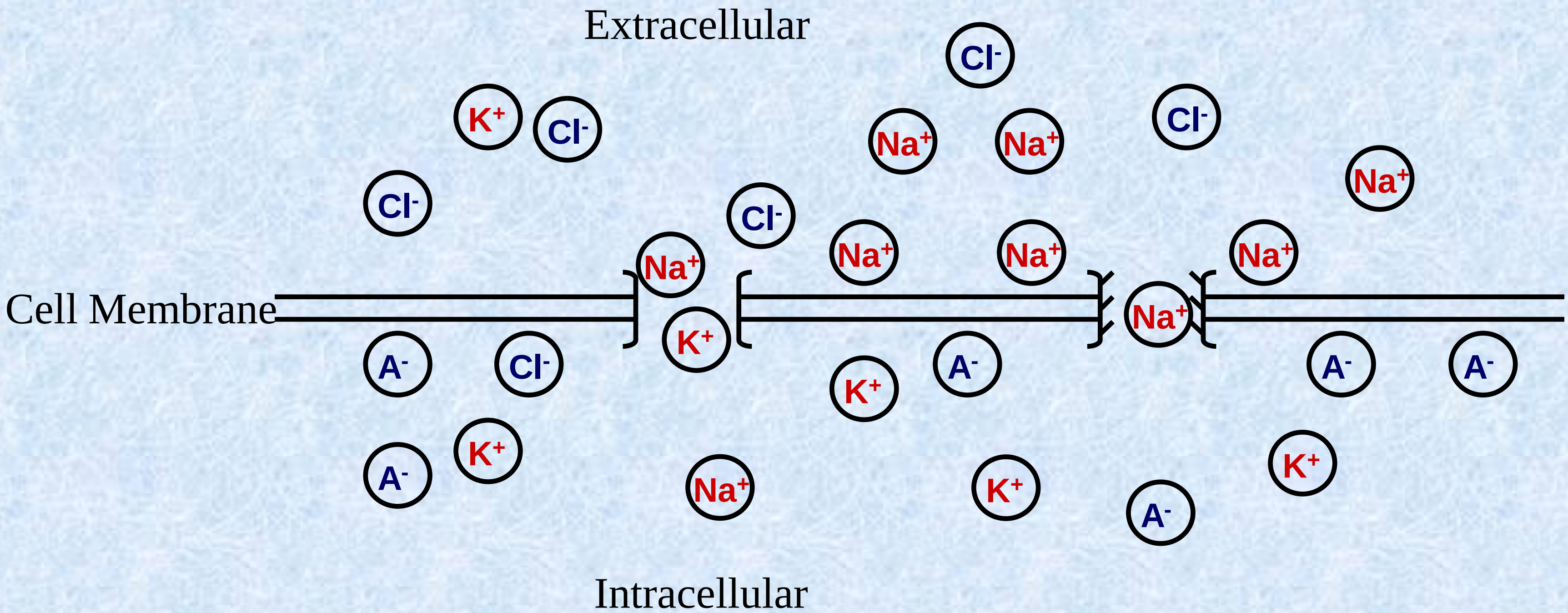
Passive Ion Channels



Non-gated (passive) ion channels are channels with fixed permeability for specific ions

These channels are also called leak channels and determine resting potential and membrane time constant

A Neuron at Rest



Inside: Potassium (+) and large proteins (-)

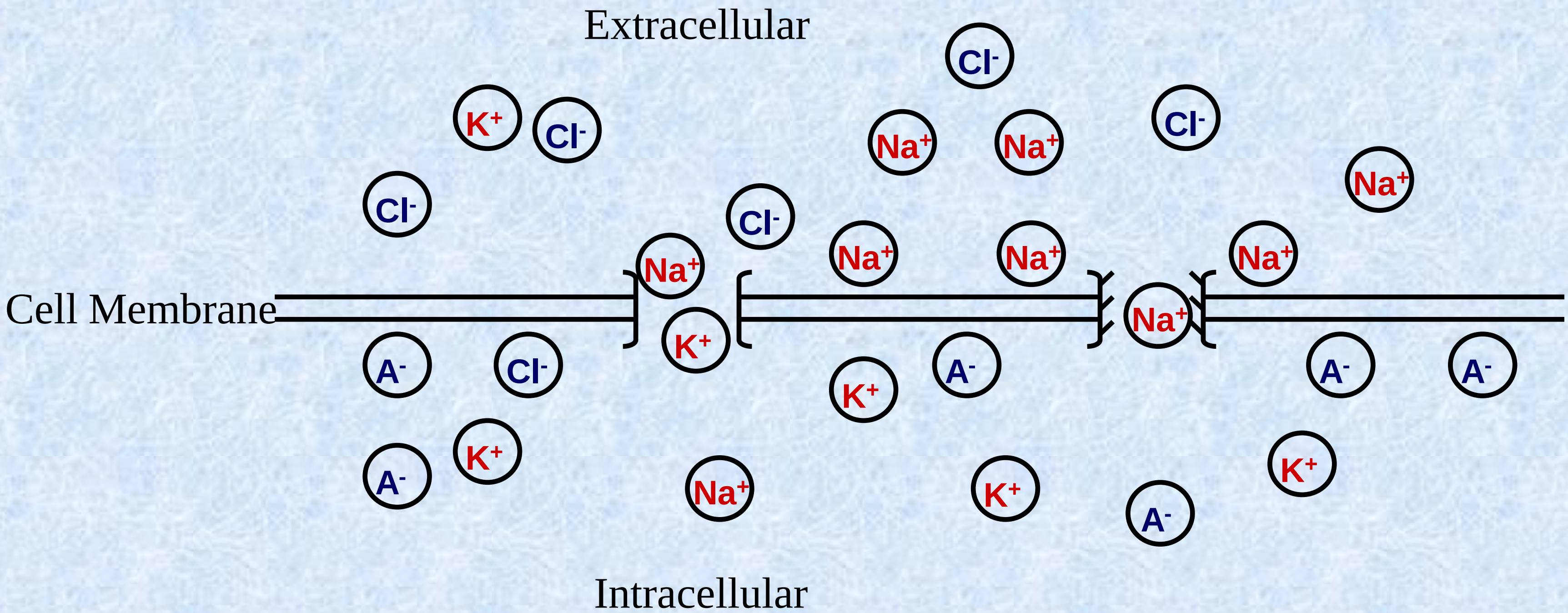
Outside: Sodium (+) and Chloride (-)

Na+: Voltage drives positive ions in, but Na pump removes sodium out of the cell

A-: Proteins are too large to pass through channels

Net effect – negative membrane potential

A Neuron at Rest

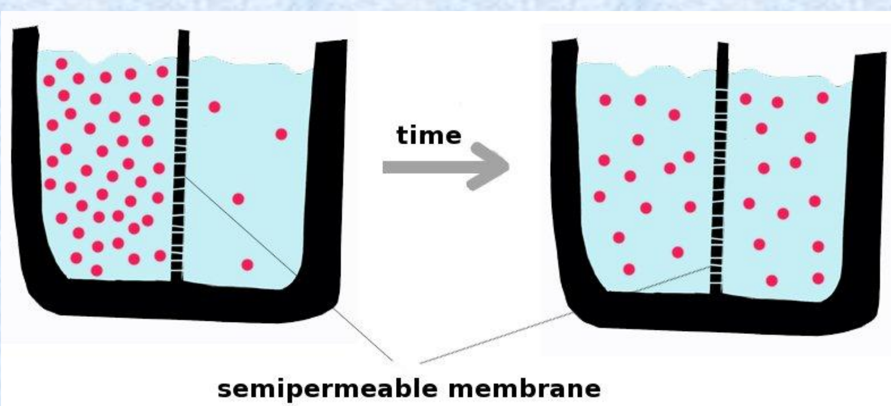


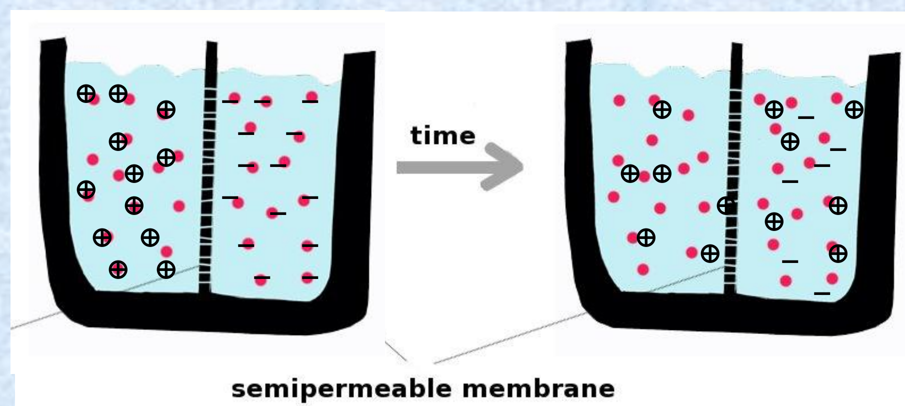
Potassium and chloride move freely in and out of the cell under two forces

Two Opposing Forces

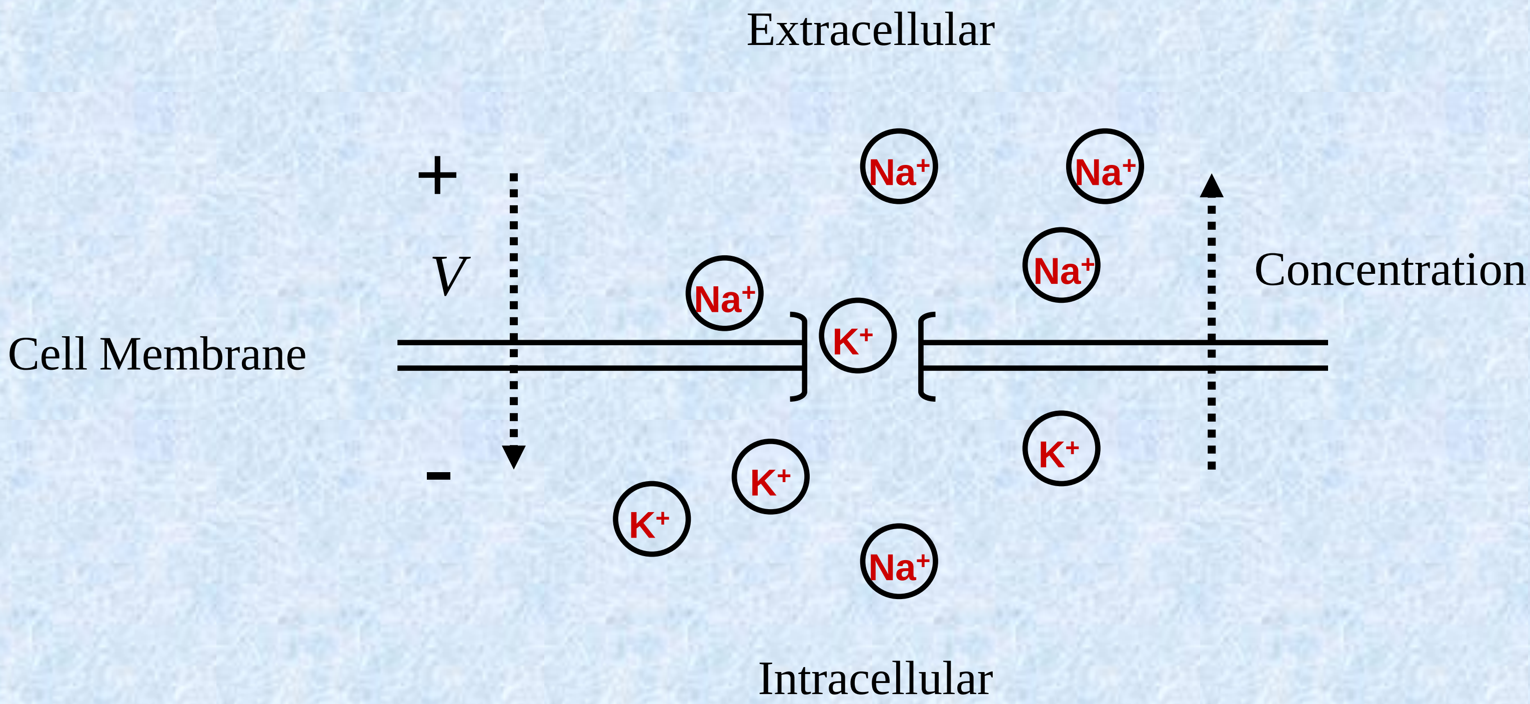
Potassium is forced into the cell (chloride out of the cell) by the voltage gradient

They are also affected by concentration gradient, which forces potassium out of the cell and chloride into the cell





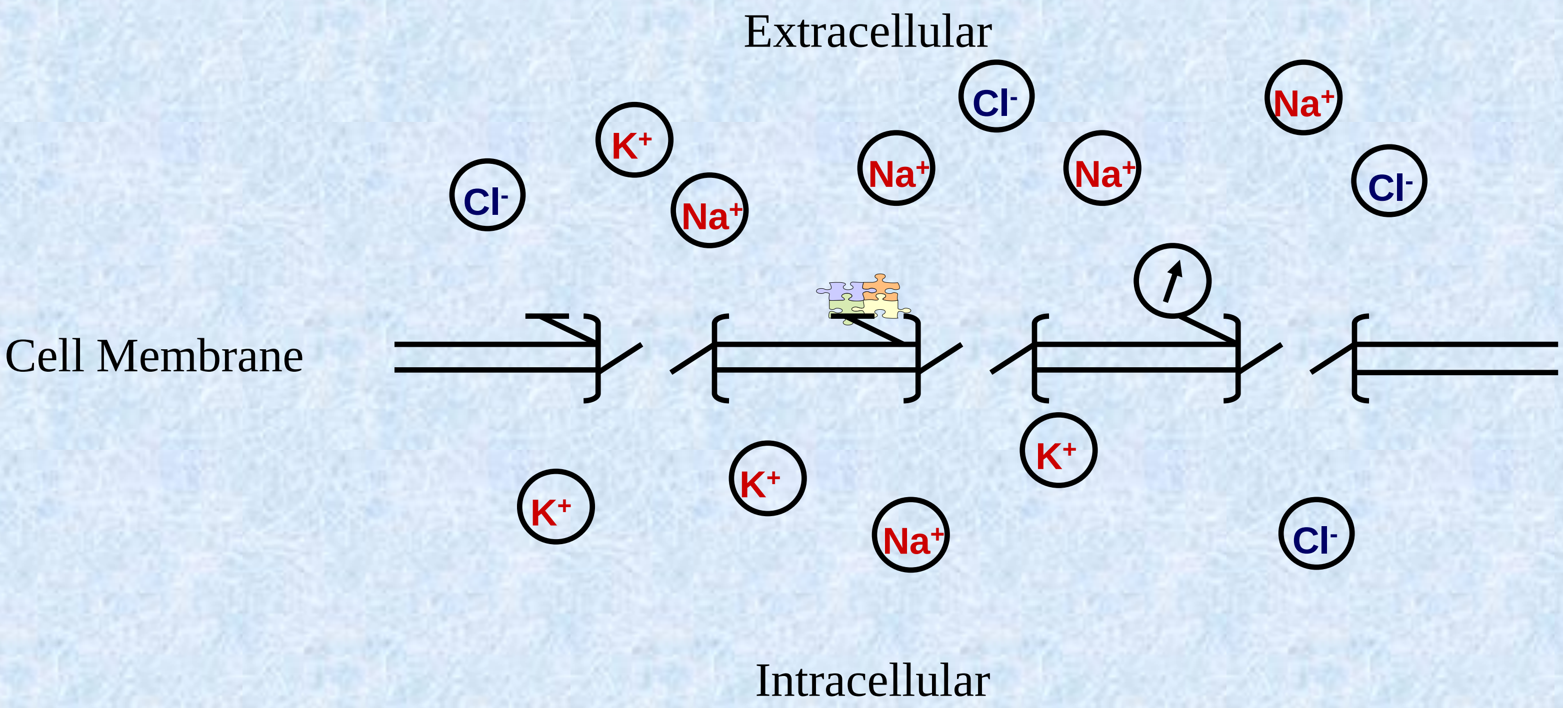
Nernst Potential



The potential that exactly balances the concentration gradient so that there is no net current of the specific ion is called Nernst potential or equilibrium potential for this ion

Notation: E_K, E_{Na}, E_{Cl}

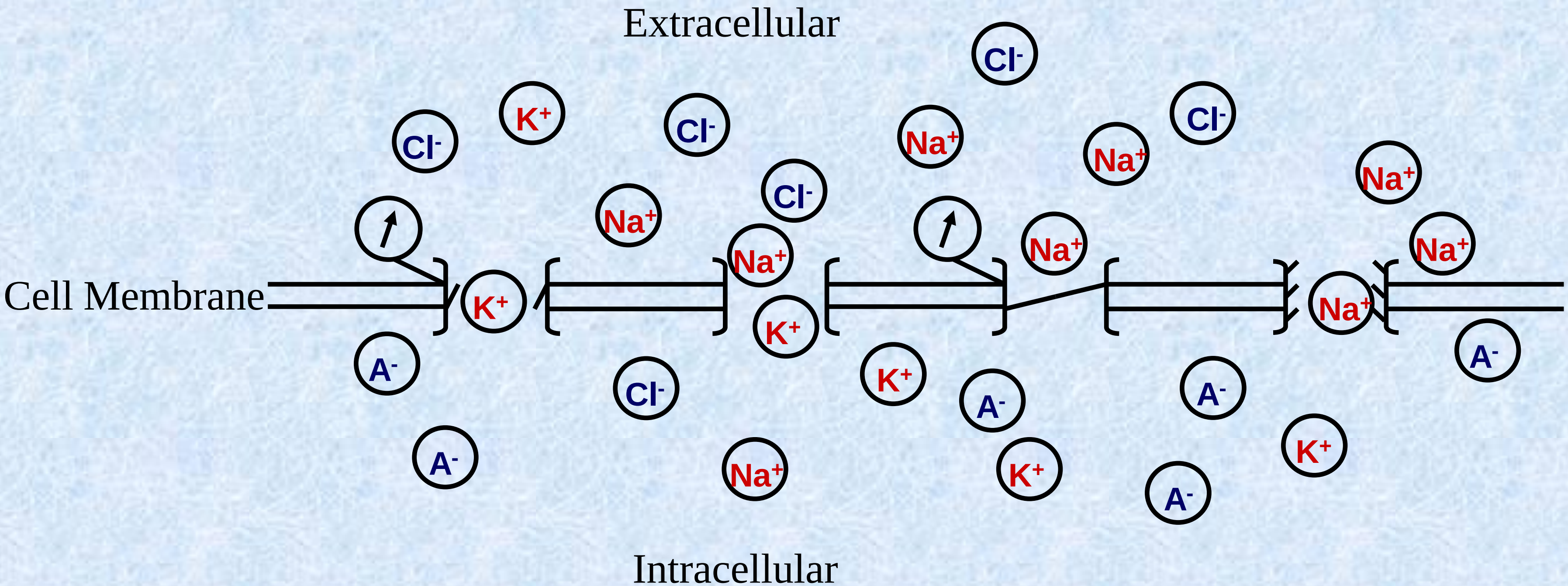
Gated Ion Channels



Gated channels can be opened by

- Mechanical stimulation: e.g. pressure receptors
- Chemical bond: most of synaptic channels and Ca activated channels
- Voltage: e.g. Hodgkin-Huxley sodium and potassium channels

A Neuron at Rest



Sodium voltage-gated channels are closed at resting potential

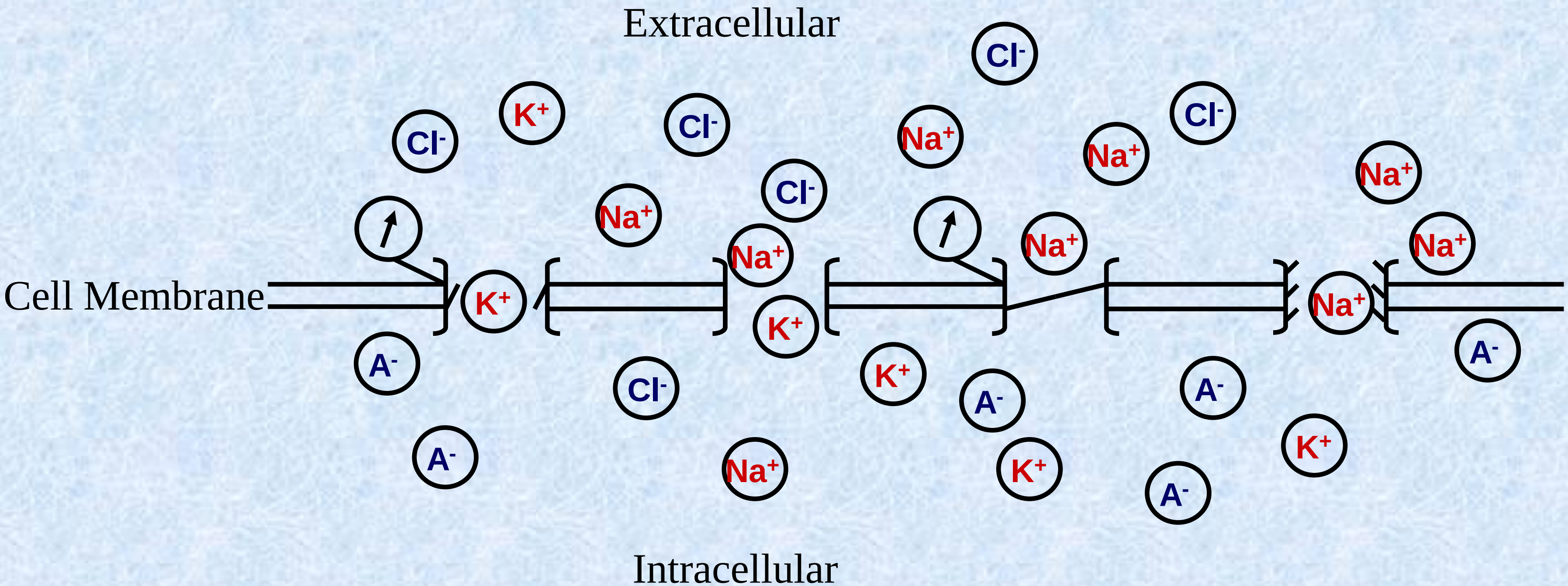
Potassium voltage-gated channels are partially open

Sodium, potassium, and chloride move through leakage channels

Potassium also moves through voltage-gated channels

Sodium is also pumped out by a sodium pump

Static vs Dynamic Equilibrium



Without sodium pump neuron would achieve static equilibrium when all currents across membrane are 0

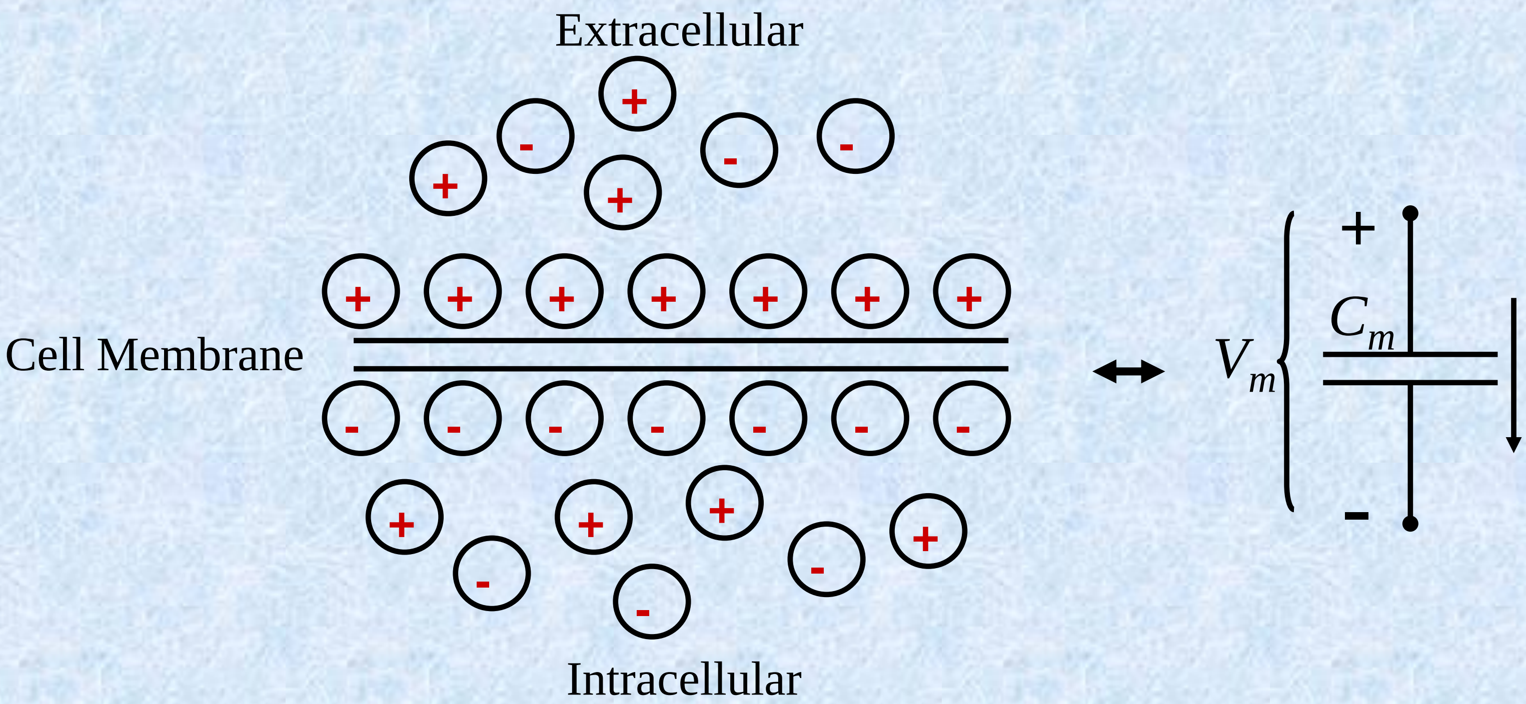
With the pump static equilibrium is impossible, there are non-zero currents that compensate for the current created by the pump, thus the equilibrium is dynamic

Parameters of the system favor oscillations in response to disturbance

What Else?

- E_K=*-80mV*, V_r=*-60mV*, so there is not enough voltage to compensate for concentration gradient, and some potassium is pushed out
- Potassium pump counteracts this efflux by sucking potassium into the cell
- Some cells also have chloride pumps
- Driving energy for all of these pumps comes from hydrolysis of ATP
- Opening extra sodium channels will push sodium in and depolarize the cell
- Opening extra potassium channels will push potassium out and hyperpolarize the cell
- Control over these channels allows producing large changes in the membrane potential with small manipulations

Equivalent Electrical Circuit for Cell Membrane

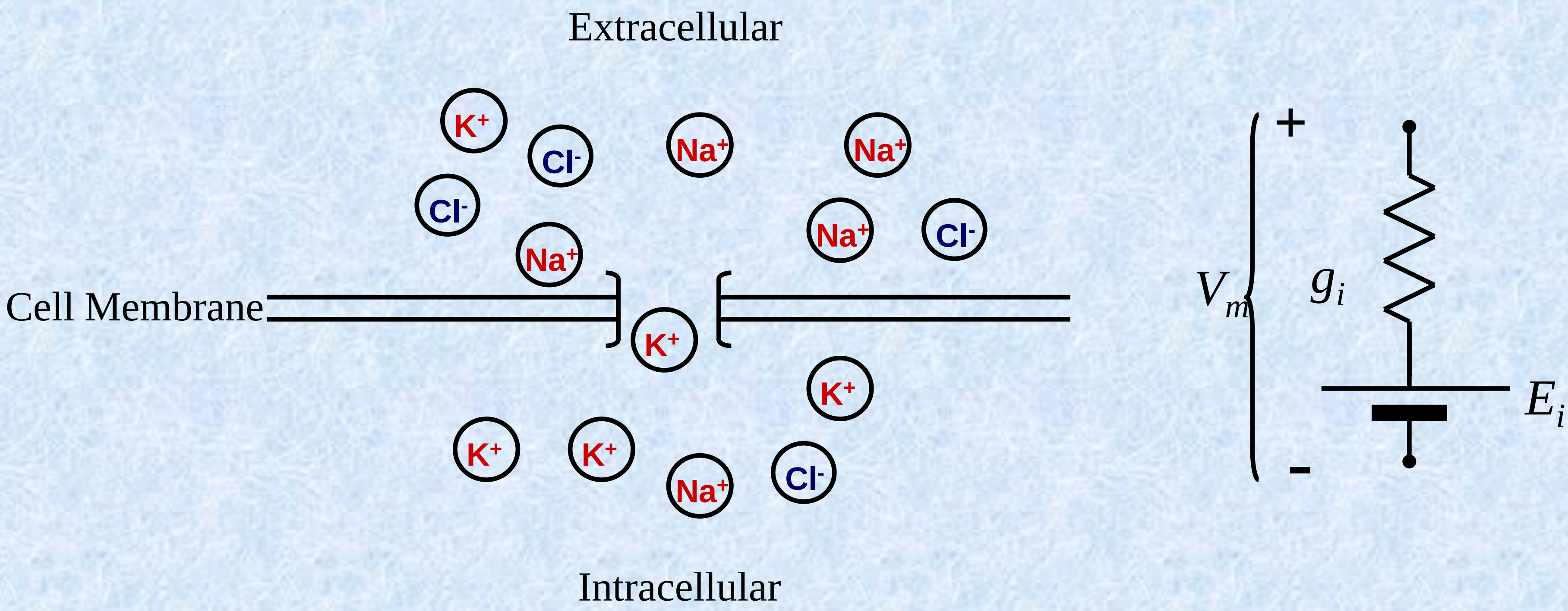


$$I = C_m \frac{dV_m}{dt}$$

Portions of membrane without channels are equivalent to the capacitor

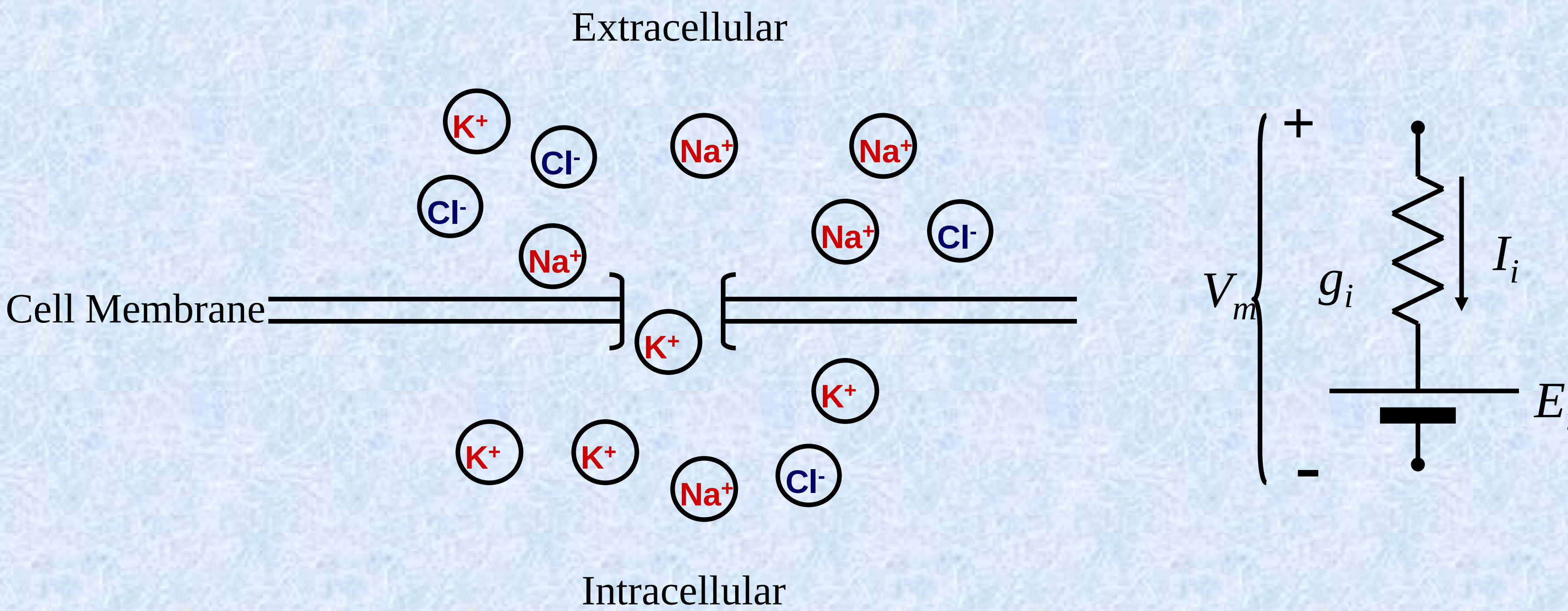
C_m is membrane capacitance V_m is membrane potential

Equivalent Electrical Circuit for Cell Membrane



Concentration gradient can be interpreted as a battery, which would set membrane potential to E_i if there are no currents across the membrane ($V_m = E_i$)

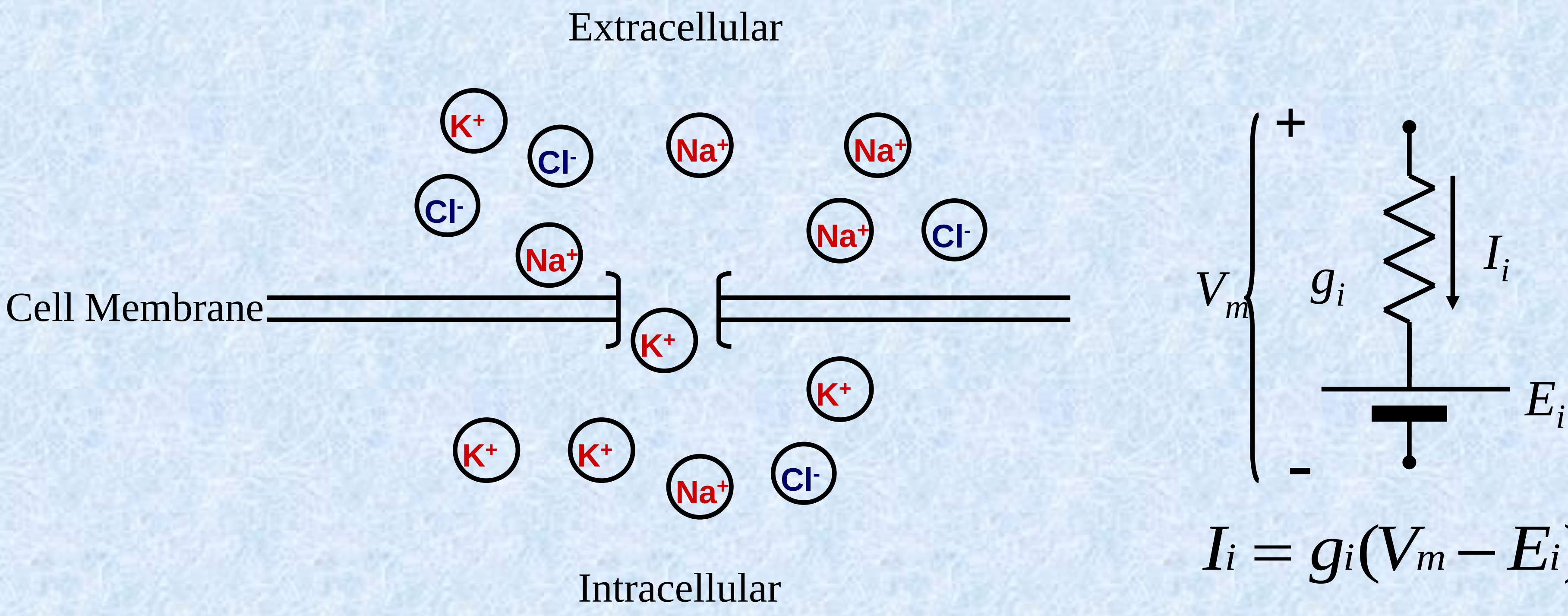
Equivalent Electrical Circuit for Cell Membrane



If there is current through the channel it will follow Ohm's law $I_i = g_i V_i$

The potential across resistor V_i is the difference $V_m - E_i$

Equivalent Electrical Circuit for Cell Membrane



$$I_i = g_i(V_m - E_i)$$

Thus, passive channel is equivalent to a constant conductance element (resistor) plus a battery defined by the Nernst potential of the respective ion

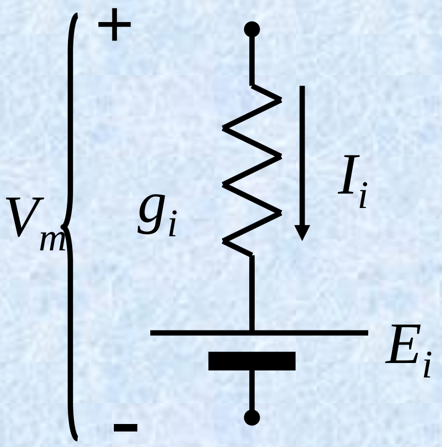
Making Sense out of Equivalent Circuit

$E_i = V_m$ => $I_i = 0$, makes sense since concentration gradient is balanced by membrane voltage

$E_i < V_m$ => $I_i > 0$ current is inhibitory, sucking negative ions in and pushing positive ions out

$E_i > V_m$ => $I_i < 0$ current is excitatory, thus sucking positive ions inside and pushing negative ions out. Makes sense: cell is so inhibited, that current becomes excitatory

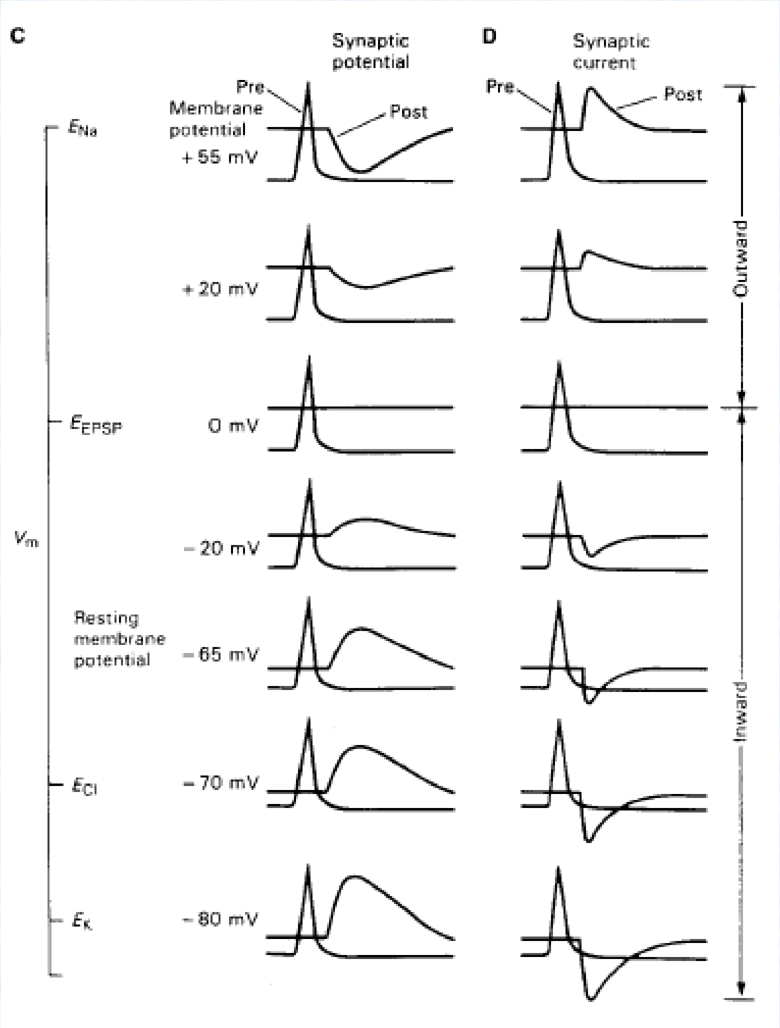
This reversal of a current (and its action) leads to the term "reverse potential"



$$I_i = g_i(V_m - E_i)$$

Reversal Potential

- In the example synapse, the membrane potential of the cell is driven toward 0 mV
- The potential E_{EPSP} is called the reversal potential because the excitatory/inhibitory effect is reversed when the membrane potential crosses E_{EPSP}
- Thus, the effect of an "excitatory" synapse is really only excitatory if V_m is below the reversal potential for that synapse

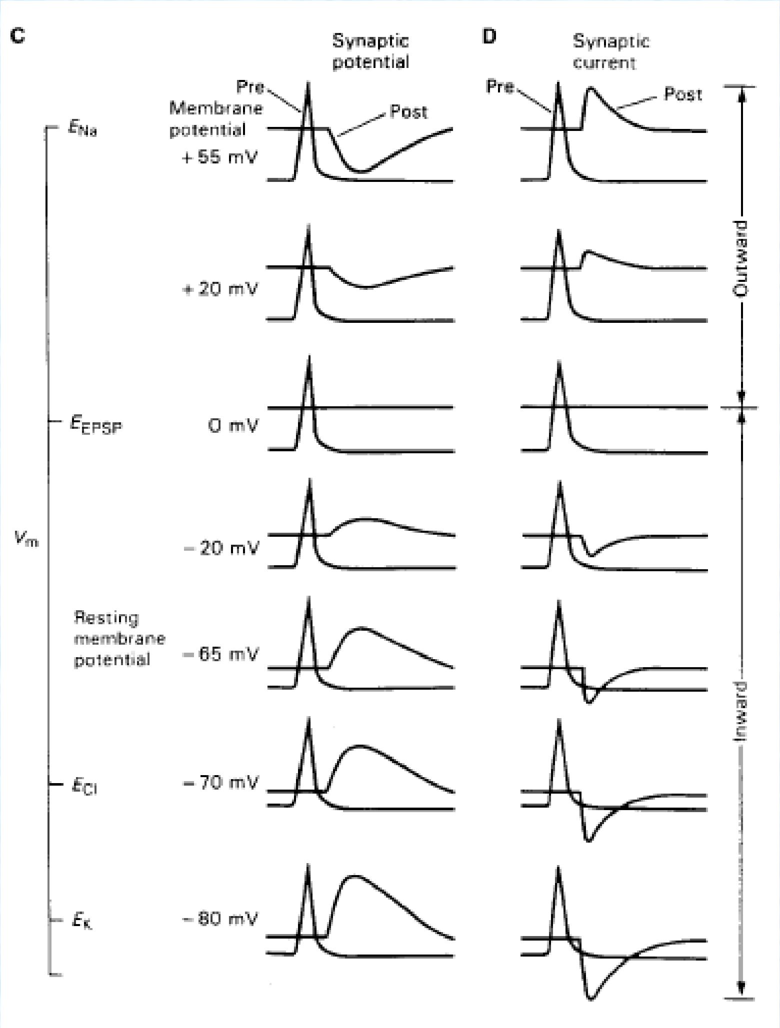


Reversal Potential

For a typical excitatory synapse, however, the reversal potential is above the threshold for voltage-gated ion channels

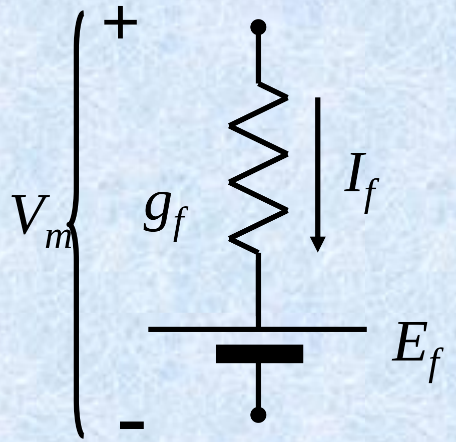
When V_m rises just above this threshold, the voltage-gated channels "take over" and an action potential is generated

Thus in normal conditions the state with V_m above reversal potential is not achievable and the channel remains purely excitatory



Reverse Potential and Polarity of the Battery

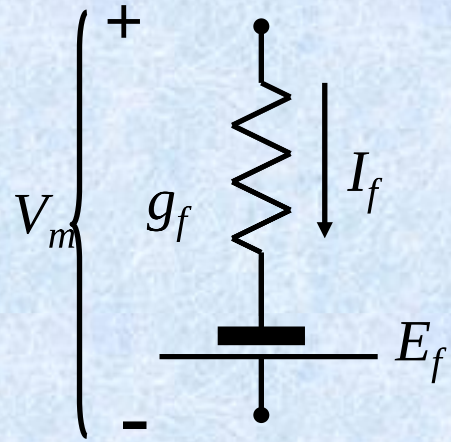
The reverse potential is negative



$$I_f = g_f(V_m + E_f)$$

$$I_f = g_f(V_m - (-E_f))$$

The reverse potential is positive



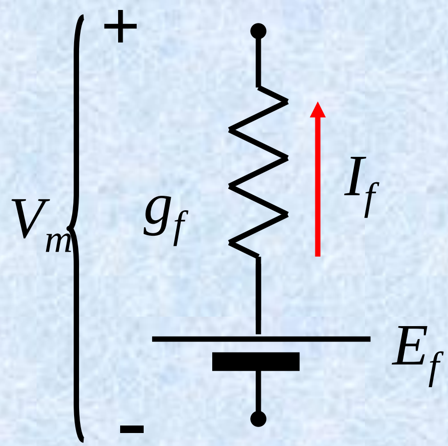
$$I_f = g_f(V_m - E_f)$$

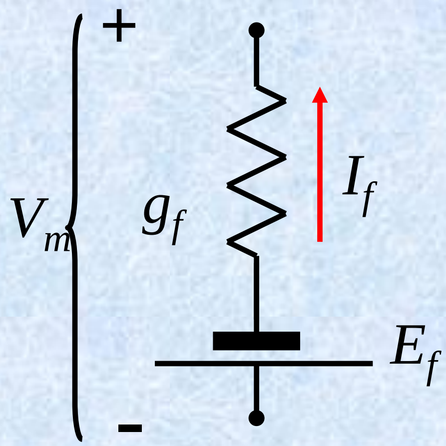
Negative battery corresponds to a positive battery plugged in upside-down

In the left circuit the battery polarity is flipped, the sign of E_f is flipped to maintain correctness ($-E_f$ is negative = r. p.)

Current Direction

The reverse potential is negative   The reverse potential is positive





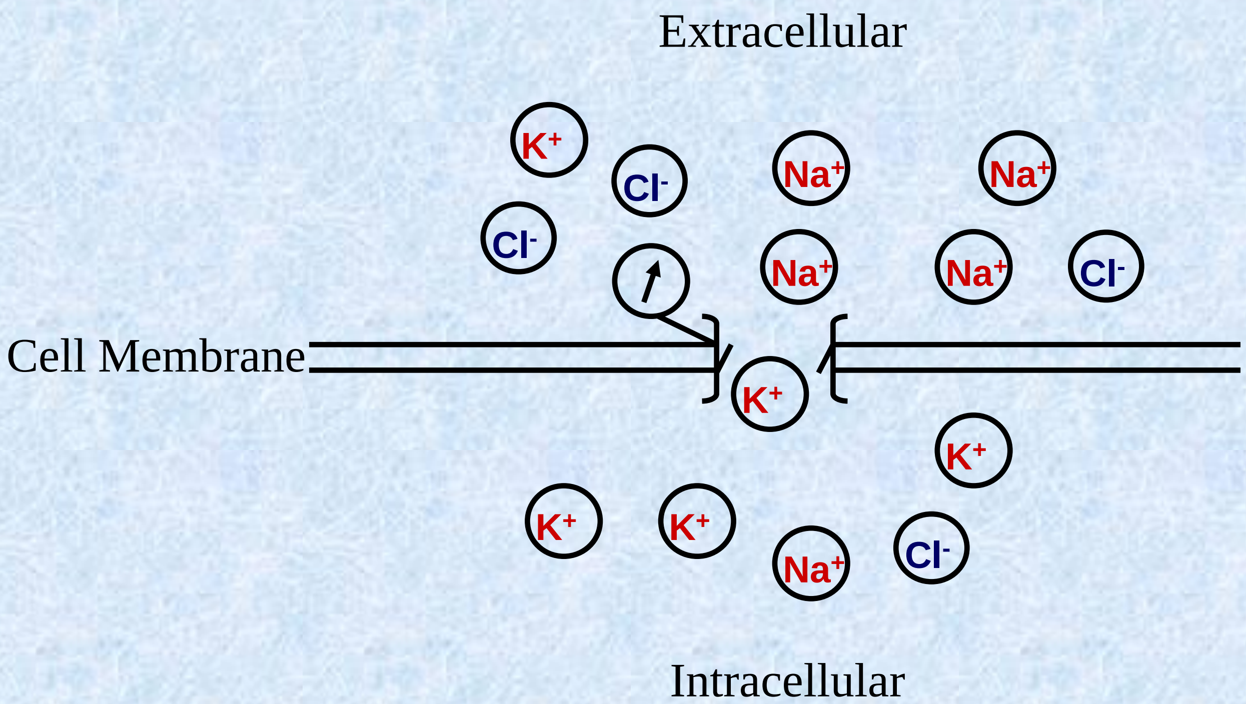
$$I_f = g_f((-E_f) - V_m)$$

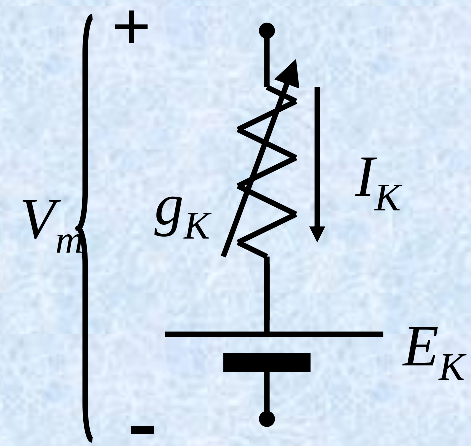
$$I_f = g_f(E_f - V_m)$$

We can flips the sign of all currents

This way positive currents are excitatory: on the left current is negative and inhibitory, on the right – positive and excitatory

Equivalent Electrical Circuit for Cell Membrane

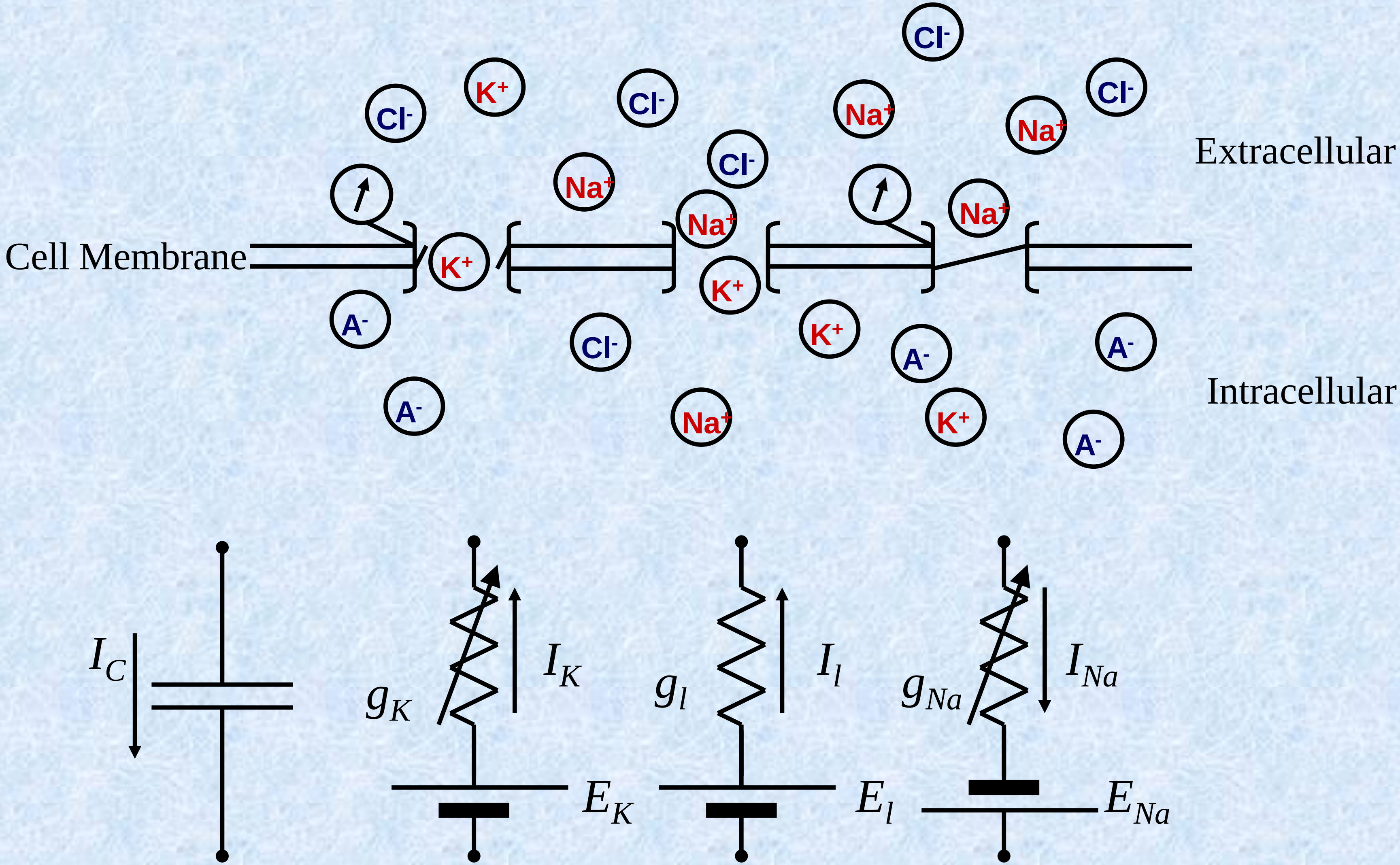




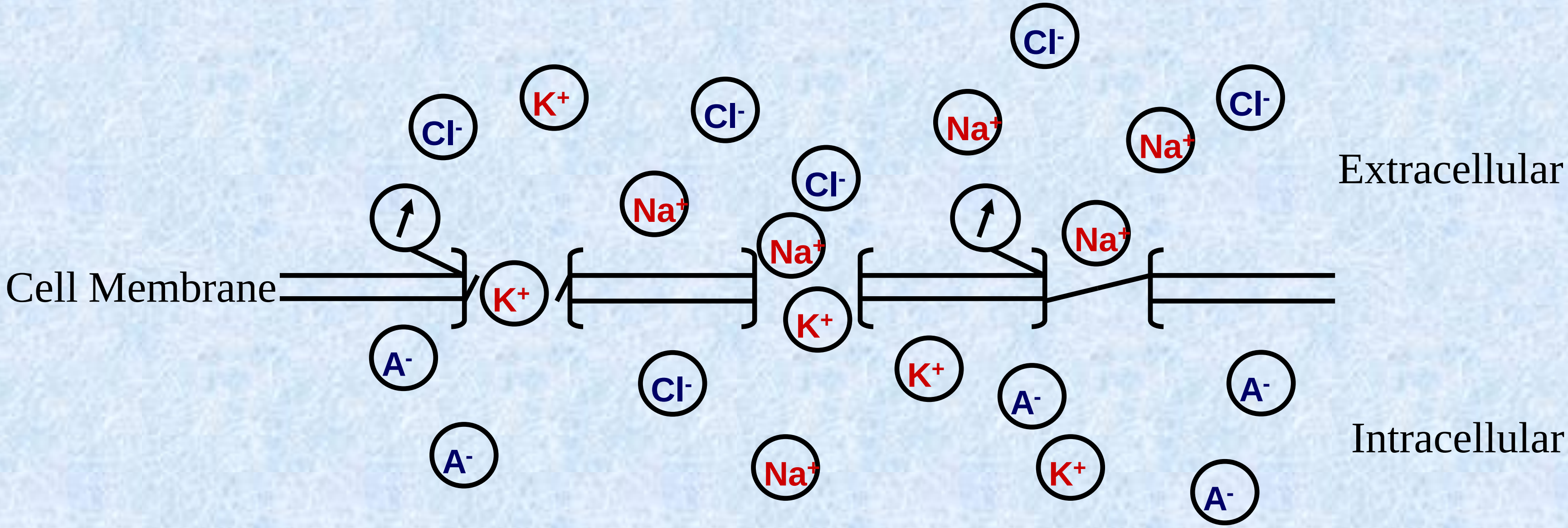
$$I_K = g_K(V_m - E_K)$$

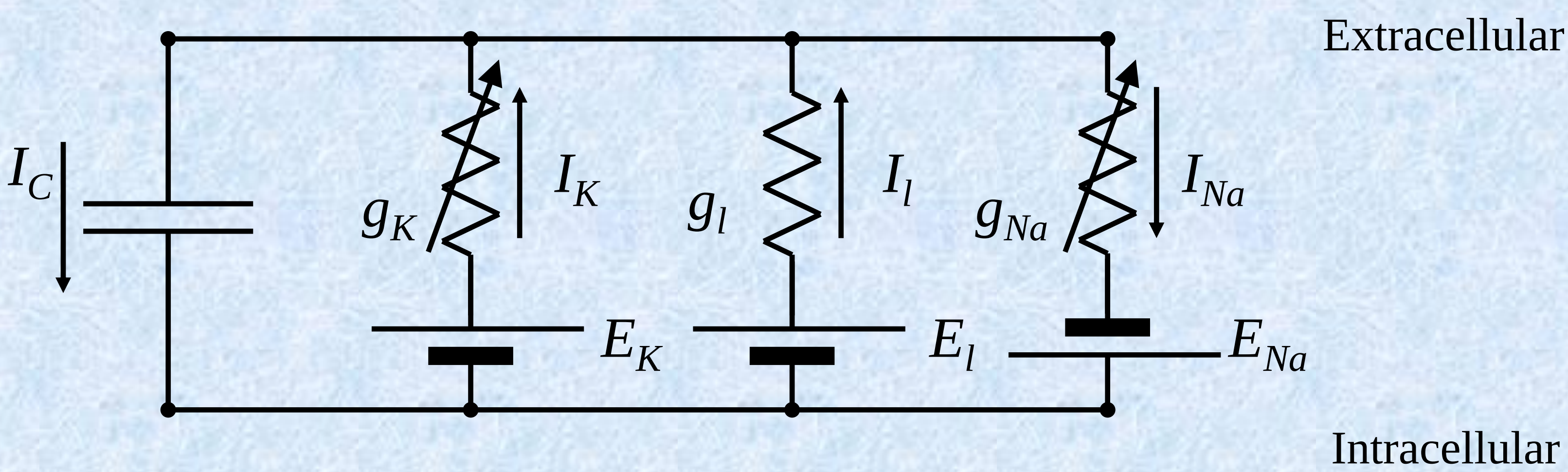
Gated channel is equivalent to an adjustable conductance element (variable resistor) plus a battery defined by the Nernst potential of the respective ion

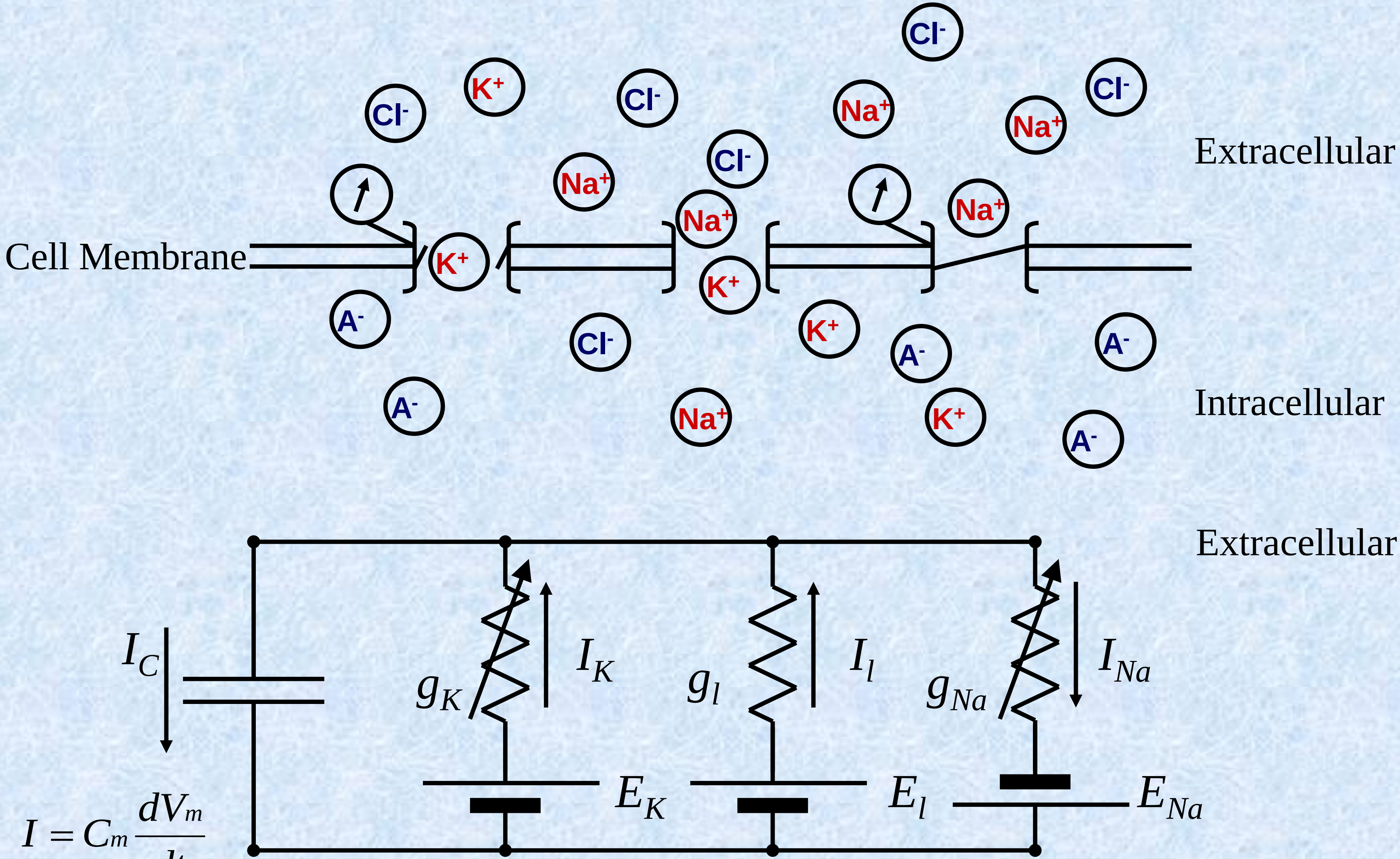
$g_K=f(V_m)$ for voltage gated channel



Extracellular
Cell Membrane
Intracellular
Cl-
K+
Na+
A-
I_C
g_K
I_K
g_l
I_l
g_{Na}
I_{Na}
E_K
E_l
E_{Na}


Extracellular
Cell Membrane
Intracellular
Cl-
K+
Na+
A-


Extracellular
I_C
g_K
I_K
g_l
I_l
g_{Na}
I_{Na}
E_K
E_l
E_{Na}
Intracellular



$$I = C_m \frac{dV_m}{dt}$$

$$I_l = g_l(V_m - E_l)$$

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

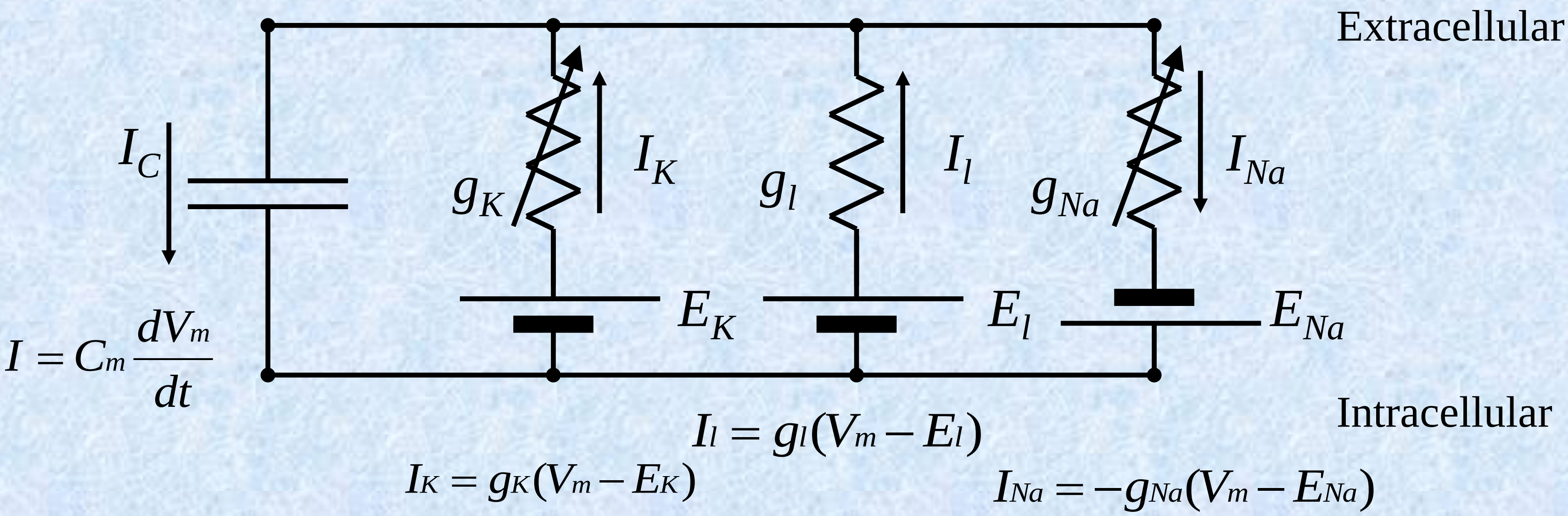
$$I_{Na} = -g_{Na}(V_m - E_{Na})$$

Finally bring it all together by using Kirchhoff current law: sum of all currents through a point is equal 0

$$0 = -C_m \frac{dV}{dt} + g_K(V_m - E_K) + g_l(V_m - E_l) - (-g_{Na}(V_m - E_{Na}))$$

Or recombining the terms

$$\boxed{C_m \frac{dV}{dt} = g_K(V_m - E_K) + g_l(V_m - E_l) + g_{Na}(V_m - E_{Na})}$$



Generalization and Some Important Points

We can expand the circuit to arbitrary number of currents, that is what simulation packages do $C_m \frac{dV}{dt} = \sum I$

We have to remember our units $C_m[\mu F]\frac{dV[mV]}{dt[ms]} = \sum I[\mu A]$

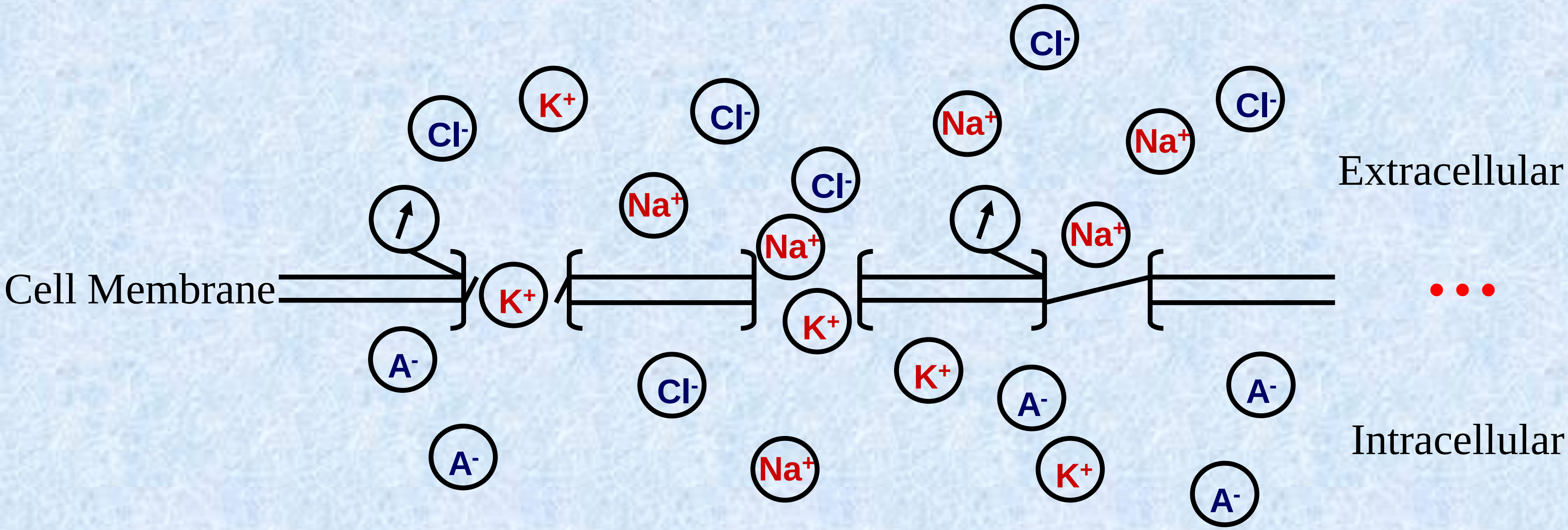
Often the parameters we are using are recorded as relative to membrane area e.g. $C_M[\mu F/cm^2]$, $g_l[mS/cm^2]$. To simplify modeling we can divide

$$C_m \frac{dV}{dt} = g_K(V_m - E_K) + g_l(V_m - E_l) + g_{Na}(V_m - E_{Na})$$

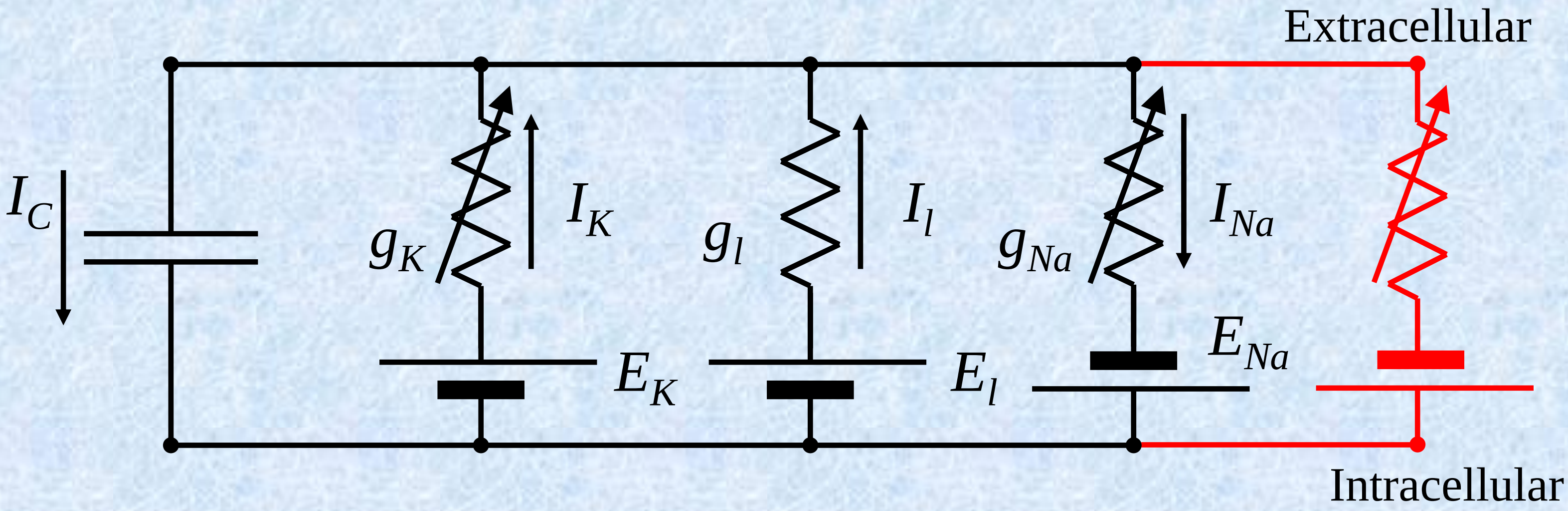
by the membrane area

$$C_M\left[\frac{\mu F}{cm^2}\right]\frac{dV}{dt}\left[\frac{mV}{ms}\right] = g_K\left[\frac{mS}{cm^2}\right](V_m - E_K)[mV] + \ldots$$

It is especially convenient since $C_M = 1\mu F/cm^2$ for most cells



$$C_m \frac{dV}{dt} = g_K(V_m - E_K) + g_l(V_m - E_l) + g_{Na}(V_m - E_{Na}) + \sum I$$

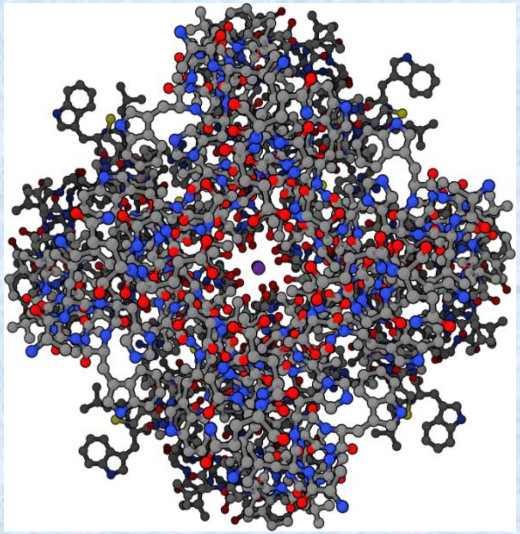


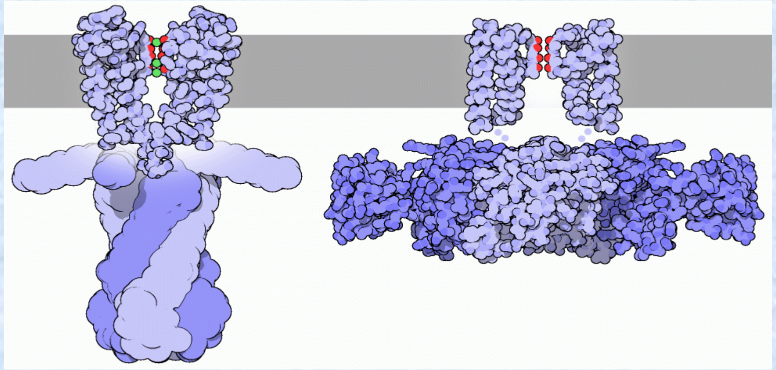
Conductance of the Channels

Individual channel can be either open or closed

Conductance is usually written as a product of:

- a maximal conductance when all channels are open $\bar{g}_i$ and
- a probability that the channel is open or the fraction of open channels $0<g_i(V_m,t,\ldots)<1$ sometimes called gating variable





Conductance of the Channels

For voltage gated channels we use some variation of HH formalism:

$$\frac{dg}{dt} = \alpha\left(1 - g\right) - \beta g$$

where $\alpha(V_m)$ is an opening rate function and $\beta(V_m)$ is a closing rate function

$$\alpha(V_m) = Ae^{\frac{B-V_m}{C}} \;\; or \;\; \frac{A - BV_m}{e^{C-DV_m} - 1} \;\; or \;\; \frac{1}{e^{A-BV_m} + 1}$$

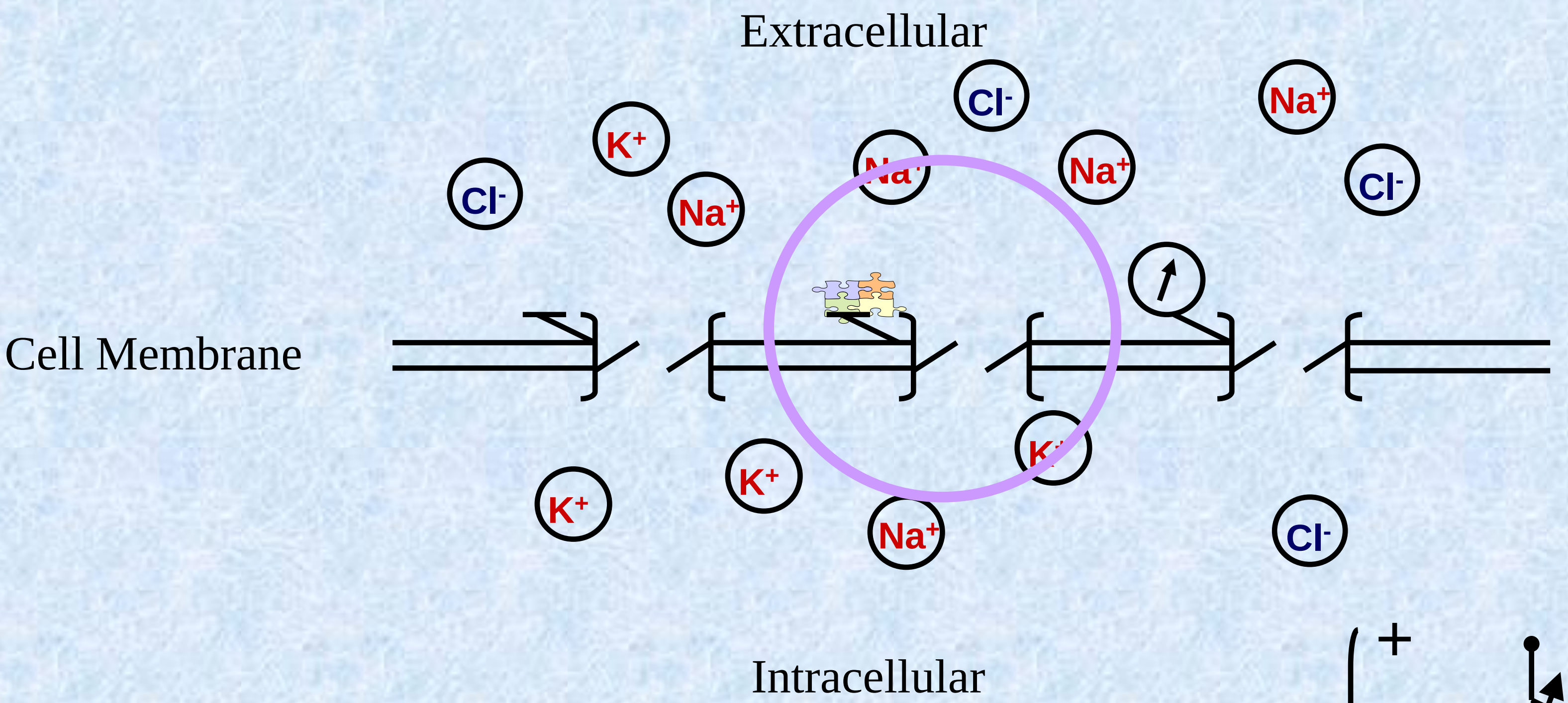
Note that for voltage gated channels the final form of conductance often involves power, e.g.

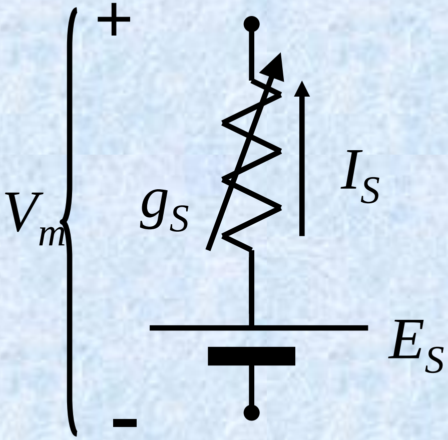
K $\quad \bar{g}_K n^4 \quad$ where n is calculated as g above

Na $\quad \bar{g}_{Na} m^3 h \quad$ where both m and h are calculated as above

Note that for Na m^3 denotes fast opening and h denotes slow closing, so the total gating is a joint probability of these two

Chemically Gated Ion Channels





Chemically gated synaptic channels are represented by the same equivalent circuit and formula as before

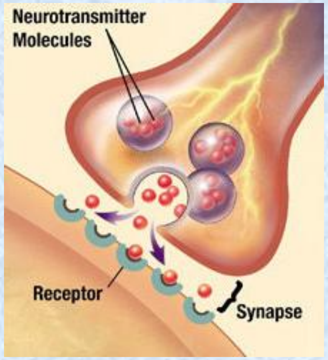
Conductance g_S depends on presynaptic activity

$$I_S = g_S(V_m - E_S)$$

Conductance of the Channels

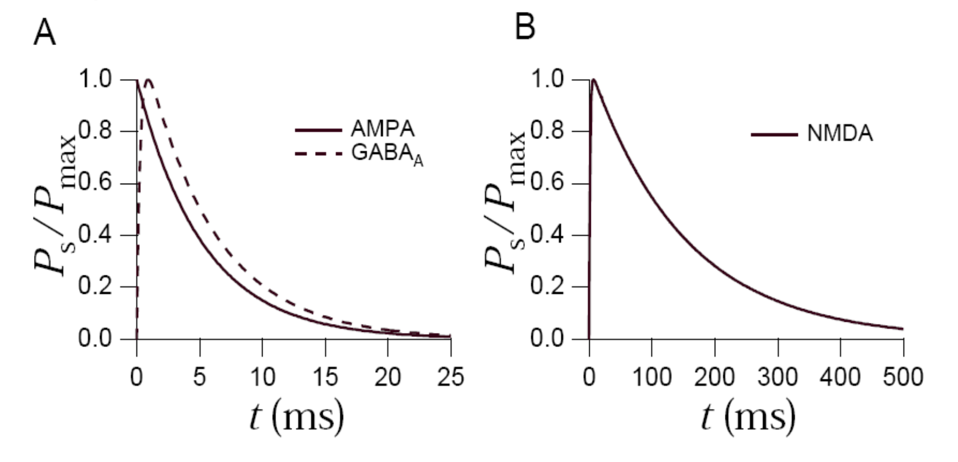
For synaptic channels we often use dual-exponential approximation:

$$g_i(t) = \begin{cases} \dfrac{p}{\tau_f - \tau_r}\left(e^{-\frac{t-t_s}{\tau_f}} - e^{-\frac{t-t_s}{\tau_r}}\right) & \text{if } \tau_f \neq \tau_r \\ \dfrac{t}{\tau_f} e^{1-\frac{t-t_s}{\tau_f}} & \text{otherwise} \end{cases}$$



so that

$$\max\left(\frac{p}{\tau_f - \tau_r}\left(e^{-\frac{t-t_s}{\tau_f}} - e^{-\frac{t-t_s}{\tau_r}}\right)\right) = 1$$

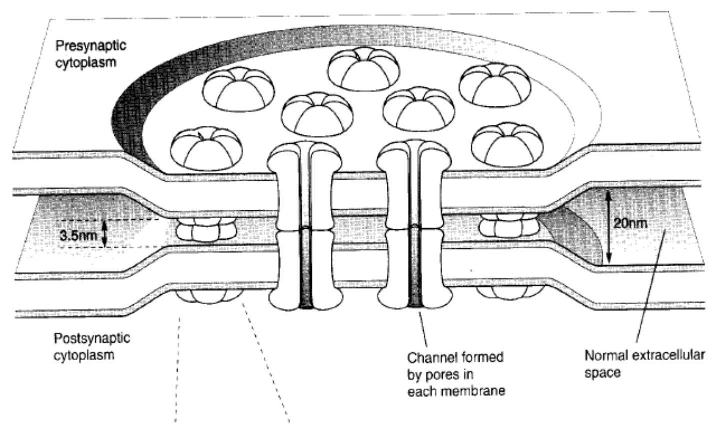


This is a solution for a critically damped pendulum

More precise model can use HH formalism with opening and closing functions matching experimental data

Gap Junctions or Electrical Synapses

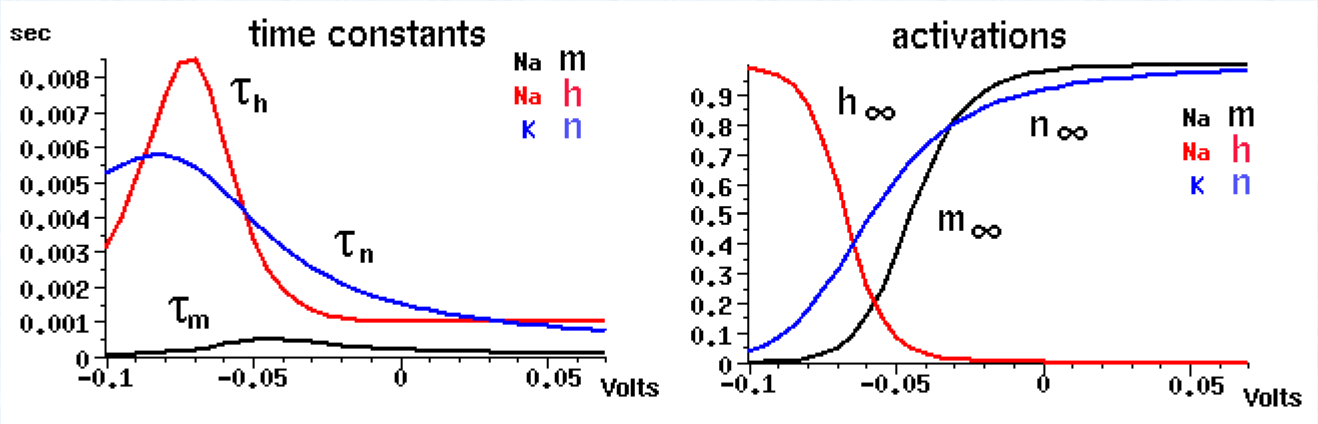
Another way to pass signal between two neurons is direct coupling, when a channel opens between two connected cells and ions pass directly from presynaptic to postsynaptic cell



These are usually modeled using some variation of diffusion equation, e.g. $I=g_j(V_{ms}-V_{mt})$

Remember that this conductance is not related to membrane area, so if you use it in the equation with relative conductances you need to divide it by cell area explicitly

Hodgkin Huxley Gatings



m is faster then *n* and *h*

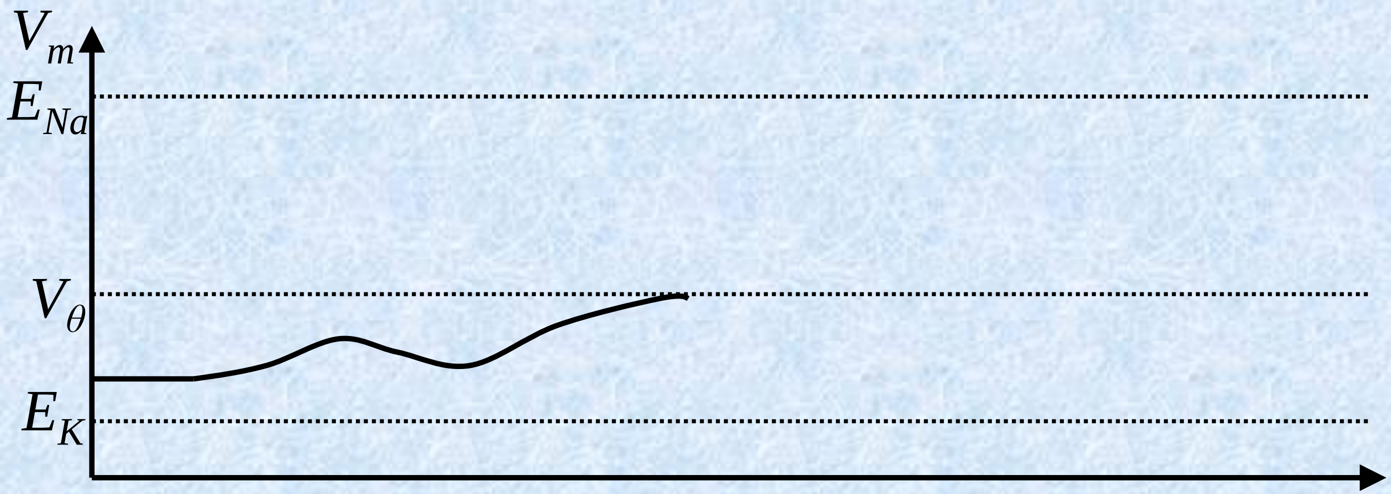
h is higher for hyperpolarized potentials, *m* and *n* are higher for depolarized potentials

If membrane potential goes up *m* increases fast, *n* increases slowly, *h* decreases slowly

So we have fast opening of Na channels followed by their slow closing and K channels opening

Generating Action Potential

- With the weak input there is a temporary increase in membrane potential
- Potential then returns to rest, often through several oscillations around resting potential
- Stronger input can bring the membrane potential to a threshold V_θ where sufficient number of voltage-gated Na channels open to continue depolarize the cell without further input

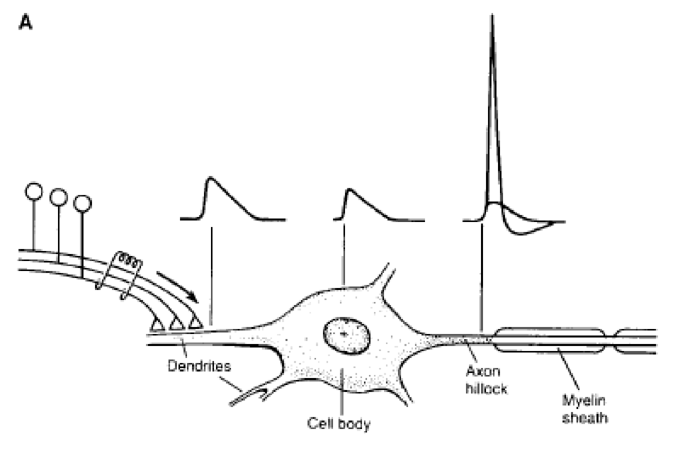


The Trigger Zone

Excitatory and inhibitory synaptic actions are combined at a low-threshold trigger zone at the axon hillock

Action potentials are generated for suprathreshold membrane potentials at the trigger zone

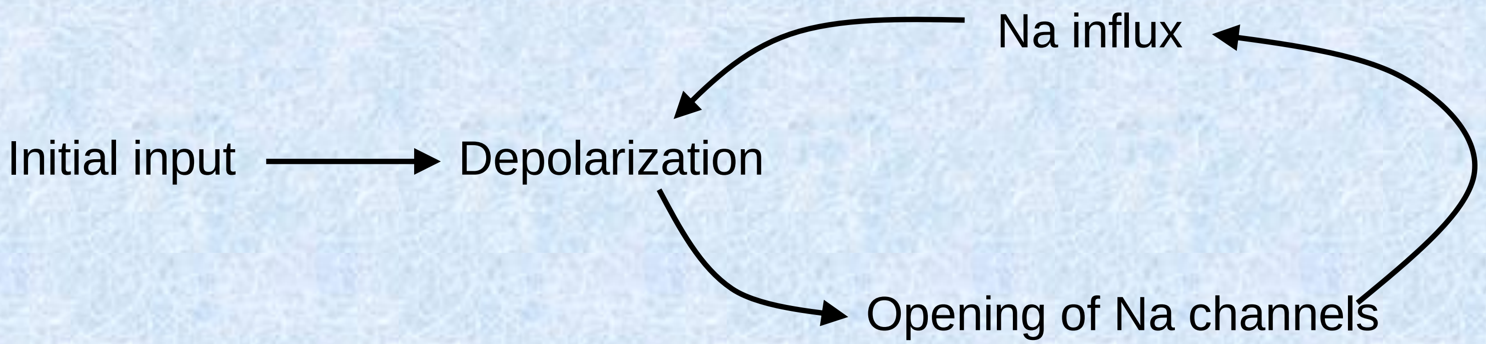
A postsynaptic potential is degraded as it travels from the synapse to the trigger zone

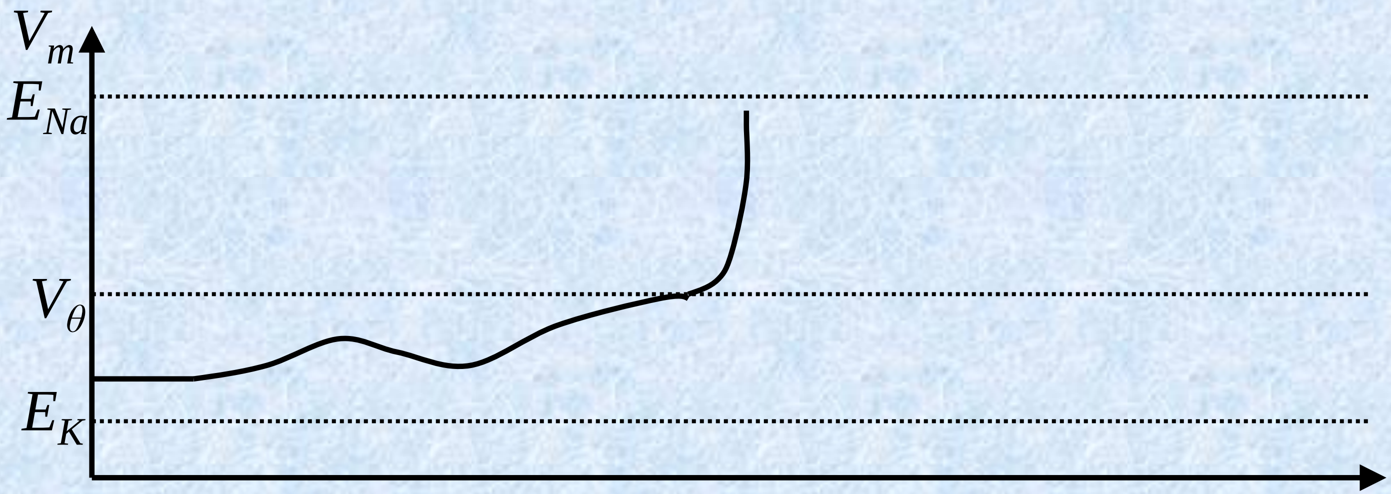


Proximity of a synapse to the trigger zone is therefore one determinant of its efficacy in causing a postsynaptic action potential

Generating Action Potential

Influx of positive Na ions further depolarizes the cell and creates a positive feedback loop



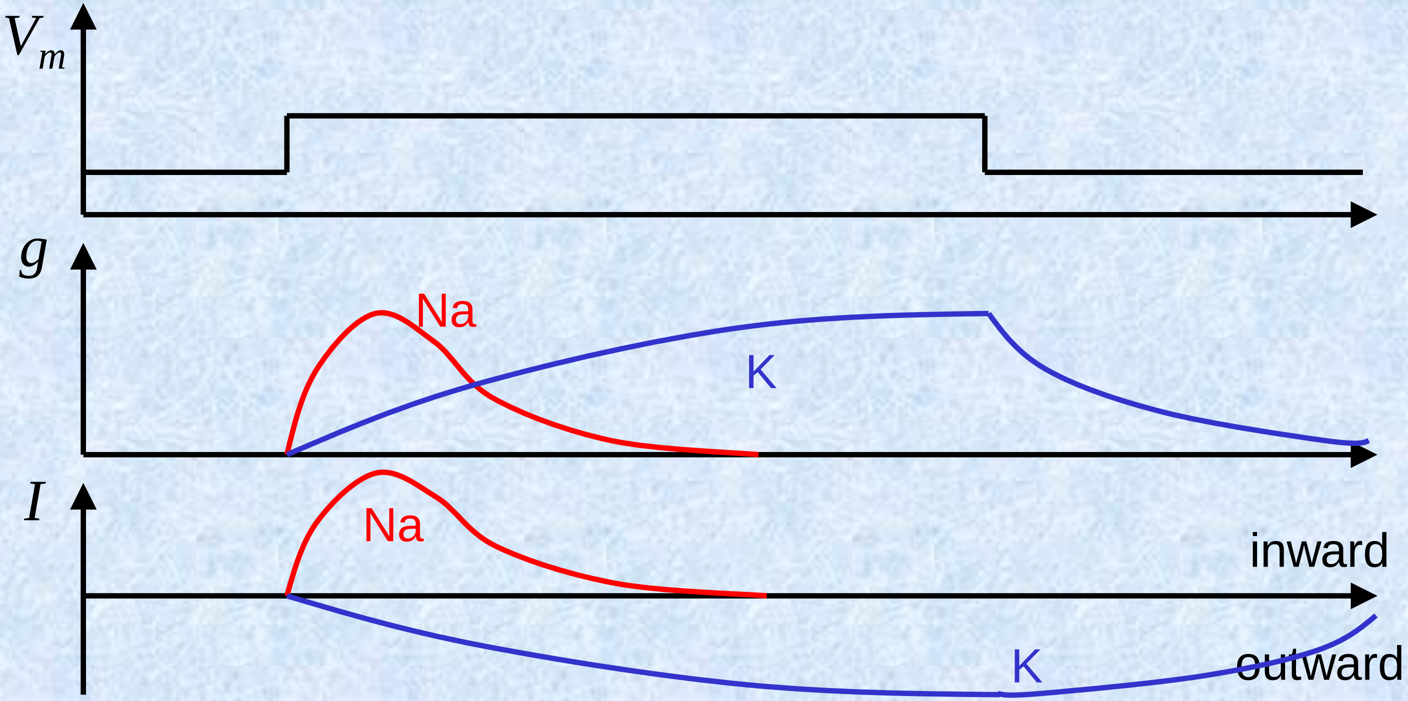


In addition to fast opening of the Na channels the increase of membrane potential causes:

Slow closing of the same voltage gated Na channels

Slow opening of the K voltage gated channels

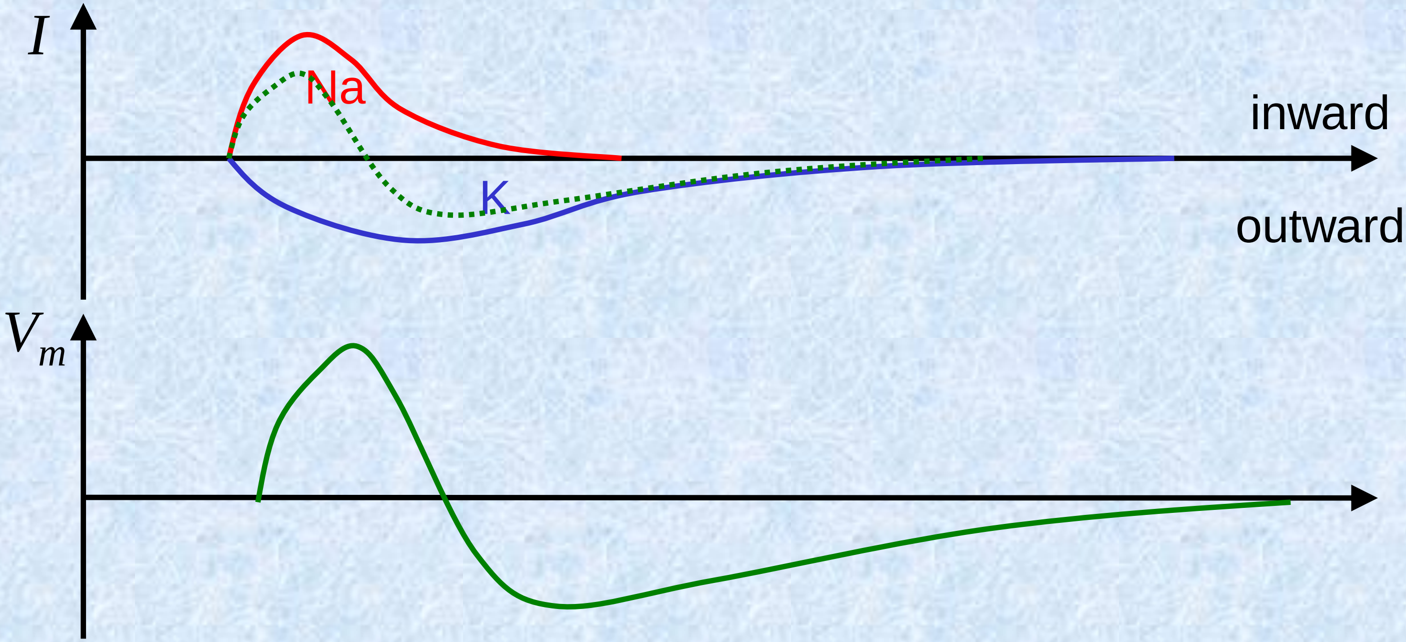
Illustrated below by providing voltage step to the cell



Net effect is fast transient inward current followed by an outward current

Potassium channels close slowly, so outward current leads to afterhyperpolarization

Note that fast upswing is caused by high Na concentration outside, and fast downswing by high K concentration inside



Action Potential Summary

Start with negative resting potential with high concentrations of Na outside and K inside

Cell gets depolarized by synaptic input, gap junction current, or release from inhibition

Membrane potential increase leads to opening of voltage-gated Na channels and strong Na influx depolarizes the cell almost to Na reverse potential

This Na current dies out due to reduction of voltage gradient and to eventual closing of Na channels

High membrane potential also leads to slower opening of K channels and efflux of K that hyperpolarizes the cell

This hyperpolarization persists for some time due to slow kinetics of K channels, but eventually wears off

Steady State Solutions

$$0 = C_m \frac{dV}{dt} = g_K(V_m - E_K) + g_l(V_m - E_l) + g_{Na}(V_m - E_{Na})$$

Rearranging the terms yields $V_m = \dfrac{g_K E_K + g_l E_l + g_{Na} E_{Na}}{g_K + g_l + g_{Na}}$

At rest g_l dominates, setting g_K and g_{Na} to 0 gives $V_m = E_l$

At the peak of action potential g_{Na} dominates, setting g_K and g_l to 0 gives $V_m = E_{Na}$

At the trough of hyperpolarization g_K dominates, setting g_l and g_{Na} to 0 gives $V_m = E_K$

Excitatory Synapses

Increasing the conductance of an ion (by opening channels) weights the ion's Nernst potential more heavily in the weighted average, thus moving the membrane potential toward the Nernst potential for that ion

So what is the effect of increasing the conductances of two ions (Na^+ and K^+)?

The potential toward which the membrane potential is driven, E_{EPSP}, will be a weighted average of the Nernst potentials of the two ions:

$$E_{EPSP} = \frac{g_K E_K + g_{Na} E_{Na}}{g_K + g_{Na}}$$

For the giant squid axon, $E_K = -75mV$, $E_{Na} = +55mV$

For a typical directly gated excitatory synapse $E_{EPSP} = 0mV$

Directly Gated Inhibitory Synapses

Most inhibitory directly-gated synapses act by opening Cl^- channels (increasing g_{Cl})

$$V_m = \frac{g_K E_K + g_{Cl} E_{Cl} + g_{Na} E_{Na}}{g_K + g_{Cl} + g_{Na}}$$

Weighting the average more toward E_{Cl} thus drives the membrane potential toward the Nernst potential for Cl^-

Because the Nernst potential for Cl^- (-60 mV) is approximately equal to the resting potential of a neuron, opening Cl^- channels will have

- an inhibitory effect if membrane potential is above the resting potential
- an excitatory effect if membrane potential is below the resting potential

This inhibition makes neuron ignore other inputs

Regarding Nernst Potentials

Given the concentrations of an ion on both sides of the cell membrane at rest, the Nernst potential is the membrane potential that would lead to zero net flux of the ion

We can calculate the Nernst potential of that ion using the Nernst equation:

$$E_{Na} = \frac{RT}{zF} \ln\left(\frac{[Na]_{out}}{[Na]_{in}} \right)$$

- where *R*, *z*, and *F* are constants, *T* is temperature, and *[]* denotes the ionic concentration

However: cell firing is mediated by changes in the ionic concentrations. Shouldn't this result in changes to the Nernst potentials?

Not really; the changes in concentrations during firing are negligible:

- e.g. the influx of Na required to change V_m from *-60mv* to *+55mv* constitutes only a 0.012% change in Na concentration inside the cell

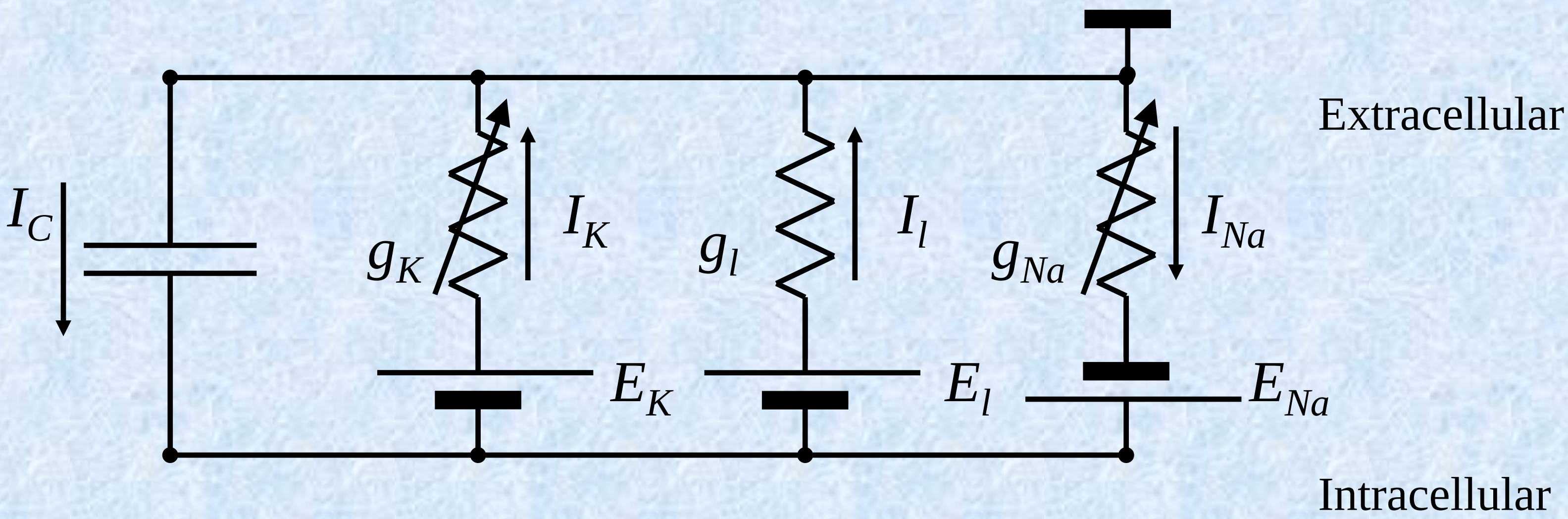
Nernst potentials can be considered constant for our purposes if we can also neglect the changes in temperature

One More Point to Consider

Neuroscientists assign "ground" or 0 potential to extracellular space

- That is where their reference electrode is
- Makes E_K=-80mV, E_{Na}=55mV, E_l=-60mV, V_r=-60mV
- But keep in mind that Hodgkin and Huxley had resting potential as 0

$$C_m \frac{dV}{dt} = g_K(V_m - E_K) + g_l(V_m - E_l) + g_{Na}(V_m - E_{Na})$$



One More Point to Consider

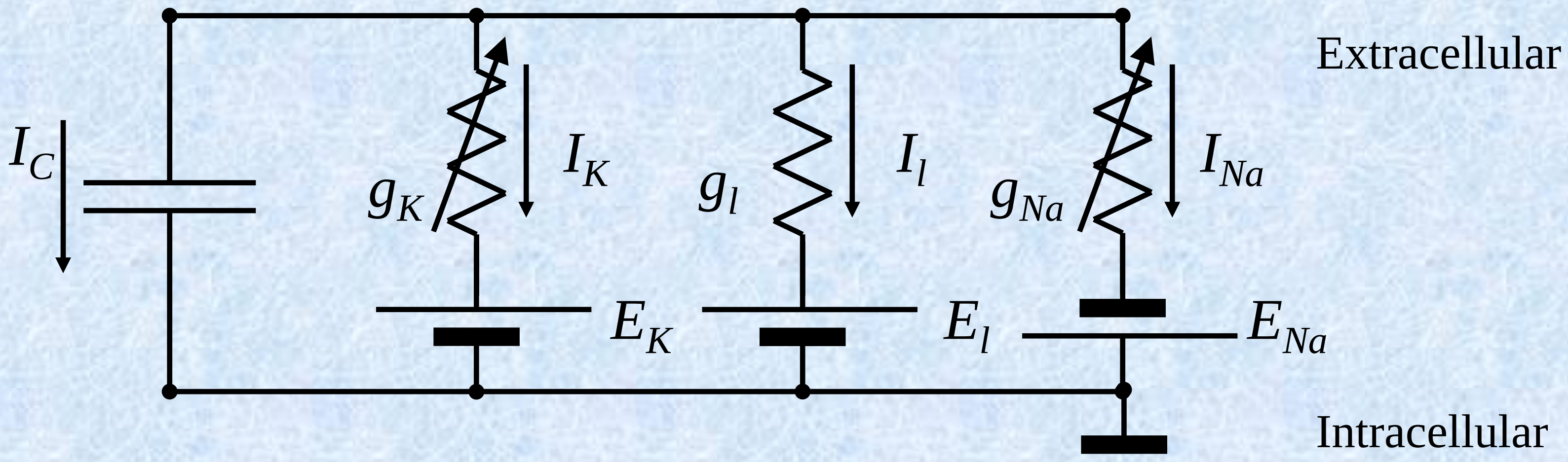
In the models it is often convenient to assign 0 potential to intracellular space at rest

- That is where the system settles if left undisturbed
- Makes E_K=-20mV, E_{Na}=115mV, E_l=0mV, V_r=0mV

$$C_m \frac{dV_m}{dt} = g_K(V_m - E_K) + g_l V_m + g_{Na}(V_m - E_{Na})$$

- And use "inward negative" convention

$$C_m \frac{dV_m}{dt} = -g_l V_m + g_K(E_K - V_m) + g_{Na}(E_{Na} - V_m)$$



Next Time

How to combine neuronal equations into a compartmental model: a brief look at cable theory for simulations of the cellular structure and Rall's law.

How to simplify Hodgkin-Huxley model of spiking to derive Izhikevich neuron.

Readings:

- Izhikevich, E.M. (2007). *Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting*. Cambridge, MA, MIT Press. Chapter 8.