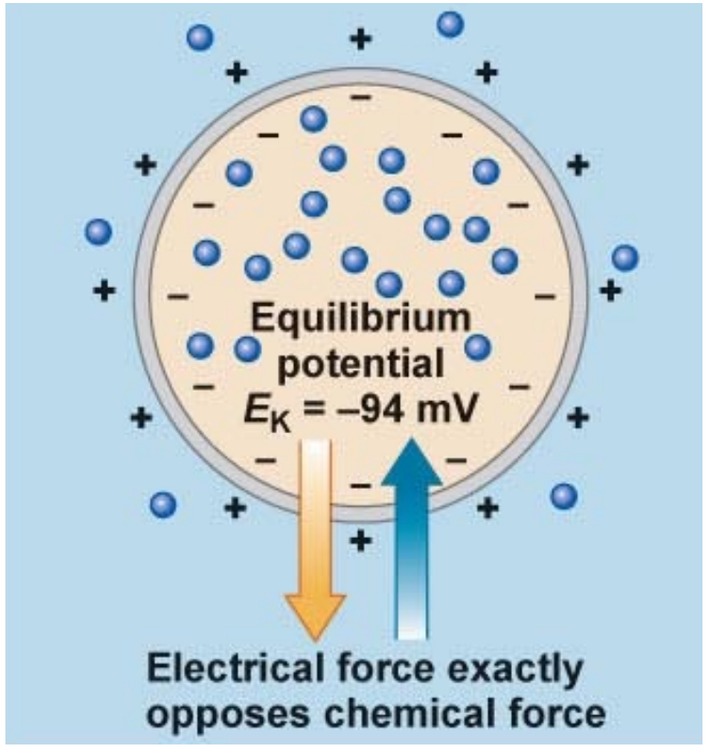
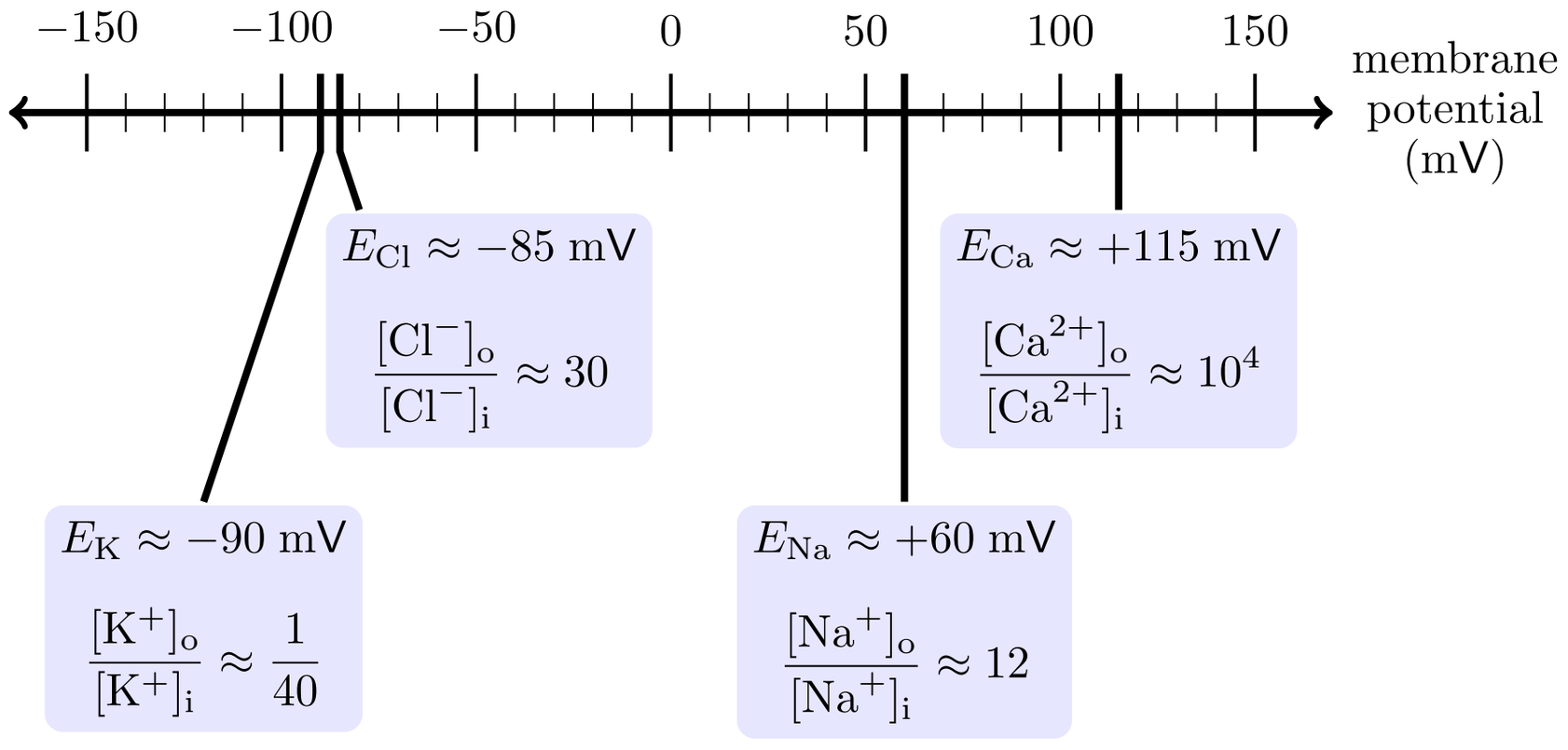
Cellular Biophysics and Modeling

Lecture 4

exponential time constants
Nernst equilibrium potentials





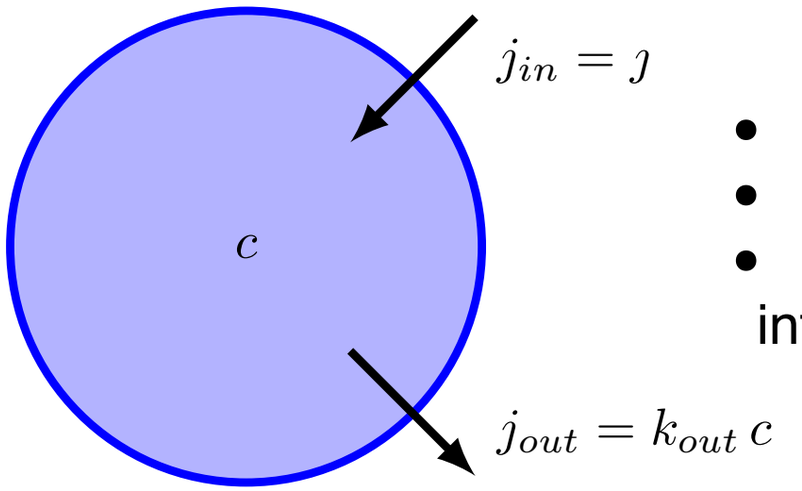
- Review exponential relaxation and phase diagram of our first model

- Discuss calcium handing in cortical neurons and mouse model of ALS

- Nernst equilibrium potential

- Goldman-Hodgkin-Katz voltage equation

our first model

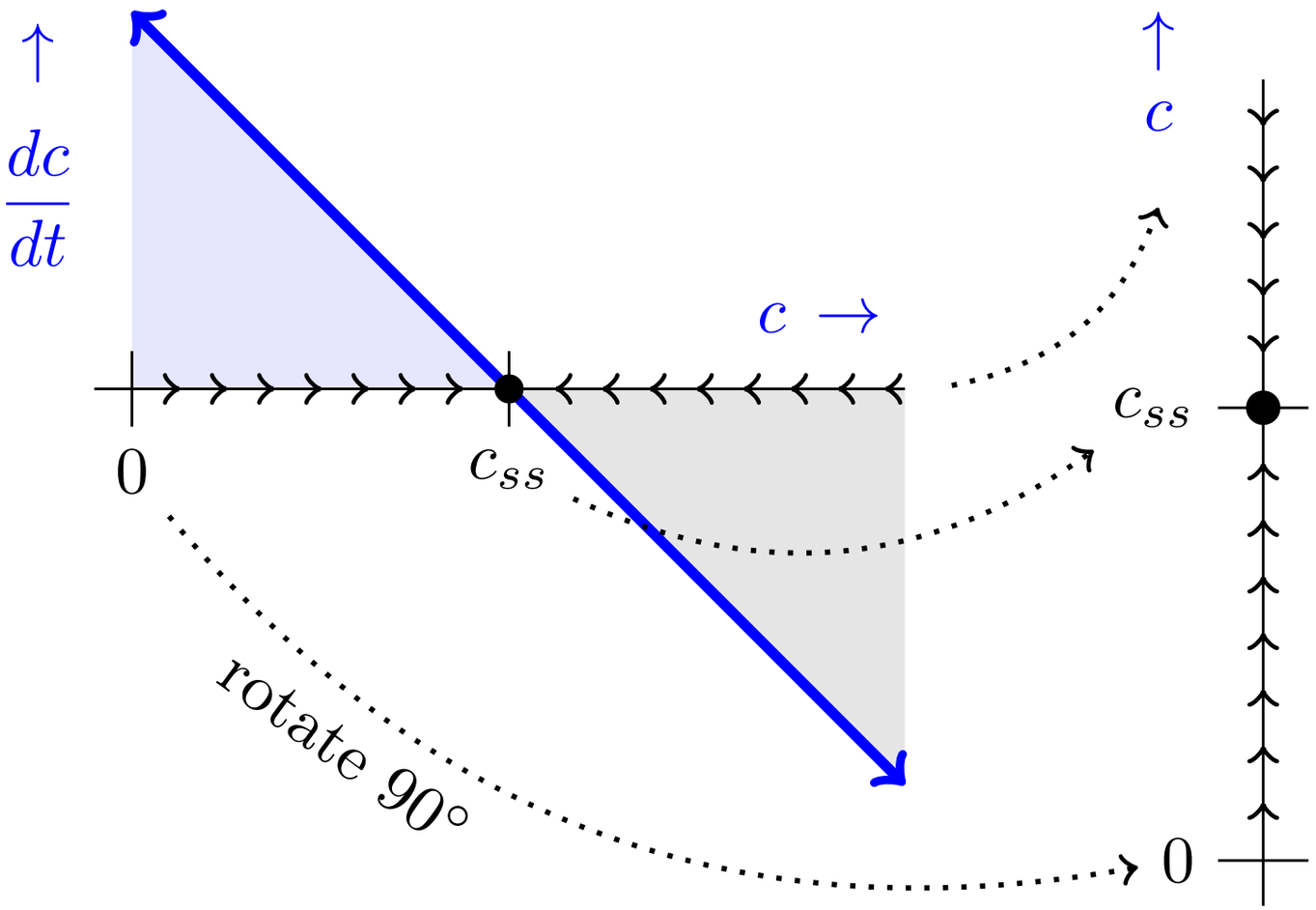


assumptions

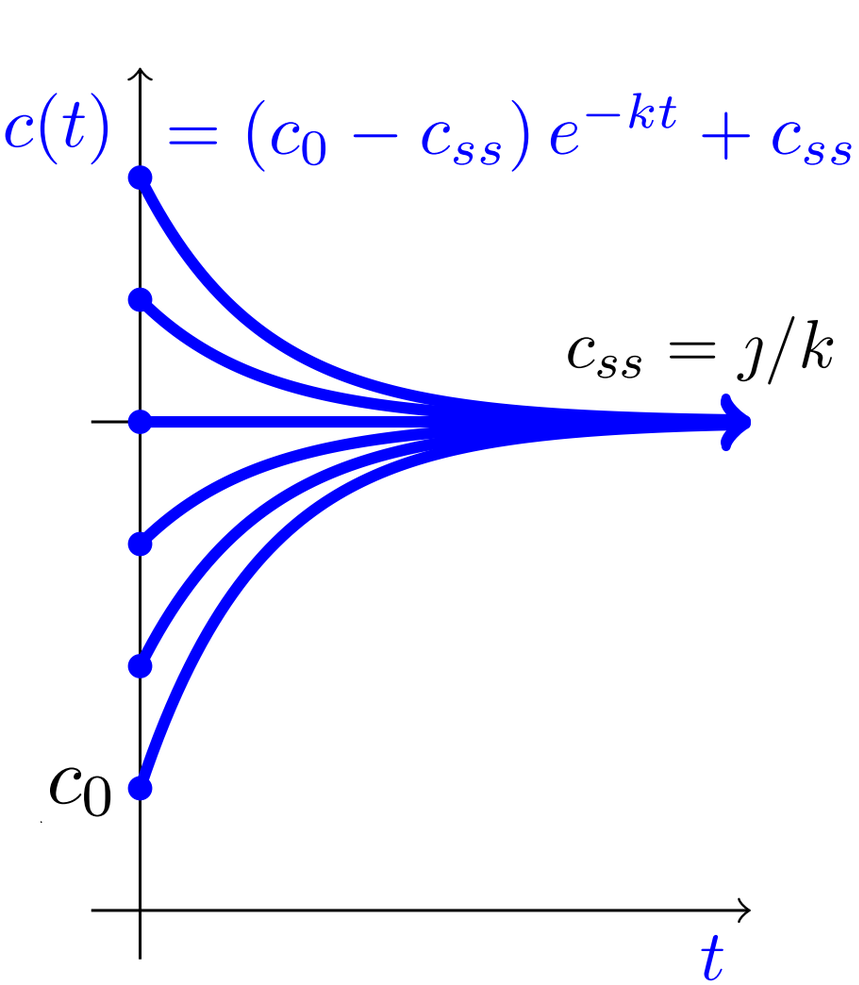
- open cell
- constant influx rate
- efflux rate proportional to intracellular concentration

ODE IVP

$$\frac{dc}{dt} = \jmath - kc \qquad c(0) = c_0$$



phase diagram



solutions of ODE IVP

Contents lists available at SciVerse ScienceDirect

Experimental Neurology

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Over-expression of N-type calcium channels in cortical neurons from a mouse model of Amyotrophic Lateral Sclerosis

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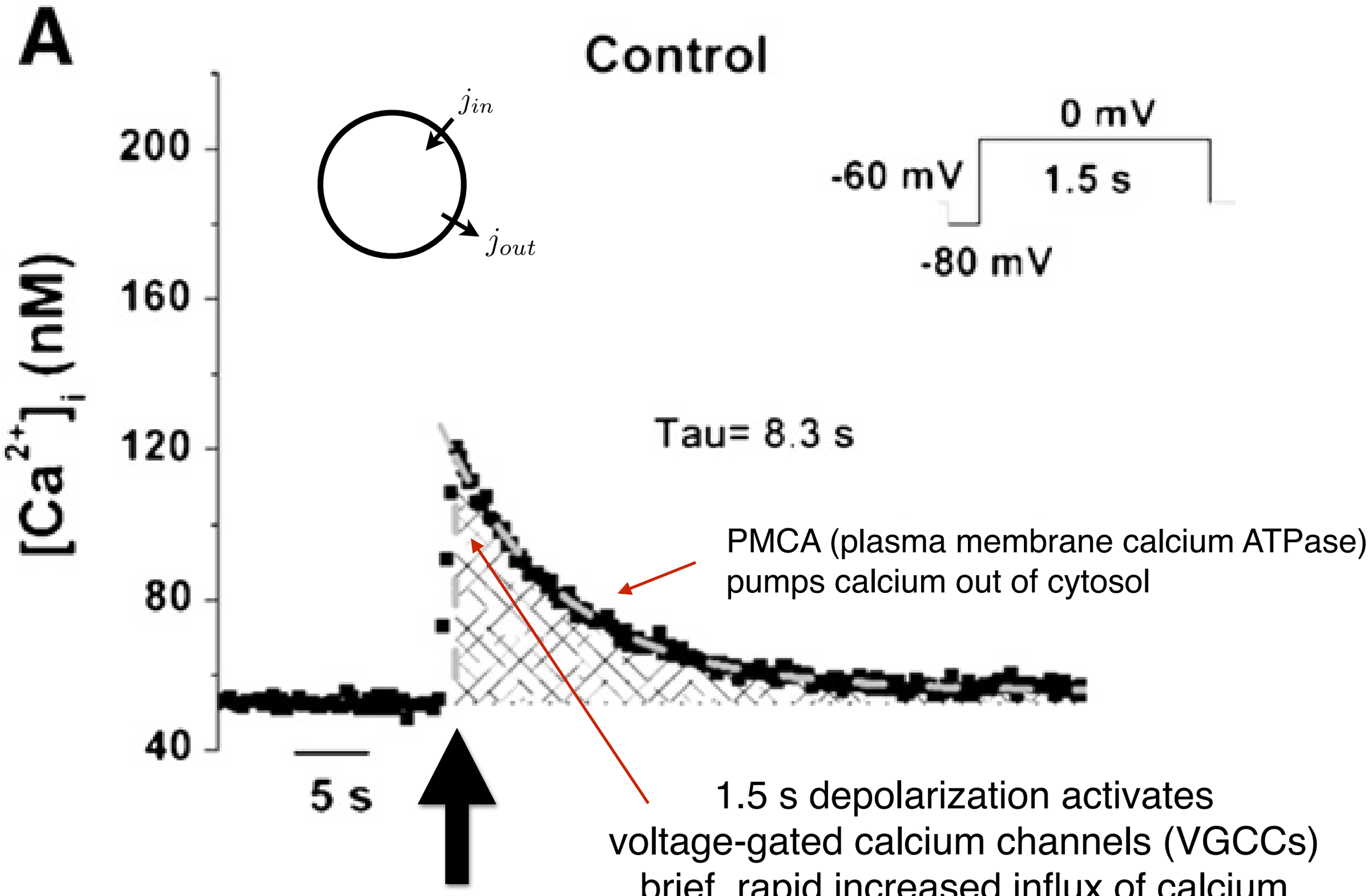
ABSTRACT

G93A transgenic mice are an experimental model of an inherited form of ALS with a Glu-to-Ala mutation in SOD1 (the gene encoding Cu, Zn superoxide dismutase). Depolarization activates VGCCs (N-type calcium channels) leading to an increase in intracellular calcium concentration that subsequent exponentially relaxes to resting values.

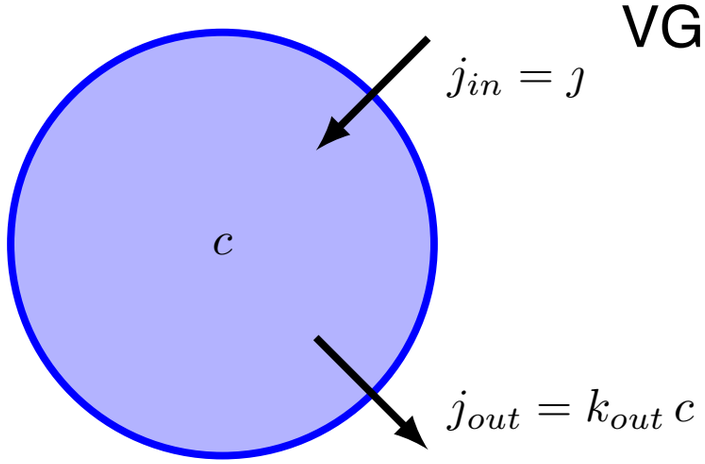
These data provide robust evidence for an excess of N-type Ca^{++} expression in G93A cortical neurons which induces a higher mortality following membrane depolarization. These results may be central to the understanding of pathogenic pathways in ALS and provide novel molecular targets for the design of rational therapies for the ALS disorder.

cultured cortical neurons - mouse



PMCA (plasma membrane calcium ATPase)
pumps calcium out of cytosol

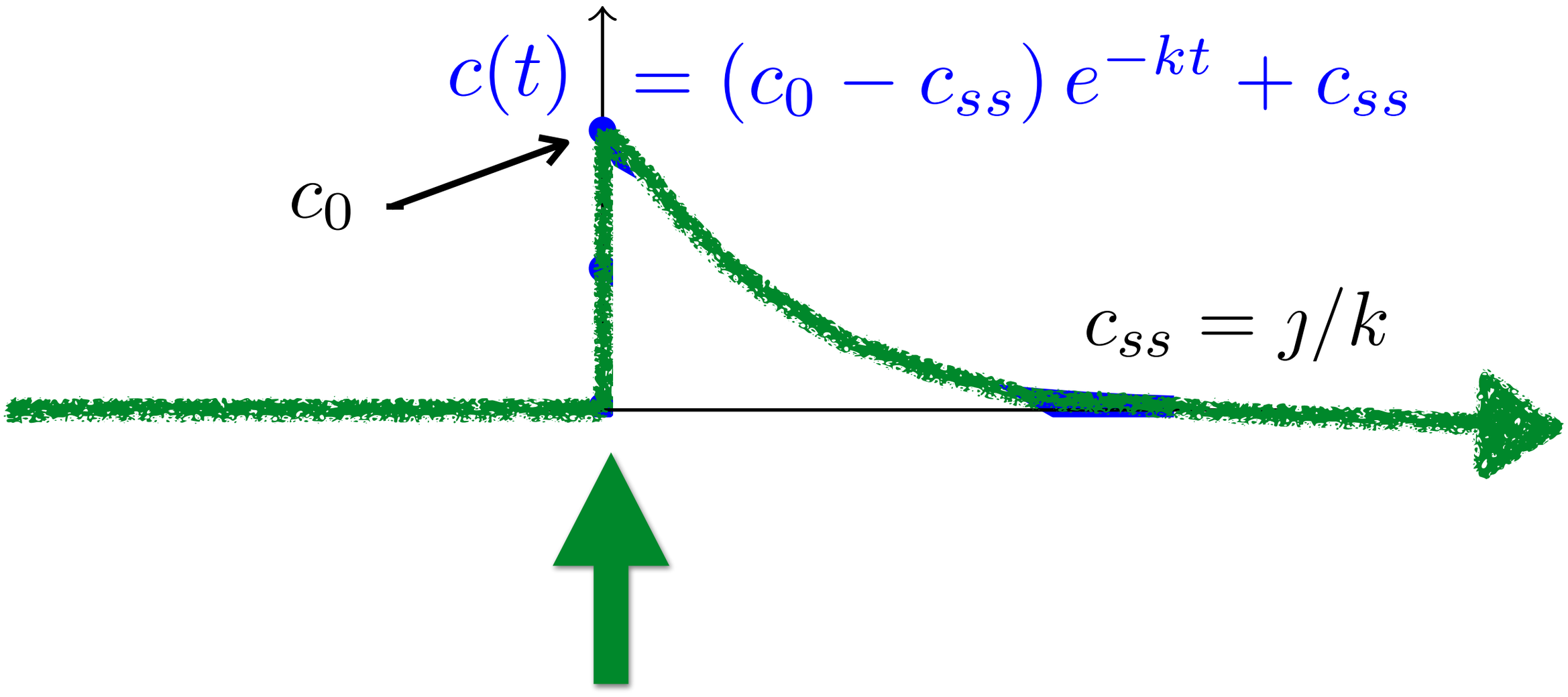
1.5 s depolarization activates
voltage-gated calcium channels (VGCCs)
brief, rapid increased influx of calcium



VGCCs (voltage-gated calcium channels)

$$\frac{dc}{dt} = \jmath - kc \qquad c(0) = c_0$$

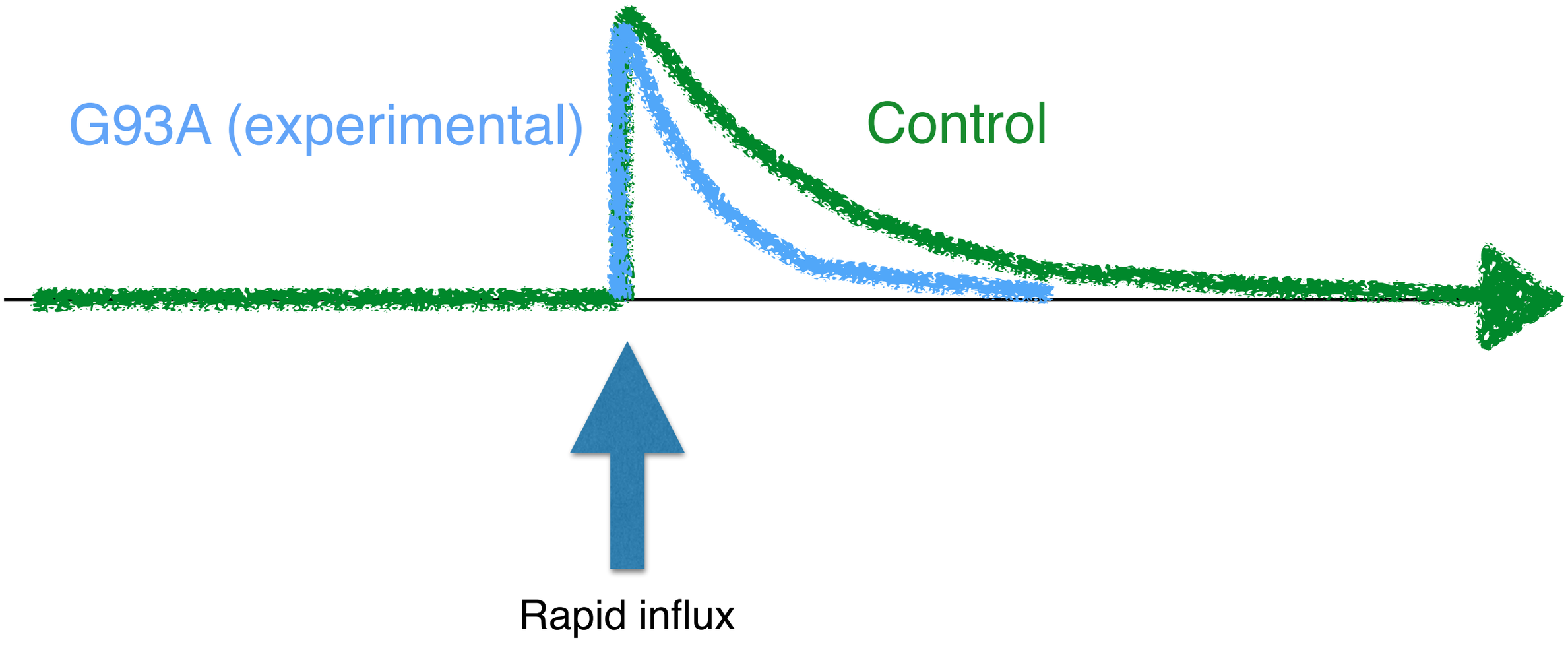
PMCA (plasma membrane calcium ATPase)



large increase in j for very short time modeled as initial calcium c_0 that is greater than steady state c_{ss}

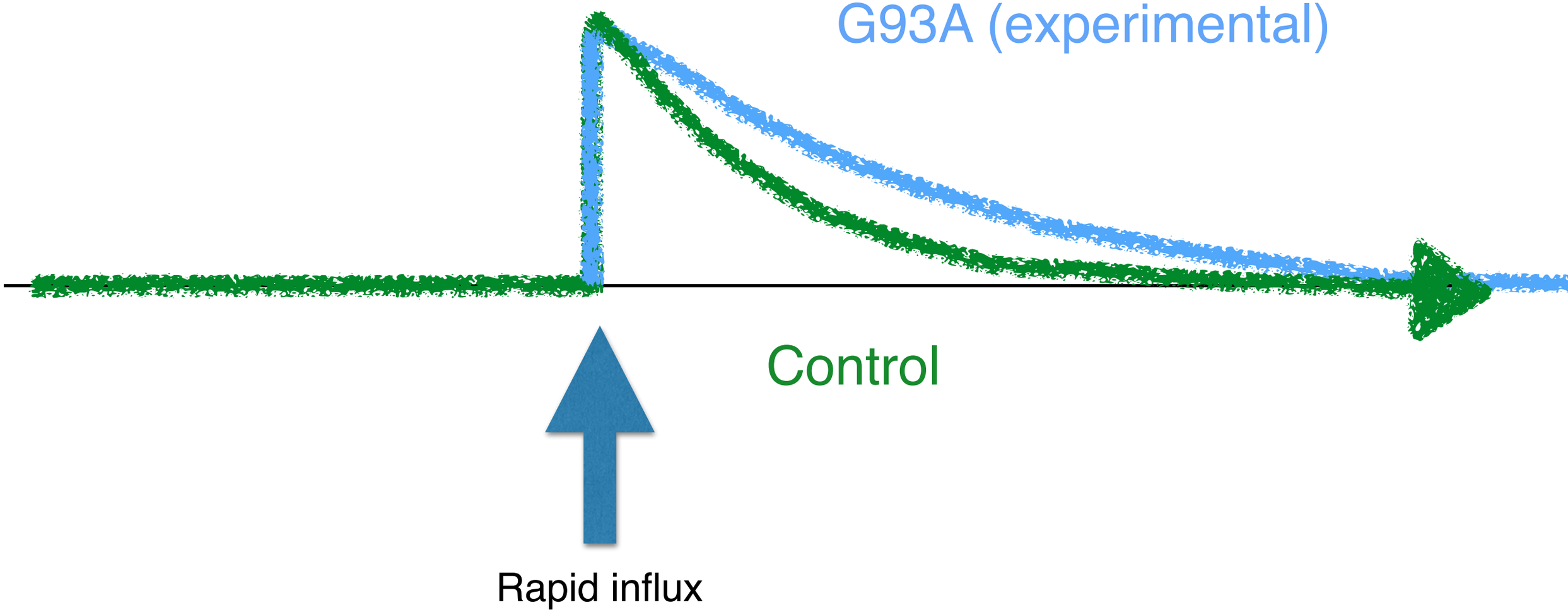
calcium influx and efflux in a transgenic mouse model of ALS

What would be your interpretation?



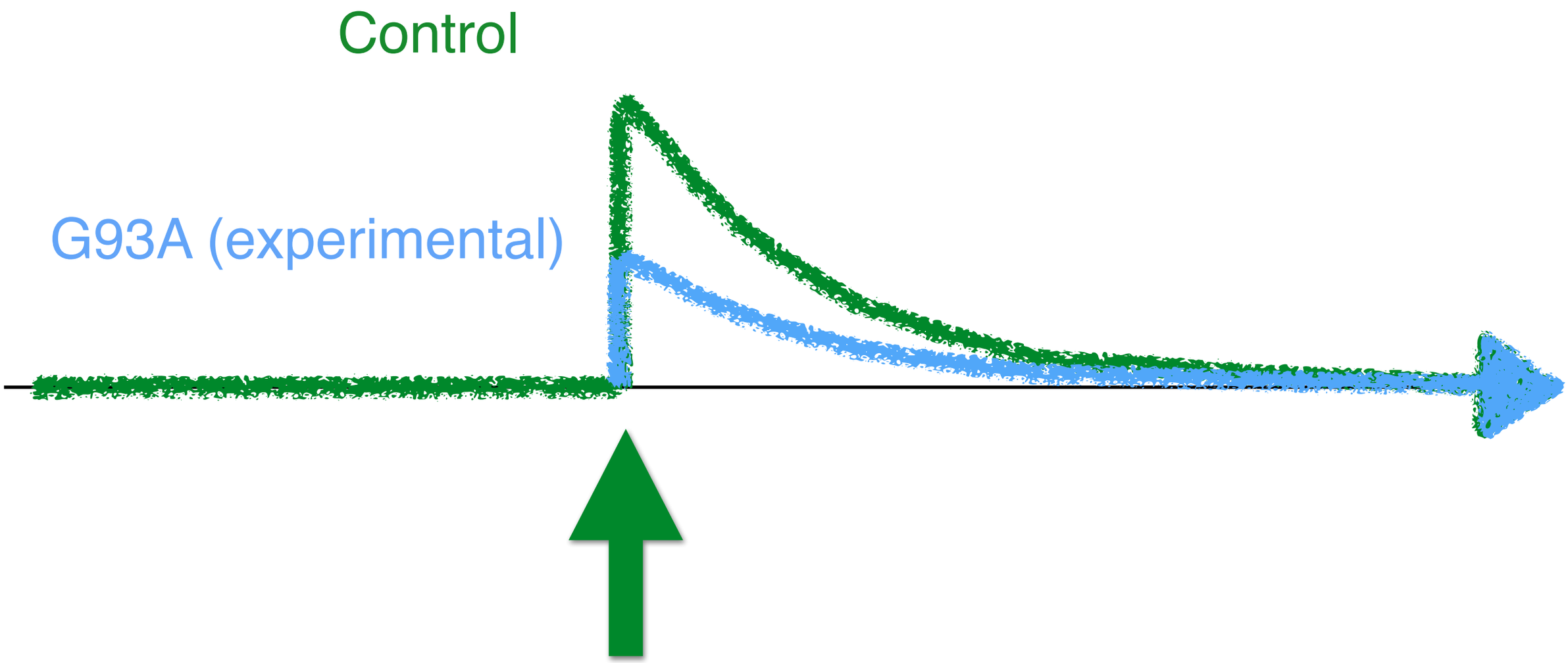
calcium influx and efflux in a transgenic mouse model of ALS

What would be your interpretation?



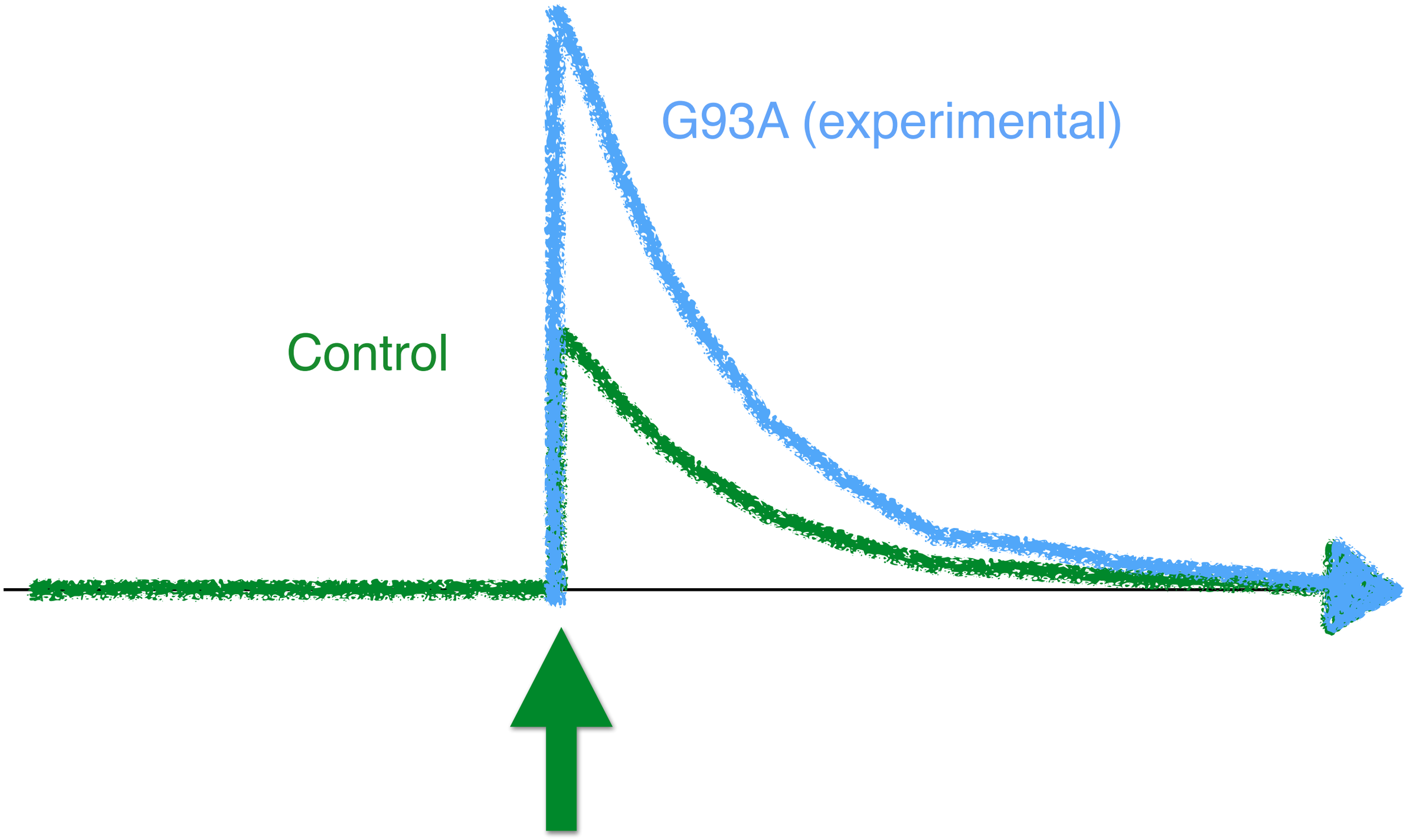
calcium influx and efflux in a transgenic mouse model of ALS

What would be your interpretation?



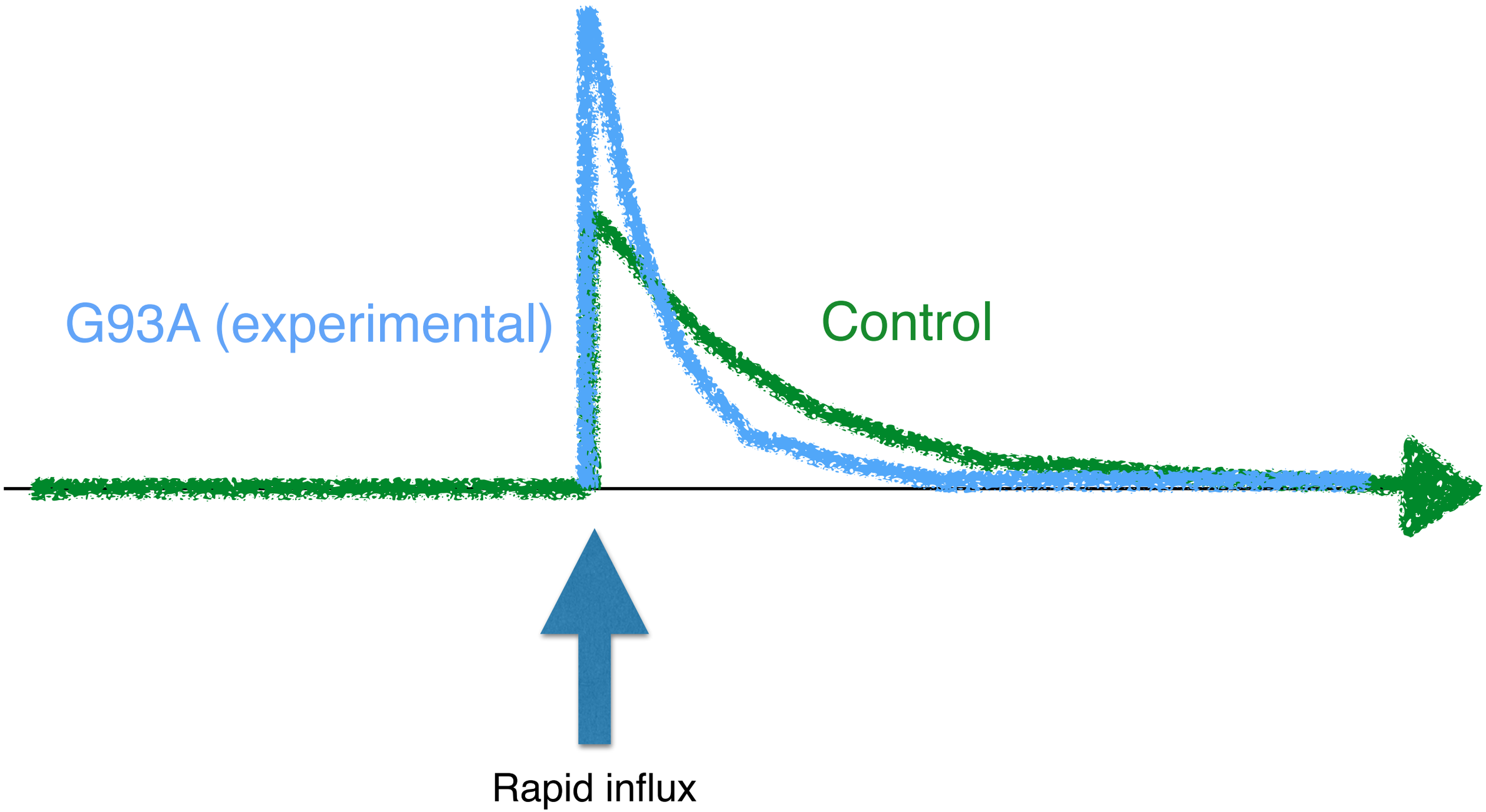
calcium influx and efflux in a transgenic mouse model of ALS

What would be your interpretation?

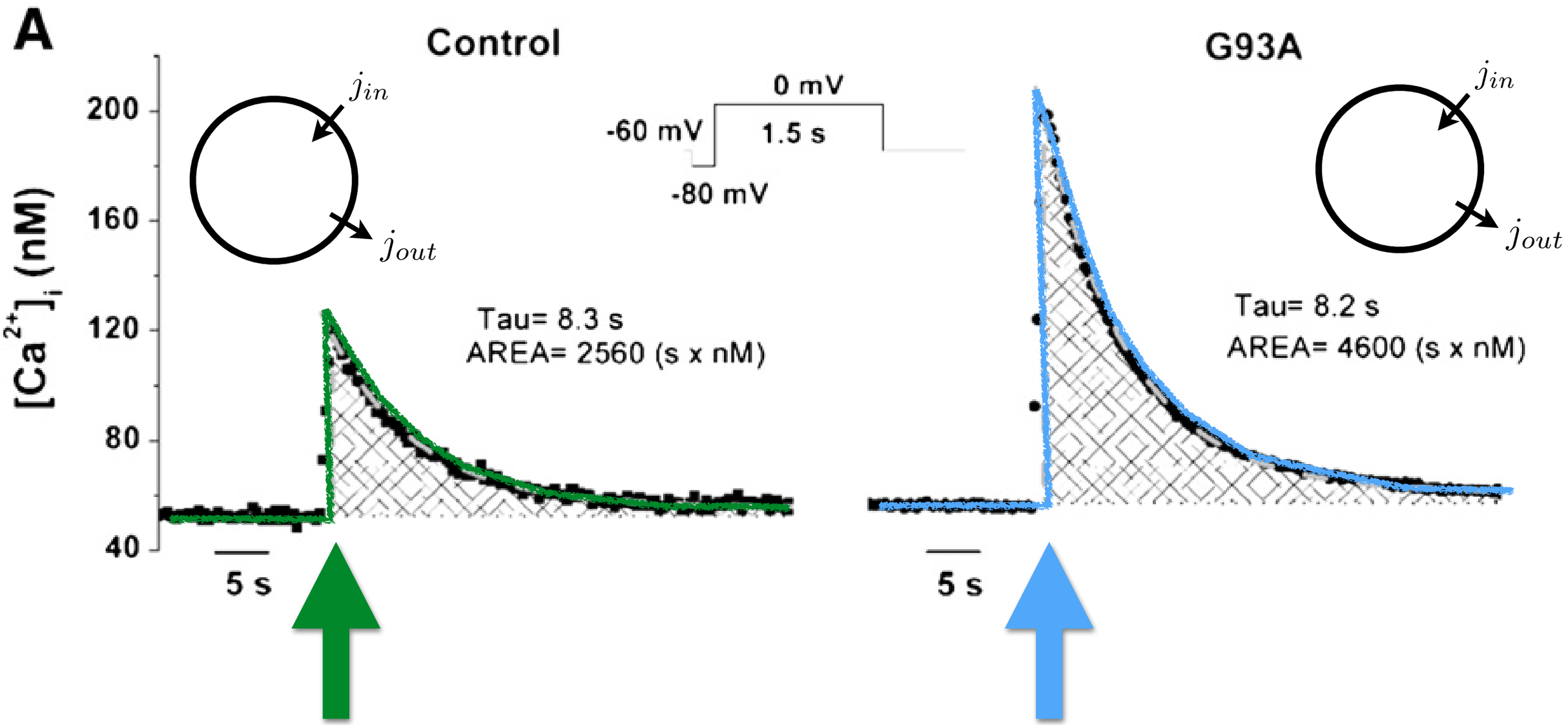


calcium influx and efflux in a transgenic mouse model of ALS

What would be your interpretation?



cultured cortical neurons - calcium influx and efflux in a transgenic mouse model of ALS (amyotrophic lateral sclerosis)



increased calcium influx during brief depolarization
unchanged **exponential time constant** of efflux

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Over-expression of N-type calcium channels in cortical neurons from a mouse model of Amyotrophic Lateral Sclerosis

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ABSTRACT

Voltage-gated Ca^{2+} channels (VGCCs) mediate calcium entry into neuronal cells in response to membrane
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G93A transgenic mice are an experimental model of an inherited form of ALS with a Glu-to-Ala mutation in SOD1 (the gene encoding Cu, Zn superoxide dismutase). Depolarization activates VGCCs (N-type calcium channels) leading to an increase in intracellular calcium concentration that subsequently exponentially relaxes to resting values. **G93A mice have more influx than Control, but similar efflux properties (the exponential time constant does not change). Conclusion: SOD1 mutation disregulates intracellular calcium by changing properties of VGCCs as opposed to plasma membrane calcium ATPases (PMCA).**

ODEs are often written with the understanding that certain parameters are positive

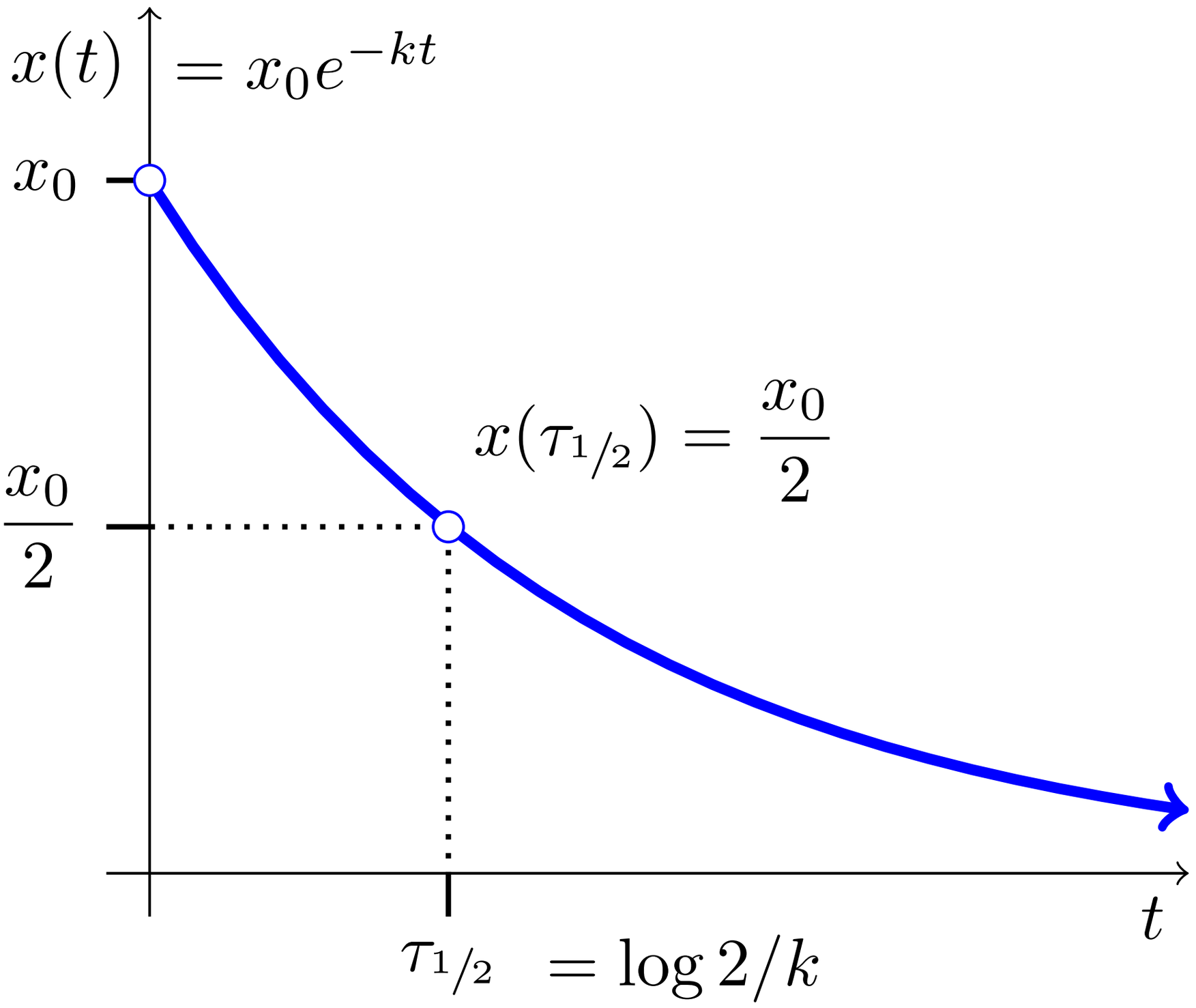
$$k > 0$$

$$\frac{dx}{dt} = -kx \qquad x(0) = x_0 \qquad (t \geq 0)$$

$$x(t) = x_0 e^{-kt}$$

knowing *k* is positive
makes it clear
that *x* is decaying

“half life” of an exponential decay



What is the half life in terms of rate constant *k* ?

$$x(\tau_{1/2}) = x_0/2$$

$$x_0 \exp\left(-k\tau_{1/2}\right) = x_0/2$$

$$\exp\left(-k\tau_{1/2}\right) = 1/2$$

$$-k\tau_{1/2} = \log 1/2$$

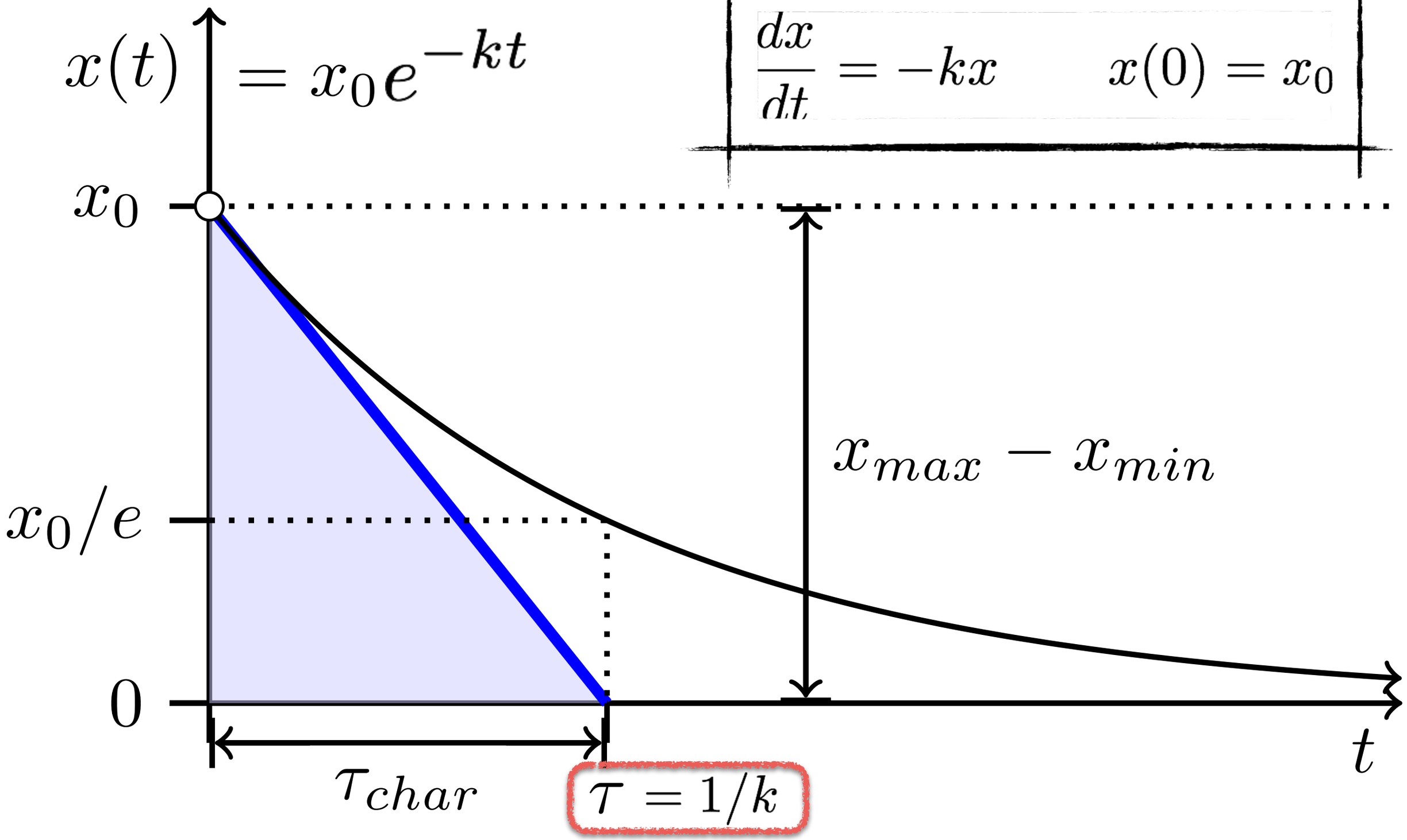
$$k\tau_{1/2} = \log 2$$

$$\text{time} \ominus \tau_{1/2} = \frac{\log 2}{k} \ominus \frac{1}{1/\text{time}}$$

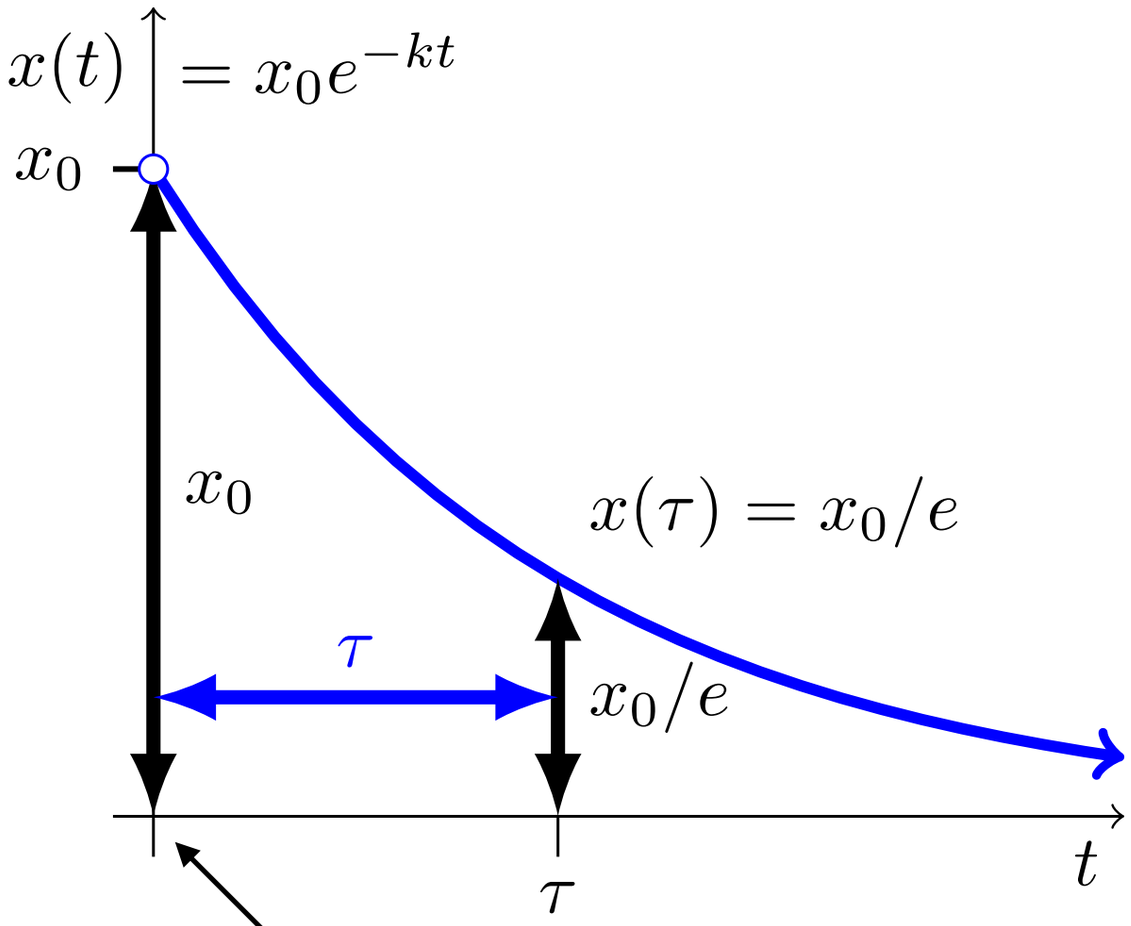
characteristic time of an exponential decay
is equal to the **exponential time constant**

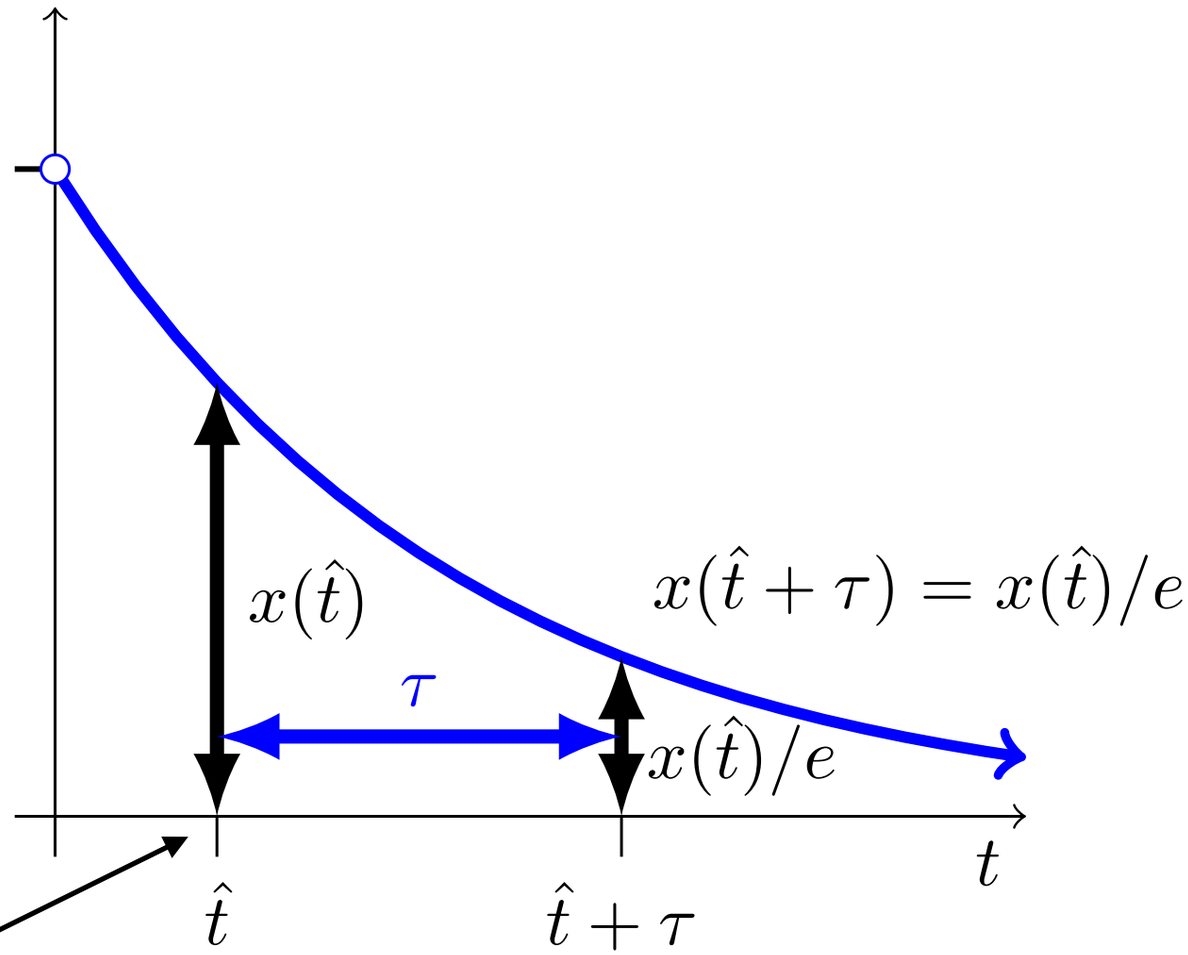
$$x(t) = x_0 e^{-kt}$$

$$\frac{dx}{dt} = -kx \qquad x(0) = x_0$$



The exponential time constant is the time required
for the decaying quantity to decrease by a factor of *e*





same answer
regardless
of where you start

These two ODE models that are equivalent,
but each highlights different aspects

growth rate

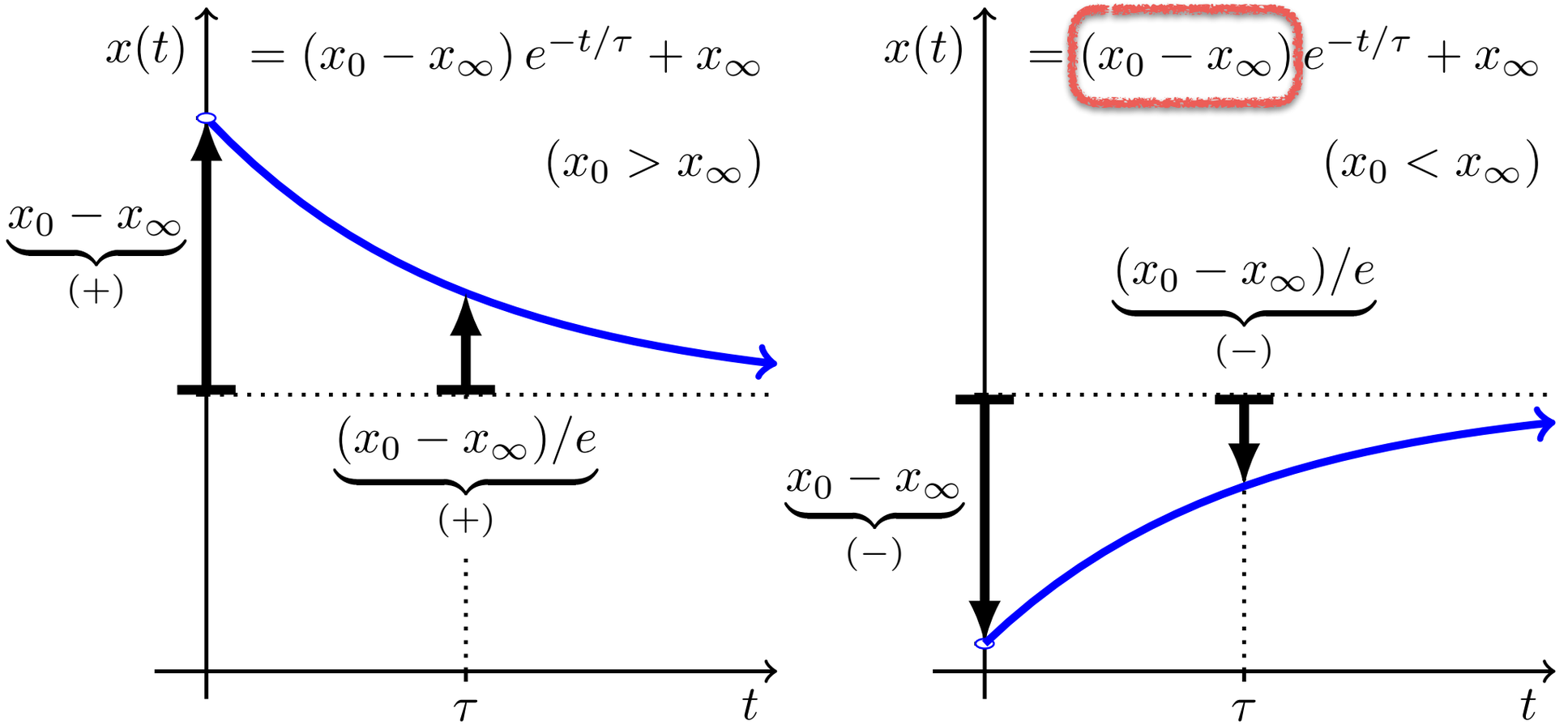
steady state value

$$\frac{dx}{dt} = j - kx \quad \rightleftharpoons \quad \frac{dx}{dt} = -\frac{x - x_\infty}{\tau}$$

exponential rate
constant of decay

exponential time
constant of decay

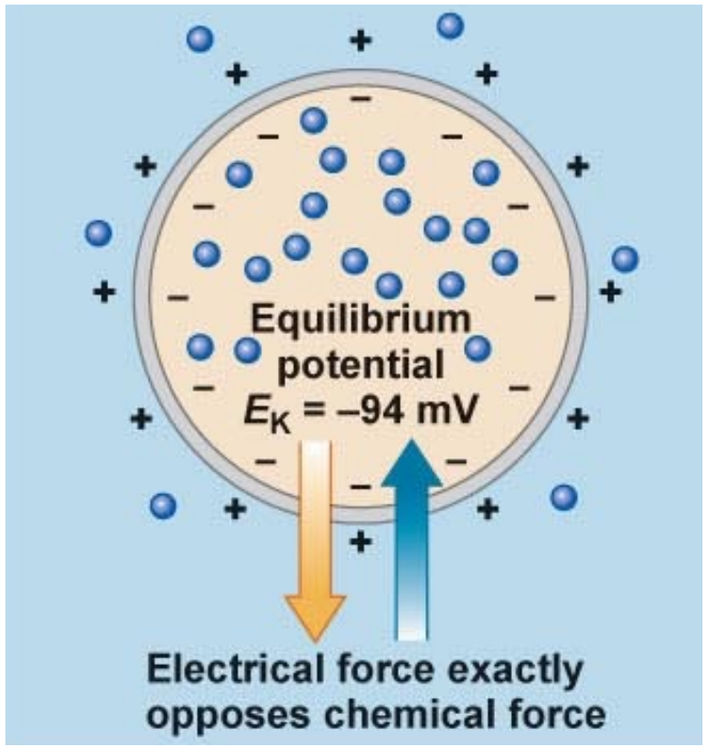
The version of the model with steady state and time constant makes clear the answer to "What exactly is decaying away?"

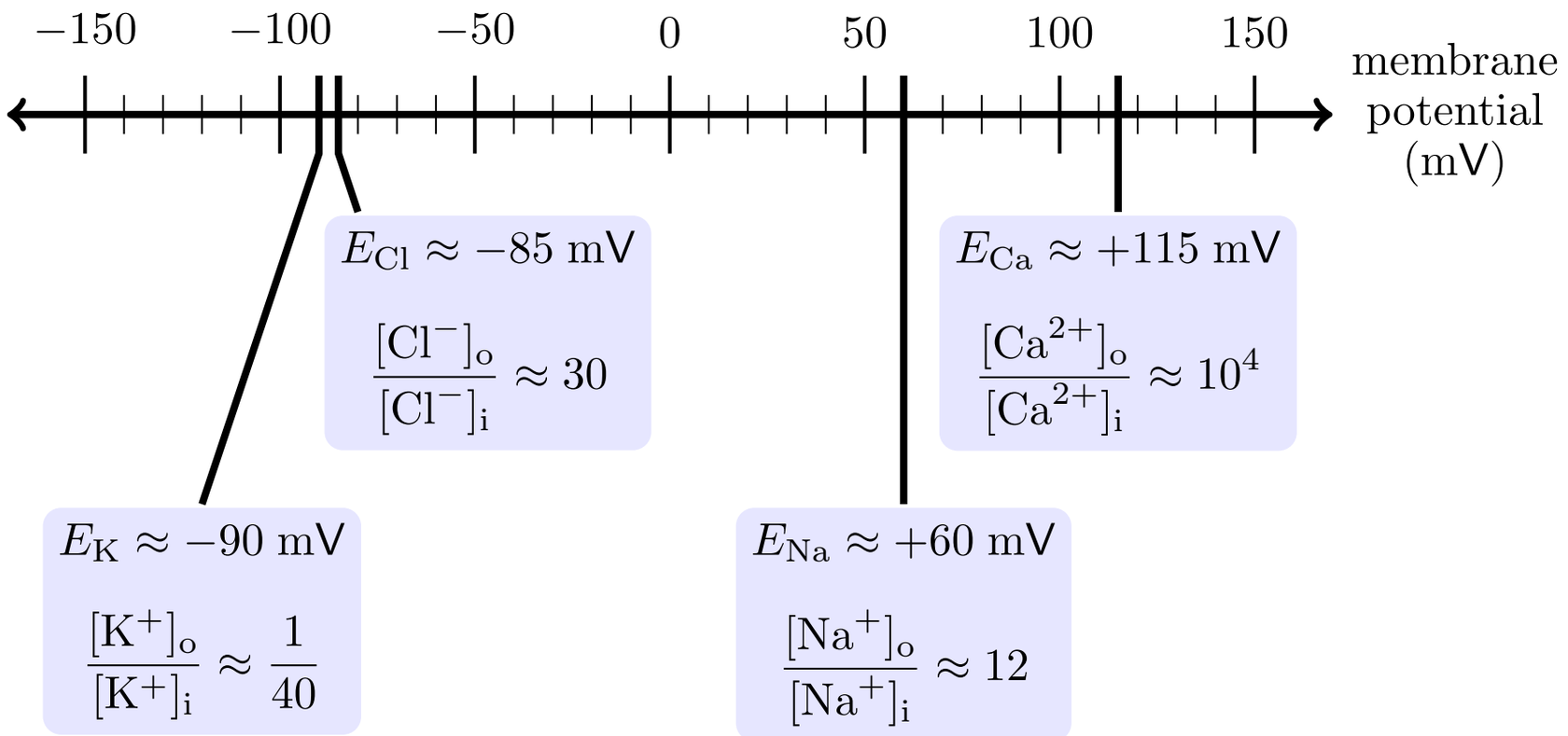


The deviation of *x* from the steady-state value x_∞ is what is decaying away

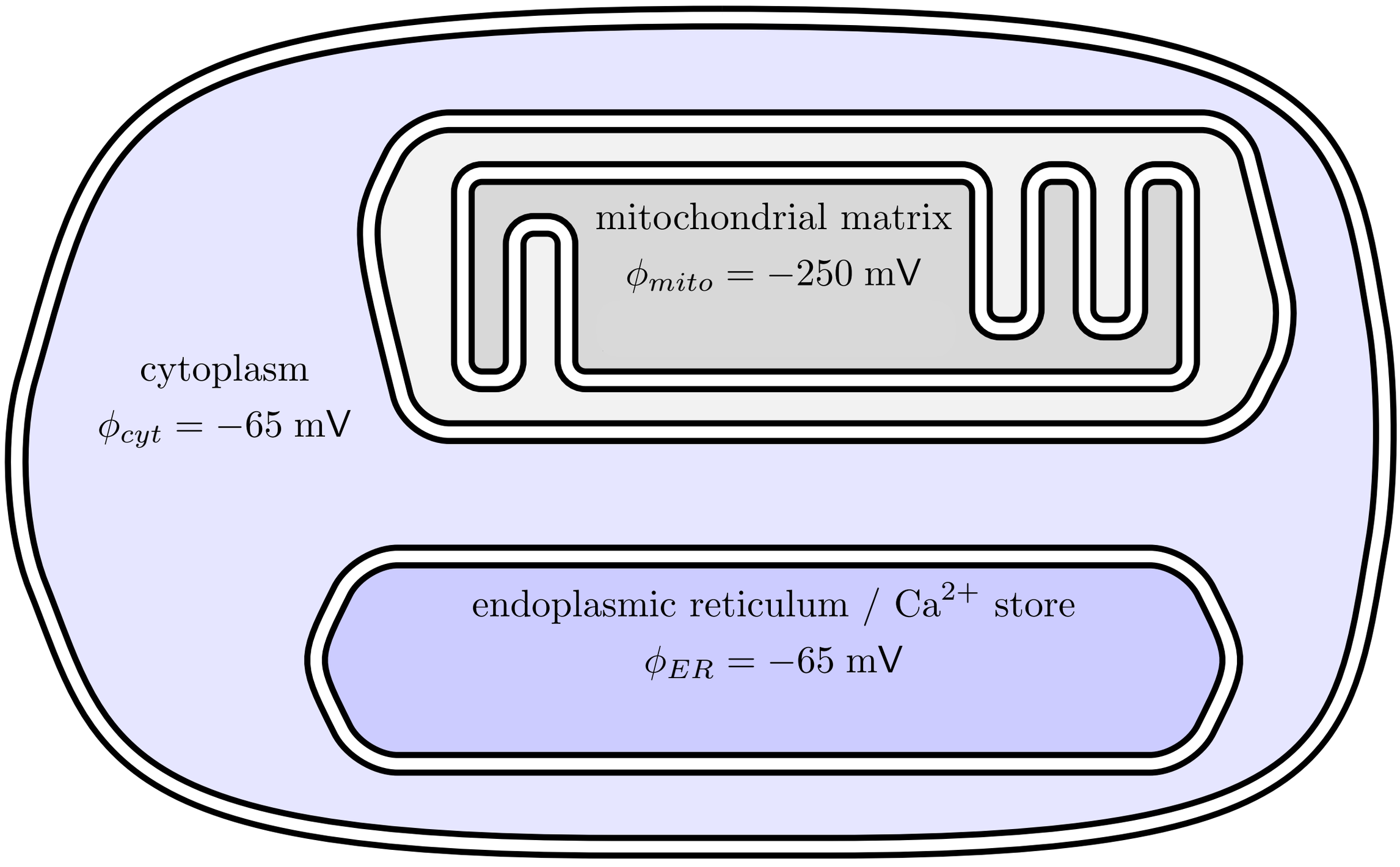
Figure 4.9 Exponential relaxation when the initial value x_0 is greater or less than the asymptotic value (x_∞). In both cases the exponential time constant τ is the time required for the deviation from the asymptotic value to decay e-fold.

Nernst equilibrium potentials



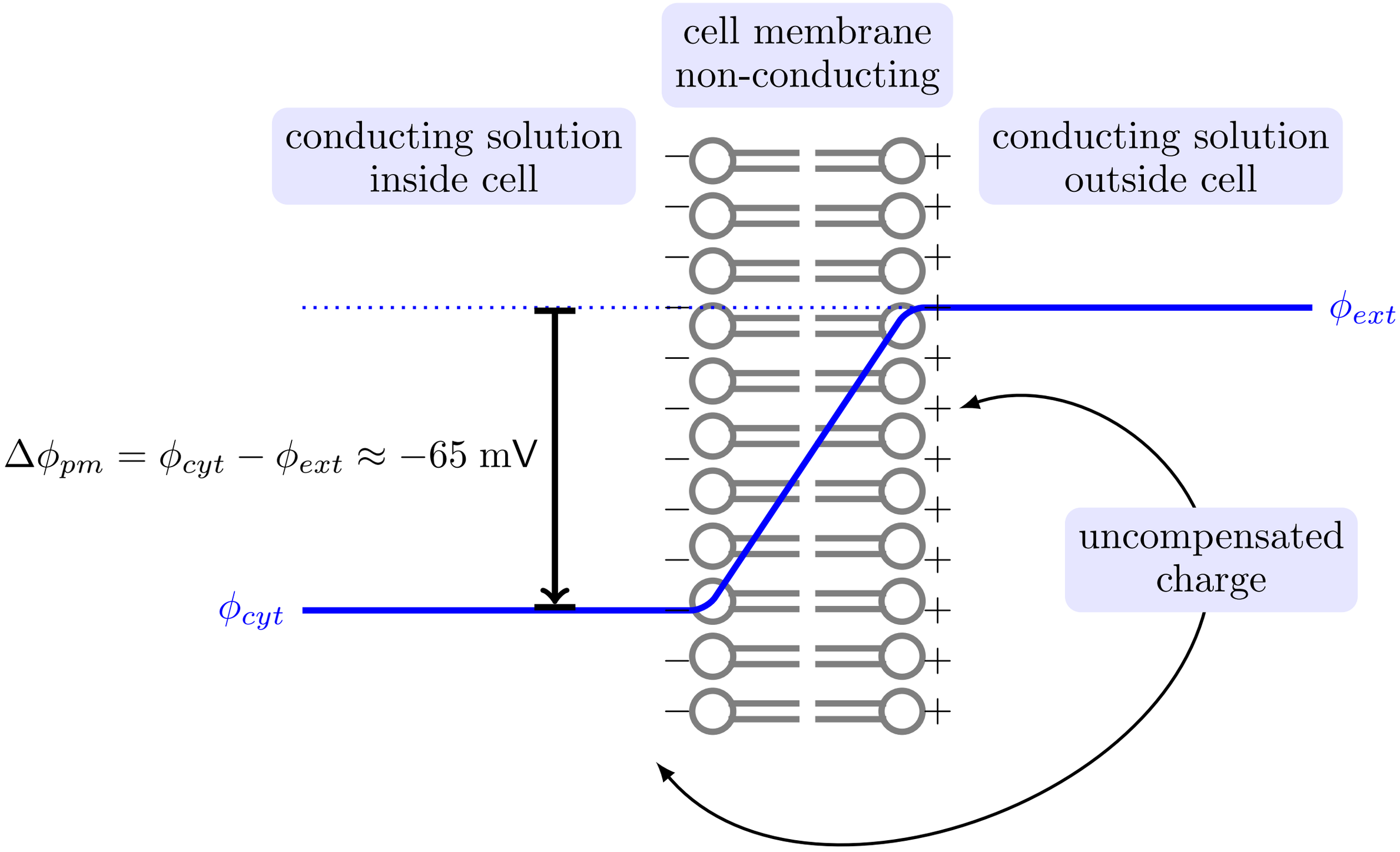


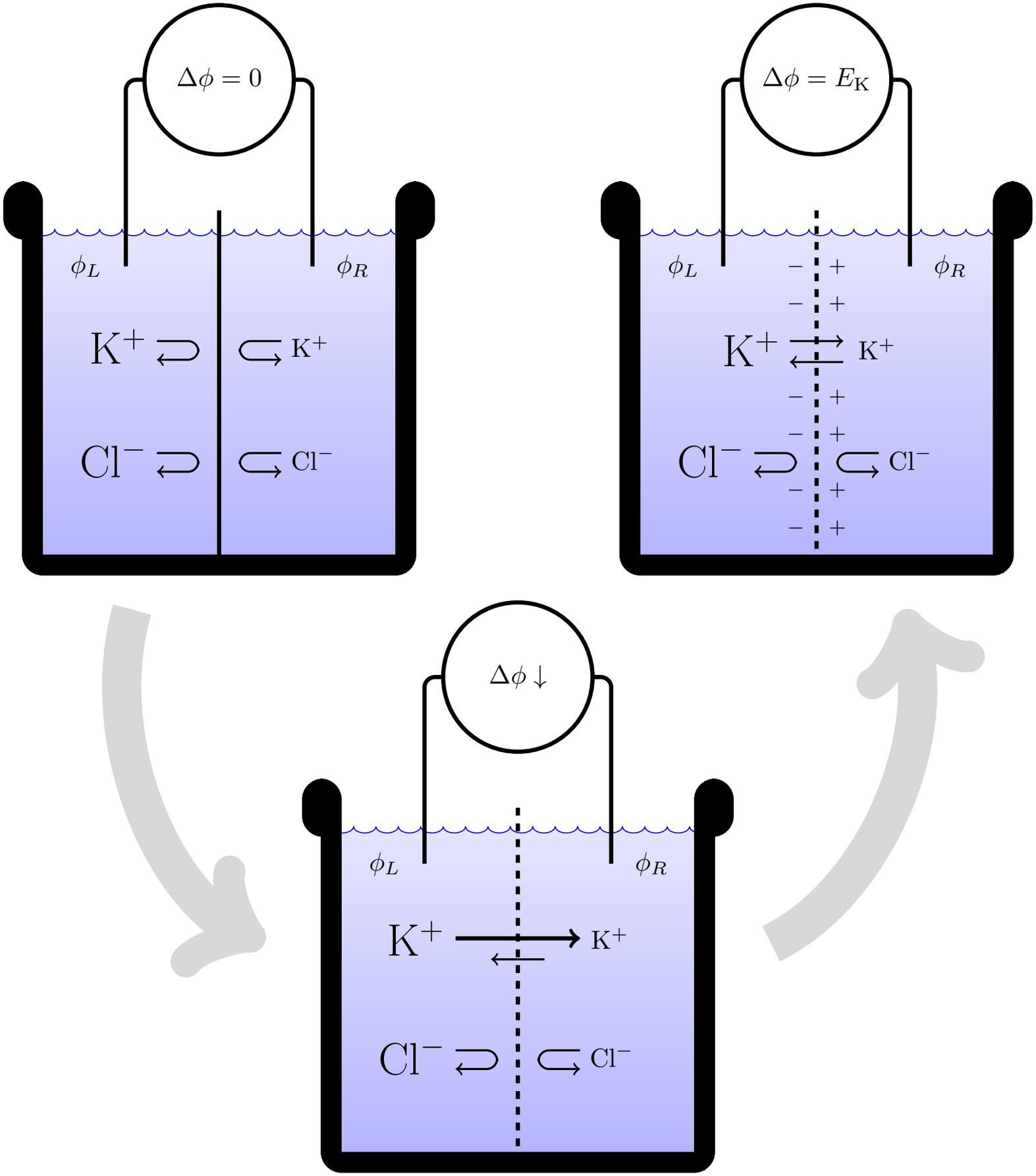
electrical potentials

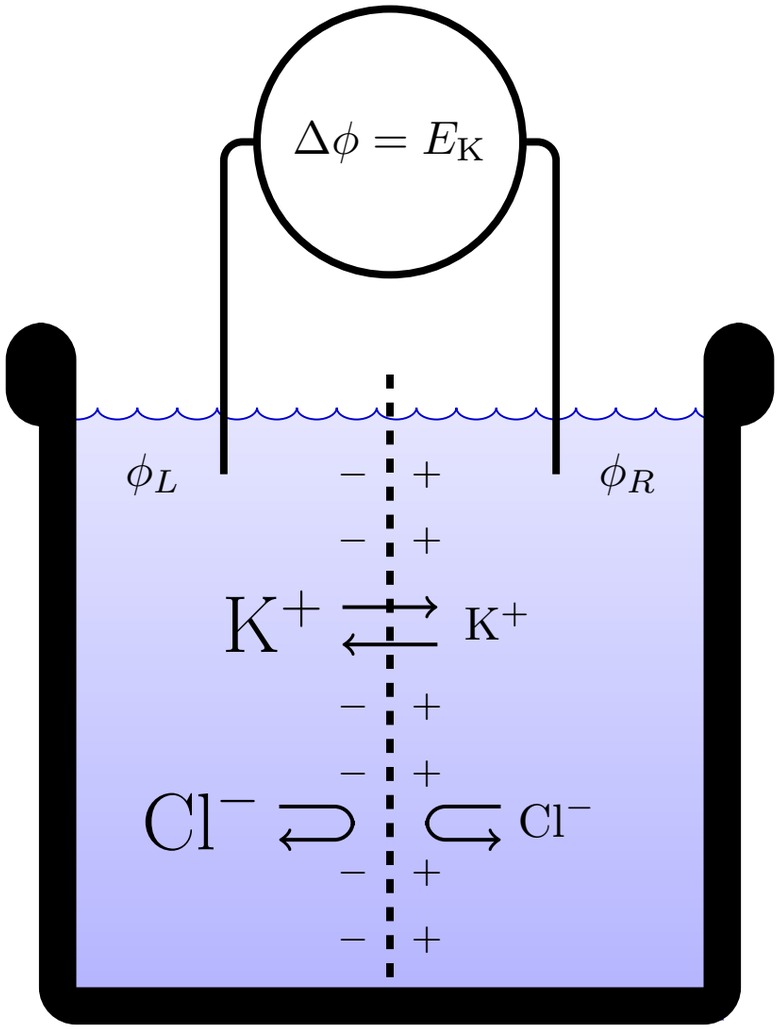


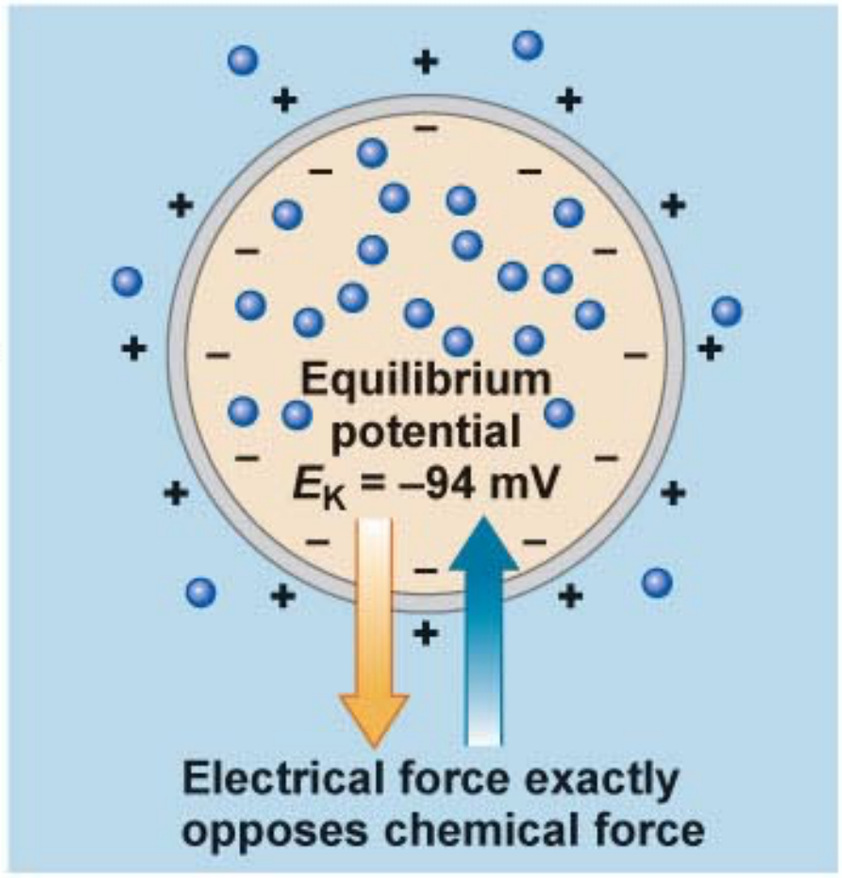
The cell plasma membrane is selectively permeable to physiological ions. This selective permeability is responsible for potential differences between the cell interior and the extracellular space.

transmembrane potential




$\Delta\phi = 0$
ϕ_L
ϕ_R
K^+
K^+
Cl^-
Cl^-
$\Delta\phi = E_K$
ϕ_L
ϕ_R
K^+
K^+
Cl^-
Cl^-
$\Delta\phi \downarrow$
ϕ_L
ϕ_R
K^+
K^+
Cl^-
Cl^-





$$V = \phi_{in} - \phi_{out}$$

When $V = E_K$ no net current

$$E_K = \frac{RT}{zF} \ln \frac{[K^+]_{out}}{[K^+]_{in}}$$

Nernst equilibrium potential

typical concentrations of physiological ions

Ion S	$[S]_o$ (mM)	$[S]_i$ (mM)
K^+	4	155
Na^+	145	12
Ca^{2+}	1.5	10^{-4}
Cl^-	123	4.2

Nernst equilibrium potential for potassium?

$$E_K = \frac{RT}{zF} \ln \frac{[K^+]_{out}}{[K^+]_{in}}$$

calculating E_K

$$E_K = \frac{RT}{zF} \ln \frac{[K^+]_o}{[K^+]_i} = \frac{\left(8.3145 \ \frac{\text{C V}}{\text{mol K}}\right) \ (310 \ \text{K})}{(+1)\left(9.6485 \times 10^4 \ \frac{\text{C}}{\text{mol}}\right)} \ \ln \left[\frac{4 \ \text{mM}}{155 \ \text{mM}}\right]$$

calculating E_K

$$E_K = \frac{RT}{zF} \ln \frac{[K^+]_o}{[K^+]_i} = \underbrace{\frac{\left(8.3145 \ \frac{\cancel{C}\ V}{mol\ \cancel{K}}\right)\ (310\ \cancel{K})}{(+1)\left(9.6485 \times 10^4 \ \frac{\cancel{C}}{mol}\right)}}_{0.0267\ V \quad 26.7\ mV} \underbrace{\ln\left[\frac{4\ \cancel{m}M}{155\ \cancel{m}M}\right]}_{\ln(0.0258) \quad -3.657}$$

$$E_K = (26.7\ mV)(-3.657)$$

$$E_K = -97.64\ mV$$

Name	Symbol	Value
Avagodro's number	N	6.02×10^{21} mol^{-1}
Boltzmann's constant	k_B	1.3807×10^{-23} J K^{-1}
Gas constant	$R = Nk_B$	8.3145 J mol^{-1} K^{-1}
Elementary charge	q	1.6022×10^{-19} C
Faraday's constant	$F = Nq$	9.6485×10^{4} C mol^{-1}

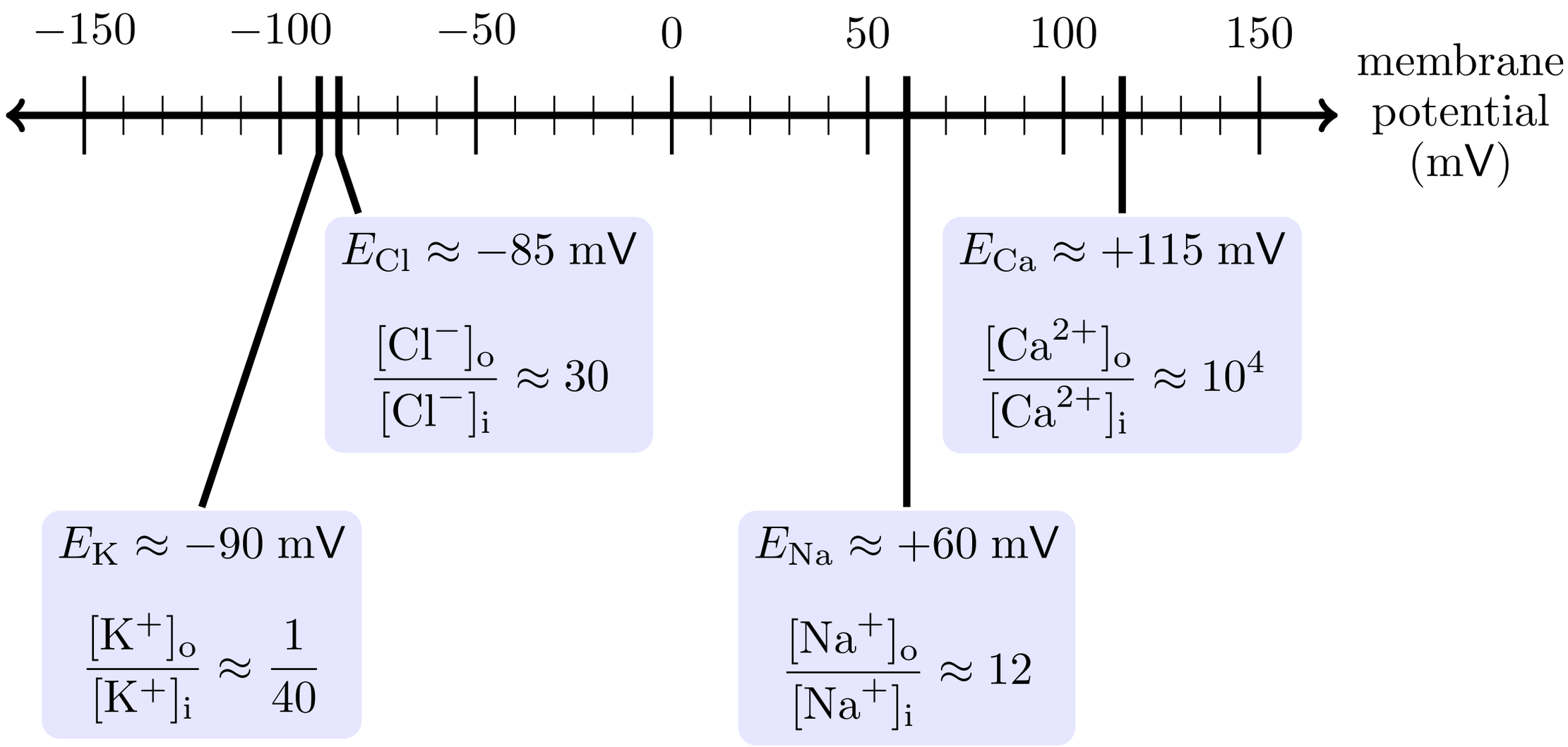
TABLE 1.2 Values of RT/F (or $k_B T/q_e$)

Temperature (°C)	RT/F (mV)	2.303 RT/F (mV)
0	23.54	54.20
5	23.97	55.19
10	24.40	56.18
15	24.83	57.17
20	25.26	58.17
25	25.69	59.16
30	26.12	60.15
35	26.55	61.14
37	26.73	61.54

$$\frac{RT}{F} \approx 25 \text{ mV at room temperature}$$

Ion S	$[\mathrm{S}]_\mathrm{o}$ (mM)	$[\mathrm{S}]_\mathrm{i}$ (mM)	E_S (mV) 21°C	37°C
K^+	4	155	−93.0	−98.1
Na^+	145	12	+63.4	+66.8
Ca^{2+}	1.5	10^{-4}	+112	+118
Cl^-	123	4.2	−85.9	−90.1

memorize **these** Nernst potentials (approximate values)



1. selective ion permeability of the plasma membrane leads to a transmembrane potential (i.e., voltage)

2. Nernst potential equals the membrane voltage at which there is no net flux (no current) of the permeant ion

3. $\frac{RT}{F} \approx 25$ mV at room temp, $\frac{RT}{F} \approx 27$ mV at physiological temperature

4. neuronal resting membrane potential is largely due to K^+ permeability of the plasma membrane

J Physiol 589.21 (2011) pp 5071–5089

Two-pore domain K^+ channels regulate membrane potential of isolated human articular chondrocytes

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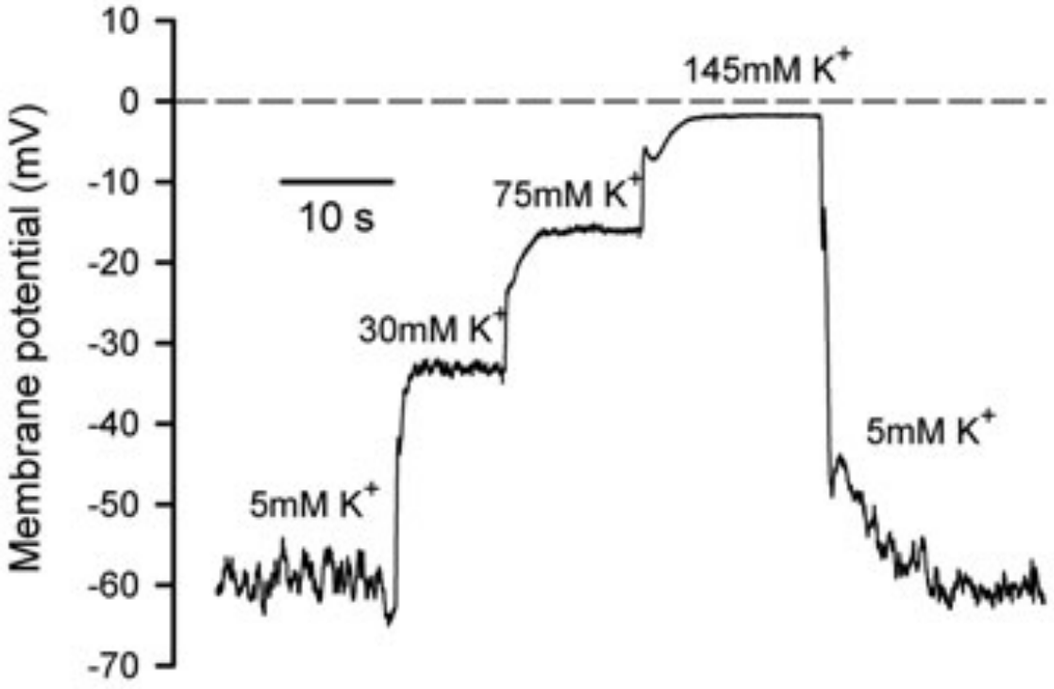
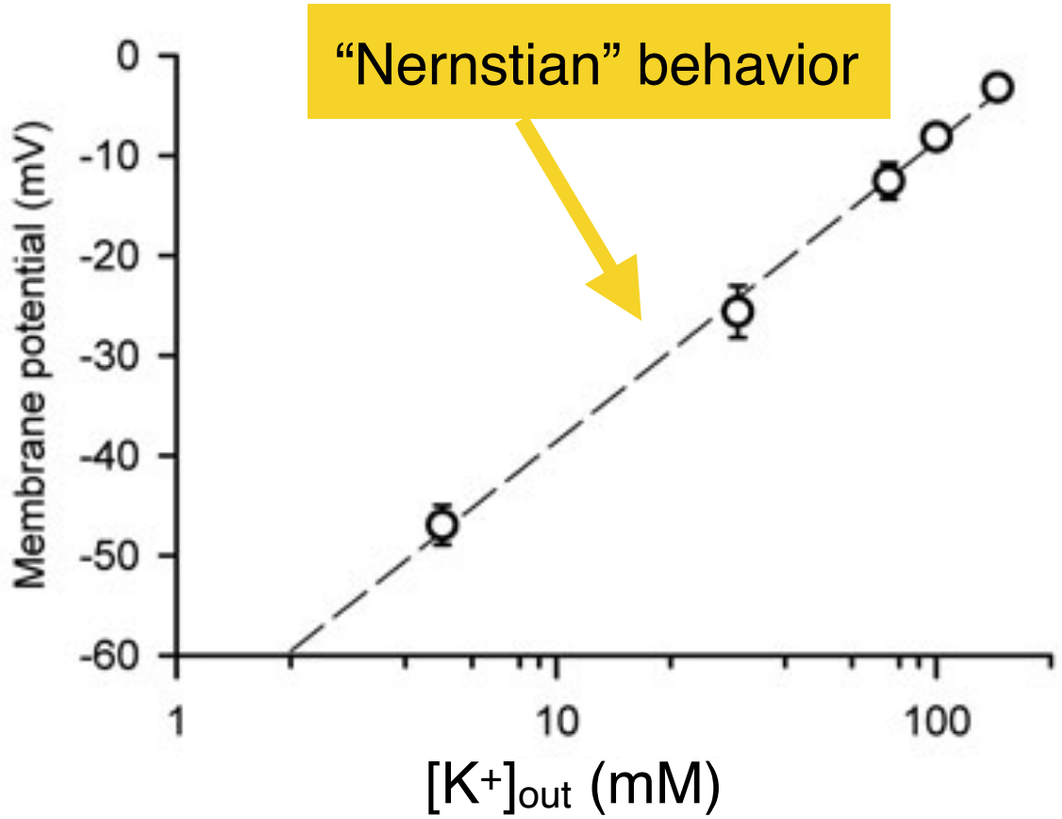
Roger Jackson Centre for Health and Wellness Research, Faculty of Kinesiology, University of Calgary, Calgary, Alberta, Canada T2N 4N1

Non-technical summary The debilitating condition of arthritis is caused by degeneration of the cartilage, a tissue that allows almost frictionless motion between the ends of bones in articulating joints such as the knee. The integrity of the cartilage is maintained by the metabolic activity of chondrocytes, the only type of cell found within the cartilage. An important factor in regulating the rate of metabolic activity of the chondrocytes is thought to be the magnitude of the electrical potential difference across the cell membrane, i.e. the 'membrane potential'. This study identifies a type of ion channel, a so-called 'two-pore potassium channel', which was not previously known to be expressed in human chondrocytes. This ion channel importantly contributes to controlling chondrocyte membrane potential. Elucidation of the factors that control chondrocyte membrane potential is important for understanding the normal and pathophysiology of the chondrocytes, and consequently the health of the cartilage.

increasing $[K^+]_{out}$ depolarizes chondrocytes

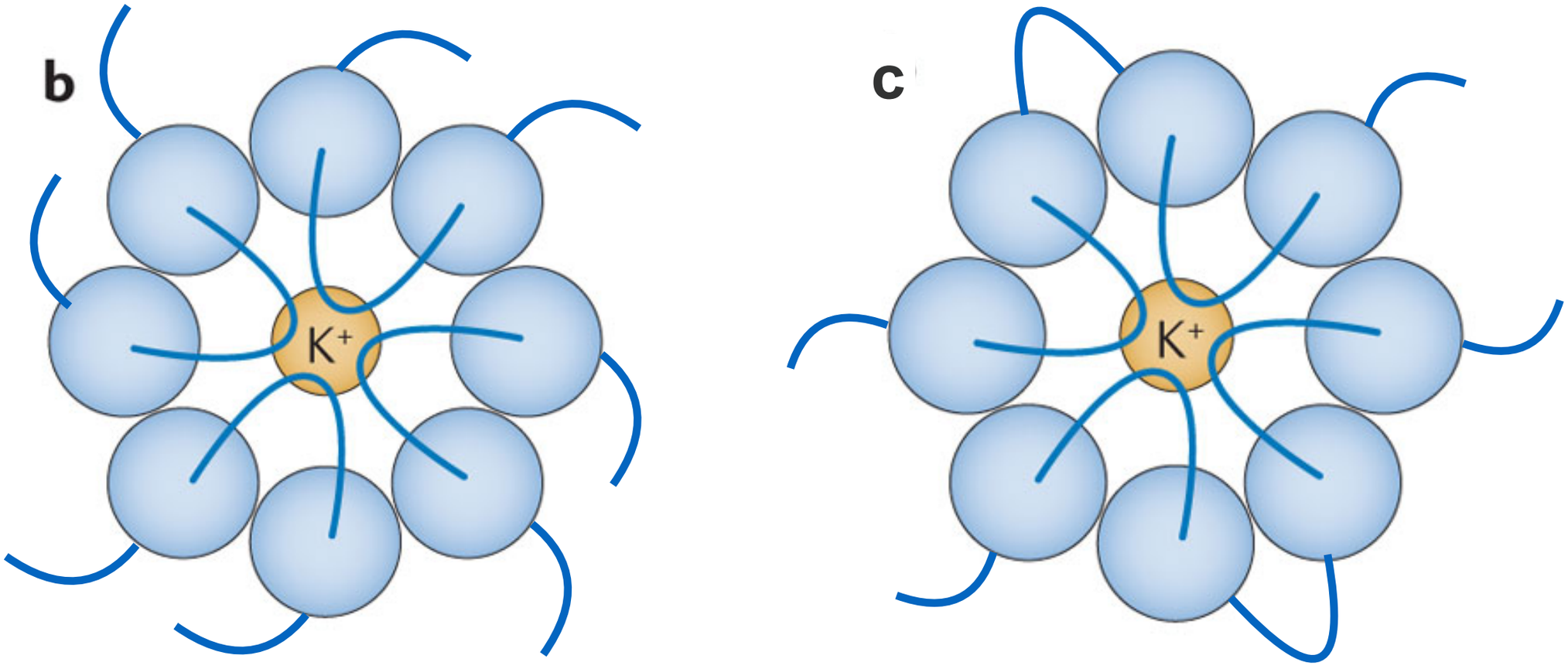




The **two-pore-domain potassium channels** form **leak channels** that are also regulated by O_2, pH, and G-proteins.

$$V_m = E_K = \frac{RT}{F} \ln \frac{[K^+]_{out}}{[K^+]_{in}}$$

Schematic structure of potassium channels



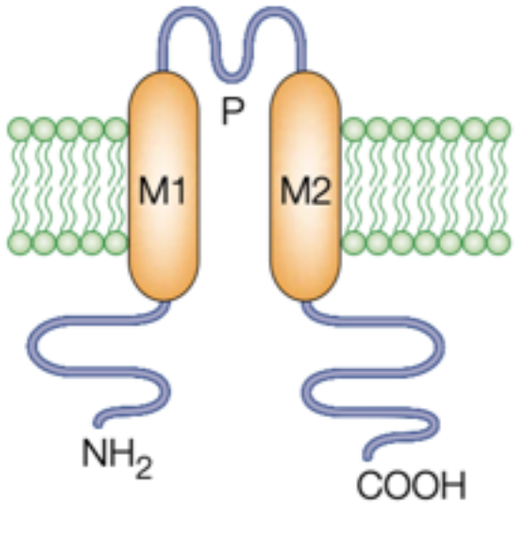
b | A top view of a Kir or Kv channel, showing the two transmembrane segments of each of the four α-subunits and their corresponding pore-forming loops (P-loops).

c | For K2P channels, four transmembrane segments of each of the two α-subunits (each with two P-loops) constituting a channel.

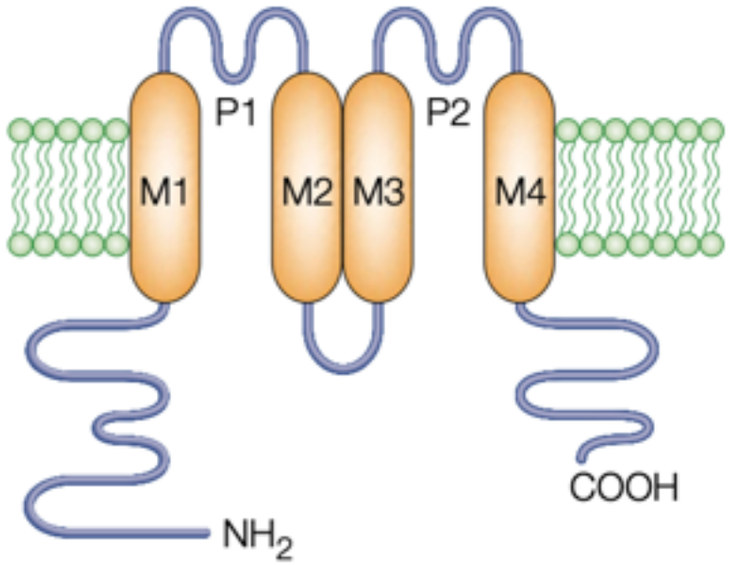
Adapted from doi:10.1038/nrc3635

structure of K^+ channel **monomers**

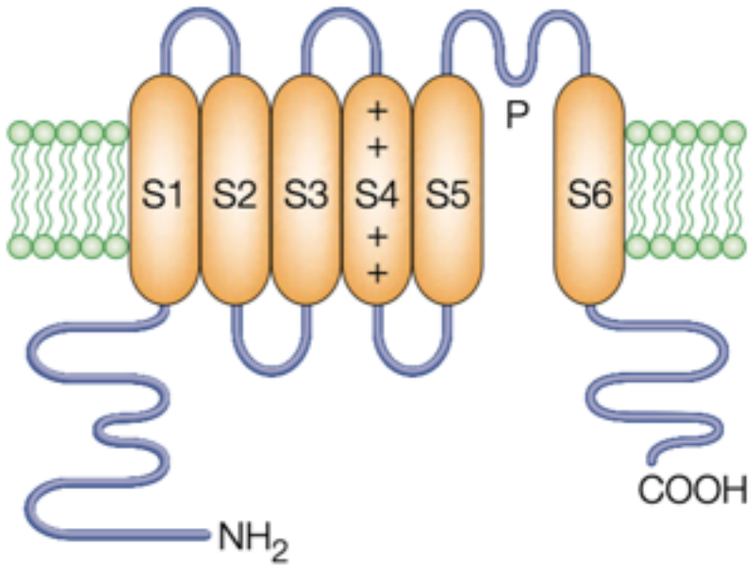
Kir, KcsA



K2P



Kv, CNG, KCa(SK), KCNQ, HCN, TRP...



open at rest

gated channels: generally closed at rest (except KCNQ activated at voltages lower than V_{rest})

TABLE 1.3 Free Ion Concentrations and Equilibrium Potentials for Mammalian Skeletal Muscle

Ion	Extracellular concentration (mM)	Intracellular concentration (mM)	$\frac{[Ion]_o}{[Ion]_i}$	Equilibrium potential[a] (mV)
Na^+	145	12	12	+67
K^+	4	155	0.026	–98
Ca^{2+}	1.5	100 nM	15,000	+129
Cl^-	123	4.2[b]	29[b]	–90[b]

[a] Calculated from Equation 1.11 at 37°C.

[b] Calculated assuming a –90-mV resting potential for the muscle membrane and that Cl^- ions are at equilibrium at rest.

$$E_S = \frac{RT}{z_S F} \ln \frac{[S]_{out}}{[S]_{in}}$$

Remember:

z_S = 2 for calcium
z_S = -1 for chloride

etc.

Commit these values to memory

$$V = \Phi_{in} - \Phi_{out}$$

$$V_{rest} \approx -65 \text{ mV}$$

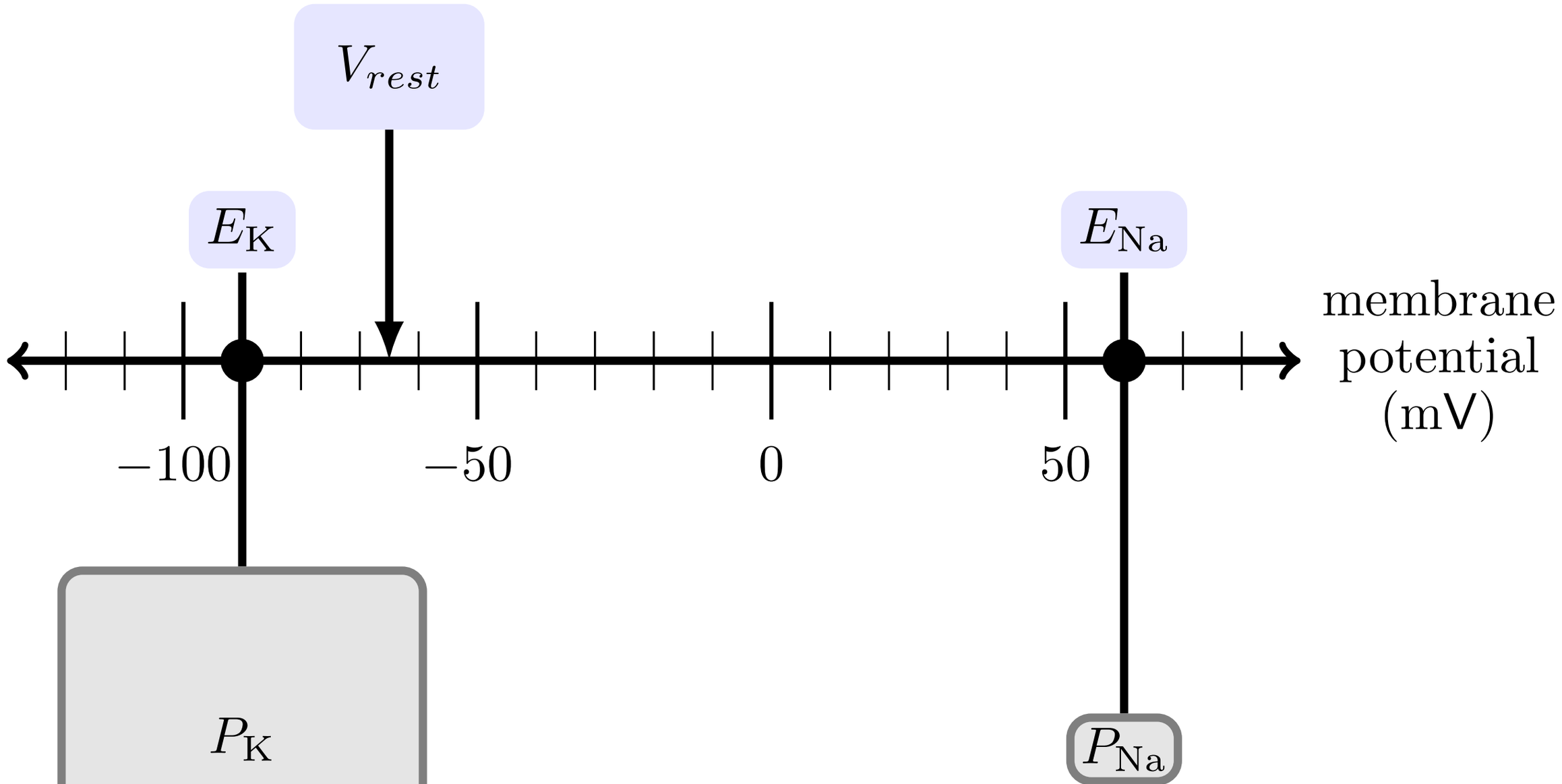
$$E_{Ca} \approx +115 \text{ mV}$$

$$E_{Na} \approx +60 \text{ mV}$$

$$E_{Cl} \approx -85 \text{ mV}$$

$$E_{K} \approx -90 \text{ mV}$$

Resting membrane potential determined by membrane permeability to potassium, sodium and chloride (in that order)



Goldman-Hodgkin-Katz voltage equation

$$V_m = \frac{RT}{F} \ln \frac{(P_K[K]_o + P_{Na}[Na]_o + P_{Cl}[Cl]_i}{(P_K[K]_i + P_{Na}[Na]_i + P_{Cl}[Cl]_o}$$

V_m is a function of the ion concentrations and relative permeability of each ion

for monovalent ions: sodium, potassium and chloride

non-Nernstian behavior of V_m

only for mature (adult) neurons and not always the case

$$V_m = \frac{RT}{F}\ln\left(\frac{P_K[K]_o + P_{Na}[Na]_o + P_{Cl}[Cl]_i}{P_K[K]_i + P_{Na}[Na]_i + P_{Cl}[Cl]_o}\right)$$

assume $E_{Cl} \approx V_m$ or $P_{Cl} \ll P_K$ so we can ignore the contributions of $P_{Cl}[Cl]$

$$V_m = \frac{RT}{F}\ln\left(\frac{P_K[K]_o + P_{Na}[Na]_o}{P_K[K]_i + P_{Na}[Na]_i}\right)$$

define $\alpha = P_{Na}/P_K$

$$V_m = \frac{RT}{F}\ln\left(\frac{[K]_o + \alpha[Na]_o}{[K]_i + \alpha[Na]_i}\right)$$

consider that $\alpha \ll 1$ and $[Na]_i \ll [K]_i$ and therefore $[K]_i + \alpha[Na]_i \approx [K]_i$

$$V_m \approx \frac{RT}{F}\ln\left(\frac{[K]_o + \alpha[Na]_o}{[K]_i}\right)$$

you should understand and be comfortable with each step here!

non-Nernstian behavior of V_m

$$V_m \approx \frac{RT}{F} \ln\left(\frac{[K]_o + \alpha[Na]_o}{[K]_i}\right)$$

non-Nernstian behavior of V_m

when $[K^+]_o$ is high... it's just E_K eq.

$$V_m \approx \frac{RT}{F} \ln\left(\frac{[K]_o + \alpha[Na]_o}{[K]_i}\right)$$

non-Nernstian behavior of V_m

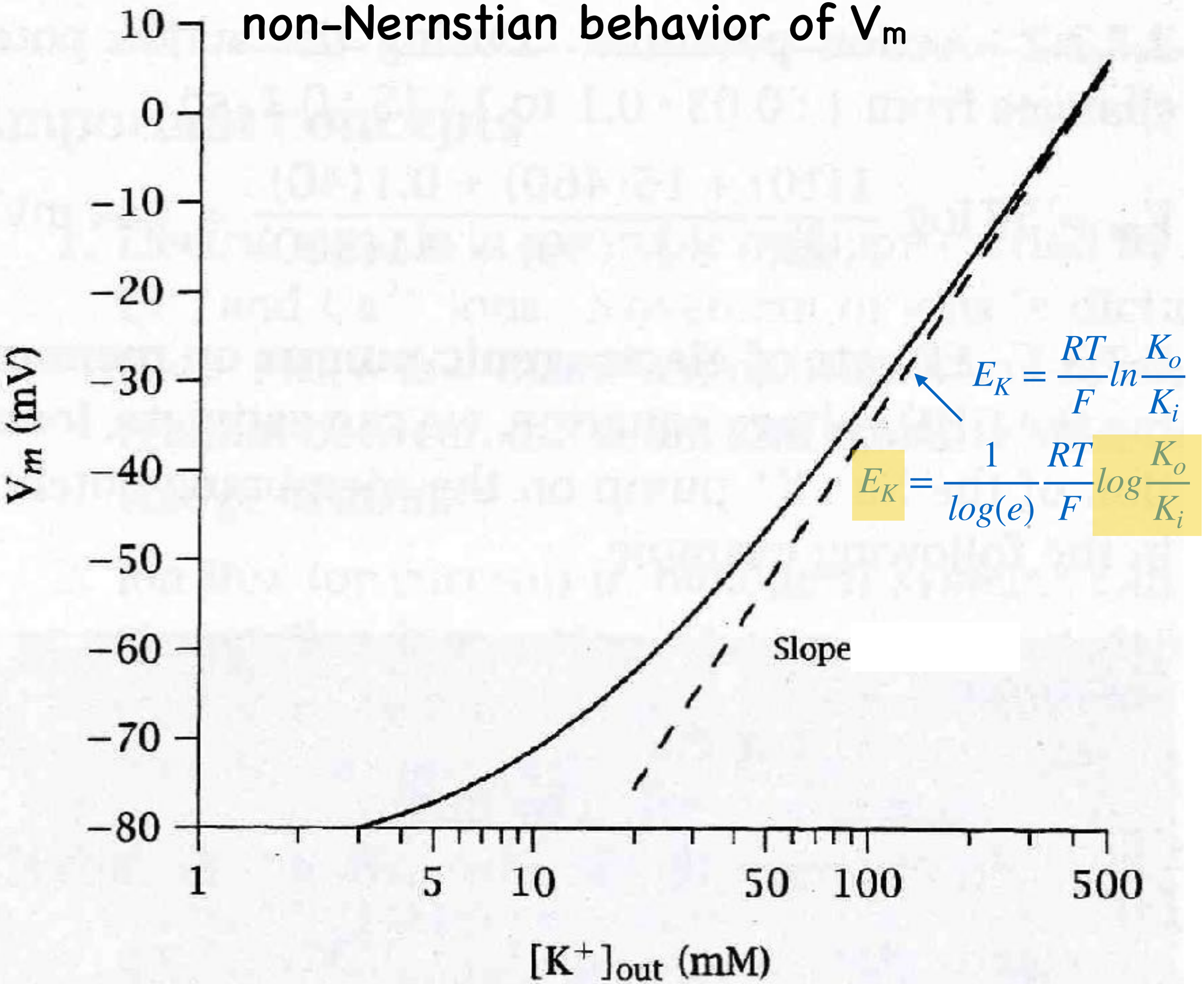
when $[K^+]_o$ is high... it's just E_K eq.

$$V_m \approx \frac{RT}{F} \ln\left(\frac{[K]_o + \alpha[Na]_o}{[K]_i}\right)$$

but when $[K^+]_o$ is low... this term is relevant

$$V_m \approx \frac{RT}{F} \ln\left(\frac{[K]_o + \alpha[Na]_o}{[K]_i}\right)$$

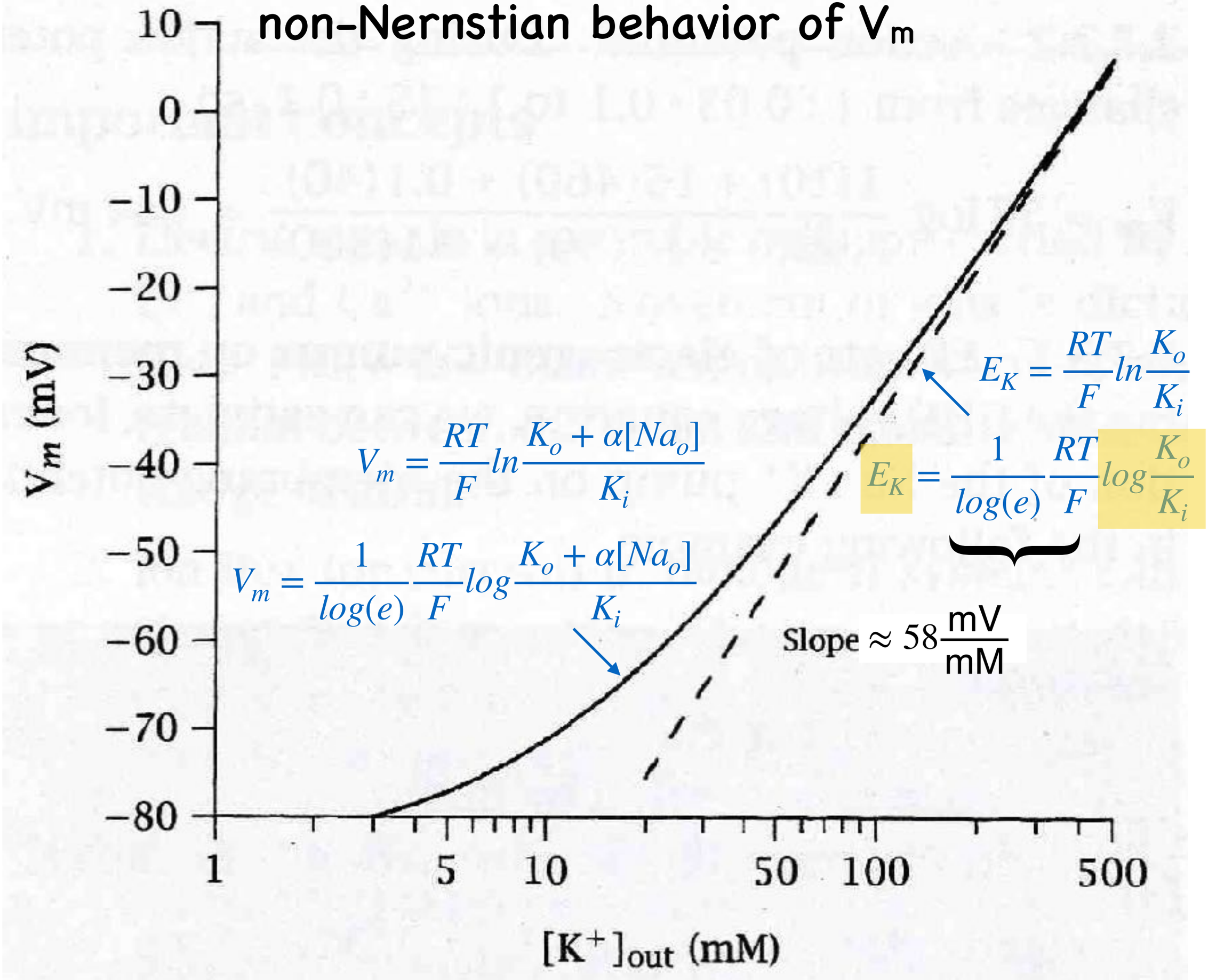
non-Nernstian behavior of V_m



$$E_K = \frac{RT}{F} ln \frac{K_o}{K_i}$$

$$E_K = \frac{1}{log(e)} \frac{RT}{F} log \frac{K_o}{K_i}$$

non-Nernstian behavior of V_m



$$V_m = \frac{RT}{F} ln \frac{K_o + \alpha[Na_o]}{K_i}$$

$$V_m = \frac{1}{log(e)} \frac{RT}{F} log \frac{K_o + \alpha[Na_o]}{K_i}$$

$$E_K = \frac{RT}{F} ln \frac{K_o}{K_i}$$

$$E_K = \underbrace{\frac{1}{log(e)} \frac{RT}{F}} log \frac{K_o}{K_i}$$

Slope $\approx 58 \frac{mV}{mM}$

1. GHK voltage equation considers all permeant ions to compute resting membrane potential (V_m)

2. GHK voltage equation requires permeabilities (or relative permeabilities and concentrations

3. resting V_m largely depends on K^+ but as $[K^+]_o$ decreases, $[Na^+]_o$ plays a larger role