Introduction to Computational Neuroscience

Biol 698
Math 635
Biol 498
Math 430

Bibliography:

"Mathematical Foundations of Neuroscience", by G. B. Ermentrout & D. H. Terman - Springer (2010), 1st edition. ISBN 978-0-387-87707-5

* "Foundations of Cellular Neurophysiology", by Daniel Johnston and Samuel M.-S. Wu. The MIT Press, 1995. ISBN 0-262-10053-3

* "Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting", by Eugene M. Izhikevich. The MIT Press, 2007. ISBN 0-262-09043-8

* "Biophysics of Computation - Information processing in single neurons", by Christof Koch. Oxford University Press, 1999. ISBN 0-19-510491-9

* "Theoretical Neuroscience: Computational and Mathematical Modeling of Neural Systems", by Peter Dayan and Larry F. Abbott. The MIT Press,2001. ISBN 0-262-04199-5

Figures were taken from some of these books

Overview

- The passive membrane equation (review)

- Goldman-Hodgkin-Katz equation

- Mechanism of action potential generation
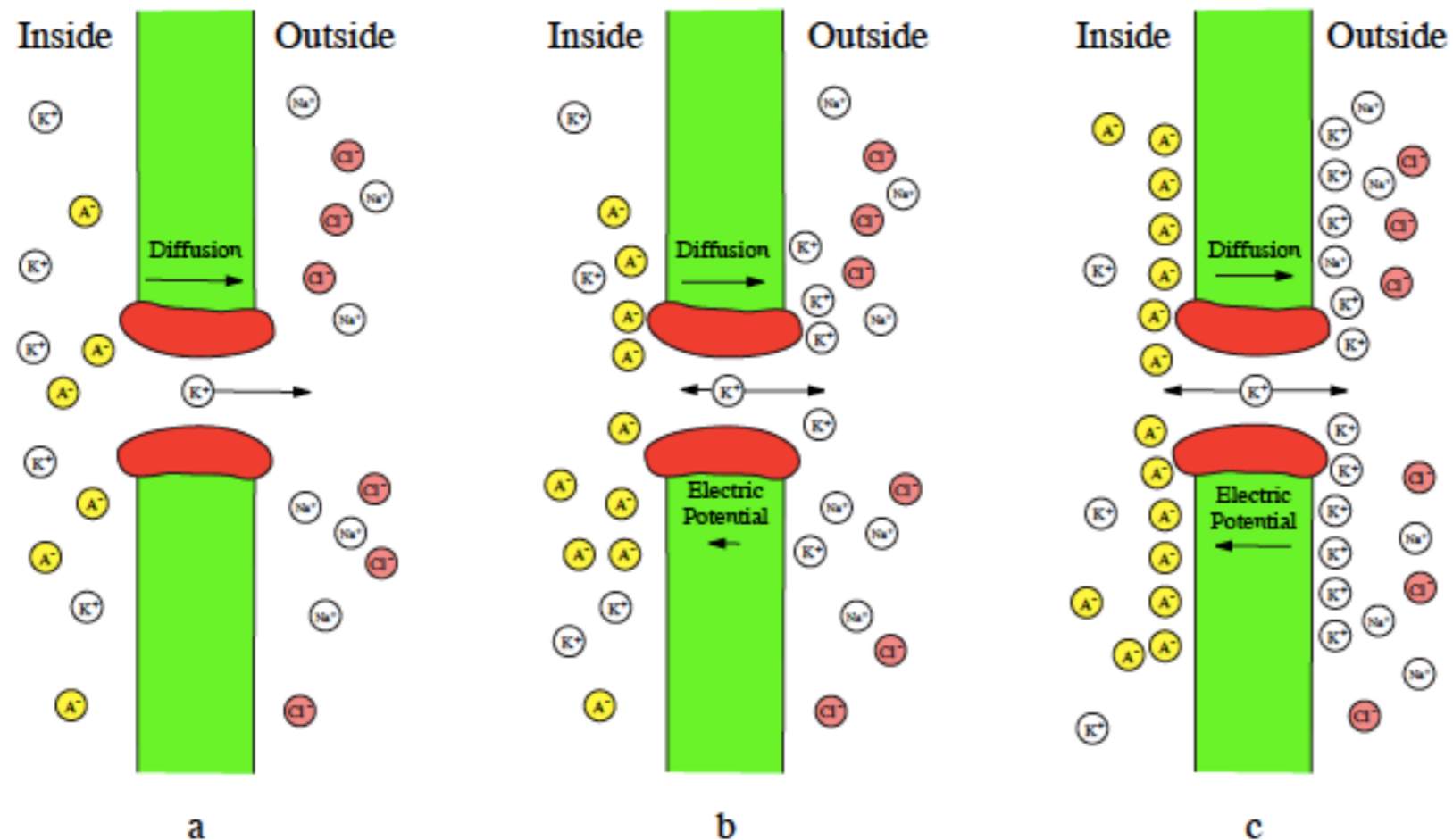
- Hodgkin-Huxley equation

Nernst equation (review)

Figure 2.2: Diffusion of K^+ ions down the concentration gradient though the membrane (a) creates an electric potential force pointing in the opposite direction (b) until the diffusion and electrical forces counter each other (c). The resulting transmembrane potential (2.1) is referred to as the Nernst equilibrium potential for K^+.

Nernst equation (review)

The membrane potential is at rest when the net cross-membrane current is equal to zero

✓ Nernst Equation:

$$E_X = \frac{R\,T}{z\,F} \ln \frac{C_{X,out}}{C_{X,in}}$$

E_X: Equilibrium potential of ion X
R: gas constant (1.98 cal/°K-mol)
F: Faraday's constant (96,480 C/mol))
z: Valence
T: Temperature (°K)

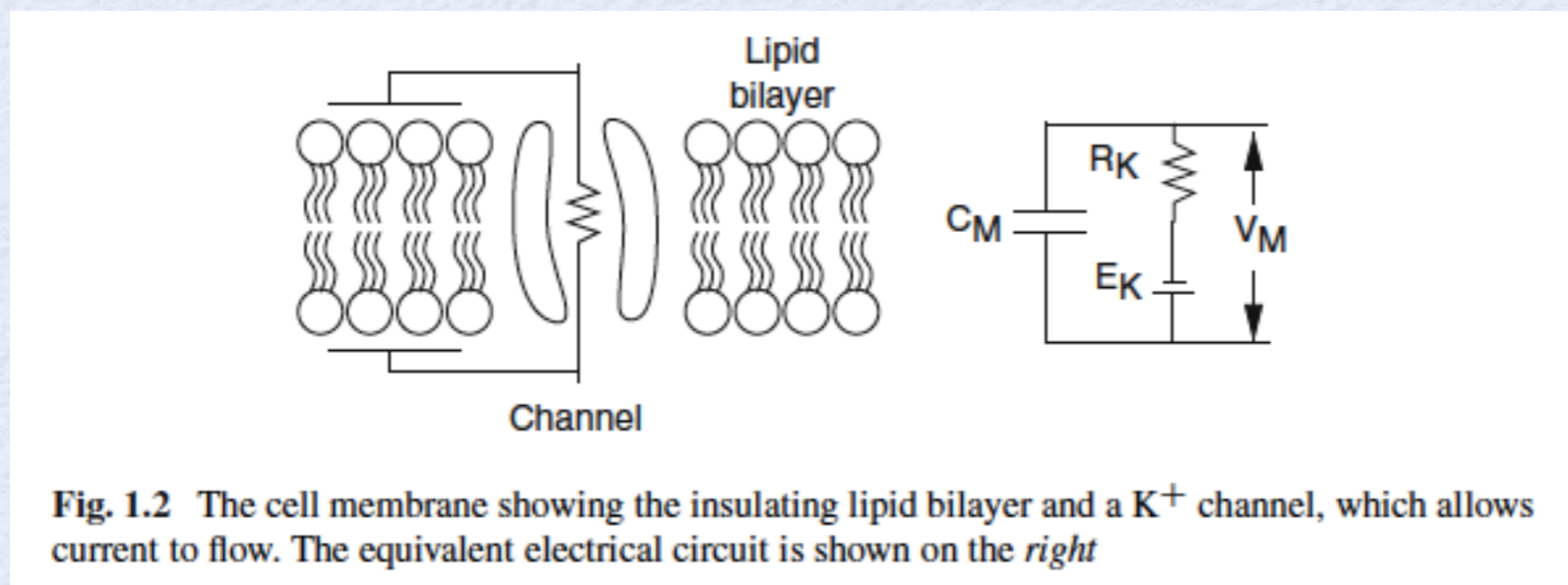# Nernst equation (review)

✓ Reversal potentials:

Table 1.1 Typical ion concentrations in cells (from Johnston and Wu [139])

Ion	Inside (mM)	Outside (mM)	Equilibrium potential (mV), $E_i = \frac{RT}{zF} \ln \frac{[C]_{out}}{[C]_{in}}$
Frog muscle			$T = 20°C$
K^+	124	2.25	$58 \log \frac{2.25}{124} = -101$
Na^+	10.4	109	$58 \log \frac{109}{10.4} = +59$
Cl^-	1.5	77.5	$-58 \log \frac{77.5}{1.5} = -99$
Ca^{2+}	10^{-4}	2.1	$29 \log \frac{2.1}{10^{-4}} = +125$
Squid axon			$T = 20°C$
K^+	400	20	$58 \log \frac{20}{400} = -75$
Na^+	50	440	$58 \log \frac{440}{50} = +55$
Cl^-	40–150	560	$-58 \log \frac{560}{40-150} = -66 \text{ to} -33$
Ca^{2+}	10^{-4}	10	$29 \log \frac{10}{10^{-4}} = +145$
Mammalian cell			$T = 37°C$
K^+	140	5	$62 \log \frac{5}{140} = -89.7$
Na^+	5–15	145	$62 \log \frac{145}{5-15} = +90 - (+61)$
Cl^-	4	110	$-62 \log \frac{110}{4} = -89$
Ca^{2+}	10^{-4}	2.5–5	$31 \log \frac{2.5-5}{10^{-4}} = +136 - (+145)$

Equivalent circuit model (review)

Components

- Capacitors: representing the ability of the membrane to store charge

- batteries: representing the concentration gradients of the ions

- conductors or resistors: representing the ion channels

Fig. 1.2 The cell membrane showing the insulating lipid bilayer and a K^+ channel, which allows current to flow. The equivalent electrical circuit is shown on the *right*

membrane only permeable to K^+

Passive membrane equation (review)

Intrinsic electric circuit + Injected (I_{inj}) or applied current (I_{app})

Kirchhoff's current law:

The total current into the cell must add up to z
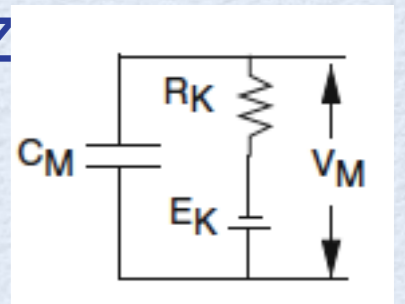
$$C\frac{dV}{dt} = -G_L(V-E_L) + I_{inj}(t)$$

$$C\frac{dV}{dt} = -G_L(V-E_L) + I_{app}(t)$$

Passive membrane equation

time constant:

$$\tau = R\,C$$

$$C\frac{dV}{dt} = -G_L(V - E_L) + I_{inj}(t)$$

$$\tau\frac{dV}{dt} = -V + E_L + I_{inj}(t)R$$

Passive membrane equation (review)

- $I_{app} = I_0$ (const) $V_\infty = R\, I_0$

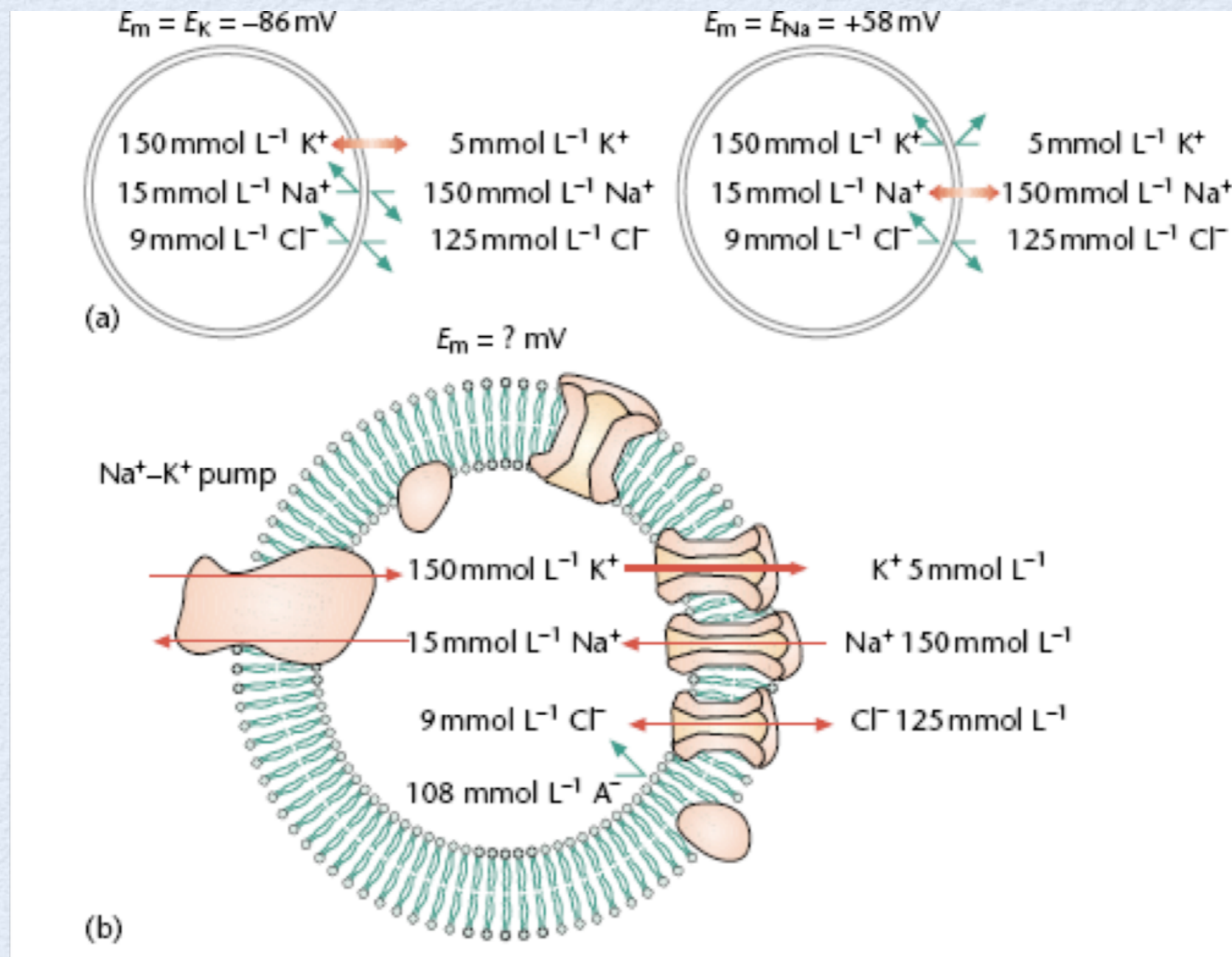$$V(t) = \boxed{V_\infty + E_L} + (V_0 - E_L - V_\infty)\, e^{-t/\tau}$$

steady state

- $V_0 = E_L$

$$V(t) = \boxed{V_\infty + E_L} - V_\infty\, e^{-t/\tau}$$

steady state

Multi-ion electrochemical equilibrium

Multi-ion electrochemical equilibrium

Goldman-Hodgkin-Katz equation:

$$E_m = \frac{R\,T}{F}\,\ln\frac{P_{K^+}[K^+]_o + P_{Na^+}[Na^+]_o + P_{Cl^-}[Cl^-]_i}{P_{K^+}[K^+]_i + P_{Na^+}[Na^+]_i + P_{Cl^-}[Cl^-]_o}$$

P_X: Permeability of ion X

R, T, F: Gas constant, Temperature (°K) and Faraday constant

Multi-ion electrochemical equilibrium

Goldman-Hodgkin-Katz equation:

$$E_m = \frac{R\,T}{F}\,\ln\frac{[K^+]_o + b\,[Na^+]_o}{[K^+]_i + b\,[Na^+]_i} \qquad b = \frac{P_{Na^+}}{P_{K^+}}$$

P_X: Permeability of ion X

R, T, F: Gas constant, Temperature (°K) and Faraday constant

Multi-ion electrochemical equilibrium

Goldman-Hodgkin-Katz equation:

$$E_m = \frac{R\,T}{F}\,\ln\frac{[K^+]_o + b\,[Na^+]_o}{[K^+]_i + b\,[Na^+]_i} \qquad b = \frac{P_{Na^+}}{P_{K^+}}$$

$$[Na^+]_o = 145\ \frac{\text{mmol}}{L} \qquad [Na^+]_i = 10\ \frac{\text{mmol}}{L} \qquad E_{Na^+} = +67\ \text{mV}$$

$$[K^+]_o = 5\ \frac{\text{mmol}}{L} \qquad [K^+]_i = 140\ \frac{\text{mmol}}{L} \qquad E_{Na^+} = -84\ \text{mV}$$

Multi-ion electrochemical equilibrium

Goldman-Hodgkin-Katz equation:

$$E_m = \frac{R\,T}{F}\ln\frac{[K^+]_o + b\,[Na^+]_o}{[K^+]_i + b\,[Na^+]_i} \qquad\qquad b = \frac{P_{Na^+}}{P_{K^+}}$$

$$[Na^+]_o = 145\ \frac{mmol}{L} \qquad [Na^+]_i = 10\ \frac{mmol}{L} \qquad E_{Na^+} = +67\ mV$$

$$[K^+]_o = 5\ \frac{mmol}{L} \qquad [K^+]_i = 140\ \frac{mmol}{L} \qquad E_{Na^+} = -84\ mV$$

Membrane 20 times more permeable to K^+ than to Na^+:

$$b = 0.05 \qquad\qquad E_m = -78\ mV$$

Multi-ion electrochemical equilibrium

Goldman-Hodgkin-Katz equation:

$$E_m = \frac{R\,T}{F} \ln \frac{[K^+]_o + b\,[Na^+]_o}{[K^+]_i + b\,[Na^+]_i} \qquad\qquad b = \frac{P_{Na^+}}{P_{K^+}}$$

$[Na^+]_o = 145\ \dfrac{mmol}{L}$ $[Na^+]_i = 10\ \dfrac{mmol}{L}$ $E_{Na^+} = +67\ mV$

$[K^+]_o = 5\ \dfrac{mmol}{L}$ $[K^+]_i = 140\ \dfrac{mmol}{L}$ $E_{Na^+} = -84\ mV$

Membrane 10 times more permeable to Na+ than to K+:

$b = 10$ $\qquad\qquad$ $E_m = +51\ mV$

Multi-ion electrochemical equilibrium

Goldman-Hodgkin-Katz equation:

$$E_m = \frac{R\,T}{F} \ln \frac{[K^+]_o + b\,[Na^+]_o}{[K^+]_i + b\,[Na^+]_i} \qquad b = \frac{P_{Na^+}}{P_{K^+}}$$

$[Na^+]_o = 145\ \dfrac{mmol}{L}$ $\qquad$ $[Na^+]_i = 10\ \dfrac{mmol}{L}$ $\qquad$ $E_{Na^+} = +67\ mV$

$[K^+]_o = 5\ \dfrac{mmol}{L}$ $\qquad$ $[K^+]_i = 140\ \dfrac{mmol}{L}$ $\qquad$ $E_{Na^+} = -84\ mV$

Membrane 5 times more permeable to K^+ than to Na^+:

$b = 0.2$ $\qquad\qquad$ $E_m = -61\ mV$

Multi-ion electrochemical equilibrium

Fig. 1.7 The action potential. During the upstroke, Na^+ channels open and the membrane potential approaches the Na^+ Nernst potential. During the downstroke, Na^+ channels are closed, K^+ channels are open, and the membrane potential approaches the K^+ Nernst potential

Membrane 5 times more permeable to K^+ than to Na^+:

b = 0.2 E_m = -61 mV

Multi-ion electrochemical equilibrium

Fig. 1.7 The action potential. During the upstroke, Na⁺ channels open and the membrane potential approaches the Na⁺ Nernst potential. During the downstroke, Na⁺ channels are closed, K⁺ channels are open, and the membrane potential approaches the K⁺ Nernst potential

Membrane 10 times more permeable to Na⁺ than to K⁺:

$b = 10$ $E_m = +51$ mV

Multi-ion electrochemical equilibrium

Fig. 1.7 The action potential. During the upstroke, Na$^+$ channels open and the membrane potential approaches the Na$^+$ Nernst potential. During the downstroke, Na$^+$ channels are closed, K$^+$ channels are open, and the membrane potential approaches the K$^+$ Nernst potential
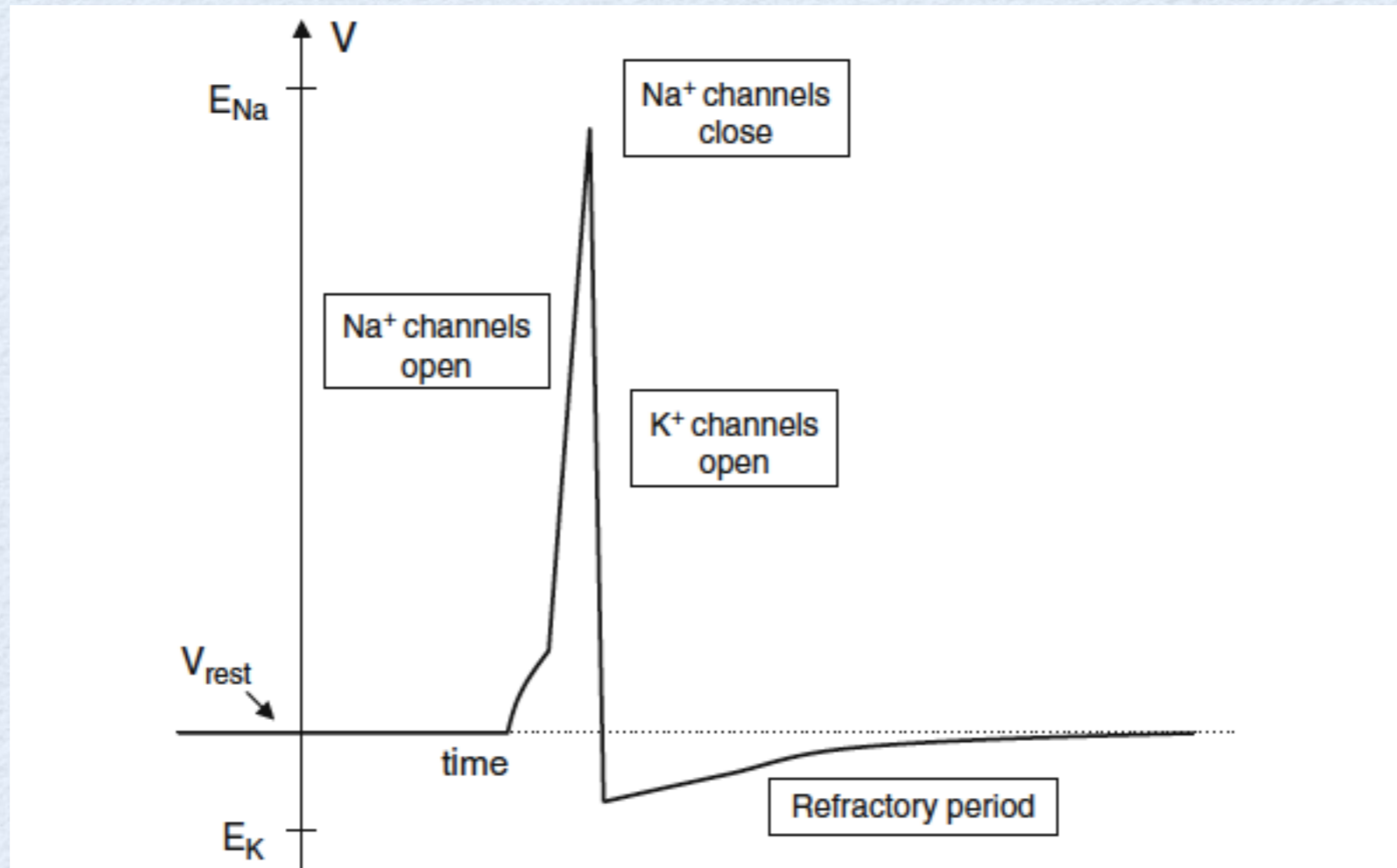
Membrane 20 times more permeable to K$^+$ than to Na$^+$:

b = 0.05 E_m = -78 mV

The Hodgkin-Huxley equation

Hodgkin & Huxley (1949) demonstrated that:

- The resting membrane of a squid axon is 25 times more permeable to K^+ than to Na^+

- At the peak of an action potential the membrane is 20 times more permeable to Na^+ than to K^+.

- During after - hyperpolarization the membrane permeability to Na^+ is very low and that of K^+ is larger than at rest

Multi-ion electrochemical equilibrium

✓ Major ionic currents:

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

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

$$I_{Ca} = g_{Ca} (V - E_{Ca})$$

$$I_{Cl} = g_{Cl} (V - E_{Cl})$$
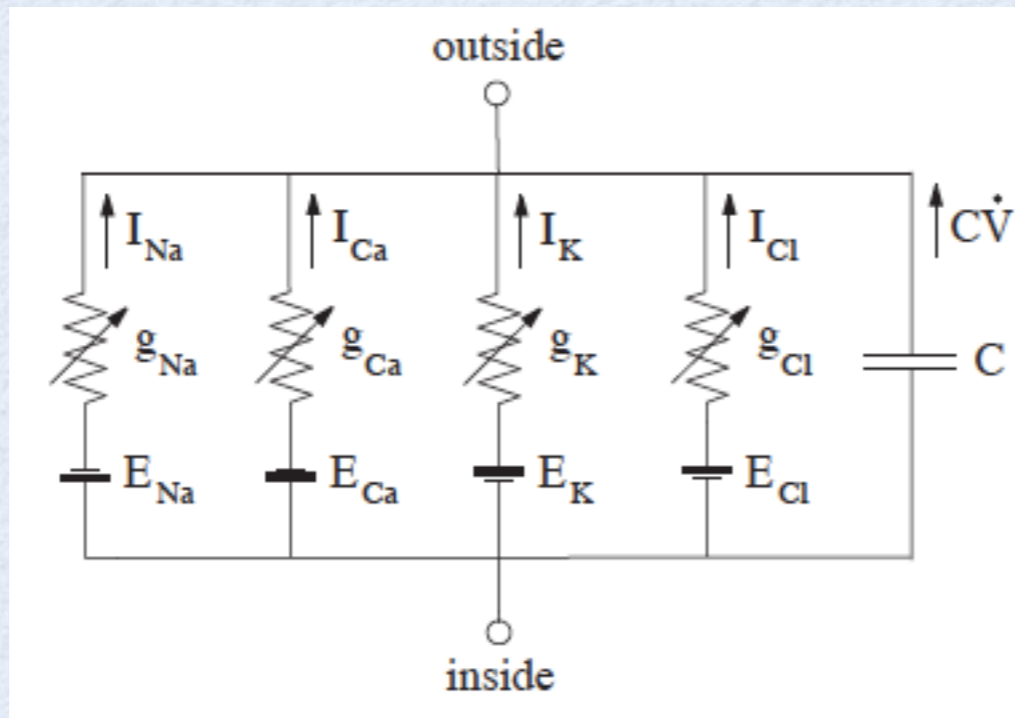
Figure 2.3: Equivalent circuit representation of a patch of cell membrane.

Multi-ion electrochemical equilibrium

Kirchhoff's current law: the total current flowing across a patch of cell membrane is the sum of the membrane capacitive current and all the ionic currents.
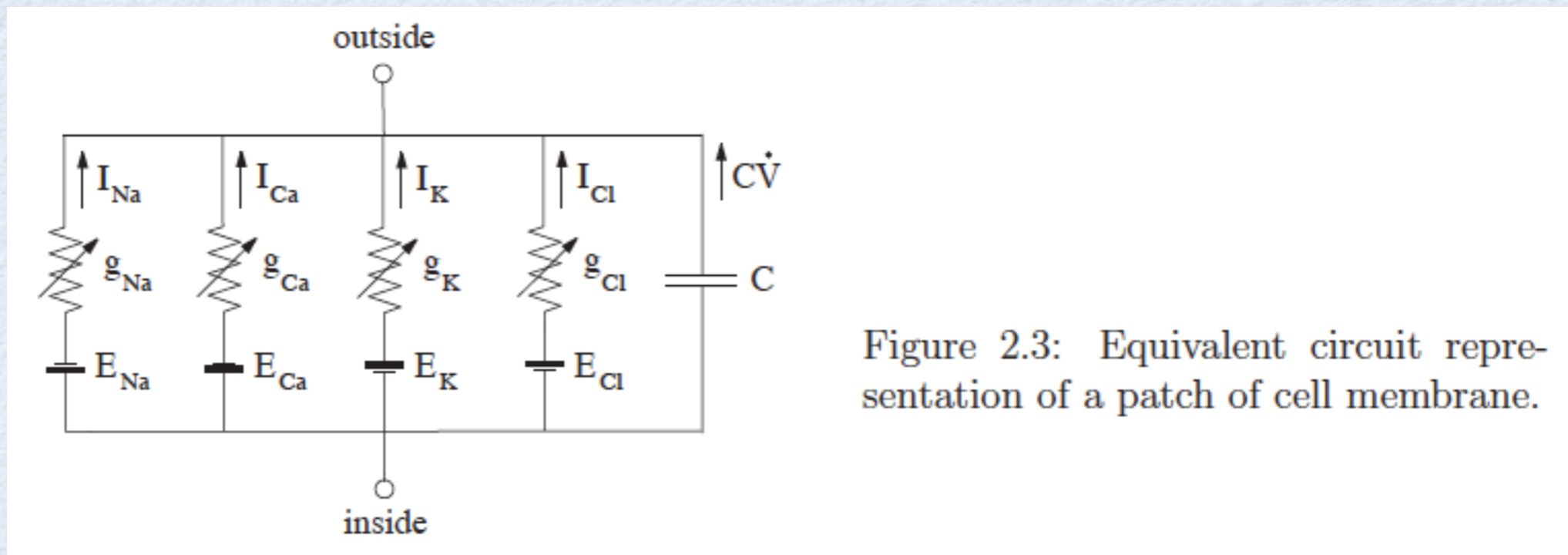
Figure 2.3: Equivalent circuit representation of a patch of cell membrane.

$$C\dot{V} = I - I_{\text{Na}} - I_{\text{Ca}} - I_{\text{K}} - I_{\text{Cl}}$$

$$C\dot{V} = I - g_{\text{Na}}\left(V - E_{\text{Na}}\right) - g_{\text{Ca}}\left(V - E_{\text{Ca}}\right) - g_{\text{K}}\left(V - E_{\text{K}}\right) - g_{\text{Cl}}\left(V - E_{\text{Cl}}\right)$$

Multi-ion electrochemical equilibrium

✓ Major ionic currents:

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

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

Fig. 1.6 Equivalent circuit underlying the Hodgkin–Huxley equations

$$C \frac{dV}{dt} = I \quad -g_{Na}(V - E_{Na}) \quad - g_K(V - E_K) \quad - g_L(V - E_L)$$
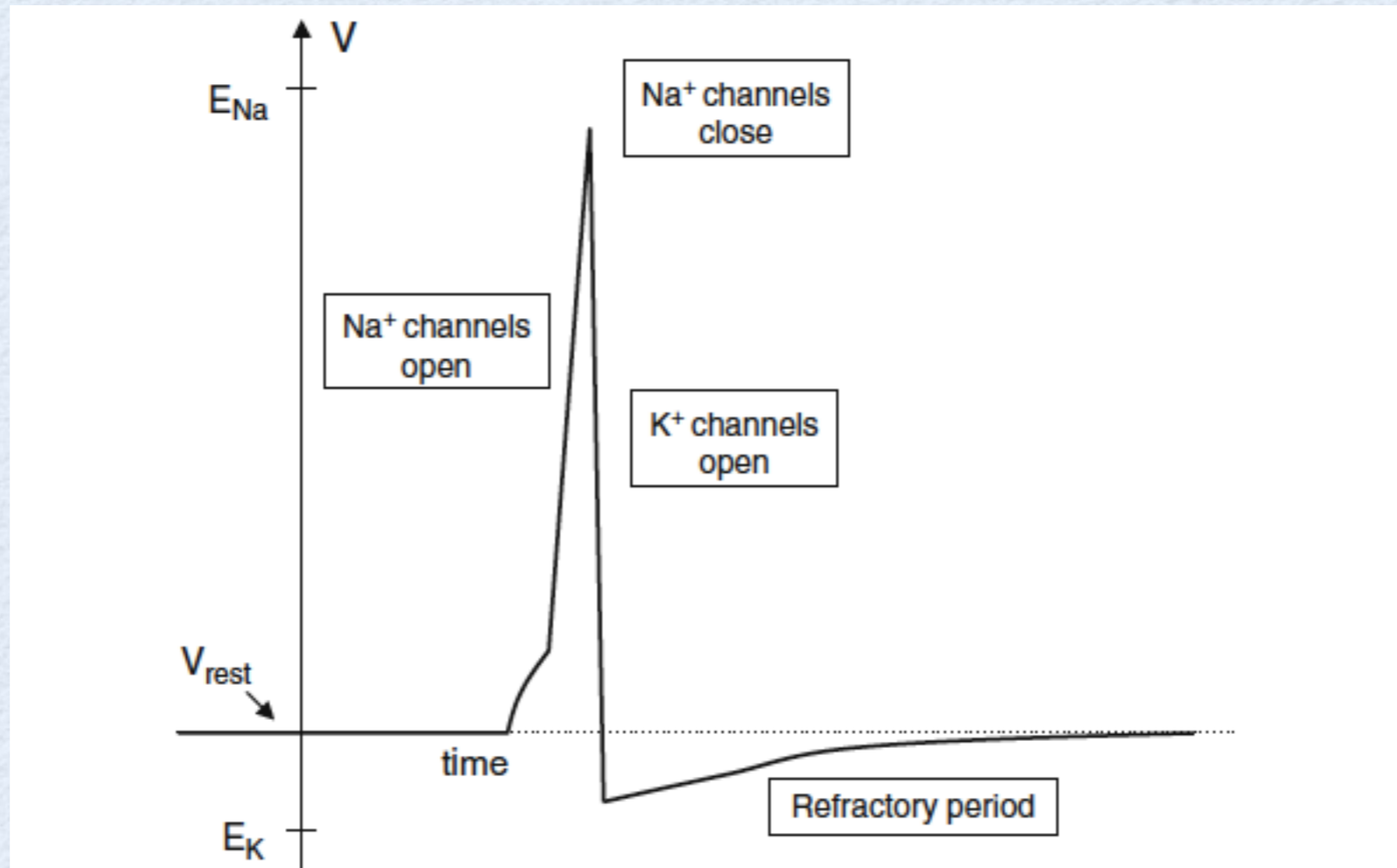
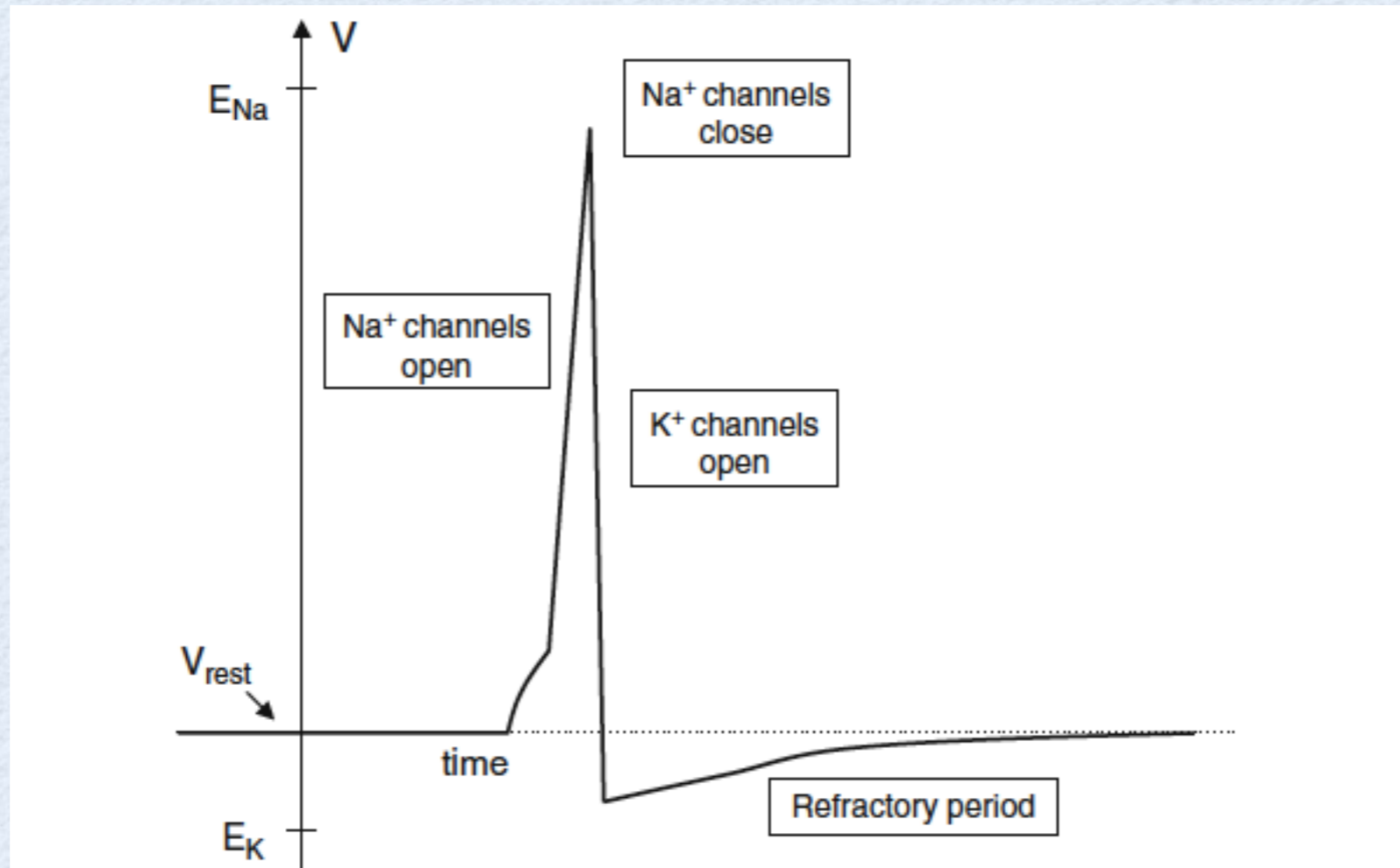# Multi-ion electrochemical equilibrium

Fig. 1.7 The action potential. During the upstroke, Na^+ channels open and the membrane potential approaches the Na^+ Nernst potential. During the downstroke, Na^+ channels are closed, K^+ channels are open, and the membrane potential approaches the K^+ Nernst potential

$$C\frac{dV}{dt} = I \quad -g_{Na}(V - E_{Na}) \quad -g_K(V - E_K) \quad -g_L(V - E_L)$$

Multi-ion electrochemical equilibrium

Fig. 1.7 The action potential. During the upstroke, Na^+ channels open and the membrane potential approaches the Na^+ Nernst potential. During the downstroke, Na^+ channels are closed, K^+ channels are open, and the membrane potential approaches the K^+ Nernst potential

$$C \frac{dV}{dt} = I \quad -g_{Na}(V - E_{Na}) \quad -g_K(V - E_K) \quad - g_L(V - E_L)$$

Multi-ion electrochemical equilibrium

Fig. 1.7 The action potential. During the upstroke, Na^+ channels open and the membrane potential approaches the Na^+ Nernst potential. During the downstroke, Na^+ channels are closed, K^+ channels are open, and the membrane potential approaches the K^+ Nernst potential

$$C \frac{dV}{dt} = I \quad -g_{Na}(V - E_{Na}) \quad - g_K(V - E_K) - g_L(V - E_L)$$

Multi-ion electrochemical equilibrium

Figure 2.3: Equivalent circuit representation of a patch of cell membrane.

$$C\dot{V} = I - g_{Na}\left(V - E_{Na}\right) - g_{Ca}\left(V - E_{Ca}\right) - g_{K}\left(V - E_{K}\right) - g_{Cl}\left(V - E_{Cl}\right)$$

$$C\dot{V} = I - g_{inp}(V - V_{rest})$$

$$g_{inp} = g_{Na} + g_{Ca} + g_{K} + g_{Cl}$$

$$V_{rest} = \frac{g_{Na}E_{Na} + g_{Ca}E_{Ca} + g_{K}E_{K} + g_{Cl}E_{Cl}}{g_{Na} + g_{Ca} + g_{K} + g_{Cl}}$$

Multi-ion electrochemical equilibrium

$$C\dot{V} = I - g_{\text{Na}}(V - E_{\text{Na}}) - g_{\text{Ca}}(V - E_{\text{Ca}}) - g_{\text{K}}(V - E_{\text{K}}) - g_{\text{Cl}}(V - E_{\text{Cl}})$$

$$C\dot{V} = I - g_{\text{inp}}(V - V_{\text{rest}})$$

$$V_{\text{rest}} = \frac{g_{\text{Na}}E_{\text{Na}} + g_{\text{Ca}}E_{\text{Ca}} + g_{\text{K}}E_{\text{K}} + g_{\text{Cl}}E_{\text{Cl}}}{g_{\text{Na}} + g_{\text{Ca}} + g_{\text{K}} + g_{\text{Cl}}}$$

$$g_{\text{inp}} = g_{\text{Na}} + g_{\text{Ca}} + g_{\text{K}} + g_{\text{Cl}}$$ input conductance

$$R_{\text{inp}} = 1/g_{\text{inp}}$$ input resistance   measures the asymptotic sensitivity of the membrane potential to injected (applied) or intrinsic currents

$$V \rightarrow V_{\text{rest}} + I R_{\text{inp}}$$

Multi-ion electrochemical equilibrium
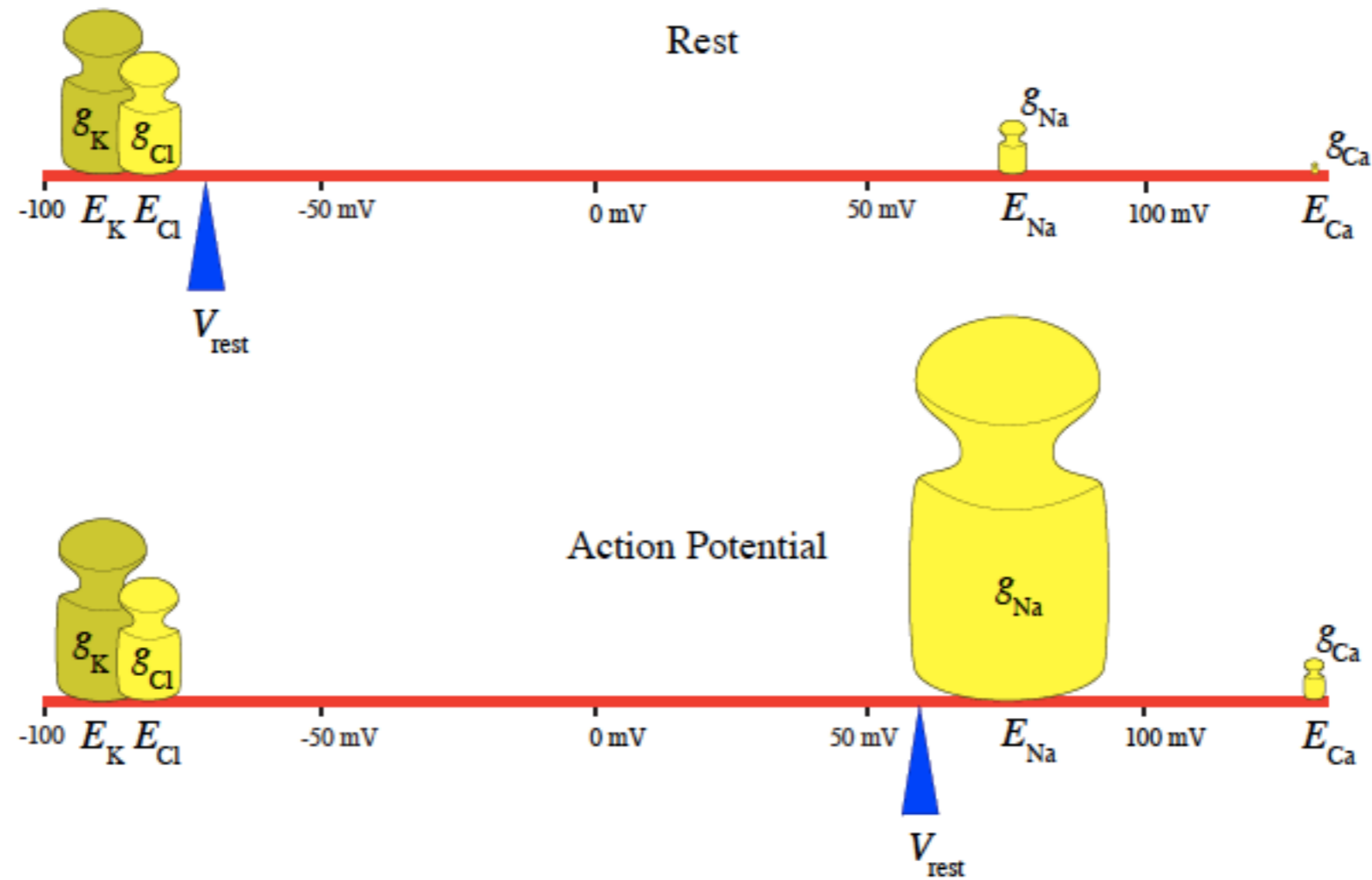
Figure 2.4: Mechanistic interpretation of the resting membrane potential (2.4) as the center of mass. Na^+ conductance increases during the action potential.

Hodgkin-Huxley equations

Ionic channels:

- Transitions between open and closed states in individual channels are stochastic

- However, the net current **I** generated by a large population or ensemble of identical channels can be reasonably be described by

$$I = G_X \, p \, (V - E_X)$$

p: average proportion of channels in the open state   →

G_X: maximal conductance of the population

E_X: reversal potential of the current (potential at which the current reverses its direction)

If the channels are selective for a single ionic species

reversal potential = Nernst potential for that ionic species

Hodgkin-Huxley equations

Ionic channels:
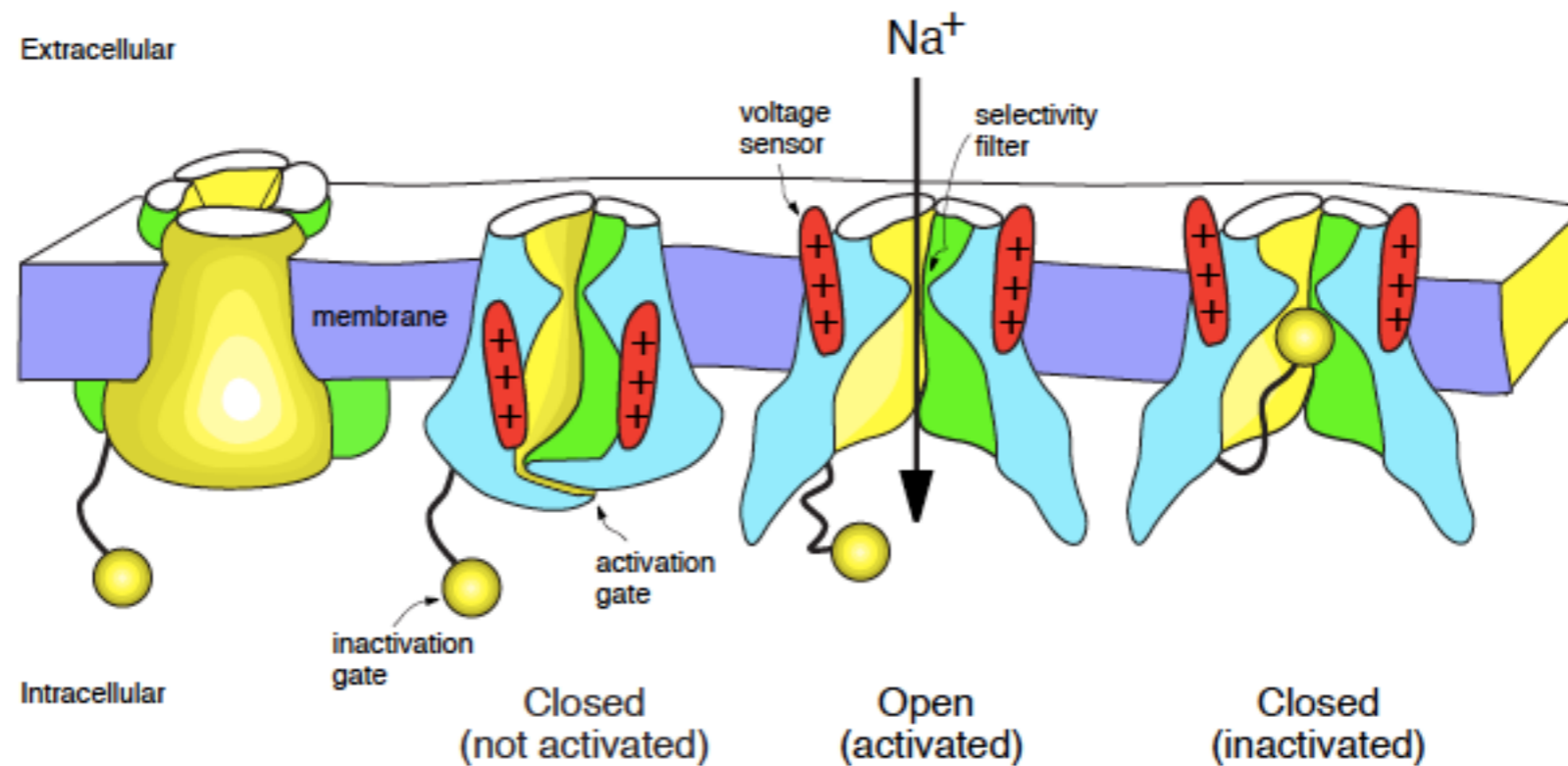
Figure 2.8: Structure of voltage-gated ion channels. Voltage sensors open activation gate and allow selected ions to flow through the channel according to their electrochemical gradients. The inactivation gate blocks the channel (modified from Armstrong and Hille 1998).

Hodgkin-Huxley equations

Voltage-gated ionic channels:

- Activating gates: open the channels

- Inactivating gates: close the channels

$$I = G_X \, p \, (V - E_X)$$

$$p = m^a \, h^b$$

- $m = 1$: activated

- $m = 0$: deactivated (not activated)

- $h = 1$: inactivated

- $h = 0$: deinactivated (released from inactivation)

Hodgkin-Huxley equations

Voltage-gated ionic channels:

- Activating gates: open the channels

- Inactivating gates: close the channels

$$I = G_X \, p \, (V - E_X)$$

$$p = m^a \, h^b$$

- persistent currents: do not inactivate (b = 0)

- transient currents: do inactivate

Hodgkin-Huxley equations

Voltage-gated ionic channels: diagram

$$C \underset{\beta(V)}{\overset{\alpha(V)}{\rightleftharpoons}} O$$
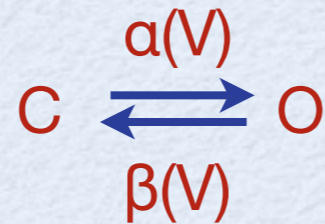
C: closed states

O: open states

α(V): rate constant at which the gate goes from the closed to the open states

β(V): rate constant at which the gate goes from the open to the closed states

Hodgkin-Huxley equations

Voltage-gated ionic channels: diagram

$$C \underset{\beta(V)}{\overset{\alpha(V)}{\rightleftharpoons}} O$$
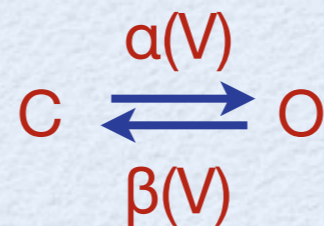
m: fraction of open gates

1-m: fraction of closed states

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha(V)(1 - m) - \beta(V)m$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = (m_\infty(V) - m)/\tau(V)$$

$$m_\infty(V) = \frac{\alpha(V)}{\alpha(V) + \beta(V)}$$

$$\tau(V) = \frac{1}{\alpha(V) + \beta(V)}$$

Hodgkin-Huxley equations

$$
\begin{aligned}
C\dot{V} &= I - \overbrace{\bar{g}_{\mathrm{K}}n^4(V - E_{\mathrm{K}})}^{I_{\mathrm{K}}} - \overbrace{\bar{g}_{\mathrm{Na}}m^3h(V - E_{\mathrm{Na}})}^{I_{\mathrm{Na}}} - \overbrace{g_{\mathrm{L}}(V - E_{\mathrm{L}})}^{I_{\mathrm{L}}} \\
\dot{n} &= \alpha_n(V)(1-n) - \beta_n(V)n \\
\dot{m} &= \alpha_m(V)(1-m) - \beta_m(V)m \\
\dot{h} &= \alpha_h(V)(1-h) - \beta_h(V)h \,,
\end{aligned}
$$

$$
\alpha_n(V) = 0.01\frac{10-V}{\exp(\frac{10-V}{10})-1}
$$

$$
\alpha_m(V) = 0.1\frac{25-V}{\exp(\frac{25-V}{10})-1}
$$

$$
\alpha_h(V) = 0.07\exp\left(\frac{-V}{20}\right)
$$

$$
\beta_n(V) = 0.125\exp\left(\frac{-V}{80}\right)
$$

$$
\beta_m(V) = 4\exp\left(\frac{-V}{18}\right)
$$

$$
\beta_h(V) = \frac{1}{\exp(\frac{30-V}{10})+1}
$$

Hodgkin-Huxley equations

$$
\begin{aligned}
C\dot{V} &= I - \overbrace{\bar{g}_{\mathrm{K}}n^4(V - E_{\mathrm{K}})}^{I_{\mathrm{K}}} - \overbrace{\bar{g}_{\mathrm{Na}}m^3h(V - E_{\mathrm{Na}})}^{I_{\mathrm{Na}}} - \overbrace{g_{\mathrm{L}}(V - E_{\mathrm{L}})}^{I_{\mathrm{L}}} \\
\dot{n} &= (n_\infty(V) - n)/\tau_n(V) , \\
\dot{m} &= (m_\infty(V) - m)/\tau_m(V) , \\
\dot{h} &= (h_\infty(V) - h)/\tau_h(V) ,
\end{aligned}
$$

$$
\begin{aligned}
n_\infty &= \alpha_n/(\alpha_n + \beta_n) , & \tau_n &= 1/(\alpha_n + \beta_n) , \\
m_\infty &= \alpha_m/(\alpha_m + \beta_m) , & \tau_m &= 1/(\alpha_m + \beta_m) , \\
h_\infty &= \alpha_h/(\alpha_h + \beta_h) , & \tau_h &= 1/(\alpha_h + \beta_h)
\end{aligned}
$$
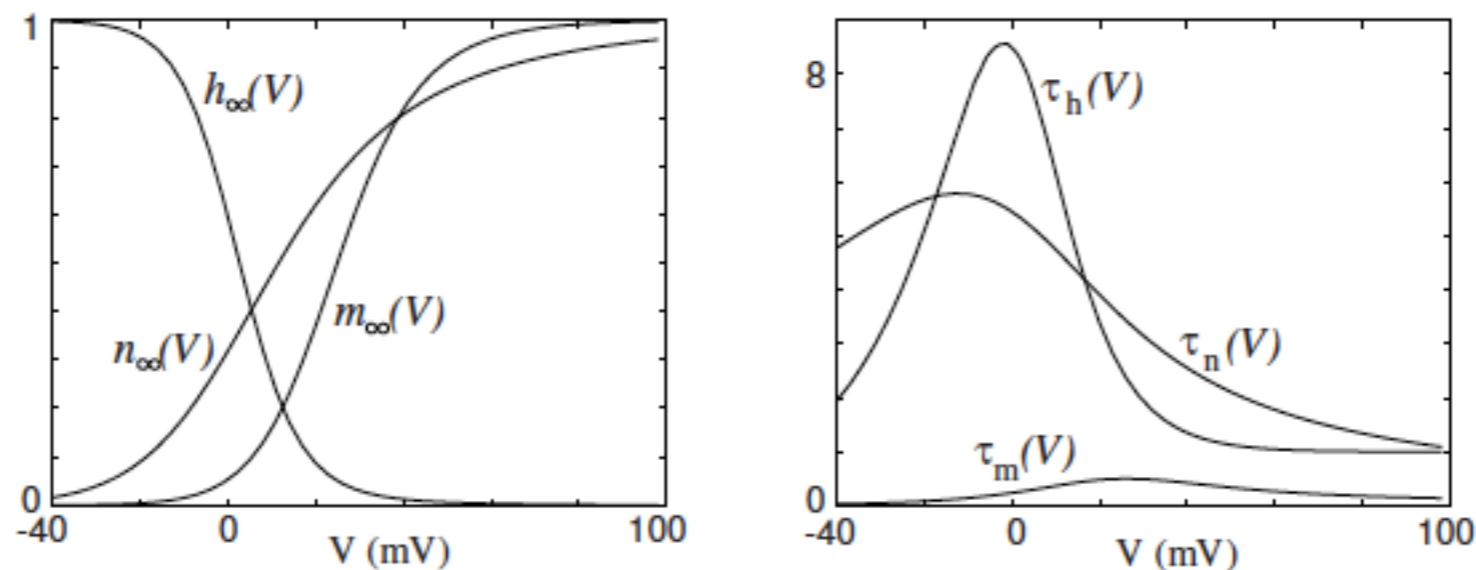
Figure 2.13: Steady-state (in)activation functions (left) and voltage-dependent time constants (right) in the Hodgkin-Huxley model.

Hodgkin-Huxley equations

$$
\begin{aligned}
C\dot{V} &= I - \overbrace{\bar{g}_\text{K}n^4(V - E_\text{K})}^{I_\text{K}} - \overbrace{\bar{g}_\text{Na}m^3h(V - E_\text{Na})}^{I_\text{Na}} - \overbrace{g_\text{L}(V - E_\text{L})}^{I_\text{L}} \\
\dot{n} &= \alpha_n(V)(1 - n) - \beta_n(V)n \\
\dot{m} &= \alpha_m(V)(1 - m) - \beta_m(V)m \\
\dot{h} &= \alpha_h(V)(1 - h) - \beta_h(V)h \, ,
\end{aligned}
$$

$E_\text{K} = -12 \text{ mV}$ $\quad$ $E_\text{Na} = 120 \text{ mV}$ $\quad$ $E_\text{L} = 10.6 \text{ mV}$

$\bar{g}_\text{K} = 36 \text{ mS/cm}^2$ $\quad$ $\bar{g}_\text{Na} = 120 \text{ mS/cm}^2$ $\quad$ $g_\text{L} = 0.3 \text{ mS/cm}^2$
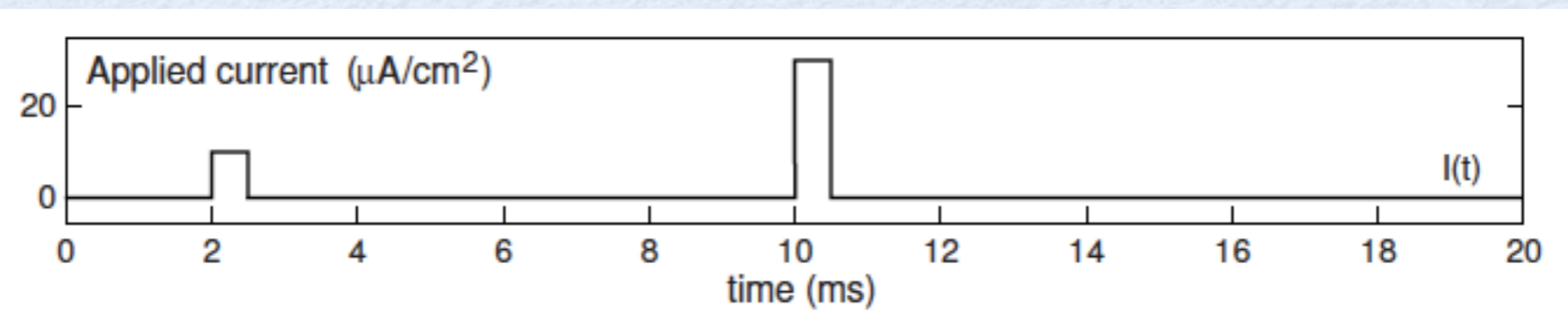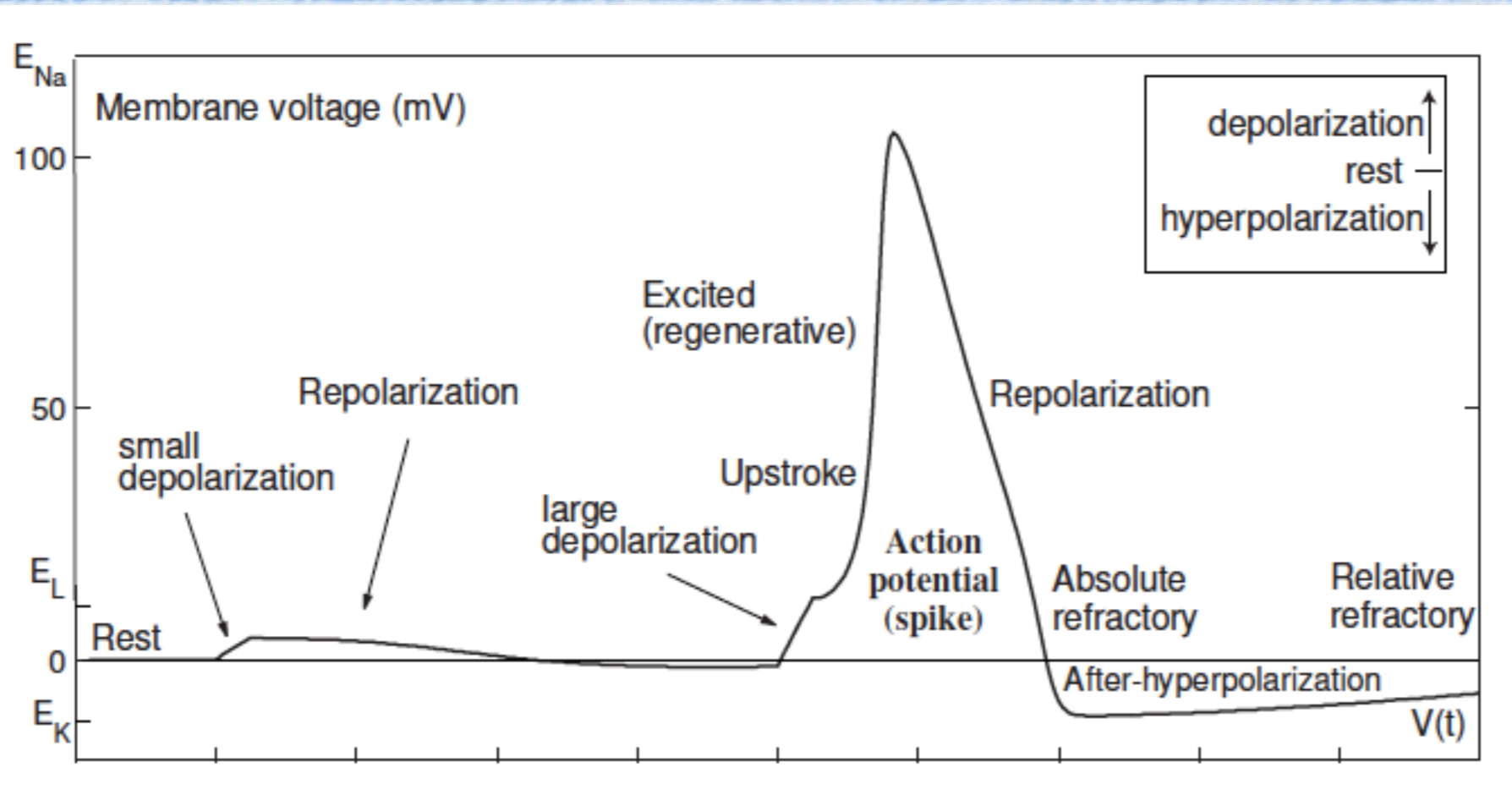
Hodgkin-Huxley equations
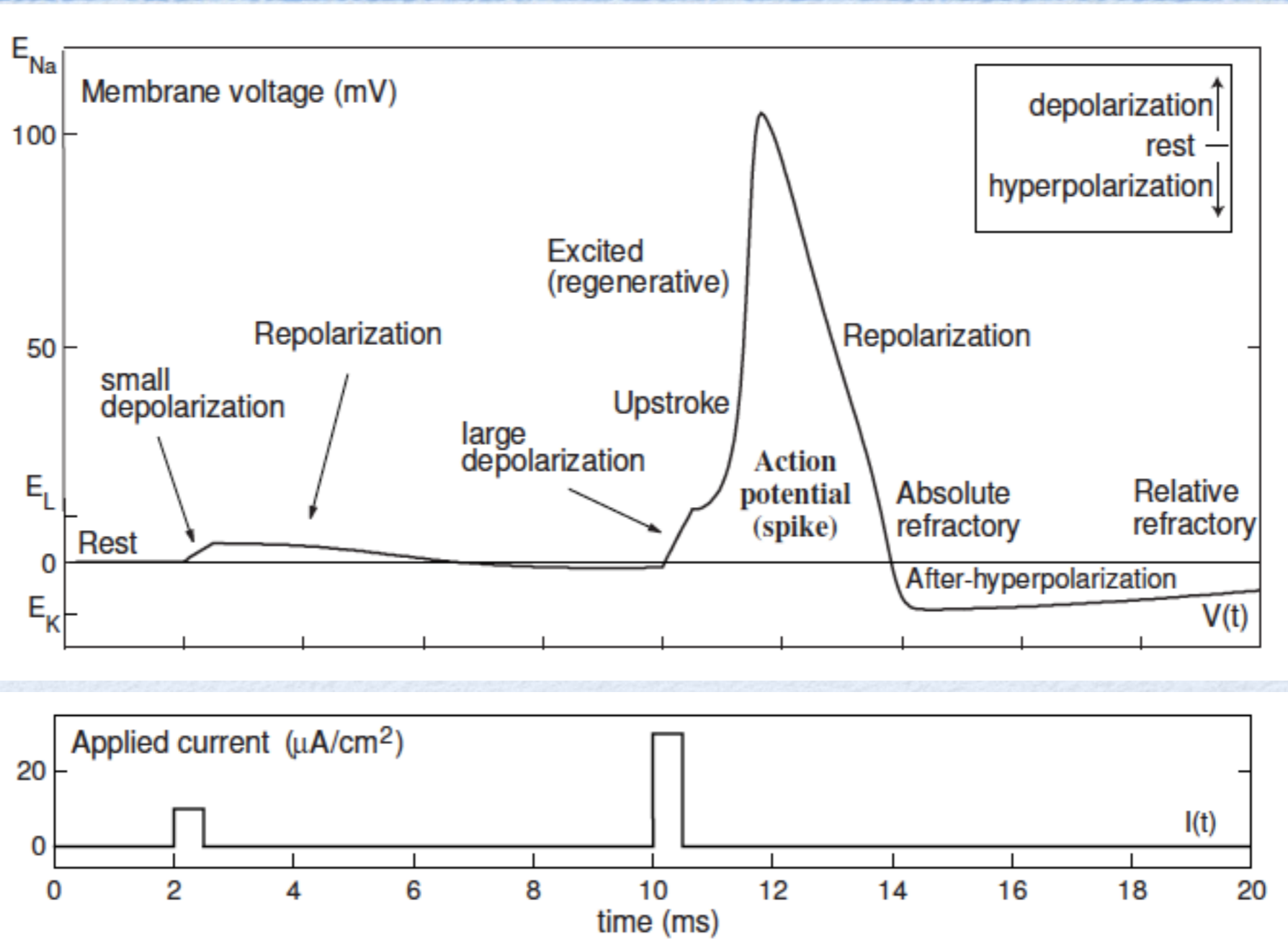
Hodgkin-Huxley equations
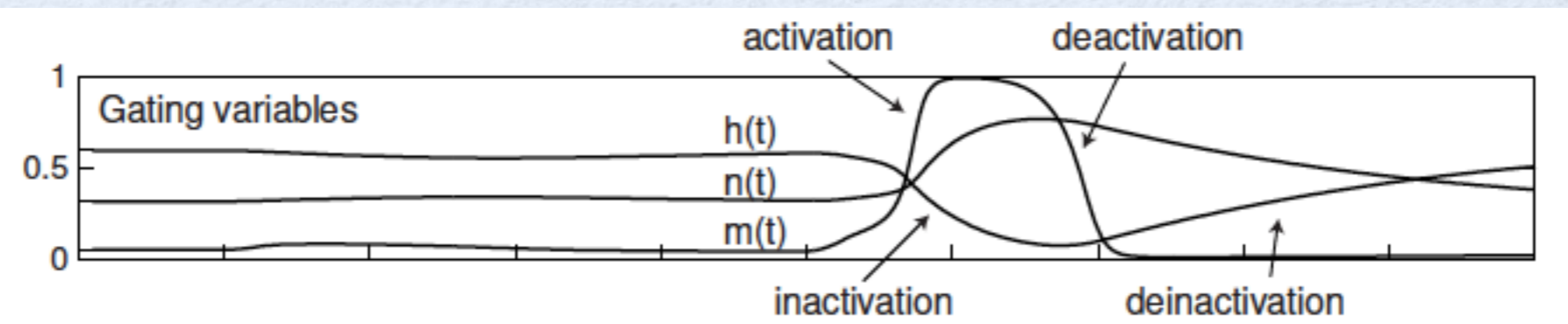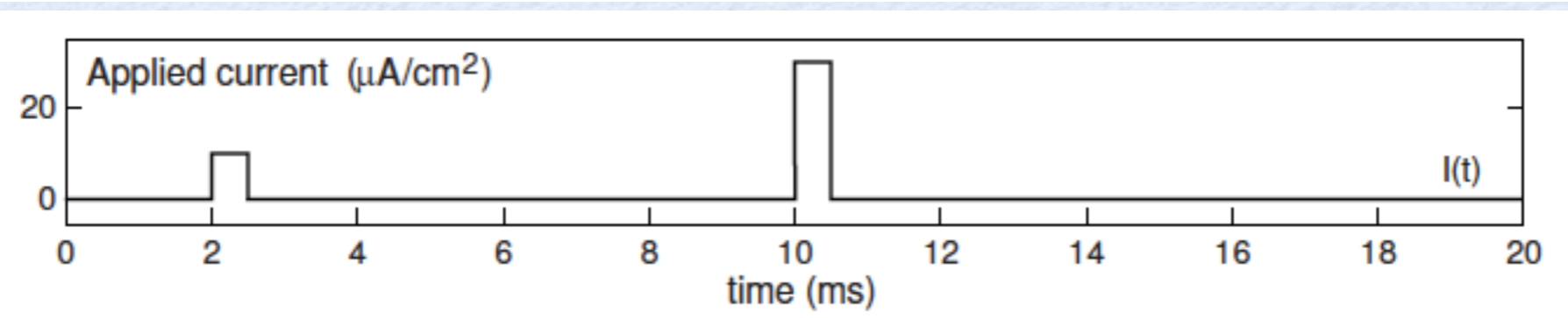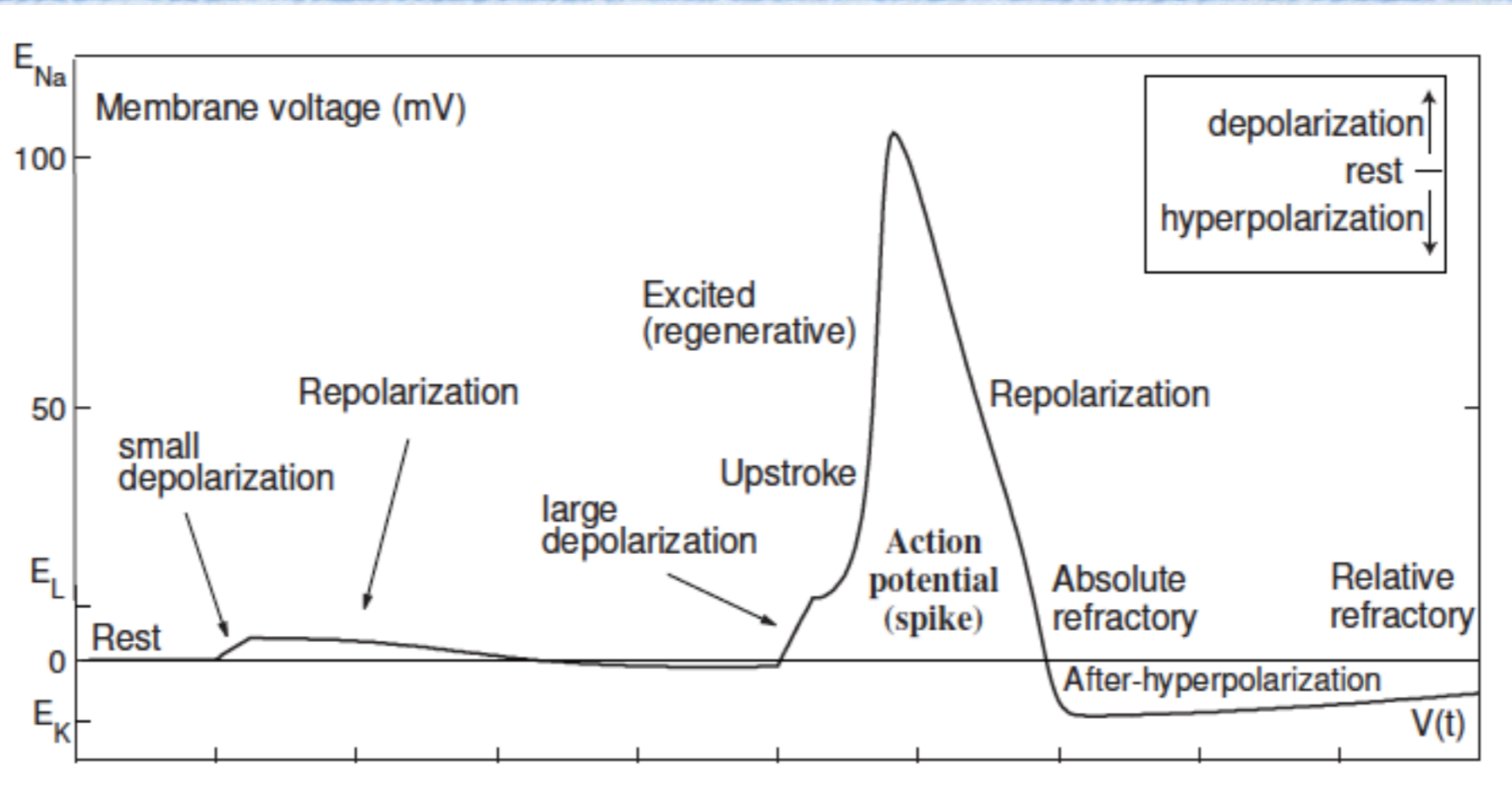
Hodgkin-Huxley equations
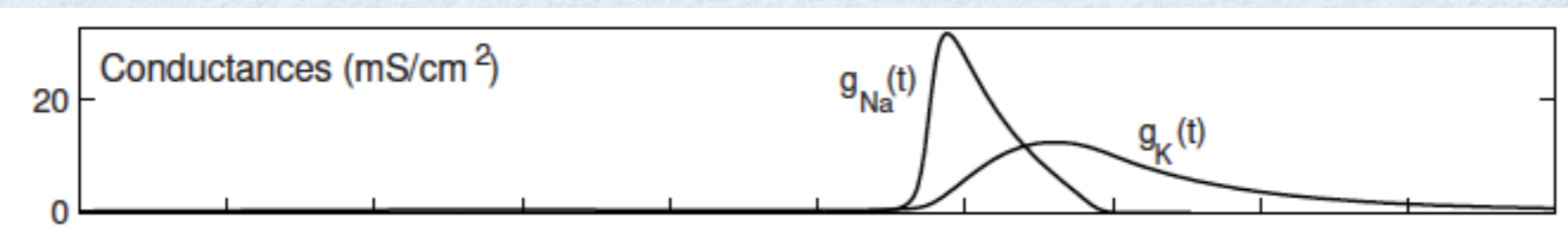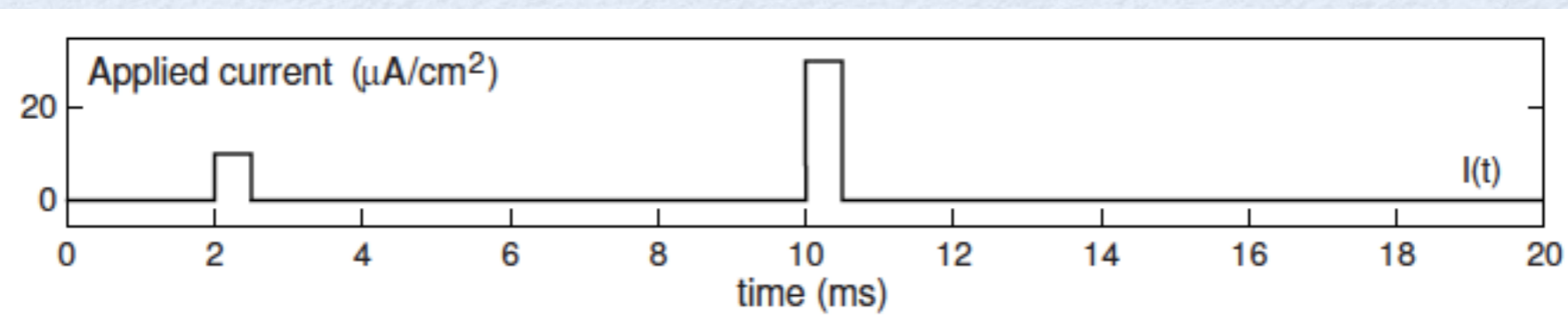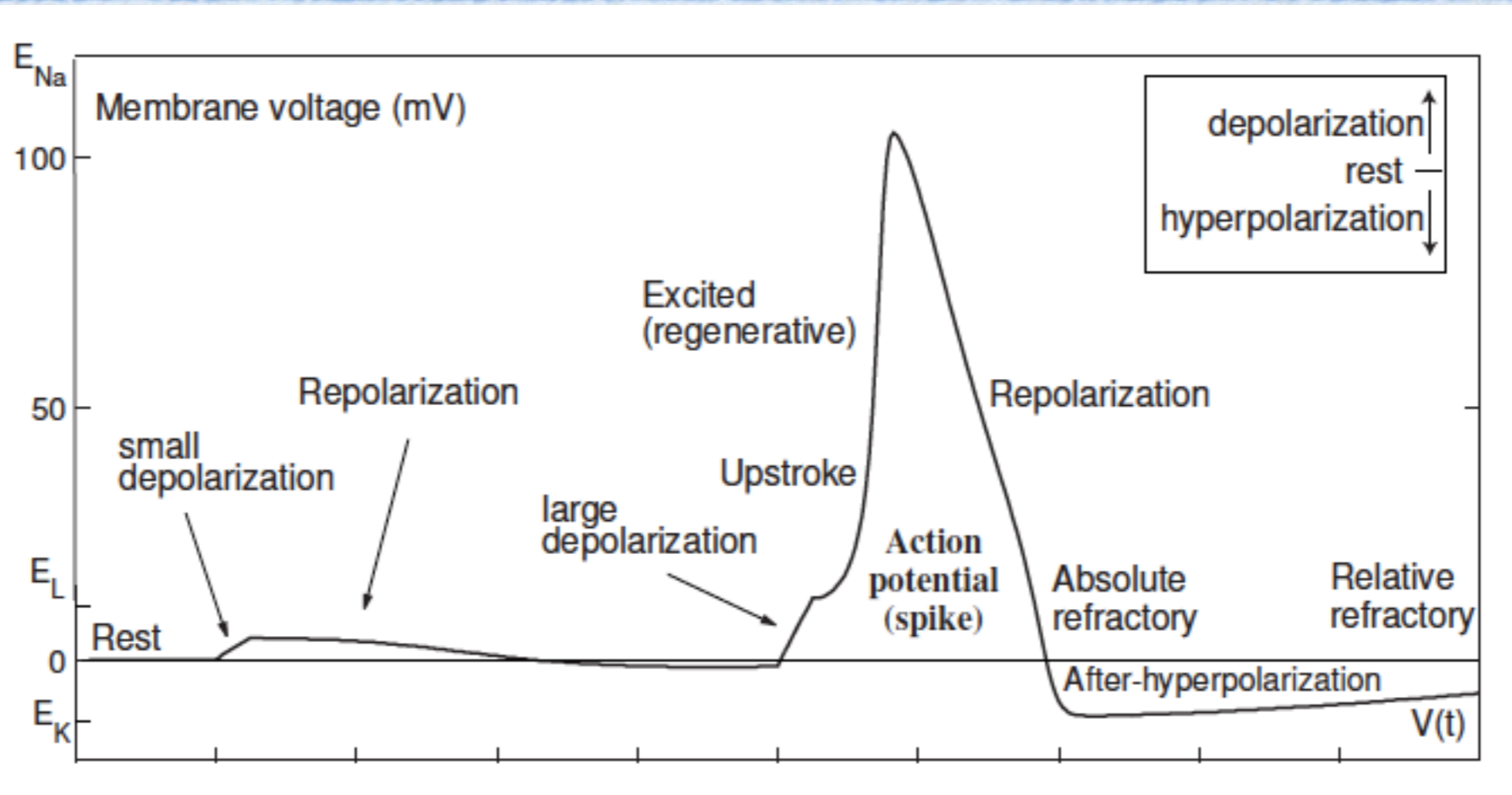
Hodgkin-Huxley equations
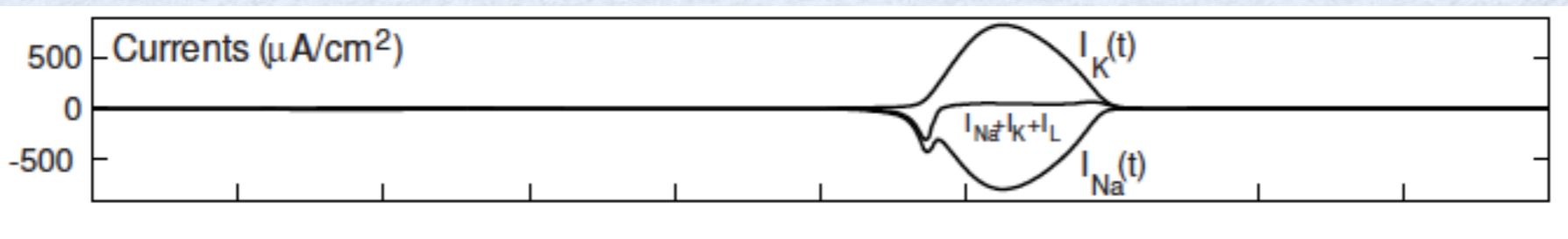
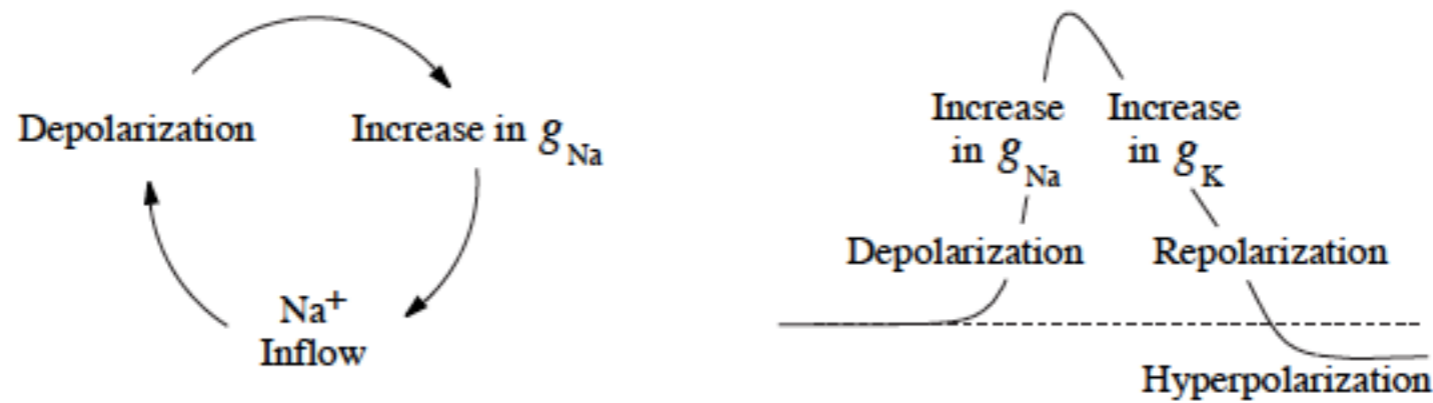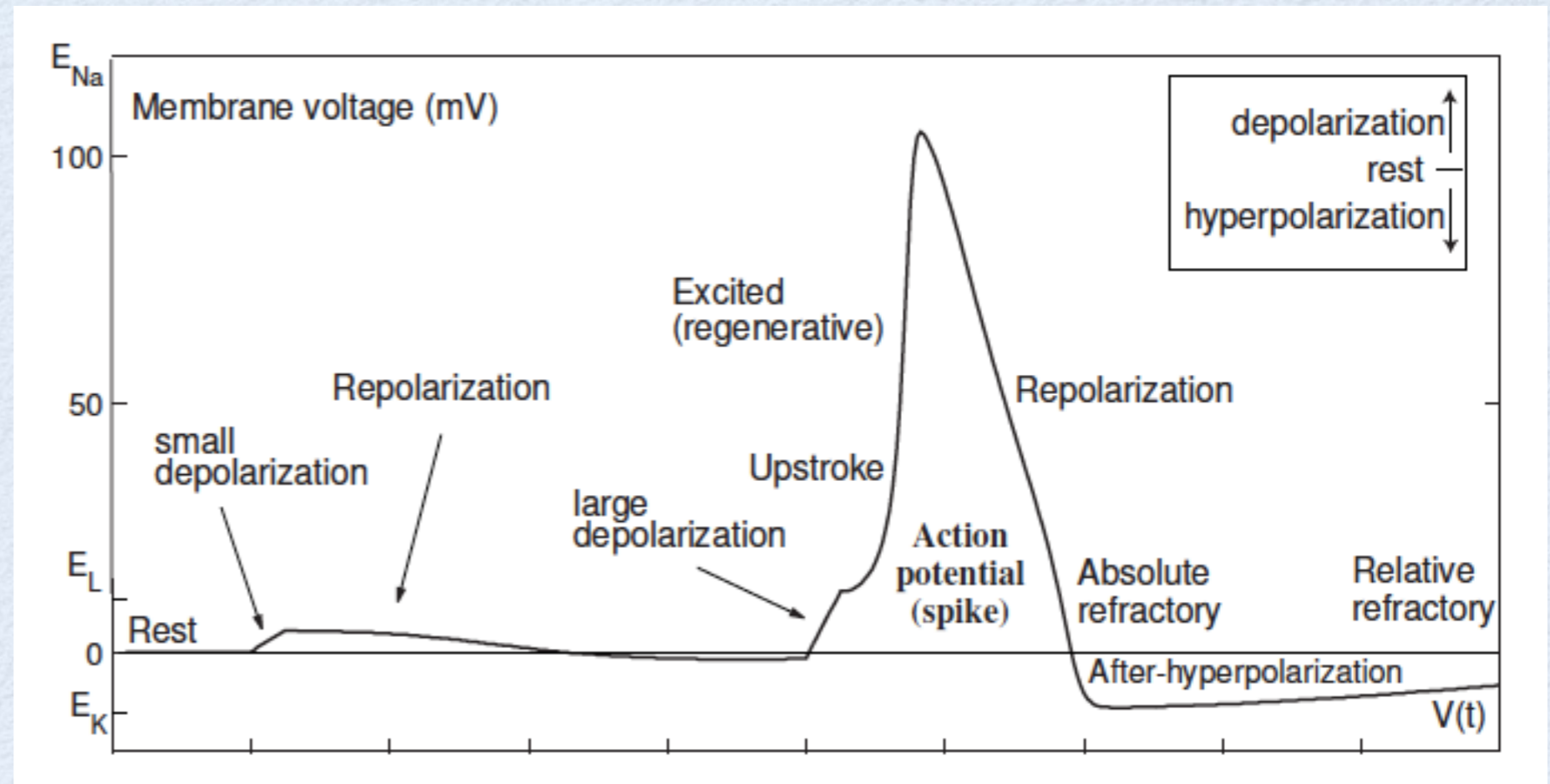# Hodgkin-Huxley equations

Action potential:

Figure 2.16: Positive and negative feedback loops resulting in excited (regenerative) behavior in neurons.