Dynamical Systems and Chaos
Part II: Biology Applications

Lecture 9: Excitability phenomena. Neurons.

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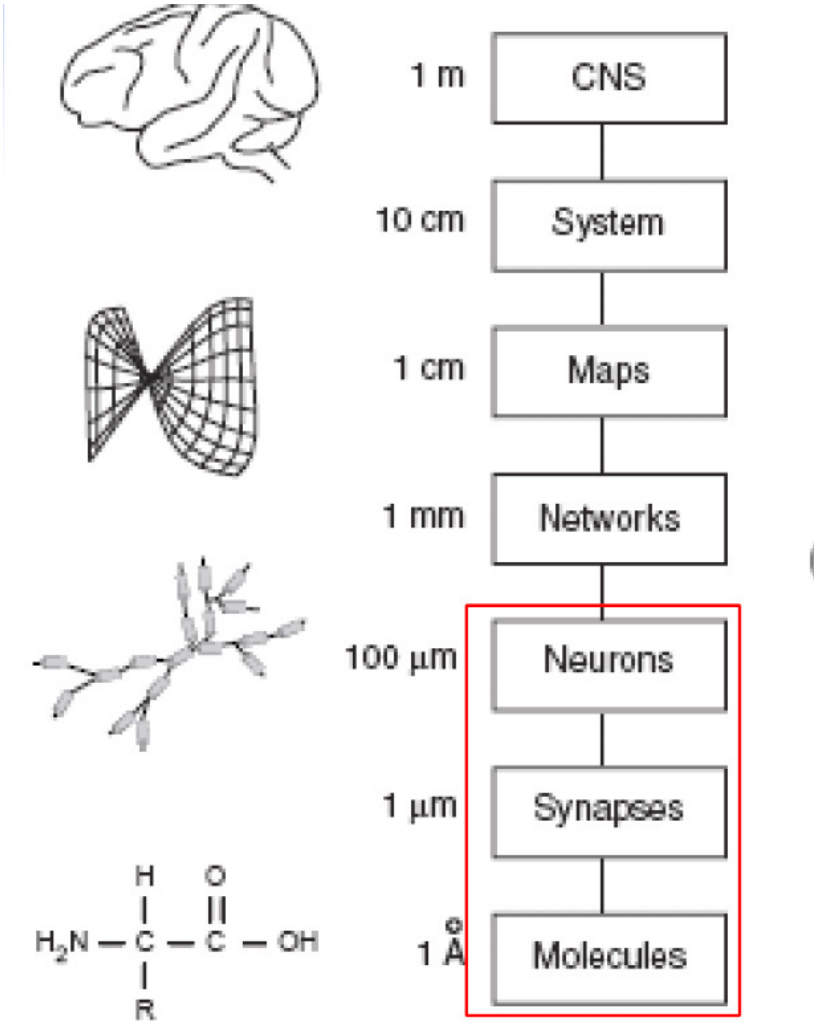
Neurons: biological background



Different scales. T. P. Trappenberg, **Fundamentals of Computational Neuroscience**, *Oxford University Press*.

Basic facts and terminology

- **Neuron** is a cell capable of transmitting **electrical signals**.
- Neurons have a **soma**, an **axon**, and **dendrites**.
  - Dendrites: input devices collecting signals.
  - Soma: central processing unit.
  - Axon: output device.
- $> 10^{11}$ neurons in the human brain and even more glial cells.
- 10^3 morphologically different neurons.
- Neurons signal to each other through the chemical synapses, where the electrical signal is transformed into the chemical one.
- Most neurons generate brief voltage pulses (**action potentials**, spikes) in response to inputs from the presynaptic neurons.
- Action potentials originate at or close to the cell body and propagate down the axon.

Spike recording

Neuron receives signals from other neurons through more than 10^4 synapses (for a typical neuron).

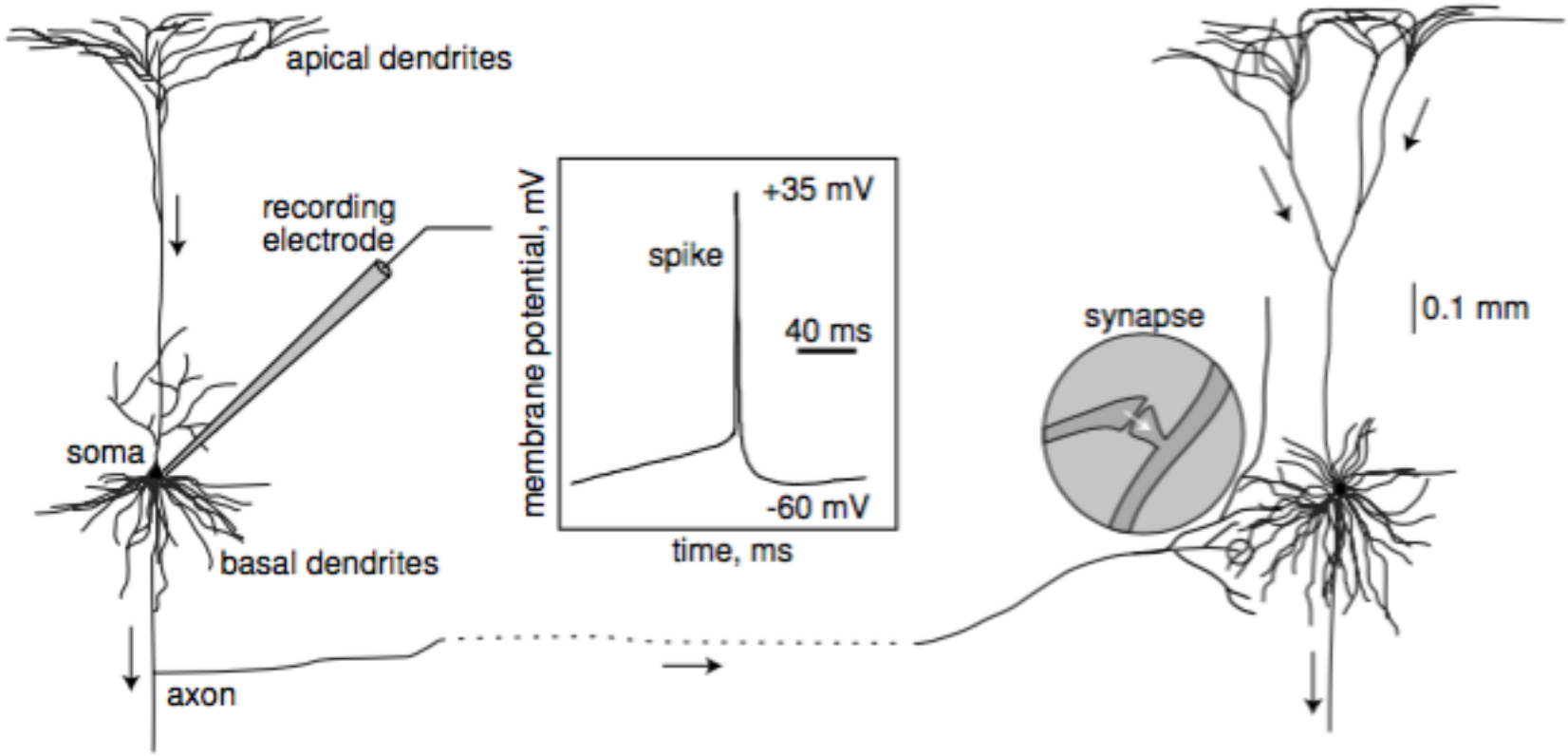
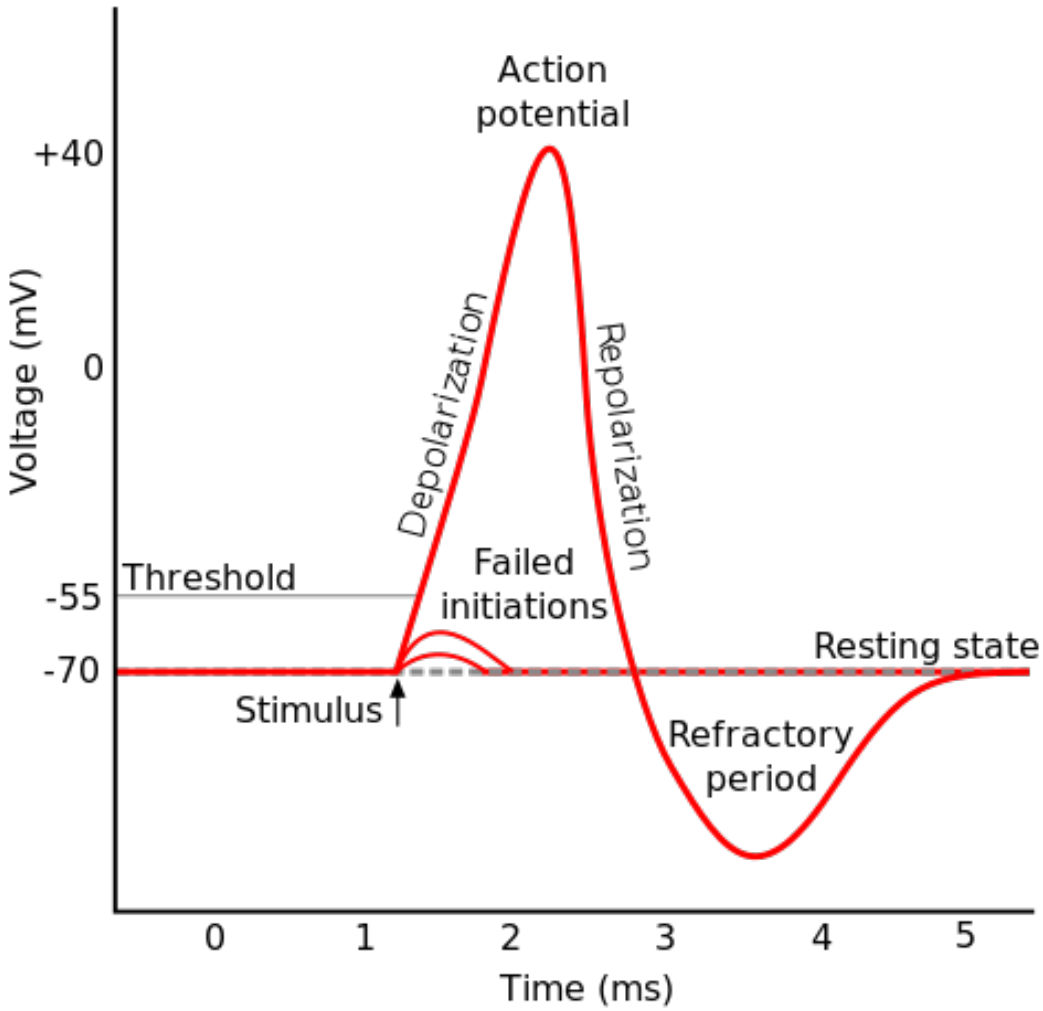


Figure: Two interconnected neurons and in vitro recorded spike. E. M. Izhikevich, *Dynamical Systems in Neuroscience*, MIT Press, 2007.

Spike/Action potential



Wikipedia.

Firing of neurons

- Fundamental question of neuroscience:
  - What makes neurons fire?
  - Why does the response to the same input signal differ in two neurons?
- One needs to understand *dynamical* properties of neurons in order to answer these questions.

Firing threshold of a neuron

For example, neurons are sometimes considered as *integrators* that sum incoming potentials and "compare" the integrated signal with a voltage value, the firing threshold.

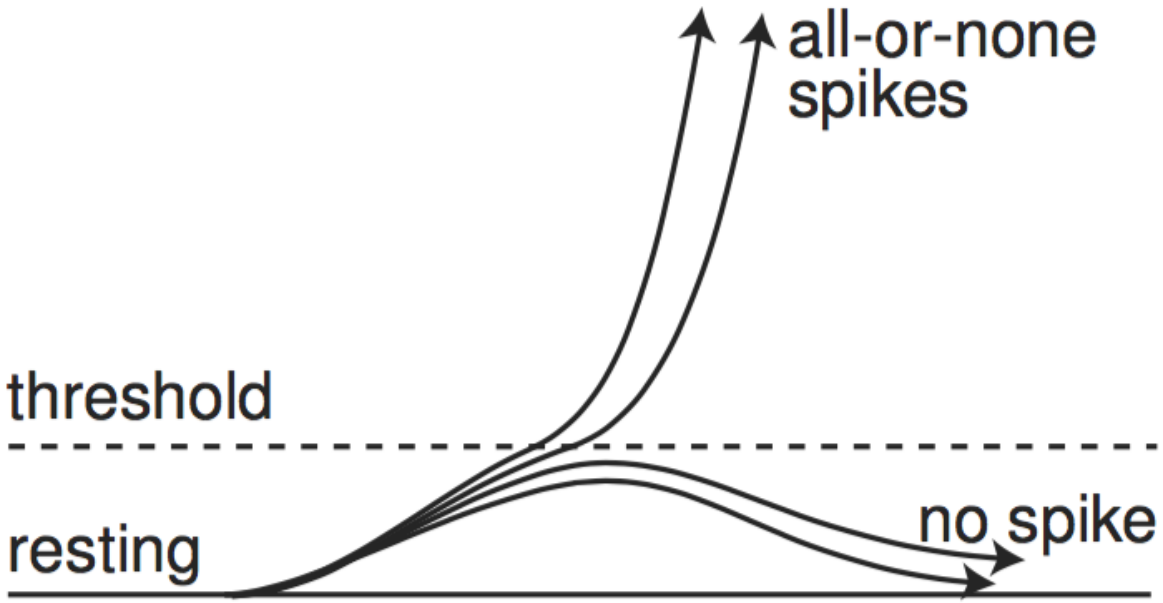


Figure: The concept of a firing threshold. E. M. Izhikevich, *Dynamical Systems in Neuroscience*, MIT Press, 2007.

Where is the threshold?

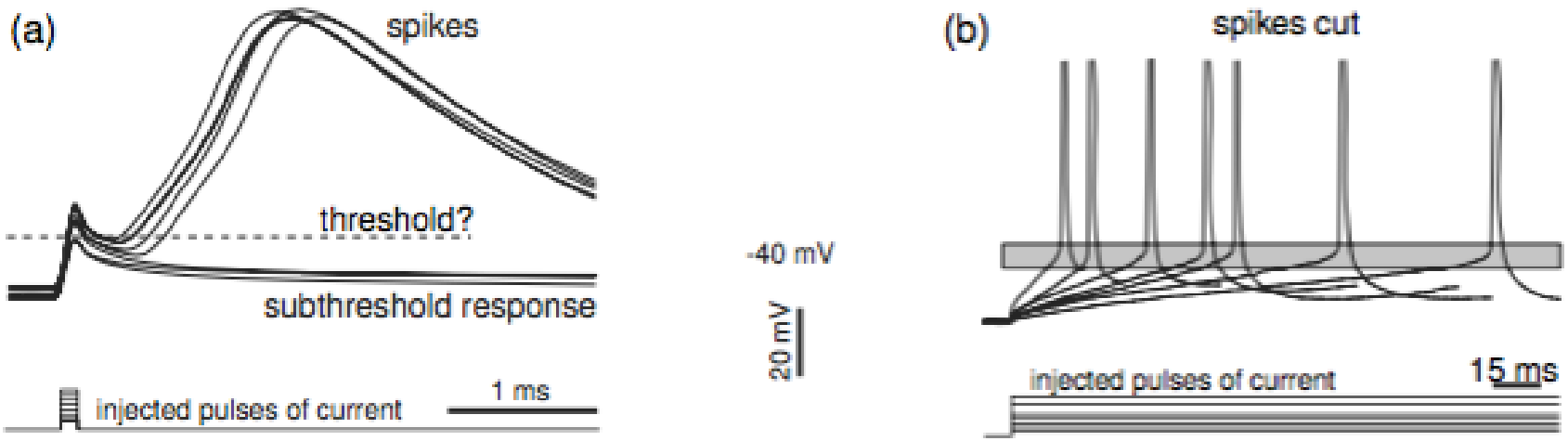


Figure 1.4: Where is the firing threshold? Shown are in vitro recordings of two layer 5 rat pyramidal neurons. Notice the differences of voltage and time scales.

E. M. Izhikevich, *Dynamical Systems in Neuroscience*, MIT Press, 2007.

Where is the threshold/rheobase?

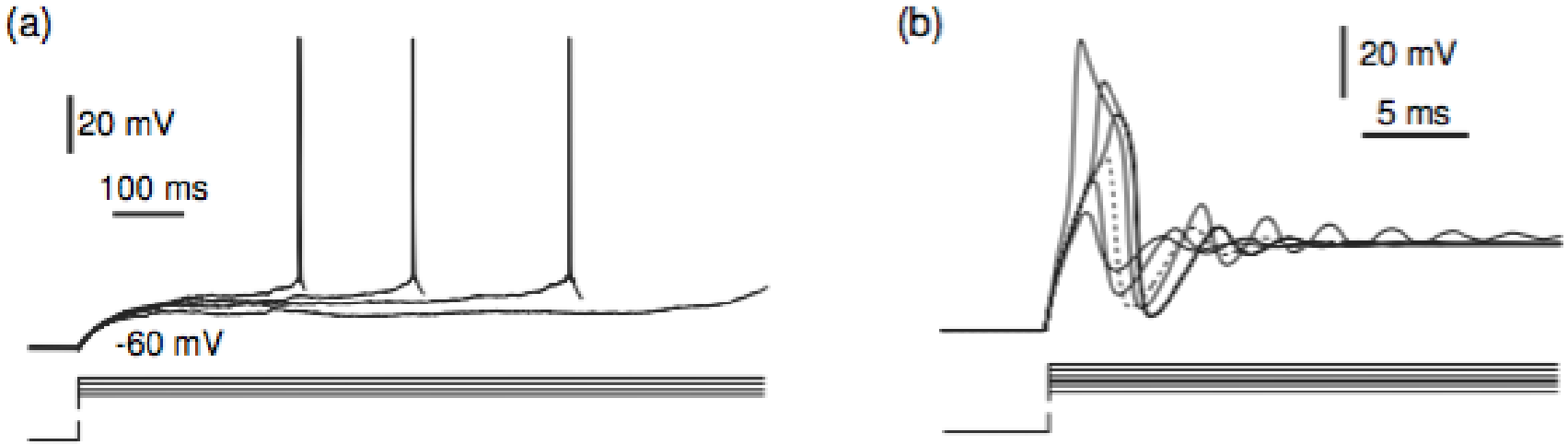


Figure 1.5: Where is the rheobase (i.e., the minimal current that fires the cell)? (a) in vitro recordings of the pyramidal neuron of layer 2/3 of a rat's visual cortex show increasing latencies as the amplitude of the injected current decreases. (b) Simulation of the $I_{\mathrm{Na,p}}+I_{\mathrm{K}}-$model (pronounced: *persistent sodium plus potassium model*) shows spikes of graded amplitude.

E. M. Izhikevich, *Dynamical Systems in Neuroscience*, MIT Press, 2007.

Resonant response

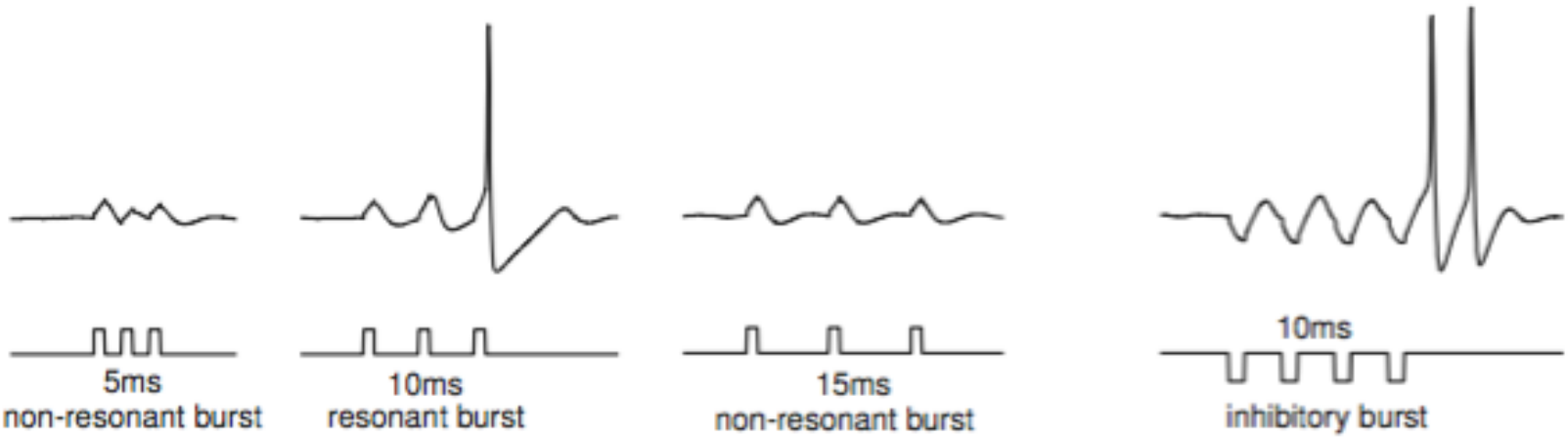


Figure 1.7: Resonant response of the mesencephalic V neuron of a rat's brainstem to pulses of injected current having a 10 ms period (in vitro).

E. M. Izhikevich, *Dynamical Systems in Neuroscience*, MIT Press, 2007.

Synapse

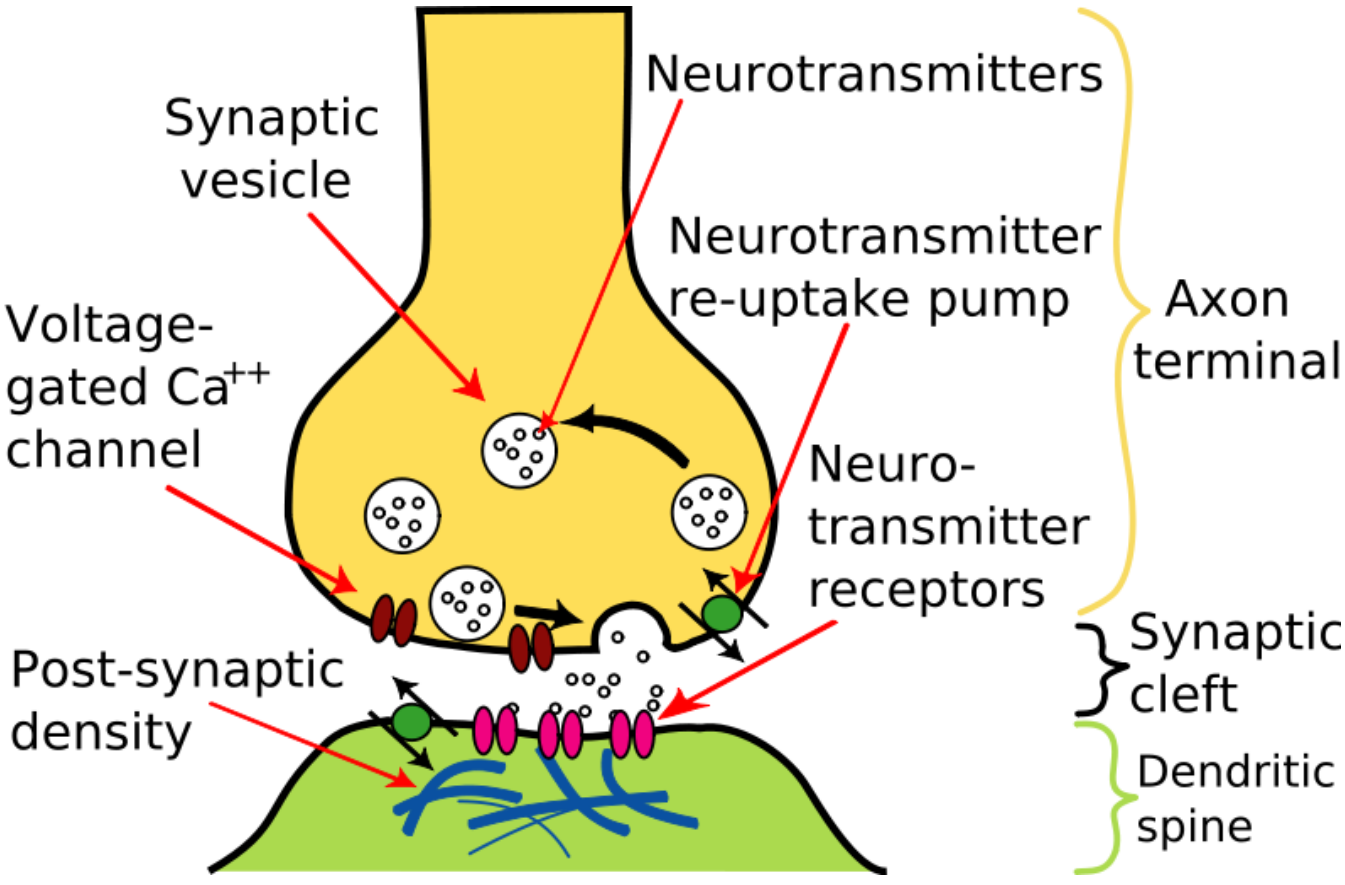


Figure: Wikimedia Commons.

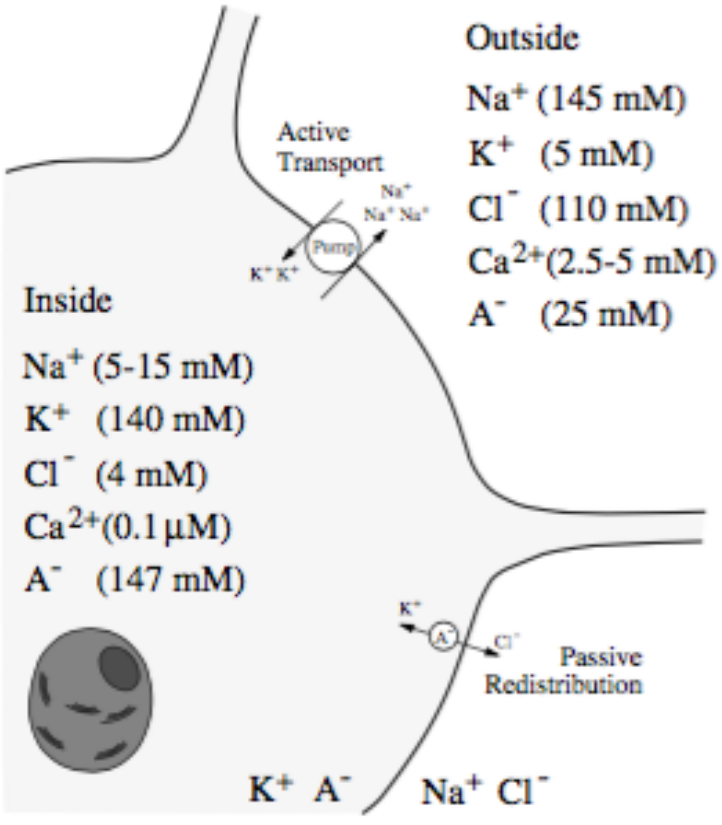
Events in synapse dynamic activity

- After the action potential has reached the end of the axon, Ca^{2+} channels open and Ca^{2+} ions flow inside the presynaptic neuron.
- The Ca^{2+} activates a set of proteins attached to vesicles with neurotransmitters.
- Neurotransmitters (e.g., **glutamate**) are released from the presynaptic neuron to the synaptic cleft.
- This means that **electrical** signal is changed to **chemical** signal.
- Neurotransmitters bind to postsynaptic receptors.
- After receptors are activated, for example, Ca^{2+} ions can flow inside the postsynaptic neuron.
- Calcium triggers many events inside the postsynaptic neuron.

Ion distribution

- Ion concentrations are different inside and outside of a cell, which creates **electrochemical gradients** — the major driving force of neural activity.
- Electrical signals are carried by Na^+, Ca^{2+}, K^+, and Cl^-, which move through membrane channels according to their electrochemical gradients.
- Ionic concentration gradients across the cell membrane are maintained by
  - **Active** transport of ions by pumps, exchangers,... (requires energy)
  - **Passive** transport of ions (`selective` permeability, electrochemical gradient, no energy required) through **channels** (large protein molecules in the membrane).
- The intracellular medium of a neuron has high concentration of K^+ ions and negatively charged molecules (denoted by A^-).

Ion distribution



Equilibrium Potentials

$$\begin{aligned}
Na^+ \quad & 62 \log \tfrac{145}{5} = 90 \text{ mV} \\
& 62 \log \tfrac{145}{15} = 61 \text{ mV} \\
K^+ \quad & 62 \log \tfrac{5}{140} = -90 \text{ mV} \\
Cl^- \quad & -62 \log \tfrac{110}{4} = -89 \text{ mV} \\
Ca^{2+} \quad & 31 \log \tfrac{2.5}{10^{-4}} = 136 \text{ mV} \\
& 31 \log \tfrac{5}{10^{-4}} = 146 \text{ mV}
\end{aligned}$$

Figure: Ion concentrations and Nernst equilibrium potential in a typical mammalian neuron. A^- are membrane-impermeant anions. Temperature 37°C (310°K) E. M. Izhikevich, *Dynamical Systems in Neuroscience*, MIT Press, 2007.

Nernst equation

- There are two forces that drive each ion species through the membrane channel: **concentration** and **electrical** gradients.

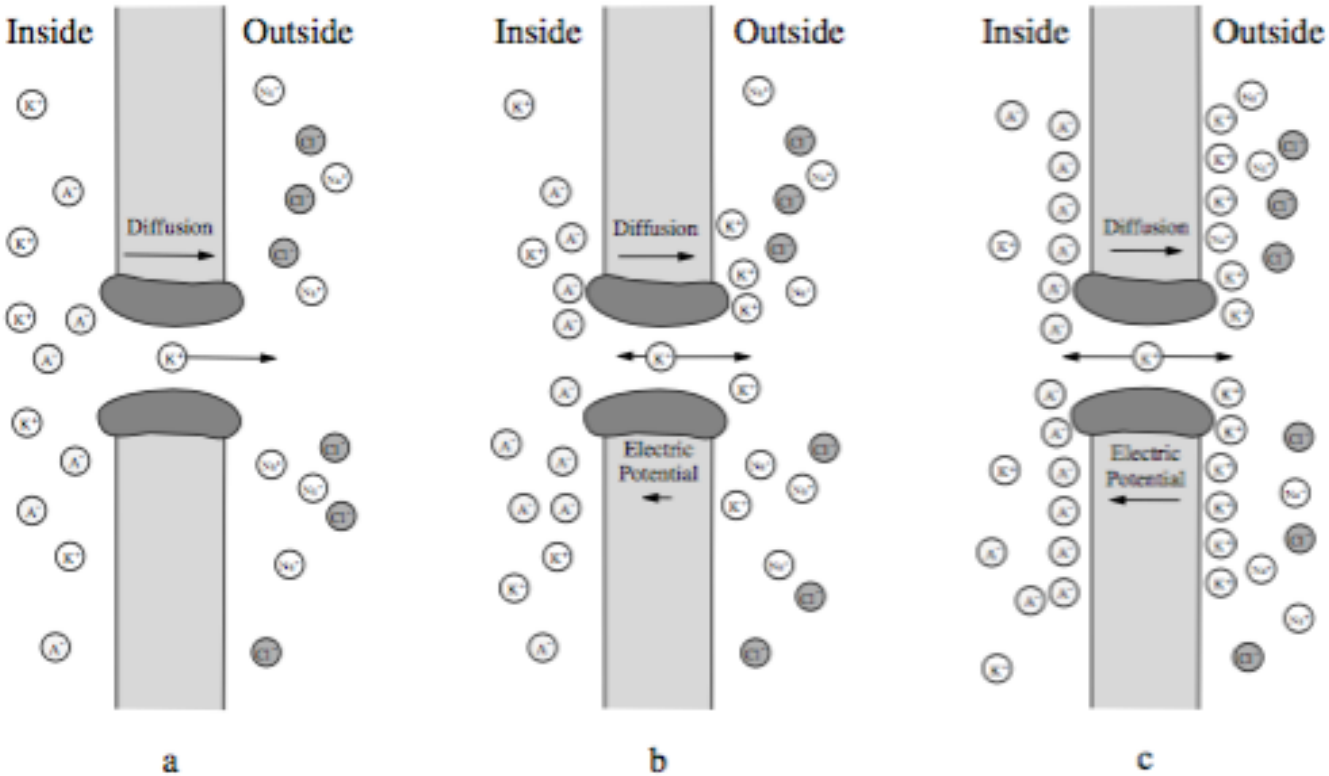


Figure: Diffusion of K^+ ion down the concentration gradient through the membrane (a) creates an electric potential force pointing in the opposite direction (b) until the diffusion and electrical forces counter each other (c). The resulting transmembrane potential is referred to as the Nernst equilibrium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

Nernst equation

- When chemical and electrical gradients are counterbalanced the equilibrium is achieved: the net cross-membrane current is zero.
- The value of such an *equilibrium potential* depends on the ionic species and it is given by the Nernst equation:

$$E_{\text{ion}} = \frac{RT}{zF} \ln \frac{[\text{Ion}]_{\text{out}}}{[\text{Ion}]_{\text{in}}},$$

  where $[\text{Ion}]_{\text{out}}$ and $[\text{Ion}]_{\text{in}}$ are concentrations of the ions outside and inside the cell, respectively; R is the universal gas constant ($8,315$ mJ/(K°·Mol)); T is temperature in degrees Kelvin; F is Faraday's constant; z is the charge value of the ion ($z = 1$ for Na^+ and K^+; $z = -1$ for Cl^-; and $z = 2$ for Ca^{2+}).
- When the membrane potential $V = E_{\text{ion}}$, the net current of the given ion $I_{\text{ion}} = 0$ by the definition of the Nernst equilibrium potential.

Ionic Currents and Conductances

- V is membrane potential and E_K, E_{Na}, E_{Ca} and E_{Cl} denote the Nernst equilibrium potential.
- In general, the net current of K^+ is proportional to the difference of potentials:

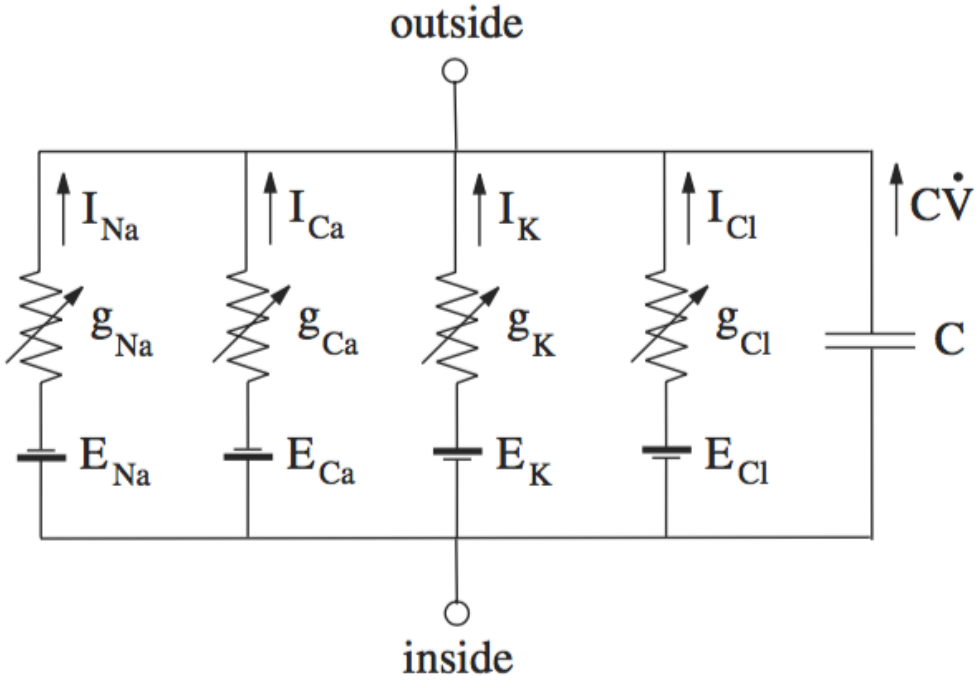
$$I_K = g_K(V - E_K)\,,$$

  where g_K (mS/cm^2) is the K^+ conductance and $(V - E_K)$ is the K^+ *driving force.*
- The other major ionic currents are

$$I_{Na} = g_{Na}(V - E_{Na})\,, \quad I_{Ca} = g_{Ca}(V - E_{Ca})\,, \quad I_{Cl} = g_{Cl}(V - E_{Cl})$$

- If g_i is constant then the current is said to be *Ohmic*. In general, g_i in neurons are not Ohmic, since they may depend on time, potential and pharmocalogical agents. ***It is these nonlinear non-constant conductances*** g_i ***that allow a neuron to generate an action potential, or spike.***

Circuit representation of cell membrane



- **Capacitors** are used to model the charge storage capacity of the cell membrane.
- **Resistors** are used to model the various types of ion channels in the membrane.
- **Batteries** are used to represent the electrochemical equilibrium (Nernst) potentials established by different intra- and extracellular ion concentrations.
- **Ohm's law**: $V = RI = \frac{1}{g}I$, V is voltage, R resistance, I electric current, g conductance.

- **Membrane potential**: $V = V_{in} - V_{out}$ (usually negative).
- **Capacitive current**: $I_c(t) = C_m \frac{\mathrm{d}V(t)}{\mathrm{d}t}$, where C_m is the membrane capacitance.
- **Ionic current**: $I_i(t) = \frac{V(t)-E_i}{R_i} \equiv g_i(V(t) - E_i)$, where E_i is the equilibrium potential for ion i from Nernst equation and R_i is the resistance.
- Cell membrane contains several different types of ion channels.
- The total current that flows across cell membrane (membrane current) represents the sum of the ion fluxes through all these different kinds of ion channels.
- The total current I_m through the cell membrane:

$$I_m(t) = I_c(t) + \sum_{ions} I_i(t) = C_m \frac{\mathrm{d}V(t)}{\mathrm{d}t} + \sum_{ions} \frac{V(t) - E_i}{R_i}$$

- Resting membrane potential can be found when setting $I_m = 0$ and $\frac{\mathrm{d}V(t)}{\mathrm{d}t} = 0$:

$$V_{rest} = \frac{\sum_{ions} g_i E_i}{\sum_{ions} g_i}.$$

Neurons are excitable

$$I_i(t) = g_i(V(t) - E_i)$$

- If g_i is a constant then the current is said to be *Ohmic*.
- In general, g_i in neurons are not Ohmic, since they may depend on time, potential and pharmocalogical agents.
- ***It is non-constant conductances*** g_i***, which are nonlinear functions of the membrane potential and time, that allow a neuron to generate an action potential, or spike.***

Ion channels

- Allow passage of charged ions through their pores.
- Direction of ion movement through ion channel is governed by the electrochemical gradient.
- Channels are named by what ions they allow to pass.
- Ion channels open in response to variety of stimuli: changes in the membrane potential V, certain chemical (ligands) outside or inside the cell.
- The electrical conductance of individual channels can be controlled by **gating particles (gates)**, which switch the channels between open and closed states:

$$I = \bar{g}p(V(t) - E),$$

where conduntance is expressed as maximum conduntance $\bar{g}$ multiplied by average proportion of channels in open state p.

- Each gate is either permissive or nonpermissive.
- Channel is open if all the gates are permissive simultaneously.
- Channel names often indicate what controls the gate (**voltage-gated, ligand-gated**).
- **Voltage-gated channels**:
  - Gates are divided into two types: those that activate the channel and those that inactivate them.
  - Probability of the activation gate to be in the permissive state is m.
  - Probability of the inactivation gate to be in the permissive state is h.
  - Proportion of open channels in large population is $p = m^a h^b$, where a is the number of activation gates and b the number of inactivation gates.
  - Some channels do not have inactivation gates and hence $p = m^a$.
  - Current produced by channels, which do not have inactivation gates, is called **persistent**. In contrast, current produced by channels, which do have inactivation gates, is called **transient**.

Gated ion channels

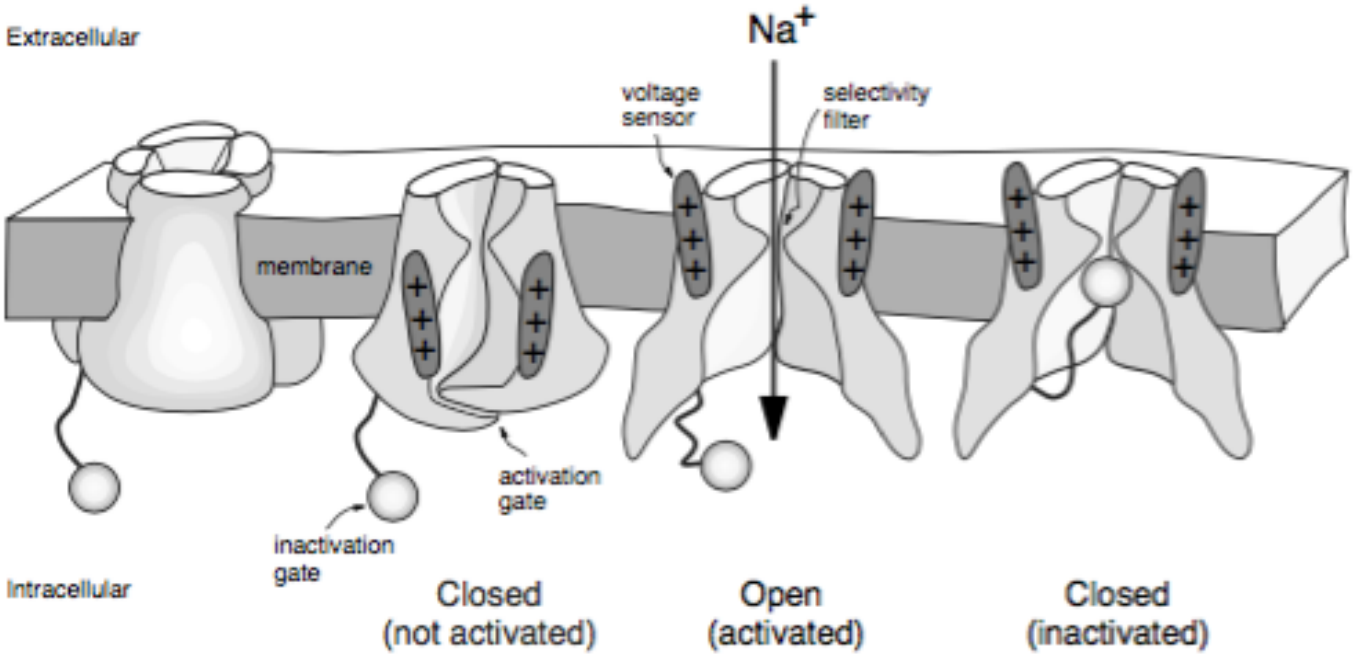


Figure 2.8: Structure of voltage-gated ion channels. Voltage sensors open an activation gate and allow selected ions to flow through the channel according to their electrochemical gradients. The inactivation gate blocks the channel. (Modified from Armstrong and Hille 1998.)

E. M. Izhikevich, *Dynamical Systems in Neuroscience*, MIT Press, 2007.

Integrate-and-fire neuron

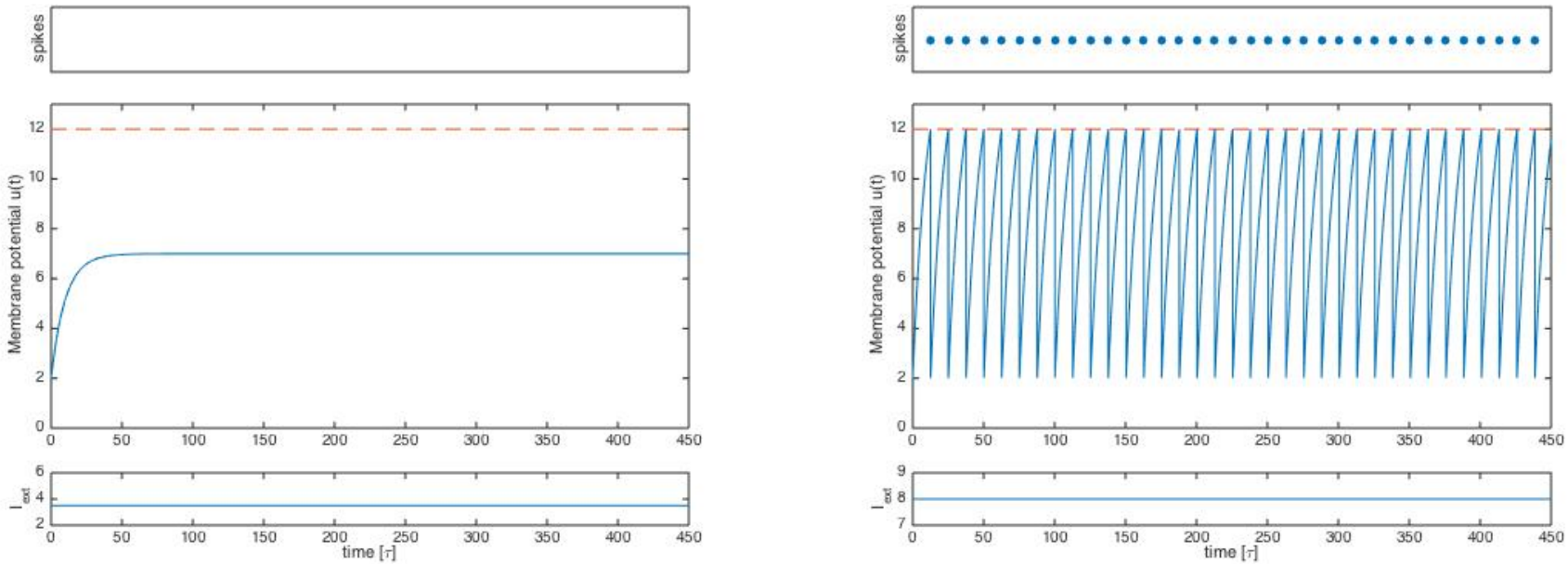
Membrane potential increases with time until it reaches a constant threshold value, at which point a spike occurs and the potential is reset to its resting potential, after which the model continues to run.
Several different types, original is:

$$C_m \frac{\mathrm{d}V}{\mathrm{d}t} = I(t).$$

Leaky integrate-and-fire neuron:

$$C_m \frac{\mathrm{d}V}{\mathrm{d}t} = I(t) - g_{leak}(V - V_{leak}).$$

Integrate-and-fire simulations



External input current below the treshold does not evoke the spiking activity (left). Input current above the threshold—spikes (right).

Gating of ion channel

Gate can be either permissive ("open") or nonpermissive ("closed"):

$$C \underset{k^-}{\overset{k^+}{\rightleftharpoons}} O.$$

- C is the nonpermissive state of the gate.
- O is the permissive state of the gate.
- Total number of gates $N = N_C + N_O$.
- Fraction (probability) of permissive gates $[O] = f_O = N_O/N$.
- Fraction of nonpermissive gates $[C] = f_C = N_C/N = (N - N_O)/N = 1 - N_O/N = 1 - f_O$.
- Flux for $O \xrightarrow{k-} C$: $k^- f_O$
- Flux for $C \xrightarrow{k+} O$: $k^+(1 - f_O)$

- Change in f_O over time:

$$\begin{aligned}
\frac{\mathrm{d}f_O}{\mathrm{d}t} &= k^+(1-f_O) - k^- f_O = k^+ - k^+ f_O - k^- f_O \\
&= k^+ \frac{k^+ + k^-}{k^+ + k^-} - k^+ f_O - k^- f_O \\
&= k^+ \frac{k^+}{k^+ + k^-} + k^+ \frac{k^-}{k^+ + k^-} - k^+ f_O - k^- f_O \\
&= (k^+ + k^-)(\frac{k^+}{k^+ + k^-} - f_O) \\
&= \frac{f_\infty - f_O}{\tau},
\end{aligned}$$

where $\tau = \frac{1}{k^+ + k^-}$, $f_\infty = \frac{k^+}{k^+ + k^-}$.

Historically, from Hodgkin-Huxley tradition $k^+ = \alpha_i(V)$ and $k^- = \beta_i(V)$ for i-th ion.

Hodgkin-Huxley model

- Giant axon of the squid.
- Action potential involves two major voltage-dependent ionic conductances, g_{Na} for sodium and g_K for potassium (independent of each other). Leak conductance do not depend on membrane potential. **Total ionic current**:

$$\sum_{ions} I_i(t) = I_{Na} + I_K + I_{leak},$$

  where $I_i(t) = g_i(V(t), t)(V(t) - E_i)$.
- Conductances are expressed as a maximum conduntance $\bar{g}_i$ multiplied by a coefficient representing the fraction of the maximum conductance available (fraction of gates in permissive state).
- Coefficient is a function of one or more activating and inactivating gates.

Hodgkin-Huxley model

- Current I_m through the cell membrane:

$$I_m(t) = I_c(t) + \sum_{ions} I_i(t) = I_c(t) + I_{Na} + I_K + I_{leak}$$
$$= C_m \frac{\mathrm{d}V(t)}{\mathrm{d}t} + \bar{g}_K n^4 (V(t) - E_K) +$$
$$\bar{g}_{Na} m^3 h (V(t) - E_{Na}) + g_{leak}(V(t) - V_{leak})$$

- $\bar{g}_i$ is maximal conductance of i-th ion,
- n, m are the probabilities to find one activation gate in permissive state, h is the probability that the inactivating gate is not in its nonpermissive state, dimensionless between 0 and 1,
- K^+ conductance is modeled using four activation gates,
- Na^+ conductance is modeled using three activation gates and one inactivation gate

- **Hodgkin-Huxley model**:

$$C_m \frac{\mathrm{d}V(t)}{\mathrm{d}t} = -\bar{g}_K n^4 (V(t) - E_K) - \bar{g}_{Na} m^3 h (V(t) - E_{Na}) - g_{leak}(V(t) - V_{leak}) + I_{app}(t),$$

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n(V)(1-n) - \beta_n(V)n = \frac{n_\infty - n}{\tau_n},$$

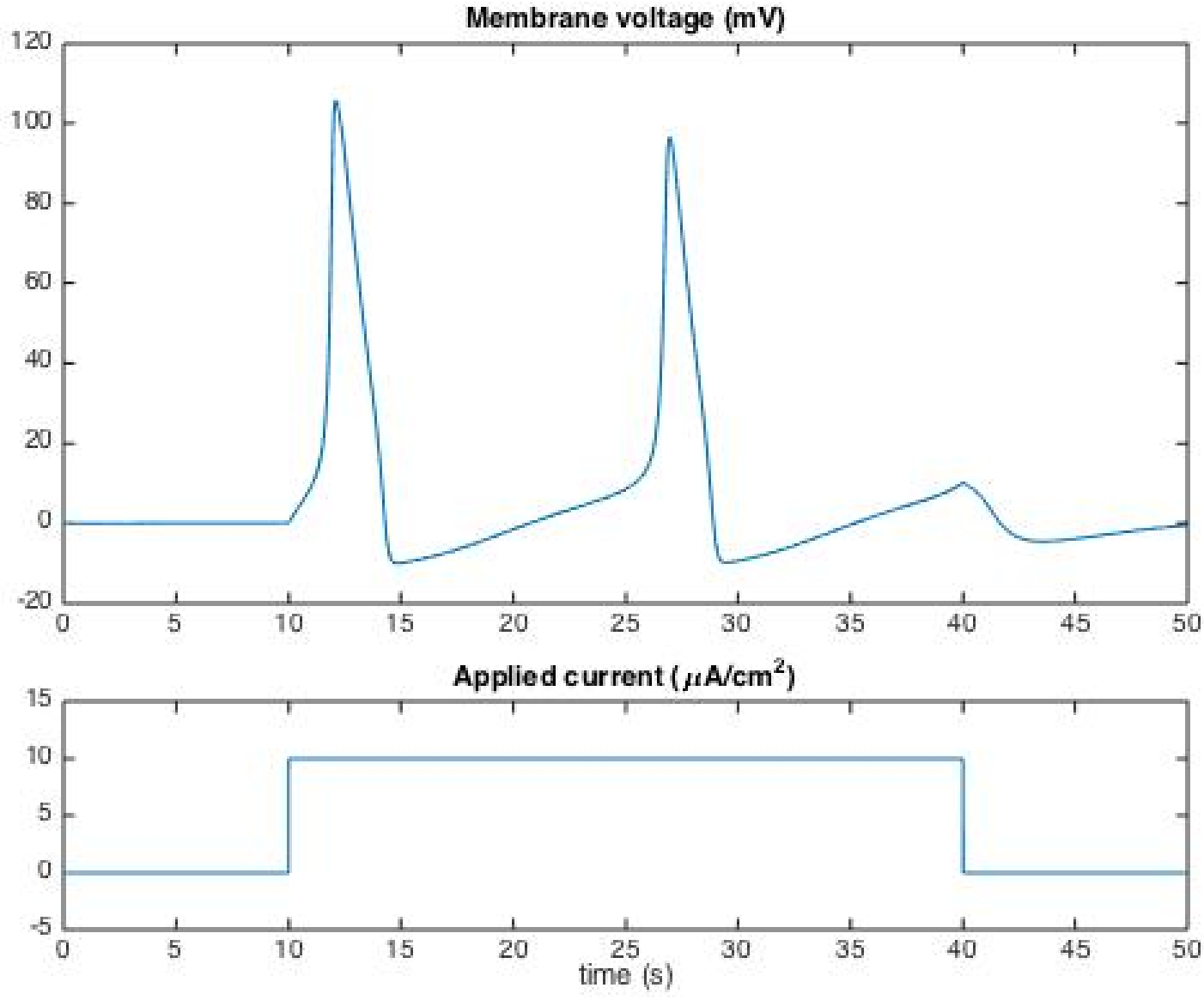
$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m(V)(1-m) - \beta_m(V)m = \frac{m_\infty - m}{\tau_m},$$

$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h(V)(1-h) - \beta_h(V)h = \frac{h_\infty - h}{\tau_h},$$

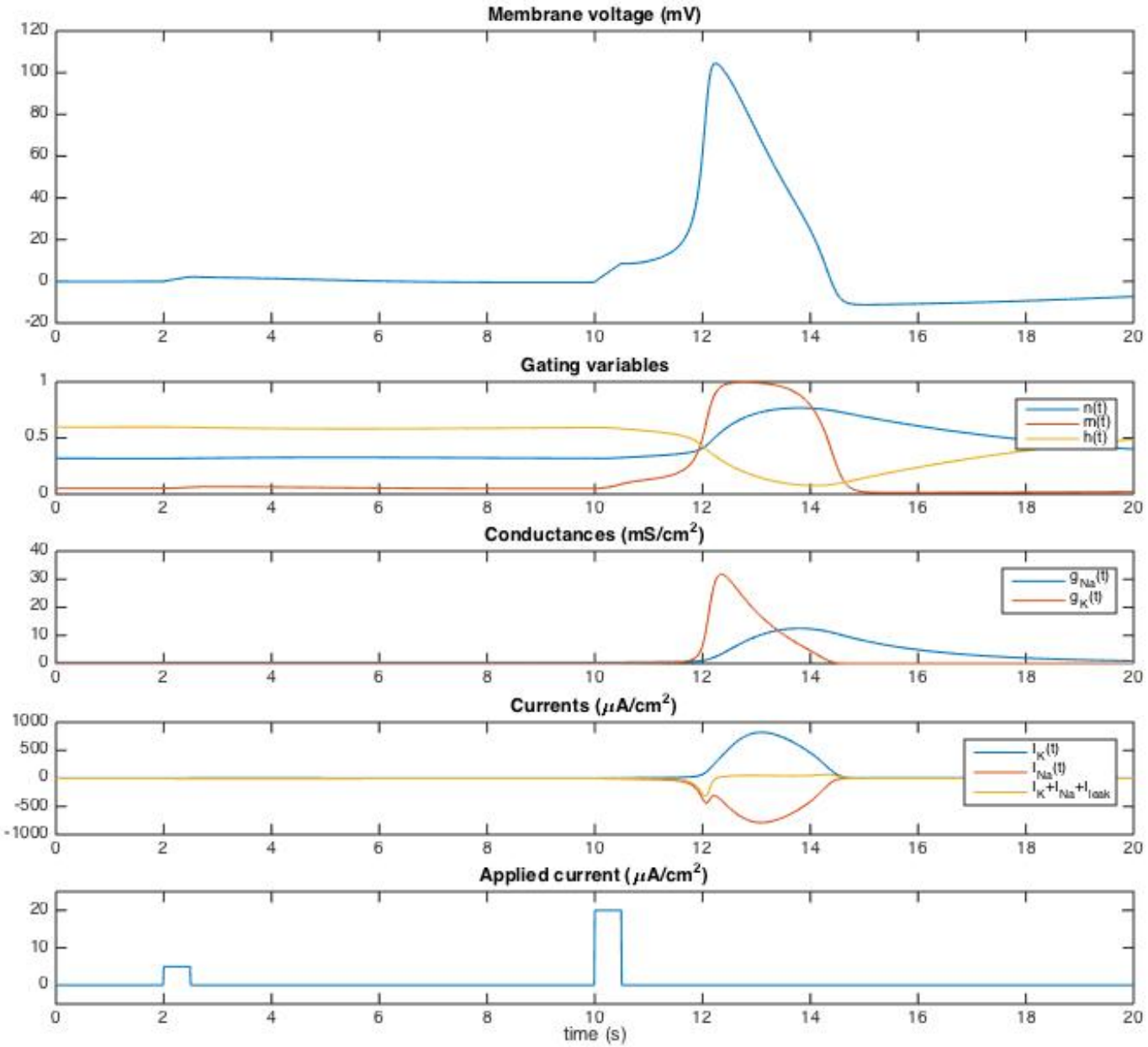
where

- $\bar{g}_K = 36$ mS/cm^2, $E_K = -12$ mV, $\bar{g}_{Na} = 120$ mS/cm^2, $E_{Na} = 115$ mV, $g_{leak} = 0.3$ mS/cm^2, $V_{leak} = 10.613$ mV, $C_m = 1$ μF/cm^2, I_{app} is applied current,

HH model: spike development



HH model: dynamics of currents



Neurons are dynamical systems

- An important result of the Hodgkin-Huxley studies is that *neurons are dynamical systems*, so they should by studied as such.
- A dynamical system consists of a set of variables that describe its state and a law that describes the evolution of the state variables with time (recall first two lectures).
- The Hodgkin-Huxley model is a four-dimensional dynamical system because its state is uniquely determined by the membrane potential, V, and gating variables n, m and h for persistent K^+ and transient Na^+ currents. The evolution law is given by a four-dimensional system of ordinary differential equations.

Neurons are dynamical systems

All variables describing neuronal dynamics can be classified into four classes, according to their functions and the time scale.

1. *Membrane potential.*
2. *Excitation variables* , such as activation of a Na^+ current. These variables are responsible for the upstroke of the spike.
3. *Recovery variables* , such as inactivation of a Na^+ current and activation of a fast K^+ current. These variables are responsible for the repolarization (downstroke) of the spike.
4. *Adaptation variables* , such as activation of slow voltage- or Ca^{2+}-dependent currents. These variables build up during prolonged spiking and can affect excitability in the long run.

E. Izhikevich, *Dynamical Systems in Neuroscience*, MIT Press, 2007.

Phase protraits

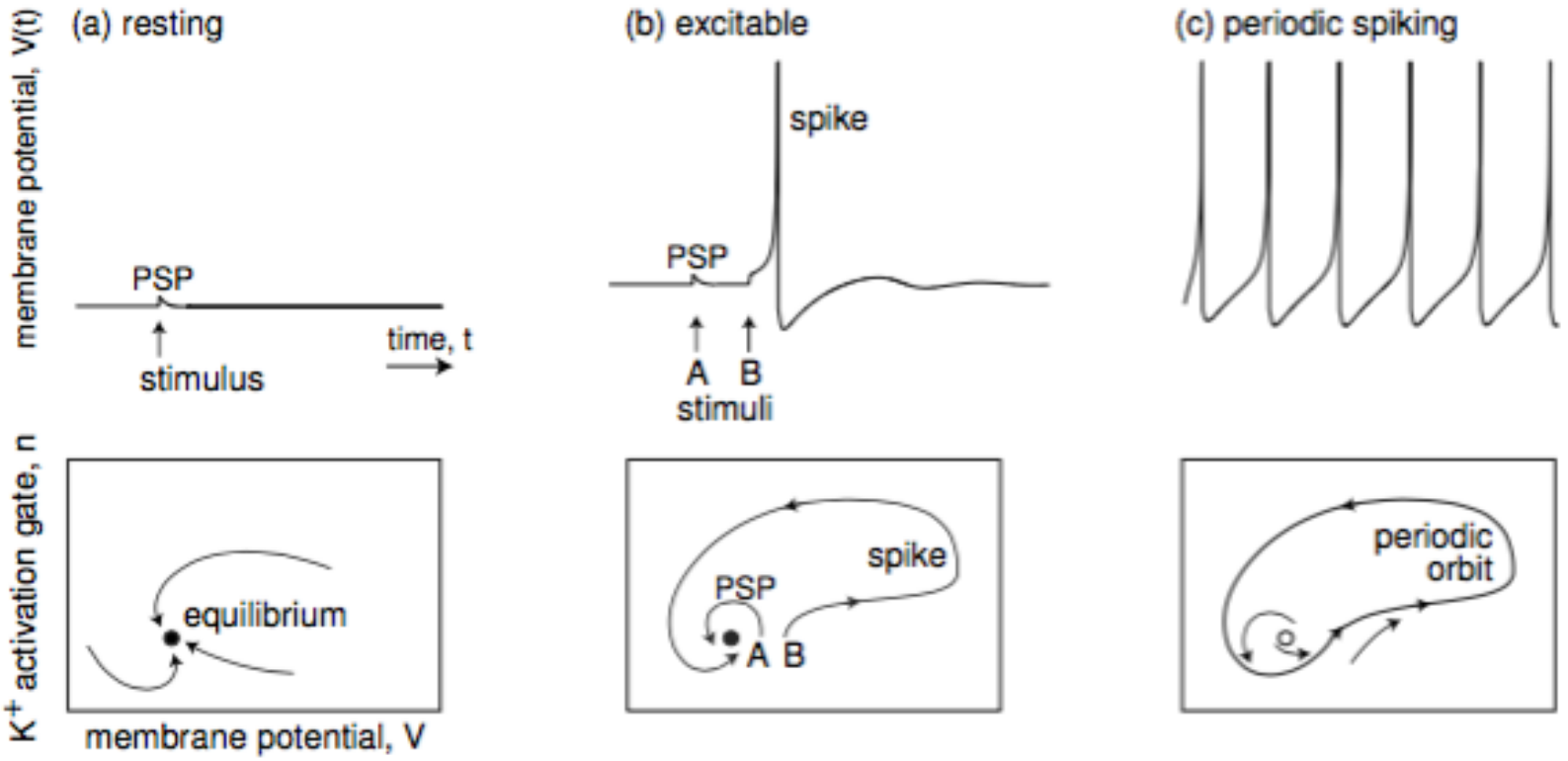


Figure: Resting, excitable, and periodic spiking activity correspond to a stable equilibrium (a and b) or limit cycle (c), respectively.
E. Izhikevich, *Dynamical Systems in Neuroscience*, MIT Press, 2007.

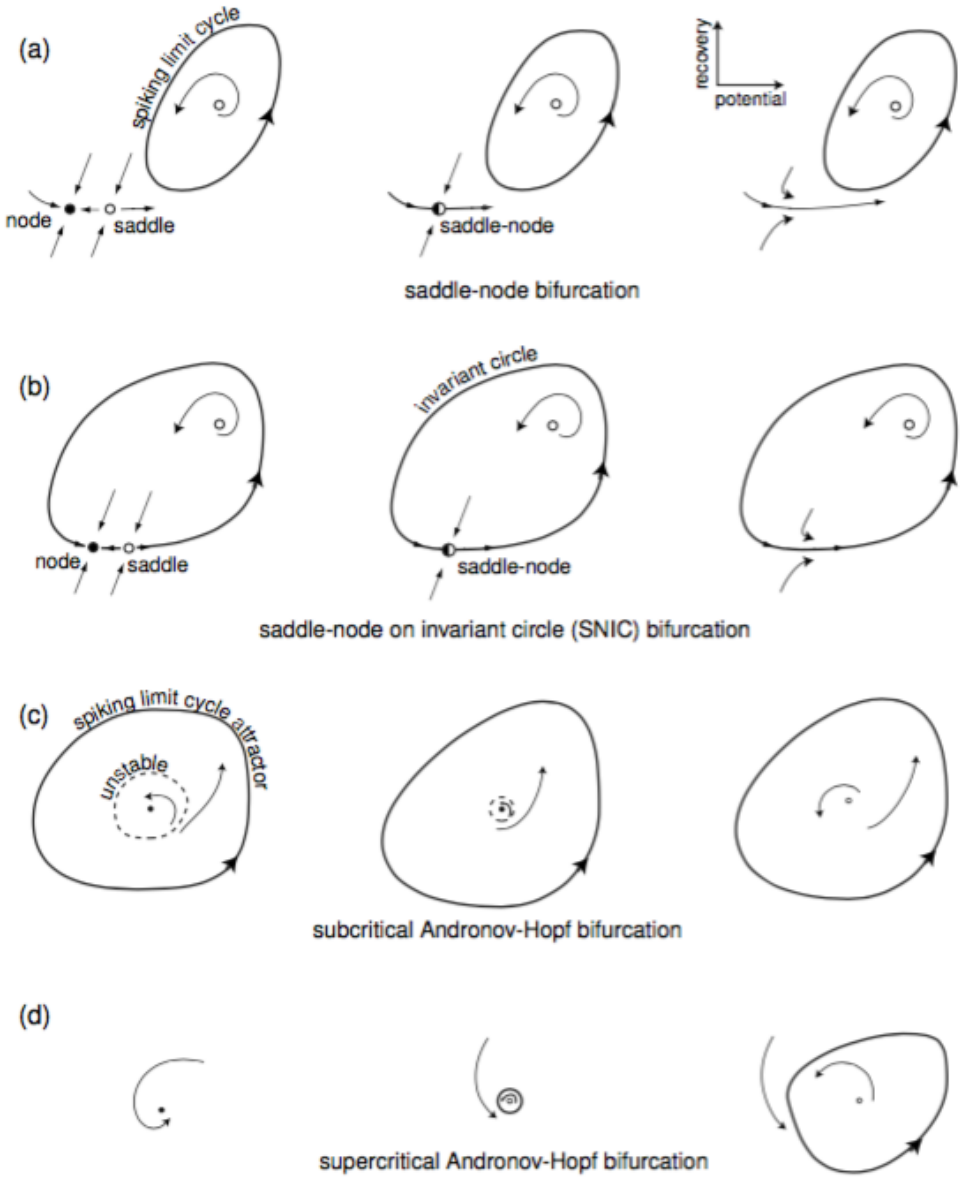


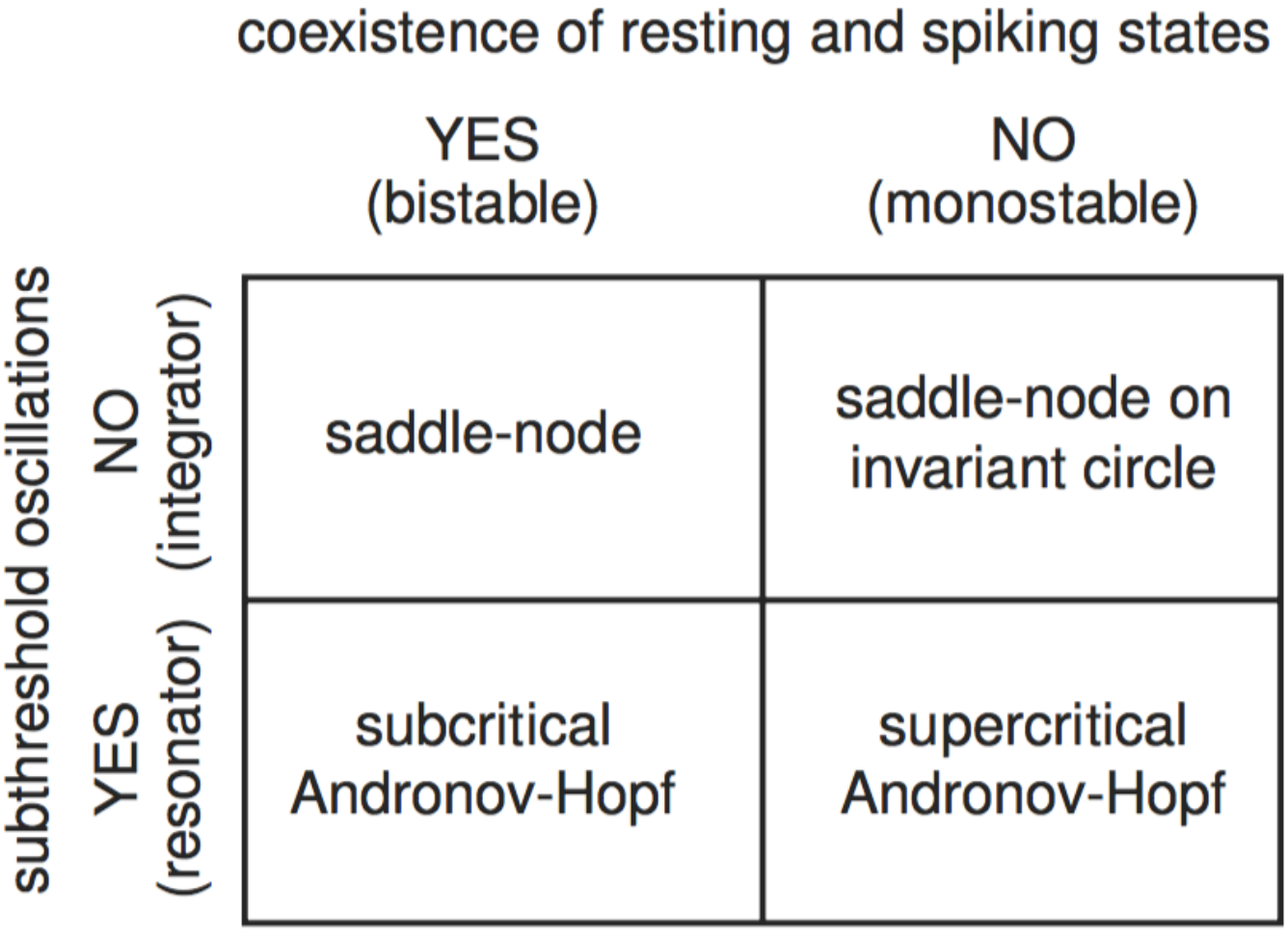
Figure: Four generic (codimension-1) bifurcations of an equilibrium state leading to the transition from resting to periodic spiking behavior in neurons. E. Izhikevich, *Dynamical Systems in Neuroscience*, MIT Press, 2007.

Classification of neurons

- Notice that there is a coexistence of resting and spiking states in the case of saddle-node and subcritical Andronov-Hopf bifurcations, but not in the other two cases. Such a coexistence reveals itself via a hysteresis behavior when the injected current slowly increases and then decreases past the bifurcation value, because the transitions "resting→spiking" and "spiking→resting" occur at different values of the current.
- Systems near Andronov-Hopf bifurcations, whether subcritical or supercritical, exhibit damped oscillations of membrane potential, whereas systems near saddle-node bifurcations do not. The existence of small amplitude oscillations creates the possibility of resonance of the frequency of the incoming pulses.

E. Izhikevich, *Dynamical Systems in Neuroscience*, MIT Press, 2007.

Classification of neurons



E. Izhikevich, *Dynamical Systems in Neuroscience*, MIT Press, 2007.

Neurocomputational properties

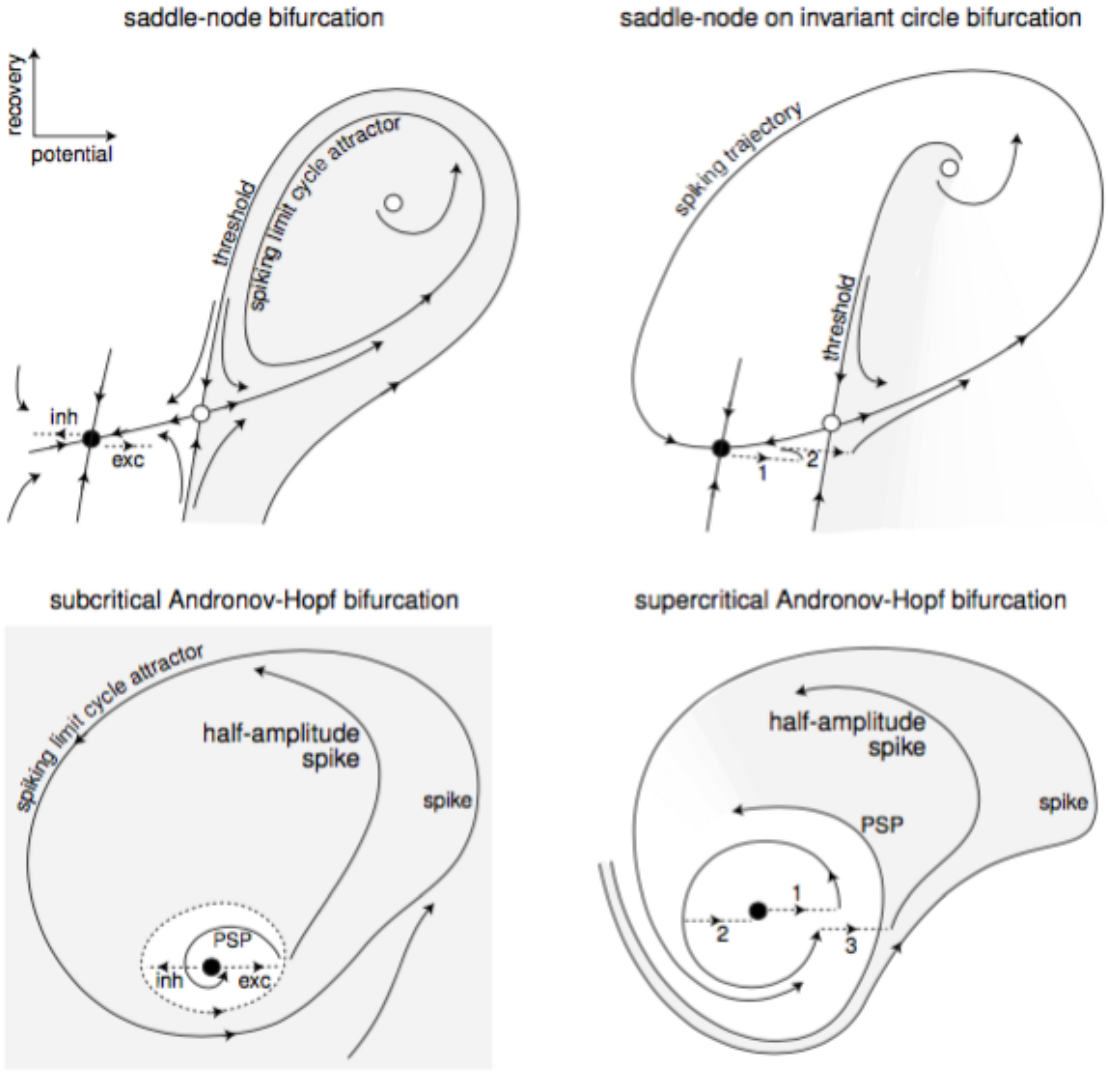


Figure 1.15: The geometry of phase portraits of excitable systems near four bifurcations can explain many neurocomputational properties (see section 1.2.4 for details).

E. Izhikevich, *Dynamical Systems in Neuroscience*, MIT Press, 2007.

Summary

In neurons...

- electrochemical gradient is the major driving force of neural activity.
- electrical charges are carried by Na^+, K^+, Ca^{2+} and Cl^-.
- current of each ion species is proportional to the membrane potential V: $I_i = g_i(V - E_i)$.
- g_i is NOT constant and is a function of V and time, which make neurons excitable.

Neurons...

- are dynamical systems.
- undergo only four (codimension-1) bifurcations between resting and spiking states.
- are uniquely classified according to these bifurcations.

Useful resources

- E. Izhikevich, Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting, The MIT Press, 2007 (**Chapters 1&2**).