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Dipartimento di Informatica
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Neural Modeling and Computational Neuroscience

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Neuroscience modeling

- Introduction to basic aspects of brain computation
- Introduction to neurophysiology
- Neural modeling:
  - Elements of neuronal dynamics
  - Elementary neuron models
  - Neuronal Coding
  - Biologically detailed models:
    the Hodgkin-Huxley Model
  - Spiking neuron models, spiking neural networks
  - Izhikevich Model
- Introduction to Reservoir Computing and Liquid State Machines
- Introduction to glia and astrocyte cells, the role of astrocytes in a computational brain, modeling neuron-astrocyte interaction, neuron-astrocyte networks,
- The role of computational neuroscience in neuro-biology and robotics applications.

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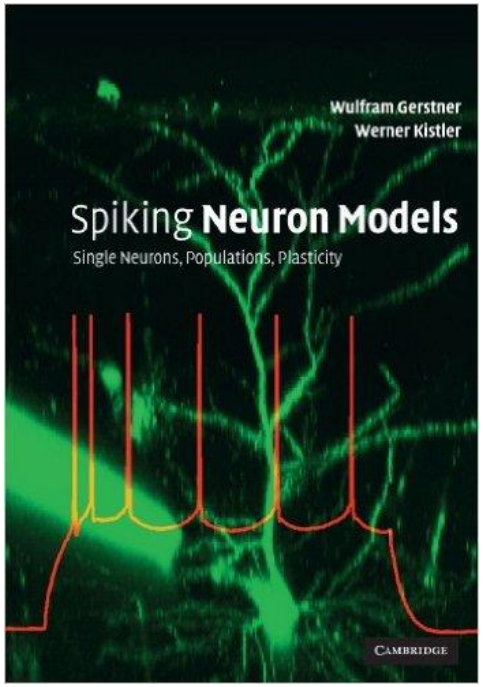
References

W. Gerstner and W.M. Kistler, Spiking Neuron Models: Single Neurons, Population, Plasticity. Cambridge Univ. Press, 2002

on-line at: http://lcn.epfl.ch/~gerstner/SPNM/SPNM.html

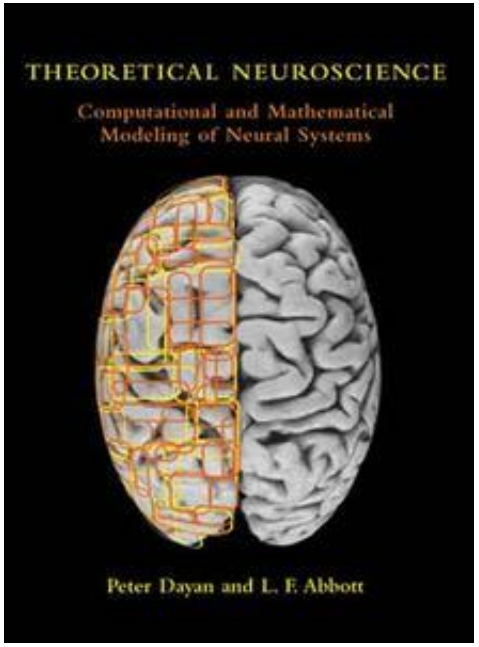


Chap. 2 – Sect. 2.1, 2.2

Chap. 4 – Sect. 4.1

References

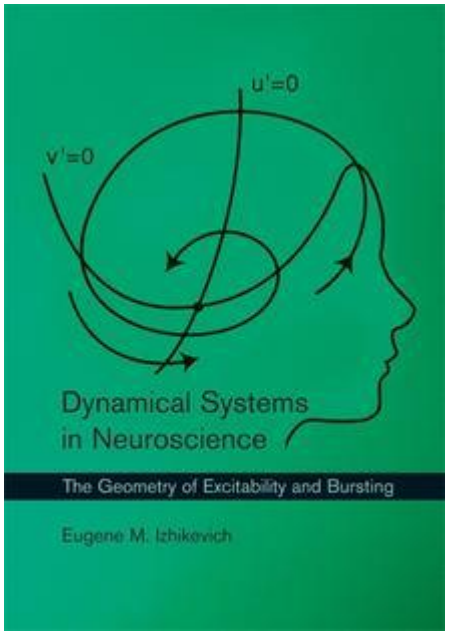
P. Dayan and L.F. Abbott. Theoretical neuroscience. Vol. 806. Cambridge, MA: MIT Press, 2001.



Chap. 5 – Sect. 5.1, 5.2, 5.4, 5.5, 5.6

References

E.M. Izhikevich, Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting. The MIT press, 2007



Chap. 1

Chap. 2

Chap. 8 – Sect. 8.1, 8.2

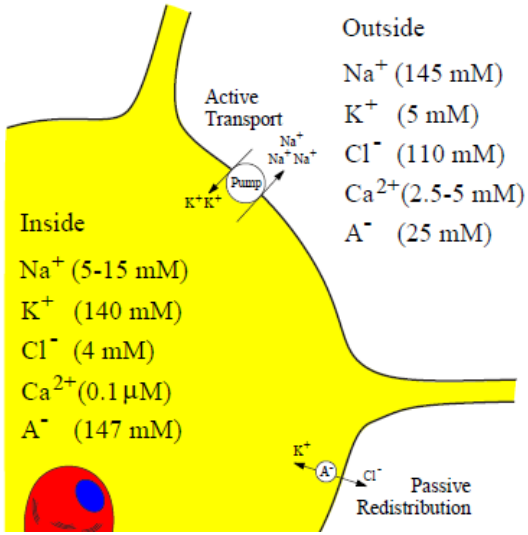
Conductance-based Neuron Models

Reversal Potential (Repetita)

- The reversal potential of an ion is its Nernst potential

$$E_{[ion]} = \frac{kT}{q_{[ion]}} \ln \frac{n_{out}}{n_{in}}$$

- If $\Delta u < E_{[\mathrm{ion}]} \Rightarrow$ ions flow into the cell
- If $\Delta u > E_{[\mathrm{ion}]} \Rightarrow$ ions flow out of the cell



Equilibrium Potentials

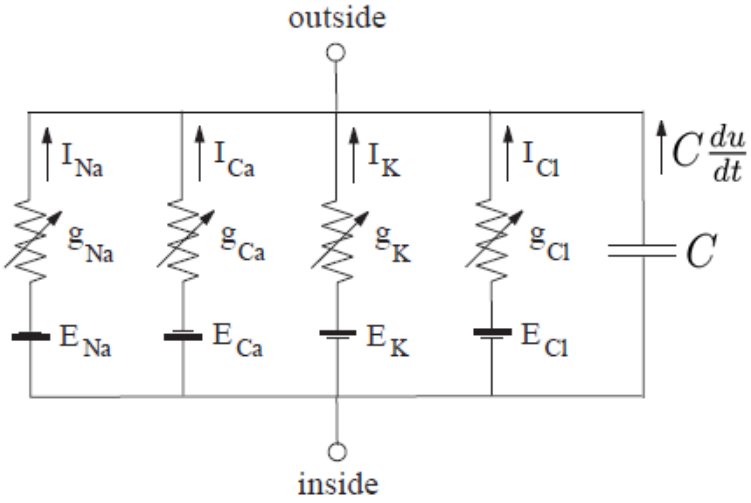
Na^+	$62 \log \frac{145}{5}$	$= 90$ mV
	$62 \log \frac{145}{15}$	$= 61$ mV
K^+	$62 \log \frac{5}{140}$	$= -90$ mV
Cl^-	$-62 \log \frac{110}{4}$	$= -89$ mV
Ca^{2+}	$31 \log \frac{2.5}{10^{-4}}$	$= 136$ mV
	$31 \log \frac{5}{10^{-4}}$	$= 146$ mV

$$E_K < E_{Cl} < \underbrace{u_{rest}}_{-65mV} < E_{Na} < E_{Ca}$$

- **Ion channels**: try to equilibrate the concentration of ions, i.e. <u>try to meet the reversal potential</u>
- **Ion pumps**: active pumps that balance the flow of ions

Equivalent Circuit (Repetita)

- Electrical properties of neurons' membranes depicted in terms of the electrical circuit

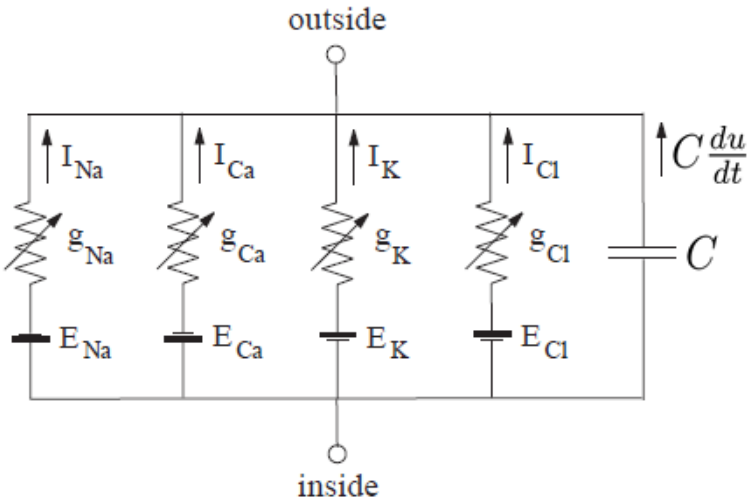


- Membrane: capacitor
- Ions' channels: resistors + battery (reversal potentials)

$$I_{Na} = g_{Na}(u - E_{Na}) \qquad I_{Ca} = g_{Ca}(u - E_{Ca})$$

$$I_K = g_K(u - E_K) \qquad I_{Cl} = g_{Cl}(u - E_{Cl})$$

Equivalent Circuit



- Membrane: capacitor
- Ions' channels: resistors + battery (reversal potentials)

$$E_K < E_{Cl} < u_{rest} < E_{Na} < E_{Ca}$$

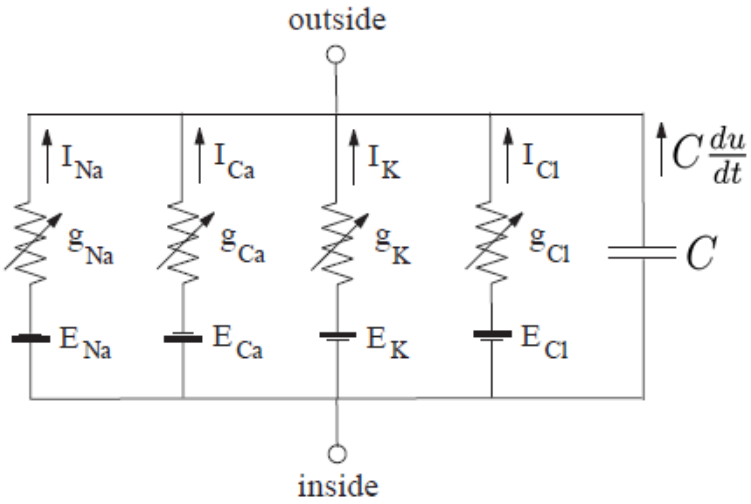
$$I_{Na} = g_{Na}(u - E_{Na}) \qquad I_{Ca} = g_{Ca}(u - E_{Ca})$$

inward current

$$I_K = g_K(u - E_K) \qquad I_{Cl} = g_{Cl}(u - E_{Cl})$$

outward current

Equivalent Circuit



- Membrane: capacitor
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$$E_K < E_{Cl} < u_{rest} < E_{Na} < E_{Ca}$$

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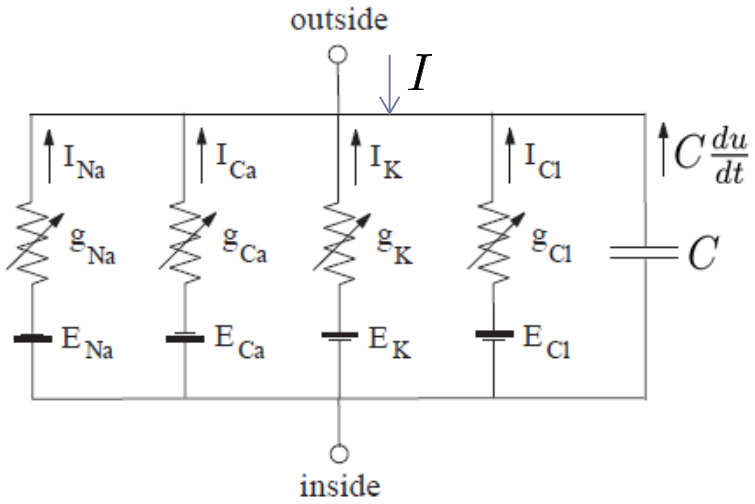
inward current

$$I_K = g_K(u - E_K) \qquad I_{Cl} = g_{Cl}(u - E_{Cl})$$

outward current

??

Equivalent Circuit



- Membrane: capacitor
- Ions' channels: resistors + battery (reversal potentials)
- Applied current I

$$I_{Na} = g_{Na}(u - E_{Na}) \quad I_K = g_K(u - E_K) \quad I_{Ca} = g_{Ca}(u - E_{Ca}) \quad I_{Cl} = g_{Cl}(u - E_{Cl}) \quad C\frac{du}{dt}$$

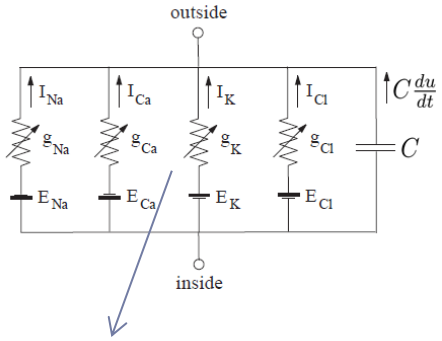
$$I$$

Using Kirchhoff's Current Law (KCL):

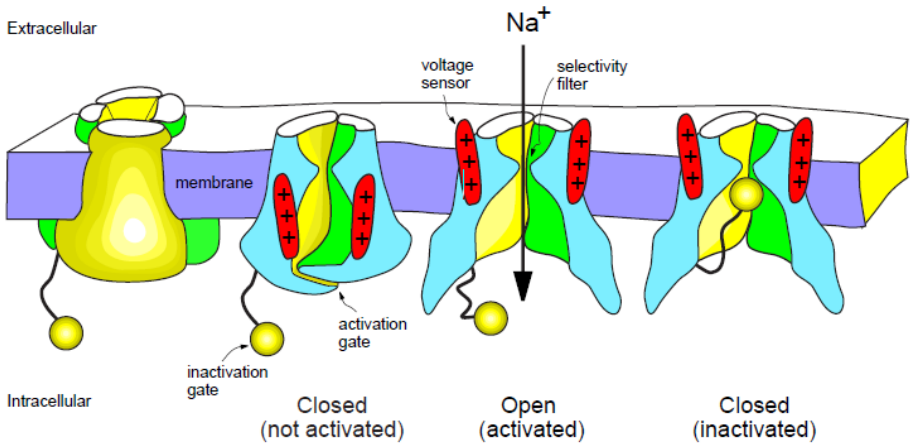
$$C\frac{du}{dt} = I - I_{Na} - I_{Ca} - I_K - I_{Cl}$$

$$C\frac{du}{dt} = I - g_{Na}(u - E_{Na}) - g_{Ca}(u - E_{Ca}) - g_K(u - E_K) - g_{Cl}(u - E_{Cl})$$

Conductances



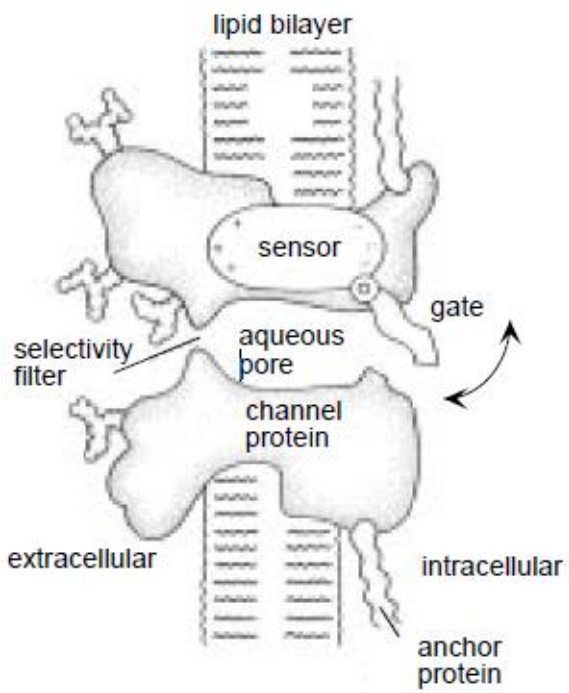
non-Ohmic currents
(conductances are not constant)



Ion channels:

- Large transmembrane proteins with aqueous pores
- Electrical conductance of individual channels is controlled by gates (gating particles)
- Gates can change the state of the channel: open/closed
- Gates can be sensitive to the membrane potential (voltage-dependent conductances), intracellular agents, neurotransmitters, ….

Persistent Conductances



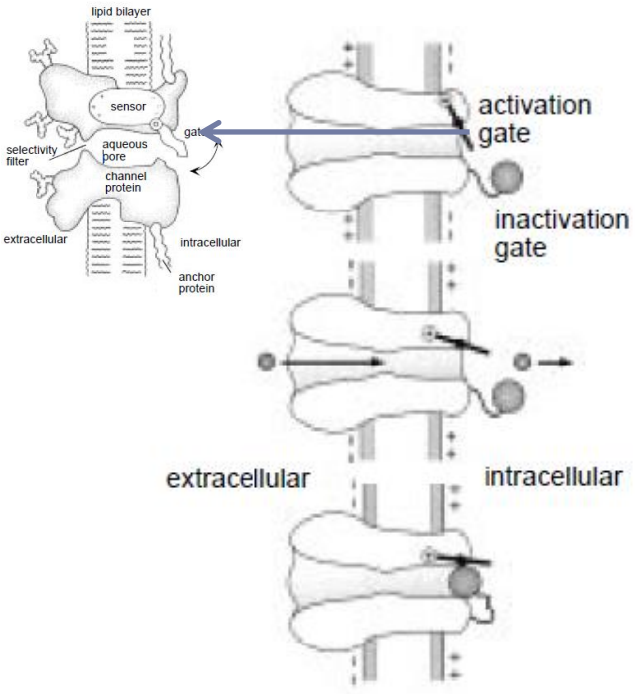
- a voltage sensor is connected to a swinging (activation) gate that can open or close the pore
- gate opening: activation of the conductance
- gate closing: de-activation of the conductance
- results in a persistent (or non-inactivating) conductance
- Probability of the channel to be opened: $p = n^k$

gating variable: the probability that one of the *k* sub-units of the gate is opened

Voltage dependency:

depolarization of the membrane leads to increasing n

Transient Conductances



- Two gates regulates the channel:
  1 activation gate & 1 inactivation gate
- The activation gate is opened with probability m^k
- The inactivation gate (the ball) does not block the channel with probability h
- The channel is opened with probability $m^k h$
- The channel opens transiently while the membrane is depolarized

Voltage dependency:

Depolarization: increasing m, decreasing h

Hyper-polarization: decreasing m, increasing h

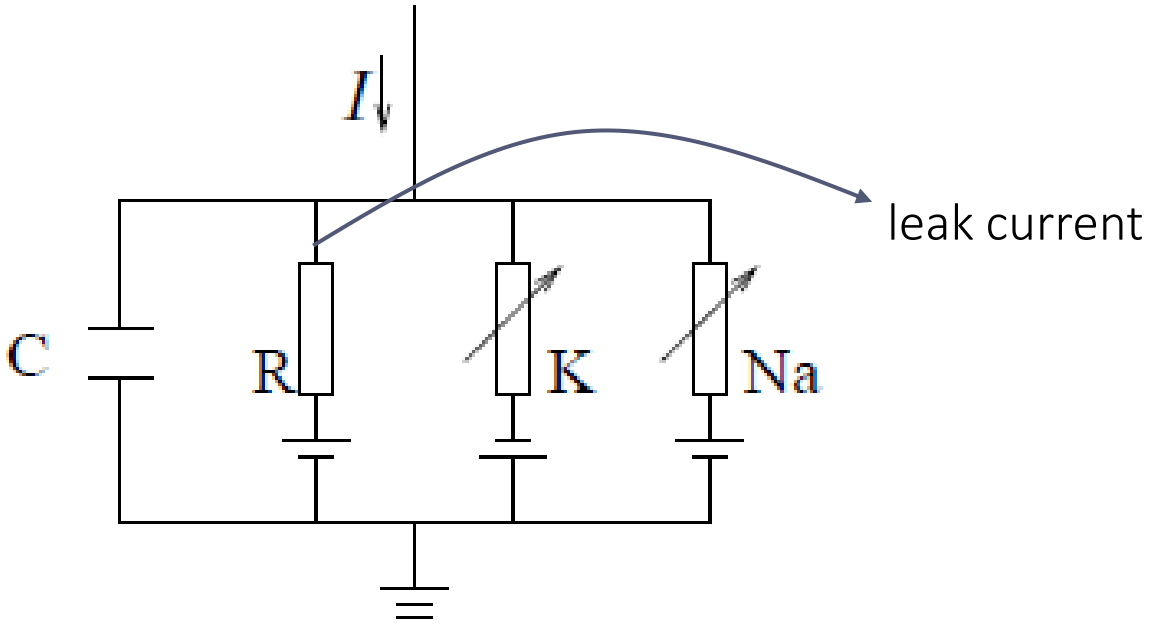
The Hodgkin-Huxley Model

The Hodgkin-Huxley Model

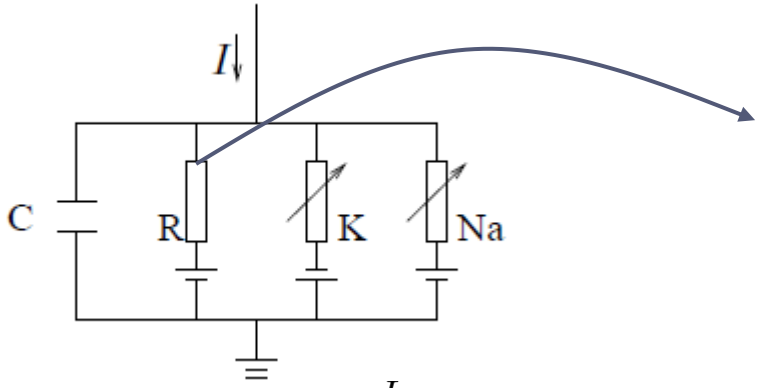
- One of the most important models in Computational Neuroscience
- Based on studies by Hodgkin and Huxley (in the 50s) on the squid axon
- The squid axon has 3 major currents:
  - Voltage-gated persistent K^+ current with 4 activation gates
  - Voltage-gated transient Na^+ current with 3 activation gates and 1 inactivation gate
  - Ohmic leak current (all the other ions)

$$I_{[ion]} = g_{[ion]}\, p\, (u - E_{[ion]})$$

Hodgkin-Huxley Model



Hodgkin-Huxley Model



leak current

$$C\frac{du}{dt} = I - \overbrace{g_k\, n^4\,(u - E_K)}^{I_K} - \overbrace{g_{Na}\, m^3 h\,(u - E_{Na})}^{I_{Na}} - \overbrace{g_L\,(u - E_L)}^{I_L}$$

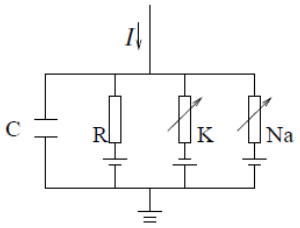
$$\frac{dn}{dt} = \alpha_n(u)(1-n) - \beta_n(u)n$$

$$\frac{dm}{dt} = \alpha_m(u)(1-m) - \beta_m(u)m$$

$$\frac{dh}{dt} = \alpha_h(u)(1-h) - \beta_h(u)h$$

- m, n, h - gating variables
- α, β – empirical functions adjusted by Hodgkin and Huxley

Hodgkin-Huxley Model



$$C\frac{du}{dt} = I - \overbrace{g_k\, n^4\,(u - E_K)}^{I_K} - \overbrace{g_{Na}\, m^3 h\,(u - E_{Na})}^{I_{Na}} - \overbrace{g_L\,(u - E_L)}^{I_L}$$

The equations for the gating variables can be rewritten as

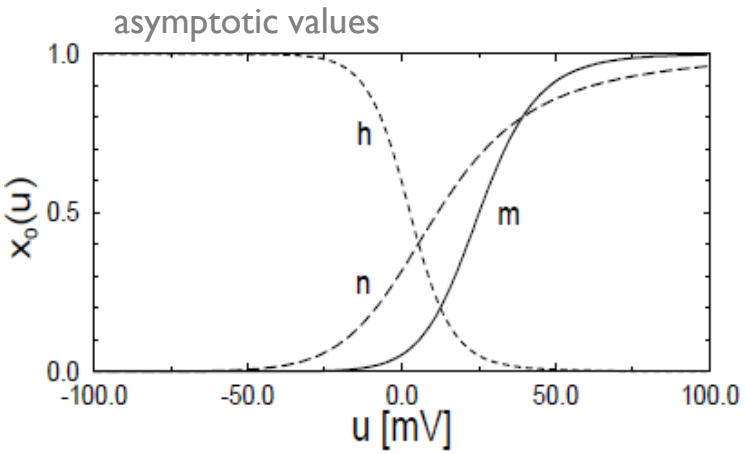
$$\frac{dn}{dt} = \frac{n_0(u) - u}{\tau_n} \qquad \frac{dm}{dt} = \frac{m_0(u) - u}{\tau_m} \qquad \frac{dh}{dt} = \frac{h_0(u) - u}{\tau_h}$$

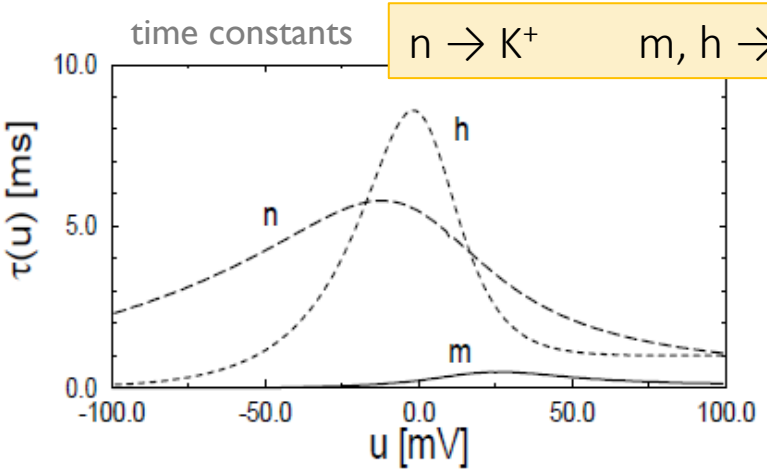
where:

$$n_0(u) = \frac{\alpha_n(u)}{\alpha_n(u)+\beta_n(u)}, \tau_n(u) = \frac{1}{\alpha_n(u)+\beta_n(u)}$$
$$m_0(u) = \frac{\alpha_m(u)}{\alpha_m(u)+\beta_m(u)}, \tau_m(u) = \frac{1}{\alpha_m(u)+\beta_m(u)}$$
$$h_0(u) = \frac{\alpha_h(u)}{\alpha_h(u)+\beta_h(u)}, \quad \tau_h(u) = \frac{1}{\alpha_h(u)+\beta_h(u)}$$

- $n_0(t), m_0(t), h_0(t)$ asymptotic values
- $\tau_n(t), \tau_m(t), \tau_h(t)$ time constants

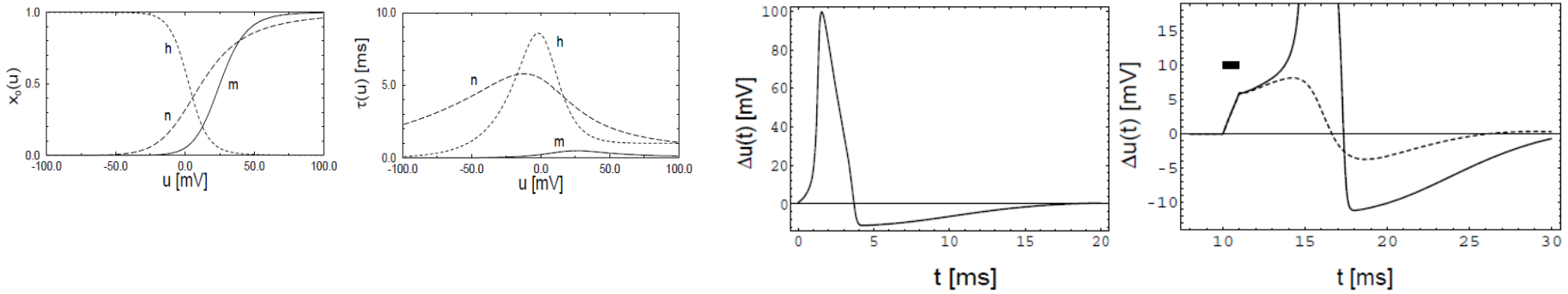
Hodgkin-Huxley Model – Dynamics





- Sodium (Na^+) – inward current:
  - Activation increases for increasing membrane potential
  - Inactivation increases for increasing membrane potential
  - BUT: activation is faster than inactivation (transient current)
- Potassium (K^+) – outward current:
  - Activation increases for increasing membrane potential
  - BUT: activation is relatively slow (slower than activation of Na^+)

Hodgkin-Huxley Model – Spike Generation



- An external input (e.g. an EPSP) leads to a depolarization (u increases)
- Conductance of Na+ increases rapidly, Na^+ ions flow in the cell and u increases even further
- If the feedback is strong enough the action potential is initiated
- At high values of depolarization, the Na^+ current is stopped by the inactivation gate ($h \rightarrow 0$), conductance of K^+ increases and K^+ ions flow outside the cell
- The membrane is re-polarized, with a negative overshoot (refractoriness)

- Threshold behavior: if the stimulating input is below a certain amplitude the action potential is not initiated and the membrane is re-polarized

The Hodgkin-Huxley Model - Summary

$$C\frac{du}{dt} = I - \overbrace{g_k\, n^4\, (u - E_K)}^{I_K} - \overbrace{g_{Na}\, m^3 h\, (u - E_{Na})}^{I_{Na}} - \overbrace{g_L\, (u - E_L)}^{I_L}$$

$$\frac{dn}{dt} = \alpha_n(u)(1-n) - \beta_n(u)n$$

$$\frac{dm}{dt} = \alpha_m(u)(1-m) - \beta_m(u)m$$

$$\frac{dh}{dt} = \alpha_h(u)(1-h) - \beta_h(u)h$$

- Conductance-based neuron model
- Processes that regulate the voltage-dependent K^+ and Na^+ conductances well described
- Biophysical mechanisms responsible for action potentials explicitly included in the mathematical model
- Accurate biological realism, BUT slow and difficult to analyze.

Formal Spiking Neuron Models

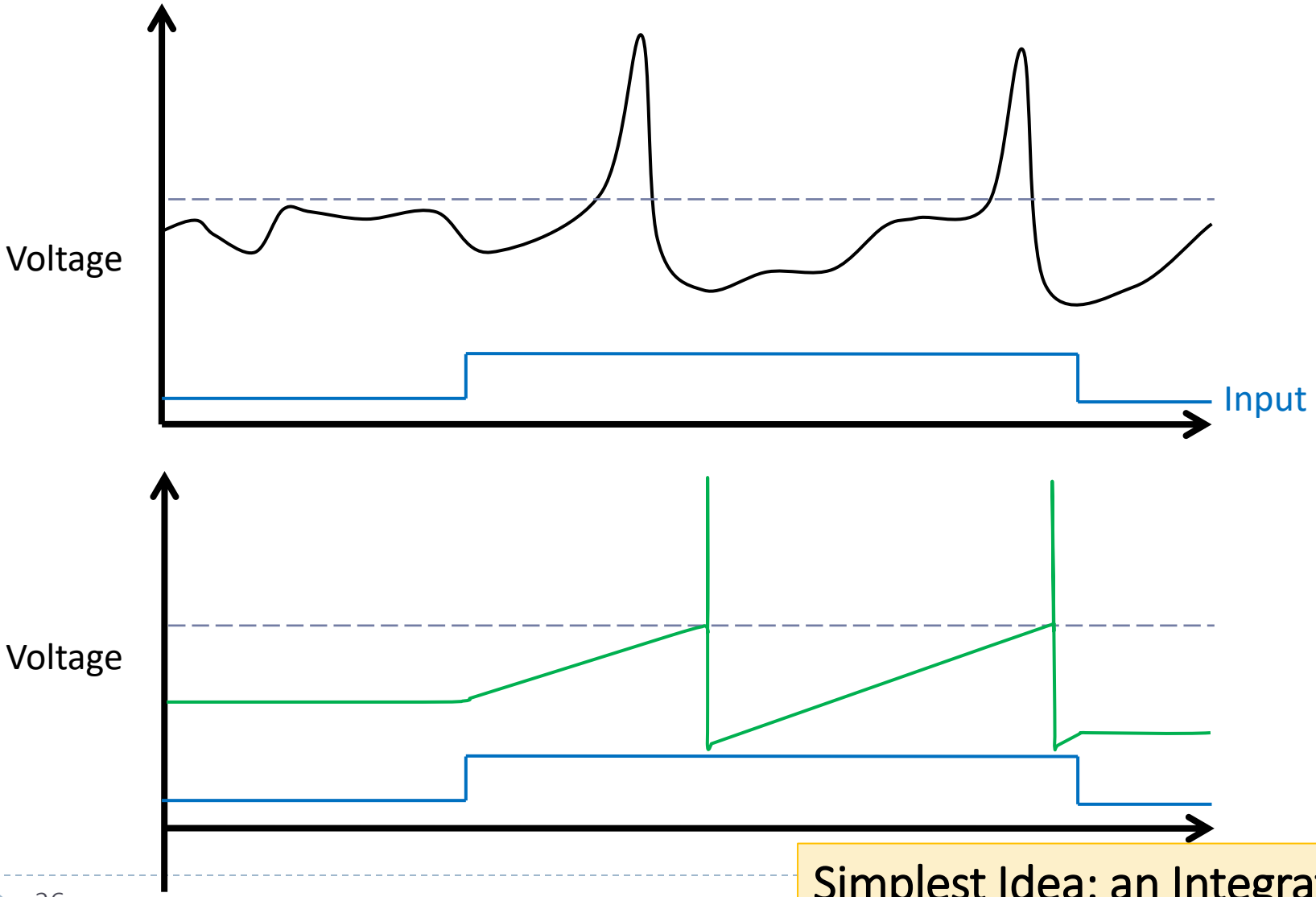
Phenomenological Spiking Neuron

- Neuron models can be simplified and simulations can be accelerated if the biophysical mechanisms of spike-generation are not included explicitly in the model
- Formal threshold models of neuronal firing:
  - Spikes are stereotyped events that occur when the membrane potential crosses the threshold from below

$$t^{(f)}: \quad u(t^{(f)}) = \vartheta \quad \text{and} \quad \left.\frac{\mathrm{d}u(t)}{\mathrm{d}t}\right|_{t=t^{(f)}} > 0$$

  - Spikes are fully characterized by their firing time
  - Model only the sub-threshold dynamics

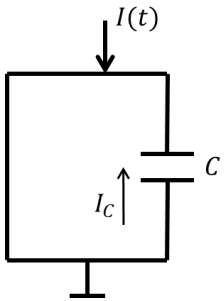
What does a neuron do?



Simplest Idea: an Integrator

Integrate-and-Fire Model

- The most simple case: all membrane conductances are ignored
- The corresponding equivalent (simplified) circuit only contains a capacitor



- From the definition of the capacity: $C = \frac{q}{u} \Rightarrow C\frac{du}{dt} = I_C$
- KCL: $C\frac{du}{dt} = I(t) \qquad \frac{du}{dt} = \frac{I(t)}{C}$
- Spikes are formal events characterized by the firing time $t^{(f)} : \; u(t^{(f)}) = \vartheta$
- After the spike the potential is reset to u_r

  $\lim_{t \to t^{(f)+}} u(t) = u_r$
- Absolute refractory period: after the spike, the integration is suspended for Δ^{abs}

Integrate-and-Fire Model

- Equations

$$\begin{cases} \frac{du}{dt} = \frac{I(t)}{C} \\ t^{(f)}: \; u(t^{(f)}) = \vartheta \\ \lim_{t \to t^{(f)}+} u(t) = u_r \end{cases}$$

u_r is often set to 0

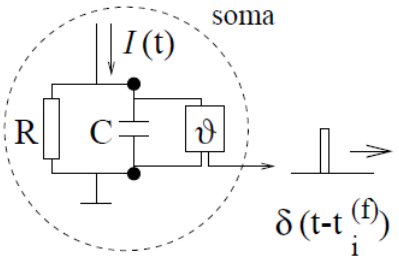
- Suppose a constant input current I_0 is applied (e.g. an EPSP), and the last spike occurred at time $t^{(1)}$:

  the time course of the membrane potential can be obtained by integration in the time interval $t^{(1)}$; t

  $$u(t) = \int_{t^{(1)}}^{t} \frac{I_0}{C} ds = \frac{I_0}{C}(t - t^{(1)})$$

Leaky Integrate-and-Fire Model

- The entire membrane conductance is modeled as a single leakage term
- Assumption: the conductances are all constant
  (true for small fluctuations around the resting membrane potential)
- Corresponding equivalent circuit: a capacitor in parallel with a resistor



Leaky Integrate-and-Fire Model

- Time course of the membrane potential?
- Suppose a constant input current I_0 is applied and the last spike occurred at time $t^{(1)}$
- $u(t)$???

$$\tau_m \frac{du}{dt} = -u(t) + RI(t)$$

First-Order linear differential equation (with initial condition $u(t^{(1)}) = u_r = 0$)

Leaky Integrate-and-Fire Model

- Time course of the membrane potential?
- Suppose a constant input current I_0 is applied and the last spike occurred at time $t^{(1)}$
- $u(t)$???

$$\tau_m \frac{du}{dt} = -u(t) + RI(t)$$

First-Order linear differential equation (with initial condition $u(t^{(1)}) = u_r = 0$)

$$u(t) = RI_0 \left(1 - e^{-\frac{t-t^{(1)}}{\tau_m}}\right)$$

(The membrane potential asymptotically approaches RI_0)

Leaky Integrate-and-Fire Model

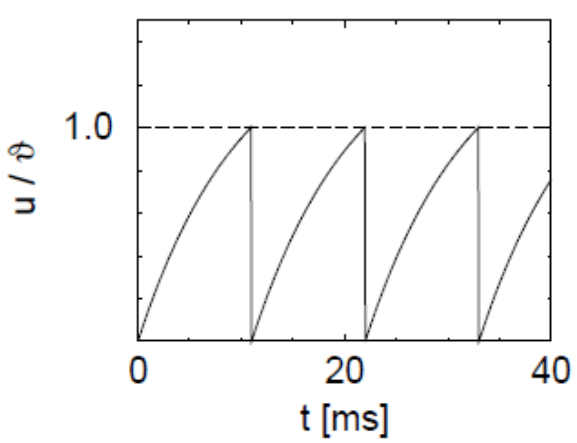
- When will next spike occur?

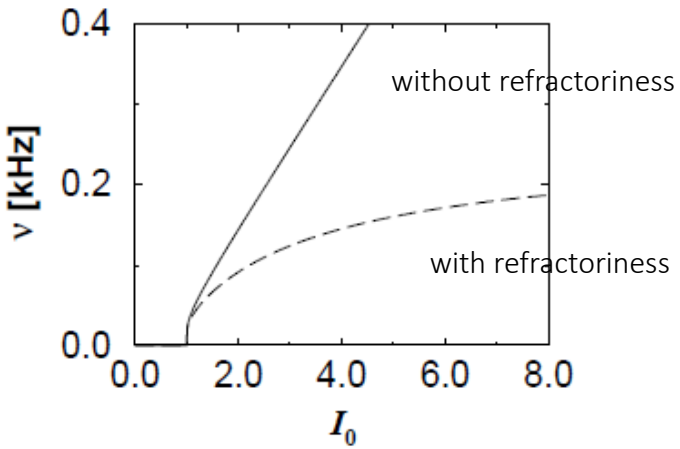
$$u(t^{(2)}) = \vartheta = RI_0\left(1 - e^{-\frac{T}{\tau_m}}\right) \qquad T = t^{(2)} - t^{(1)}$$

$$T = \Delta^{abs} + \tau_m \ln\left(\frac{RI_0}{RI_0 - \vartheta}\right)$$

$$\nu = \left[\Delta^{abs} + \tau_m \ln\left(\frac{RI_0}{RI_0 - \vartheta}\right)\right]^{-1}$$

Firing rate (with refractory period)



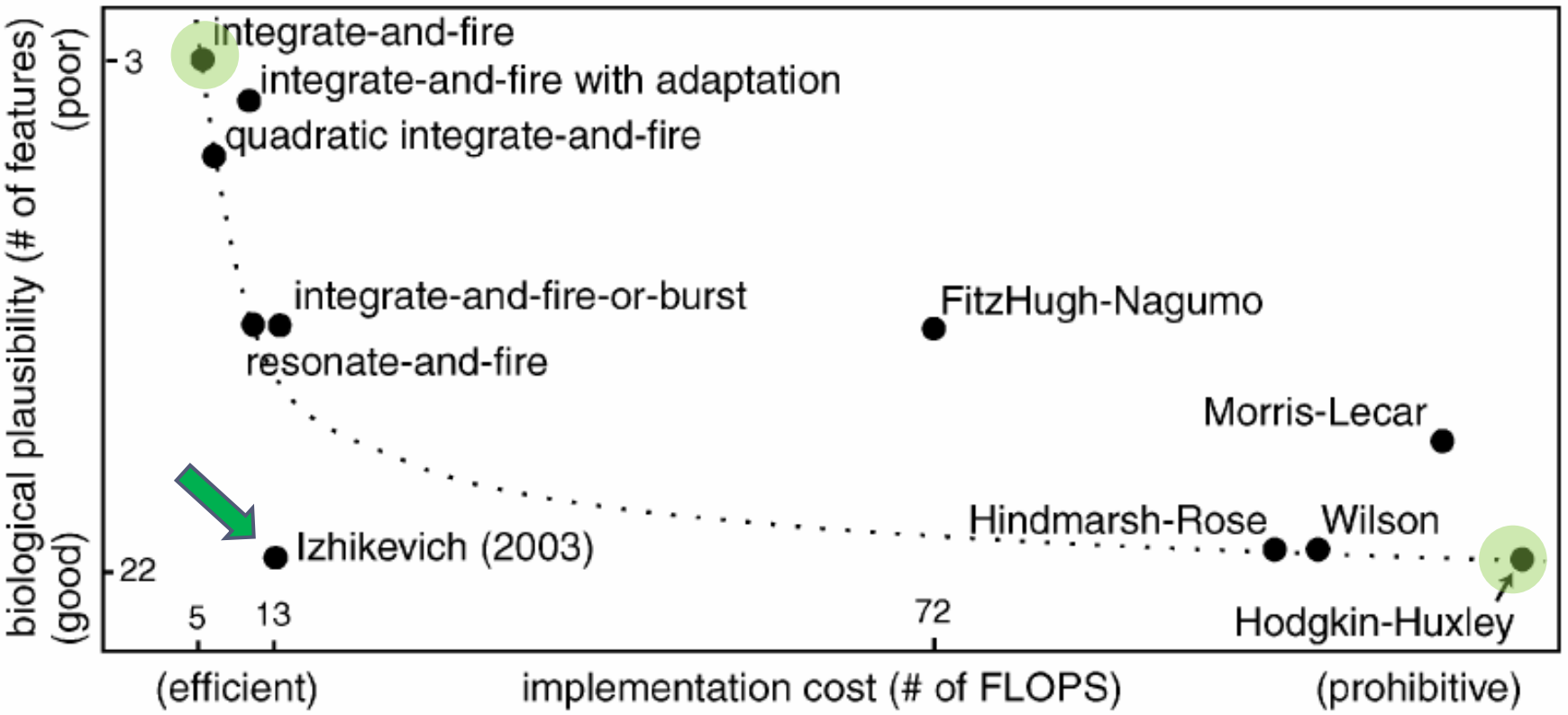


Izhikevich Model

Simple Spiking Models

- Modeling the dynamics of excitable neurons
  - Fast activation of Na^+ channels
  - Slow inactivation of Na^+/activation of K^+
- Dynamical system with 2 variables
  - One variable for the fast voltage increase
  - One recovery variable for slow voltage decrease
- In many cases the sub-threshold dynamics leading to the action potential are more important than the shape of the action potential itself
- Izhikevich model

Neuron Models – Biological Plausibility vs Cost



Izhikevich Model

- Two dimensional system of ordinary differential equations

$$\begin{cases} \frac{du}{dt} = 0.04\,u(t)^2 + 5u(t) + 140 - r(t) + I \\ \frac{dr}{dt} = a(bu(t) - r(t)) \end{cases}$$

If $u(t) \geq 30$ mV

$$\begin{cases} u = c \\ r = r + d \end{cases}$$

- u is the membrane potential,
- r is a recovery variable (Na+ inactivation/K+ activation) provides negative feedback to u
- a, b, c, d are the parameters of the model
- I is the applied current

Izhikevich Model

- Two dimensional system of ordinary differential equations

$$v' = 0.04v^2 + 5v + 140 - u + I$$
$$u' = a(bv - u)$$

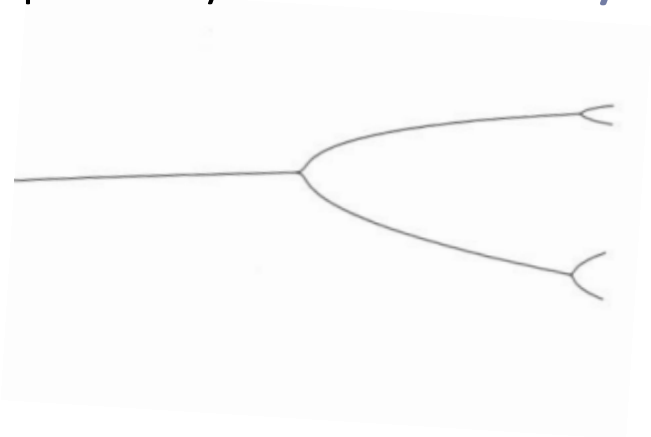
if $v = 30$ mV,
then $v \leftarrow c, \quad u \leftarrow u + d$

Often in literature:

- v is the membrane potential
- u is the recovery variable

Neuronal Dynamics

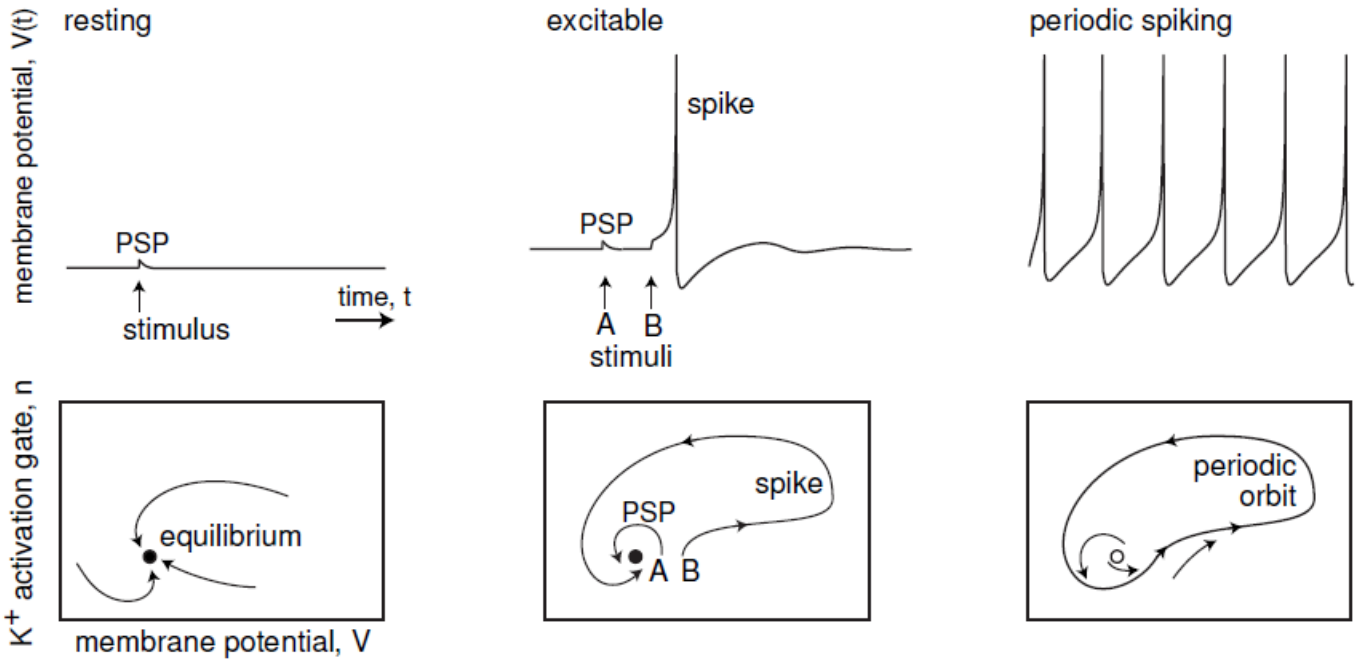
- The behavior of a neuron does not depends only on its electrophysiological properties
- Two neurons with the same electrophysiological properties can respond differently to the same input
- Neurons can be thought as dynamical systems
- Dynamical properties of the neurons have a major role Especially bifurcation dynamics



A bifurcation occurs when a small change to the parameter values of a system results in a sudden qualitative change in its behavior

Neuronal Dynamics

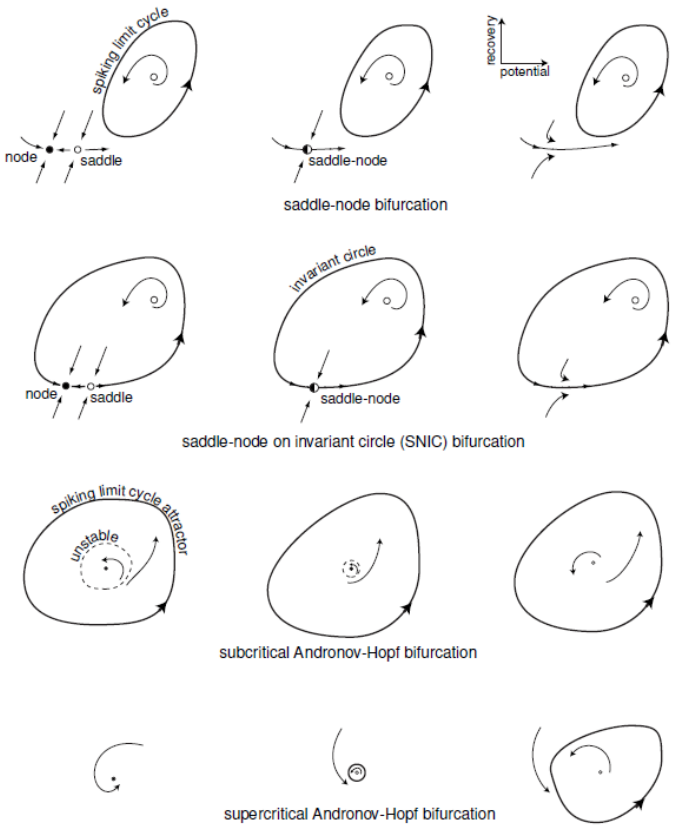
- Neurons are excitable because they are near a transition (bifurcation) between resting and sustained spiking activity



The system is excitable because its equilibrium is near a bifurcation

Neuronal Dynamics

- Four generic bifurcations



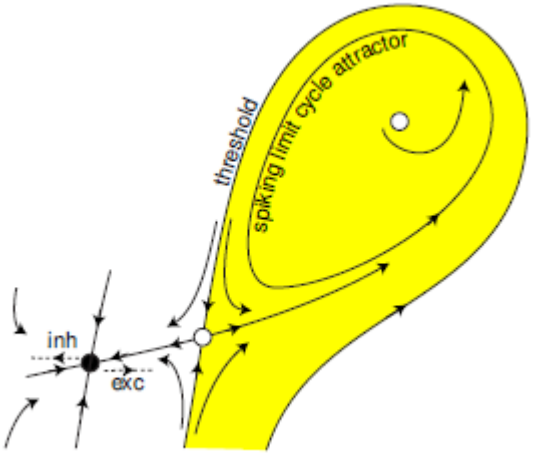
co-existance of resting and spiking states

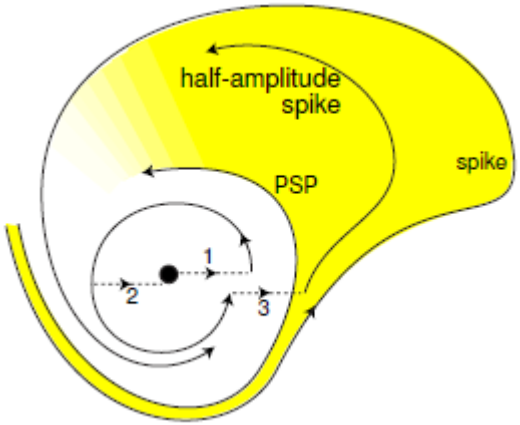
subthreshold oscillations	YES (bistable)	NO (monostable)
NO (integrator)	saddle-node	saddle-node on invariant circle
YES (resonator)	subcritical Andronov-Hopf	supercritical Andronov-Hopf

- Monostable: the neuron does not exhibits the presence of resting and tonic spiking
- Resonator: there exist small amplitude oscillations of membrane potential

Neuronal Dynamics

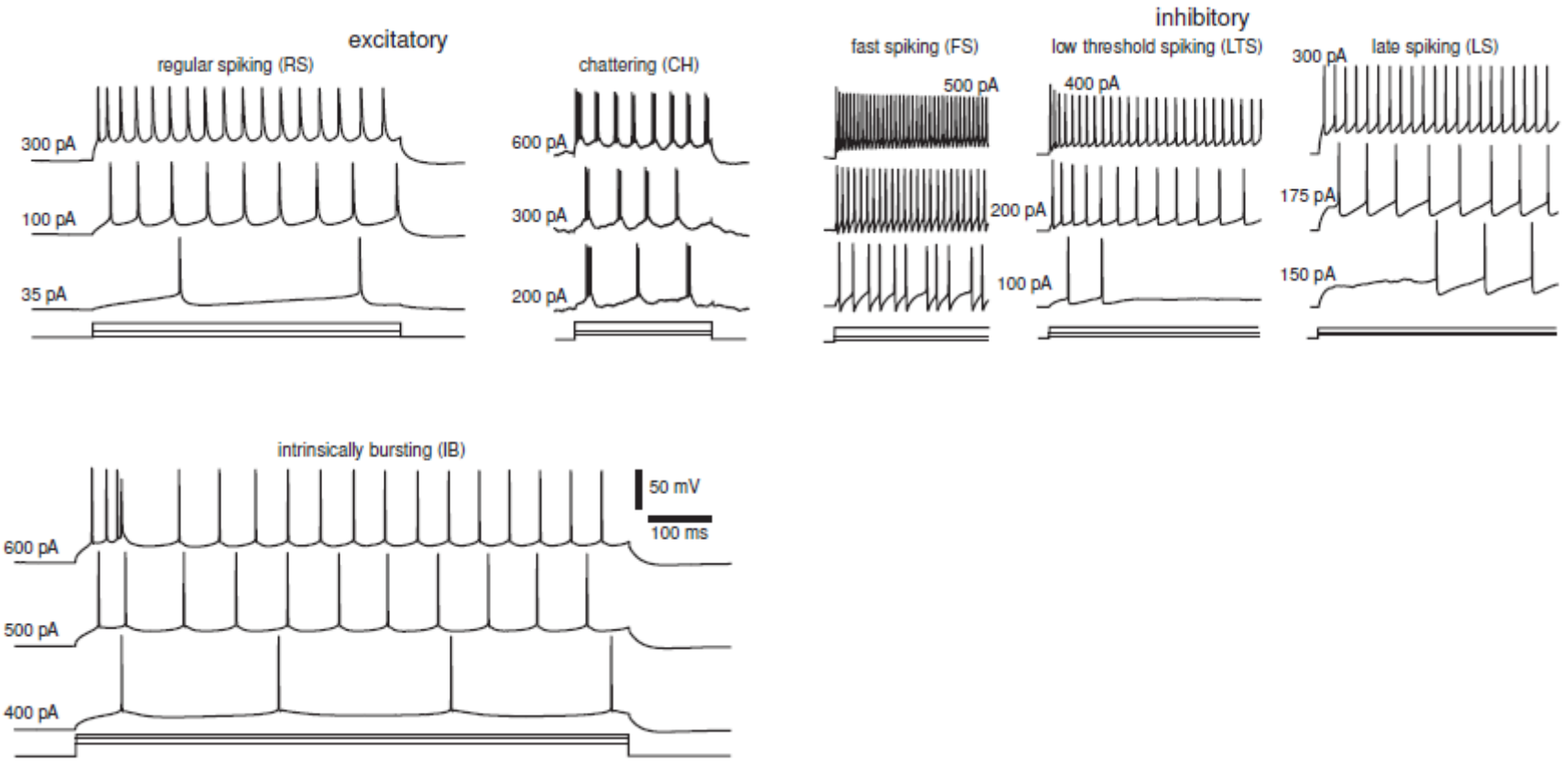
- Integrators vs Resonators



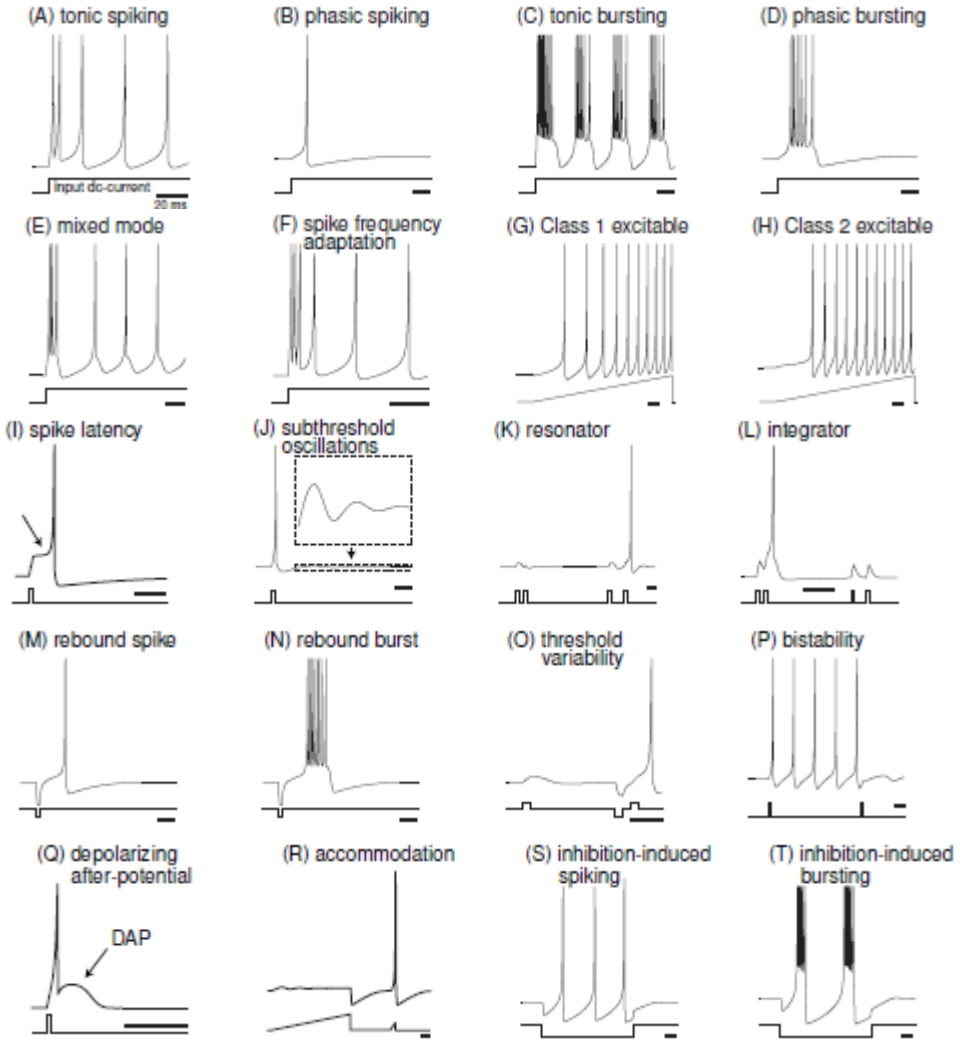


Firing Patterns

- The most fundamental classes of firing patterns are just 6



Neuro-Computational Features



- 20 Most prominent features of biological spiking neurons
- The Izhikevich model can simulate all of them

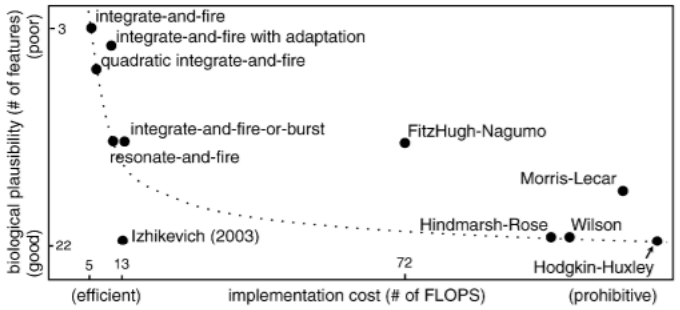
- Izhikevich's book – Chapter 8
- Papers:

  E.M. Izhikevich, "Which model to use for cortical spiking neurons?." *IEEE transactions on neural networks* 15.5 (2004): 1063-1070.

  E.M. Izhikevich, "Simple model of spiking neurons." IEEE Transactions on neural networks 14.6 (2003): 1569-1572.
- web:

  http://izhikevich.org/publications/whichmod.htm

Which Model to Use for Cortical Spiking Neurons?



Models	biophysically meaningful	tonic spiking	phasic spiking	tonic bursting	phasic bursting	mixed mode	spike frequency adaptation	class 1 excitable	class 2 excitable	spike latency	subthreshold oscillations	resonator	integrator	rebound spike	rebound burst	threshold variability	bistability	DAP	accommodation	inhibition-induced spiking	inhibition-induced bursting	chaos	# of FLOPS
integrate-and-fire	-	+	-	-	-	-	-	+	-	-	-	-	+	-	-	-	-	-	-	-	-	-	5
integrate-and-fire with adapt.	-	+	-	-	-	-	+	+	-	-	-	-	+	-	-	-	-	+	-	-	-	-	10
integrate-and-fire-or-burst	-	+	+		+	-	+	+	-	-	-	-	+	+	+	-	+	+	-	-	-		13
resonate-and-fire	-	+	+	-	-	-	-	+	+	-	+	+	+	+	-	-	+	+	+	-	-	+	10
quadratic integrate-and-fire	-	+	-	-	-	-	-	+	-	+	-	-	+	-	-	+	+	-	-	-	-	-	7
Izhikevich (2003)	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	13
FitzHugh-Nagumo	-	+	+	-		-	-	+	-	+	+	+	-	+	-	+	+	-	+	+	-	-	72
Hindmarsh-Rose	-	+	+	+			+	+	+	+	+	+	+	+	+	+	+	+	+		+		120
Morris-Lecar	+	+	+	-		-	-	+	+	+	+	+	+		+	+	-	+	+	-	-		600
Wilson	-	+	+	+			+	+	+	+	+	+	+	+	+		+	+					180
Hodgkin-Huxley	+	+	+	+			+	+	+	+	+	+	+	+	+	+	+	+	+		+		1200