Single neuron models

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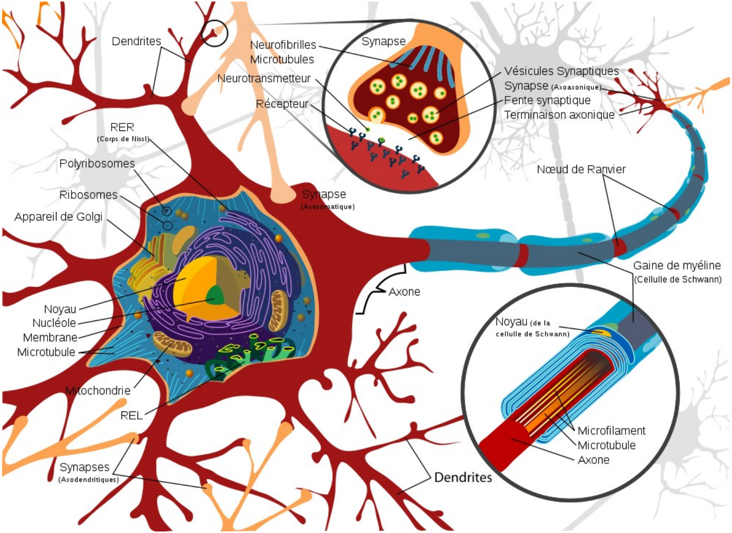
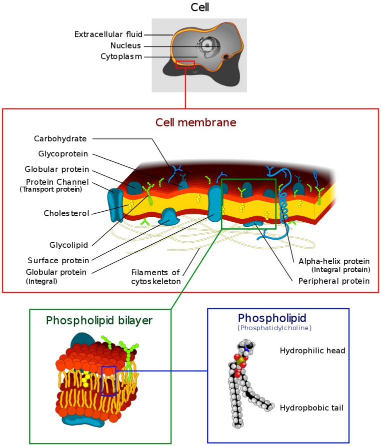
Biological neuron



The membrane



Electro-diffusion laws

Fick's law:

$$J_d = -D\,\frac{\partial c}{\partial x}$$

Ohm's law:

$$J_e = -\mu z c\,\frac{\partial V}{\partial x}$$

Einstein's relation:

$$D = \frac{\mu k_B T}{q}$$

Nernst-Planck equation

Ionic form:

$$J = -(\mu z c \, \frac{\partial V}{\partial x} + \frac{\mu k_B T}{q} \, \frac{\partial c}{\partial x})$$

Molar form:

$$\mathbf{J} = J/\mathcal{N} = -(u z c \, \frac{\partial V}{\partial x} + u \, \frac{RT}{\mathcal{F}} \, \frac{\partial c}{\partial x})$$

Current density:

$$I = \mathbf{J} \cdot z\mathcal{F} = -(u z^2 \mathcal{F} c \, \frac{\partial V}{\partial x} + u z R T \, \frac{\partial c}{\partial x})$$

Nernst's equation

At equilibrium (I=0):

$$V_2 - V_1 = -\frac{RT}{z\mathcal{F}} \ \ln(\frac{c_2}{c_1})$$

Conventions of electrophysiology:

1. $V_m = V_i - V_e = V$
2. Positive currents: from inside to outside

Equilibrium potential for an ion (k):

$$E_k = V(I_k = 0) \qquad \text{thus} \qquad E_k = \frac{RT}{z\mathcal{F}} \ln(\frac{c_e}{c_i})$$

Ionic distributions

Cell of Mammal ($T = 37^o C$):

Ions	c_i	c_e	E_k
K^+	140	5	$\approx -90\,\mathrm{mV}$
Na^+	from 5 to 15	145	≈ 60 to $90\,\mathrm{mV}$
Cl^-	4	110	$\approx -90\,\mathrm{mV}$

Gradients maintenance:

- Active processes: pump (ATP-ases), exchanger, co-transporters
- Donnan's equilibrium

Membrane potential is the result of a stationary regime of exchanges based on transmembrane ionic currents

Ionic currents

Ionic channels:

- Non-gated channels
- Gated channels

Models:

- Electrodiffusion
- Barriers models
- State models (kinetics and stochastics)

Characteristic:

- I-V curve

Goldman-Hodgkin-Katz model

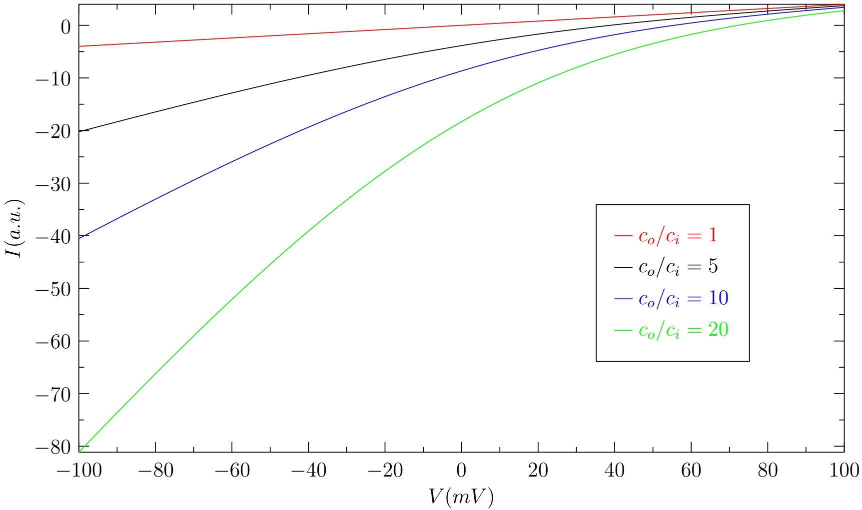
Hypothesis:

1. Electrodiffusion in the membrane
2. No interaction between ions
3. Constant electric field ($dV/dx = V/l$)

Current I(V):

$$I_k = P_k z \mathcal{F} \xi \, \frac{c_i - c_e e^{-\xi}}{1 - e^{-\xi}} \quad \text{et} \quad \xi = \frac{z\mathcal{F}V}{RT}$$

I-V curves for GHK model

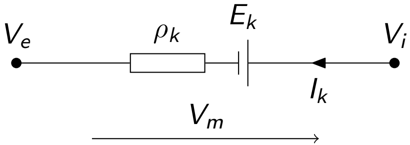


Ohmic (linear) model

Hypothesis:

1. Equivalent circuit
2. Currents follow Ohm's law

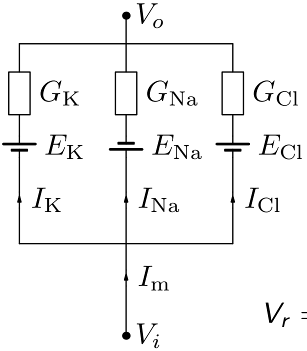
Equivalent circuit:



Current $I(V)$:

$$I_k = \gamma_k(V - E_k) \qquad \text{with} \qquad \gamma_k = 1/\rho_k$$

Resting potential



Linear model:

$$V_r = \frac{G_{\mathrm{Na}} E_{\mathrm{Na}} + G_{\mathrm{K}} E_{\mathrm{K}} + G_{\mathrm{Cl}} E_{\mathrm{Cl}}}{G_{\mathrm{Na}} + G_{\mathrm{K}} + G_{\mathrm{Cl}}}$$

Constant field (GHK):

$$V_r = -\frac{RT}{\mathcal{F}} \ln\left(\frac{P_{\mathrm{K}}[\mathrm{K}]_i + P_{\mathrm{Na}}[\mathrm{Na}]_i + P_{\mathrm{Cl}}[\mathrm{Cl}]_e}{P_{\mathrm{Na}}[\mathrm{Na}]_e + P_{\mathrm{K}}[K]_e + P_{\mathrm{Cl}}[\mathrm{Cl}]_i}\right)$$

$$I_m = I_{\mathrm{Na}} + I_{\mathrm{K}} + I_{\mathrm{Cl}} = 0$$

Passive and active currents

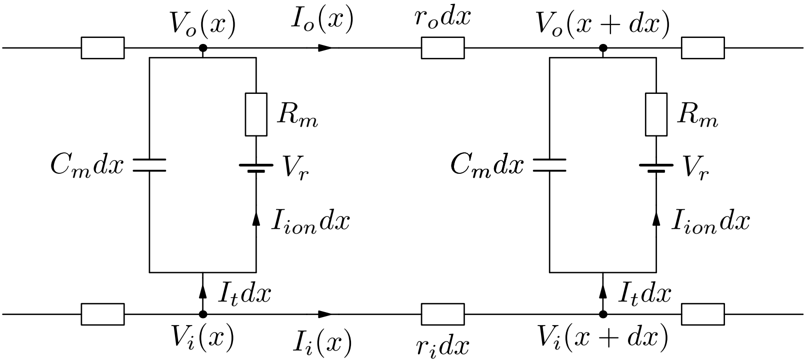
Definitions:

1. *Passive* currents have a *constant* conductance
2. *Active* currents have a *variable* conductance (voltage, stimulus or chemical sensitive). They are the basis of *cell excitability*.

Formalism:

1. Passive:
$$I_k = g_k(V - E_k)$$
2. Active:
$$I_k = \bar{g}_k p(\cdot)(V - E_k)$$

Cable equation (Rall, 1957-1969)

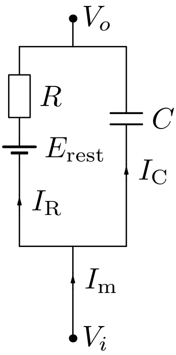


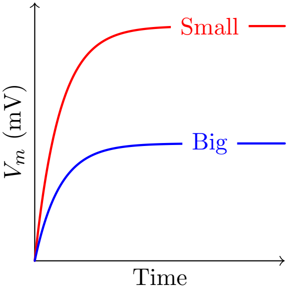
$$\tau_m \frac{\partial V}{\partial t} + R_m I_{ion} = \lambda_m^2 \frac{\partial^2 V}{\partial x^2} \qquad \text{with:} \quad \tau_m = R_m C_m \quad \text{and} \quad \lambda_m = \sqrt{\frac{R_m d}{4 R_c}}$$

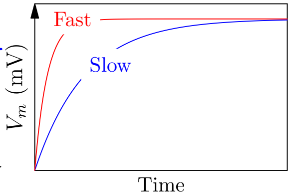
Temporal properties

$$\tau \frac{dV}{dt} = V_r + RI - V \qquad \text{with} \quad \tau = R_m C_m$$

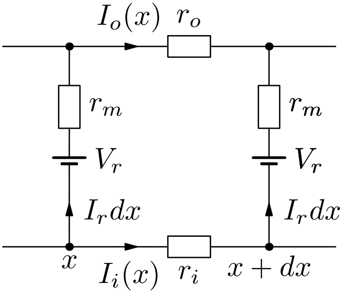
$$V(t) = V_r + RI(1 - e^{-t/\tau}) \qquad \text{and} \quad R = R_m/S$$

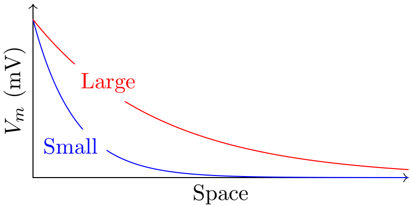






Spatial properties

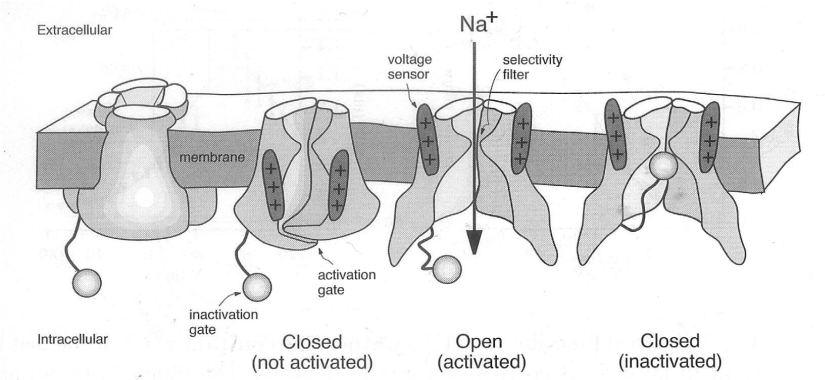




$$\lambda^2 \frac{d^2 V}{dx^2} = V(x) - V_r$$

$$V_m(x) = V_r + V_\infty e^{-x/\lambda}$$

Sodium gated channel



Formalism for gated channels

$$I_k = \bar{g}_k p(\cdot)(V - E_k) = \bar{g}_k m^a h^b (V - E_k)$$

- Probability of opening for *activation* (m) and *inactivation* (h) gates.
- Number of *activation* (a) and *inactivation* (b) gates
- Independence of the gates:

$$p(\cdot) = \underbrace{m \times m \times \cdots \times m}_{a \text{ times}} \times \underbrace{h \times h \times \cdots \times h}_{b \text{ times}}$$

- *Open / activated channel:*

$$m = 1 \text{ (partially activated: } 0 < m < 1) \text{ and } h = 1.$$

- *Closed channel:*
  - Not activated: $m = 0$ and $h = 1$
  - Inactivated: $m = 1$ and $h = 0$

Action potential

Hodgkin & Huxley (1952):

Experimental analysis and theoretical model that explains the genesis of action potential in the squid giant axon.

Hypothesis:

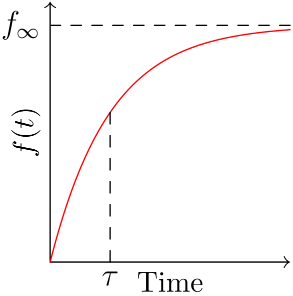
1. No spatial dependency
2. Ohmic currents
3. Sodium, potassium and leak
4. First order kinetics for activation and inactivation gates

First order kinetics

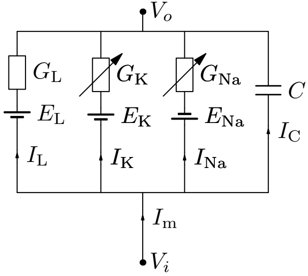
$$\text{Closed} \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} \text{Open}$$

$$\frac{df}{dt} = \alpha(1 - f) - \beta f$$

$$f(t) = f_\infty(1 - e^{-t/\tau}) \qquad \text{with} \quad f_\infty = \frac{\alpha}{\alpha + \beta} \quad \text{and} \quad \tau = \frac{1}{\alpha + \beta}$$



Circuit for Hodgkin and Huxley model



$$I = I_{\mathrm{Na}} + I_{\mathrm{K}} + I_{\mathrm{L}} + I_C$$
$$= I_{\mathrm{Na}} + I_{\mathrm{K}} + G_L(V - E_{\mathrm{L}}) + C\frac{dV}{dt}$$

Active currents:

- *Transient sodium current:*
  $I_{\mathrm{Na}} = \bar{g}_{\mathrm{Na}} m^3 h (V - E_{\mathrm{Na}})$
- *Persistent potassium current:*
  $I_{\mathrm{K}} = \bar{g}_{\mathrm{K}} n^4 (V - E_{\mathrm{K}})$

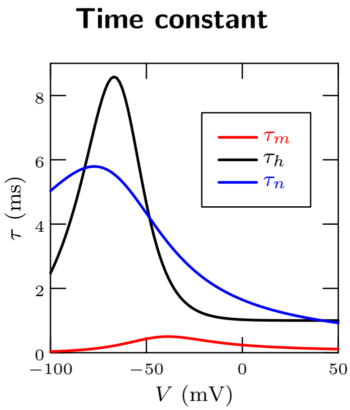
Historical Hodgkin-Huxley model

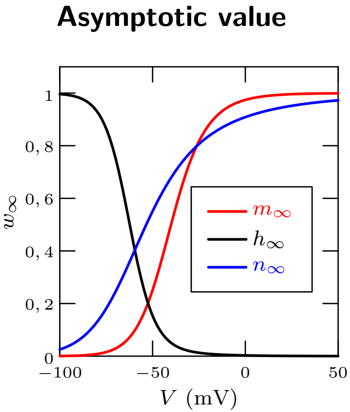
$$
\begin{aligned}
C\dot{V} &= I - \bar{g}_{\mathrm{Na}} m^3 h (V - E_{\mathrm{Na}}) - \bar{g}_{\mathrm{K}} n^4 (V - E_{\mathrm{K}}) - g_{\mathrm{L}} (V - E_{\mathrm{L}}) \\
\dot{m} &= \alpha_m(V)(1-m) - \beta_m(V) m \\
\dot{h} &= \alpha_h(V)(1-h) - \beta_h(V) h \\
\dot{n} &= \alpha_n(V)(1-n) - \beta_n(V)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

and

$$
\begin{aligned}
\alpha_n(V) &= 0.01\ (10 - V)/(\exp((10 - V)/10) - 1) \\
\beta_n(V) &= 0.125\ \exp(-V/80) \\
\alpha_m(V) &= 0.1\ (25 - V)/(\exp((25 - V)/10) - 1) \\
\beta_m(V) &= 4\ \exp(-V/18) \\
\alpha_h(V) &= 0.07 \exp(-V/20) \\
\beta_h(V) &= 1\ /\ (\exp((30 - V)/10) + 1)
\end{aligned}
$$

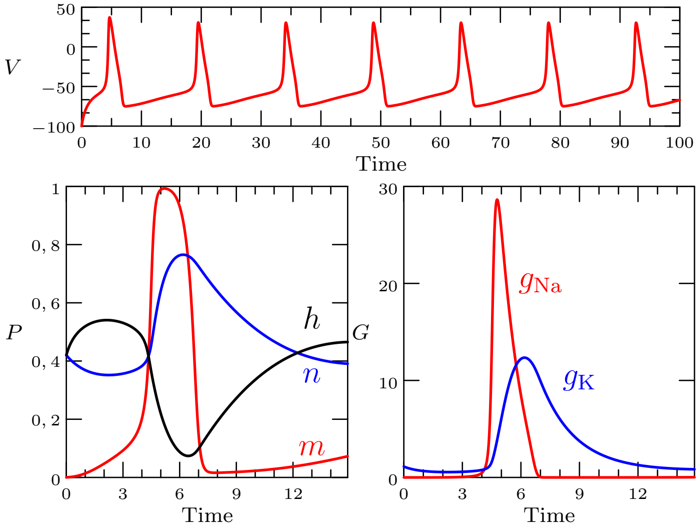
Potential dependence of kinetics parameters





$$\tau_x(V) = \frac{1}{\alpha_x(V) + \beta_x(V)} \qquad x_\infty(V) = \frac{\alpha_x(V)}{\alpha_x(V) + \beta_x(V)}$$

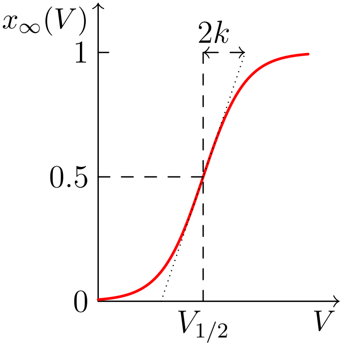
Hodgkin-Huxley model

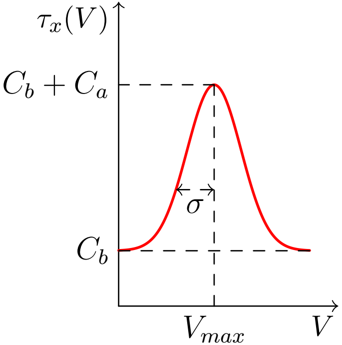


Standard Hodgkin-Huxley model

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

Standard kinetic parameters

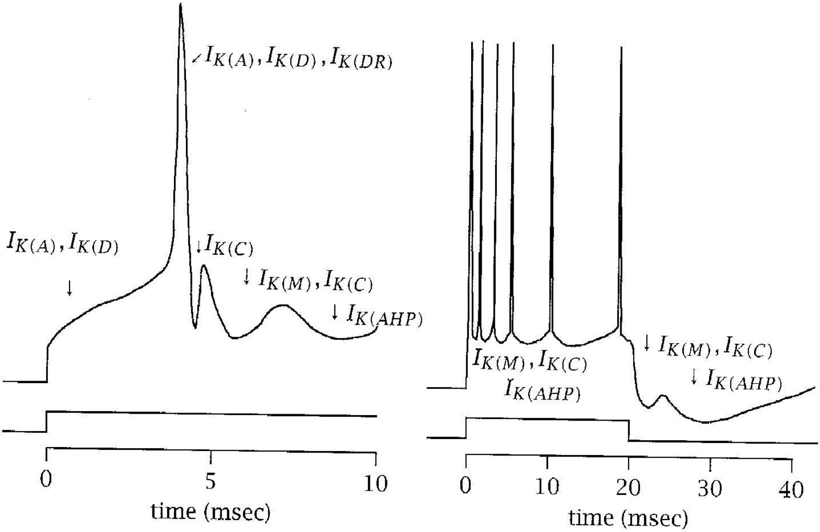




$$x_\infty(V) \approx \frac{1}{1 + e^{\frac{V_{1/2}-V}{k}}}$$

$$\tau_x(V) \approx C_b + C_a\, e^{\frac{-(V_{max}-V)^2}{\sigma^2}}$$

"Zoology" of ion channels



Neuronal models

Criteria:

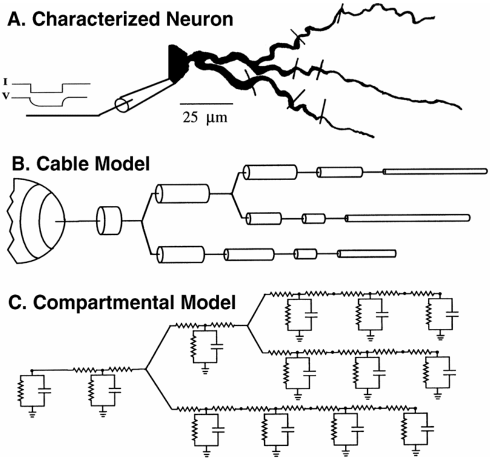
1. Biological plausibility
2. Computational load

Categories:

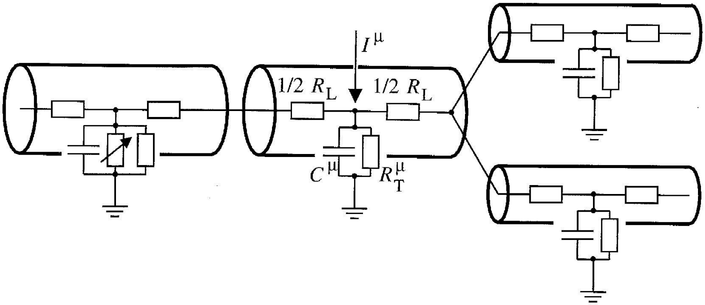
1. Compartmental models
2. Differential models (simplified HH)
3. Hybrid models
4. Discrete state automata

Compartmental models

Principle:



Compartmental models



Simulation environments:

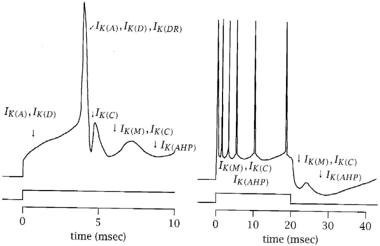
NEURON, GENESIS

Zoology of channels

Channels types:

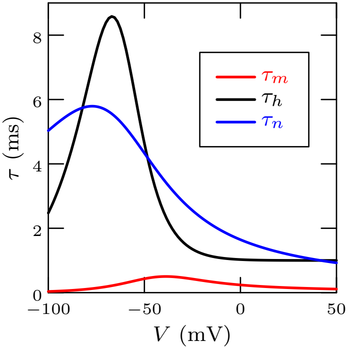
- INa(fast), INa(slow), ICa(L), ICa(T), ICa(N), ICa(P), IK(DR), IK(A), IK(D), IK(M)
- IQ, Ih, If, IK(IR), ICl(V)
- IK(C), IK(AHP), ICl(Ca)
- IK(L), ICl, IK(ATP), IK(Na)

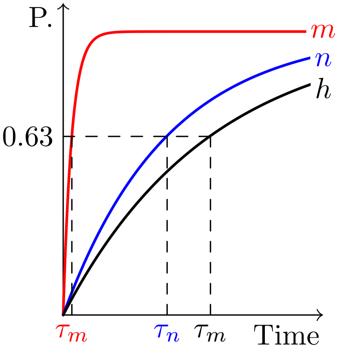
Potassium channels:



Reduction of Hodgkin-Huxley model: step 1

Separation of time scales: $m = m_\infty(V)$



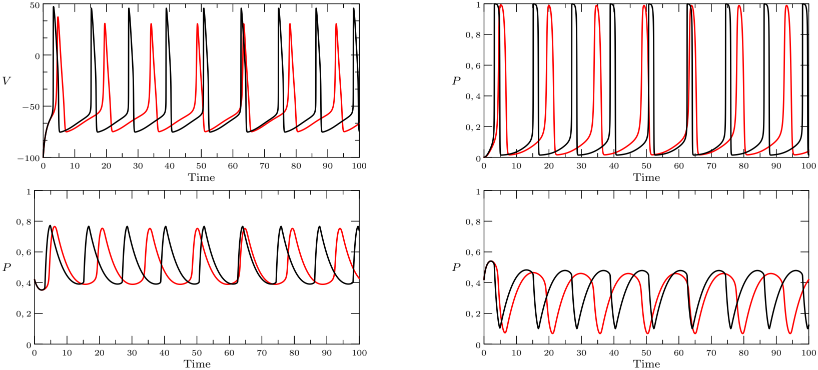


Thus:

$$C\dot{V} = I - \bar{g}_{\mathrm{Na}} m_\infty(V)^3 h (V - E_{\mathrm{Na}}) - \bar{g}_{\mathrm{K}} n^4 (V - E_{\mathrm{K}}) - g_{\mathrm{L}}(V - E_{\mathrm{L}})$$

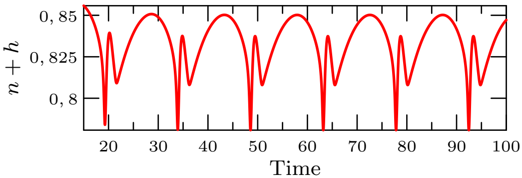
$$\dot{h} = (h_\infty(V) - h)/\tau_h(V) \qquad \text{and} \qquad \dot{n} = (n_\infty(V) - n)/\tau_n(V)$$

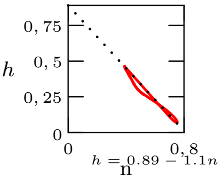
Comparison of HH models: 4D vs. 3D



Reduction of Hodgkin-Huxley model: step 2

Comparison of h and n: $h + n \approx 0.8$

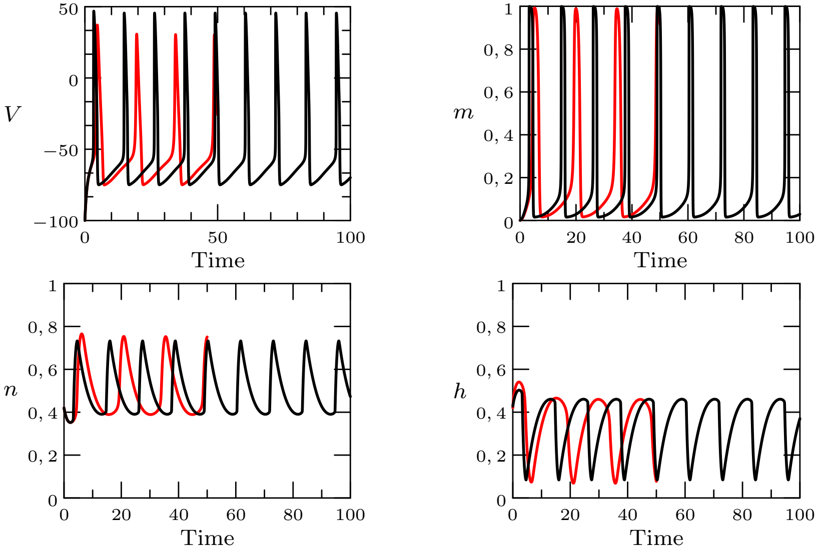




Thus:

$$
\begin{aligned}
C\dot{V} = & I - \bar{g}_{\mathrm{Na}} m_\infty(V)^3 (0.8 - n)(V - E_{\mathrm{Na}}) - \bar{g}_{\mathrm{K}} n^4 (V - E_{\mathrm{K}}) \\
& - g_{\mathrm{L}}(V - E_{\mathrm{L}}) \\
\dot{n} = & (n_\infty(V) - n) \,/\, \tau_n(V)
\end{aligned}
$$

Comparison of HH models: 4D vs. 2D



Two-dimensional models

Morris-Lecar model:

$$C\dot{V} = I - \bar{g}_{\mathrm{Ca}} m_\infty(V)(V - E_{\mathrm{Ca}}) - \bar{g}_{\mathrm{K}} n(V - E_{\mathrm{K}}) - g_L(v -$$
$$\dot{n} = (n_\infty(V) - n)/\tau_n(V)$$

INa,p+IK model:

$$C\dot{V} = I - \bar{g}_{\mathrm{Na}} m_\infty(V)(V - E_{\mathrm{Na}}) - \bar{g}_{\mathrm{K}} n(V - E_{\mathrm{K}}) - g_{\mathrm{L}}(V -$$
$$\dot{n} = (n_\infty(V) - n)/\tau_n(V)$$

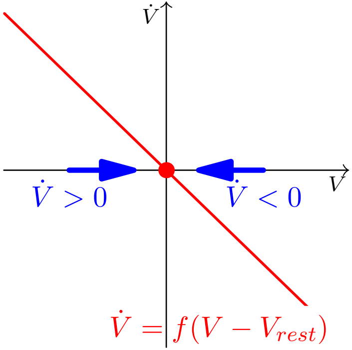
Fitzhugh-Nagumo model:

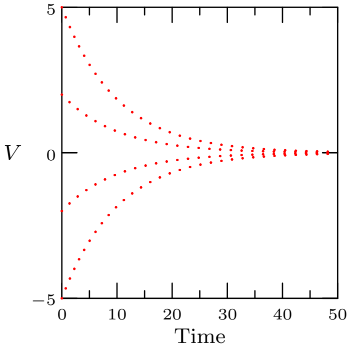
$$\dot{x} = x(a - x)(x - 1) - y + I$$
$$\dot{y} = bx - cy$$

Qualitative analysis of dynamical systems

Example of 1D linear system:

$$C\frac{dV}{dt} = -G(V - V_{rest}) = C\dot{V}$$

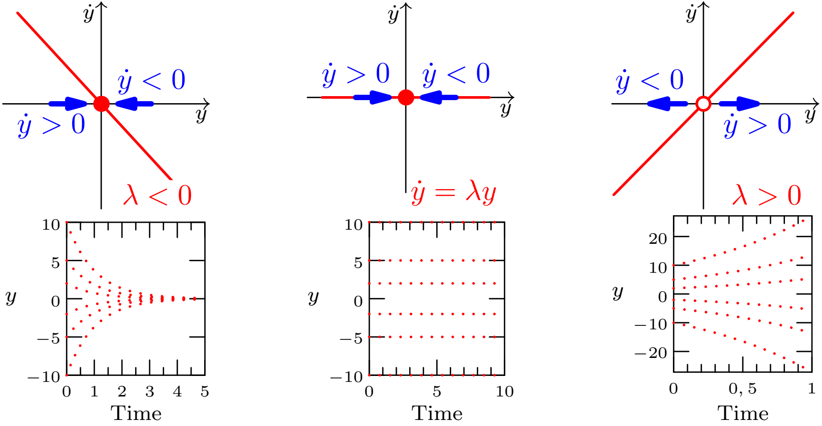




Qualitative analysis of dynamical systems

General 1D linear system:

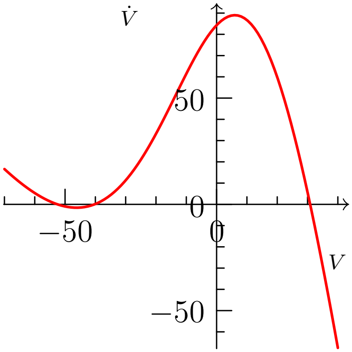
$$\dot{y}(t) = \lambda y(t) \qquad \text{Solution:} \quad y(t) = y_0 e^{\lambda t}$$

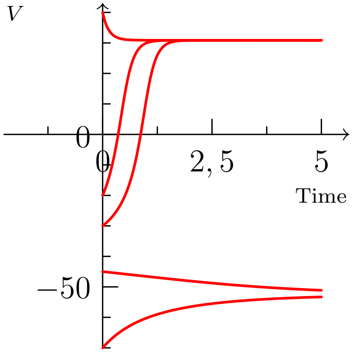


Qualitative analysis of dynamical systems

Example of 1D nonlinear system: persistent sodium model.

$$C\dot{V} = I - g_{\mathrm{L}}(V - E_{\mathrm{L}}) - g_{\mathrm{Na}} m_\infty(V)(V - V_{\mathrm{Na}})$$

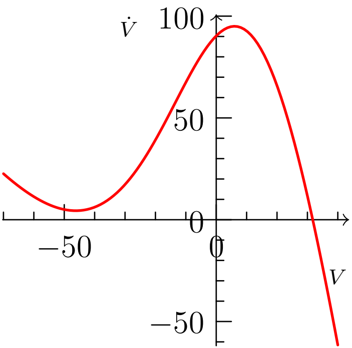


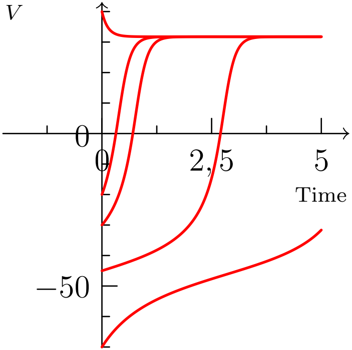


Qualitative analysis of dynamical systems

Example of 1D nonlinear system: persistent sodium model $(I = 60)$

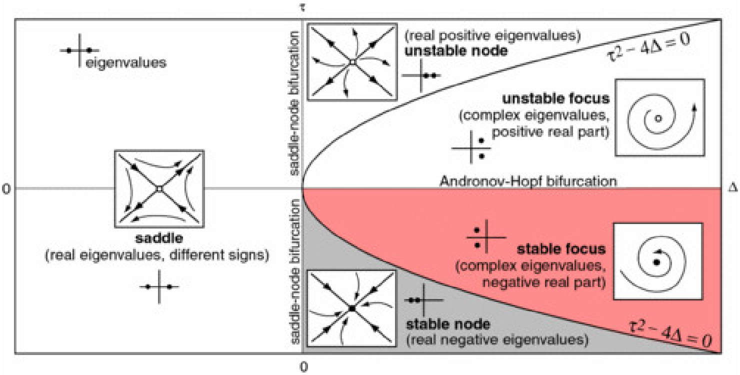
$$C\dot{V} = I - g_{\mathrm{L}}(V - E_{\mathrm{L}}) - g_{\mathrm{Na}} m_{\infty}(V)(V - V_{\mathrm{Na}})$$





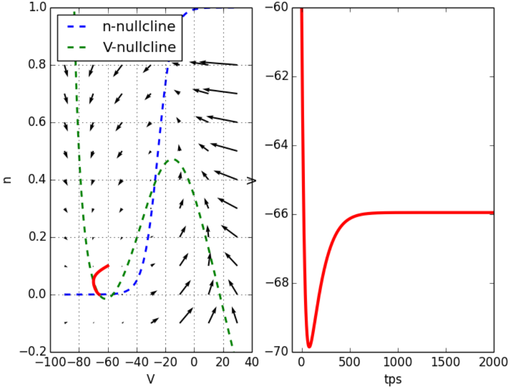
Qualitative analysis of dynamical systems

2D system:



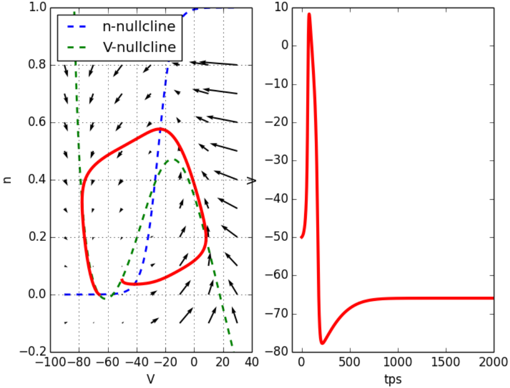
INa,p+IK model: high threshold

General behavior: $I = 0$



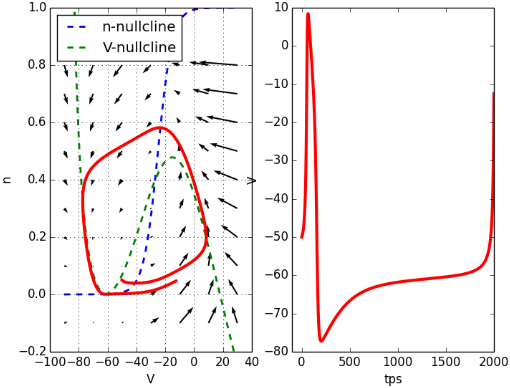
INa,p+IK model: high threshold

General behavior: $I = 0$



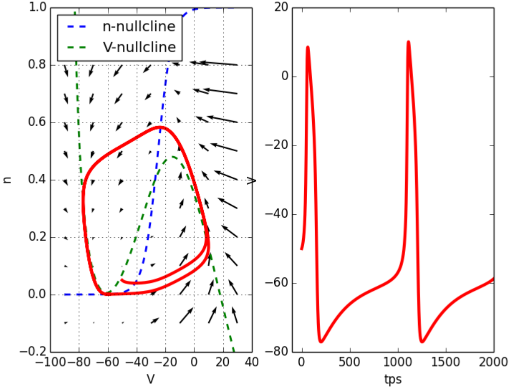
INa,p+IK model: high threshold

Saddle-node bifurcation: $I = 4.75$



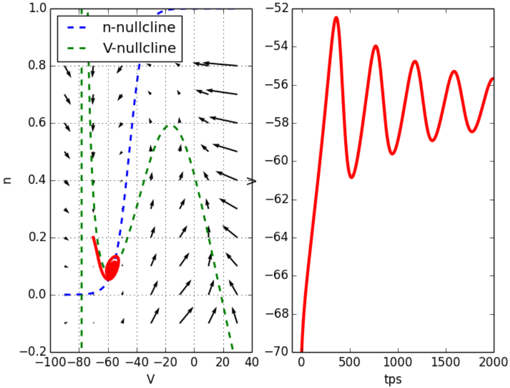
INa,p+IK model: high threshold

Saddle-node bifurcation: $I = 6$



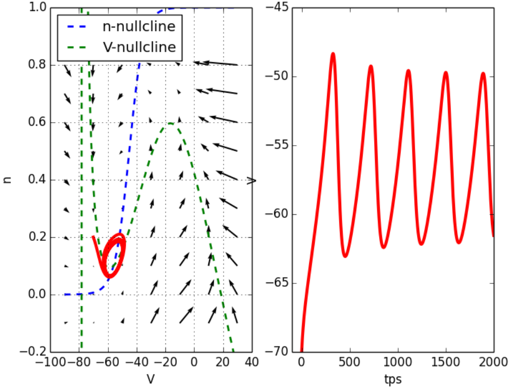
INa,p+IK model: low threshold

Supercritical Hopf bifurcation: $I = 18.5$



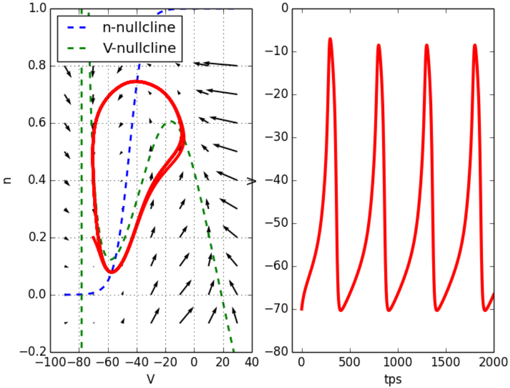
INa,p+IK model: low threshold

Supercritical Hopf bifurcation: $I = 21$



INa,p+IK model: low threshold

Supercritical Hopf bifurcation: $I = 27$



Hodgkin's classification (1948)

Type I neurons:

- Variable frequency
- Saddle-node / high threshold

Type II neurons:

- Constant frequency
- Hopf / low threshold

Bursting models (3D)

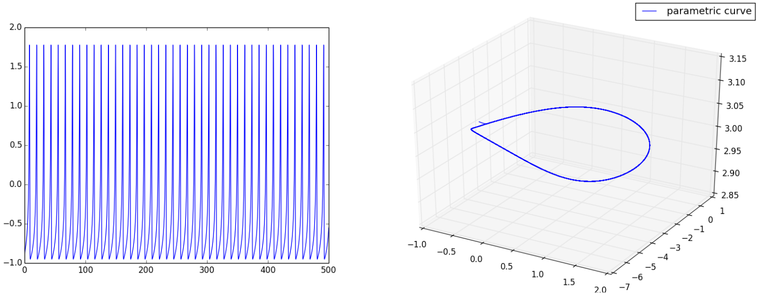
Fast-slow system:

Hindmarsh-Rose model:

$$
\begin{aligned}
\dot{x} &= y - ax^3 + by^2 - z + I \\
\dot{y} &= c - dx^2 - y \\
\dot{z} &= r[s(x - x_0) - z]
\end{aligned}
$$

Hindmarsh-Rose model (1984)

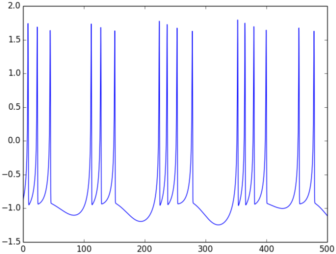
Two-dimensional: $r = 0$

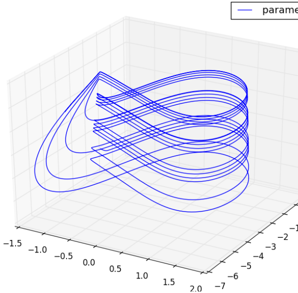


Periodic behavior (limit cycle)

Hindmarsh-Rose model (1984)

Three-dimensional: $r = 0.006$





Chaotic behavior (strange attractor)

Hybrid models

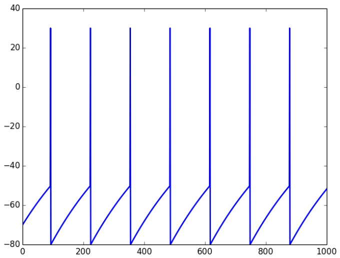
Characteristics:

- Continuous part
- Discrete part

Leaky "integrate and fire" (Lapicque, 1909)

$$\tau_m \dot{V} = -V + RI(t)$$

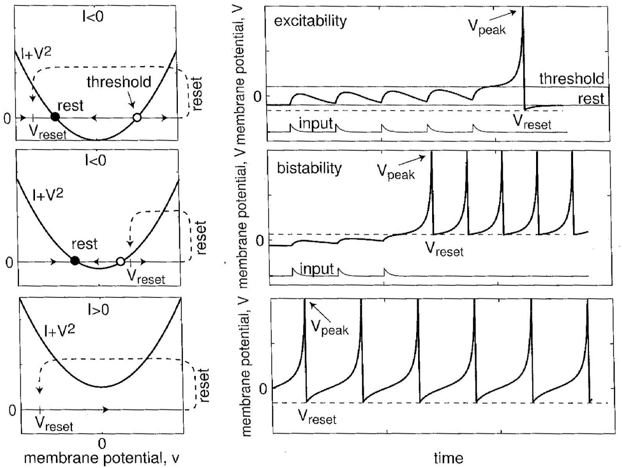
$$\text{If} \quad V > V_{th} \quad \text{then} \quad V \leftarrow V_{reset}$$



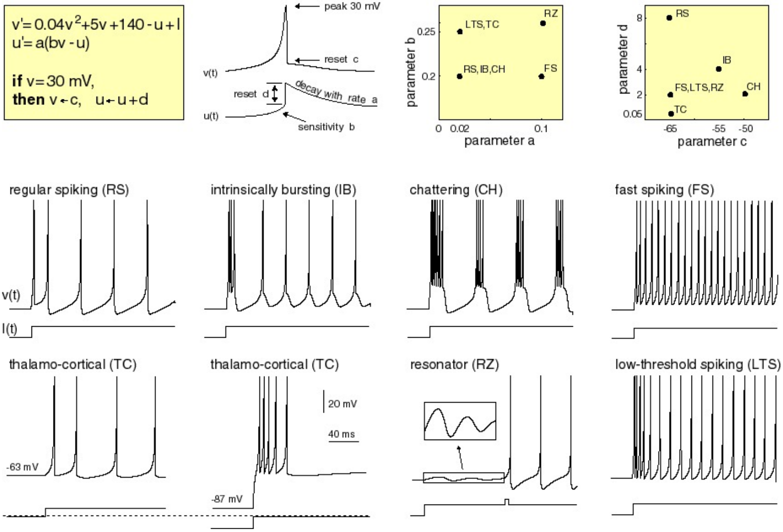
No spike generation mechanism

Quadratic integrate and fire

$$\tau \dot{V} = V^2 + RI(t)$$

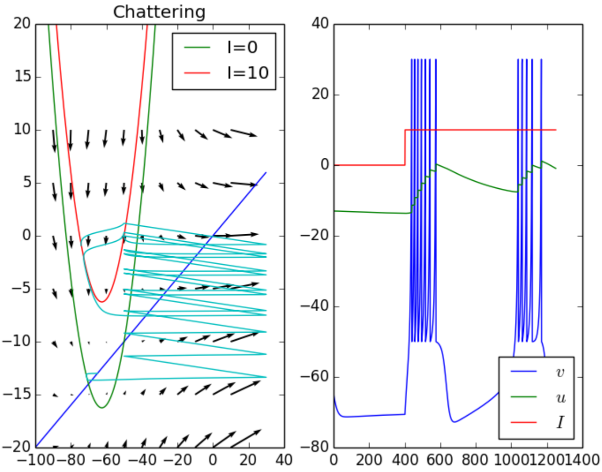


Two-dimensional hybrid model

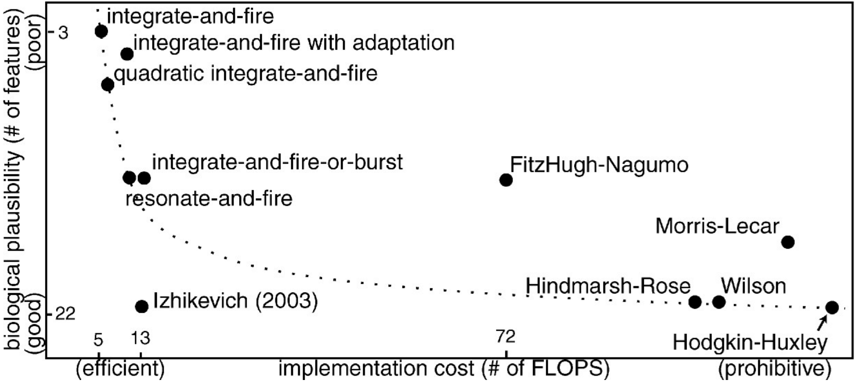


Izhikevich (2003)

Two-dimensional hybrid model



Simplified models



Izhikevich (2004)

Discrete state automata

Binary models:

Excitable systems:

- Quiescent
- Active
- Refractory

Generic models:

Models of synapses

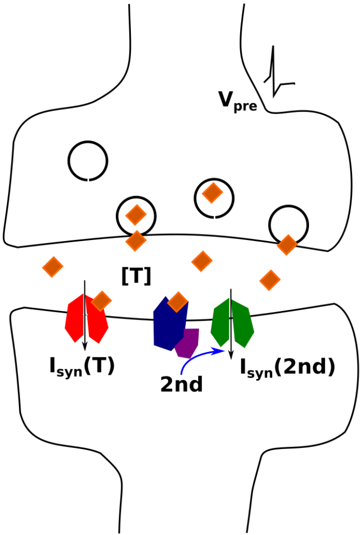
- Synaptic weights: matrix representation
- Synaptic currents:
  - Kinetic models
  - Simplified models
- Learning rules:

Synaptic weights

$$W = [w_{ij}]$$

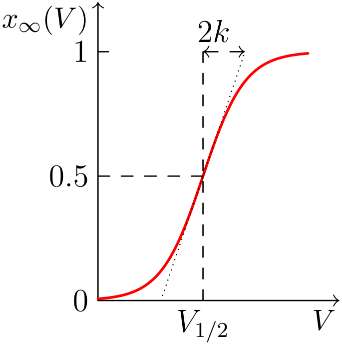
- $w_{ij} > 0$ for excitatory connections.
- $w_{ij} < 0$ for inhibitory connections.
- With quantal release (n sites, p probability of release, q size of the quantum):
$$w \approx npq$$

Synaptic mechanisms



Transmitter release

$$[T](V_{pre}) = \frac{T_{max}}{1 + e^{\xi}} \qquad \text{with} \quad \xi = \frac{-(V_{pre} - v_{1/2})}{K_p}$$



Synaptic currents: kinetic models

$$I_{syn}(t) = g_{syn}(t)(V_m(t) - E_{syn}) \qquad \text{with} \qquad g_{syn}(t) = \bar{g}_{syn}s(t)$$

- Dependency to transmitter concentration
- Kinetics of current changes

Ionotropic receptors

$$C + T \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} O \tag{1}$$

with C for "Closed" and O for "open". We get the equation:

$$\frac{ds}{dt} = \alpha\,[T]\,(1 - s) - \beta s \tag{2}$$

$$I_{\mathrm{AMPA}} = \bar{g}_{\mathrm{AMPA}}\, s(V_m - E_{\mathrm{AMPA}}) \tag{3}$$

$$I_{\mathrm{GABA}_A} = \bar{g}_{\mathrm{GABA}_A}\, s(V_m - E_{\mathrm{GABA}_A}) \tag{4}$$

$$I_{\mathrm{NMDA}} = \bar{g}_{\mathrm{NMDA}}\, sM(V)(V - E_{\mathrm{NMDA}}) \tag{5}$$

and:

$$M(V) = \frac{1}{1 + \exp(-0.062V)\,[\mathrm{Mg2+}]_o\,/3.57} \tag{6}$$

Metabotropic receptors

$$R_i + T \underset{K_2}{\overset{K_1}{\rightleftharpoons}} R \tag{7}$$

$$R + G_i \xrightarrow[K_3]{} R + G \tag{8}$$

$$G \xrightarrow[K_4]{} G_i \tag{9}$$

$$I_{\mathrm{GABA}_B} = \bar{g}_{\mathrm{GABA}_B} \frac{s^n}{s^n + K_d}(V - E_{\mathrm{K}}) \quad \text{with} \quad n = 4 \tag{10}$$

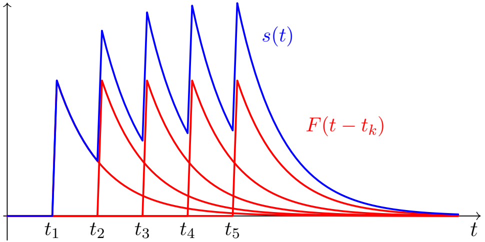
$$\frac{dr}{dt} = K_1 [T] (1 - r) - K_2 r \tag{11}$$

$$\frac{ds}{dt} = K_3 r - K_4 s \tag{12}$$

Synaptic currents: simplified models

$$I_{syn}(t) = g_{syn}(t)(V_m(t) - E_{syn}) \qquad \text{with} \qquad g_{syn}(t) = \bar{g}_{syn}s(t)$$

$$s(t) = \sum_k F(t - t_k) \qquad \text{with} \qquad \begin{cases} F(t) = 0 & \text{for} \quad t < 0 \\ F(t) > 0 & \text{otherwise} \end{cases}$$



The α function:

$$F(t) = \frac{f_r f_d}{f_r - f_d}(e^{-f_d t} - e^{-f_r t})$$