Computer Lab 2: Synapses and small networks

- Izhikevich 2D LIF model neuron
- Models of synaptic currents
- 2 cell networks

- **READINGS:**
  - Izhikevich IEEE 2003, www.izhikevich.org/publications/spikes.htm
  - Modeling synapses: Chapter 6 of Computational Modeling Methods for Neuroscientists
  - Modeling papers of invertebrate CPG neurons

Hodgkin-Huxley Equations

$$C_m \frac{dV}{dt} = -g_{Na} m^3 h (V - E_{Na}) - g_K n^4 (V - E_K) - g_L (V - E_L) + I_{app}$$

$$\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)\, m, \quad \frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V)\, h$$

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

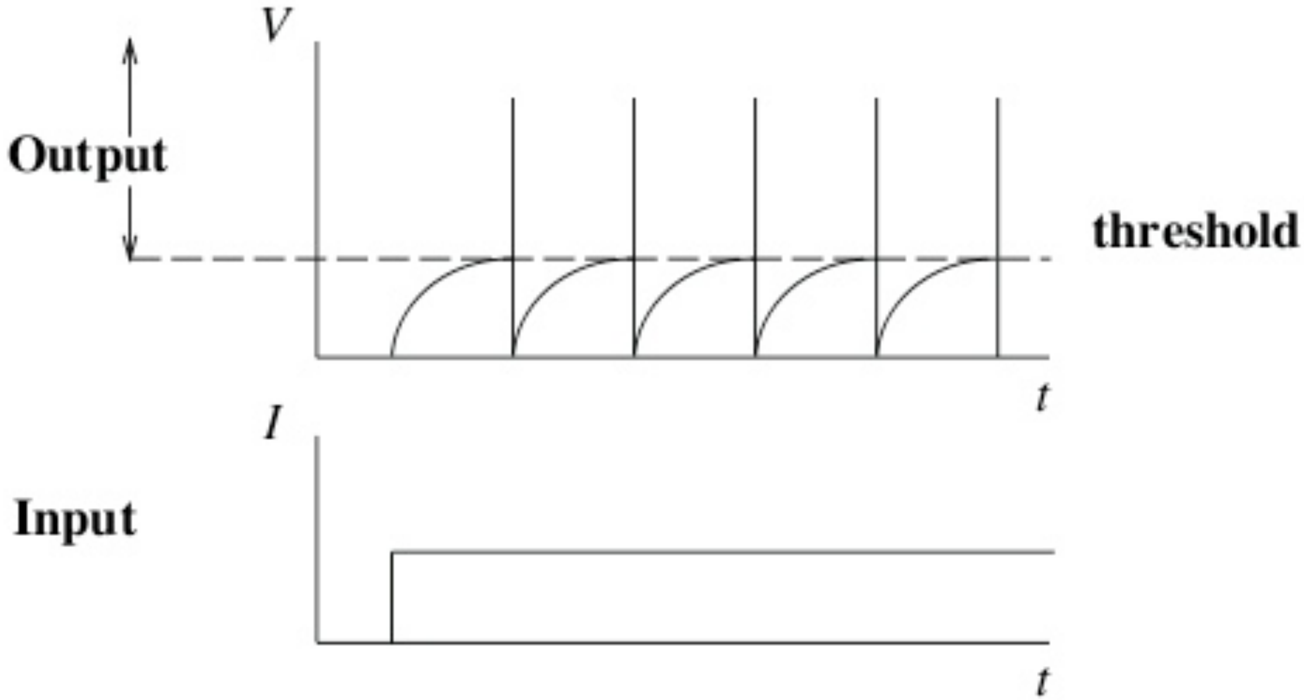
$$\alpha_m(V) = 0.1(25-V)/(e^{\frac{25-V}{10}} - 1), \quad \beta_m(V) = 4 e^{\frac{-V}{18}}$$

$$\alpha_h(V) = 0.07\, e \frac{-V}{20}, \quad \beta_h(V) = 1/(e^{\frac{30-V}{10}} + 1)$$

$$\alpha_n(V) = 0.01(10-V)/(e^{\frac{10-V}{10}} - 1), \quad \beta_n(V) = 0.125\, e^{\frac{-V}{80}}$$

All equations and parameter values in handout on

Leaky Integrate & Fire model



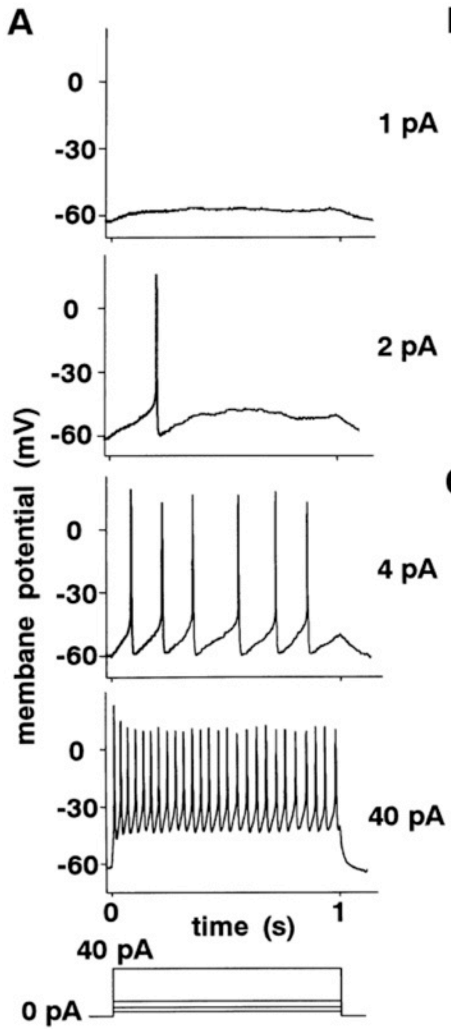
- In response to input, voltage increases exponentially
- When voltage reaches spike threshold, it is reset to hyperpolarized value
- When no input present, voltage decays exponentially to rest value

Leaky Integrate & Fire model

- Equation includes only capacitive and leak currents

$$C_m \frac{dV}{dt} = -g_L\,(V - E_L) + I_{app}$$

- Reset Condition: When $V = V_{th}$= -55 mV, set $V = V_{reset}$ = -70 mV



Izhikevich 2D LIF (ILIF) Model

- 2 variables:
  - V = membrane voltage
  - u = membrane recovery variable, which provides negative feedback to v like K^+ currents
  - No explicit modeling of AP biophysics
  - No units but V takes on realistic voltage values and time may be assumed to be ms

$$\frac{dV}{dt} = 0.04\,V^2 + 5V + 140\; - u + I$$

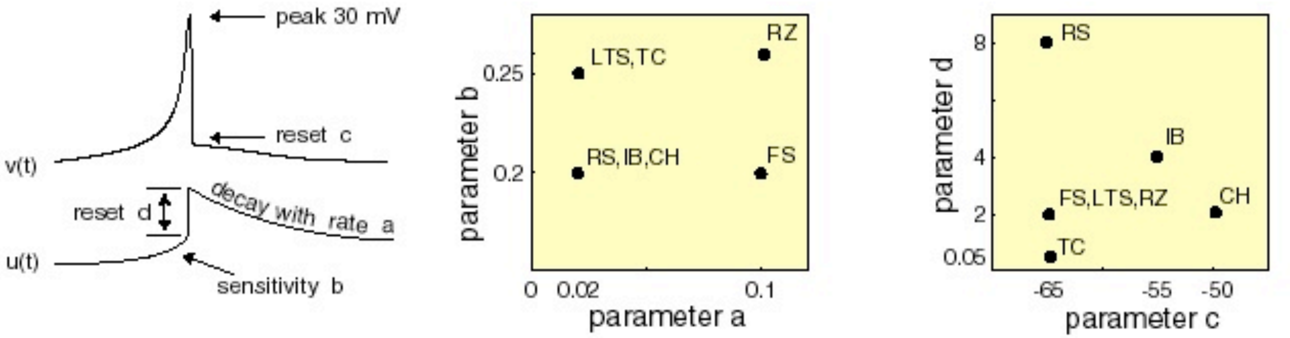
$$\frac{du}{dt} = a(bV - u)$$

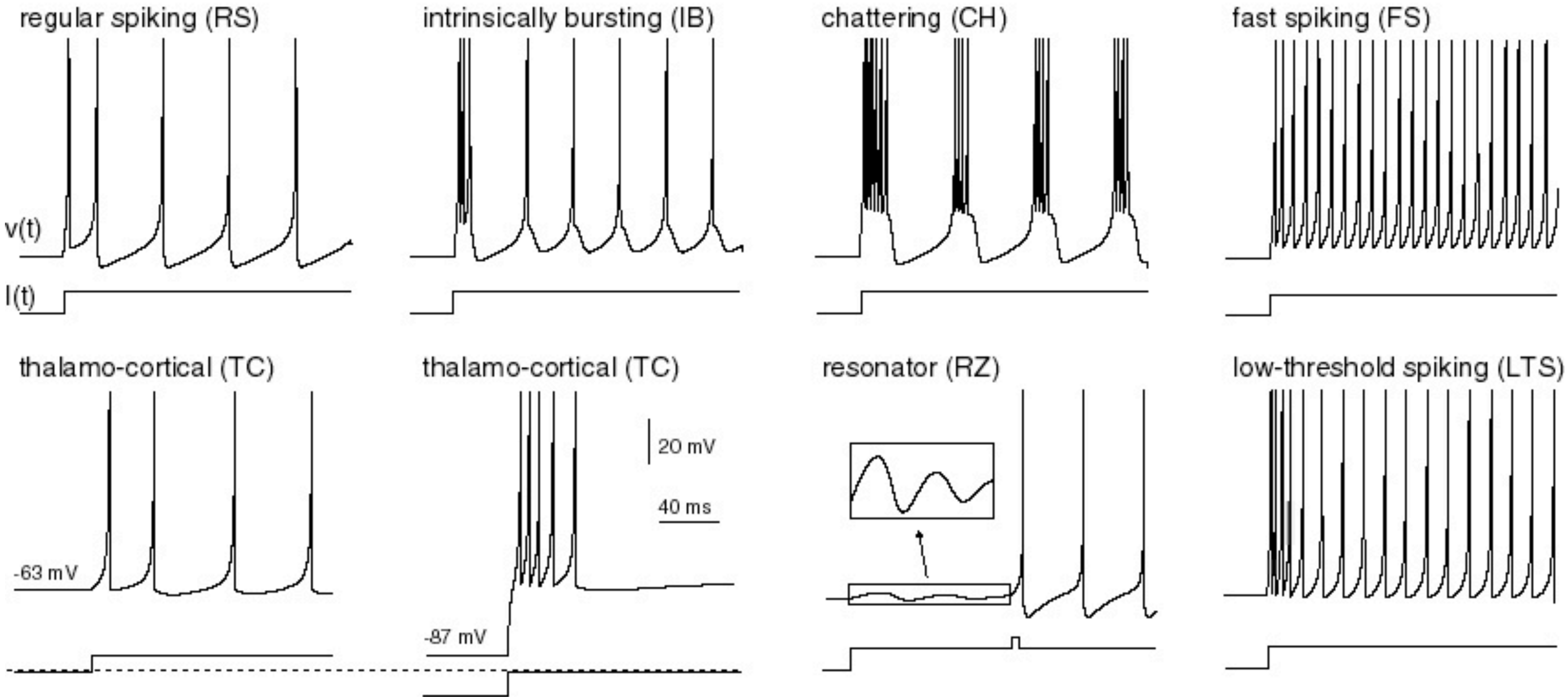
Reset condition: If V ≥ 30, then set V = c and u = u + d

ILIF model

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

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





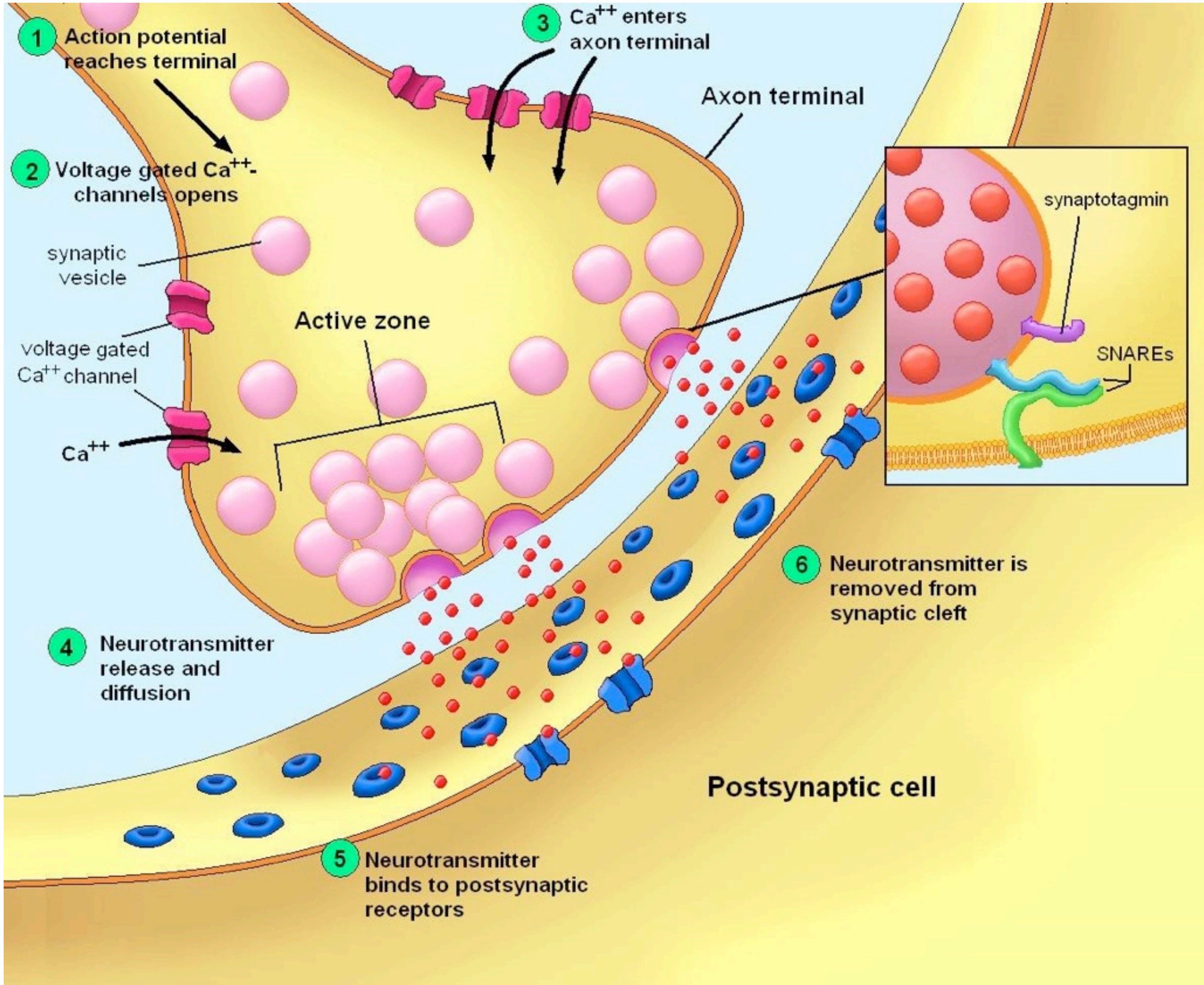
General form of neuron model equations

- • Current balance equation

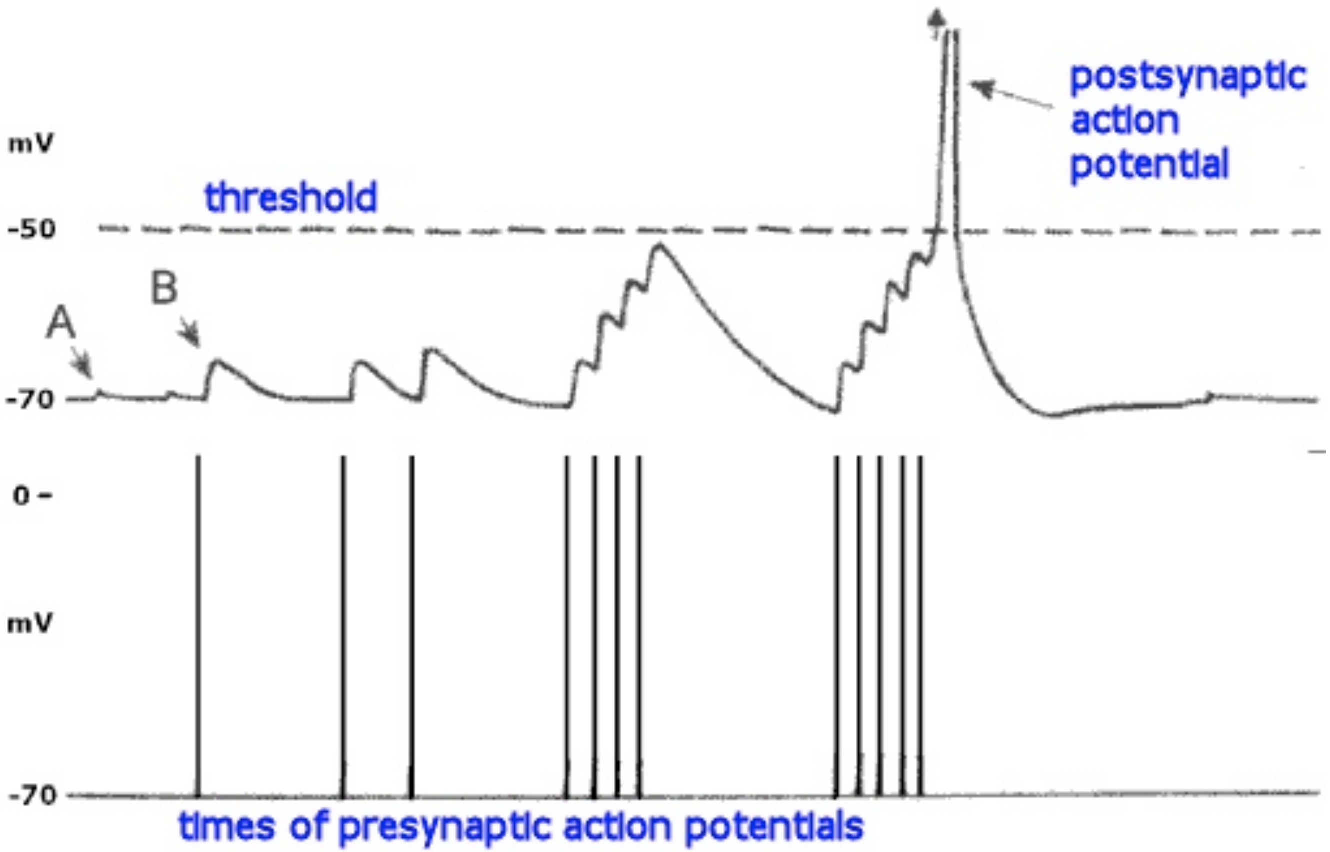
$$C_m \frac{dV}{dt} = I_{ion}(V, m, h) + I_{app} + I_{syn}$$

- Differential equation for change of voltage over time
- Contains terms for all intrinsic and external factors that affect membrane voltage
- Equations for gating variables m, h depend on V

Synaptic transmission



Modeling Excitatory Post-Synaptic Potentials (EPSPs)



Modeling synaptic currents

- IDEA: when a presynaptic cell spikes, initiate a time-varying input to the postsynaptic cell

  In current balance equation for V of post-synaptic cell:

$$\frac{dV_{post}}{dt} = I_{ion}(V_{post}, t) + I_{app} + \sum_j I_{syn}(V_j, t)$$

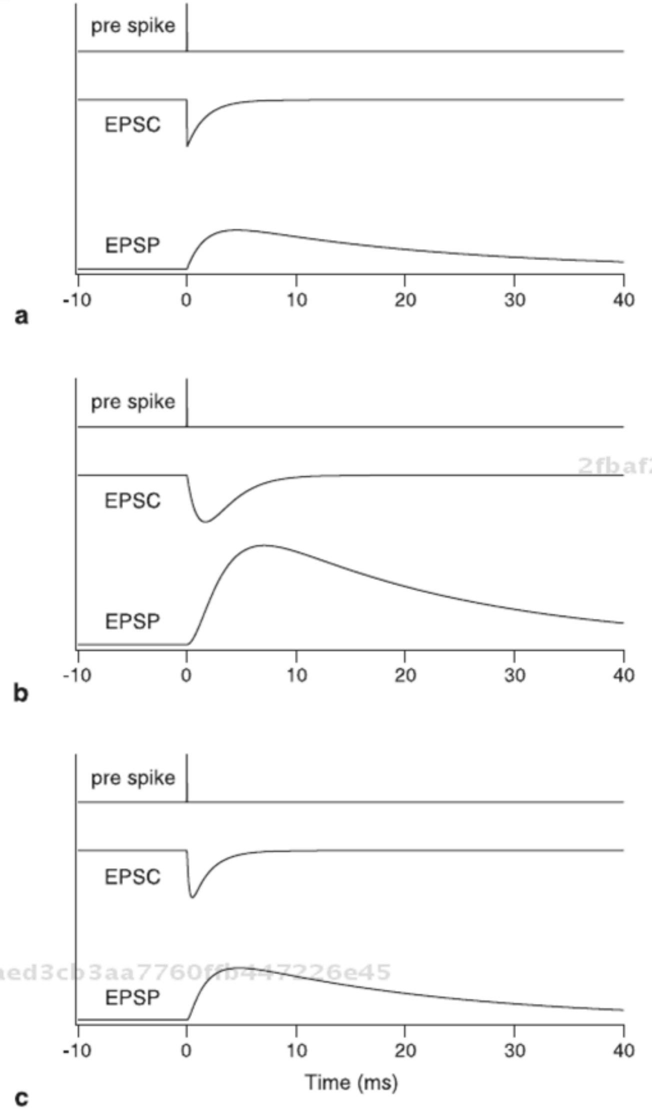
  where sum is over all presynaptic cells

Simplified models of synaptic currents

- $I_{syn} = I_{syn}(t)$ only depends on time of presynaptic spike

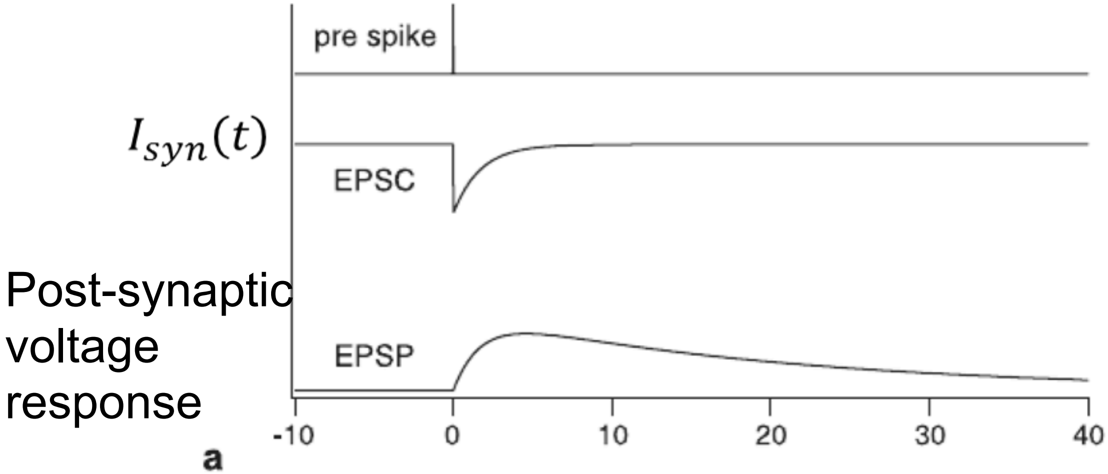
Possible profiles of synaptic input:

- Instantaneous rise and exponential decay
- Alpha function
- Double exponential



Instantaneous rise and exponential decay

- $$I_{syn}(t) = g_{syn} e^{-(t-t_{pre})/\tau}$$

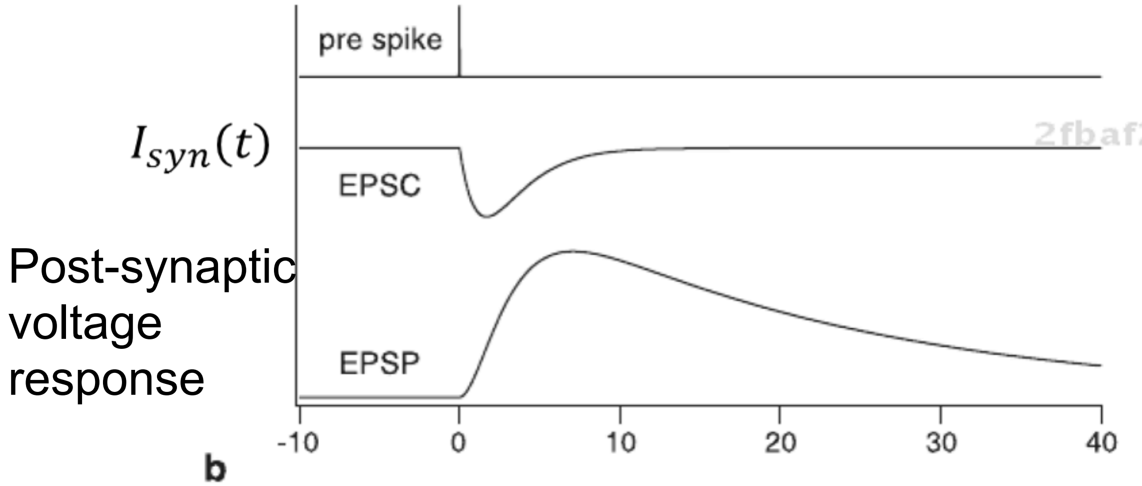


Where

- t_{pre} = time of presynaptic spike
- g_{syn} = synaptic strength
- τ = time constant of decay of synaptic current (large τ = slow decay)

Alpha function

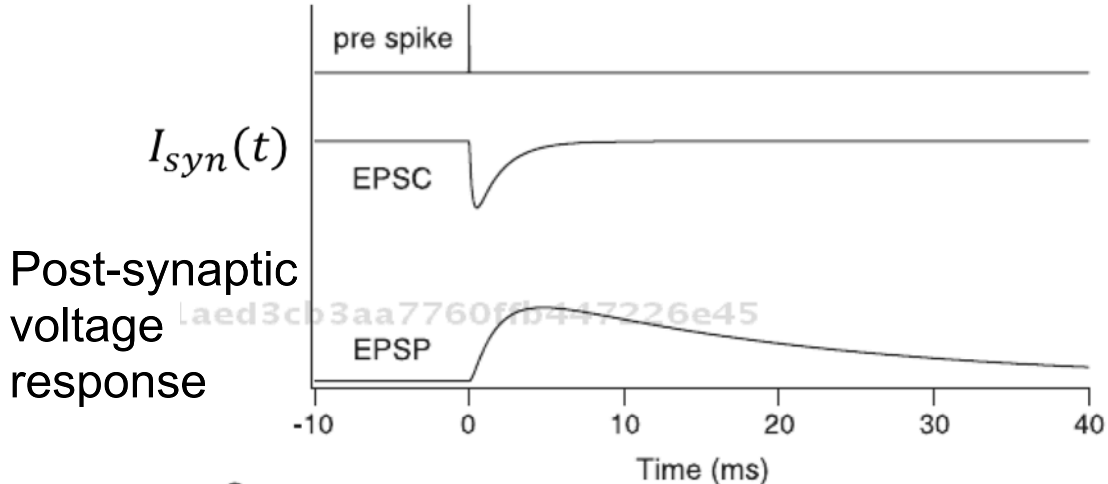
- $$I_{syn}(t) = g_{syn} \frac{t - t_{pre}}{\tau} e^{1-(t-t_{pre})/\tau}$$



- Rise time is slower
- Peak is at time t = τ
- Rise and decay time constants are related

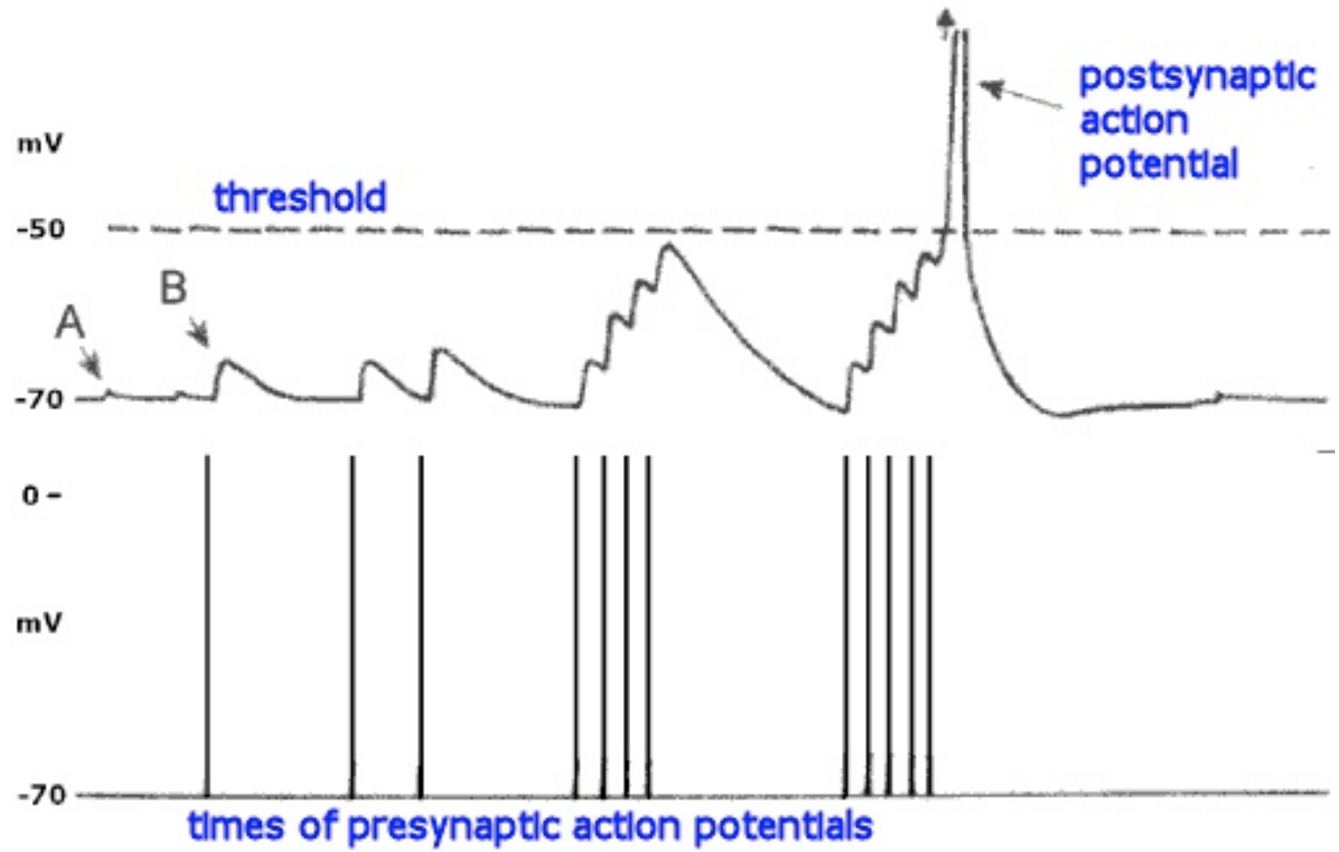
Double exponential

- $I_{syn}(t)$
  $= g_{syn} f \left(e^{-(t-t_{pre})/\tau_{decay}} - e^{-(t-t_{pre})/\tau_{rise}}\right)$



- f normalizes exponential term so max is 1
- Can specify different rise and decay time constants

Assume linear summation of I_{syn} for each presynaptic spike



Conductance based synaptic currents

- Models synaptic current in H-H formalism

$$I_{syn,j}(V_j, t) = \; g_{syn}\, s_j\, (V_{post} - E_{syn})$$

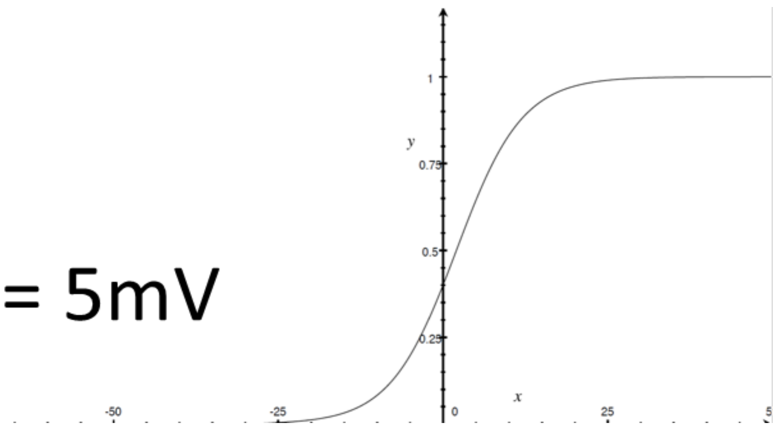
- s_j = synaptic gating variable, varies between 0 and 1, depends on presynaptic voltage V_j
- E_{syn} = reversal potential of synaptic current (0 mV for excitatory synapses, -75 mV for inhibitory synapses)

Synaptic gating variable

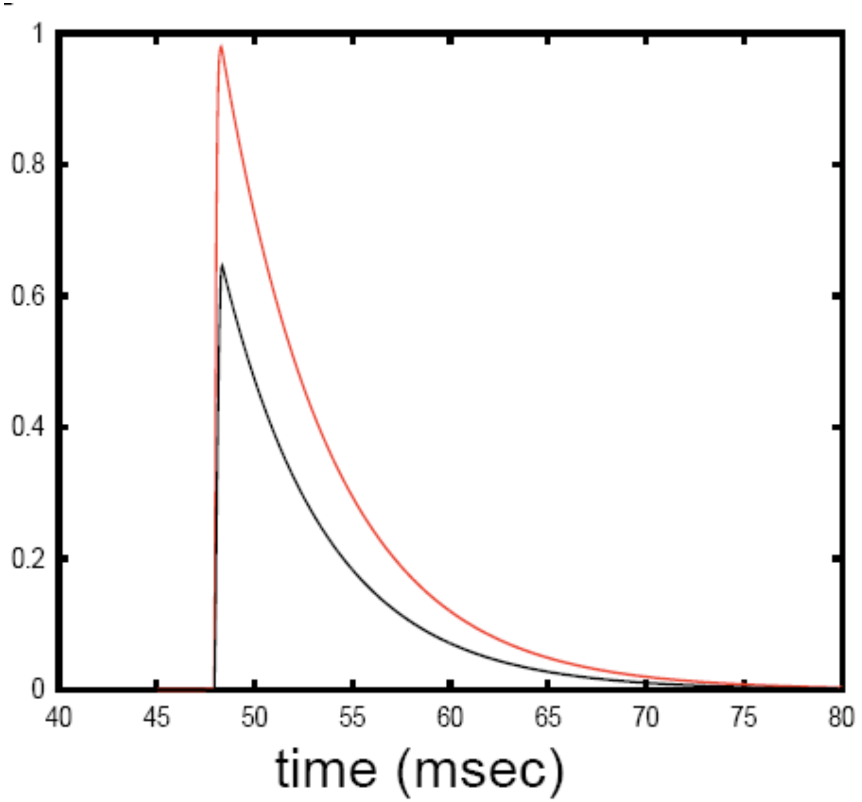
- Dynamics of s_j reflect amount of transmitter released by presynaptic cell

$$\frac{ds_j}{dt} = \alpha T(V_j)(1 - s_j) - \beta s_j$$

  - α = rate of synaptic current activation
  - β = rate of synaptic current decay
  - $T(V_j) = \frac{T_{max}}{1+e^{-(V_j - V_T)/k}}$
  - T_{max} = 1mM, V_T = 2mV, k = 5mV



AMPA (black) and $GABA_A$ (red) synaptic current gating *s* for a single pre-synaptic



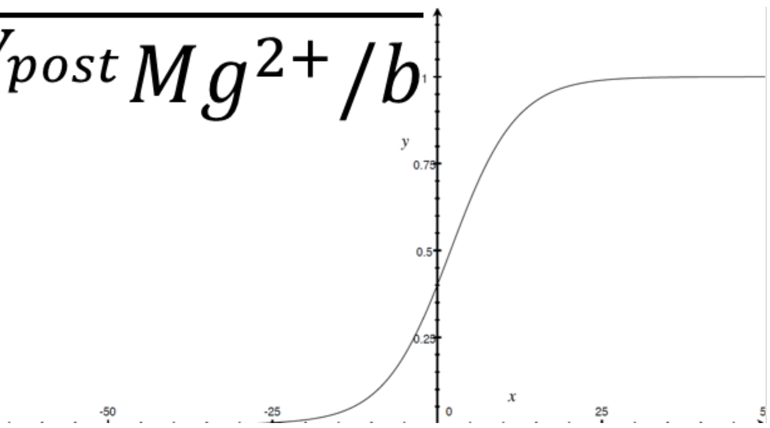
- For AMPA: α = 1.1 $(\text{mM ms})^{-1}$, β = 0.19 ms^{-1}
- For $GABA_A$: α = 5 $(\text{mM ms})^{-1}$, β = 0.18 ms^{-1}

Adaptation for NMDA synapses

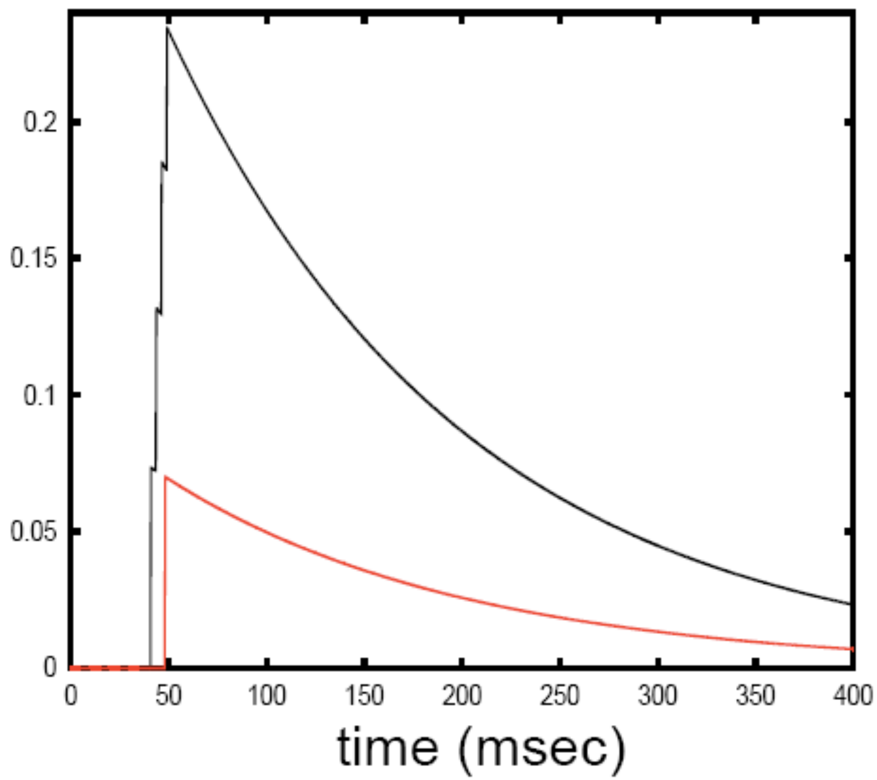
- $I_{syn} = g_{syn}\, s_j\, u(V_{post}, Mg^{2+})(V_{post} - E_{syn})$

Function $u(V_{post}, Mg^{2+})$ reflects fraction of NMDA channels not blocked by Mg^{2+}

$$u(V_{post}) = \frac{1}{1 + e^{-aV_{post}} Mg^{2+}/b}$$



NMDA synaptic gating *s* for a single pre-synaptic spike (red) and a burst of 4 pre-synaptic spikes (black)



Slower activation (= smaller response amplitude) and decay compared to AMPA

2 cell network model

- ILIF2cells.m

$$\frac{dV_1}{dt} = 0.04\, {V_1}^2 + 5V_1 + 140 \; - u_1 + I_{app} + I_{syn,2\ to\ 1}$$

$$\frac{du_1}{dt} = a(bV_1 - u_1)$$

$$\frac{dV_2}{dt} = 0.04\, {V_2}^2 + 5V_2 + 140 \; - u_2 + I_{app} + I_{syn,1\ to\ 2}$$

$$\frac{du_2}{dt} = a(bV_2 - u_2)$$

- Implemented in matlab in vector format

$$v = \begin{bmatrix} V_1 \\ V_2 \end{bmatrix}, u = \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}$$

- Using Euler's method

Synaptic currents in 2 cell

- Use instantaneous rise and exponential decay profile
- For each cell, compute sum of synaptic currents generated for each spike it fires

$$s_1(t) = \sum_{t_k} e^{-(t-t_k)/\tau}$$

$$s_2(t) = \sum_{t_m} e^{-(t-t_m)/\tau}$$

where t_k are all the spikes fired by Cell 1 and t_m are all the spikes fired by Cell 2 up to time t

Vector format for equations

- $$\frac{d}{dt}\begin{bmatrix} V_1 \\ V_2 \end{bmatrix} = 0.04 \begin{bmatrix} {V_1}^2 \\ {V_2}^2 \end{bmatrix} {V_1}^2 + 5\begin{bmatrix} V_1 \\ V_2 \end{bmatrix} + 140 - \begin{bmatrix} u_1 \\ u_2 \end{bmatrix} + \begin{bmatrix} I_1 \\ I_2 \end{bmatrix} + g_{syn} \begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix} \begin{bmatrix} s_1 \\ s_2 \end{bmatrix}$$
- Connectivity or adjacency matrix $\mathrm{W} = \begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix}$ sets coupling between cells

2 cell network behaviors

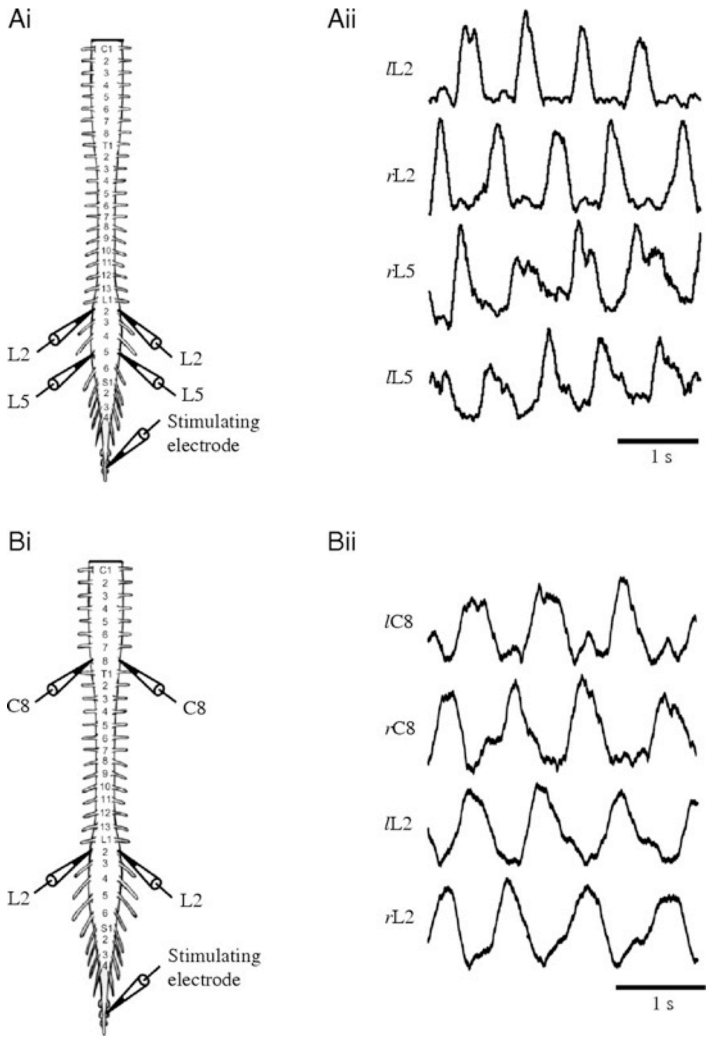
- Excitatory synapses generate
  - Synchronous firing when cells have same firing frequency
  - Phase locked behavior when cells have different firing frequencies
- Inhibitory synapses generate
  - Anti-phase firing
  - Suppress firing of 1 cell
  - Synchronous firing

  Depending on decay of synaptic current

Anti-phase firing in central pattern generator networks

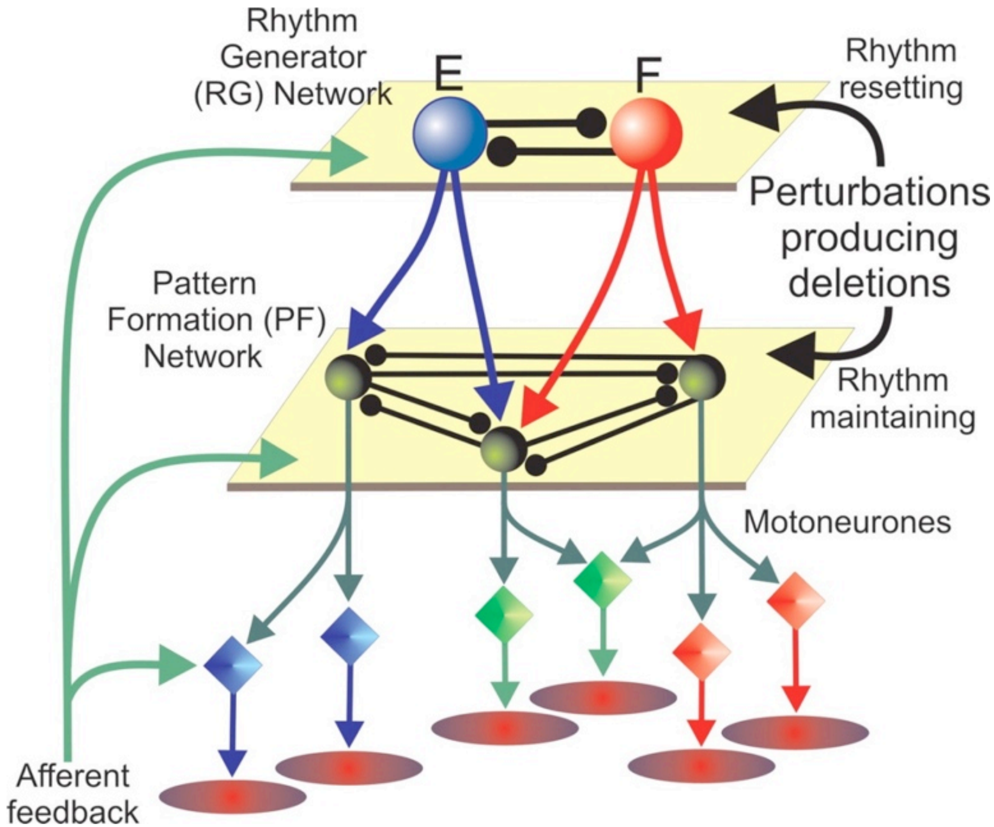
- Modeling papers
  - Spinal CPG in lamprey eel (Kotaleski etal Biol Cybernetics 1999)
  - Lateral pyloric neuron in crab stomatogastric ganglion (Taylor etal J Neurosci 2009)
  - Neuromodulation of synapses in crab stomatogastric ganglion (Oh etal J Comput Neurosci 2012)

(Ai) In the neonatal mouse, electrical stimulation (4 Hz, 40 pulses) of the cauda equina is capable of evoking coordinated lumbar locomotor-like activity.



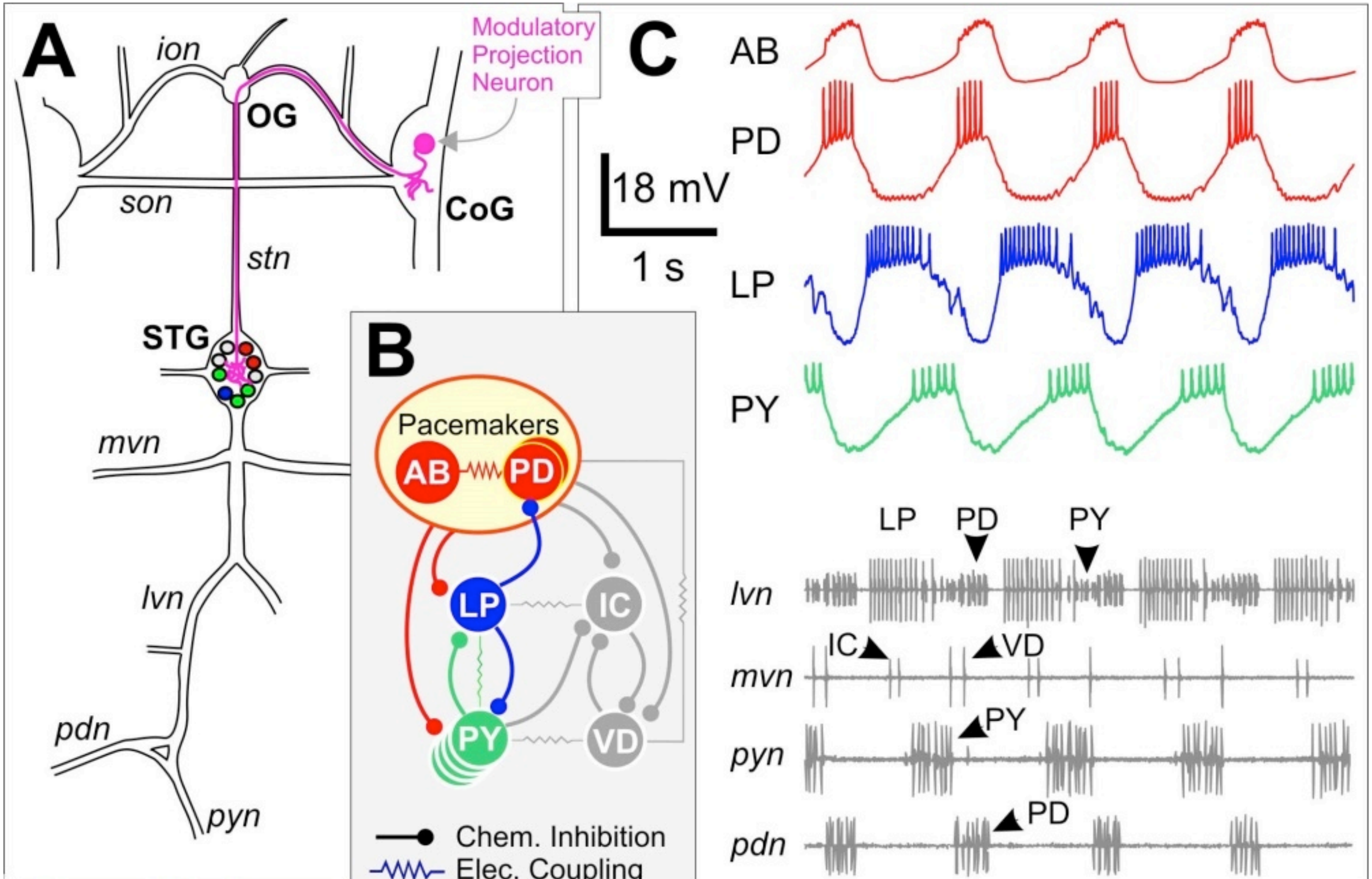
Gordon I T , and Whelan P J J Exp Biol 2006;209:2007-2014

The Journal of Experimental Biology



- Schematic illustration of the two-level central pattern generator (CPG) concept The locomotor CPG consists of a half-centre rhythm generator (RG) and a pattern formation (PF) network. The RG defines the locomotor rhythm and the durations of flexor and extensor phases and controls the activity of the PF network. The PF network contains interneurone populations (green spheres), each of which provides excitation to multiple synergist motoneurone pools (diamonds) and is connected with other PF populations via a network of inhibitory connections. Activation of a particular PF population activates the corresponding muscle synergy. The PF network mediates rhythmic input from the RG to motoneurones and distributes it among the motoneurone pools. Depending on the input from the RG and the interactions within the PF network, each PF population is active within particular phase(s) of the step cycle and produces a phase-specific, synchronized activation of the corresponding group of synergist motoneurone pools. Afferent feedback and spontaneous perturbations may affect the CPG either at the level of the RG, producing alterations (e.g. phase shifting or resetting) of the locomotor rhythm, or at the level of PF, altering the level of motoneurone activation and/or the timing of phase transitions without shifting the phase of (or resetting) the locomotor rhythm generated by the RG.

The pyloric circuit of the crab stomatogastric nervous system



- *The pyloric circuit of the stomatogastric nervous system.* **A.** Schematic diagram of the STNS including a modulatory projection neuron that innervates the STG. Abbreviations: Ganglia - CoG, commissural ganglion (bilateral pair); OG, oesophageal ganglion; STG: stomatogastric ganglion. Nerves - *ion*, inferior oesophageal nerve; *son*, superior oesophageal nerve; *stn*, stomatogastric nerve; *mvn*, medial ventricular nerve; *lvn*, lateral ventricular nerve; *pdn*, pyloric dilator nerve; *pyn*, pyloric constrictor nerve. **B.** Circuit diagram showing connectivity among pyloric neurons. Neurons AB: anterior burster; PD: pyloric dilator (2), LP: lateral pyloric; IC: inferior cardiac; PY: pyloric constrictor (3-5); VD: ventricular dilator. **C.** Tri-phasic pyloric oscillations shown in simultaneous intracellular recordings of 4 pyloric neurons and 4 motor nerves containing axons of pyloric neurons. The AB and PD neurons are the pyloric pacemaker group. Colors show the 3