Mathematical Foundations of Neuroscience - Lecture 3. Electrophysiology of neurons - continued

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Winter 2009/2010

Short summary

- We know from elsewhere that in the steady state equilibrium the total current across the membrane is $I_{\text{total}} = 0$.
- We know the Nerst potentials of Ions, we only need to know the respective conductances to get the equation:

$$C\frac{dV(t)}{dt} = I(t)_{\text{total}} - I_{Na} - I_K - I_{Cl} - I_{Ca}$$

  running and find out what is the steady state membrane voltage.
- Sadly this is where the neuronal story begins...

Equivalent circuit

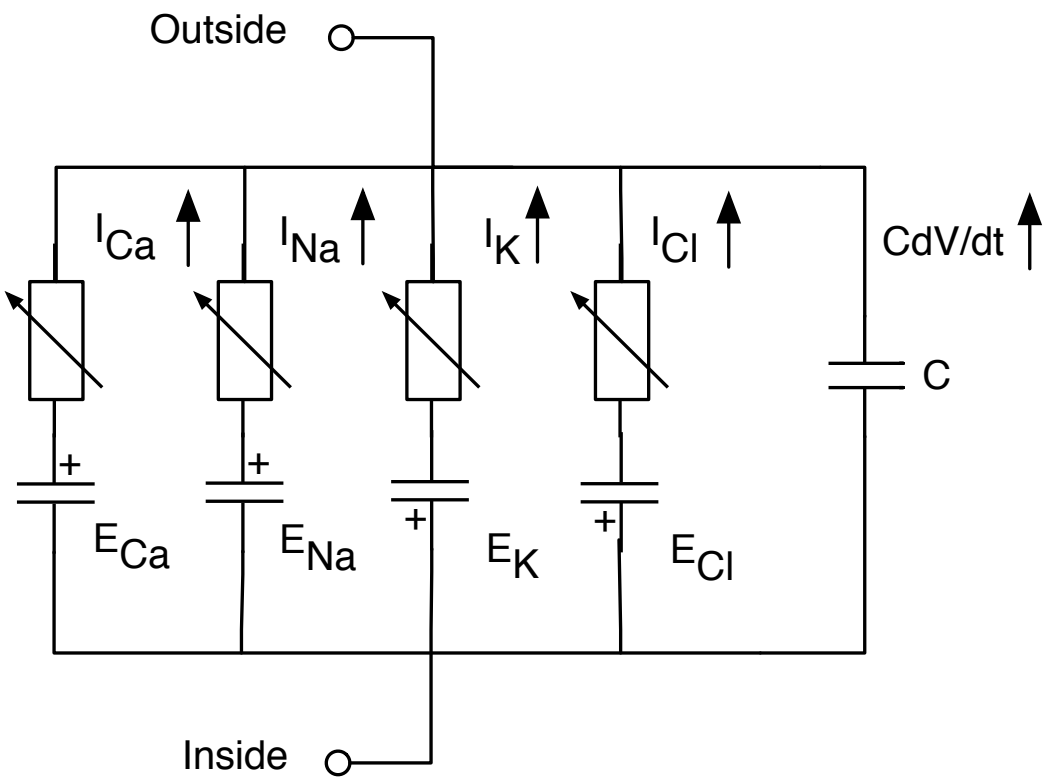

Figure: Electrical circuit equivalent to a patch of neuronal membrane.

Resting potential

- At what level the Voltage across the membrane is in equilibrium? That is to say when is $\frac{dV}{dt} = 0$?
- It is easy to see, that if there were only one ionic current (e.g. sodium) the resting potential would be equal to its Nerst potential

$$0 = \frac{dV}{dt} = -I_{Na} = -g_{Na}(V - E_{Na})$$

since $g_{Na} \neq 0$ it follows that $V_{\text{rest}} = E_{Na}$

- But there are unfortunately more currents.

Resting potential

- We can solve the equation

$$C\frac{dV(t)}{dt} = I(t)_{\text{total}} - I_{Na} - I_K - I_{Cl} - I_{Ca}$$

by setting $\frac{dV(t)}{dt}$ and $I(t)$ to zero. We then come up with a solution

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

- It is easy to verify that V_{rest} indeed satisfies the equation. Note that V_{rest} is a weighted (by conductances) average of all equilibrium potentials!

Conversely the equation

$$C\frac{dV(t)}{dt} = I(t)_{\text{total}} - I_{Na} - I_K - I_{Cl} - I_{Ca}$$

can be expressed

$$C\frac{dV(t)}{dt} = I(t) - g_{\text{inp}}(V - V_{\text{rest}})$$

where $g_{\text{inp}} = g_{Na} + g_{Ca} + g_K + g_{Cl}$. The quantity $R_{\text{inp}} = \frac{1}{g_{\text{inp}}}$ is called the input resistance. It follows that

$$V \to V_{\text{rest}} + IR_{\text{inp}}$$

Ionic conductances

- So if we have the equations, we only need to get the conductances and were done!
- Unfortunately the ionic conductances are the source of neuronal excitability and various behaviors!
- Conductances are not constants (Ohmic), they are functions of time and voltage itself!
- That creates a closed loop, voltage depends on conductances which depend on voltage and so on... Smells like trouble...
- How than can we measure the conductances?

Voltage clamp experiment

- The idea is to artificially alter membrane voltage by the so called voltage clamp
- One electrode is used to measure membrane voltage while the other is used to apply appropriate current.
- The current variates with time, approaching steady state asymptotic value. That way the so called I-V (current-voltage) curves can be obtained.
- Further variants of the experiment have beed devised in order to measure conductances of particular ions etc.

Voltage clamp experiment

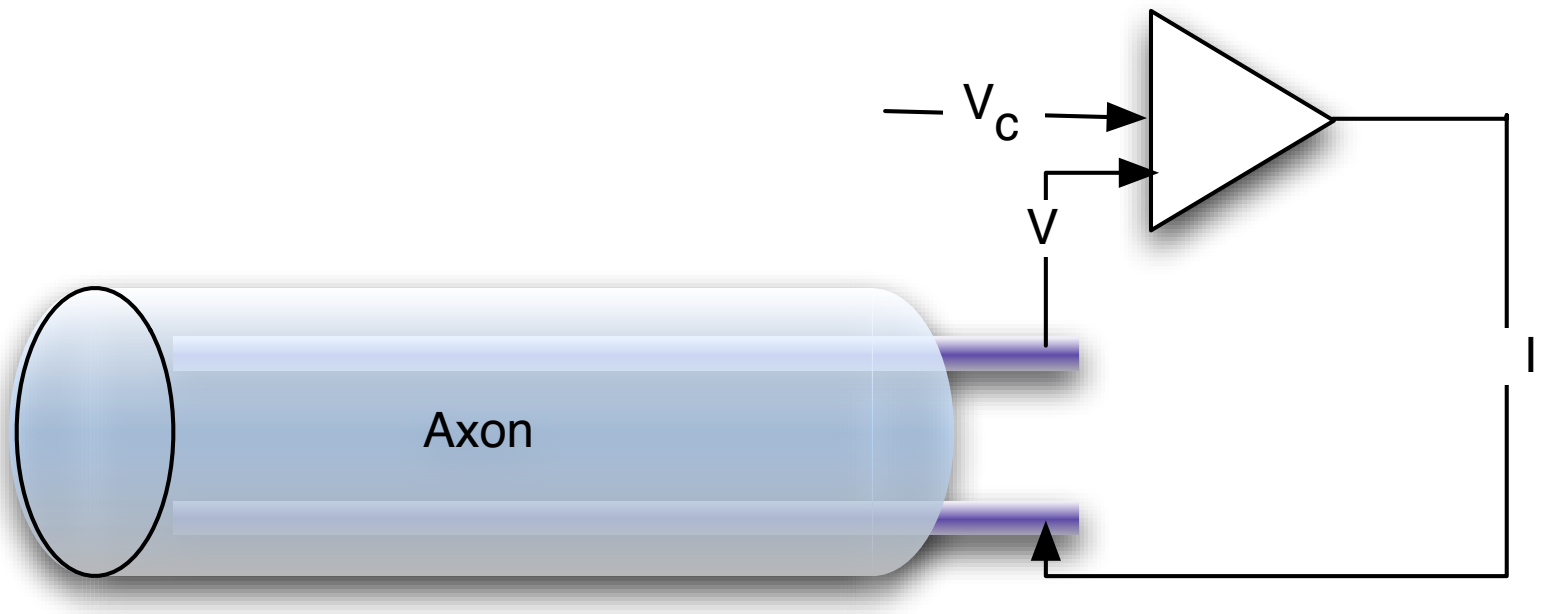

Figure: Voltage clamp scheme

Voltage clamp experiment

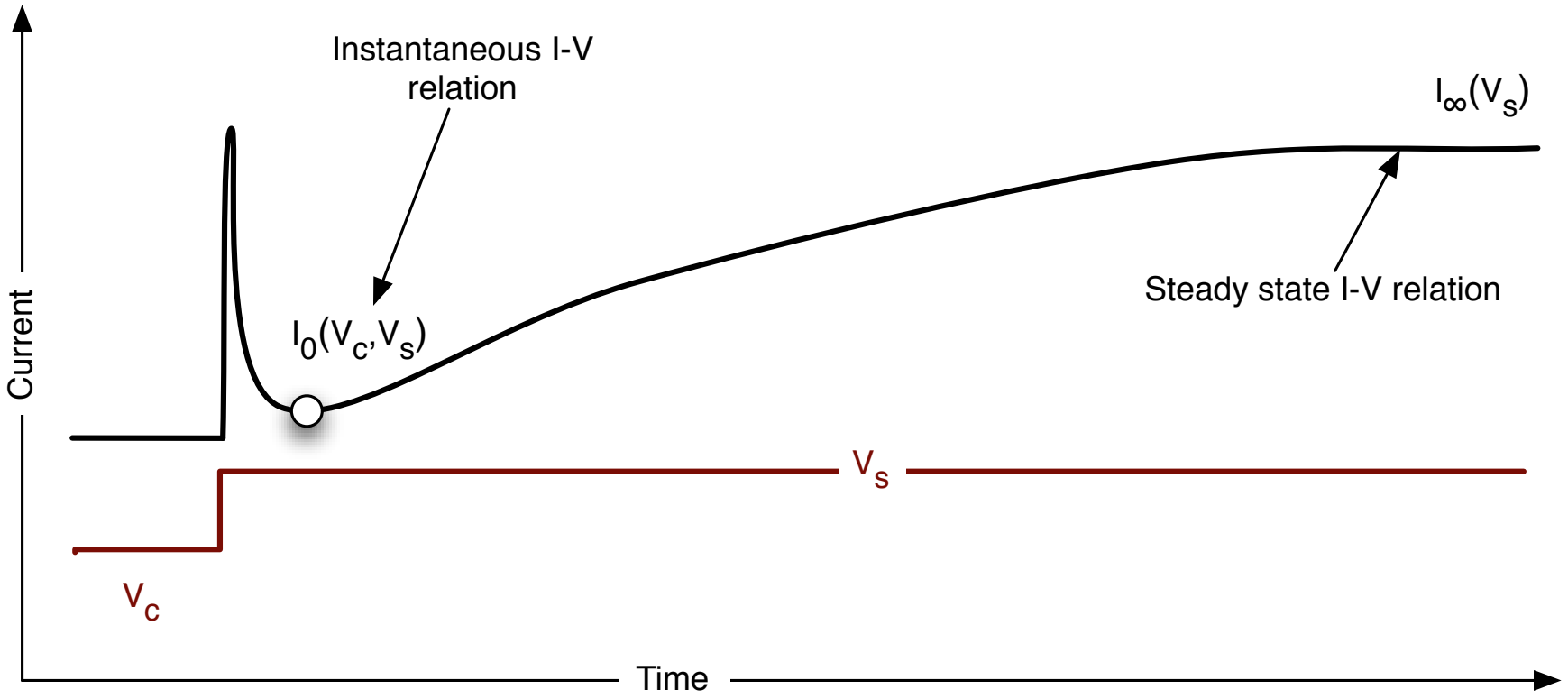

Figure: Typical outcome of the voltage-clamp experiment.

Conductances

- The ionic conductances are variable which makes the neuronal activity complex (if they weren't, things would be very simple)
- The conductance variability is due to the so called gates - large particles in the neural membrane that open or close a particular ionic channel. The gates may be sensitive to:
  - Membrane voltage - *voltage gated channels* e.g. $Na^+$and K^+
  - Secondary messengers (intracellular agents) - e.g. Ca^{2+}-gated K^+channels
  - Extracellular agents (neurotransmitters and neuromodulators) - e.g. AMPA, GABA, NMDA receptors in synapses.
- Gating is a stochastic process, nevertheless since there are lots of channels on each membrane piece, globally gating can be averaged and approximated via a differential equation

Conductances

Variable conductances can be employed to our equation in a following manner:

$$I = \overline{g} p (V - E)$$

where $\overline{g}$ is the maximal conductance (with every channel open) and $p \in [0, 1]$ is average proportion of open channels. E is the reverse potential, that is the potential at which the current reverses direction. If the channels are selective to a single ionic species (which is the case), then E is the Nerst potential of that ion.

Voltage gated currents

- The most important for neural excitability a the voltage gated currents, that is currents dependent on conductances which themselves depend on membrane voltage.
- These conductances may be
  - deactivated (the channels are closed)
  - activated (the ions may flow freely)
  - inactivated (another process closes the channel)
  - deinactivated (released from inactivation)
- If the channel can only be activated and deactivated it results in *persistent* (long lasting) currents
- The channel that can be inactivated results in *transient* (short lasting) currents.

Voltage gated currents

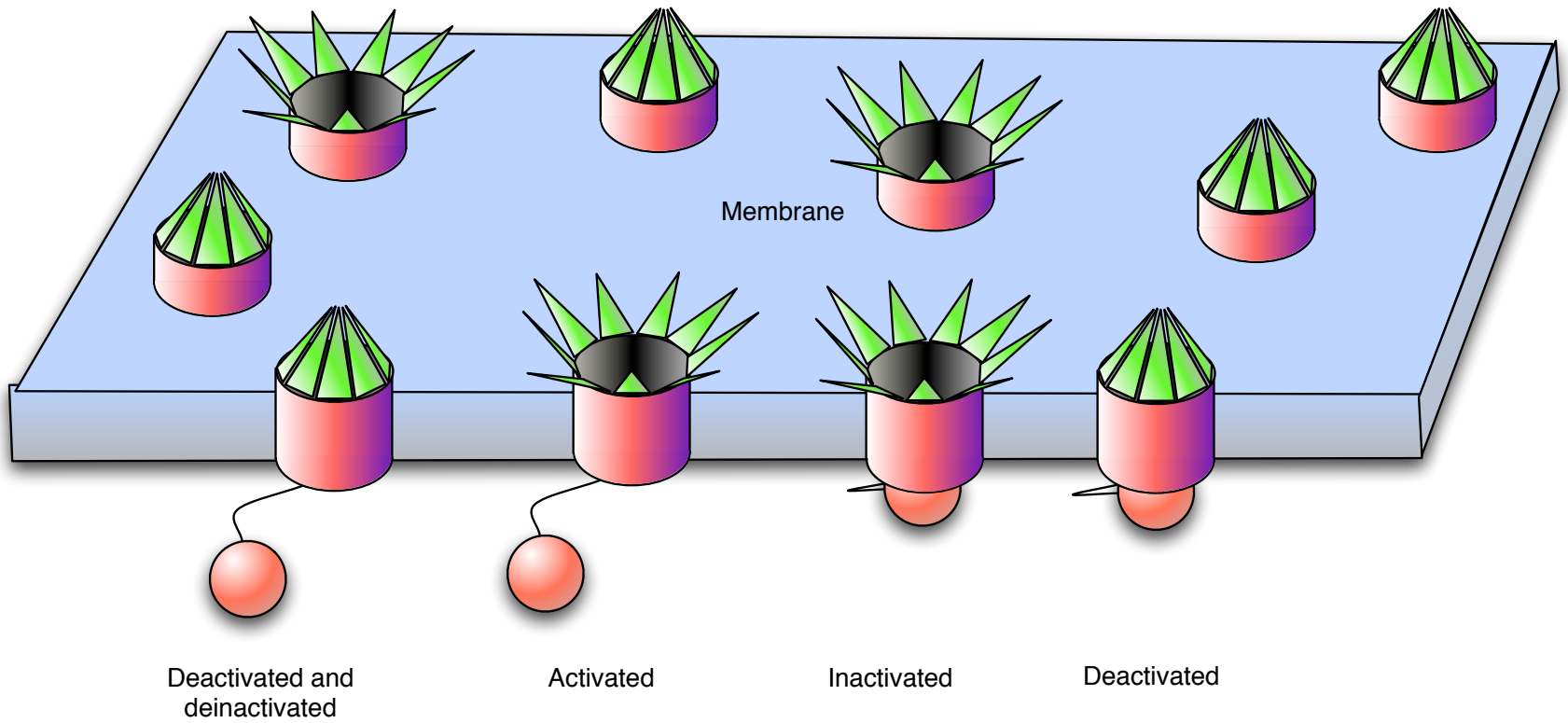

Figure: Channels that can be activated and inactivated.

Voltage gated currents

- Activation and inactivation are a processes that take some time, historically the activation is denoted with variable m (or n) while the inactivation is denoted with h.
- Consequently the total conductance of a channel is expressed

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

  where a and b are numbers of activation and inactivation gates per channel (activities of gates are assumed to be independent)
- If the channel has no inactivation gates then $b = 0$.
- The only thing needed to have a decent model of neuronal membrane is to investigate the activation and inactivation dynamics!

Hodgkin-Huxley neuron

- The pioneering measurements leading to fairly full description of neuronal excitability were conducted by Alan Lloyd Hodgkin and Andrew Huxley in 1952.
- In 1963 they both received Nobel Prize in Physiology or Medicine for the work.
- They've worked on a giant squid axon - a particularly convenient neuronal cell to study due to it's large size.
- They managed to measure all the parameters required to formulate a complete model of neuronal membrane, and that could simulate excitability and spike generation mechanisms.

Activation kinetics

- The averaged activation can be approximated with a following differential equation

$$\frac{dm(V,t)}{dt} = (m_\infty(V) - m)/\tau_m(V)$$

- $m_\infty(V) \in [0,1]$ is the asymptotic steady state activation function. That is with voltage V activation approaches $m_\infty(V)$.
- $\tau_m(V)$ is the rate at which m converges to its asymptotic value.

Hodgkin and Huxley came up with a set of equations:

$$
\begin{aligned}
C_m \frac{dV}{dt} &= -g_L(V - E_L) - g_{\mathrm{Na}} m^3 h (V - E_{\mathrm{Na}}) - g_{\mathrm{K}} n^4 (V - E_{\mathrm{K}}) \\
\frac{dm}{dt} &= (m_\infty(V) - m)/\tau_m(V) \\
\frac{dn}{dt} &= (n_\infty(V) - n)/\tau_n(V) \\
\frac{dh}{dt} &= (h_\infty(V) - h)/\tau_h(V)
\end{aligned}
$$

Where C_m is the membrane capacitance (typically $1\mu F/cm^2$), $g_L = 0.3 = mS/cm^2$ is the leak conductance and $E_L - 55.4mV$ is the leak potential, $g_{\mathrm{Na}} = 120mS/cm^2$, $E_{\mathrm{Na}} = 55mV$, $g_{\mathrm{K}} = 36mS/cm^2$, $E_{\mathrm{K}} = -77mV$ are conductances and Nerst potentials of sodium and potassium respectively

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m, n and h are gating variables, $m_\infty(V)$, $n_\infty(V)$, $h_\infty(V)$ are steady state activation functions, $\tau_m(V)$,$\tau_n(V)$,$\tau_h(V)$ are volatge dependent convergence rates. These functions have been estimated empirically and approximated by sigmoidal and unimodal exponential functions.

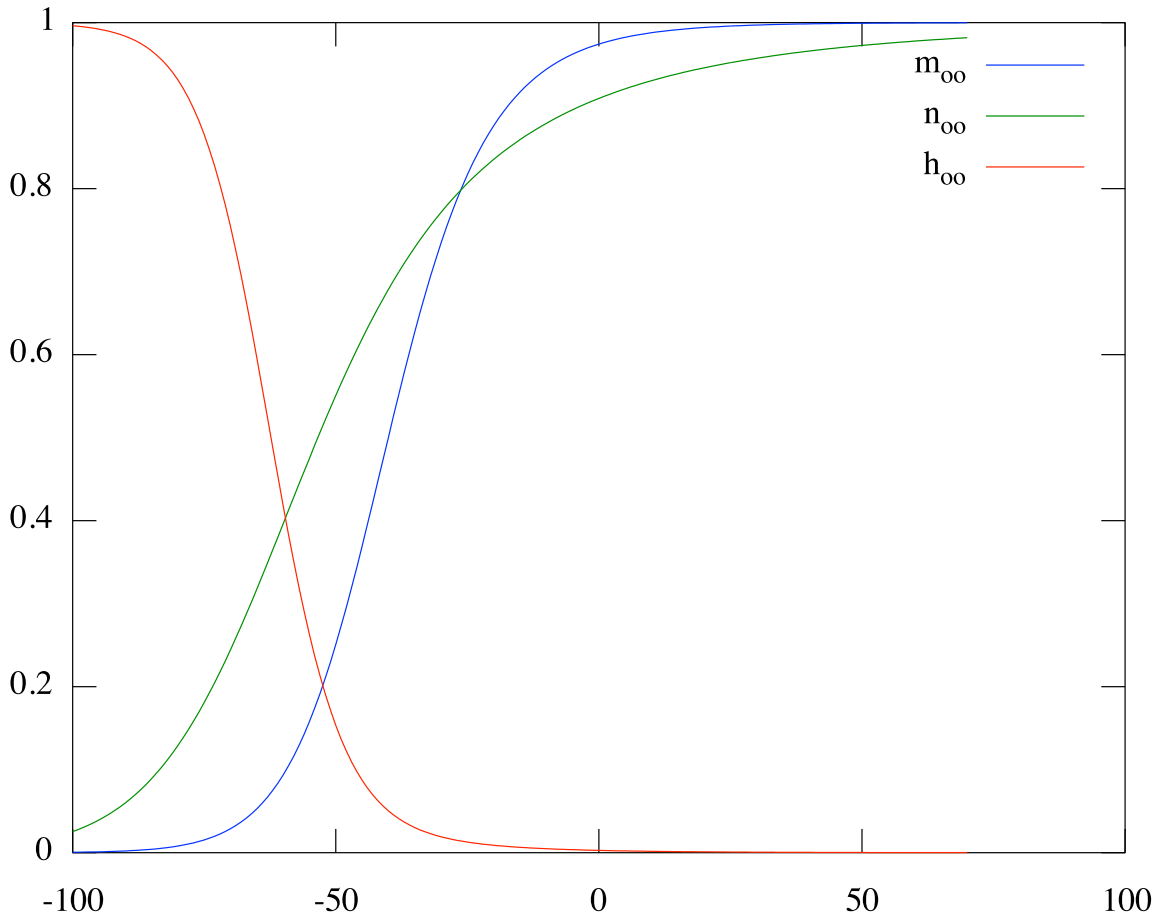

Figure: Steady state activation functions in Hodgkin-Huxley model (horizontal axis stands for voltage)

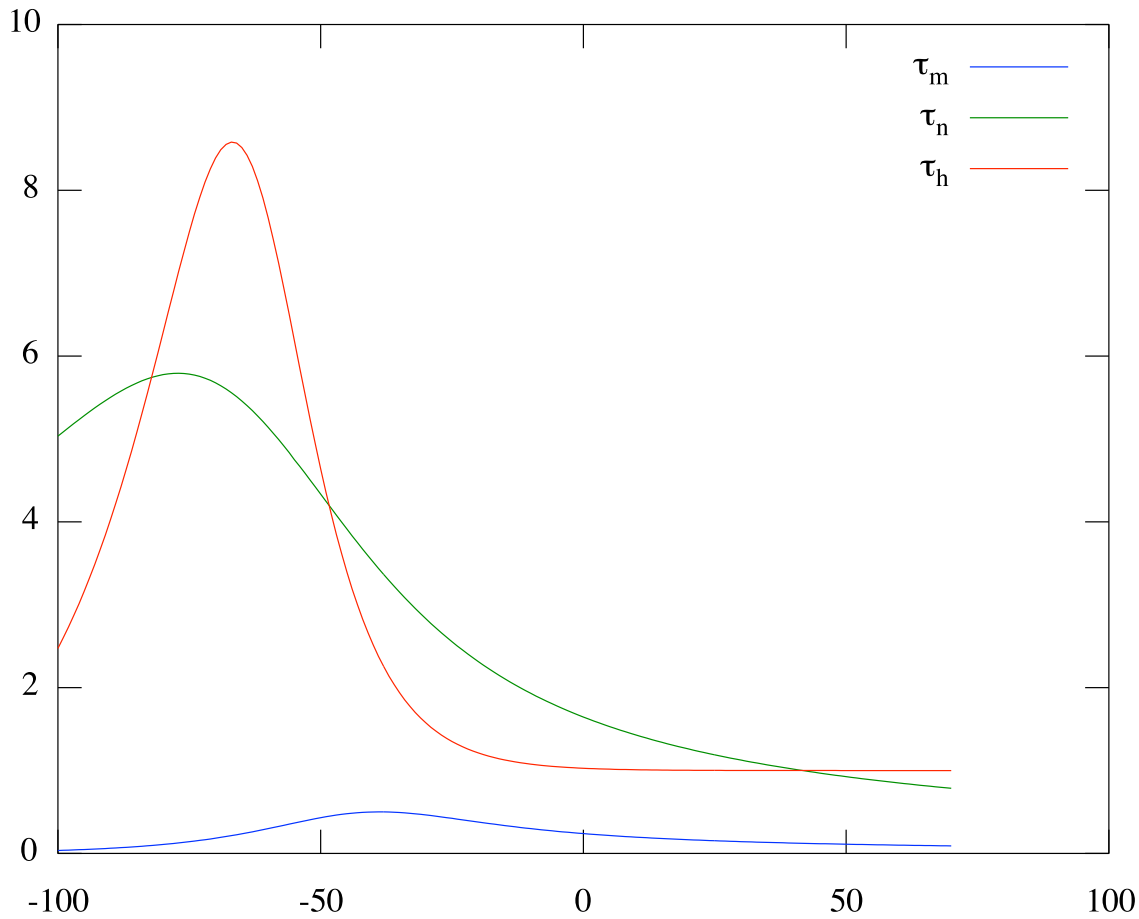

Figure: Voltage dependent convergence rates in Hodgkin-Huxley model (horizontal axis stands for voltage)

Action potential

- What happens to the Hodgkin-Huxley model when some stimulating current is applied to the membrane?
- The current causes the voltage to jump according to $V \to V_{\text{rest}} + IR_{\text{inp}}$.
- Voltage changes alter ionic conductances, consequently m, n and h variables start to follow their new asymptotic values $m_\infty(V)$, $n_\infty(V)$, $h_\infty(V)$ with rates $\tau_m(V)$,$\tau_n(V)$,$\tau_h(V)$.
- Sodium Na^+has the fastest kinetics, therefore initial voltage jump quickly increases Na^+conductance. If the jump was strong enough it may ignite a self perpetuating process, since the inflow of sodium increases membrane polarization (further increase in V) !

Action potential

- If the process ignites, then membrane voltage quickly jumps up to say $50mv$ before other gates start their action.
- After a while sodium inactivation catches up, and inactivates the sodium channel.
- In the mean while, slow potassium activation variable n grows, causing huge outflow of K^+ions. Consequently membrane voltage falls down below the rest state, that is it hyperpolarizes.
- Next the potassium channel slowly inactivates, and the membrane gets back to the rest state.
- The whole process is called an action potential or a spike (due to a sudden spike like increase in membrane potential).

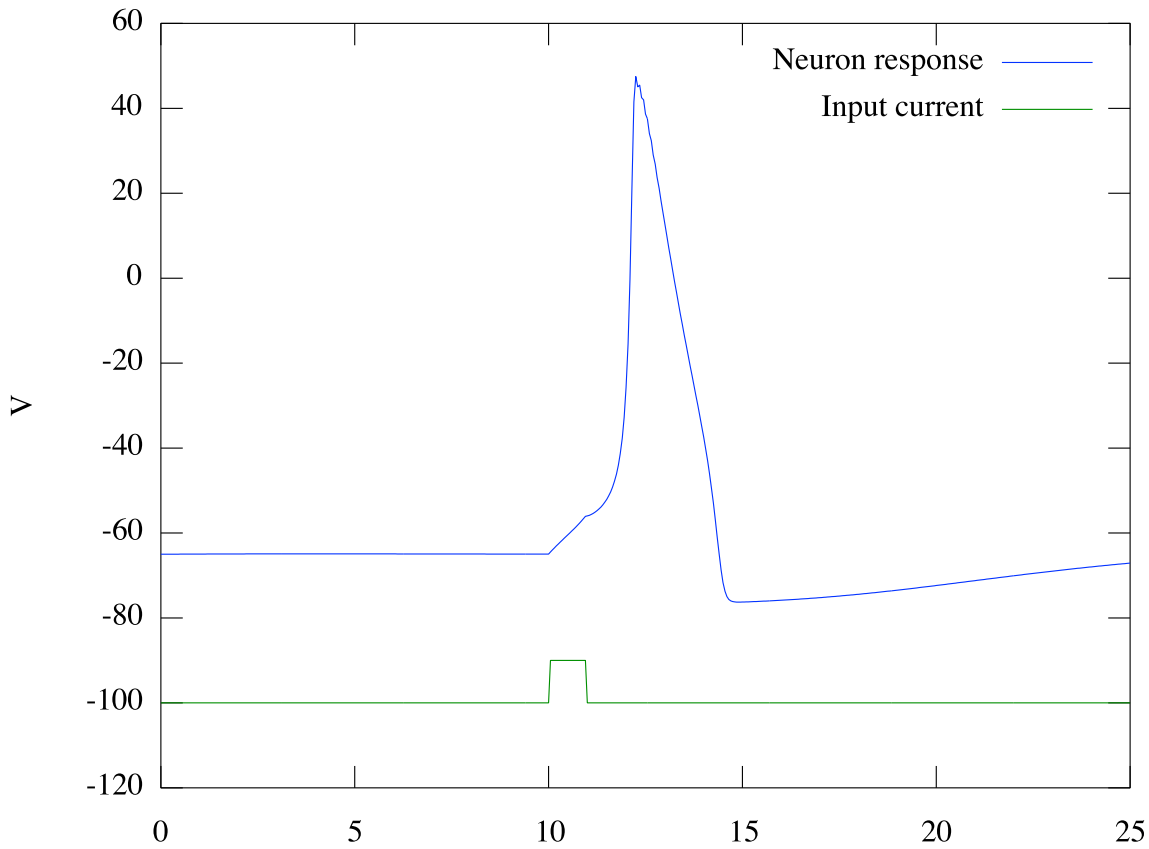

Figure: A spike in HH model. In response to a $1ms$ stimulation of $10pA$, the neuron ignites a huge jump in the membrane voltage.

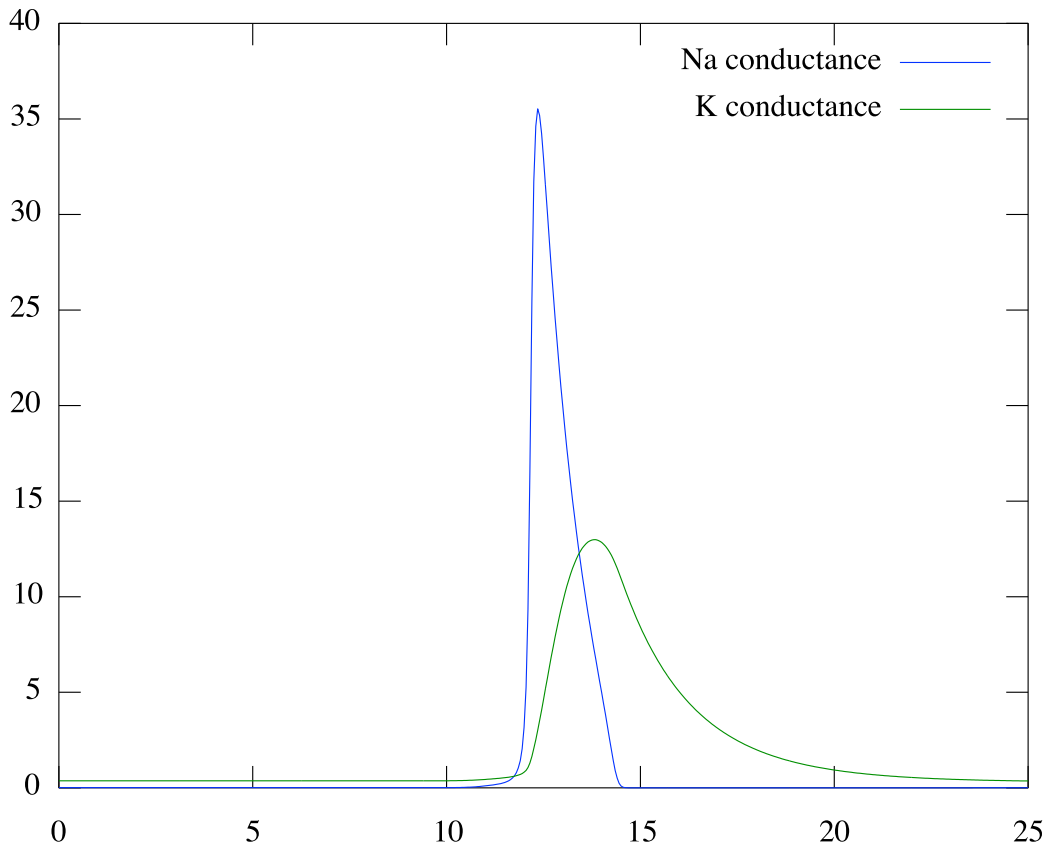

Figure: Na^+ and K^+ conductances during a spike (time scale as on previous figure).

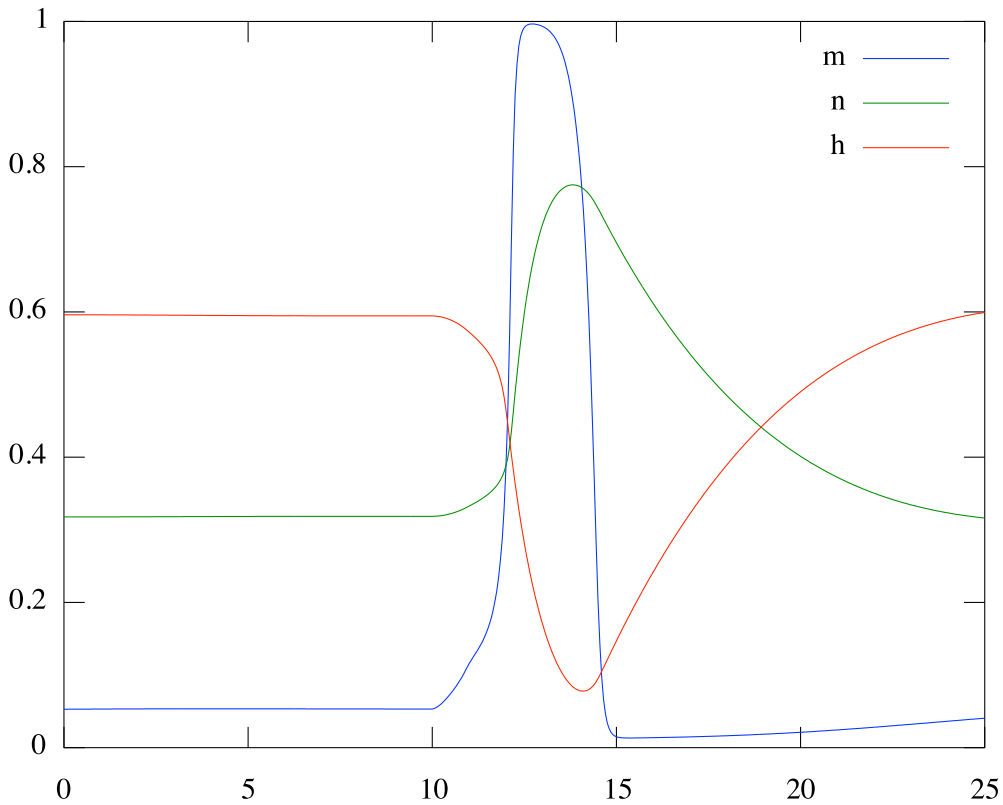

Figure: Activation and inactivation variables during a spike (time scale as on previous figure). Blue and red are Na^+activation and inactivation respectively, green is the slow K^+activation.

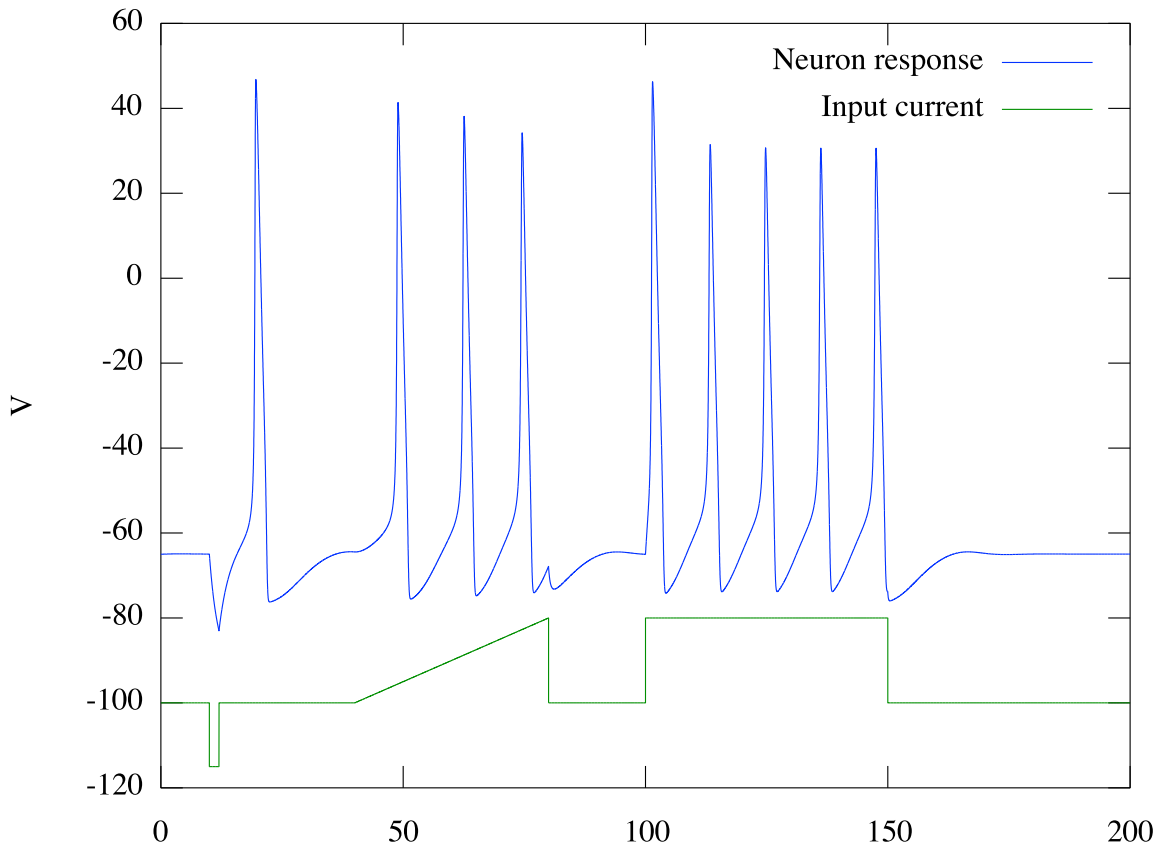

Figure: Neuronal voltage (HH model) in response to a stimuli depicted with green line. Note the post inhibitory spike!

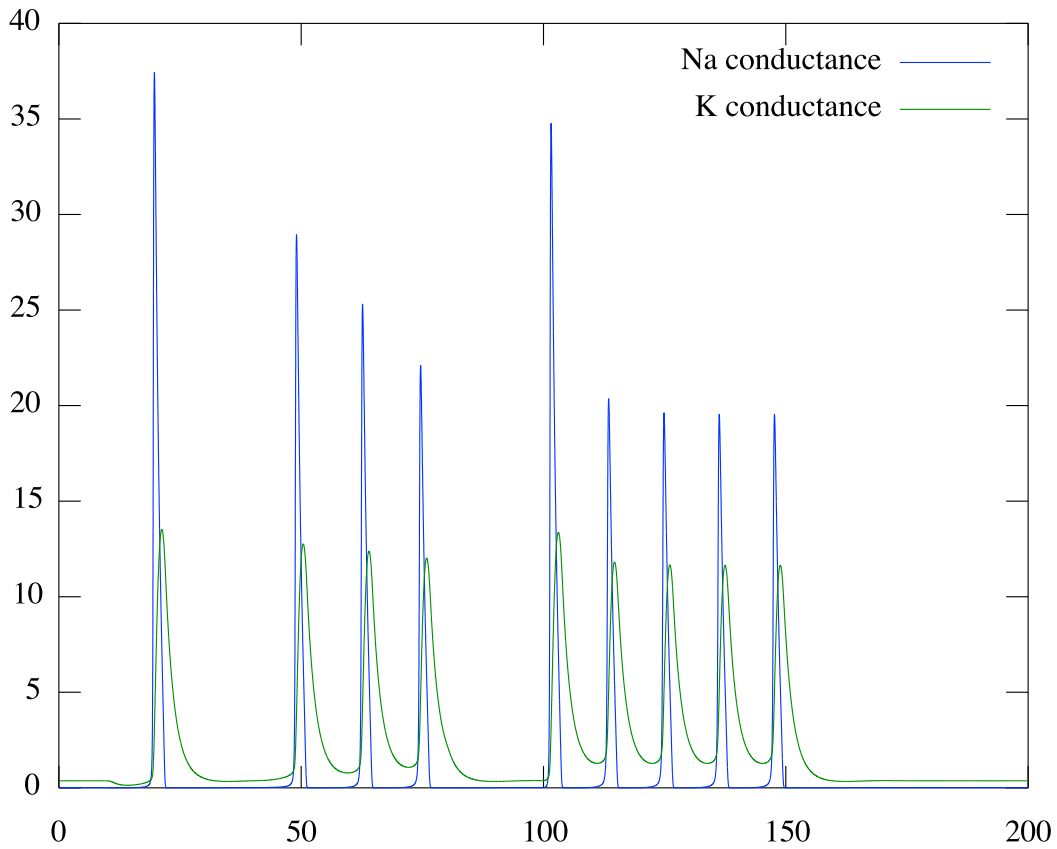

Figure: Ionic conductances of Na^+ and K^+ in HH model in response to a stimuli from previous figure.

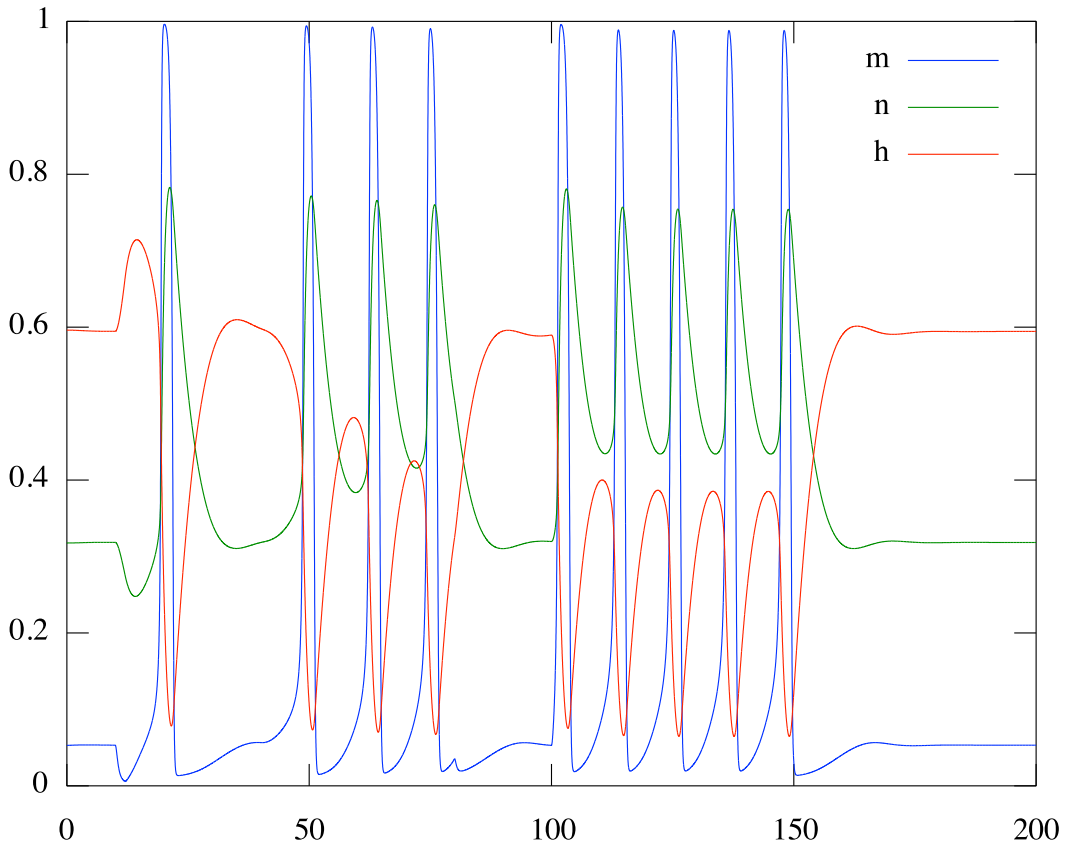

Figure: Activation and inactivation variables in HH model in response to a stimuli from previous figure.

After spike excitability

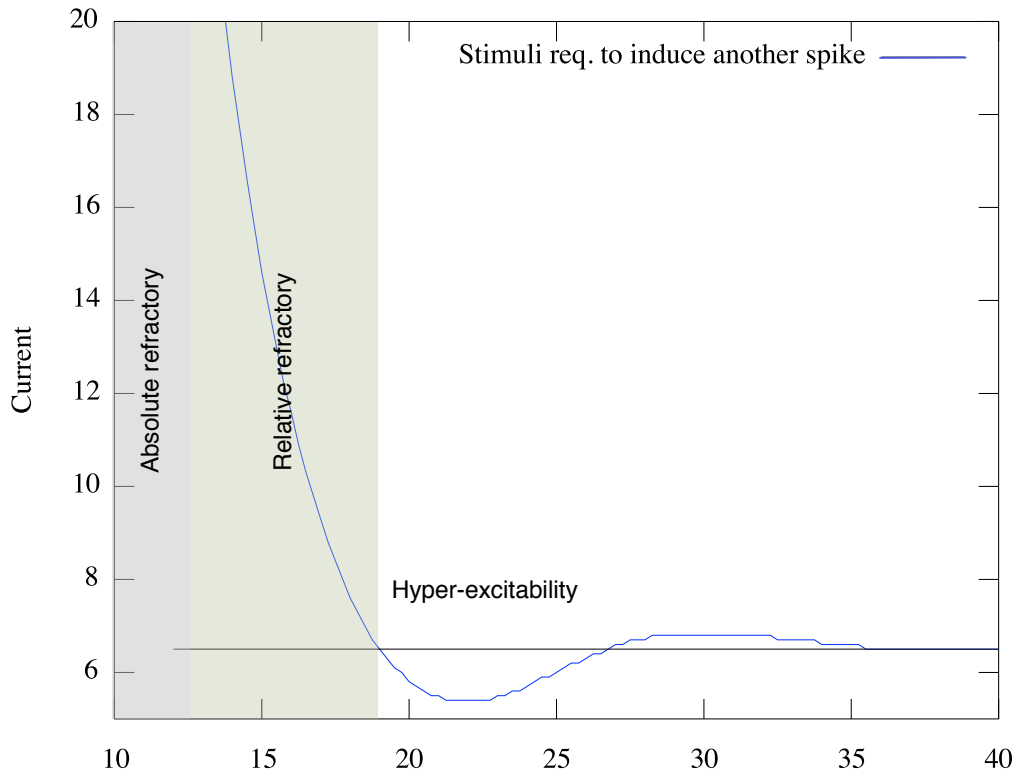

Figure: Magnitude of stimulation required to fire another spike as a function of time from the previous spike inducing stimulus.

Remarks

Originally Hodgkin-Huxley equation was formulated as follows:

$$\begin{aligned} C_m \frac{dV}{dt} &= -g_L(V - V_L) - g_{Na} m^3 h (V - V_{Na}) - g_K n^4 (V - V_K) \\ \frac{dm}{dt} &= \alpha_m(V)(1 - m) - \beta_m(V) m \\ \frac{dh}{dt} &= \alpha_h(V)(1 - h) - \beta_h(V) h \\ \frac{dn}{dt} &= \alpha_n(V)(1 - n) - \beta_n(V) n \end{aligned} \tag{1}$$

where (see next slide)

Remarks continued

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

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

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

and typically:

$$E_k = -12mV, \quad E_{Na} = 120mV, \quad E_L = 10.6mV,$$

$$g_K = 36mS/cm^2, \quad g_{Na} = 120mS/cm^2, 7 \quad g_L 7 = 0.3mS/cm^2,$$

$$C = 1\mu F/cm^2$$

Remarks continued

The ionic potentials were shifted, so that membrane rest potential would be at 0mV. Instead we are adopting the modern formulation, in which the rest potential is at -65mV. Also note that

$$n_\infty = \alpha_n/(\alpha_n + \beta_n), \qquad \tau_n = 1/(\alpha_n + \beta_n)$$
$$m_\infty = \alpha_m/(\alpha_m + \beta_m), \qquad \tau_m = 1/(\alpha_m + \beta_m)$$
$$h_\infty = \alpha_h/(\alpha_h + \beta_h), \qquad \tau_h = 1/(\alpha_h + \beta_h)$$

(remember to shift the voltage in expressions for α and β before trying to implement this model!)

Spatial propagation of spikes

- Everything derived up until now relates to infinitesimal piece of neuronal membrane and time evolution of its potential
- However neurons are spacial entities (some axons can be up to a meter long!)
- There are two approaches available for simulation of the whole neuron:
  - Via the cable equation (most adequate, but computationally demanding)
  - Via compartments connected by conductances (faster but less accurate).

Cable equation

The cable equation adds an extra term to the voltage/current relation. The term is proportional to the second order partial derivative of V with respect to spacial variable x.

$$C\frac{dV}{dt} = \frac{a}{2R}\frac{\partial^2 V}{\partial x^2} + I - I_K - I_{Na} - I_L \tag{2}$$

Where a (cm) is the radius of the cell (dendrite,axon etc...), and R $\Omega \cdot cm$ is intracellular resistivity. It is easy to understand that equation: it basically says that the rate of change of the membrane at some point (dV/dt) depends on what happens at that particular point $I - I_K - I_{Na} - I_L$, but also depends on the rate of change of the difference between the voltage at current point and a neighboring point.

Multi compartment model

- Another somewhat easier approach is to simulate a neuron as a set of compartments.
- Each compartment has the dynamics defined by the Hodgkin-Huxley equation, with an extra current coming from neighboring comparments
- Eventually the equation is:

$$C\frac{dV}{dt} = -I(V,t) + \sum_{n \in \text{neighbors}} g_n(V_n - V)$$

where g_n is the conductance from neighboring compartment n and V_n is the value of voltage at that compartment.

- Neurons exhibit very peculiar electric activity. The charge is not transferred directly (like in copper wires), but instead causes inward and outward ionic currents across the membrane.
- Depolarization of the membrane propagates along neuronal fibers. The propagation is rather slow of order 1m/s unlike metallic conductors where voltage changes propagate at nearly speed of light.
- The mechanism is active, that is whenever input signal is strong enough, the spike generation process is ignited which amplifies the action potential.
- The first mathematical description of action potentials were introduced in 1952 by Alan Lloyd Hodgkin and Andrew Huxley.