Summary: The Membrane Tutorial
How Currents Depolarize Excitable Membranes

J Rinzel, Feb 2, 2009

Goals of this Tutorial

- To understand, through experimentation, how a current pulse changes the voltage across a membrane:
  - when it is only a plain lipid bilayer
  - when it has only a Na/K pump that establishes a resting potential
  - when it has, in addition to the pump, a voltage-insensitive, non-selective "leakage" conductance
  - when it has, in addition to the pump and leakage channels, the voltage-sensitive Na and K channels described by Hodgkin and Huxley
- To understand capacitance and capacitive currents and why they are important for understanding neuronal signaling

Highlights of some computational experiments:

1. The plain lipid bilayer. $Q = CV$, $Q$ is charge, the integral of injected/applied current $I(t)$ and $C$ is capacitance. $C$ is total capacitance: $C = A \times C_m$ where $A$ is patch area (in cm$^2$) and $C_m$ is specific capacitance, 1 microF/cm$^2$. Equivalently, the current equals the time derivative of $Q$ (charge per unit time): $I = \frac{dQ}{dt} = C \frac{dV}{dt}$.

The equation for capacitive current, $I_{cap}$.

\[
I_{cap} = C \times [\frac{dV}{dt}]
\]

or

\[
\frac{dV}{dt} = \frac{I_{cap}}{C}
\]

Note for a step current input:

a. $V$ remains constant after the I-step returns to zero. There are no ionic/leakage channels through which the accumulated charge can leave the cell.
b. The rising ramp is linear (constant slope), during the stimulus because the current is constant (const influx of charge).
c. Smaller $C$ means slower ramp for given I-step.
d. For given $C$, the ramp speed is proportional to $I$. 
e. We can estimate $C$ by measuring $V=V_{ss}$ (steady state) after the I-step, knowing the total charge injected: $C = Q/V = I*T/V$, where $T$ is the step duration.

f. **JR query:** Suppose we wish to restore $V$ to $V=0$ after the depolarizing I-step, with an oppositely directed current-step $I_{off}$ with duration $T_{off}$. What should the value of $I_{off}$ be? Notice, if $T_{off}$ is chosen very small then $dV/dt$ becomes very large and negative. In the limit as $T_{off}$ goes to zero the stimulus tends to a “delta pulse” of current: zero duration and infinite amplitude to give finite charge.

JR did not discover how to “tack on” more time to a simulation like the above by changing the stimulus to a negative square step: $I_{off}=-10$ and $T_{off}=2$ ms that would begin at $t=11$ ms. Rather I had to redo the simulation from “reset Voltage” of 200 mV. See next page.

Can you come up with a scheme to use “Continue for ms” after changing the Current Params?
2. Adding $V_{\text{rest}} = -70 \text{ mV}$ and leakage conductance. There are now 2 parallel pathways for membrane current: the capacitive current and the leakage current. 

$$I = C \frac{dV}{dt} + G_{\text{leak}} (V - V_{\text{leak}}).$$

Here $G_{\text{leak}}$ is total leakage conductance. Within NIA “membrane params” control window $g_{\text{leak}}$ (lower case or with overbar) is expressed as per unit area, specific conductance, so that $G_{\text{leak}} = A \times g_{\text{leak}}$ where $A$ is patch area.

a. The response (see next Fig) no longer rises linearly (as for a plain lipid bilayer) for I-step input. If I-step is held for very long time $V(t)$ levels off to a steady state value: $V_{ss}$ rather than continue rising. All of the injected current in that case exits the membrane through $I_{\text{leak}}$; that is, zero capacitive current at steady state (i.e., $dV/dt = 0$) and we have $I = G_{\text{leak}} (V_{ss} - V_{\text{leak}})$ from which we see that $V_{ss} = V_{\text{leak}} + I / G_{\text{leak}}$.

b. Initially, all of I-step is capacitive current (and $I_{\text{leak}}$ is zero); that is, $I=2 \text{ nA}$ and, from the plot of $I_{\text{cap}}$ (density) below, we have $I_{\text{cap}}$ (per unit area) $\times A \text{ (area)} = 0.02 \text{ mA/cm}^2 \times 0.0001 \text{ cm}^2 = 2 \text{ nA/cm}^2$. 

V_{\text{leak}}=-75 \text{ mV}, for setting the resting potential.
c. For intermediate times, \( I_{\text{cap}} \) decays as \( I_{\text{leak}} \) grows, proportional to \( V(t) - V_{\text{leak}} \) with an exponential approach of \( V(t) \) toward \( V_{\text{ss}} \):

\[
V(t) = V_{\text{ss}} + (V_{\text{leak}} - V_{\text{ss}}) \exp(-t/\tau)
\]

where \( \tau = C/G_{\text{leak}} \) -- \( \tau \) is the membrane time constant, also written as \( \tau = R_{\text{leak}} C \) where \( R_{\text{leak}} \) is the membrane resistance = \( 1/G_{\text{leak}} \).

d. We can use this theoretical result, this formula, to estimate \( \tau \). That is, at time \( \tau \) the depolarization of \( V \) (from rest) toward \( V_{\text{ss}} \) (from rest) is 62.3\% (= 1-1/e) complete. From this estimate of \( \tau \) we can estimate \( R_{\text{leak}} \) and thereby \( G_{\text{leak}} \)… Experimentally it is very difficult to estimate \( G_{\text{leak}} \) without such a formula/theory … why? You would need single channel conductance and then channel density…

e. **JR query.** The pt d, just above, leads to an estimate for \( G_{\text{leak}} \) based on a measurement of a single time point. We can do better. Since we know that the approach is exponential we could plot the time course on a log scale. To illustrate: let’s focus on the deviation of \( V \) from \( V_{\text{leak}} \) and call it \( v(t) \). Then the current balance eqn for \( v(t) \) is:

\[
I = C \frac{dv}{dt} + G_{\text{leak}} v.
\]

Suppose we start from some initial depolarization \( v(0) = v_0 \) then \( v(t) \) will decay toward is resting (steady) state with an exponential time course:

\[
(*) \quad v(t) = v_0 \exp(-t/\tau).
\]
To illustrate this see the following simulation in which I change $V_{\text{leak}}$ and $V_{\text{reset}}$ to zero and $g_{\text{leak}}=0.4 \text{ mS/cm}^2$ and duration of $I_{\text{step}}$ is 20 ms.

Now, at the end of the $I_{\text{step}}$ we see that $v=50 \text{ mV}$ (is it the correct value?) and the return to rest is a pure exponential, as in our formula (*) above.

If we knew how to plot log of $v(t)$ vs $t$ in NIA we would get a straightline: $\log v(t) = \log v_0 - \frac{t}{\tau}$ with negative slope $1/\tau$. This procedure to estimate $\tau$ is more robust since it uses the entire time course, not just a measurement at one time point.

Can someone discover how to make plots of log $V$ vs $t$ in NIA or Neuron?