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:

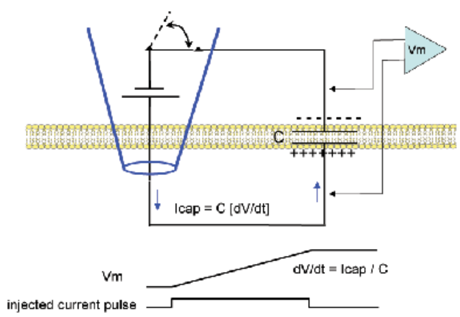
1. **The plain lipid bilayer.** Q = C V, Q is charge, the integral of injected/applied current I(t) and C is capacitance. C is total capacitance: $C=A * C_m$ where A is patch area (in cm^2) and C_m is specific capacitance, 1 microF/cm^2. Equivalently, the current equals the time derivative of Q (charge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

The equation for capacitive current, Icap.

Icap = C * [dV/dt]

or

dV/dt = Icap / C

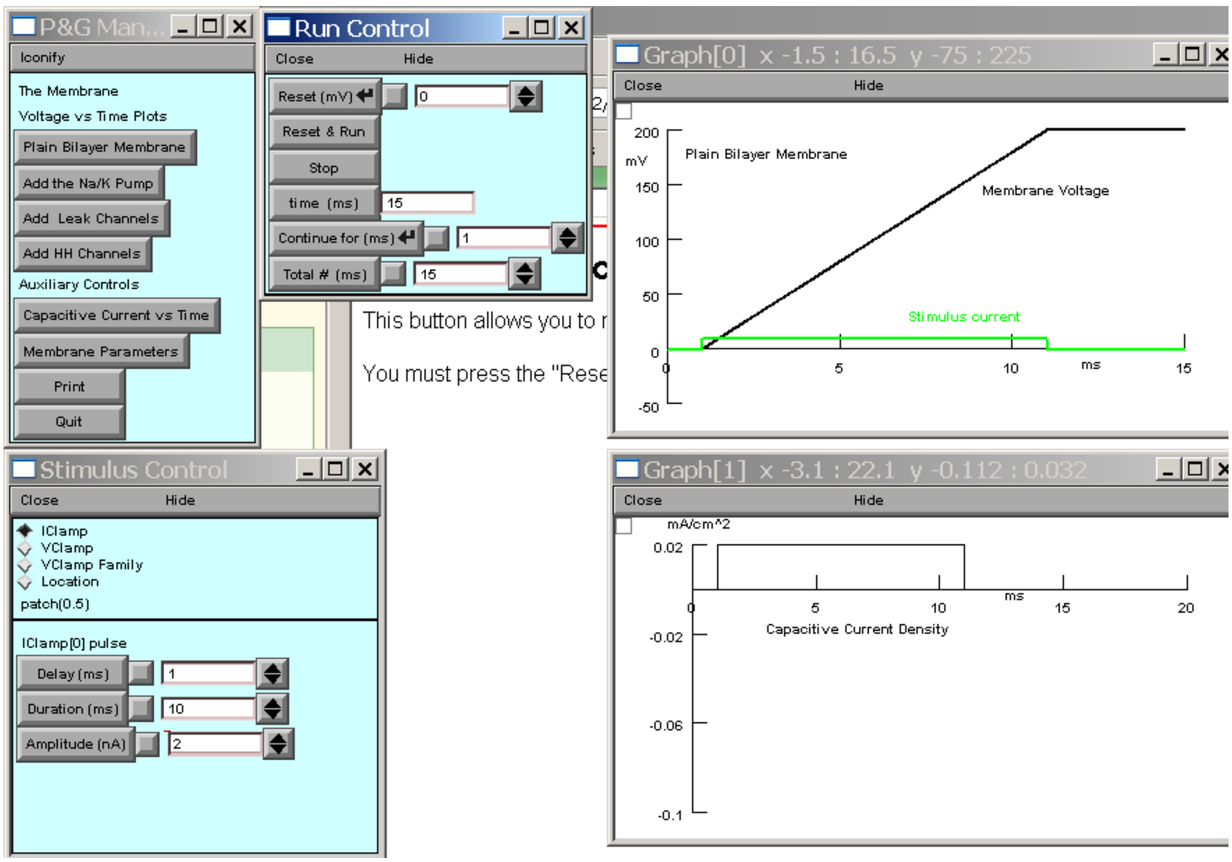


Note for a step current input:

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.

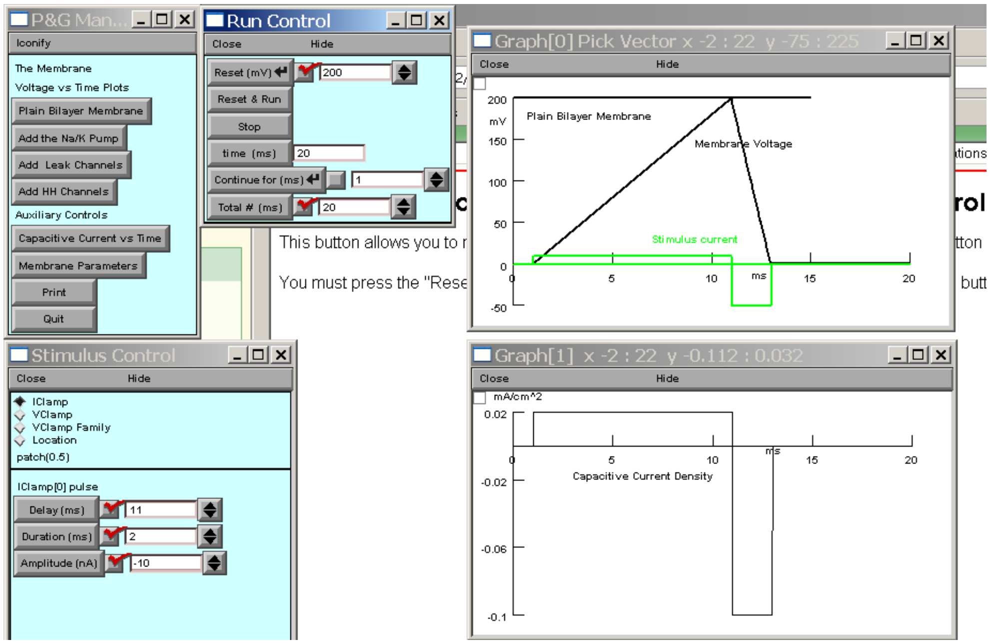
e. We can estimate C by measuring V=Vss (steady state) after the I-step, knowing the total charge injected: C=Q/V = I*T/V, where T is the step duration.

f. **JR query:** Suppose we wish to restore V to V=0 after the depolarizing I-step, with an oppositely directed current-step Ioff with duration Toff. What should the value of Ioff be? Notice, if Toff is chosen very small then dV/dt becomes very large and negative. In the limit as Toff 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: Ioff=-10 and Toff=2 ms that would begin at t=11ms. Rather I had to redo the simulation from "reset Voltage" of 200 mV. See next page.

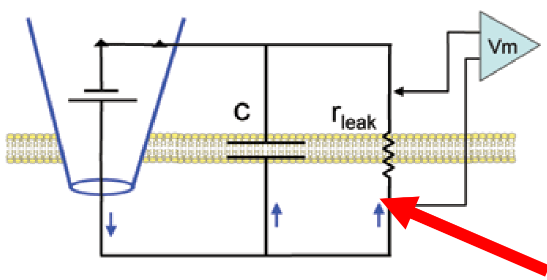
Can you come up with a scheme to use "Continue for ms" after changing the Current Params?



2. **Adding V_{rest}= - 70 mV and leakage conductance.** There are now 2 parallel pathways for membrane current: the capacitive current and the leakage current.

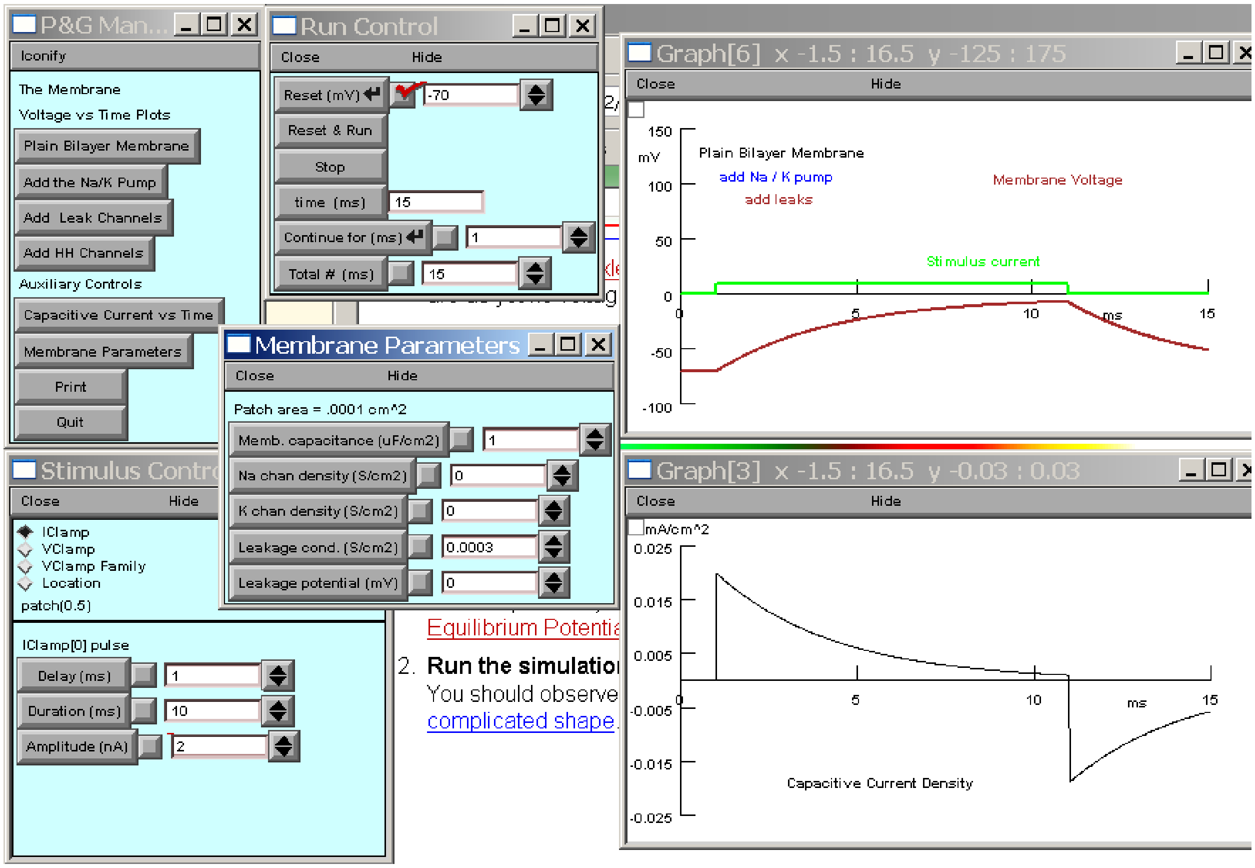
$$I = C\, dV/dt + G_{leak}\,(V-V_{leak}).$$

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



There should be a leakage battery here Vleak=-75 mV, for setting the resting potential.

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_{leak}; that is, zero capacitive current at steady state (ie, dV/dt=0) and we have $I = G_{leak}\,(V_{ss}-V_{leak})$ from which we see that $V_{ss} = V_{leak} + I/G_{leak}$.
b. Initially, all of I-step is capacitive current (and I_{leak} is zero); that is, I=2 nA and, from the plot of Icap (density) below, we have Icap (per unit area) * A (area) = $0.02\ mA/cm^2 * 0.0001\ cm^2 = 2\ nA/cm^2$.



c. For intermediate times, Icap decays as I_{leak} grows, proportional to $V(t)-V_{leak}$ with an exponential approach of V(t) toward V_{ss}: $V(t)= V_{ss} + (V_{leak} - V_{ss}) \exp(-t/\tau)$ where $\tau=C/G_{leak}$ -- τ is the membrane time constant, also written as $\tau=R_{leak} C$ where R_{leak} is the membrane resistance = $1/G_{leak}$.

d. We can use this theoretical result, this formula, to estimate τ. That is, at time τ the depolarization of V (from rest) toward V_{ss} (from rest) is 62.3% (= 1-1/e) complete. From this estimate of τ we can estimate R_{leak} and thereby G_{leak} … Experimentally it is very difficult to estimate G_{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_{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_{leak} and call it v(t). Then the current balance eqn for v(t) is:

$I= C\, dv/dt + G_{leak}\, v$. Suppose we start from some initial depolarization $v(0) = v_o$ then v(t) will decay toward is resting (steady) state with an exponential time course:

(*) $v(t) = v_o \exp(-t/\tau)$.

To illustrate this see the following simulation in which I change V_{leak} and V_{reset} to zero and g_{leak}=0.4 mS/cm^2 and duration of I_{step} is 20 ms.

Now, at the end of the I_{step} we see that v=50 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: $\log v(t) = \log v_o - t/\tau$ with negative slope $1/\tau$. This procedure to estimate τ 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?