Spike Threshold

The exact value of the depolarization required to trigger an all-or-none spike can be found by solving the Hodgkin-Huxley equations numerically on a computer. However, valuable insight into the underlying mechanism can be gained by considering a simplified version of the equations graphically. We will assume that a short current pulse has been applied which depolarizes the membrane to near threshold. The question is, will the membrane potential trajectory after the end of the current pulse be *hyperpolarizing* (as it would be in a passive cell, since the potential tends to return to its resting value) or *depolarizing*?

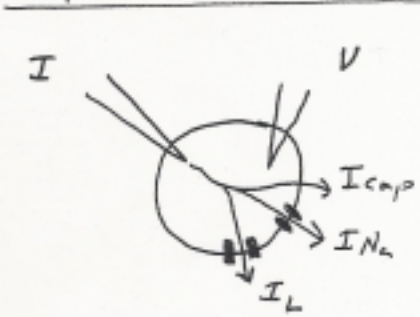
We will assume, for the moment, that inactivation of the sodium channels and activation of potassium channels is much slower than activation of sodium channels, which we will approximate as instantaneously activating (on the time scale of the passive membrane time constant). These are reasonable approximations.

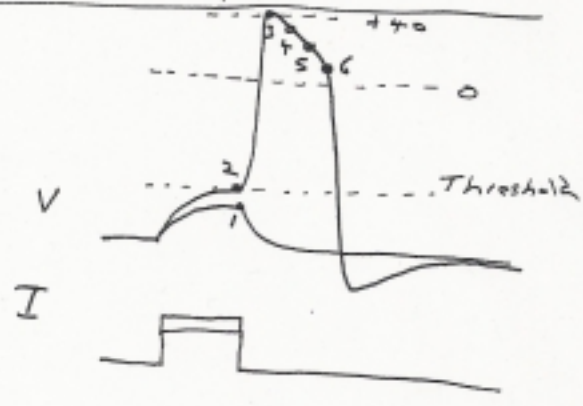
We can diagram the current-voltage relation for the leakage channels as a shallow straight line passing through the resting potential (see I_L on handout). We can also, on the same graph, diagram the I-V relation for the sodium channels (see I_{Na}). The curve for I_{Na} follows from the voltage dependence of m^3. Make sure you understand the shape of this curve.

Figure Legend The top left diagram shows the experimental situation with a small isopotential patch of membrane (for example the cell body of a nerve cell, or a squid giant axon with a wire along its axis). Current is applied through one electrode and voltage recorded with another electrode. We assume that the potassium channels activate very slowly, so they can be ignored. We also assume that the sodium channels activate very fast, and that they inactivate very slowly (i.e. the HH rate constants for *m* are much faster than the *n* and *h* rate constants). The applied current can either flow through the leak channels, through the sodium channels or through the membrane capacity. The diagram on the top right shows the way the membrane potential will change following small depolarizing current pulses that are either just subthreshold or just suprathreshold. The lower graph shows current-voltage relations for the leak current (straight line) or the sodium current (solid curve, a).

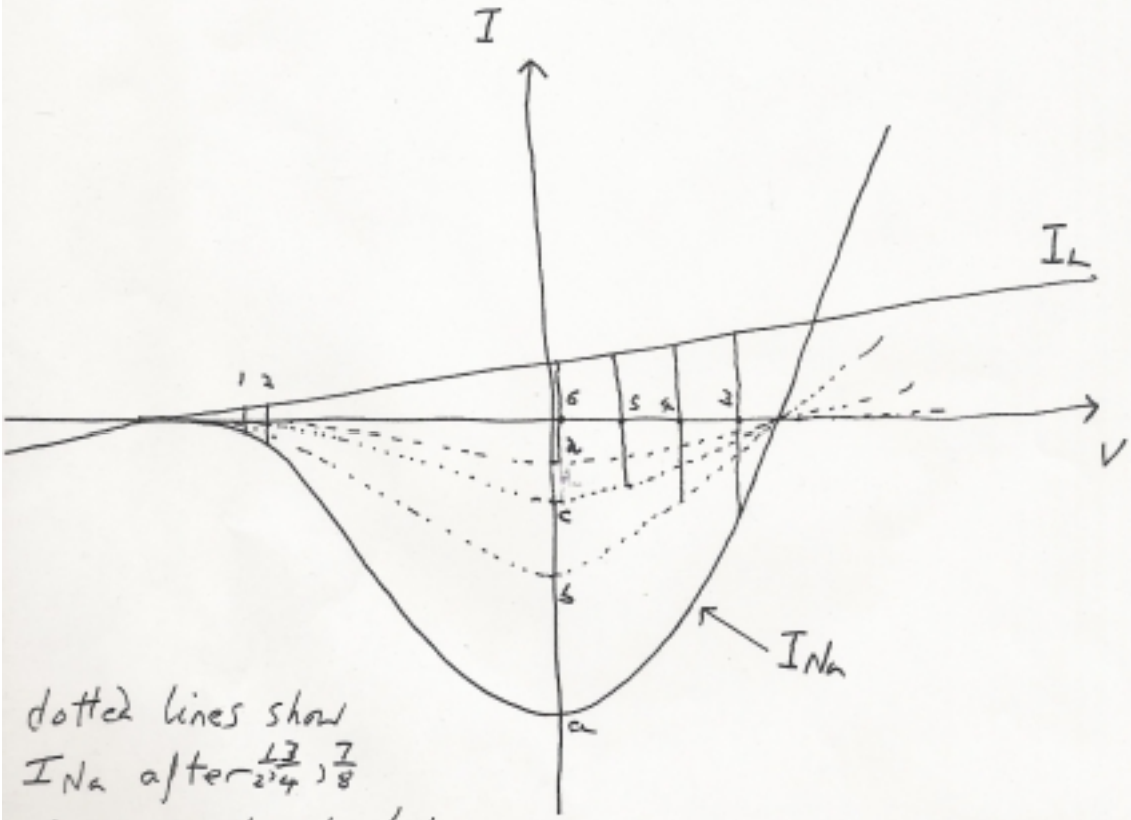
At the end of the current pulses, there is no net current crossing the membrane. Therefore the capacity current must equal the net ionic current. The net ionic current is equal to the sum of the (typically outward) leak current and the (typically inward) sodium current. For the just subthreshold condition, the membrane voltage at the end of the pulse is at level 1, which corresponds to a net outward ionic current, which will therefore generate a hyperpolarisation, back towards the resting potential where the net ionic current is zero. But for the just suprathreshold current pulse, the membrane potential at the end of the pulse is at level 2, where the small inward sodium current just exceeds the small outward leak current, generating a net inward current, which will depolarize the membrane potential. As the potential depolarizes, the net ionic current will become even more inward, causing further depolarization. The membrane potential will continue to depolarize until point 3 is reached, where the outward current again balances the inward current. If the sodium channels did not inactivate, and potassium channels did not activate, the membrane potential would stay at this new stable point indefinitely; however, the inactivation of the sodium channels reduces the inward current , forcing the membrane potential to change to points 4 (when half the Na channels inactivate, dotted curve b), and then point 5 (three quarter inactivation, curve c). When all but 1/8 of the sodium channels have inactivated, the potential shifts to point 6, where the leak current always exceeds the sodium current, causing rapid regenerative repolarisation to the *only* potential at which inward and outward now balance, the original resting potential. (Actually, there is also potassium activation, which causes additional outward current, and an afterhyperpolarisation).

Spike Threshold and Repolarization





Assume
$\alpha_m, \beta_m \gg \alpha_h \beta_h, \alpha_n \beta_n$



dotted lines show
I_{Na} after $\frac{1}{2}, \frac{3}{4}, \frac{7}{8}$
of sodium channels have inactivated

Imagine the cell is depolarized to various potentials (see handout). If the depolarization is very small, reaching only the level marked 1, then the net ionic current at the end of the current pulse will be outward (since the outward leak current exceeds the inward sodium current). Since the total membrane current is zero, this outward leak current must be balanced by an inward capacity current, which means that the membrane must be hyperpolarizing at the end of the current step. If the applied depolarization is slightly larger (point 2), the net ionic current is inward, and the membrane will depolarize at the end of the pulse. This depolarisation will cause an immediate increase in I_{Na} which causes further depolarisation, until the net ionic current becomes zero (point 3) at a voltage just short of E_{Na}. These depolarisations correspond to the rising phase of the spike (which will be limited by the maximum possible size of I_{Na} and the membrane capacity). At the peak of the spike the membrane potential is briefly stable, but now the sodium channels start to inactivate (dotted curves). For the dotted curve labeled b, half the sodium channels have inactivated, shrinking the available sodium current, so that the membrane potential is briefly stable at point 3. As I_{Na} inactivates further, the stable membrane potential falls to 5 then 6. At this point, even the maximum possible remaining I_{Na} is smaller than the corresponding leakage current, so the net ionic current becomes outward, and the membrane repolarises further. It will repolarise regeneratively until all the sodium channels close and the membrane potential turns to rest. It will take some time for channels to recover from inactivation, so in the immediate aftermath of a spike, a second spike cannot be elicited (absolute refractory period). When sufficient Na channels have recovered, a reduced amplitude spike is possible, although it will have an increased threshold (relative refractory period). Eventually all sodium channels will recover, and a normal spike can be elicited again.

Solving HH equations on the computer.

In the HH equations dV/dt depends on I_{Na} which depends on G_K which depends on m which depends on α which depends on V. This vicious circle means that the equations cannot be “solved” except approximately, on a computer. To do this we approximate dV/dt as $\Delta V/\Delta t$, where ΔV is the (hopefully) small voltage change occurring in a small time interval Δt. To a first approximation the change in V in the small time step will be proportional to the ionic current, which can be calculated from the initial values of m,h and n appropriate to the resting potential. We can then calculate small changes in m,h and n using an analogous approximation to their kinetic equations, and update their values ready for the next small time step. In this way the whole time course of the membrane potential can be reconstructed. It is necessary to check that the time intervals chosen are sufficiently small that the results do not depend on the time interval. One could view the real membrane as “solving” the HH equations using an infinitely small time step.