Lecture notes computational neuroscience 2012: lecture 2

In this lecture we will be looking at neural models at various levels of complexity and arrive at a simple, computationally effective model for representing the variety of spike patterns of neurons. We follow the discussion in the Izhikevich book [1].

The simplest spiking model is the leaky integrate and fire (LIF) neuron. The membrane potential is given by the following equation

$$C\dot{V} = -g_L(V - E_L) + I$$

together with the prescription that when V crosses the threshold value V_{thr} (typical value -50 mV), a spike is called and it is reset to V_{reset} (typical value -65 mV). The parameters in these equations are the capacitance C (typical value 300 pF), leak conductance g_L (typical value 10 nS), reversal potential E_L (typical value -60 mV), depolarizing current I (in the nA range). This leads a time scale $RC=C/g_L$ of about 30 ms, which is representative for pyramidal cells.

We can perform a dynamical analysis on this equation as before by setting the time derivative to zero: $C\dot{V} = 0 \Rightarrow I - g_L(V - E_L) = 0$ which gives a fixed point value of $V_{FP}=(I/g_L + E_L)$. The stability of this point is given by the derivative $f(V)=-g_L$, which is always negative, hence this FP is stable. When V_{FP} is lower than V_{thr}, the neuron will not spike because the membrane potential will be stuck at the fixed point. If it is higher the neuron will go through threshold before reaching the fixed point, and at that point it will be reset to V_{reset} after which the cycle starts again (the membrane potential will again increase towards V_{FP} and hit threshold). A periodic sequence of spikes will result (Figure 0). One can interpret this behavior as a limit cycle.

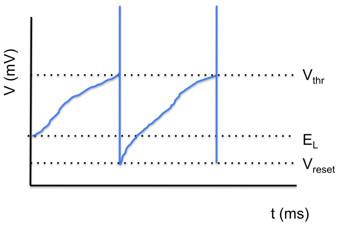

Figure 0. Leaky integrate-and-fire neuron

Self-test 1: What is the mean firing rate of such a neuron as a function of I?

In the Hodgkin-Huxley model, the leak current is augmented with terms representing voltage-activated channels. To see what this does, we start by including one current:

$$C\dot{V} = -g_L(V - E_L) - gp(V - E) + I$$

with $\dot{p} = (p_\infty(V) - p)/\tau(V)$.

Here g is the maximum conductance when all the channels are open, and p represents the fraction of them that are open at a particular time. For a constant membrane potential V, this fraction converges to $p_\infty(V)$ with a time constant $\tau(V)$. To make the analysis simpler, we assume that the voltage varies at a slower time scale compared to the time scale of the p dynamics, so that we can use the asymptotic value for the latter:

$$C\dot{V} = -g_L(V - E_L) - gp_\infty(V)(V - E) + I = I - I_\infty(V)$$

For persistent sodium we have E=60 mV and

$$p_\infty(V) = \frac{1}{1+e^{-(V-V_{1/2})/k}}$$

(note that the convention is to use m as the symbol for persistent sodium instead of p, in our example we set the midpoint $V_{1/2}$ to -54mV and k is 9mV).

Figure 1 shows the activation function m_∞ as a function of V. The channel opens when the voltage exceeds -54 mV, and because it does not inactivate it stays open.

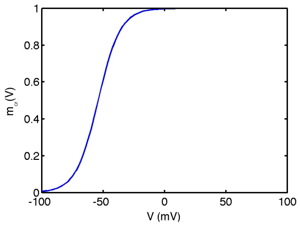

Figure 1. Activation function

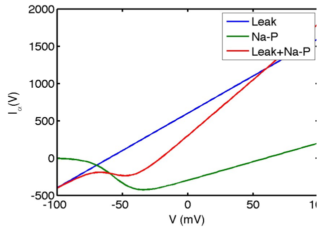

Figure 2. Currents charging the membrane are comprised of a leak and persistent sodium current.

Figure 2 shows $I_\infty(V)$ as a sum of the linear leak current (leak) and the nonlinear persistent sodium (Na-P) current.

Figure 3 shows $F(V) = I - I_\infty(V)$ for three different values of I. The fixed points are defined by the solution to F(V)=0, because then the voltage does not change anymore in time. Depending on the value of I there are either 1 or 3 V values for which this holds. The stability of the fixed points is determined by the derivative of F(V) at the fixed point. Negative means stable, this is indicated by the direction of tangent. For the highest current value, there is only a stable high voltage FP, whereas for the lowest current there is only a stable low voltage FP.

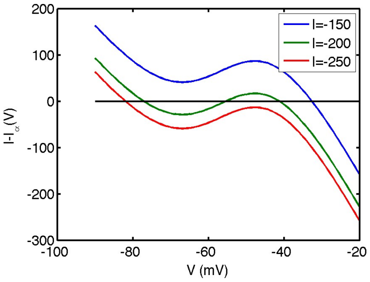

Figure 3. The number of zeros of F(V) depends on current offset.

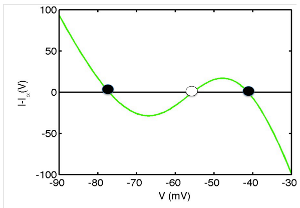

Figure 4. Stability of FP for I=-200.

Figure 4: For an intermediate current value there is a low and high voltage stable FP and an intermediate voltage unstable FP.

Figure 5. The unstable FP acts as a separatrix. When a voltage starts below the unstable FP, it will converge to the low-V stable FP, whereas when it starts above the unstable FP will converge to the high-V stable FP. Hence, one could view the voltage value for the unstable FP as the action potential threshold.

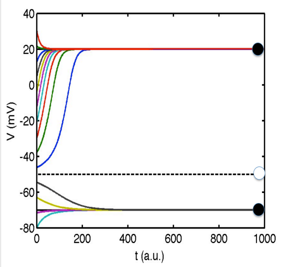

Figure 5. Convergence to stable FPs (filled circles) away from the unstable FP (open circle).

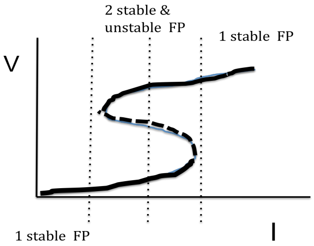

Figure 6. Bifurcation diagram.

Figure 6. The behavior as a function of I can be summarized in a bifurcation diagram where the voltage value of the FPs is plotted for each value of V, with their stability indicated by the line style (unstable: dashed, stable: solid line). From this we recover the features shown in Figure 3: low I and high I only one stable FP and for intermediate I values, 2 stable FPs and 1 unstable FP.

Although the one-dimensional model has something like an action potential threshold, is does not have an action potential. Once the neuron is in the high voltage FP it will stay there. For action potentials, we need limit cycles, hence a two-dimensional model such as the Morris-Lecar model introduced earlier. We need to take a gating variable as the second variable and we need another current to counterbalance the sodium current that generates the high-voltage stable FP. The potassium current will return the neuron to near the resting potential, in a way similarly to the resetting in the leaky integrate-and-fire model. The assumption is that the sodium current is fast, hence that the slower gating variable n of the potassium current is the second variable. This variable activates for high voltage values.

$$C\dot{V} = I - g_L(V - E_L) - g_{Na}m_\infty(V)(V - E_{Na}) - g_K n(V - E_K)$$

$$\dot{n} = (n_\infty(V) - n)/\tau(V)$$

Note: for numerical exploration you can use, in standard units, C=1, E_L=-80, g_L=8, g_K=10; $V_{1/2}$=-20, k=15 for m_∞(V); $V_{1/2}$=-25, k=5 for n(V) and τ=1, E_{Na}=60,E_K=-90.

To understand the resulting limit cycle, we need to construct the null clines. The first one, $\dot{V} = 0$ yields $n = f(V)$ whereas the second one yields $n = n_\infty(V)$. Note that

$$f(V) = (I - g_L(V - E_L) - g_{Na}m_\infty(V)(V - E_{Na}))/g_K(V - E_K)$$

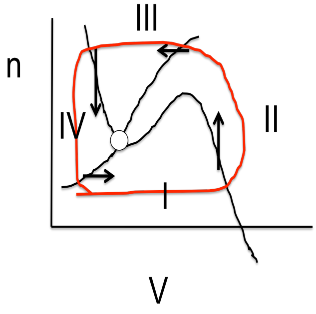

Figure 7. Phase plane of model with high threshold potassium current.

The details of these functions are not relevant except for their typical shape. The first one is similar to the case discussed before, and can be approximated by a cubic polynomial, whereas the second one is sigmoidal. These null clines are sketched in Figure 7. There is a limit cycle when the FP at the intersection between the null clines is unstable. The limit cycle corresponding to an action potential then has four stages. I: The upstroke, where the voltage increases, but n does not yet increase. II: At the peak the n gate is open and balances the current coming in through the sodium channels. III: repolarisation, the potassium current dominates and brings the V back to near resting values; IV: relative refractory period, the n variable needs to decrease so that the neuron can spike again.

In general the analysis of these null clines is difficult and it is helpful to approximate them by simple functions that have approximately the same shape. The Fitzhugh-Nagumo is an example of this

$$\begin{aligned}\dot{V} &= V(a-V)(V-1) - w + I \\ \dot{w} &= bV - cw\end{aligned}$$

The V null cline is replaced by a cubic polynomial and the sigmoid by a linear function. Because this form has only a few parameters a systematic analysis can be attempted. Figure 8 illustrates what happens with the number of fixed points when the slope of the w null cline is reduced (by reducing c/b).

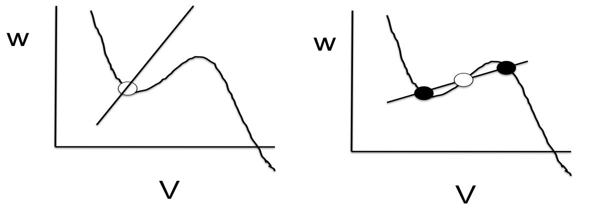

Figure 8. Number of fixed points in Fitzhugh-Nagumo model depends on the tangent of the w null cline.

The next step is to recognize bifurcations that occur in neuroscience context.

Case 1. In the saddle-node bifurcation a stable equilibrium disappears in the presence of a stable limit cycle, as illustrated in Figure 9-top. In the bottom panel, the voltage trace is shown when the current is increased over time. When the voltage is near rest, and the current is increased, it stays near rest until the stable FP defining the rest potential disappears when it merges with the unstable FP (saddle-node). At this point the neuron converges to the stable limit cycle and starts spiking. This scenario has the following properties: (1) no subthreshold oscillations, (2) nonzero amplitude of the action potentials after the bifurcation, (3) firing starts at nonzero frequencies. This bifurcation occurs at I=4.51 in the aforementioned V-n system.

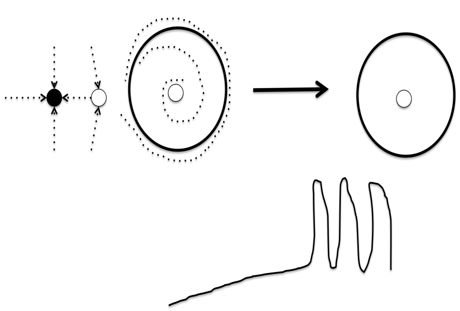

Figure 9. Saddle-node bifurcation, outside the limit cycle

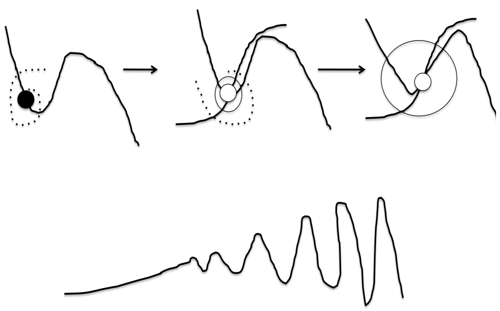

Figure 10. Supercritical Hopf.

Case 2. Supercritical Hopf bifurcation. Below the bifurcation point there is a stable FP (an inward spiral), which bifurcates into an unstable FP and a stable limit cycle, which grows in amplitude. This bifurcation is characterized by (1) subthreshold oscillations because of the spiral, (2) amplitude at bifurcation is zero, growing roughly as the square root of the bifurcation variable; (3) spiking frequency jumps directly to a nonzero value.

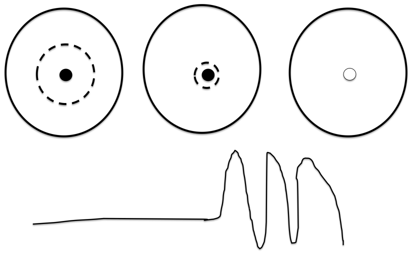

Figure 11. Subcritical Hopf (stabilized)

Case 3. A subcritical Hopf is also possible, but does not change much. Initially, there is a stable FP, inside an unstable LC, which itself is inside a stable LC (this needs to be the case for stability reasons, otherwise the system will diverge for some initial condition. The radius of the unstable LC will shrink until it merges with the stable FP. At the point all that remains is an unstable FP, together with the stable LC. Hence, the neuron will jump from its rest potential directly to a finite amplitude periodic spike train. The bifurcation has the following features: (1) subthreshold oscillations, (2) firing starts at a non-zero amplitude, (3) spiking frequency jumps directly to a nonzero value.

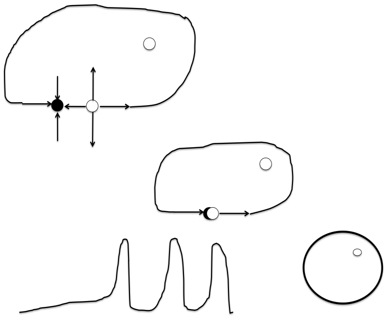

Figure 12. SNIC bifurcation.

Case 4. A saddle-node on an invariant circle (SNIC). Initially there is a heteroclinic orbit from the unstable FP to the stable FP, going around the high-V unstable FP. The unstable and stable FP merge (saddle-node), generating a homoclinic orbit at the bifurcation. Above the bifurcation the saddle-node has disappeared and only the stable limit cycle remains. The bifurcation has the following features: (1) no subtreshold oscillations, (2) amplitude at onset nonzero, (3) frequency starts at zero at the bifurcation as it is proportional to the square root of the distance to the bifurcation point.

We can now relate this transition to the behavior of real neurons.

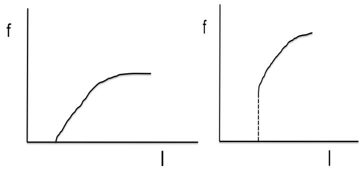

Figure 13. (Left) Class I and (right) II firing rate vs current curves.

First, some terminology. A neuron is excitable, when you can push it out of its stable FP, to which it then returns via an action potential. Hence, it will not fire spontaneously, because for each action potential you need to stimulate it. It is oscillatory when there is a stable LC and the neuron then fires a repetitive train of action potentials. It is bistable when it has both a stable FP and a stable LC. Hence it can go from quiescent to periodically spiking and vice versa, using a current pulse.

Nobel Laureates Hodgkin & Huxley distinguished two (actually three) classes of firing based on the firing rate versus current curve. For the class 1 neuron, the neuron can fire at an arbitrarily low firing rate, whereas for a class 2 neuron, it jumps from zero to a finite firing rate, and it can not fire at rates between 0 and the onset firing rate. The question is whether this implies that class 1 and class 2 have a different bifurcation from quiescent (non-spiking, stable low V FP) to spiking. From our discussion above we have that class 1 is consistent with SNIC (saddle-node on invariant circle) because that one starts at arbitrarily low frequencies, whereas class 2 is consistent with the other three (super/subcritical Hopf and saddle-node not on the circle)

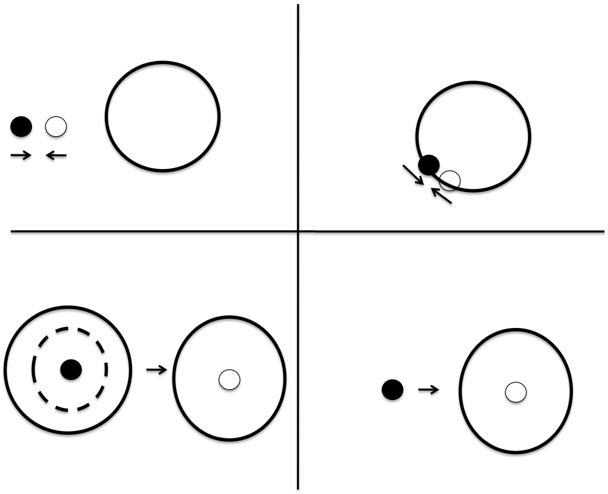

Figure 14. Schematic of the four bifurcation involving loss of stability of the quiescent state.

There are two other defining characteristics. These are whether a neuron is a resonator, displaying subthreshold oscillations, or an integrator in which case it does not display subthreshold oscillations. And whether the neuron is bistable or not. These map onto the four bifurcations we encountered, as shown in the table and illustrated schematically in Figure 14.

	Bistable (coexisting quiescent state)	Monostable
integrator	SN	SNIC
Resonator (subthreshold oscillations)	Subcritical Hopf	Supercritical Hopf

Self-test 2. Describe the scenario for each of the bifurcations in Figure 14 and how they account for being an integrator/resonator or being monostable/bistable.

The distinction resonator/integrator is an important one. When a resonator is perturbed in its quiescent state, it will return to it via an inward spiral in the phase plane, which means that an oscillatory membrane potential is obtained. Furthermore, noise, which will perturb the neuron away from the fixed point, will therefore lead to sustained subthreshold oscillations. When a periodic current is injected, the amplitude of the corresponding oscillation will depend on the frequency. This can be plotted in an amplitude versus frequency graph. For a resonator a curve with a peak at finite frequencies is obtained, this frequency value is referred to as the resonance frequency. Likewise, when the neuron gets inputs in the form of a periodic train of postsynaptic conductances, the response of the neuron will depend on the period. Under the circumstances where the neuron is quiescent, it may respond with a spike for intermediate frequencies near the resonant frequency, but for much higher frequencies it will not spike.

The integrator behaves in the opposite way: it will spike most for input spike trains with the highest frequency. Furthermore, its amplitude versus frequency curve will have its maximum value for zero frequency, hence it looks like a low-pass filter.

To represent these properties, a model more complicated than the leaky integrate-and-fire neuron is needed. One example would be the Fitzhugh-Nagumo or Morris-Lecar model. Unfortunately, these models are complicated to parameterize. The Izhikevich models are also two-dimensional, but are characterized by only a few parameters.

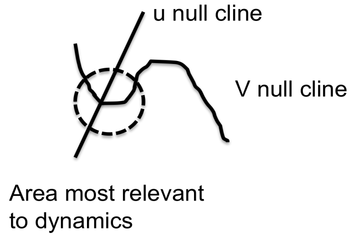

Figure 15. Reduction of dynamics to a quadratic function by focusing on the left knee.

The V null cline has a cubic character with two knees (local minimum for low V, local maximum for high V). The key realization is that the behavior is mostly determined by the left knee, which can then be parameterized in terms of a quadratic function. The problem is that we only have half of the limit cycle, because neurons will have membrane potentials going to infinity. To solve this a voltage threshold is set, and a reset introduced. The standard notation is to use lower case v in this model. Taken together, this yields:

$$\begin{aligned}\dot{v} &= I + v^2 - u \\ \dot{u} &= a(bv - u)\end{aligned}$$ together with if v larger than or equal 1 it is reset $$\begin{aligned}v &= c \\ u &= u + d\end{aligned}$$

The parameters are: the depolarizing current I (bifurcation parameter), which could also be time-varying; the time scale 1/a of u relative to v; the tangent b of u null cline, this determines how many intersections there are (and where); the reset value c of the voltage; the addition d to u after reset, this can incorporate the effect of adaptation. Here adaptation means that in a repetitive spike train the firing rate decreases over time, saturating at a lower value.

The above form is unit less, and has therefore the fewest parameters and is best suited for analysis. For comparison to experiment it is useful to have the correct voltage (mV), time (ms) and current scale (pA):

$$\begin{aligned} C\dot{v} &= I + k(v - v_r)(v - v_t) - u \\ \dot{u} &= a(b(v - v_r) - u) \end{aligned}$$ together with if $v > v_{peak}$ it is reset to $$\begin{aligned} v &= c \\ u &= u + d \end{aligned}$$

For a L5 pyramidal cells the following parameters are representative a=0.03, b=-2,c=-50 mV (reset), d=100, v_{peak}=35 mV, v_r=-60 mV (rest voltage), v_t=-40 mV (threshold), k=0.7, C=100 pF. This model is characterized by the following experimentally measurable quantities. The model was fitted to have a threshold current I=50 pA (current at which the neuron starts spiking), the input resistance 80 MΩ (voltage change divided by the current change producing it) and an RC time (membrane time constant) of approximately 8 ms.

Self-test 3: Show how you can extract these quantities from the model parameters. This can be done analytically, but if you wish, you could also simulate the model.

1. Izhikevich EM (2007) Dynamical systems in neuroscience : the geometry of excitability and bursting. Cambridge, Mass.: MIT Press. xvi, 441 p. p.