School of Mathematical Sciences

XPP Worksheet - to be handed in to the School office by 2pm Feb 15th.

In this worksheet we will explore the properties of a number of single neuron models using XPP and a set of pre-written .ode files. These are available at

http://www.maths.nott.ac.uk/personal/sc/cnn/#ODE

Conductance based models are all written in the form of a current-balance nonlinear differential equation:

$$C\frac{dV}{dt} = I_{ion} + J,$$

where C is the membrane capacitance, V the membrane voltage, I_{ion} represents all ionic membrane currents and J represents externally injected current. Ionic currents have the generic form

$$I_{ion} = g_{ion} m h (V_{ion} - V).$$

Here g_{ion} is the conductance of the ionic current, m, h are (activating, inactivating) gating variables, and V_{ion} is the reversal potential. The gating variables are *dynamic*, and evolve in time according to nonlinear differential equations. The art of ionic current modelling is in finding the best set of gating dynamics!

The Hodgkin-Huxley model – `HodgkinHuxley.ode`

This is the standard model of excitable neural membrane, and forms the basis for many detailed biophysical single neuron models. It has three ionic currents, due to the flow of sodium (I_{Na}), potassium (I_K), and all other ions (I_L), so that $I = I_L + I_{Na} + I_K$, with

$$I_L = g_L(V_L - V), \qquad I_{Na} = g_{Na} m^3 h (V_{Na} - V), \qquad I_K = g_K n^4 (V_K - V).$$

1. Run the .ode file (`Initialconds - Go`) to see a periodic train of action potentials. Plot the gating variables m, n, h and the currents I_L, I_{Na}, I_K (use `Xi vs t` and `Window - Fit`). Describe their evolution during an action potential and comment on the relative values of the membrane reversal potentials V_L, V_{Na}, V_K. Plot n vs h (using `Viewaxes - 2D`) during an action potential and show that there is a roughly linearly relationship between n and h.

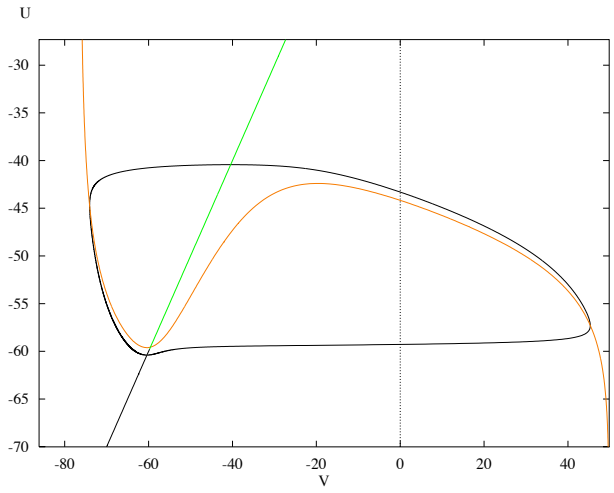
2. Evolve the model with the external input J at $J = 0$ and $J = 200$. Comment on what you see, and then find the window of J values that allow the model to fire periodically.

3. Comment on how the frequency of firing changes with increasing J.

4. Vary the reversal potentials for Na and K, namely V_{Na} and V_K, to more hyperpolarised values to see if you can abolish action potential generation. How might you achieve this experimentally?

A reduced Hodgkin-Huxley model – `HHReduced.ode`

The Hodgkin-Huxley model is described by four nonlinear differential equations (one for the voltage V, and three for the gating variables m, n, h). However, the dynamics of m is fast compared to that of n and h and so it can be set to its steady-state value (called m_∞). Numerical experiments also show that n and h are slaved (i.e. if we know one of them we can work out the other - see Q1. of Hodgkin-Huxley model). Thus we arrive at a reduced version of the Hodgkin-Huxley model, described by only two variables – one for the voltage V, and the other for the variable U.



1. Run the reduced model and compare it with the full Hodgkin-Huxley model. Comment on the similarities and differences for various values of I.

2. 2-D models are much easier to visualise than 4-D models! Plot an action potential in the (V, U) plane (similar to the one shown). Nullclines are boundaries between regions where V or U is increasing and decreasing. Nullclines can be found in XPP using `Nullclines - New`. The intersections between V and U nullclines are equilibrium or rest points.

   Plot the nullclines for $I = 0, 50, 200$ and comment on the behaviour you see when evolving the model in time. Can you explain what you see using the geometry of the figure?

3. For $I = 0$ evolve initial data with $(V, U) = (-65, -40)$ and $(V, U) = (-20, -60)$ and explain the different behaviours you observe.

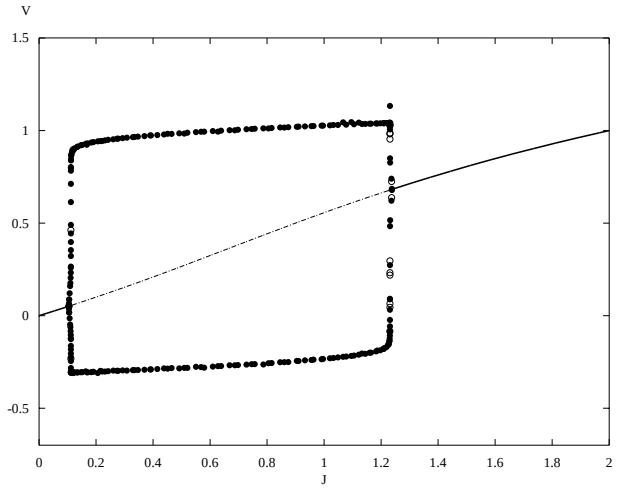
The FitzHugh-Nagumo model – `FitzHughNagumo.ode`

The FitzHugh-Nagumo is also a 2D model, with variables (v, w). Although not directly derived from the original Hodgkin-Huxley model it has many of the same qualitative features. v is like the membrane potential V, and w plays the role of a recovery variable incorporating the dynamics of the three variables m, n, h.

1. Plot action potentials and nullclines (with varying I) for this model and compare with both the full and reduced Hodgkin-Huxley models

2. For $I = 0$ and $(v, w) = (0, 0)$ run the AUTO program using `File - Auto`. This program can track steady states as a function of the drive I. It can also detect *Hopf bifurcations* -

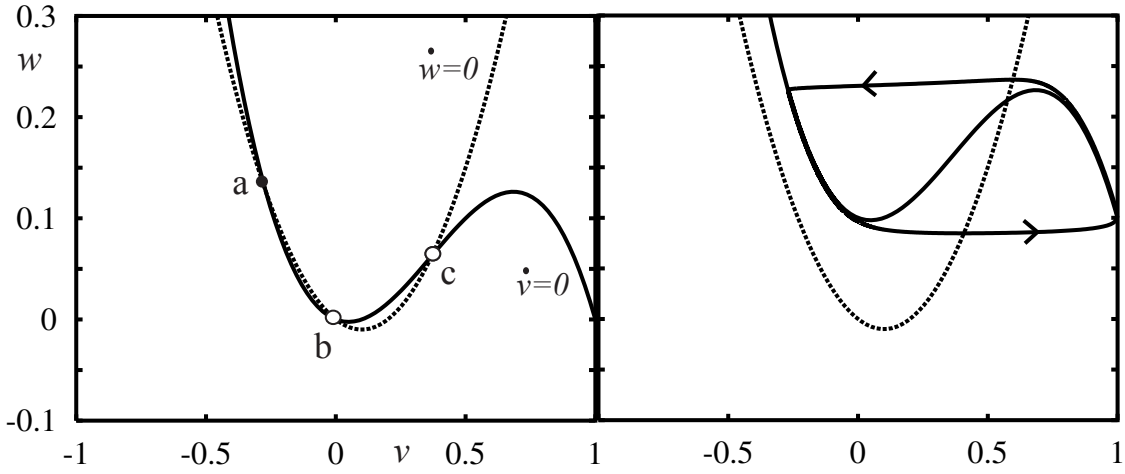
points where the steady state goes unstable and a stable limit cycle (periodic train of action potentials) emerge. Choose `Run - Steady state`, then `Grab` and the tab to the point labelled 2, then `Run - Periodic` to obtain a bifurcation diagram like the one below. Thick (dashed) lines denote stable (unstable) rest states. The filled circles denote the amplitude of periodic orbits (action potentials). Check that this diagram summarises the behaviour you have seen in XPP. Can you repeat the process for the Hodgkin-Huxley model?



A cortical neuron model – `cortical.ode`

Many of the properties of a real cortical neuron can be captured by making the dynamics for the recovery variable of the FitzHugh-Nagumo equations *nonlinear* (in fact quadratic).

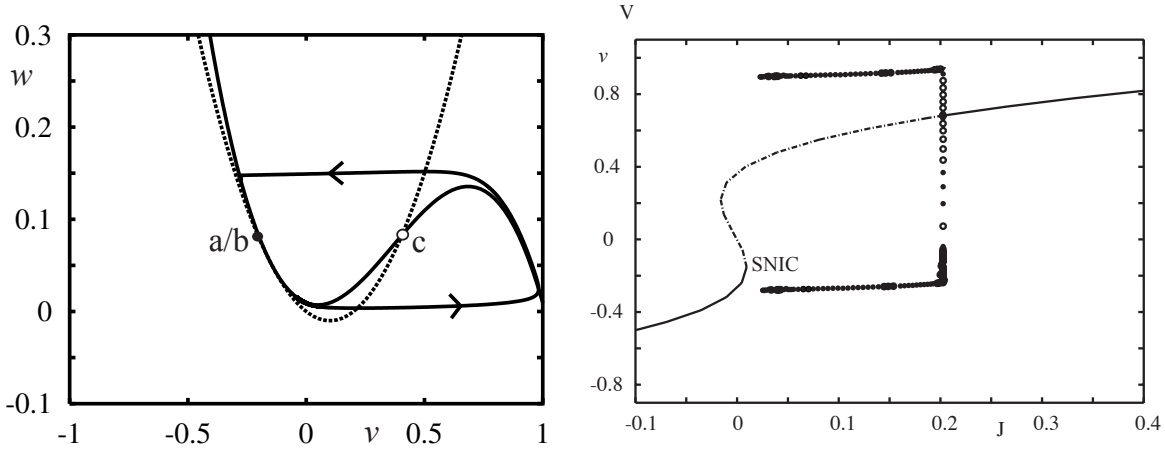
1. Use XPP to check that in addition to the single fixed point of the FitzHugh-Nagumo model (denoted by (c)) it is possible to have another pair of fixed points denoted by (a) and (b). As J increases (a) and (b) can anhilate in a saddle node bifurcation - see figure.



Phase portrait for cortical neuron model with quadratic recovery variable. Left: J=0. Right: J=0.1, with stable limit cycle.

2. Use XPP to check that for large enough J there is only one fixed point (c) on the middle branch of the cubic. In this instance an oscillatory solution occurs via the same mechanism

as for the FitzHugh-Nagumo model - see figure.



Left: Saddle-node on invariant (limit) cycle (SNIC) bifurcation at $J_c \sim 0.009396$. Right: Full bifurcation diagram.

3. Comment on the frequency of oscillations as the point SNIC is approached with decreasing J. Contrast the frequency trend with that of the Hodgkin-Huxley model.

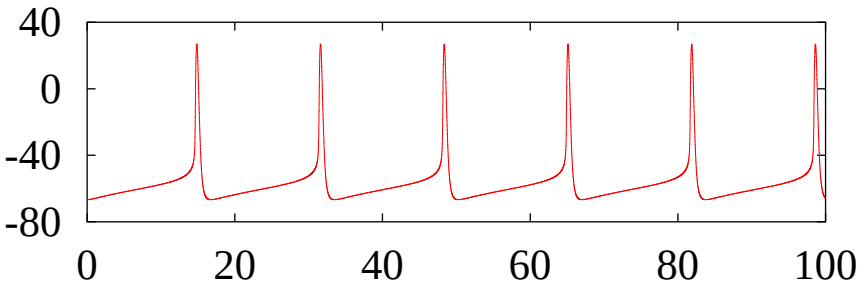
The Pinsky-Rinzel model – `PinskyRinzel.ode`

The two-compartment Pinsky-Rinzel model of a hippocampal CA3 pyramidal neuron consists of electrically coupled soma and dendritic compartments, each with active ionic conductances. The soma compartment contains a fast inward sodium current I_{Na} and an outward potassium delayed rectifier current I_{K-DR}. The dendritic compartment contains an inward calcium current I_{Ca} and two outward potassium currents, the voltage-activated potassium current I_{K-C} and the calcium activated after hyperpolarization current I_{AHP}.

1. Quantify the change in frequency as a function of J (from $J = 0$ to $J = 30$) for this model. Use AUTO to obtain a bifurcation diagram.

The Wang-Buzsaki model – `WangBuzsaki.ode`

The Wang-Buzsáki model has the form of the Hodgkin-Huxley model, but the gating variable m is replaced by its steady-state value (i.e. activation is assumed to be *fast*). It displays two salient properties of hippocampal and neocortical fast-spiking interneurons. First, the action potential in these cells is followed by a brief afterhyperpolarization. Second, the model can fire repetitive spikes at high frequencies.

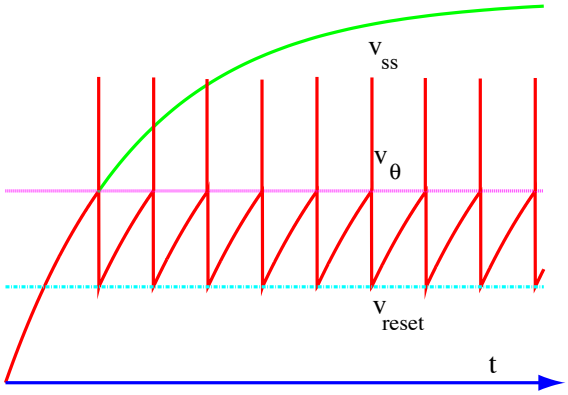


$J = 1$.

1. Quantify the change in frequency as a function of J for this model.

The integrate-and-fire (IF) model – `IF.ode`

This is a simple phenomenological model of a spiking neuron. It is a 1-D model, with just a voltage variable V, that is *reset* whenever V reaches some threshold. It can not represent the shape of an action potential - just the time that it occurs (though idealised spike are often added to plots):



Since it is both computationally cheap (allowing large network studies) and analytically tractable it is a very popular model.

1. Evolve the model and comment on how the period of oscillation varies with increasing J.

IF model with I_T – `IFB.ode`

Inclusion of the so-called I_T current can result in a burst of spikes. This current is often found in thalamic relay (TC) cells (in the thalamus). It is thought to be involved in relaying sensory information from the brainstem and periphery to the cortex. These cells have at least two modes of operation.

- During wakefulness or REM sleep, the cells resting potential is around -63 mV, and a small pulse of injected current does not evoke spikes. If the cell is depolarized to around -53 mV, then the same small pulse of injected current evokes a train of spikes.
- During slow wave sleep, the cells resting potential is around -75 mV. In this mode (sometimes called burst mode), the same small pulse of injected current initiates a low-threshold Ca spike (via the I_T current), which results in a burst of spikes.

A movie of intracellular recordings from a thalamic relay cell can be found at the McCormick lab http://info.med.yale.edu/neurobio/mccormick/movies/rly_exp.mpg

A simple model of this current is given by

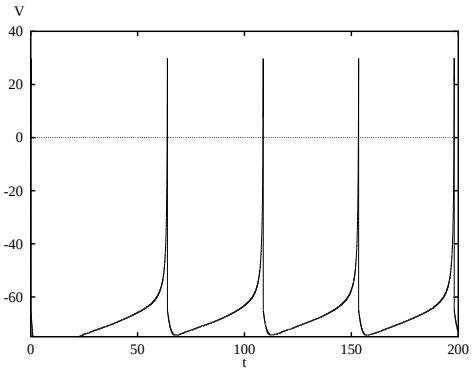
$$I_T = g_T \Theta(V - V_h) h_T (V_T - V),$$

where $\Theta(V - V_h)$ is a *switch* in the sense that it is one if $V > V_h$ and zero otherwise. The reversal potential is that for calcium ions ($V_T = 120$ mV), whilst $V_h = -70$ mV, and h_T is an inactivating gate.

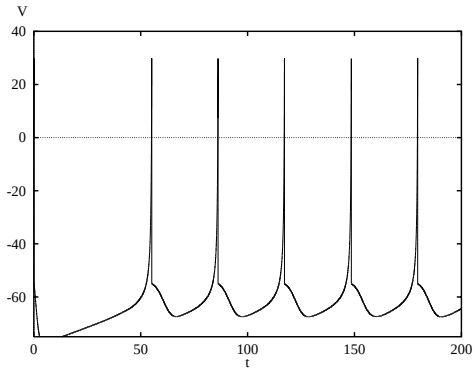
1. For $J = 0$ vary the value of the external current step J_P (a pulse of amplitude J_P and duration 300 ms) to evoke a spiking output.
2. For $J = 0$ and $J_P < 0$ show that I_T can generate a so-called *rebound burst*, and comment on its duration.
3. Adjust J until the resting potential is -75 mV and explore the firing modes of the model.

The Izhikevich spiking model[1] – `Izhikevich.ode`

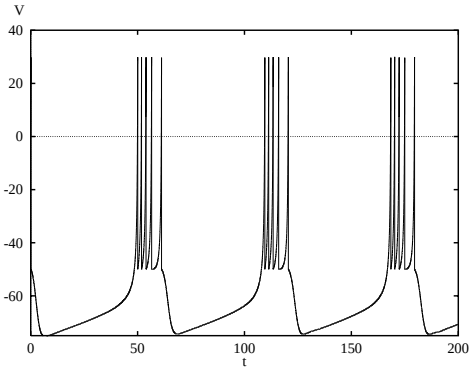
Like the IF model this is also a threshold model - this time possessing two variables v and u, which we may interpret as a voltage and a recovery variable. Upon reaching threshold the voltage is reset as in the IF model to a value c, and u is reset as $u \to u + d$. Two further parameters describe the sensitivity (b) and decay rate (a). It can capture a number of neuronal firing patterns including i) regular spiking (RS), ii) intrinsically bursting, iii) chattering (CH), and iv) fast spiking (FS).



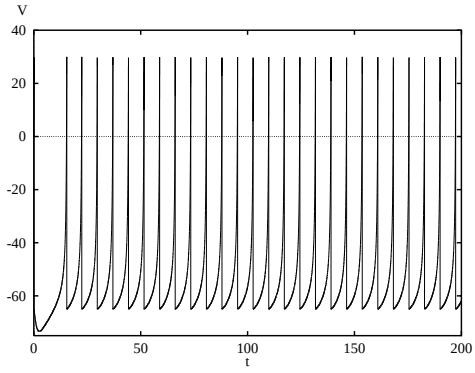
Regular Spiking (RS).
$a = 0.02,\ b = 0.2,\ c = -65,\ d = 8.$



Intrinsically Bursting (IB).
$a = 0.02,\ b = 0.2,\ c = -55,\ d = 4.$



Chattering (CH).
$a = 0.02,\ b = 0.2,\ c = -50,\ d = 2.$



Fast Spiking (FS).
$a = 0.1,\ b = 0.2,\ c = -65,\ d = 2.$

1. Evolve the model in various parameter regimes and obtain the plots above.

[1] http://vesicle.nsi.edu/users/izhikevich/publications/spikes.htm

This last question is **optional!**

Exploring a cortical model with multiple conductances – `McCormick.ode`

Here we will explore the role of different currents on the firing properties of cortical neurons[2]. There are 11 conductances that are used. By changing them, you can look at different currents, turning them on and off as you'd like. The conductances (and two permeabilities) are

g_{Na} sodium	g_{Nap} persistent sodium	g_K delayed rectifier
g_{K2} slow potassium	p_T permeability for T-type Ca	p_L permeability for L-type Ca
g_C fast Ca/voltage dependent potassium	g_A A-current	g_H sag current
g_M slow muscarinic potassium current	g_{AHP} slow Ca-dependent potassium	g_{Kleak} potassium leak
g_{Naleak} sodium leak		

1. The initial file is set up for a passive membrane. Change ip to 0.25 nA. Run the simulation. You will see the potential rise. Find the equilibrium potential with this much current.

2. Spikes! Now set $g_{Na} = 12$ and $g_K = 2$. Rerun the simulation. How many spikes? What is the firing frequency of the cell? Block the potassium current by setting $g_K = 0$. What happens? The cell is "bistable" there are two stable states a high potential and a low potential. What accounts for the initial drop in the potential shortly after the stimulus is turned on?

3. A-Current. Set $g_K = 1$, $g_A = 1$, $g_{Na} = 12$. What does the A-current do? Compare the actual currents (called I_A and I_K in the program).

4. After-hyperpolarization. Set the total simulation time to 1000 msec (using `Numerics - Total`). Set the stimulus, $t_{on} = 50$, $t_{off} = 250$, $ip = 1$. Now turn on the L-type calcium current, $p_L = 40$ and set $g_k = 1$, $g_{naleak} = 0.0024$. Run the simulation. Now add a small AHP current g_{AHP}=0.02. Compare the two. There is a large after-hyperpolarization that lasts for a second or so! Spike adaptation has also occurred. The first interspike interval is much smaller than the next several.

5. Rebound burst with T-current. Set $ip = 0$, $t_{on} = 50$, $t_{off} = 150$, $p_T = 40$, $p_L = 70$, $g_K = 1$, $g_A = 1$, $g_{Na} = 12$ Integrate the equations and then reintegrate them using `Initial conditions - Last` to get rid of any transients. Now set $ip = -0.25$ and thus hyperpolarize the membrane. You will get a rebound burst. Plot ht the inactivation of the T-current. Notice that hyperpolarization increases the value of this gate. Plot mt the activation gate on the same plot. Notice that the inactivation is slow so that when the hyperpolarization is removed, the channel is now open sufficiently to allow calcium to enter

[2]following the tutorial of Bard Ermentrout at http://www.math.pitt.edu/~bard/classes/tutorial/tutorial.html

the cell and we get a burst. This is important for the workings of the thalamus which is surrounded by a thin layer of cells that are strictly inhibitory called the reticularis (RE). The thalamo-cortical (TC) units that project from the thalamus to the cortex have a large T-current. When they are inhibited by the RE cells, they produce a rebound burst. These bursts are believed to be responsible for sleep spindles.

6. Calcium oscillations. Thalamic relay cells can generate intrinsic oscillations via an interaction between the T-current and the sag current, I_h. Set all conductances to zero and then set $ip = 0$ and the total integration time to 1500 msec. Set $g_{naleak} = 0.00025$, $g_{kleak} = 0.007$, $g_{K2} = 0.2$, $p_T = 60$, $p_L = 80$, $g_C = 0.2$, $g_A = 1$, $g_H = 0.01$. Integrate the equations. Turn of the sag $g_H = 0$ and reintegrate them. What happens to the behavior? Turn the sag back on and add sodium spikes by setting $g_{Na} = 14$. Describe the behavior. Why is the period longer? (Hint - it has to do with the sag current.)