Modeling synapses

Comp Neuroscience

February 10, 1998

1 A final word on compartmental modeling

In attempting to model the behavior of whole neurons, detailed microscopy and staining are required to produce a full three-dimensional picture of the cell. This picture is then broken down into a series of cylinders with varying diameters and lengths. These are then used to create a mathematical and computational description of the cell. In order to write equations for the compartments, we must determine the axial and the transmembrane resistances as well as the membrane capacitance. For a given cylindrical compartment, the membrane resistance is related to the area of the compartment as is the capacitance. Given a specific resistivity in Ohm-cm^2, R_M the total resistance is just this value divided by the area, $R_m = R_M/A$ whare A is the area. Similarly, if there are active channels with conductances in millisiemens per square centimeter, the total conductance is the specific conductance times the area. (Note that the resistance is divided by the area and the conductance multiplied – more are means more conductance and less resistance.) The capacitance for the compartment is also proportional to the area.

However, when we connect two compartments together, how do we define the axial resistance between them if they have different lengths and/or diameters? Obviously, if the two cylinders are identical, then you can use either of the axial resistances as they are both the same. If they are not the same, then there are several different possibilities:

- If both are cylinders, average the two resistances and use the average.
- If one is a cylinder and the other is a sphere, use the cylindrical value
- Order the compartments and use the resistance corresponding to the lower or higher number in the ordering

We will always use the first 2 algorithms. GENESIS lets you choose which algorithm to use. I am not sure how NEURON resolves this.

EXAMPLE

Suppose that the two compartments have dimensions (length X diameter) 100 $\mu m \times 5\ \mu m$ and 200 $\mu m \times 2\ \mu m$ respectively. Then

$$\begin{aligned}
A_1 &= 500\pi = 1571\mu m^2 \\
A_2 &= 400\pi = 1257\mu m^2 \\
Ri_1 &= R_I 100/(\pi 2.5^2) = 5.1 R_I \\
Ri_2 &= R_I 200/(\pi 1^2) = 63.66 R_I \\
R_i &= 34.4 R_I
\end{aligned}$$

Thus, the two equations are

$$\begin{aligned}
C_M A_1 \frac{dV_1}{dt} &= (V_M - V_1)/(R_M/A_1) + (V_2 - V_1)/R_i \\
C_M A_2 \frac{dV_2}{dt} &= (V_M - V_2)/(R_M/A_1) + (V_1 - V_2)/R_i
\end{aligned}$$

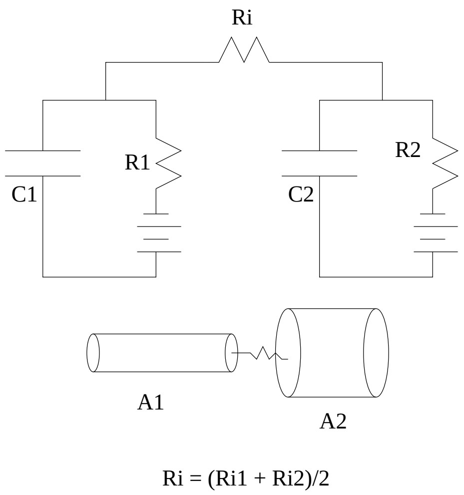

Figure 1: Two different cylinders coupled by the average axial resistance

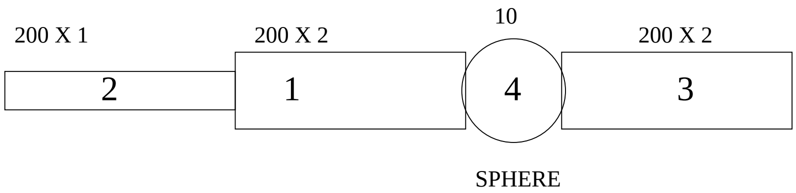

Figure 2: A 4 compartment model representing a pyramidal cell

Dividing these by the area, we get

$$\begin{aligned} C_M \frac{dV_1}{dt} &= (V_M - V_1)/R_M + (V_2 - V_1)/(A_1 R_i) \\ C_M \frac{dV_2}{dt} &= (V_M - V_2)/R_M + (V_1 - V_2)/(A_2 R_i). \end{aligned}$$

In other words the two equations for the voltages look identical except for the coupling strength between them. (If the specific resistances and potentials and channel densities were different for the two cells, the noncoupling coefficients would also be different.) The key point is that the effect of a big compartment on a little compartment is asymmetric. In this example, since compartment 1 is larger than compartment 2, the influence of compartment 2 on compartment 1 is less than that of compartment 1 on compartment 2 since the former coupling is divided by a bigger number. Often in modeling a 2 compartment system with compartment 1 bigger than compartment 2, it is convenient to write the couplings as:

$$\begin{aligned} \text{coupling}_{2\to 1} &= G(V_2 - V_1) \\ \text{coupling}_{1\to 2} &= G(V_2 - V_1)/(1-p) \end{aligned}$$

where G is a fixed conductance and $p = 1 - A_2/A_1$ is an asymmetry parameter. $p = 0$ if the compartments have the same area. As p gets closer to 1, the ratio of the small to the big goes to zero. Big dendrites have strong effects on little somas. This is why when the soma spikes, there is little propagation back up the dendrite unless the dendrites themselves have active channels.

Homework

Write the equations for a compartmental model of a neuron with 4 compartments that are arranged as follows with dimensions given in the figure (length and diameter in microns). Compartments 1 and 2 are apical dendrites with $R_M = 10000\Omega/cm^2$, $C_M = 1\mu F/cm^2$, $R_a = 100\Omega cm$. Compartment 3 is a basal dendrite with the same properties and compartment 4 is the *spherical* soma that has a transient sodium conductance and delayed rectifier as well as a leak. Assume that it has a transient sodium channel with a density of $100mS/cm^2$ a persistent potassium channel with density of $80mS/cm^2$, a leak conductance $.1mS/cm^2$ and $V_{Na} = 50mV, V_K = -100mV, V_l = -67mV$. (Note that if one uses millisiemens and microfarads as the dimensions, then the times will be in milliseconds which is convenient.) (Also note that a leak conductance of $0.1mS/cm^2$ corresponds to a membrane resistance of $10000\Omega cm^2$.) You do not have to simulate this (yet); I am mainly interested in seeing that you understand how to put the compartments together with the dynamics. The resting potential is -67mV.

2 The action potential

We have now derived the fundamental models for cables and active membranes and thus should be able to produce models of individual neurons and banched neuronal structures such as dendrites and axons. Networks of neurons communicate in a variety of means but by far the most common is through synapses. Synapses are exceeding complex and involve a large number of biochemical steps, can be modified and modulated by external substances, and are capable of undergoing slow adaptation and facilitation. Nevertheless, we will blunder on in order to describe ways in which one might model them; for without synapse, we cannot model networks and without networks, we are nothing. Indeed, to paraphrase Dorothy Parker, *you can put a cell in culture but you can't make it think.* The first step in this process of communication is the action potential; abbreviated as "AP." The action potential occurs when we combine the active membrane theory of "channeling" with the passive cable theory. The compartmental model is then:

$$C_m \pi l d \frac{dV_j}{dt} + I_{act}\pi l d = \frac{\pi (d/2)^2}{R_a l}(V_{j+1} - 2V_j + V_{j-1})$$

where I_{act} contains all of the active channels with conductances given in terms of density per unit area and l is the length of the compartment and d is the diameter of the cylinder. Dividing by $2\pi l d$ and letting $l \to 0$ to approximate a continuous axon, we obtain:

$$C_m \frac{\partial V_j}{dt} + I_{act} = \frac{d}{4R_a}\frac{\partial^2 V}{\partial x^2}$$

which is the model for the continuous axon originally modeled by HH. One can numerically simulate this partial differential equation and it is found that for each set of parameters, there is a solutions that is a travelling wave. That is, there is a solution that keeps the same spatial profile translated in time. Specifically, $V(x,t) = U(x - ct)$ where U is a particular function and c is the velocity of the wave. (See illustration of the wave.) A natural question to ask is how does the velocity depend on say, the geometry or the coupling? This is easily seen from the above. The term d multiplies two spatial derivatives of V, thus, the velocity depends on d as the square-root. That is, quadrupling the diameter doubles the velocity. Similarly quadrupling the intrc-axonal resistance halves the velocity. The rigorous existence of traveling waves to the HH equations was independently proven in the 70's by Stuart Hastings and Gail Carpenter.

The AP provides the means of communicating between neurons by activating the axon and causing a signal to travel unattenuated down the cable. It is possible to block this by various means. For example, if the diameter of the axon increases drastically (say at a branch point) then the impuls can be blocked. Since there is no intrinsic anisotropy in the axon, it is possible to initiate an impulse any where and it will propagate outward (see Figure.) Because of the refractory period following the AP, the conducting medium behind the AP is very hyperpolarized and remains so until the sodium-potassium pump is able to rebalance the ionic concentrations. As a consequence of this two propagating action potentials that collide annihilate unlike more common physical waves such as boles or light waves which pass through each other unchanged. (Note that for linear waves, this is a trivial observation, but for boles this requires some amount of mathematics.)

Repeated stimuli can have somewhat complicated effects. The simplest is to produce a train of waves that are equally spaced dowm the axon. If we let ν denote the velocity of the waves and T their period,

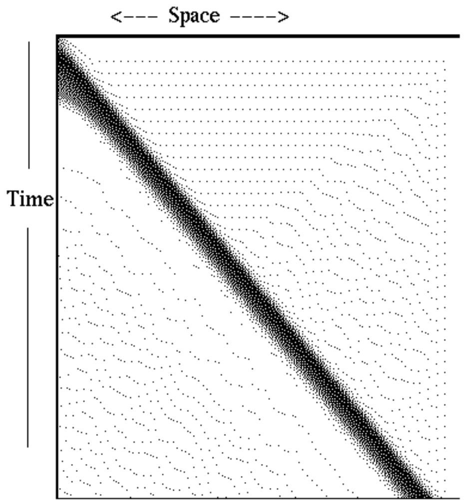

Figure 3: Voltage contour of an action potential in space-time

then there is a relationship between ν and T called the dispersion relation. Any nonlinear medium capable of producing waves has sucg a relationship. You have probably observed it in water; waves with different magnitudes have different velocities and thus tend to disperse through the medium. Generally, the higher the temporal frequency, the smaller is the amplitude and velocity. The fastest wave is the one with zero frequency; the solitary pulse. The quantity, $1/(T\nu)$ has dimensions of $1/dist$ and is called the wavenumber or spatial frequency of the waves. Nonmonotone dispersion relations have profound consequences for the spacing of waves and it is possible to get doublets and other complicated spacings of impulses. The mathematical analysis of this type of phenomena has led to some striking insights into propagation of the lowly action potential.

In spite of all this interesting behavior, when it comes time to model networks of neurons, most people ignore it and model the action potential via a conduction delay. The range of velocities are from 2-10 meters/second for a typical impulse, the faster occuring in myelinated axons. In a small piece of cortical tissue a millimeter on the side, the maximum of these delays is less than a millisecond so that for purposes of modeling we will generally neglect them. However, in parts of the olfactory cortex, there appear to be instances where conduction delays are important.

3 Synapses

Assuming we have built a neuron such as the one in your homework above, then we can connect these together to form a neural network. This requires a model for the synapses that connect the cells. Later on, we will create "connectionist" type models that mimic synapses by directly producing PSPs, but here we are interested in a more rigorous and directly biophysical approach. The synapse is remarkably complex and involves many simultaneous processes such as the production and degradation of neurotransmitter, the sequestration in the vesicles, release, binding to the postsynaptic membrane, and opening of the channels.

The basic story is that the action potential travels down the axon and terminates at many presynaptic sights invading regions called synaptic terminals. These terminals contain calcium channels which when depolarized cause (a) release of calcium; (b) calcium activates a calcium binding protein which promotes release by binding to vesicles containing the transmitter; (c) these "docked" vesicles release their transmitter into the synaptic cleft. This type of detail is all well and good, but if we are going to model many cells, then we want to simplify things quite a bit. In the chapter by Destexhe, Mainen, and Sejnowski, a detailed description of this model is provided as well as simulations.

We adopt here a cruder approach that can be viwed as a mean field or average over many individual synapses. Our simple model is to treat the synapse as just another ionic channel that will be modeled by Ohms law. For every synapse between two neurons, we will add a current of the form:

$$I_{syn} = g_{syn}s(t)(V - V_{syn}) \tag{1}$$

to the right-hand side of the current balance equation for voltage. (Note that the NMDA synapse discussed below is more complex since the conductance is dependent on the post-synaptic potential.) Here $s(t)$ is the time-dependent proportion of open channels, g_{syn} is the maximum conductance, and V_{syn} is the reversal potential for the synapse. The quantity, $s(t)$ will always be nonnegative and is zero if the presynaptic cell is not firing. For "excitatory" synapses, V_{syn} larger than the resting potential so that it will produce an inward current. "Inhibitory" synapses will be close to the reversal potential of potassium and negative relative to rest. "Shunting " synapses have a reversal potential close to the resting potential.

Homework

I would like you to explore a simple 5 compartment model of a dendrite that is passive and has one synapse in compartment 3. In this case, $s(t)$ is a pulse that turns on to 1 at t_{on} and then back to 0 at t_{off}. The XPP file is

```
# pas_syn.ode
init v1=5.08  v2=4.33  v3=3.8  v4=3.46  v5=3.3
par c=1  i=1  gl=0.05  vsyn=0  gsyn=0.1  gc=1
par ton=10  toff=15
v1'=-gl*v1+gc*(v2-v1)+i
v2'=-gl*v2+gc*(v1-2*v2+v3)
v3'=-gl*v3+gc*(v2-2*v3+v4)-gsyn*heav(t-ton)*heav(toff-t)*(v3-vsyn)
v4'=-gl*v4+gc*(v3-2*v4+v5)
v5'=-gl*v5+gc*(v4-v5)
done
```

and is called `pas_syn5.ode`. Plot `v1,v3,v5` against time for `vsyn=-20mV,0mV,50mV` and a variety of different times on/off and maximal conductances. Integrate the equations for 100 msec and define an appropriate window. Note the difference at the ends and at the site of the synapse. The time units are in milliseconds. What are the units of `i` in this equation? Note also, that the coupling conductances and the leak and the synapses are all in mS/cm^2. Observe that even though compartment 1 receives input via a current injection, that the synapse that is downwind from it exerts a significant effect on the membrane potential at that point.

Now that you have explored the effects of these transient conductance changes, I return to modeling the synapse. How do we determine $s(t)$ from the presynaptic activity? As we have noted above, the release of transmitter is quite complex. However, a good fit to the total amount of transmitter release by a single action potential is given by the expression:

$$[T](V_{pre}) = T_{max}/(1 + exp(-(V_{pre} - V_p)/K_p)) \tag{2}$$

where T_{max} is the maximal concentration of transmitter in the synaptic cleft and K_p, V_p determine the stiffness and threshold for the release. A good value for these constants is $V_p = 2\ mV$ and $K_p = 5\ mV$. Typically, we will assume that 1 mM of transmitter is the maximum concentration released.

3.1 Post synaptic behavior

Given that a certain amount of transmitter is released from the synaptic terminal, we want to now model the current that appears in the postsynaptic site. To do this we need to model $s(t)$ the fraction of open channels open due to the transmitter T. The typical way to model these is via a series of reactions or so called Markov models in which the probability of channels opening and closing is described by a series of rate constants. This kind of detail is well beyond what one wants for simple modeling, thus, instead, we will describe a couple of simple models for the 4 primary types of postsynaptic response induced by the two principle neurotransmitters.

3.2 Glutamate

The neurotransmitter glutamate activates two different kinds of receptors: AMPA/kainate which are very fast and NMDA which is implicated in memory and long-term potentiation of synapses. Both of these receptors lead to excitation of the membrane. We will introduce simple models for these receptors and then simulate them.

3.2.1 AMPA/Kainate

A simple first order kinetic model works well for the fast excitatory AMPA receptor:

$$\begin{aligned} I_{AMPA} &= \bar{g}_{AMPA} s(t)(V - V_{AMPA}) && (3) \\ \frac{ds}{dt} &= \alpha[T](1-s) - \beta s && (4) \end{aligned}$$

where $[T]$ is the concentration of transmitter given by (2). The data taken from cortical cells is best fit by setting $\alpha = 1.1\ mM^{-1}ms^{-1}$, $\beta = .19\ ms^{-1}$ and $V_{AMPA} = 0\ mV$. If we suppose that that transmitter occurs in a square pulse (not too bad an approximation), then the equation for s is just linear with constant coefficents and can be solve. If the transmitter is released at $t = t_0$ and lasts until $t = t_1$ then

$$s(t - t_0) = s_\infty + (s(t_0) - s_\infty)e^{-(t-t_0)/\tau_s} \qquad \text{for } t_0 < t < t_1$$

where

$$\begin{aligned} s_\infty &= \frac{\alpha T_{max}}{\alpha T_{max} + \beta} \\ \tau_s &= \frac{1}{\alpha T_{max} + \beta} \end{aligned}$$

After the pulse turns off at $t = t_1$,

$$s(t - t_1) = s(t_1)e^{-\beta(t-t_1)}.$$

Thus, the synapse rises exponentially with a time constant τ_s and decays with a time constant β^{-1}. This simple form has led many modelers to dispense with the differential equations altogether and use the so-called "alpha" functions for $s(t)$ which have the form

$$\alpha(t - t_s) = K(e^{-(t-t_s)/\tau_2} - e^{-(t-t_s)/\tau_1})$$

where t_s is the time of the presynaptic spike (when the presynaptic voltage crosses some set threshold), τ_1 is the rise time of the synapse (approximately τ_s) and τ_2 is the decay of the synapse (approximately β^{-1}). In particular, if the rise time is very fast, then

$$\alpha(t - t_s) = Ke^{-(t-t_s)/\tau_2}$$

while if the decay and rise times are close,

$$\alpha(t - t_s) = K(t - t_s)e^{-(t-t_s)/\tau_2}.$$

The problem with using the so called "alpha" functions is that there is some question what to do when there are multiple spikes. Multiple spikes can either be added or the most recent taken. This approach requires monitoring the presynaptic cells and then setting/resetting the synaptic time-courses, $s(t)$ for each synapse. This method of modeling has the advantage that no real dynamics must be computed; once the synapse is set in motion, it follows the prescribed time course. However, Destexhe et al show that using the actual differential equations and the assumption that the pulse of transmitter released is a square pulse, then the formulae above for $s(t)$ lead to a computationally efficient scheme for computing the synaptic gates without having to keep track of all prior spikes. In my opinion, the "alpha" functions are useful only for certain types of exactly solvable models called integrate and fire models.

The AMPA synapses can be very fast. For example in some auditory nuclei, they have submillisecond rise and decay times. In typical cortical cells, the rise time is 0.4 to 0.8 milliseconds. Using the above model with a transmitter concentration of 1 mM, the rise time would be $1/(1.1+.19) = .8$ msec. Decay is about 5 msec. As a final note, AMPA receptors onto inhibitory interneurons are about twice as fast in rise and fall times.

3.2.2 NMDA

An important receptor found in cortical pyramidal neurons is the NMDA receptor. They are quite slow with rise times of about 20 msec and decay times of 25 to 120 msec. A fairly good simple model for NMDA is

$$I_{NMDA} = \bar{g}_{NMDA} B(V) s(t)(V - V_{NMDA})$$

where $s(t)$ obeys first order dynamics. There is an important difference between NMDA and AMPA. The conductance depends in a complex fashion on the postsynaptic potential via the term $B(V)$. This voltage dependent conductance depends on the level of external magnesium ions. Here is a physiological correlate of the Hebb rule that both pre- and postsynaptic cells must be coincidently active. The voltage dependence is mediated by magnesium ions which normally block the NMDA receptors. Thus, the postsynaptic cell must be sufficiently depolarized to knock out the magnesium ions. This is modeled in Jahr and Stevens, J. Neuroscience 10, 1830-1837:

$$B(V) = \frac{1}{1 + e^{-.062V}[Mg^{2+}]/3.57}$$

By blocking the magnesium, it is possible to eliminate the voltage dependence and measure the kinetic parameters. A simple first order model is

$$\frac{ds}{dt} = \alpha[T](1-s) - \beta s$$

as in the AMPA current, but , $\alpha = 0.072\ mM^{-1}ms^{-1}$, $\beta = 0.0066\ ms^{-1}$ and $V_{NMDA} = 0\ mV$.

3.3 GABAergic synapses

γ-aminobutyric acid (GABA) is the principle inhibitory neurotransmitter in the cortex. There are two main receptors for GABA, GABA_A and GABA_B.

3.3.1 GABA$_A$

GABA-A is responsible for fast inhibition and require only brief stimuli to produce a response. The same simplified type of kinetic model used for AMPA synapses can be used for GABA-A. The current is

$$\begin{aligned} I_{GABA_A} &= \bar{g}_{GABA_A} s(t)(V - V_{GABA_A}) \\ \frac{ds}{dt} &= \alpha[T](1-s) - \beta s \end{aligned}$$

with $\alpha = 5\ mM^{-1}ms^{-1}$, $\beta = .18\ ms^{-1}$ and $V_{GABA_A} = -80\ mV$.

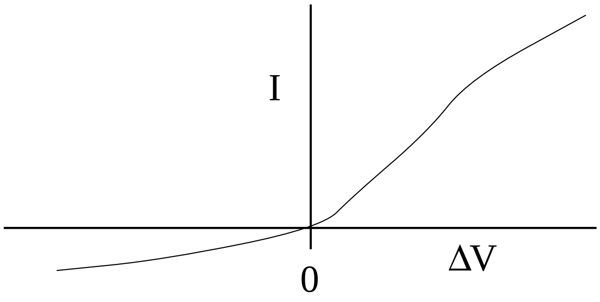

Figure 4: Rectifying gap junction

3.3.2 GABA$_B$

GABA-B is a much more complex receptor. It involves so-called second messengers. For the other three receptors, the receptor and the ion channel are part of the same protein complex. GABA-B responses occur when the GABA binds to another compound (the G-protein) which in turn binds to a potassium channel and opens it up. It takes 4 of the activated G-proteins to open the channel. For this reason, we must use a second order kinetic scheme to properly model the GABA-B dynamics. The equations are:

$$\begin{aligned} I_{GABA_B} &= \bar{g}_{GABA_B} \frac{s^n}{s^n + K_d}(V - E_K) \\ \frac{dr}{dt} &= \alpha[T](1-r) - \beta r \\ \frac{ds}{dt} &= K_3 r - K_4 s \end{aligned}$$

where $n = 4$, $K_d = 5$, $\alpha = .09\ mM^{-1}ms^{-1}$, $\beta = .0012\ ms^{-1}$, $K_3 = .18\ ms^{-1}$, and $K_4 = .034\ ms^{-1}$.

3.4 Gap junctions.

These are not chemical synapses but electrical in nature. They produce a current proportional to the difference between pre- and postsynaptic potential. No transmitter or action potential is involved:

$$I_{gap} = G(V_{post} - V_{pre})$$

Sometimes these act as rectifiers so that the positive and negative current flow is not equal for potential differences of the same magnitude

Many non-neural cells are coupled in this manner; muscle, glia, and most humoral cells.

3.5 More complex synapses

There are many other types of synapses that can have more complex behavior. For example in the bullfrog sympathetic ganglion, synaptic cotransmission occurs in which a cocktail of several neurotransmitters is released which then bind to several different receptor types. With such complex synapses, it is possible to get an initial brief depolarization followed by hyperpolarization and then by a long lasting low amplitude depolarization.

Many cortical neurons have AMPA synapses which depress. That is, when given repeated stimuli, the synapse produces less and less transmitter. We can readily model this by adding a desensitized state to the standard two-state model for the synapse. Instead of the open state going directly back to the closed state, we allow there to be an intermediate state (desensitized) which then returns to the closed state.

$$\begin{array}{ccc} C & \xrightarrow{\alpha[T]} & O \\ O & \xrightarrow{\beta} & X \\ X & \xrightarrow{\beta_2} & C \end{array}$$

Since $C+O+X=1$ (that is the probability of being any of these three states is 1) we eliminate the equation for the closed states and are left with the following pair of equations:

$$\begin{aligned}\frac{ds}{dt} &= \alpha[T](1-s-x)-\beta s \\ \frac{dx}{dt} &= \beta s-\beta_2 x\end{aligned}$$

The slower is β_2, the longer the synapse remains in the desensitized state, x.

3.6 Playing around with synapses

In this little section, you should examine the time courses of the different synaptic types. In the file below, I describe a simple active cell that synapses onto a passive compartment V_{post}. There are 5 different synaptic currents simulated (the depressed synapse is among them). The equations are based on the models presented in the Destexhe et al paper. Here is th ODE file

```
# Synapse exercises
# presynaptic cell
v'=-(gna*h*m^3*(v-ena)+gk*n^4*(v-ek)+gl*(v-el) -i-ip*heav(t-ton)*heav(toff-t))/c
m'=am(v)*(1-m)-bm(v)*m
h'=ah(v)*(1-h)-bh(v)*h
n'=an(v)*(1-n)-bn(v)*n
# post synaptic cell
vpost'=-.2*(vpost-vp0)-iampa-igaba-inmda-igabb-idep
# transmitter released
trans=tmax/(1+exp(-(v-2)/5))
# synaptic types
s_ampa'=al_ampa*trans*(1-s_ampa) -s_ampa*bet_ampa
s_nmda'=al_nmda*trans*(1-s_nmda) -s_nmda*bet_nmda
s_gaba'=al_gaba*trans*(1-s_gaba) -s_gaba*bet_gaba
r'=al_gabb*trans*(1-r) -r*bet_gabb
s_gabb'=k3*r-k4*s_gabb
# depressed AMPA synapse
s_dep'=al_ampa*trans*(1-s_dep-xx) -s_dep*bet_ampa
xx'=s_dep*bet_ampa-beta2*xx
# synaptic currents
idep=g_dep*s_dep*(vpost-vex)
iampa=g_ampa*s_ampa*(vpost-vex)
inmda=g_nmda*s_nmda*(vpost-vex)/(1+exp(-.062*vpost)*(mg/3.57))
igaba=g_gaba*s_gaba*(vpost-vin)
igabb=g_gabb*(s_gabb^4/(s_gaba^4+kd))*(vpost-ek)
# make them plottable
aux i_ampa=iampa
aux i_nmda=inmda
aux i_gaba=igaba
aux i_gabb=igabb
aux i_dep=idep
# functions
am(v)=.32*(54+v)/(1-exp(-(v+54)/4))
bm(v)=.28*(v+27)/(exp((v+27)/5)-1)
ah(v)=.128*exp(-(50+v)/18)
bh(v)=4/(1+exp(-(v+27)/5))
an(v)=.032*(v+52)/(1-exp(-(v+52)/5))
```

```
bn(v)=.5*exp(-(57+v)/40)
# parameters
par ek=-100,ena=50,el=-67,vp0=-70
par gl=.1,gk=80,gna=100
par c=1,i=0
par bet_ampa=.19,al_ampa=1.1, g_ampa=.038
par bet_nmda=.0066,al_nmda=.072, g_nmda=.0,mg=0
par bet_gaba=.18,al_gaba=5, g_gaba=.0
par bet_gabb=.0012,al_gabb=.09, k3=.18,k4=.034,kd=4,g_gabb=.0
par g_dep=0.0,beta2=.01
par tmax=3.2, vex=0,vin=-80
par ton=0,toff=10,ip=1
init v=-67.68,m=.0128,h=1,n=.0332,vpost=-70
@ method=qualrk,toler=.0001,total=40,dt=.25
@ xhi=40,yp=vpost,ylo=-72,yhi=-62
done
```

The file is set up to simulate 40 msec of time. The presynaptic cell is injected with a small or large pulse of current to elicit either 1 or many action potentials. The parameter **ip** controlls the magnitude of ther current. To get 1 presynaptic spike and to get 4 presynaptic spikes, set it to 35. The conductance parameters are **g_ampa, g_nmda, g_gaba, g_gabb, g_dep** for each of the four types and depressed AMPA synapse. The graph is set up to show the post-synaptic cell which is passive and receives a synapse from the presynaptic cell with magnitude 0.038 mS/cm^2. (This strange number results in 1 nS of conductance for a 10 by 10 micron cylinder.)

Exercises

1. Run the given ODE file and simulate the effects of a single AMPA spike and on the same graph the GABA-A and the depressed synapse. (Make sure you set the non-active synaptic conductances to 0 and the active conductance to 0.038.) Although the amplitude of the conductances for both the AMPA and the GABA-A synapse are close, there is greater depolarization due to the AMPA synapse. Why? Does synaptic depression have an effect on the AMPA single spike response?

2. Look at the response of NMDA (in zero magnesium – the parameter **mg=0** and at GABA-B. Why is the response to NMDA small? Why is the GABA-B response almost no-existent?

3. Set **ip=35** to give a burst of action potentials. Compare the AMPA and the depressed AMPA. What is the difference?

4. Set the time of integration to 1000 msec. Set the x-axis length to be 1000 and the y-axis window between -75 and -60. Now reintegrate the equations and look at the responses to GABA-B and NMDA synapses. Why is the GABA-B so much larger with a burst of action potentials?

5. Now set all the synapses to zero except for the NMDA synapse. Set the total integration time to 500. Set the magnesium **mg=1**. Integrate the equations and take note of the NMDA current by plottin I_NMDA. Now change the resting potential of the post-synaptic cell by changing the parameter **vp0**. Change the initial value of the post-synaptic voltage to the resting potential. Change it to -60, -50, -30, -10, 0. Plot the peak NMDA current. Why is it non-monotonic? How would the peak NMDA current change if you block magnesium and change the resting potential of the cell?

3.7 Exercise 2

In this example, we will take the model from Figure 1 and actually add the kinetics. We will then add 4 synapses whose conductances and whose onsets can be individually set (although they will all have the same time courses). The object of this little exercise is to explore thresholds and timing of synapses. The file is called `trcomp4.ode` and you should integrate it at least for 80 msec. I have used alpha functions for the synapses since there is no post-synaptic cell and these fire only once. The sodium and potassium dynamics are those of Traub's cortical cell model. The parameters you will vary are called `gsyn1,gsyn2,gsynb,gsyns` which are the conductances for the two apical dendrite compartments, the basal dendrite compartment, and the soma compartment. The other parameters of interest are `ts,tb,t1,t2` which are the onset times of the 4 synapses. The voltages are `v, va1,va2,vb` for the soma, the two apical dendrites, and the basal dendrite. I have chosen the coupling between the compartments for you for the purposes of this exercise. Here are some things to do:

1. Find the minimum value of the synaptic conductance on each compartment in order to elicit a spike at the soma.
2. Fix the conductance on the basal dendrite to be below the threshold to elicit a spike. Now increase the conductance on the terminal apical dendrite (labeled `gsyn2`) until the two of them elicit a spike.
3. With the paired synapses of the above, alter the timing by increasing `t2` from 5 to higher values. How close do the two stimuli have to be to elicit a spike. Increase the conductance `gsyn2` and repeat this.
4. Note that the alpha functions are normalized so that their integral in time is 1. Set all the synaptic conductances to 0 except `gsyn2`. Make a table showing the minimum conductance to elicit a spike at the soma as a function of `tau_s` the time constant of the synapse. Try fast synapses `tau_s=5` and slow `tau_s=40` as well as those in between.
5. Hold `gsyn2=4`. Now vary `tau_s` from 1 msec (really fast) to 20 msec. Which stimulus evokes the most action potentials.

Here is the file:

```
# traub sodium and potassium kinetics and 3 compartments with synapses
# v va1,va2,vb
v'=-(gna*h*m^3*(v-ena)+gk*n^4*(v-ek)+gl*(v-el)+gas*(v-va1)+gbs*(v-vb)+\
     alphas(t)*(v-vsyn))/c
va1'=-(gl*(va1-el)+g21*(va1-va2)+gsa*(va1-v)+alpha1(t)*(va1-vsyn))/c
va2'=-(gl*(va2-el)+g12*(va2-va1)+alpha2(t)*(va2-vsyn))/c
vb'=-(gl*(vb-el)+gsb*(vb-v)+alphab(t)*(vb-vsyn))/c
m'=am(v)*(1-m)-bm(v)*m
h'=ah(v)*(1-h)-bh(v)*h
n'=an(v)*(1-n)-bn(v)*n
init v=-67,va1=-67,va2=-67,vb=-67,m=0,n=0,h=1
am(v)=.32*(54+v)/(1-exp(-(v+54)/4))
bm(v)=.28*(v+27)/(exp((v+27)/5)-1)
ah(v)=.128*exp(-(50+v)/18)
bh(v)=4/(1+exp(-(v+27)/5))
an(v)=.032*(v+52)/(1-exp(-(v+52)/5))
bn(v)=.5*exp(-(57+v)/40)
par ek=-100,ena=50,el=-67
par gl=.1,gk=80,gna=100
par c=1,i=0
par gsyns=0,gsynb=0,gsyn1=0,gsyn2=0,vsyn=0
par ts=5,tb=5,t1=5,t2=5
par tau_s=5
par g12=2,g21=1,gsa=.5,gas=2,gbs=2,gsb=.5
alpha(t)=t*exp(-t/tau_s)/(tau_s^2)
alpha1(t)=gsyn1*alpha(max(t-t1,0))
alpha2(t)=gsyn2*alpha(max(t-t2,0))
```

```
alphab(t)=gsynb*alpha(max(t-tb,0))
alphas(t)=gsyns*alpha(max(t-ts,0))
@ dt=.25,meth=qualrk,total=80,xhi=80,ylo=-80,yhi=25
done
```

4 Synapses in a network setting

The above exercises illustrate the different effects of synapses and how they sum in concert with each other. However, the main reason for synapses is for neurons to communicate with each other within networks. One of the big theoretical and experimental interests of the last several years is the behavior of networks of neurons which oscillate and whether or not they syncronize. This interest arose due to some theoretical ideas by Christof von der Malsberg in the late 70's and early 80's. He was interested in how multiple aspects of a visual image such as color, texture, etc could be "bound" together to form a coherent whole. How can you seperate an figure from the background? He came up with the idea that oscillatory neurons could use phase information (that is the timing between the firing of the cells) to encode features of an object. All the cells that fire synchronously would correspond to the same object. The theory was viewed with great excitement when in the late 80's and early 90's Singer and Gray discovered that some cortical neurons would fire together synchronously over long distances in the cortex when presented with a continuous bar. If the bar was broken into two smaller bars, then the cells would fire but not synchronously. This spawned an industry of theory and experiment in synchronization of cortical oscillators. The firing rates of the cells during stimulation is around 40 Hz and this is called "gamma" rhythm. Thus, one of the major theoretical questions that has been asked is what kind of synaptic interactions lead to synchrony in networks of cortical and thalamic cells. In the following exercise, you will study a two-cell network of neurons coupled by synapses. The synapses are modeled by the first order dynamics above.

The ode file is :

```
# Two traub cells coupled together with synapses
# cell 1
v1'=-(gna*h1*m1^3*(v1-ena)+gk*n1^4*(v1-ek)+gl*(v1-el) -i1+gsyn2*s2*(v1-vsyn2))/c
m1'=am(v1)*(1-m1)-bm(v1)*m1
h1'=ah(v1)*(1-h1)-bh(v1)*h1
n1'=an(v1)*(1-n1)-bn(v1)*n1
s1'=alpha1*tmax*(1-s1)/(1+exp(-(v1-vt)/vs))-beta1*s1
# cell 2
v2'=-(gna*h2*m2^3*(v2-ena)+gk*n2^4*(v2-ek)+gl*(v2-el) -i2+gsyn1*s1*(v2-vsyn1))/c
m2'=am(v2)*(1-m2)-bm(v2)*m2
h2'=ah(v2)*(1-h2)-bh(v2)*h2
n2'=an(v2)*(1-n2)-bn(v2)*n2
s2'=alpha2*tmax*(1-s2)/(1+exp(-(v2-vt)/vs))-beta2*s2
am(v)=.32*(54+v)/(1-exp(-(v+54)/4))
bm(v)=.28*(v+27)/(exp((v+27)/5)-1)
ah(v)=.128*exp(-(50+v)/18)
bh(v)=4/(1+exp(-(v+27)/5))
an(v)=.032*(v+52)/(1-exp(-(v+52)/5))
bn(v)=.5*exp(-(57+v)/40)
par ek=-100,ena=50,el=-67
par gl=.1,gk=80,gna=100
par c=1,i1=0,i2=0,
par gsyn1=0,gsyn2=0,vsyn1=0,vsyn2=0
par vt=2,vs=5,tmax=3.2
par alpha1=1,beta1=.2,alpha2=1,beta2=.2
init v1=-67,v2=-67,h1=1,h2=1
```

```
@ dt=.25,meth=qualrk,total=100,xhi=100,ylo=-85,yhi=25
done
```

HOMEWORK The model is of two point neurons coupled together by first order synapses like we have already explored. The neurons are labeled 1 and 2 and neuron 1 synapses onto 2 with synapse `s1` and maximal conductance `gsyn1` and reversal potential `vsyn1`. Neuron 2 synapses onto neuron 1 with synapse `s2` and maximal conductance `gsyn2` and reversal potential `vsyn2`. The synaptic parameters, α, β are `alpha1, alpha2, beta1, beta2`. Neuron 1 receives an applied current `i1` and neuron 2 receives an applied current `i2`. Other than these parameters, the neurons are identical. Both neurons are at rest.

1. Change the initial value of neuron 1 `v1` from -67 to -60. This will cause the neuron to fire a pulse. Use the "graphics" "add curve" option to add the voltage of cell 2 (`v2`) to the plot. It should be flat. Increase the synaptic conductance `gsyn1=.05` which impinges on cell2 from cell 1. Reintegrate the equations. Note that a spike occurs in both cell1 and cell2 since the firing of cell 1 depolarizes cell 2. Lower the conductance until there is no more spike. Observe a slight depolarization of cell 2 but no firing. What is the minimal conductance needed to elicit a spike? Now set `gsyn1=.1, gsyn2=.1` Integrate the equations. What happens? Set both conductances to 0.15. Integrate the equations. What happens? Can you explain what is going on? What is the phase difference between the cells? Are they synchronized or not? Would this behavior happen if the cells were mutually inhibitory ? How about if one is excitatory and the other inhibitory?

2. Now set `i1=1,i2=1.05, gsyn1=.05,gsyn2=.05` and integrate the equations with mutual excitatory coupling. What sort of behavior is observed? To see the steady state behavior, you may want to integrate for a longer period of time.

3. Make cell 2 inhibitory by changing `vsyn2=-80`. Change `i1=.5, i2=0, gsyn1=.1,gsyn2=.2` Integrate for 400 msec. Calculate the period of the oscillation. Change the decay rate of the inhibitory synapse (`beta2=.1` and recalculate the period. Also do the same thing for `beta2=.05`. Explain why the period is getting longer.

4. Here is a last example of the complexities of network behavior. Set `vsyn1=0, vsyn2=-80, alpha2=.5,beta2=.01, gsyn1=.01 gsyn2=1, i1=3,i2=0`. Set the total integration time to 1000. Integrate the equations. What do you see? Explain the behavior. How would you modify `gsyn1` to get fewer cell 1 spikes per cell 2 spike? How would you get more cell 1 spikes per cell 2 spike?

This exercise should give you an appreciation of how complex even simple networks can get. Synapses provide a powerful computational tool for sculpting complex behaviors out of simple networks. You can now imagine how complex behavior can be when all of the channels that we have previously described are added to the network. The fact that such models are tremendously complex and that solving these "detailed" (not really as fasr as the real biology is concerned) models is computationally expensive makes one ask how can one distinguish between models and how useful can these methods be? For this, reason, in the next set of lectures, we will look at simplified versions of these models and their computational properties.