

## Stochastic\_Models

**16-1.** The modeling that we have discussed thus far is deterministic modeling governed by differential equations. However opening of ion channels is essentially a stochastic process. We use the deterministic approach when the number of channels is large so that individual variations that may occur are averaged out, and this is valid in most cases. However, there are situations when the deterministic approach is not entirely adequate. A stochastic approach is needed if the number of channels is small, and stochastic variations may influence whether a neuron fires an action potential when the voltage is near threshold.

How does one do stochastic models? What is Monte Carlo modeling? Monte Carlo is a location known for race cars and gambling and Monte Carlo modeling is the “invention of games of chance whose behavior and outcome can be used to study interesting phenomena”.

Some examples of Monte Carlo modeling are

--to compute the odds of winning at solitaire following a given strategy

--Numerical integration (pick random numbers in a space of known area. The proportion of random numbers in the region of interest compared to the total area given the integral!)

--population growth. Population growth can be described deterministically by  $N(t) = N_0 \exp(kt)$ . To model population growth stochastically we pick a random number between 0 and 1. We can say a birth has occurred to increase the population by 1 if the random number is between 0 and 0.2, a death has occurred to decrease the population by 1 if the random number is between 0.2 and 0.38, and there is no change in the population (no birth and no death, or both) if the random number is between 0.38 and 1. We can illustrate this on a number line.

The basis of stochastic modeling or Monte Carlo modeling is to select random numbers to make decisions. This requires that we have very good random number generators. Unfortunately it is very difficult to generate a very good random number generator. Every random number generator repeats its sequence of numbers after a while. In addition, rare events will require random number generators that have many digits of precision.

**16-2.** We have already seen examples of stochastic models in this course. Here is a binding scheme for glutamate binding to NMDA receptors. There is one open state on the upper right and many closed states. From the rate constants we can compute transition probabilities.

Transition probabilities are usually computed as rate constant times  $\Delta t$ .

Here are two examples of stochastic simulations. In the upper graph the number of open NMDA channels reached as high as 9 even though the peak with a deterministic simulation was near 3. In the lower graph, the peak number was 4 but this was achieved more than 20 ms after the peak in the deterministic calculation. Note also in both graphs that the number of open channels drops to 0 at a few different time points. The dashed line in these plots is the deterministic solution and the solid line is the average of 10 stochastic simulations. You can see that the average of the stochastic simulations approaches the deterministic solution.

**16-3.** How do we get transition probabilities from rate constants. Suppose we look at the reaction illustrated here for an open channel closing with rate  $\alpha$ .

The probability that the channel is closed at time  $t+\Delta t$  given that it is open at time  $t$  is what? The closing rate times  $\Delta t$  or  $\alpha\Delta t$ .

The probability that the channel remains open at time  $t+\Delta t$  given that it is open at time  $t$  is what?

Just 1 minus the previous probability or  $1 - \alpha\Delta t$

These are conditional probabilities.

The probability the channel is open at  $t+\Delta t$  is equal to the probability the channel is open at  $t$  times the probability that the channel is open at  $t+\Delta t$  given it is open at time  $t$ . We can say  $P_o(t+\Delta t) = P_o(t) * (1 - \alpha\Delta t)$  where  $P_o$  is the probability of being open

If we expand this, move the  $P_o(t)$  to the left hand side, divide by  $\Delta t$ , and take the limit as  $\Delta t$  goes to zero we can get a differential equation

$dP_o/dt = -\alpha P_o(t)$  This is easily solved  $P_o(t) = \exp(-\alpha t)$ . Then the probability the channel is closed  $P_c(t) = 1 - \exp(-\alpha t)$ . We can think of this latter function as the distribution function for closing.

So if we are doing a simulation, there are 2 approaches we can use: 1) We can increment the simulation by  $\Delta t$  and ask at each time step whether the channel closed, or 2) we can determine the time when the channel closes.

For the first method, the distribution function for closing is  $1 - \exp(-\alpha t)$  (which says that the channel is closed for very large  $t$ ). Then given  $\alpha$  and  $t$  (actually  $\Delta t$ ) we can pick a random number and compare it to the probability of closing. The probability of closing is just  $1 - \exp(-\alpha\Delta t)$ . Now exponential functions are computationally expensive.

Recall the Taylor expansion for  $\exp(x) = 1 + x + x^2/2! + x^3/3! + \dots$  so

$1 - \exp(-\alpha\Delta t) = 1 - (1 - \alpha\Delta t + (\alpha\Delta t)^2/2 - (\alpha\Delta t)^3/6 + \dots)$  which is  $\approx \alpha\Delta t$  particularly since  $\Delta t$  is usually very small. So the probability of closing is  $\alpha\Delta t$ . If our random number is less than the probability of closing, then the channel closes. If not it remains open.

For the second method we determine the time when the channel closes. Here we pick a random number  $r_0$  and let  $r_0 = 1 - r_1$  (another random number between 0 and 1). Then we set the probability of closing  $1 - \exp(-\alpha\Delta t) = 1 - r_1$ . Then  $\exp(\alpha t) = 1/r_1$ . We solve for  $t$ , the time of closing and get  $t = 1/\alpha \ln(1/r_1)$

**16-4.** A few years ago there were several papers that studied the effect of channel noise. A review is given by White et al in Trends in Neuroscience in March 2000. Channel noise is generated by the random gating of voltage-gated ion channels.

The hypothesis is: Channel noise has measurable effects under normal conditions on the reliability and precision of spike timing.

Recall how we defined  $I_{Na}$ , the sodium current.  $I_{Na} = g_{Na}(V - E_{Na}) = \overline{g_{Na}} m^3 h(V - E_{Na})$

Now let's define  $g_{Na} = \gamma N p(V)$

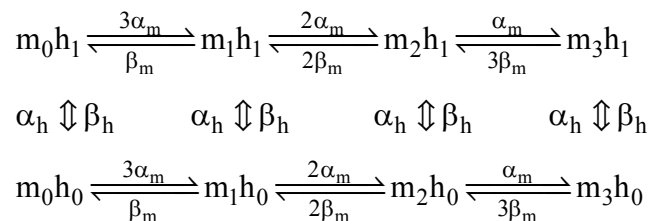
Where  $\gamma$  is the single channel conductance of a Na channel,  $N$  is the total number of Na channels, and  $p(V)$  is the probability (voltage-dependent) that the channel is open.

So how do we determine  $p(V)$ ?

**16-5.** To do this we have to consider the kinetic scheme for the transitions from the closed state to the open state. For the HH K channel such a scheme is

$n_0 \xrightleftharpoons[\beta_n]{4\alpha_n} n_1 \xrightleftharpoons[2\beta_n]{3\alpha_n} n_2 \xrightleftharpoons[3\beta_n]{2\alpha_n} n_3 \xrightleftharpoons[4\beta_n]{\alpha_n} n_4$  where  $n_4$  is the open state where all 4 gates are open. Each gate opens with rate  $\alpha_n$  and closes with rate  $\beta_n$  and the coefficient in the above scheme merely indicates the number of available gates that can do the indicated transition.

For the HH Na channel the kinetic scheme is a bit more complicated.



The only open state is the  $m_3 h_0$  state. The  $\alpha$  and  $\beta$  functions are the HH  $\alpha$  and  $\beta$  functions as indicated on this overhead for sodium.

**16-6.** Here is an example where there is no applied current and the membrane area is as indicated. Note that when the membrane area is small, the number of channels is small and the stochastic variations allow action potentials to occur quite often. When the membrane area is  $400 \mu\text{m}^2$  there is a sufficiently large number of channels so that voltage does not exceed threshold. The channel densities in this figure are standard HH densities.

**16-7.** With  $g_{\text{Na}} = \gamma N p(V)$ , if  $N$  is large, what is the problem?

--What the simulations show is that neurons do not have a precise threshold and this is due to channel noise (Sigworth). This accounts for the non-deterministic threshold. Small numbers of channels changing state can make a big difference near threshold.

--The contributions of noise tend to be important when the probability of opening is low—below threshold the number of open channels is relatively small.

--Random Na openings can be regenerative.

--Noise goes down only as the square root of  $N$ , so noise can be significant even with  $N$  large. A very large  $N$  would be costly to the cell.

DC input (response to current injection) has low reliability and low accuracy. The information is exclusively in the spike rate and not in the timing of the spikes.

However, reliability and precision of spike timing are high for strongly fluctuating inputs whose variations override the inherent channel fluctuations. The channel fluctuations are more significant for smooth inputs (i.e. DC) and firing time becomes less reliable. Neurons fire most reliably in response to stimuli with significant frequency content close to the preferred firing frequency of the cell.

**16-8.** This figure from the White article illustrates these points regarding the uncertainty in threshold that comes with channel noise.

In A we see the response to constant current input for 5 ms. The current is set to be near the threshold. We see that when a spike is produced, it does not always occur at exactly the same time.

In B we see the probability of a spike as a function of current amplitude. If channel openings were deterministic there would be a precise threshold at 100%. However, because of channel noise, there is some spread in the probability around 100 %.

In C we see the spread of the probability response for different numbers of sodium channels, where the different spread numbers were due to different membrane areas. The spread is proportional to the square root of N.

In D we see results similar to those we saw earlier. There is much spontaneous activity when the number of channels is low, but not when the number is high.

In E we see the firing frequency as a function of current. In the deterministic case there is no firing until the current exceeds a minimum and then the firing frequency jumps directly, in this case, to 50 Hz and then increases with further current injection. However in the stochastic simulations there is a smoother increase in spike frequency with current depending on the number of Na channels.

**16-9.** How do we do the models? (See Box 2 in White et al article)

There are several methods. Students in Peter Jung's lab have reported results with various methods in the past. I will discuss Methods similar to those mentioned earlier.

The first method is to follow the fate of each channel.

Given Voltage, compute transition probabilities

For each channel

Get its state

Pick a RN

Determine if a change of state occurs

Update state

Get next channel and repeat

Compute the new voltage given the new conductance given by  $\gamma N_{\text{open}}$

Repeat for the next  $\Delta t$

This method involves lots of bookkeeping and so is computationally expensive

It needs a random number for each channel at each  $\Delta t$

You still need a small  $\Delta t$  ( $\sim 1\mu\text{s}$ ) because Na transitions are rapid

This method is inefficient for N large.

There is a binomial variation on this approach where you keep track of the total number of channels in each state. Then compute the probabilities that 0, 1, 2, etc change state in  $\Delta t$ . Pick a random number and update.

A second method is the Gillespie method. Here you keep track of the total number of channels in each state and then determine 1) the time to the next transition and 2) which transition occurred.

Given the total number of channels in each state

Given voltage, compute the effective rate for the next transition,  $\lambda$ . To do this compute  $\lambda$  where  $\lambda = \sum N_i \alpha_{ij}$  where  $\lambda$  is the overall rate constant,  $N_i$  is the number of channels in state  $i$  and  $\alpha_{ij}$  is the rate constant to go from state  $i$  to state  $j$

Pick a random number to determine the time of the next transition. (No transition with Probability  $\exp(-\lambda t)$  and a transition with probability  $1 - \exp(-\lambda t)$ . Let  $1 - \exp(-\lambda t) = 1 - \text{random number}$  and solve for  $t$ . As before  $t = 1/\lambda \ln(1/\text{RN})$ .

Now that you know the time of the next transition, pick a RN to determine the particular Transition that occurred.  $\text{Transition}(k) < \lambda * \text{RN} < \text{transition}(k+1)$

Update the number of channels in the appropriate states

Compute the new voltage

Repeat

Only 2 random numbers are needed per  $\Delta t$  with this method, but  $\Delta t$  could be very, very small, particularly with lots of channels. This is a disadvantage of this approach.

**16-11.** I mentioned MCell to you earlier this quarter. MCell is software that uses Monte Carlo techniques to simulate diffusion and ligand binding to receptors. It is available from <http://www.mcell.cnl.salk.edu> or <http://www.mcell.psc.edu> (sites where the authors Bartol and Stiles reside!)

There is an outstanding problem with stochastic models of this type and that is that diffusion and reaction when both reactants can diffuse is a difficult problem. The next version of MCell is supposed to be able to handle this.

If we look at reaction and diffusion in a dendritic spine, we can see this problem. The Gillespie algorithm applies to homogeneous volumes only. We may not have this in spines. One way around this is to divide the volume into voxels and consider diffusion between voxels as a special reaction.

**16-12.** On this overhead I give some more details about the Gillespie algorithm to justify the method. This involves looking at the time evolution via what is called the Master Equation. I won't go into this at this time, but the details are here if you are interested.