Stochastic Homework

1. Run the Gillespie algorithm on the Brusselator. I have put an XPP file on the web `bruss_gill.ode` for you to try if you do not want to implement it yourself. The ode file is well annotated. Note in the simulation, that the limit cycle is quite regular. This is because there are many molecules. Cut the num,ber of molecules by a factor of 100. (This will mean that you may have to change the parameters, `c1a,c2b,c3,c4`; it is your job to figure out which ones based on the scaling arguments from class.) You should also change the initial conditions by a factor of 100. Go into the Numerics menu and change the total number of reactions from 1000000 to 10000 and the output nOut from 1000 to 10. Rerun the simulation. You should see a limit cycle but it is much noisier.

   The Schnakenberg oscillator is another simple chemical model that have the following form:

   ```
   # u -> *  (c1)
   # A -> v  (c2)
   # 2 u + v -> 3u (c3)
   # B -> u  (c4)
   ```

   Write the deterministic equations for this assuming rate constants that are all 1. Next, how do the rate constants scale with the number of molecules. Finally, implement it using the Gillespie algorithm. Here are parameters that have worked for me `c2a=90,c1=1,c3=.0001,c4b=10` with initial data `u=100,v=100`.

2. In this next rather lengthy problem, we will simulate and then analytically solve for a membrane model with a stochastic channel. We considered a stochastic model with a random sodium channel in class. Instead, we will look at a simpler but essentially identical problem:

   $$\frac{dx}{dt} = -x + z(2 - x)$$

   where z flips between 0 and 1. The rate $0 \to 1$ is α and the rate $1 \to 0$ is β. We will first simulate this for a long period of time and collect a histogram of the variable x under the conditions that $z = 1$ and $z = 0$. This will approximate the probability distribution of x when the channel is open or closed. Here is an ODE file if you want to use XPP:

   ```
   x'=-x+z*(2-x)
   par a=4,b=4
   markov z 2
   {0} {a}
   {b} {0}
   @ total=5000,dt=.1,maxstor=100000,meth=euler
   done
   ```

Now, here is how to collect the histogram:

(a) Run the ODE file and integrate the equations. You have just collected 50000 points for the process.

(b) Click on nUmerics, stocHastic, Histogram. Fill in the numbers as follows

- Number of bins: 100
- Lo: 0
- Hi: 1
- Variable: X
- Condition: z==1

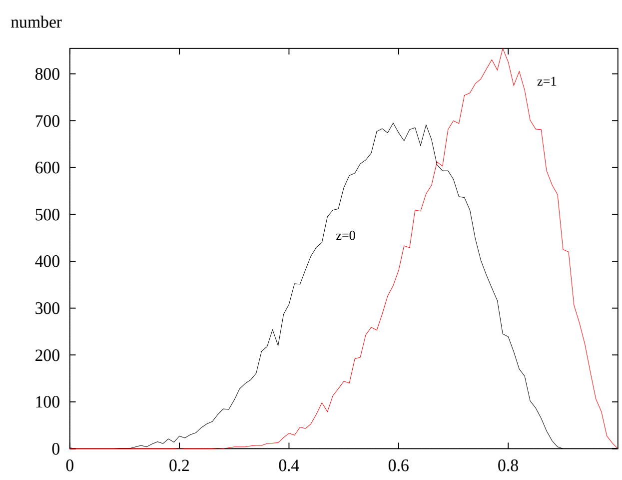
and the histogram is computed.

(c) Click Escape to leave the numerics menu. Click on Xi-vs-t and you will see a the histogram. This is the histogram for the open state.

(d) Click on Graphics, Freeze, Freeze, and change the color to 1, then click OK to permanently store this curve.

(e) Click on nUmerics, stocHastic,Data to restore the data. Then Click on stocHastic Histogram again and fill it in exactly as above, except for the Condition, which should be set to `z==0`. Escape to the main menu and click on Restore to get the distribution for the off state `z=0`.

(f) Make a hard copy of this - you can save it as postscript if you want – click on Graphics Postscript



You have a nice stochastic approximation of the distributions. It will look a little like the figure in the book but not as smooth. Repeat this same procedure, but this time change α, β from 4 to 1. You will see quite a different pair of histograms.

Next we write probability distribution function, $P_j(x,t)$ which is the probability for x at time t given channel state $j = 0, 1$. From the book, the equations are

$$\begin{aligned}
\frac{\partial P_0}{\partial t} &= -\frac{\partial}{\partial x}\left(f_0(x)P_0\right) + \beta P_1 - \alpha P_0 \\
\frac{\partial P_1}{\partial t} &= -\frac{\partial}{\partial x}\left(f_1(x)P_1\right) - \beta P_1 + \alpha P_0
\end{aligned}$$

where

$$f_z(x) = -x + z(2-x)$$

and $z = 0, 1$. Since $0 < x < 1$, that is the variable x always lies between the two equilibria, this equation is defined on the interval $0 < x < 1$. In addition to the equations there are two boundary conditions that must be imposed. We point out that if the channel is open $z = 1$, then $x = 0$ can never be reached, so that $P_1(0,t) = 0$ and if the channel is closed, then $x = 1$ can never be reached, so $P_0(1,t) = 0$. We could try to solve these numerically and then let the solutions to evolve to a steady state, but instead, I want you to compute the steady state distribution. This satisfies the pair of ordinary differential equations:

$$\begin{aligned}
\frac{d}{dx}\left(f_0 P_0(x)\right) &= \beta P_1 - \alpha P_0 \\
\frac{d}{dx}\left(f_1 P_1(x)\right) &= -\beta P_1 + \alpha P_0
\end{aligned}$$

along with boundary conditions $P_0(1) = P_1(0) = 0$. How can we solve these? Here is a hint. First add them together to obtain:

$$\frac{d}{dx}\left(f_0P_0 + f_1P_1\right) = 0.$$

This implies that

$$f_0P_0 + f_1P_1 = C$$

where C is a constant. Use the definition of f_j and the boundary conditions to show that $C = 0$. This means

$$P_1 = -(f_0/f_1)P_0.$$

Thus, we get

$$\frac{d}{dx}\left(f_0P_0(x)\right) = -(\beta\frac{f_0}{f_1} + \alpha)P_0.$$

Evaluating the derivative of f_0P_0, we get

$$-x\frac{dP_0}{dx} - P_0 = -(\beta\frac{f_0}{f_1} + \alpha)P_0$$

which then becomes

$$\frac{dP_0}{dx} = \frac{\beta\frac{f_0}{f_1} + \alpha - 1}{x}P_0$$

This is a linear separable differential equation! Solve it for $P_0(x)$ up to a normalization constant and use it to get $P_1(x)$. The normalization is just so that the integral of $P_0(x) + P_1(x)$ is 1 and does not change the shapes of the functions. Graph $P_j(x)$ for $\alpha = \beta = 4$ and for $\alpha = \beta = 1$ and compare the shapes to the simulated histograms. Find the critical values of the rates, α, β which lead to qualitatively different distributions. (For example, peaks in the middle or singular at the end points).

3. Simulate the stochastic Morris-Lecar system for $N = 10, 25, 50, 100, 500$ channels to get the last figure in Chapter 11. I have included the file, `stoch_ml.ode` on the web for you. Here is the XPP code

```
v(0)=-40
w(0)=1
wiener b
par n=100
minf=.5*(1+tanh((v-v1)/v2))
winf=.5*(1+tanh((v-v3)/v4))+.05
tau=1/(phi*cosh((v-v3)/(2*v4)))
gam=((1-2*winf)*w+winf)/(n*tau)
dv/dt=(iapp-gl*(v-vl)-gk*max(w,0)*(V-Vk)-gca*minf*(v-vca))/c
dw/dt=(winf-w)/tau+sqrt(gam)*b
par iapp=10,vk=-70,c=1,gk=2,vca=100,gca=1.333,vl=-50,gl=.5,v1=-1,v2=15
par phi=.333,v3=10,v4=14.5
@ total=500,dt=.01,nout=10,meth=euler
@ xlo=0,xhi=500,ylo=-60,yhi=50,maxstor=10000
done
```

4. This last problem is a chemical reaction one and not really a stochastic problem. However, it does have to do with the distribution of lengths of a polymer. Suppose that we have a fixed amount of cellular free actin, A. This can polymerize. The dimerization is different from the subsequent polymerization. Here are the reaction steps:

$$\begin{aligned} A + A &\rightleftharpoons D_2 \\ D_n + A &\rightleftharpoons D_{n+1} \quad \text{for} \quad n \geq 2 \end{aligned}$$

Assume the forward and backward dimerization reaction rates are k_d^+, k_d^- respectively and that the forward and backward rates for subsequent polymerization are k^+, k^- respectively. Write equations for the concentrations of $A, D_2, D_3, \ldots, D_j$. Make sure you note that the breakup of the dimer produces two A's and that the dimerization uses up two A's. Let B be the total actin both polymerized and free. Show that

$$A + 2D_2 + 3D_3 + \ldots + nD_n + \ldots = B.$$

Note that this had better be the case since this is just the total monomerized actin! Now we will look for a steady state solution to this. We can ignore the A equation since we have the above constraint on total actin. Write down the steady state solution for the $j-$mer, D_j by showing it satisfies (for $j < 2$):

$$k^+ AD_{j-1} + k^- D_{j+1} - (k^- + k^+ A)D_j = 0$$

Show that $D_j = C\lambda^j$ is a solution to this problem and show that $\lambda = 1, rA$ are the roots where $r = k^+/k^-$. Since the total actin is the infinite sum above, conclude that λ cannot be 1. Use the equation for the dimer D_2 to find the unknown constant C in terms of A and the parameters. Finally use the following summation formula,

$$\sum_{j=1}^{\infty} jx^j = \frac{x}{(1-x)^2}$$

to show that the free actin satisfies an equation of the form:

$$f(A) = B$$

where $f(A)$ is a function of A and the parameters. Show that $rA < 1$ so that the infinite series converges. Plot $f(A)$ given $k^+ = 2, k^- = 1, k_d^+ = .25, k_d^- = .05$.