Problem Set 2 for Biomath 202: Due May 3, 2011

1. Analyze the robustness of the steady state level of $X$ with respect to cell-cell variation in the production rate, $\beta$, for the autorepression, studied in class, with Hill function $1/(1+(X/K)^n)$ in the limit $X \gg K$. Calculate the parameter sensitivity coefficient of the steady state concentration, $X_{st}$, with respect to $\beta$. The parameter sensitivity coefficient of property $A$ with respect to parameter $B$, denoted $S(A,B)$, is defined as the relative change in $A$ for a given small relative change in $B$, that is,

$$S(A,B) = (\Delta A / A) / (\Delta B / B) = (B / A)(dA / dB).$$

How does this change as $n$ increases?

2. During development from an egg to an embryo, cells need to make irreversible decisions to express the genes appropriate to their designated tissue types and repress other genes. One common mechanism is positive transcriptional feedback between two genes. There are two types of positive feedback made of two transcription factors. The first type is of two positive interactions $X \rightarrow Y$ and $Y \rightarrow X$. The second type has two negative interactions $X \rightarrow |Y$ and $Y \rightarrow |X$. Describe the stable steady states in each type of feedback? Which type of feedback would be useful in situations where genes regulated by both $X$ and $Y$ belong to the same tissue? Which would be useful when genes regulated by $X$ belong to different tissues than the genes regulated by $Y$?

3. The four-node diamond pattern occurs when $X$ regulates $Y$ and $Z$, and both $Y$ and $Z$ regulate $W$.
   a. How does the mean number of diamonds scale with network size in random ER networks?
   b. What are the distinct type of sign combinations of the diamond (where each
edge is either activation or repression)? How many of these are coherent?

4. a. Derive the first two results in Table 1 of Itzkovitz and Alon. That is, show for the geometric model that $\langle G_x \rangle = N(k)^2 / 2$ in both 1d and 2d. This matches the Erdos-Renyi (ER) result, but it is incorrect to use the ER formula. Instead, start with the analogous formula to Eq. 2 (but for wedges instead of triangles) and use $F_g$ as defined by Eqs. 3 and 4. (Hint: Use or derive results for Gaussian integrals.)

b. Why do the geometric and ER models match in this case? Compare the formula for $\langle G_\Delta \rangle$ to $\langle G_x \rangle$ and think about the calculation in (a) for help.

5. a. The Fibonacci rule is $a_{n+1} = a_n + a_{n-1}$. Show that in the limit $n \to \infty$, the ratio of consecutive coefficients is the Golden Ratio $\frac{1 \pm \sqrt{5}}{2}$. What is the trajectory of the coefficient if the ratio starts out at -1, -1/2, 1, or 2?

b. If we extend the Fibonacci rule to $a_{n+1} = a_n + a_{n-1} + a_{n-2}$, what is the value of the ratio of consecutive coefficients in the limit $n \to \infty$? The Fibonacci rule and Golden ratio appear often in nature. Do you think our new rule would also appear often in nature?
6. Discuss how you would construct equations like those in Mileyko et al. for the feed forward loop.

For the connections X->Y and X->Z, which circuit and equations in Mileyko et al. does this most resemble? Which equations or terms would change? What about for Y->Z? What about for the production of Z? Which equation would best describe that?

7. We have seen in Mileyko et al. that zeros can play an important role in determining the dynamics of a system. Show that the power series \( \sum_{n=0}^{\infty} a_n x^n \)

representation of \( \sum_{n=0}^{\infty} \frac{x^n (x-1)^{2n}}{n!} \) cannot have three consecutive zero coefficients?

(Hint: Derive the differential equation for this series.)

EXTRA CREDIT

8. Rewriting series in terms of integrals and vice versa is often central to approximations for our modeling approach. Show that we can express the ratio of the following two series as a Gaussian-type integral

\[
\frac{x + \frac{x^3}{3 \cdot 1} + \frac{x^5}{5 \cdot 3 \cdot 1} + \frac{x^7}{7 \cdot 5 \cdot 3 \cdot 1} + \ldots}{1 + \frac{x^2}{2 \cdot 1} + \frac{x^4}{4 \cdot 2 \cdot 1} + \frac{x^6}{6 \cdot 4 \cdot 2 \cdot 1} + \ldots} = \int_0^\infty e^{-\frac{t^2}{2}} dt
\]