Student Name:

7.32/7.81J/8.591J: Systems Biology

Final Exam, 2013

Instructions
1) Please do not open the exam until instructed to do so.
2) This exam is closed-book and closed-notes.
3) Please do all problems.
4) Please show all work.
5) Use the back of sheets if you need more space.
6) Have a good holiday.

Scores

1 (out of 8):

2 (out of 7):

3 (out of 9):

4 (out of 6):

5 (out of 5):

6 (out of 9):

7 (out of 6):

8 (out of 14):

9 (out of 12):

10 (out of 12):

11 (out of 15):

12 (out of 15):

13 (out of 15):

Total (out of 133):

1) Response Time (8 points)

a. Compared to simple regulation, which of these strategies may decrease the time necessary to increase protein concentration to the (non-zero) equilibrium? (4 pt)

Faster division   Negative autoregulation

Increased degradation   Coherent FFL

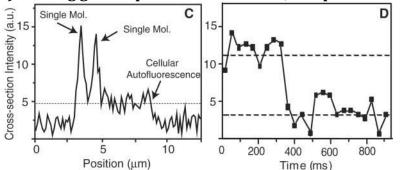Positive autoregulation   Incoherent FFL

b. Compared to simple regulation, which of these strategies may decrease the time necessary to decrease the protein concentration to the equilibrium of zero? (4 pt)

Faster division   Negative autoregulation

Increased degradation   Coherent FFL

Positive autoregulation   Incoherent FFL

2) Diffusion through a pore (7 points)

a. Consider a membrane that separates two fluid reservoirs. The membrane is impermeable to protein which is present at concentration c on the right side, but there is a small round hole in membrane with radius R. Use dimensional analysis to determine how the flow rate of protein scales with the concentration c, radius R, and diffusion constant D. (4 pt)
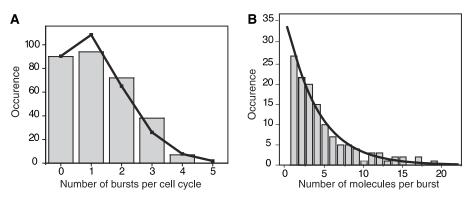
b. How does the total flow rate change if a second identical pore is added far from the first pore? (3 pt)

3) Probing gene expression in live cells, one protein molecule at a time (9 points)

a. In subplot (D), what are the authors trying to show? (3 pt)

b. Consider the black fits in each of the two plots above analyzing bursts of protein production. (6 pt)

Figure A:

1. Name of distribution:

2. Equation describing distribution:
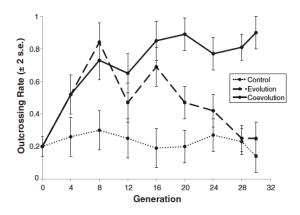
3. Approximate parameter value(s) in the fit:

Figure B:

1. Name of distribution:

2. Equation describing distribution:

3. Approximate parameter value(s) in the fit:

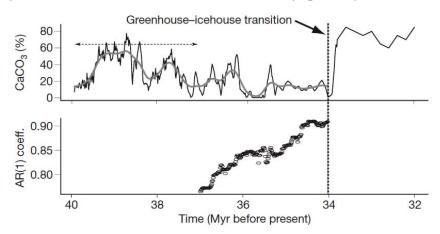**4) The Evolution of Sex: Running with the Red Queen (6 points)**

a) In one sentence, summarize the main argument of this paper. (2 pt)

b) Figure 1 of the paper is below. What is the experimental difference between the three conditions listed? (4 pt)

5) Bifurcations and critical transitions (5 points)

a. What are the authors trying to demonstrate in this plot? (3 pt)

b. Name one other proposed early warning indicator of an impending bifurcation that is based on critical slowing down. (2 pt)

6) Populations in space (9 points)

You are interested in studying the expansion in space of a population that can be described by the following equation:

$$\frac{\partial n}{\partial t} = rn(1 - n^2) + D\frac{\partial^2 n}{\partial^2 x}$$

a. How is this population different from a population that experiences standard logistic growth? Starting from a uniform population $n(x,t=0) = 0.1$, will this population saturate more rapidly, less rapidly, or at the same rate as a logistically growing population? Why? (3 pt)

b. Will this population expand as a "pull" wave or as a "push" wave? Why? (2 pt)

c. Using dimensional analysis, approximately what will be the velocity with which this population expands into new territory? (2 pt)

d. As compared to a logistically growing population, will this population's wave velocity be larger, smaller, or the same? Why? (2 pt)

7) Neutral Theory in Ecology (6 points)

Figure 1 Data on tree species abundances in 50-hectare plot of tropical forest in Barro Colorado Island, Panama[4]. The total number of trees >10 cm DBH in the data set is 21,457 and the number of distinct species is 225. The red bars are observed numbers of species binned into $\log_2$ abundance categories, following Preston's method[5]. The first histogram bar represents $\langle \phi_1 \rangle/2$, the second bar $\langle \phi_1 \rangle/2 + \langle \phi_2 \rangle/2$, the third bar $\langle \phi_2 \rangle/2 + \langle \phi_3 \rangle + \langle \phi_4 \rangle/2$ the fourth bar $\langle \phi_4 \rangle/2 + \langle \phi_5 \rangle + \langle \phi_6 \rangle + \langle \phi_7 \rangle + \langle \phi_8 \rangle/2$ and so on. The black curve shows the best fit to a lognormal distribution $\langle \phi_n \rangle = \frac{N}{n}\exp(-(\log_2 n - \log_2 n_0)^2/2\sigma^2)$ ($N = 46.29$, $n_0 = 20.82$ and $\sigma = 2.98$), while the green curve is the best fit to our analytic expression equation (7) ($m = 0.1$ from which one obtains $\theta = 47.226$ compared to the Hubbell[2] estimates of 0.1 and 50 respectively and McGill's best fits[3] of 0.079 and 48.5 respectively).

Volkov, I., J. Banavar, et al. "Neutral Theory and Relative Species Abundance in Ecology." *Nature* 424 (2003): 480–81. Courtesy of Nature Publishing Group. Used with permission.

a. What is the mean number of individuals per species in this data set? (2 pt)

b. What is the most likely number of individuals for a species to have? (2 pt)

c. In the neutral theory of ecology, how would the above histogram shift if the researchers studied the distribution of species abundance on the mainland? (2 pt)

8) Binding and unbinding (14 points)

Consider two proteins X and Y which bind with dissociation constant K (units of concentration).

a. If $[X]_T = [Y]_T = 2K$, what fraction of X is bound? (3 pt)

b. Assuming that $[X]_T = 2K$, plot the fraction of X bound as a function of the total concentration of Y. You do not need to do the calculation if you can draw an accurate plot with the correct limits labeled. (4 pt)

c. Assuming that $[X]_T = 2K$, plot the fraction of Y bound as a function of the total concentration of Y. (4 pt)

d. Assume that the mean lifetime of the XY complex is 1ms. Draw the probability distribution for the time that a complex will dissociate if it was formed 0.5ms ago. What is the mean of this distribution? (3 pt)

9) Understanding dimensionless models (12 points)

Consider the following model describing the interaction between two proteins u and v.

$$\frac{du}{dt} = \frac{\alpha_1}{1 + v^\beta} - u$$
$$\frac{dv}{dt} = \frac{\alpha_2}{1 + u^\beta} - \delta v$$

a. What is the biological interaction between these two proteins? (2 pt)

b. What does u = 1 correspond to? (2 pt)

c. What is the definition of time? (2 pt)

d. How does the effective lifetime of protein v compare to the lifetime of protein u? (2 pt)

e. If we add a degradation tag to protein u then which parameters in the model change? Do the numerical values increase or decrease? (4 pt)

10) Games in populations (12 points)

Consider the following pay-off matrix describing a game, with b > c > 0:

$$
\begin{array}{c c}
 & \begin{array}{cc} A & B \end{array} \\
\begin{array}{c} A \\[1.5em] B \end{array} &
\left(\begin{array}{cc} b - \dfrac{c}{2} & b - c \\[1em] b & 0 \end{array}\right)
\end{array}
$$

a. In a population of cells in which all cells interact with all others via this game, plot the resulting payout of genotype A and genotype B as a function of f_A, the fraction of the population that is genotype A. (4 pt)
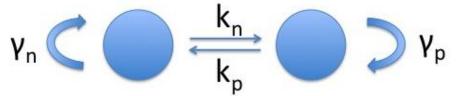
b. If A and B are heritable genotypes, then what is the final composition of the population? (3 pt)

c. Is either pure strategy a Nash Equilibrium? Why or why not? (2 pt)

d. In the context of a two-person game, what is the Nash Equilibrium Strategy? How does this relate to the outcome that you found in part (b)? No calculation is required. (3 pt)

11) Persister formation and antibiotics (15 points)

A classic example of bet-hedging within the microbial realm is the formation of persister cells, which divide slowly but are resistant to antibiotics. In this problem we will consider a simple model of persistence in which normal cells (n) switch reversibly into persister cells (p). The division rate of the normal and persister cells are γ_n and γ_p, respectively.

a. Write down the two differential equations describing the rate of change of the number of normal and persister cells. (3 pt)

b. Set $\gamma_n = 1$, $\gamma_p = 0$, and assume that $k_p = 1$. Calculate the rate of exponential growth of the population and the equilibrium fraction of persister cells. Simplify your expressions assuming $k_n \ll 1$. One possible way to solve: Your answer to part a can be expressed as $\dot{\vec{x}} = A\vec{x}$. The largest eigenvalue of the matrix A and its associated eigenvector tell us about the rate of growth of the population as well as the equilibrium composition of the population. (7 pt)

c. If every time T (large compared to equilibration time) the population is briefly exposed to an antibiotic that kills all normal cells, what is the optimal switching rate k_n? (5 pt)

12) Predator-prey oscillations and the Lotka-Volterra model (15 points)

$$\frac{du}{dt} = au - buv$$

$$\frac{dv}{dt} = -cv + duv$$

a. Which is the predator and which is the prey? (2 pt)

b. In the Lotka-Volterra model there are predator-prey oscillations. What determines the amplitude of these oscillations? (3 pt)

c. Which parameters determine the period of the oscillations? You do not need to show work to get credit, but you may find it helpful to calculate the eigenvalues around the fixed point. (4 pt)

d. In the paper by Yoshida et al. the authors claimed that there were two primary differences between the predator-prey oscillations that they observed experimentally and those that they were expecting from models. What were they? (4 pt)

e. What was the explanation for these differences? (2 pt)

13) The evolution of virulence (15 points)

Consider the set of equations proposed by Nowak to model the evolution of virulence, where x is the number of non-infected hosts, y_1 is the number of hosts infected with parasite 1, and y_2 is the number of hosts infected with parasite 2:

$$\dot{x} = k - ux - x\left(b_1 y_1 + b_2 y_2\right)$$
$$\dot{y}_1 = y_1\left(b_1 x - u - v_1\right)$$
$$\dot{y}_2 = y_2\left(b_2 x - u - v_2\right)$$

a. At equilibrium only one of the two parasites will typically survive. Why? (2 pt)

b. Begin by considering the dynamics in the absence of parasite 2. Find an expression for equilibrium 1 (E1), in which parasite 1 survives and parasite 2 does not. (3 pt)

c. Parasite 1 is endemic (non-zero) when R_1, the basic reproductive ratio of parasite 1, is larger than one. What is the expression for R_1 and how can it be interpreted? (3 pt)

d. Show that if $R_2 > R_1 > 1$ then parasite 2 can invade equilibrium 1 and that parasite 1 cannot invade equilibrium 2 (when parasite 2 is present at non-zero number). (4 pt)

e. If infectivity is proportional to virulence $b = av$, then how will virulence evolve over time? (3 pt)

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