**Comprehensive Exam 2015**
**Biomath 202: Structure, Function, and Evolution of Biological Systems**

Consider a system of species, such as autotrophic (resource) species in an ecosystem or microbes in the gut. Also consider a set of stressors (e.g., predators/consumers, drugs, or abiotic factors like fires and drought) for which each stressor affects the growth rates of the species in the system.

1. Write down the expression for pairwise interactions given in class in terms of the relative fitness (i.e., growth rate) of a single bacteria species in the presence of a drug A, a drug B, and of the pairwise drug combination of A and B. What is the relative fitness measured "relative" to? If the relative fitnesses were replaced by absolute fitnesses, would you necessarily obtain the same categorization—synergistic, antagonistic, or additive—of pairwise drug combinations? Explain.
2. For the remainder of the test, you will consider interactions among the species, not among stressors (e.g., antibiotics) as we did in class. For interactions between two species, the growth rates that could be measured (in some standardized units) are the wild type growth rate of each species, the growth rate of each species in the presence of a stressor, the growth rate of both species together with no stressor, and the growth rate of each species when both are grown together in the presence of a stressor. This represents 6 potentially relevant growth rates. For this test, the interaction metric between two species will be based on the growth rate of one species relative to the growth rate of the other species. No interaction between two species is defined to be the case that the relative growth rate of the species grown together in the presence of the stressor is the same as the relative growth rate of the two species when each is grown in isolation in the presence of the stressor. That is, the growth rate of one species relative to the other is affected by the same amount whether the species are grown together or in isolation. Provide an equation that captures this definition. How many growth rates are needed for this equation? Can categories like antagonistic and synergistic still apply? If not, what categories might you use to describe the possible cases that correspond to different signs for this interaction metric? Try to still keep only 3 categories, counting no interaction as a category. You can assume that no 2 species have exactly the same growth rate.
3. Construct a color-coded interaction network that captures all of the pairwise interactions among 6 different species exposed to a single stressor, with data for this given in the table below. As for antibiotic interactions, let no interaction correspond to no link and no color, and let the other categories correspond to their own specific colors. In the table below, labels (S1...S6) are for each of the species. Assume wild-type growth rates in isolation for the 6 species are respectively (1, 2, 1.5, 0.7, 1.2, 2.3). Assume growth rates are ½ of this when two species are grown together with no stressor present. For the cells below, the two numbers

are the growth rates of each species, ordered by label (e.g., S1 growth rate is listed before S2 growth rate), for the two species grown together in the presence of the stressor. For cells that align a species with itself, the number given is the growth rate of the species grown in isolation in the presence of the stressor. The matrix is symmetric, so only values along the diagonal or below are given. You can give calculations for how you determine the interactions, but remember that you only need to determine the sign of the metric (positive or negative), not its value.

| | S1 | S2 | S3 | S4 | S5 | S6 |
|---|---|---|---|---|---|---|
| S1 | 0.8 | ---- | ---- | ---- | ---- | ---- |
| S2 | 0.6, 1.2 | 1.5 | ---- | ---- | ---- | ---- |
| S3 | 0.5, 0.4 | 1, 0.33 | 0.5 | ---- | ---- | ---- |
| S4 | 0.4, 0.3 | 1, 0.33 | 0.3, 0.1 | 0.6 | ---- | ---- |
| S5 | 0.4, 0.5 | 1.2, 0.8 | 0.4, 0.8 | 0.4, 0.8 | 1 | ---- |
| S6 | 0.6, 1.2 | 0.9, 1.2 | 0.3, 1.2 | 0.3, 0.9 | 0.7, 1.4 | 2 |

4. Can you monochromatically cluster the above network? Is the clustering unique? If not, give at least two examples of clustering (the trivial clustering of each species by itself does not count), and try to find examples in which the clusters have the same numbers of species. For drug interactions, the clusters seem to roughly correspond to mechanisms of action. Discuss what the clusters here might correspond to. Do you expect that other stressors would lead to similar interaction networks? Under what conditions might it be similar or different?
5. If there is a measurement error of 10% for each growth rate, how would you include this as uncertainty in the calculation for the interaction metric? Can you give one example for part 3 where the interaction metric identified an interaction that may not be statistically significant?
6. As in parts 3 and 4, construct a color-coded interaction network for the data in the table below. These data can be considered as either corresponding to a different stressor or to the same stressor with a different magnitude, such as a different concentration of a drug, more frequent fires, or higher temperatures. Note that the values in a few cells have changed in comparison to part 3. In addition, a seventh species has been added that has a wild type growth rate of 4 when it is in isolation and no stressor is present. Try to cluster this network by building on the clusters from your answer to part 4. Does this change your clustering from part 3 or just add in a species to a cluster that already existed?

| | S1 | S2 | S3 | S4 | S5 | S6 | S7 |
|---|---|---|---|---|---|---|---|
| S1 | 0.8 | ---- | ---- | ---- | ---- | ---- | ---- |
| S2 | 0.6, 1.3 | 1.5 | | | | | |
| S3 | 0.5, 0.4 | 1, 0.33 | 0.5 | ---- | ---- | ---- | ---- |
| S4 | 0.4, 0.3 | 1, 0.33 | 0.4, 0.1 | 0.6 | ---- | ---- | ---- |
| S5 | 0.4, 0.5 | 1., 0.8 | 0.4, 0.8 | 0.4, 0.8 | 1 | ---- | ---- |
| S6 | 0.6, 1.2 | 0.9, 1.2 | 0.3, 1.2 | 0.3, 0.9 | 0.7, 1.4 | 2 | ---- |
| S7 | 0.27, 1 | 0.6, 1.2 | 0.3, 2.1 | 0.3, 1.5 | 0.4, 1.6 | 1.2, 2 | 3 |

7. Forgetting the colors of the edges/links, and recalling the network motifs we learned about in class, how many triangle motifs are in your network in parts 3 and 6? How many square motifs are in your networks? Are these numbers more or less than you would expect for a random Erdos-Renyi network? Are self edges possible for this type of network?
8. If there is spatial heterogeneity or stochasticity in the magnitude of the stressor (e.g., concentration of a drug administered), how would you express the time evolution of the probability density of the magnitude of the stressor in terms of a Fokker-Planck (or Kolmogorov) equation? Derive or write down the equilibrium solution for the Fokker-Planck equation. Discuss what the form of the coefficients to the first- and second-order derivative terms might be. If there are multiple stressors/drugs, each with stochasticity in their concentration, how would you express a modified Fokker-Planck equation for that case?