List of problems, Math Systems Biology, Part 1

It is OK to discuss the problems with other students, but you should write your own solutions. I encourage use of the "wiki" to discuss, actually.

(**Note:** If you are having lots of trouble proving some formula, there is always the chance that I made a mistake!)

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1. Suppose that we have built a chemostat and we model it as usual, with a Michaelis-Menten growth rate. Moreover, we have measured all constants and, in appropriate units, have:

   $$V = 2 \quad \text{and} \quad k_{\max} = F = k_n = 1\,.$$

   What should the concentration of the nutrient in the supply tank be, so that the steady state concentration of bacteria is exactly 20? (Don't worry about units. Assume that all units are compatible.)

   Answering this question should only take a couple of lines. You may use any formula from the notes that you want to.

2. Suppose that we use a Michaelis-Menten growth rate in the chemostat model, and that the parameters are chosen so that a positive steady state exists.

   (a) Show that

   $$N = f(V, F, C_0) = \frac{C_0(F - VK_m) + FK_n}{\alpha\,(F - VK_m)}$$

   and

   $$C = \frac{FK_n}{F - VK_m}$$

   at the positive steady state.

   (b) Show that either of these: (a) increasing the volume of the culture chamber, (b) increasing the concentration of nutrient in the supply tank, or (3) decreasing the flow rate, provides a way to increase the steady-state value of the bacterial population. (Hint: compute partial derivatives.)

3. Suppose that we use $K(C) = kC$ (for some constant k) instead of a Michaelis-Menten growth rate, in the chemostat model.

   (a) Find a change of variables so that only *one* parameter remains.

   (b) Find the steady state(s). Express it (them) in terms of the original parameters. Determine conditions on parameters so that a positive steady state exists, and explain intuitively why these conditions make sense.

   (c) Compare the conditions you just obtained with the ones that we got in the MM case.

   (d) Determine the stability of the positive steady state, if it exists.

4. This is purely a modeling problem (there is no one "correct" answer!). We ask about ways to generalize the chemostat - just provide sets of equations, no need to solve anything.

(a) How would you change the model to allow for two growth-limiting nutrients? Now $K(C_1, C_2)$, the rate of reproduction per unit time, depends on two concentrations.[1] It is a little harder to write how the nutrients are being consumed in this multiple nutrient case. Think about this and be creative.[2]

(b) Suppose that at high densities the microorganism secretes a chemical that inhibits growth. How would you model that?

(c) Model the case when two types of microorganisms compete for the same nutrient.

5. This is yet another variation on the chemostat. Suppose that there is a membrane that filters the outflow, so that the microorganism never flows out (only the nutrient does). Assume, however, that the microorganism dies at a certain rate μN.

   (a) Write down a model, assuming $K(C)$ is Michaelis-Menten.

   (b) Find a change of variables that leads to a system with three parameters as follows:

$$\begin{aligned} \frac{dN}{dt} &= \alpha_1\left(\frac{C}{C+1}\right)N - \alpha_3 N \\ \frac{dC}{dt} &= -\left(\frac{C}{C+1}\right)N - C + \alpha_2 \end{aligned}$$

   (c) Show that there are two steady states, one with $N = 0$. Show that the second one has positive coordinates provided that:

$$\alpha_1 > \alpha_3 \quad \& \quad \alpha_2 - \frac{\alpha_3}{\alpha_1 - \alpha_3} > 0\,,$$

   (d) Show that this second equilibrium is always stable (if it has positive coordinates).

6. Consider the chemotherapy model (section "Effect of Drug on Cells in an Organ"). Suppose that $K(C)$ is Michaelis-Menten.

   (a) Show how to reduce the model to having just three constants.

   (b) There are again two steady states, one with $N = 0$. Find conditions under which there is a second one that has positive coordinates. Interpret biologically what your conditions mean.

   (c) In contrast to the chemostat (where the objective is to get the microorganisms to grow), it would be desirable if the equilibrium with $N = 0$ is stable and the second one either doesn't exist (in the positive quadrant) or is unstable. Why would a stable second equilibrium be bad? (Just one sentence, please.)

   (d) Find conditions guaranteeing that the equilibrium with $N = 0$ is stable and show that, under these conditions, the second equilibrium, if it is in the first quadrant, must be unstable.

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[1] One possibility if to use $K(C_1, C_2) = \max\{K_1(C_1), K_2(C_2)\}$, in the case in which the bacteria decide to use the nutrient that is in most abundance preferentially (this actually happens with certain sugar consumptions - a beautiful example of bacterial computation; search "lac operon" on the web). Another would be to take K as some linear combination of C_1 and C_2, etc. What is the least that one should assume about K, though?

[2] It is amusing to see can be found by typing

multiple nutrients chemostat

into Google (you might recognize some of the authors of the first paper that comes up :).

7. For the chemotherapy model discussed above, write a computer program in your favorite package (MATLAB, Mathematica, Maple, whatever) to simulate it (or use "Jode"), and plot solutions from several different initial conditions (show $N(t)$ and $C(t)$ versus t on the same plot, using different line styles such as lines and dots or dashes or different colors). Do so for sets of parameters that illustrate a few of the possible cases (second equilibrium exists as a positive solution or now; equilibrium with $N = 0$ is stable or not)

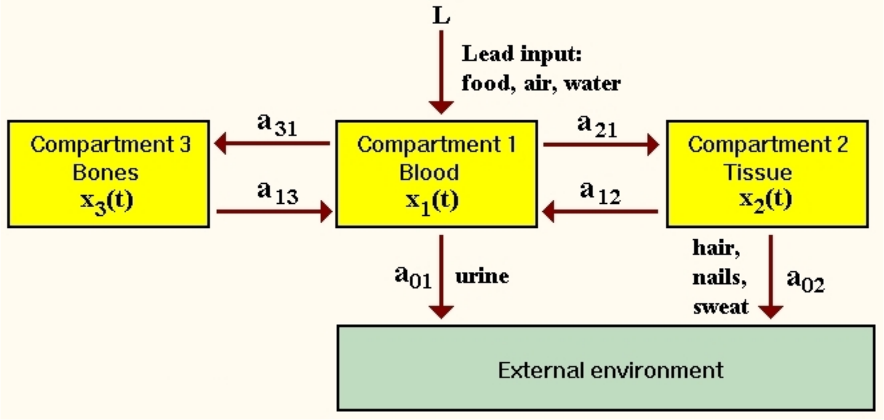
8. For the chemotherapy model discussed above, and assuming that parameters are so that the equilibrium with $N = 0$ is stable and the one in the positive orthant is unstable, there are two possibilities: (a) all solutions (except for a set of measure zero of initial conditions) converge to the equilibrium with $N = 0$ is stable; (b) there is set of initial conditions with nonzero measure for which solutions do not converge to the equilibrium with $N = 0$. Determine which is the case, and prove your conclusions rigorously. (Some numerical experimentation will be useful, of course.) *Warning: I just made up the problem and didn't work it out myself. I hope that it is not too hard!*

9. We base this problem on the following paper:

   M.B. Rabinowitz, G.W. Wetherill, and J.D. Kopple, "Lead metabolism in the normal human: stable isotope studies," in *Science*, vol. 182, 1973, pp. 725 - 727.

   as well as a writeup from the Duke Connected Curriculum Project (by L.C. Moore and D.A. Smith) (we use the wording from this writeup):

   Lead enters the human body from the environment by inhalation, by eating, and by drinking. From the lungs and gut, lead is taken up by the blood and rapidly distributed to the liver and kidneys. It is slowly absorbed by other soft tissues and very slowly by the bones. Lead is excreted from the body primarily through the urinary system and through hair, nails, and sweat:



   We model the flow of lead into, through, and out of a body with separate compartments for blood, bones, and other tissues, plus a compartment for the external environment. For $i = 1, 2, 3$, we let $x_i(t)$ be the amount of lead in compartment i at time t, and we assume that the rate of transfer from compartment i to compartment j is proportional to $x_i(t)$ with proportionality constant a_{ji}.

   We assume that exposure to lead in the environment results in ingestion of lead at a constant rate L.

   The units for amounts of lead are micrograms (μg), and time t is measured in days.

Rabinowitz et. al. (paper cited above) measured over an extended period of time the lead levels in bones, blood, and tissue of a healthy male volunteer living in Los Angeles. Their measurements produced the following transfer coefficients for movement of lead between various parts of the body and for excretion from the body. Note that, relatively speaking, lead is somewhat slow to enter the bones and very slow to leave them. The estimated rates are (units are days$^-1$):

$$a_{21} = 0.011, a_{12} = 0.012$$

(from blood to tissue and back),

$$a_{31} = 0.0039, a_{13} = 0.000035$$

(from blood to bone and back), and

$$a_{01} = 0.021, a_{02} = 0.016$$

(excretion from blood and tissue), and they estimated that the average rate of ingestion of lead in Los Angeles over the period studied was $L = 49.3\mu g$ per day.

(a) Find the steady state of the corresponding system. (You need to solve a set of three linear equations.)

(b) Now repeat the problem assuming that the coefficient for blood to tissue transfer is ten times bigger: $a_{21} = 0.11$.

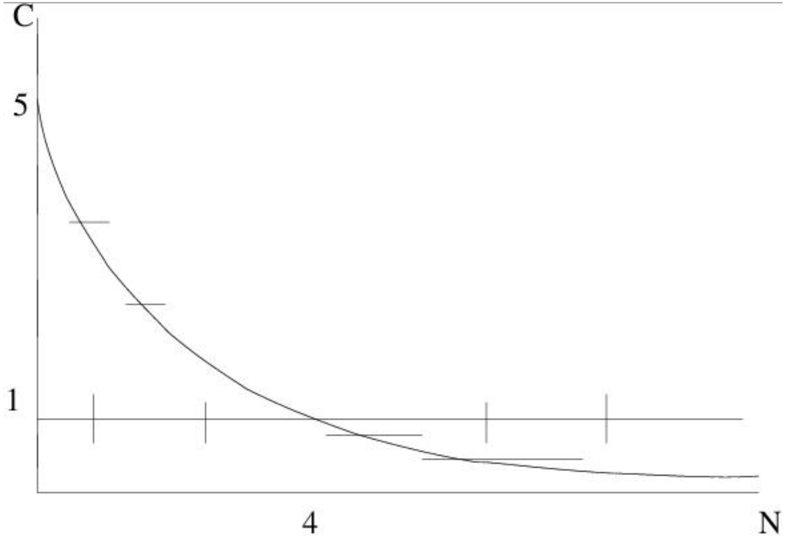
(c) Find the steady state of the modified system, and conclude that in steady state the amount of lead in the tissue is about three times higher than in the original model.

(d) Use a computer (MATLAB, Maple, Mathematica, JOde, whatever you prefer) to plot the amount of lead in the tissue, starting from zero initial conditions, for the original ($a_{21} = 0.011$) model, for two years. Notice that even after two years, the amount is not quite near steady state (it is about 620 μg). What is it after 100 years?

10. Consider this system of equations (which corresponds to a chemostat with $K(C) = C$):

$$\begin{aligned}\frac{dN}{dt} &= CN - N \\ \frac{dC}{dt} &= -CN - C + 5\,.\end{aligned}$$

The sketch below has the nullclines (there are vertical arrows on the C axis too).



(a) Label the C and N nullclines, and put directions on all arrows. Assign directions to the flows ("NE", "SE", "NW", "SW") in each of the sections of the positive quadrant, partitioned by the nullclines.

(b) Sketch on this diagram a rough plot of the trajectory which starts with a concentration $N = 4$ of bacteria and $C = 2$ of nutrient.

(c) For the system in part **A**, what is the linearization at the equilibrium $N = 4$, $C = 1$?

(d) For the system in part **A**, is the equilibrium $(4, 1)$ stable or unstable? Classify the equilibrium (saddle, spiral, etc). (You are not asked to compute eigenvalues and eigenvectors. It is OK to answer by referring to the trace/determinant plane picture in the notes.)

11. Take the SIRS model, and suppose that the parameters are so that a positive steady state exists. Now assume that a new medication is discovered, which multiplies by 20 the rate at which people get cured (that is, become "removed" from the infectives). However, at the same time, a mutation in the virus which causes this disease makes the disease 5 times as easily transmitted as earlier. How does the steady state number of susceptibles change?

    (The answer should be stated as something like "it is doubled" or "it is cut in half".)

    Answering this question should only take a couple of lines. You may use any formula from the notes that you want to.

12. Consider the following chemical reaction network, which involves 4 substances called M, E, C, P:

$$3M + 2E \underset{1}{\overset{1}{\rightleftharpoons}} C \xrightarrow{1} 2E + P\,.$$

(a) Find the species vector S and the reaction vector $R(S)$ (assuming mass action kinetics).

(b) Find the stoichiometry matrix Γ.

(c) Compute the product $\Gamma R(S)$ and show the set of 4 differential equations for M, E, C, P.

(d) Find the rank of Γ.

(e) What is the dimension of the left nullspace of Γ?

(f) Find a basis of the left nullspace of Γ (conservation laws).

13. As in the notes, we study a virus that can only be passed on by heterosexual sex. There are two separate populations, male and female: we use $\bar{S}$ to indicate the susceptible males and S for the females, and similarly for I and R.

    The equations analogous to the SIRS model are:

$$\begin{aligned}
\frac{d\bar{S}}{dt} &= -\bar{\beta}\bar{S}I + \bar{\gamma}\bar{R} \\
\frac{d\bar{I}}{dt} &= \bar{\beta}\bar{S}I - \bar{\nu}\bar{I} \\
\frac{d\bar{R}}{dt} &= \bar{\nu}\bar{I} - \bar{\gamma}\bar{R} \\
\frac{dS}{dt} &= -\beta S\bar{I} + \gamma R \\
\frac{dI}{dt} &= \beta S\bar{I} - \nu I \\
\frac{dR}{dt} &= \nu I - \gamma R\,.
\end{aligned}$$

This model is a little difficult to study, but in many STD's (especially asymptomatic), there is no "removed" class, but instead the infecteds get back into the susceptible population. This gives:

$$\begin{aligned}
\frac{d\bar{S}}{dt} &= -\bar{\beta}\bar{S}I \qquad + \bar{\nu}\bar{I} \\
\frac{d\bar{I}}{dt} &= \bar{\beta}\bar{S}I - \bar{\nu}\bar{I} \\
\frac{dS}{dt} &= -\beta S\bar{I} \qquad + \nu I \\
\frac{dI}{dt} &= \beta S\bar{I} - \nu I\,.
\end{aligned}$$

Writing $\bar{N} = \bar{S}(t) + \bar{I}(t)$ and $N = S(t) + I(t)$ for the total numbers of males and females, and using these two conservation laws, we then concluded that one may just study the following set of two ODE's:

$$\begin{aligned}
\frac{d\bar{I}}{dt} &= \bar{\beta}(\bar{N} - \bar{I})I - \bar{\nu}\bar{I} \\
\frac{dI}{dt} &= \beta(N - I)\bar{I} - \nu I\,.
\end{aligned}$$

Parts (a)-(c) refer to this reduced model.

(a) Prove that there are two equilibria, the first of which is $I = \bar{I} = 0$ and a second one, which exists provided that:

$$\sigma\bar{\sigma} = \left(\frac{N\beta}{\nu}\right)\left(\frac{\bar{N}\bar{\beta}}{\bar{\nu}}\right) > 1$$

and is given by $I = \frac{N\bar{N} - (\nu\bar{\nu})/(\beta\bar{\beta})}{\nu/\beta + \bar{N}}$, $\bar{I} = \frac{N\bar{N} - (\nu\bar{\nu})/(\beta\bar{\beta})}{\bar{\nu}/\bar{\beta} + N}$.

(b) Prove that the first equilibrium is unstable, and the second one stable.

(c) What vaccination strategies could be used to eradicate the disease?

(d) Now consider the full model (six dimensional, with removeds). How many linearly independent conservation laws are there?

(e) Again for the full model. Reduce by conservation to a system of 5 or less equations (how many, depends on how many conservation laws you found in (d)). Pick some set of numerical parameters (any you want) such that $\sigma\bar{\sigma} = 2$. Determine, using computer simulations, what the solutions look like. (You may be able to find the steady states algebraically, too.)

For your answer, attach some plots of solutions $I(t)$ and $\bar{I}(t)$ as a function of time.

14. We discussed the chemical kinetics formulation of an example that may be represented as in Figure 1(a).

Many cell signaling processes involve double instead of single transformations such as addition of phosphate groups. A model for a double-phosphorylation as in Figure 1(b) corresponds to reactions as follows (we use double arrows for simplicity, to indicate reversible reactions):

$$\begin{array}{ccccccccc}
E + S_0 & \leftrightarrow & ES_0 & \rightarrow & E + S_1 & \leftrightarrow & ES_1 & \rightarrow & E + S_2 \\
F + S_2 & \leftrightarrow & FS_2 & \rightarrow & F + S_1 & \leftrightarrow & FS_1 & \rightarrow & F + S_0
\end{array} \tag{1}$$

where "ES_0" represents the complex consisting of E bound to S_0 and so forth.

Figure 1: *(a) One-step and (b) two-step transformations*

(a) Find the stoichiometry matrix and write a corresponding system of ODE's.

(b) Show that there is a basis of conservation laws consisting of three vectors.

15. In the quasi-steady state derivations, suppose that, instead of $e_0 \ll s_0$, we know only the weaker condition:

$$e_0 \ll (s_0 + K_{\mathrm{m}})\,.$$

Show that the same formula for product formation is obtained. Specifically, now pick:

$$x = \frac{s}{s_0 + K_{\mathrm{m}}}\,, \quad y = \frac{c}{e_0}\,, \quad \varepsilon = \frac{e_0}{s_0 + K_{\mathrm{m}}}$$

and show that the equations become:

$$\begin{aligned} \frac{dx}{dt} &= \varepsilon\Big[k_{-1}\,y \;-\; k_1(s_0 + K_{\mathrm{m}})\,x\,(1-y)\Big] \\ \frac{dy}{dt} &= k_1\Big[(s_0 + K_{\mathrm{m}})\,x \;-\; \big(K_{\mathrm{m}} + (s_0 + K_{\mathrm{m}})\,x\big)\,y\Big]\,. \end{aligned}$$

Now set $\varepsilon = 0$. In conclusion, one doesn't need $e_0 \ll s_0$ for the QSS approximation to hold. It is enough that K_{m} be very large, that is to say, for the rate of formation of complex k_1 to be very small compared to $k_{-1} + k_2$ (sum of dissociation rates).

16. We consider a simplification of allosteric inhibition, in which binding of substrate can always occur, but product can only be formed (and released) if I is not bound. In addition, we will also assume that binding of S or I to E are independent of each other. (If we don't assume this, the equations are still the same, but we need to introduce some more kinetic constants k's.)

A reasonable chemical model is, then:

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \xrightarrow{k_2} P + E$$

$$EI + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} EIS$$

$$E + I \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} EI$$

$$ES + I \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} EIS$$

where "EI" denotes the complex of enzyme and inhibitor, etc.

Prove that there results under quasi-steady state approximation a rate

$$\frac{dp}{dt} = \frac{V_{\max}}{1 + i/K_{\rm i}} \cdot \frac{s^2 + as + b}{s^2 + cx + d}$$

for some suitable numbers $a = a(i), \ldots$ and a suitably defined $K_{\rm i}$.

17. Do this problem:

    http://www.math.rutgers.edu/∼sontag/JODE/gardner_cantor_collins_toggle.html