MATH 495: Homework #1
Spring 2019

Due: Tuesday, February 12, 2019

Solve the below questions related to both cancer biology and differential equations. Most mathematical concepts should be familiar from Math 252 and Linear Algebra; please review any concepts that are difficult and/or unfamiliar; I will also be happy to meet and discuss any questions you may have either in office hours or via appointment. There is also an introductory MATLAB problem.

1. (a) Give an example of an **oncogene**. That is, find a specific oncogene, describe its function (including protein(s) it regulates), and the role mutations in it participate in the progression towards cancer. Describe at least one cancer in which mutations of the gene are prevalent . Note that this will probably require some Googling (see also the articles listed from 01/19 in the Course Calendar).

   (b) Repeat part (a) for a **tumor suppressor gene**.

2. Consider the first-order ordinary differential equation (ODE)
$$\dot{y} = y^4 - y^2.$$

   (a) Find the steady states (also known as equilibria, fixed points, etc.).

   (b) Use the graph of $f(y) = y^4 - y^2$ to determine the stability of the steady states found in (a). That is, draw the **phase line** from the graph of $f(y)$.

   (c) Suppose that $y(0) = 0.2$. Find $\lim_{t\to\infty} y(t)$ and $\lim_{t\to-\infty} y(t)$.

   (d) Suppose that $y(0) = 1.2$. Find $\lim_{t\to\infty} y(t)$.

   (e) Draw representative solution curves (in the ty-plane) for all qualitatively distinct initial conditions. Don't forget to include $t \to \pm\infty$.

3. Solve the following first-order initial-value problems (IVPs):

   (a) $\dot{y} = -\frac{t}{y-3}, \quad y(0) = 1.$

   (b) $\frac{dy}{dt} = -2y + 3e^{-2t}, \quad y(1) = e^2.$

4. Consider the linear system

$$\dot{x} = -4x - 2y,$$
$$\dot{y} = -x - 3y.$$

Find the general solution (in vector form), and plot the phase portrait. Note that you should be as accurate as possible, including all qualitatively distinct types of solutions, as well as the correct tangencies as $t \to \pm\infty$.

5. (10 points) Recall that second-order equations can be recast in an equivalent manner as **second-order systems** (in general this is true in higher dimensions as well). As an example, consider the second-order linear initial value problem (IVP)

$$\ddot{y} - 6\dot{y} + 25y = 0, \quad y(0) = 1, \quad \dot{y}(0) = \frac{1}{3}.$$

Convert the above into a first-order system of equations, with initial condition. That is, find a 2×2 matrix A and vectors $\mathbf{Y} = \begin{pmatrix} y_1 \\ y_2 \end{pmatrix}$ and $\mathbf{Y}_0$ such that the IVP takes the equivalent form

$$\dot{\mathbf{Y}} = A\mathbf{Y}, \quad \mathbf{Y}(0) = \mathbf{Y}_0.$$

Hint: $y_1 := y$, $y_2 := \dot{y}$.

6. Consider the nonlinear system

$$\dot{x} = x(2 - x - y),$$
$$\dot{y} = y(y - x^2).$$

(a) Find all equilibrium solutions (i.e. fixed points, steady states, etc.).

(b) Classify, **if possible**, each equilibrium found in part (a) via Jacobian analysis. That is, as a stable node, saddle, spiral sink, etc. Note that it may be the case that your analysis here is inconclusive (when does linearization fail?). **Use this information to plot the phase portrait locally near each equilibrium solution.**

(c) In the phase plane, plot the nullclines of the system, and hence the direction of the vector field in each region.

(d) Use your results from parts (b) and (c) to plot a reasonable phase portrait for the system.

7. Molecular biology is, in essence, the study of networks of chemical reactions. That is, cell dynamics (and hence cancer) can be viewed as a series of inter-connected chemical reactions. In this exercise, we introduce the concepts and physical laws which allow us to study such systems quantitatively.

Chemical reactions will be represented in the following manner:

$$aA + bB \xrightarrow{k_1} cC + dD.$$
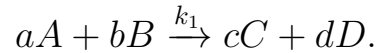
In words, this means that a molecules of A combine with b molecules of B to form c molecules of C and d molecules of D. Here A, B, C, D are the species, and a, b, c, d are non-negative integers. k_1 is a rate constant, discussed in the next paragraph.

A fundamental physical law allows us to form differential equations, **if the reaction is elementary**. Specifically, **Mass Action** says that the overall rate of the above reaction takes the form

$$R = k_1[A]^a[B]^b,$$

where $[\cdot]$ denotes concentration. Intuitively, the speed of elementary re-action is **proportional to the product of the concentration of the reactants**. Note that this is not true for non-elementary reactions, for example those involving catalysts.
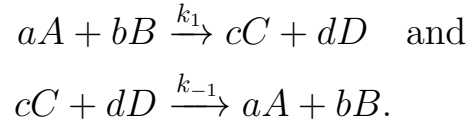
Differential equations can then be obtain for the concentrations of each component. For species A, since every time the reaction occurs, it loses a molecules, we obtain

$$\frac{d[A]}{dt} = -aR,$$
$$= -ak_1[A]^a[B]^b.$$

Similar equations can be written for B, C, and D, to obtain a system of differential equations. Networks of multiple reactions can be modeled by adding the representative rates from each individual reaction. As a last note, "double harpoons" indicate that the reaction is occurring in both directions (i.e. there are two reactions, a forward and a reverse):
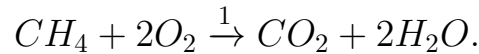
$$aA + bB \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} cC + dD.$$
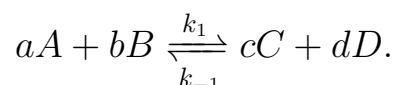
is equivalent to the set of **two** reactions,

$$aA + bB \xrightarrow{k_1} cC + dD \quad \text{and}$$

$$cC + dD \xrightarrow{k_{-1}} aA + bB.$$

For more information, see Section 2.6 in Professor Sontag's "Lecture Notes on Mathematical Systems Biology" (Resources section on the webpage).

(a) Consider the combustion of methane:

$$CH_4 + 2O_2 \xrightarrow{1} CO_2 + 2H_2O.$$

Using the Law of Mass Action, write down a system of differential equations for the four species $A = CH_4, B = O_2, C = CO_2, D = H_2O$. Note that for simplicity, I assumed units such that the rate constant is 1.

(b) Simulate for 10 units of time (time units dictated by choice of constant normalization to 1) the system of differential equations obtained in (a), assuming that there was initially 1 M of methane and 2 M of oxygen molecule, with all other chemical species absent. Provide your result as a time plot for all four species.

(c) Find a set of conservation laws to reduce the four dimensional system to one dimension only. That is, you should obtain a scalar ODE that captures the same dynamics.

(d) Similarly as to (b), simulate the 1 dimensional ODE found in part (c), and find the corresponding concentrations of all species (all four) in time. Again, you should represent your answer pictorially in a time plot as in (b). **Are your results for (b) and (d) consistent?**

(e) How would your equations from part (a) change if we also considered the electrolysis of water:

$$2H_2O \xrightarrow{k_1} 2H_2 + O_2?$$
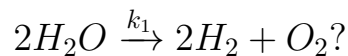
Note that you do **NOT** need to repeat the complete analysis, but simply change your system of ODEs from part (a) to incorporate this reaction.

The following code may be useful **for parts (b) and (d)**, but be aware that it is **not complete**. I have written it in MATLAB, but please feel free to use any language. Your fundamental command will be **ode45**, which numerically solves ODEs (*scipy.integrate.odeint* in Python). Please read up on **ode45**, and/or come talk to me about it if you have questions.

```matlab
%Clear all previous plots and variables
clear all; close all;

% Initial and final times
tI=0;
tF=10;

% Chemical species ICs (A=methane, B = oxygen, C = carbon dioxide, D = water)
A0 = 1;
B0 = ;
C0 = ;
D0 = ;

% Rate constants
k1 = ;

% Total species vector N, with following IC
N0 = [A0; B0; C0; D0];

% Solve the system of ODEs on time interval [tI,tF] with ICs N0
% Note that I am passing the parameter k1 here as well (special syntax [])
[T,N]=ode45(@chemReactionsRHS, [tI tF], N0, [], k1);

% Get the 4 components from the matrix
% Here rows correspond to a fixed time, and columns to a fixed species (A,B,C, or D)
A = N(:,1);
B = N(:,2);
C = N(:,3);
D = N(:,4);

% Plot the time trajectories on the same set of axes
figure(1)
plot(T,A,'-k','LineWidth',2);
hold on;
plot(,'LineWidth',2);
plot(,'-.g','LineWidth',2);
plot(,':r','LineWidth',2);
legend('CO_{4}','O_{2}','CO_{2}','H_{2}O');
xlabel('time (a.u.)');
ylabel('cocentration (M)');
title('Combustion of Methane Dynamics');
```

This will be the main source code that runs your program (i.e. what you actually execute), saved as (say) *chemReactions.m*. However, you must create an additional **function** *m-file*, where the right-hand side (RHS) of the equation is defined. This function should be called *chemReactionsRHS.m*

(note the same name in the code above), and must be saved in the same directory as *chemReactions.m.* Inside this function, define the RHS of system of chemical reactions as below:

```matlab
function dNdt=chemReactionsRHS(t,N,k1)
% Right-hand side (RHS) for system of chemical reactions (i.e. the
% vector field)
% Write in terms of components A,B,C,D
A = N(1);
B = N(2);
C = N(3);
D = N(4);

% Overall reaction rate
R = k1*A.*B.^2;
% Each component of the vector field
dAdt = -R;
dBdt = -2*R;
dCdt = ;
dDdt = ;

% Put it as a vector
dNdt=[dAdt; dBdt; dCdt; dDdt];
end
```

Note the text preceded by a % (green text) is ignored by the computer, and is there to help clarify (known as a *comment*). Complete both files, and hand in the corresponding plots for part (b). For part (d), write similar files, but now using conservation laws so that **only one ODE is solved**, and the rest of the species are obtained from the found conservation laws in (c).

See the Resources section on the webpage for more tutorials, and see me if you have further questions. Also, Google can be a good friend here.