Exercise set 4 (covering lectures 8-10)
Due 5/7/21

1. **Ovulation simulation**

   The goal of this exercise is to go a bit deeper into how to solve differential equation models, and to have fun playing with the ovulation race.

   N follicles start the race, with N=10. The initial size of each follicle is a random number between 0 and 0.1. They grow and compete according to the model discussed in class.

   a. Here is a "sketch" of a simulation code:

```
N=10 % number of follicles
h=0.01  % time step in unit of days
T=1400  % end of simulation, at 14 simulated days
%Initial conditions
For i=1 to N
        x(i,1) = rand (0,0.1);   %random initial sizes
End
%Solve the equations
For t=1 to T
        X_tot(t) = 0
        For i=1 to N
            X_tot(t) = X_tot(t) + x(i,t)    % X_tot is sum of all sizes
        End

        For i=1 to N
            x(i,t+1) = x(i,t) + h (x(i,t)/X_tot(t)) φ(x(i,t)/X_tot(t))    % heart of the code
        End
End
```

   where ϕ is defined as in the lecture notes: $\phi(x) = (1 - M_1 x)(x\, M_2 - 1)$. Ovulation is defined by follicles with size larger than 3 at the end of the simulation.

   b. Explain how this code solves the differential equations, in the line marked "heart of the code". What might happen if the time step h is too large? (50 words) If you need more background here is a video from Khan Academy https://www.khanacademy.org/math/ap-calculus-bc/bc-differential-equations-new/bc-7-5/v/eulers-method.

   c. Choose values for M_1 and M_2 that give more than two ovulating follicles. Simulate the race (using python, R, or any other language) and plot the follicle sizes as a function of time. Simulate the race again and plot the sizes again with new random initial sizes. Discuss the differences and similarities [50 words]. (If you need help with the simulations, please write to Avi and Alon)

   d. Does the size of the largest follicle grow approximately linearly with time? Measure its velocity from the simulation. Explain analytically using the symmetric solution.

   e. First sit down. Mazal Tov! You have twins! Set $M_1 = 0.9, M_2 = 6$. Repeat the simulation 100 times. How many twins events do you observe? Plot the follicle sizes as a function of time in one of the twins events. (Hint: use an extra For loop to run the simulation and count twin events if they occur).

2. In the thyroid lecture, we focused on T4. Read about the more active form, T3, and how it is produced in the body tissues by enzymes called deiodinases. What might be the advantage of having T3 and T4 instead of a single hormone? [50 words].

3. Theories for autoimmunity:

a. Read about the hypothesis of 'molecular mimicry' for autoimmune diseases.
b. Read about the 'hygiene hypotheses' for autoimmune diseases.
c. Discuss their pros and cons, and compare to the 'surveillance of hypersecreting mutant' theory discussed in the lecture (200 words)

4. Viral dynamics:

In the autoimmunity lecture we discussed the immune system, and here is an example of how it operates against a virus, and how it is fooled in autoimmune disease. Consider a model for viral infection. The concentration of virus is V(t), and it multiplies at a rate α_0 . It is killed by activated T-cells, T(t), which are inhibited by regulatory T-cells called T_{regs} , R(t). Both T-cells and Tregs are activated by the presence of the virus:

$$(1) \quad \frac{dV}{dt} = (\alpha_0 - c\,T)V$$

$$(2) \quad \frac{dR}{dt} = V - R$$

$$(3) \quad \frac{dT}{dt} = \frac{V}{k+R} - T$$

a. Explain the equations and the parameters k, c and α_0.
b. Calculate the steady-state solution.
c. Numerically solve the equations for various values of the viral growth rate α_0. What do we mean by various? You are scientists, and you decide ☺ . Use $c = 1, k = 1$, and initial conditions $R(0) = T(0) = 0$, and $V(0) = 1$. Explain the meaning of these initial conditions.
d. Assume that when the virus concentration goes below a minimal concentration, $V_0 = 0.01$, it is eliminated by the innate immune system. What is the maximal value of α_0 for which the virus is eliminated? What happens if α_0 is larger than this value?
e. In autoimmune disease, the T cells kill healthy cells. The killed cells and their antigens are presented to new inactive T cells and activate them. Thus, the more T cell killing, the more antigen is presented. The body thinks there is more "virus " V, where now V represents the antigen level. This changes equation 1 to something like $dV/dt = c\,T - r\,V$. Here r is the removal rate of antigen. How does this change the model results? Interpret in terms of autoimmune disease.