Exercise set 4 (covering lectures 6,7 and 8)
Due July 5
Adaptive immunity, Autoimmunity, Inflammation and Fibrosis

1. **Viral dynamics:**

Consider the model for the concentrations of virus, u(t), T-cells, T(t), and T_{regs} ,R(t):

$$\frac{du}{dt} = (\alpha_0 - c\,T)u$$
$$\frac{dR}{dt} = u - R$$
$$\frac{dT}{dt} = \frac{u}{k+R} - T$$

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 α_0. Use $c = 1, k = 1$, $R(0) = T(0) = 0$, and $u(0) = 1$. Explain the meaning of these initial conditions.
d. Assume that when the virus concentration goes below a minimal dose, $u_0 = 0.01$, it is killed by the innate immune system. What is the maximal value of α_0 for which the virus is killed by the immune system? What happens if α_0 is larger than this value?

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

3. Bistability in a simple model for autoimmunity:
Consider this simple model: The immune system attacks a healthy tissue. This releases auto-antigens, making the immune killing stronger, in a cooperative way, with Hill coefficient n=2. The variable is the amount of autoantigen a(t). The autoantigen is removed at rate γ.

(a) Explain the equation:
$$\frac{da}{dt} = c\frac{a^n}{k^n+a^n} - \gamma\, a.$$
(b) Draw a rate plot showing the fixed points. Consider (graphically) different scenarios (different parameters) with different number of fixed points. When is there bistability?
(c) Which scenario corresponds to an autoimmune disease? Which corresponds to no autoimmune disease?
(d) Suppose that individuals vary in their genetics in a way that affects the parameters of the equation. Does an increase in the parameter c increase the risk for autoimmune disease? Repeat for the parameters k and gamma.

4. Paradoxical effect of macrophage depletion:
Consider the model for injury repair and fibrosis. Experiments have shown that depleting macrophages (setting M to M=0) at different timepoints after an injury can result in improved healing or excessive fibrosis. Explain this 'paradoxical' effect using the phase portrait.