Systems medicine

Uri Alon

Exercise 4.

1. Stem-cell feedback that keeps a constant S population: Consider the following feedback loop in a labile tissue. Both stem cells S and differentiated cells D secrete factors (like $TGF\beta$) that increase differentiation rate, and both cell types die at rates d_1 and d_2. The differentiation rate is $q(S,D) = q_0 SD$.
(a) Write the equations for this circuit.
(b) Simulate this circuit for different initial conditions (or use linear stability analysis) and test whether the steady-state is stable.
(c) Show that the steady-state concentration of S cells is independent on S proliferation rate, p, until a catastrophe happens.
(d) What is the concentration of D cells as a function of p?
(e) When might the behavior of this feedback loop be biologically useful?

2. Death rates: In healthy alveoli tissue there are approximately twice as many AT2 cells (S) than AT1 cells (D). Since S cells are smaller they make up only 7% of the surface area. Estimate using the simple calculations in the lecture what is the ratio between S proliferation and death rates. In the knee joint, progenitor cells (S) amount to about 4% of the total cell population, rising to about 8% in OA. What is the ratio of proliferation to death rates?

3. Nullclines and directions of motion: Consider the model for inflammation and fibrosis presented in the lecture. The nullcline $dM/dt = 0$ is the line where macrophage concentration M does not change. On one side of the nullcline in phase plane, $dM/dt > 0$ which means that M grows, and on the other side $dM/dt < 0$ which means that M shrinks.
(a) Why is this statement true?
(b) Which side of the nullcline corresponds to $dM/dt > 0$ and which to $dM/dt < 0$?
(c) Repeat for the $dF/dt = 0$ nullcline. Explain why this U-shaped nullcline separates the phase plane to a middle region where myofibroblasts F flow to higher levels, and regions at low and high F where F flows to lower levels.
(d) Use these results to sketch the arrows in the phase portrait and to explain the stability of the fixed points.

4. **paradoxical effect of macrophage depletion:**
Experiments have shown that depleting macrophages at different timepoints after an injury can result in improved healing or excessive fibrosis. Explain using the phase portrait.