Systems medicine

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Exercise 5.

1 Pareto optimality- Too few traits measured: Suppose a system has four tasks, but only two traits are measured experimentally. What kind of shapes would describe the optimal phenotypes in the 2D trait space?

2 Empty regions in the polytope: The theorem we discussed in lecture 9 is silent on the question of where in the polytope the points can lie. This exercise will show that some regions of the polytope can be empty (forbidden) if the performance functions have certain curvatures. We will use a 1D example, with a single trait T and two tasks. Thus, fitness F is an increasing function of two performance functions P_1 and P_2, which are functions of T.

(a) Show that the Pareto front is the line segment between the two archetypes.

(b) Show that a condition for optimality is $\frac{d^2F}{dT^2} < 0$.

(c) Show that this requires a condition on the curvature of the performance functions d^2P_i/dT^2.

(d) Show that when both curvatures are positive, there is an empty region with no allowed phenotypes.

(e) What happens when the performance functions are Gaussians that decay with distance from the archetype?

(f) What other reasons might explain an empty region inside a polytope (hint: consider physical constraints on the phenotype).

3. Liver transplantation In liver transplantation the donor donates a liver lobe to the recipient. After donation, the recipient liver regenerates faster than the donor liver. Explain this using the growth hormone axis model, with n=1/3:

$$\frac{dP}{dt} = P(c_P P^{-\frac{n}{2n+1}} L^{-\frac{1}{2n+1}} - a_P)$$

$$\frac{dL}{dt} = L(c_L P^{\frac{1}{2n+1}} L^{-\frac{2}{2n+1}} - a_L)$$

a) Simulate the donor liver trajectory. Use the HPS model with the initial conditions P=1 (healthy pituitary), L=1/2 (half a liver).

b) Compare the simulation above to the recipient liver trajectory, for the recipient use the initial conditions P > 1, L=1/2. Explain why these are the initial conditions for the recipient. Which hormone levels are expected to be high or low before the transplantation in the recipient?

c) Explain intuitively why recipient's liver regenerates faster than donor's liver.

4. **Model for major depression.** The 'toggle switch' model for depression was described in class by the following equations, where A is the adrenal functional size and h is the hippocampus functional size:

$$\frac{dA}{dt} = b_A\, A\left(\left(\frac{u}{hA}\right)^{1/3} - a_A\right)$$

$$\frac{dh}{dt} = D + c - \left(a + b\,\theta\left(\left(\frac{u}{h}\right)^{1/3} A^{2/3} > T\right)\right) h$$

(a) Find conditions on the parameters for three fixed points.

(b) What is the minimal level of stress input u, present for a long time, which can cause a shift to the depressed state?

(c) What level of stress input is required to return to the euthymic fixed point?

(d) What is the minimal drug level D which can cause recovery?