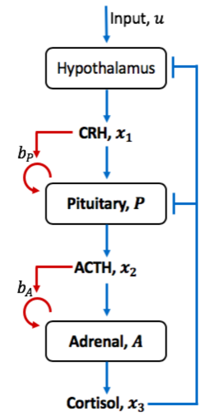
Exercise set 3 (covering lectures 6-7)
Due 15/6

1. The goal of this exercise is to flex your algebra muscles, and to see the mathematical origin of robustness. The **HPA axis,** can be described by the following equations:



$$(1)\ \frac{dx_1}{dt} = q_1\frac{u}{x_3} - a_1x_1$$

$$(2)\ \frac{dx_2}{dt} = q_2\frac{x_1}{x_3}P - a_2x_2$$

$$(3)\ \frac{dx_3}{dt} = q_3x_2A - a_3x_3$$

$$(4)\ \frac{dP}{dt} = P(b_Px_1 - a_P)$$

$$(5)\ \frac{dA}{dt} = A(b_Ax_2 - a_A)$$

(a) Explain the meaning of each parameter (for example, b_p is the P cell proliferation rate per unit CRH, x_1)
(b) Fast time scale steady-state: Solve the steady state of Eq 1-3, assuming that the gland masses A and P are constant. What are the steady-state values of the hormone concentrations x_1, x_2 and x_3?
(c) Full solution steady state: Solve the steady state of the full model, equations 1-5. Start with Eq 4 and 5, to show that x_1 and x_2 must reach specific values. Then use these values in Eq 1-3 to find the steady states of x_3, A and P.
(d) Compare the solutions of b and c. Which solution has hormone levels that are more robust (insensitive) to variations in model parameters? Explain biologically what mechanism provides this robustness (50 words).

2. Steroid withdrawal
Many medical situations are treated by drugs that mimic cortisol called corticosteroids (such as dexamethasone or prednisone), to reduce inflammation, swelling and autoimmune diseases. Millions of people take such drugs at high doses for many months.
(a) Model such a drug by adding its dose D to x_3 in the inhibitory terms in the equations (1-2), so that the $1/x_3$ terms become $1/(x_3 + D)$. Explain. Solve Eq 1-5 for the effect of the drug on the steady-state hormone levels. What is the effect on the gland sizes?
(b) Why is it dangerous to stop taking the drug all at once? This effect is called steroid addiction or steroid withdrawal. (50 words).

3. The HPA model – numerical simulation of the COVID crisis
(a) Lets (just for the fun of it) model the impact of the COVID crisis on the HPA axis as high stress input u for a year. Numerically simulate the HPA equations (1-5) for a step change in which $u = 1$ goes to $u = 2$ at time $t = 0$. Run the simulation until the model reaches its new steady state. Use $q_1 = q_2 = q_3 = b_P = b_A = 1, a_1 = 1/(5\,min), a_2 = 1/(30\,min),\ a_3 = 1/(90\,min)\ \ and\ a_P = a_A = 1/(60\,days)$.
use the steady state values of the system with $u = 1$ that you computed in question 1 as the initial conditions.
(b) What happens to the levels of the three hormones after this step? Does x_3 behave differently from the other two hormones? Does this make sense biologically?
(c) Suppose that the crisis lasts one year and is suddenly over. Simulate the effect of a down-step of u from $u = 2$ to $u = 1$ at time $t = 1$ year. What do you observe happens to the hormones and the glands? How long does it take the gland masses to return to their original state? What might you conclude about how long it takes to fully recover from a long stress period? (50 words)
(d) Brief crisis: supposed there is a brief crisis that lasts one week. Start at steady state at $u = 1$ and simulate a pulse of u that rises to $u = 2$ and then back to $u = 1$. Compare the impact of the brief crisis on the glands and hormones to the prolonged stress of (a-c), both during the stress pulse and in the recovery period. What explains the difference?