Exercise set 3 (covering lectures 4-5)

Due June 9-th

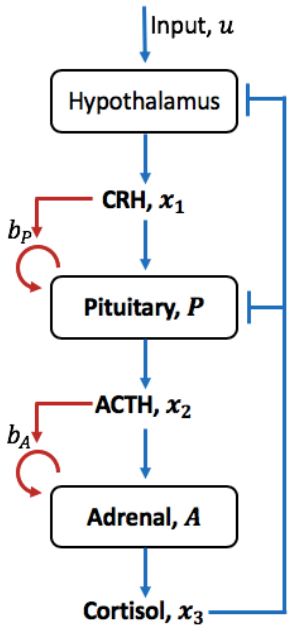
The HPA axis, and addiction

1. HPA model equations: To model the HPA axis, we can write the following 5 equations:

$$\frac{dx_1}{dt} = \frac{q_1 u}{x_3} - a_1 x_1$$

$$\frac{dx_2}{dt} = \frac{q_2 P x_1}{x_3} - a_2 x_2 \ , \qquad \frac{dP}{dt} = P(b_P x_1 - a_P)$$

$$\frac{dx_3}{dt} = q_3 A x_2 - a_3 x_3 \qquad \frac{dA}{dt} = A(b_A x_2 - a_A)$$



(a) Explain the equations and the parameters.
(b) What are the steady-state values of the hormone concentrations x_1,x_2 and x_3, and gland total masses A and P? Which of these depend on the steady-state input level? Explain (100 words)
(c) Rare cancers in the lung can secrete high constant levels of x2 (ACTH) that is not under control of x1 or x3. This secretion is due to mutations that occur in the cancer cells. Assume that the secretion is constant over time. What will such cancers do to the levels of cortisol and to the HPA gland masses? (100 words).

2. The HPA model – numerical simulation
(a) Numerically simulate the HPA equations of question 1 for a step change in which $u = 1$ goes to $u = 2$ at time t=0. Start the simulations at steady-state initial conditions (that you obtained in question 1a, or by simulating the system for a longtime). Run the simulation until the model reaches its new steady-state. Then do a second input step from u=2 to u=4. Use the following parameter values: $q_1 = q_2 = q_3 = b_P = b_A = 1, a_1 = 1/5\ min, a_2 = 1/30\ min,\ a_3 = 1/90\ min\ \ and\ a_P = a_A = 1/60\ days$.
(b) What happens to the levels of the three hormones? Does x_3 behave differently from the other two hormones?
(c) Invent a new question about the HPA axis that you are curious about, (for example, an input u(t) that you specify), and simulate the model to see what happens.

3. Addiction initiation after withdrawal:
a. Discuss the duration of the initiation phase if relapse occurs (i) a few days after withdrawal, (ii) after total recovery. Use logic and/or simulations.
b. Watch the Osmosis video about opiate addiction. Choose a topic not covered in class, read about it and summarize in 100 words. https://www.youtube.com/watch?v=VldsyyybBRw.

4. Dual addiction: suppose that two addictive substances activate the HPA pathway. The doses taken are d_1 and d_2. The effect on the HPA axis is an input $u = (1 + d_1)(1 + d_2)$, where $u = 1$ is the baseline input before substance use. Use logic and/or simulations to answer:
(a) Discuss how the two substances affect each other's tolerance and withdrawal.
(b) What is the effect of stopping one substance while still using the other?
(c) What happens if one increases drug 1 dose from d1=9 to d1=19, and decreases simultaneously drug 2 dose from d1=9 to d1=4?