Systems medicine

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Exercise 2.

1. Concepts about the origins of diabetes.

In class we discussed fundamental origins of type-2 and type-1 diabetes from tissue-size control circuits and mutant resistance mechanisms. To learn about the current state-of-the-art in understanding these diseases, watch this 18-min video, made for medical students.

https://www.youtube.com/watch?v=XAnMhq_dX0k&vl=en

Compare the explanations for type-1 and type-2 diabetes in the video to the mechanisms we learned in class (100 words).

PS: this video might answer additional biomedical questions you have about the material in class. I recommend Osmosis.org for similar videos for biological background.

2. **Effect of mutant cell expansion on homeostasis**

In this exercise we will compute the effect of mutant beta cells on the homeostasis (effort to maintain a good glucose set point) by beta cells.

(a) Read the lecture notes for lecture 3, and understand equations 1-7.
(b) To model the effect of mutant cells, we use the model of lecture 1 for insulin-glucose.

Glucose is produced at rate m and removed by insulin I,

$$\frac{dG}{dt} = m - s\, I\, G$$

And insulin is produced by beta cells

$$\frac{dI}{dt} = qBf(G) - \gamma\, I$$

With $f(G) = G^2$.

For the beta-cells, use the equation from the lecture notes

$$\frac{dB}{dt} = B[\mu_0(G - G_0) - a]$$

(c) What is the effect of the auto-immune surveillance of hypersecreting mutants (ASHM) strength parameter a on the steady state glucose level, on insulin levels and the steady state cell population B?
(d) If auto-immune disease is modelled by a very large parameter a, what happens to the glucose blood levels?
(e) A mutant cell population B_m arises, together with the non-mutant (wild-type) cell population B. A s result, insulin production is a sum of production from the two cell types

$$\frac{dI}{dt} = qBf(G) + qB_m f(uG) - \gamma\, I$$

Were u is the mis-sensing factor of the mutant cells.

For the mutant beta-cells, use the equation from the lecture notes

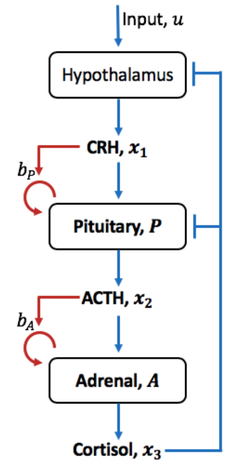
$$\frac{dB_m}{dt} = B_m[\mu_0(uG - G_0) - au^{2n}]$$

(f) Consider different values of the parameter a (ASHM strength), using n=7. Find values in which the mutant population with u=1.5 grows and values of a for which it shrinks. What happens to the glucose levels in these cases?

3. In the **HPA axis,** we derived the following equations:

$$\frac{dx_1}{dt} = \frac{q_1 u}{x_3} - a_1 x_1$$
$$\frac{dx_2}{dt} = \frac{q_2 P x_1}{x_3} - a_2 x_2 \ ,$$
$$\frac{dx_3}{dt} = q_3 A x_2 - a_3 x_3$$

$$\frac{dP}{dt} = P(b_P x_1 - a_P)$$
$$\frac{dA}{dt} = A(b_A x_2 - a_A)$$



(a) What are the steady-state values of the hormone concentrations x_1,x_2 and x_3, and gland sizes A and P?

(b) What would be the steady states if A and P were constant (only the x_i's equations)? Which case is more robust (insensitive) to changes in parameters? Explain.

(c) Many people take a drug to suppress the immune system which is an analogue of cortisol (x_3), for many months (such as dexamethasone). Model this drug by adding its dose D to x_3 in the inhibitory terms in the equations for x_1 and x_2, so that the $1/x_3$ terms become $1/(x_3 + D)$. Explain. Solve for the effect on the steady-state hormone levels? What is the effect on the gland sizes?

(d) Why is it dangerous to stop taking the drug D at once? This effect is called steroid addiction or steroid withdrawal.

4. The HPA model – numerical simulation

(a) Numerically simulate the HPA (1-5) equations 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 $q_1 = q_2 = q_3 = b_P = b_A = 1, a_1 = 1/(5\, min), a_2 = 1/(30\, min),\ a_3 = 1/(90\, min)\ and\ a_P = a_A = 1/(60\, days)$. Explain the difference between a_A and a_P to the rest of the parameters.

(b) What happens to the levels of the three hormones after this step? Does x_3 behave differently from the other two hormones?

(c) Numerically simulate (or solve analytically using linearized equations) with a periodic input that represents the seasons: $u = 1 + u_0\, sin\,(\omega\, t)$, with $\omega = \frac{2\pi}{1\, years}$. This describes an input with a scale of one year, like day-length variations over the seasons. What do you observe about the resulting dynamics of the hormones and glands (when do they peak?).