Systems medicine

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Exercise 2.


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. As a result, insulin production is a sum of production from the two cell types

\[
\frac{dI}{dt} = qBf(G) + qB_mf(uG) - \gamma I
\]
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:
\[
\begin{align*}
\frac{dx_1}{dt} &= q_1 u - a_1 x_1 \\
\frac{dx_2}{dt} &= q_2 P x_1 - a_2 x_2 \\
\frac{dx_3}{dt} &= q_3 A x_2 - a_3 x_3 \\
\frac{dP}{dt} &= P (b_P x_1 - a_P) \\
\frac{dA}{dt} &= A (b_A x_2 - a_A)
\end{align*}
\]

(a) What are the steady-state values of the hormone concentrations \( x_1, x_2, x_3 \), 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 \( q_1 = q_2 = q_3 = b_P = b_A = 1, a_1 = 1/(5 \text{ min}), a_2 = 1/(30 \text{ min}), a_3 = 1/(90 \text{ min}) \) and \( a_P = a_A = 1/(60 \text{ days}) \). 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 \( \omega = \frac{2\pi}{1 \text{ years}} \). 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?).