Systems Medicine 2022

Exercise set 1

Due Dec 4, 2022

Exercises can be submitted in pairs.

Please submit in electronic form such as pdf to **urialonsb@gmail.com**

1. Additional biological features of the glucose-insulin circuit and diabetes.

The goal of this exercise is to expand your knowledge of the glucose circuit, and acquaint you with a nice video resource used by medical students.

Watch the 19-minute video from osmosis.com, for medical students, on diabetes.

Diabetes mellitus (type 1, type 2) & diabetic ketoacidosis (DKA)

https://www.youtube.com/watch?v=-B-RVybvffU

(a) Choose one element of the glucose system or diabetes (except glucagon) that we did not cover in class in detail. Read about it and summarize its role in the glucose control and/or diabetes in 100 words.
(b) Read about the hormone glucagon. Describe its role in 100 words.
(c) Speculate on why the body needs two opposing hormones, insulin and glucagon? (100 words)

2. Brain uptakes of glucose

The original equations for the BIG model are:

$$dG/dt = m - s\ I\ G$$
$$dI/dt = qBf(G) - \gamma I$$
$$dB/dt = \mu B(G - G_0)$$

The brain takes up glucose from the blood at an **insulin-independent** rate.

(a) Add to the BIG model a term describing this effect.

(b) Write a formula for the steady states of glucose, insulin and beta-cells, G_{st}, I_{st} and B_{st} in the BIG model with this effect. Use $f(G) = G^2$. Is the steady-state blood glucose level G_{st} affected by the brain's uptake rate in the new BIG model?

(c) The minimal model assumes constant total mass of beta cells, B, that is - no third equation in the BIG model. Is the steady-state blood glucose level G_{st} affected by the brain's uptake rate in the minimal model?

(d) Discuss why the BIG model design might be biologically useful when organs like the brain have varying fuel demands (50 words).

3. The BIG model – numerical simulation

The goal of this exercise is to develop your ability to simulate biological circuits. Write a computer code to numerically solve the BIG model equations (without brain uptake):

$$dG/dt = m - s\,I\,G$$
$$dI/dt = qBf(G) - \gamma I$$
$$dB/dt = \mu B(G - G_0)$$

Use parameters $s = q = \gamma = 1$, m_0=1. Use $f(G) = G^2$, beta-cell growth rate $\mu = 0.003$ and $G_0 = 5$ Note that due to $\mu = 0.003$, the rate of change of B(t) is much slower than the rate of change of G(t) and I(t). This represents the slow rate of beta-cell turnover compared to the fast hormone reactions. For the simulations, use time unit $dt = 1$

Tutorials on solving and simulating the minimal model using python can be found here:
https://www.weizmann.ac.il/mcb/UriAlon/system-medicine-2022-2023

(a) Solve the steady state values of B, G and I in two ways:
(1) Exactly from the equations.
(2) Numerically by simulating for a sufficient time to reach steady-state.
(3) Compare the simulation to the exact solution.
You should get G=5, I=⅕=0.2 and B=1/125=0.008.

(b) The system is at steady state with s=1, when suddenly, at time t=1000, there is a drop of insulin sensitivity from s=1 to s=0.2. Plot G(t), B(t) and I(t) from t=0 to t=3000. The plot should show the transition of B(t) from one steady-state to another. Explain in 50 words.

(c) Plot G(t) and I(t) in response to a meal, in the situation of (b). Model a meal by a pulse of glucose input. Thus, m(t) goes from an initial value $m_0 = 1$ to a higher value $m_1 = 2$ for one time-unit then back down to m_0. Let the meal begin at three different times, before, right after and long after the drop of insulin sensitivity: t_{meal}=900, 1100 and 2000.

(d) In order to compare the response to the three meals, overlay three plots of glucose and and three plots of insulin from three different timeframes: t=850 to t=950, t=1050 to t=1150 and t=1950 to t=2050. Interpret the results in terms of the concept of "dynamical compensation" defined in the lecture notes (100 words).

(For some solvers, like the "odeint" function in python, it is best to include t=900, 1100, 3000 as "critical points". In "odeint" this is done by the "tcrit" argument)

Open research question (not for credit, just for interest, feel free to ignore)
Type-1 diabetes and the honeymoon period
Type-1 diabetes is an autoimmune disease in which immune cells kill beta cells. It occurs in about 1% of children and adolescents. Type-1 diabetes is usually discovered when someone shows up at the hospital with symptoms caused by very high blood glucose levels. Soon after

starting insulin treatment, blood glucose returns and stays near normal levels, and symptoms mostly vanish. In many patients, there is sometimes no need for further insulin treatment. Doctors call this the **honeymoon phase**. Unfortunately, after several weeks to a year or so, blood glucose rises again and beta-cells collapse. Thereafter, insulin treatment is needed for life. How might one explain the phenomenon of the honeymoon phase in type-1 diabetes?