Exercise set 2 (covering lectures 3-5)

Due 25.5.21

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 brain takes up glucose from the blood at an insulin-independent rate. Write a BIG model with a term describing this effect.

(a) Write formula for the steady states of glucose, insulin and beta-cells, G_{st}, I_{st} and B_{st}.
(b) Is the steady-state blood glucose level G_{st} affected by the brain's uptake rate?
(c) What would be the answer to (b) in the minimal model? Use $f(G) = G^2$. The minimal model assumes constant total mass of beta cells, B, that is - no third equation in the BIG 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 secure your ability to simulate biological circuits, which you developed in the previous exercise. Write a computer code to numerically solve the BIG model equations. Use parameters $s = q = \gamma = 1$, $m_0=1$. Use $f(G) = G^2$, and beta-cell growth rate $dB/dt = 0.01\, B\,(G - 5)$. Note that due to the "0.01", 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.

(a) Plot G(t), B(t) and I(t) when at time t=100, there is a drop of insulin sensitivity from s=1 to s=0.2. The plot should show the transition of B(t) from one steady-state to a new one. (Hint: the initial steady state of B is determined by setting all the time derivatives in Eq.4-6 in lecture notes 4 to 0). Explain in 50 words.

(b) Plot G(t) and I(t) in response to a meal, in the situation of (a). 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: $t_{meal}=90$, 110 and 300. Plot a comparison of the response in the three meals in terms of how high and how quickly glucose rises and falls. Interpret 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=90, 110, 300 as "critical points". In "odeint" it 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.
   (a) Explain what effect this killing has on the B versus G plot of lecture 5.
   (b) Assume that the killing rate of beta cells by the immune cells starts at zero and rises relentlessly and slowly with each passing year. What happens to the stable and unstable fixed points over time?
   (c) What happens when the two fixed points collide? What happens after?
   (d) 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?