Systems medicine

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Exercise 1.

1. The minimal model- steady state solution (repeating what we did in class).
In class we studied the minimal model for insulin and glucose:

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

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

Where the meal input is m(t). Assume that $f(G) = G^2$.

(a) Explain each parameter.

(b) Solve the steady state of G and I for a steady-state glucose input m_0 (hint: steady state occurs when $dG/dt = 0$ and $dI/dt = 0$).

(c) How does the steady-state glucose level change upon insulin resistance in which s is reduced by a factor of 8?

(d) Many people with obesity have insulin resistance, but do not suffer from abnormal glucose levels. Can the minimal model explain this phenomenon?

2. The minimal model – numerical simulation

(a) Write a computer code to numerically solve the minimal model equations (if you need advice on software, please email avi.mayo@weizmann.ac.il).

(b) A meal is modelled by a pulse of m(t): m(t) goes from initial value m_0 to a higher value m_1 at time t=1, and then back to m_0 at time t=2. Use parameters $s = q = B = \gamma = m_0 = 1$, and $m_1 = 2$. Plot G(t) and I(t) for initial conditions at steady state (use the answer to question 1b).

(c) Repeat for a situation with insulin resistance, s=0.1. Compare the two solutions in terms of insulin and glucose levels, and their response times (times to reach halfway to steady state).

3. The BIG model: steady-state solution (repeating what we did in class)
In class we extended the minimal model by adding an equation for beta cells B(t):

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

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

$$\frac{dB}{dt} = B\,\mu(G)$$

Where beta cell growth rate $\mu(G)$ equals zero at G=Go=5, the glucose set-point.

(a) Solve the steady state for B,G and I.

(b) Does the steady state glucose depend on insulin sensitivity s? Other parameters?

(c) Why does the answer to (b) offer a physiological advantage?

4. The BIG model numerical simulation

(a) Repeat the numerical simulation question 2 for the BIG model, by inputting a meal as a pulse of m(t). Use $\mu(G) = 0.01 * (G - 5)$. Start from steady state initial conditions.

(b) What is the biological meaning of the small number 0.01 in (a)? (Hint: consider tissue turnover rates compared to insulin secretion/action rates).

(c) Simulate a step change in s, from s=1 to s=0.1, with a constant glucose supply $m=m_0=1$. Plot G(t),I(t) and B(t), over a long enough time so that B reaches its new steady state. Interpret the results.

(d) Simulate a meal by a supply term m that goes from m_0 =1 to m_1=2 for one time unit, and then back to m_0. Compare the dynamics G(t) in response to a meal before the change in s (when B is its initial steady state), shortly after the change in s (when B is still not at steady state), and long after the change in s when B is at its new steady state.

(e) How do changes in insulin sensitivity s affect the glucose G(t) and insulin I(t) dynamics following a meal?

(f) Can the BIG model explain how people with insulin resistance can have normal glucose dynamics?

(g) Repeat c and d for a step change in the parameter q from 1 to 2. Interpret the results.

(h) *Dynamic compensation (DC)* is the ability of a system to show dynamics of a variable (like G(t)) that are independent of certain parameters (like s and q), in response to an input signal (like m(t)) provided you start at steady state initial conditions. Doe the BIG model have DC? What about the minimal model?

5. Brain uptakes of glucose

The brain takes up glucose from the blood at an insulin-independent rate.
  (a) Write a BIG model with a term describing this effect.
  (b) Compute the steady states of glucose, insulin and beta cells.
  (c) Is the steady-state blood glucose level affected by the brains uptake?

6. Biphasic mechanism: position of the unstable point

The biphasic mechanism balances between two evils: (i) dynamical instability- if glucose rises above the unstable point, type-2 diabetes can set in. (ii) mutation takeover – mutant cells can expand if they mis-sense 5mM glucose as slightly higher levels that range between 5mM and the unstable fixed point.
  (a) (*repeating what we did in class*) Sketch the beta-cell death curve and proliferation curves, including glucotoxicity, as a function of G. Indicate their crossing points. Explain why the 5mM point is stable whereas the higher point is not. Explain what happens if the unstable point is crossed. Sketch the range of mis-sensing mutants that can expand in this mechanism.
  (b) Suppose that natural selection can select for changes that move the glucotoxicity arm of the death curve. What situations (e.g. nutrition) cause selection pressure to evolve higher or lower values for the unstable fixed point? How would that affect the chances for diabetes given a shift to a high fat&sugar diet?
  (c) A desert rodent *(psammomys obesus)* quickly gets obesity and diabetes in the lab when fed on a normal mouse diet. Provide an explanation based on the biphasic mechanism.