Basic Toolkit for Bioinformatics - final project

Zofia Sikorska Kinga Kurowska Wiktor Rorat

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1 Introduction

This semester, in Systems Biology class we have learned about using differential equations to model behavior of biological systems. We have found this method especially interesting. Modeling can help us better understand human physiology and how different diseases can come about. For our project, we decided to closely examine three different models of glucose-insulin dynamics, hoping to see their limits and differing applicability.

2 Methods

We have researched and recreated three models:

- Bergman's Minimal Model[1]
- Li and Kuang's Dynamical Model [2]
- Topp at al.'s βIG Model[3][4]

We have numerically simulated each using deSolve library for R. For visualization, we have used ggplot2 and R's builtin tools. To get a better sense of these systems, we have made an Shiny app to see how each one reacts to changes in initial conditions. We found parameters in papers discussing said models[1][2][4].

3 Bergman's Minimal Model

Model most widely used in clinical practice today. It is described by following equations:

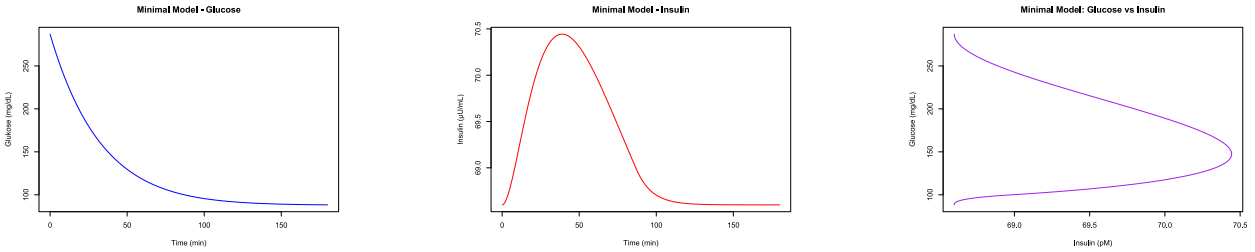
$$\frac{dG(t)}{dt} = -[p_1 + X(t)]G(t) + p_1 G_b, \qquad G(0) = p_0 \tag{1}$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3[I(t) - I_b], \qquad X(0) = 0 \tag{2}$$

$$\frac{dI(t)}{dt} = p_4[G(t) - p_5]^+ t - p_6[I(t) - I_b] \qquad I(0) = p_7 + I_b, \tag{3}$$

G(t) and I(t) represents levels of glucose and insulin respectively in plasma. X(t) represents a "distant" compartment, later understood to be interstitial fluid[5][6]. Introduction of the X(t) term was the breakthrough that made this model widely used, it accounted well for the delay between change in insulin level and increased consumption of glucose.

One issue with the model immediately stands out, insulin response gets progressively stronger with time! It makes sense in context, the model was developed to analyze data from Intravenous Glucose Tolerance Tests, where glucose is injected into the veins and then measured several times to see how it's concentration changes with time. This model can fit really well into experimental data.

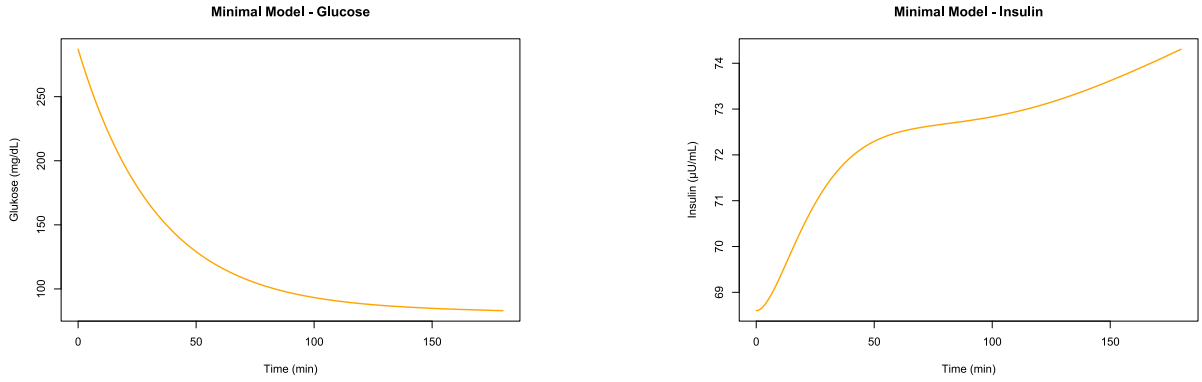


(a) Glucose dynamics (b) Insulin dynamics (c) Insulin vs Glucose

Figure 1: Minimal Model simulation results: (a) Glucose clearance pattern showing rapid decay; (b) Insulin response; (c) Phase portrait demonstrating the inverse relationship between insulin and glucose concentrations.

3.1 Critical Limitations of the Minimal Model

The Minimal model assumes a steady state before injection where G_b results from a balance between insulin's glucose-lowering effect and the liver's glucose production (p_5). The problem arises when $G_b > p_5$. In that case if glucose stays above p_5, the model predicts that insulin action X grows without bound ($\limsup_{t\to\infty} X(t) \to \infty$), which is biologically impossible.



(a) Glucose dynamics (b) Insulin dynamics

Figure 2: Minimal Model critical Limitation: (a) Glucose clearance; (b) Insulin response which is biologically impossible

4 Li and Kuang's Dynamical Model

Delay in the Minimal Model is implicit, as it is caused by existance of a "distant" compartment X. The idea here was to deal with the delay explicitly. As such, this model has not only Ordinary Differential Equations (ODEs), but a Delayed Differential Equation (DDE) as well.

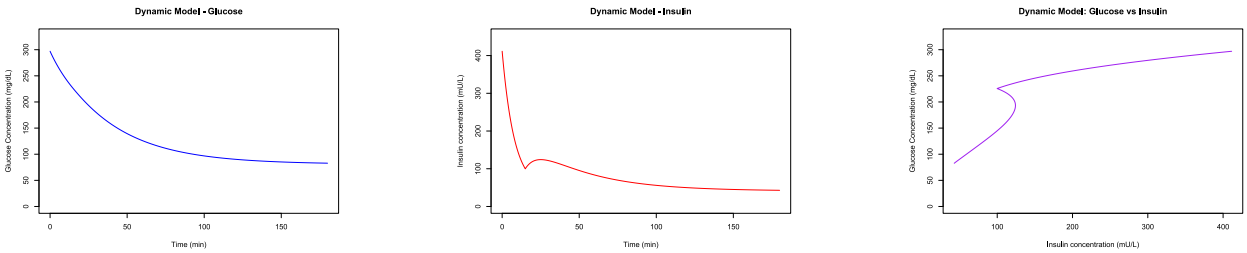
$$\frac{dG(t)}{dt} = -b_1 G(t) - \frac{b_4 I(t) G(t)}{\alpha G(t) + 1} + b_7, \tag{4}$$

$$G(t) \equiv G_b \;\forall\; t \in [-b_5, 0), \qquad G(0) = G_b + b_0 \tag{4}$$

$$\frac{dI(t)}{dt} = b_6 G(t - b_5) + b_2 I(t) \qquad I(0) = I_b + b_3 b_0 \tag{5}$$

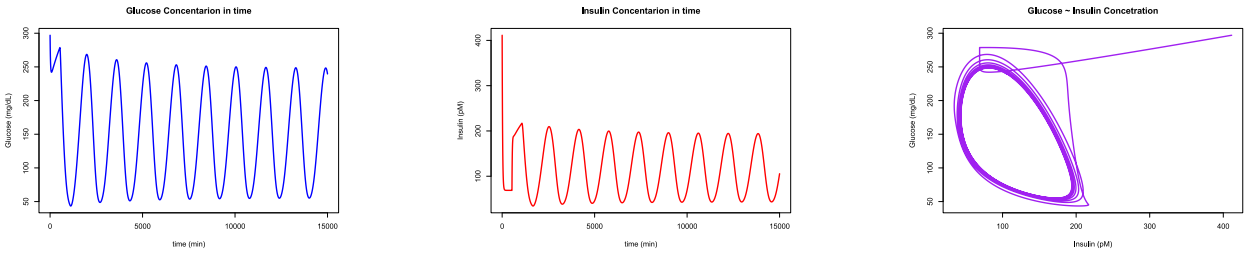
Value $G(t - b_5)$ depends on the past state of the system! This has some consequences, for example, we can now see that lines can intersect in the phase space, something that is not normally possible.

This system can also exhibit more complex behaviors for certain sets of values, for b_5 larger than a critical value, system enters stable oscillations. It is not unseen for biological systems to oscillate, but this one does so only for values well outside of physiological range[2].



(a) Glucose dynamics (b) Insulin dynamics (c) Insulin vs Glucose

Figure 3: Dynamic Model simulation results: (a) Glucose clearance; (b) Insulin response; (c) Phase portrait.



(a) Glucose oscillation (b) Insulin oscillation (c) Insulin vs Glucose

Figure 4: Oscillation Model simulation results

5 Topp at al.'s βIG Model

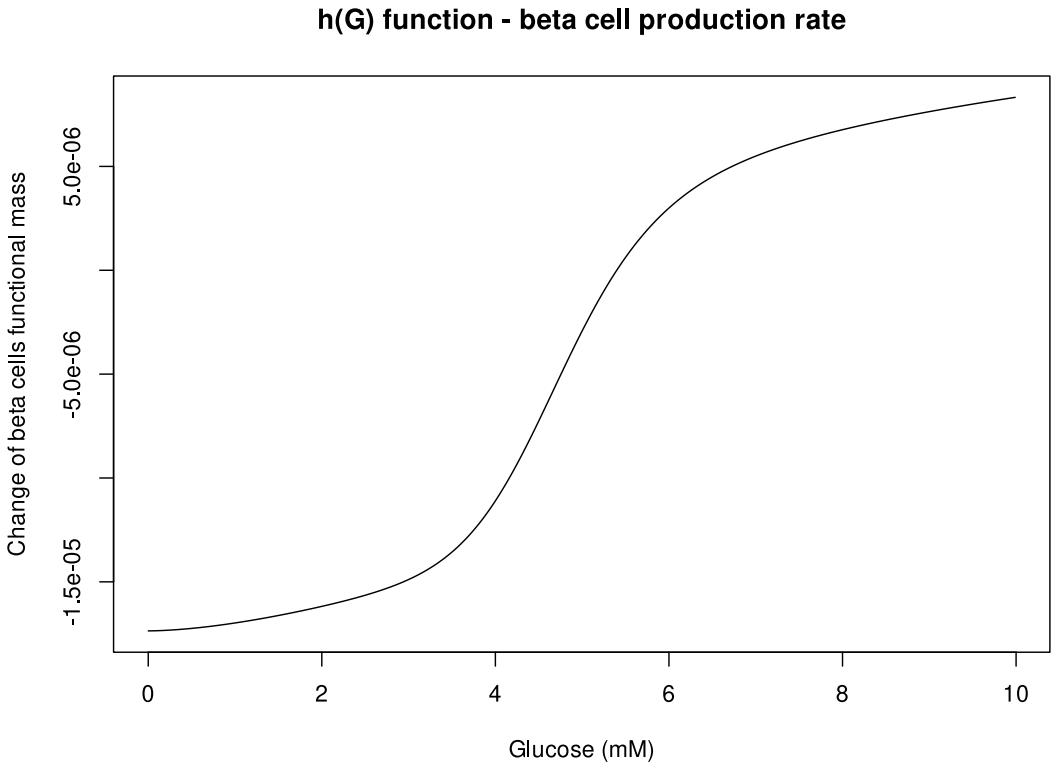
Both examples above have their merits, but they cannot maintain stable glucose when parameters, most importantly insulin sensitivity, is changed. To account for this, new closed loop can be added.

$$\frac{dG(t)}{dt} = u_0 + u(t) - (C + S_i I)G \tag{5}$$

$$\frac{dI(t)}{dt} = p\beta \cdot \rho(G) - \gamma I \tag{6}$$

$$\frac{d\beta(t)}{dt} = \beta h(G) \tag{7}$$

Where β is the functional mass of beta cells, u(t) represents meal intake, and ρ is a monotonically increasing function of glucose, here we have used $\frac{G^2}{\alpha+G^2}$. Third equation is what setts this model apart. Beta cells mass changes strongly in response to glucose levels, creating a way to dynamically adapt the system until a desired glucose level is reached. Reaction of cells to glucose is modeled with a empirically determined function:



We had issues with modeling this system ourselves, but the theory behind it is very interesting. Growth of beta cells protects body from too high glucose concentrations. This mechanism could also apply to thyroid for example, growth of cells could help change hormone levels back to acceptable range.

6 Conclusion

Through examination of these models we have seen different issues that can arise when modeling. Issues like applicability for example, first model is good at what it does, but it does not show how insulin-glucose system works in general. With more complex systems we have seen issues like bifurcations appear. There is much more to do than just write down the equations, models need to be robust to wide range of problems.

References

[1] R.N. Bergman, C. Cobellit, and G. Toffolo. "Minimal models of glucose/insulin dynamics in the intact organism: A novel approach for evaluation of factors controlling glucose tolerance". In: *Transactions of the Institute of Measurement and Control* 3.4 (Oct. 1981), pp. 207–216. ISSN: 0142-3312, 1477-0369. DOI: 10.1177/014233128100300404. URL: https://journals.sagepub.com/doi/10.1177/014233128100300404.

[2] Fateme Mohabati and MohammadReza Molaei. "Bifurcation analysis in a delay model of IVGTT glucose–insulin interaction". In: *Theory in Biosciences* 139.1 (Feb. 2020), pp. 9–20. ISSN: 1431-7613, 1611-7530. DOI: 10.1007/s12064-019-00298-y. URL: http://link.springer.com/10.1007/s12064-019-00298-y.

[3] Brian Topp et al. "A Model of -Cell Mass, Insulin, and Glucose Kinetics: Pathways to Diabetes". In: *Journal of Theoretical Biology* 206.4 (Oct. 2000), pp. 605–619. ISSN: 00225193. DOI: 10.1006/jtbi.2000.2150. URL: https://linkinghub.elsevier.com/retrieve/pii/S0022519300921507.

[4] Omer Karin et al. "Dynamical compensation in physiological circuits". In: *Molecular Systems Biology* 12.11 (Nov. 2016), p. 886. ISSN: 1744-4292, 1744-4292. DOI: 10.15252/msb.20167216. URL: https://www.embopress.org/doi/10.15252/msb.20167216.

[5] Richard N. Bergman. "Origins and History of the Minimal Model of Glucose Regulation". In: *Frontiers in Endocrinology* 11 (Feb. 15, 2021), p. 583016. ISSN: 1664-2392. DOI: 10.3389/fendo.2020.583016. URL: https://www.frontiersin.org/articles/10.3389/fendo.2020.583016/full.

[6] Jiaxu Li et al. "Analysis of IVGTT glucose-insulin interaction models with time delay". In: *Discrete & Continuous Dynamical Systems - B* 1.1 (2001), pp. 103–124. ISSN: 1553-524X. DOI: 10.3934/dcdsb.2001.1.103. URL: http://aimsciences.org//article/doi/10.3934/dcdsb.2001.1.103.