Modelling Hyperglycemia in Patients with Monogenic Forms of Diabetes

Winner Sotthivej (ws322 | CID: 02228489)

Department of Mathematics, Imperial College London

Imperial College London

Introduction

Monogenic forms of diabetes are forms of diabetes caused by mutations/changes in a single gene. The NHS [1] estimates that these are much rarer than the familiar Type 1 and Type 2 diabetes, with a prevalence of 8 confirmed cases per 100,000 in the UK. They also note that the two main forms of monogenic diabetes are neonatal diabetes mellitus (NDM) and maturity-onset diabetes of the young (MODY). The pathway into diabetes for people with permanent NDM and GCK-MODY (a form of MODY) will be investigated, using the βIG model proposed by Topp et al. [2]

The βIG Model

Topp et al. [2] proposed a model for insulin kinetics, involving a coupled system of 3 non-linear ODEs based on pancreatic β-cell mass (β), blood insulin concentration (I), and blood glucose concentration (G) kinetics:

$$\frac{dG}{dt} = R_0 - (E_{G0} + S_I I)G \tag{1}$$

$$\frac{dI}{dt} = \frac{\beta\sigma G^2}{\alpha + G^2} - kI \tag{2}$$

$$\frac{d\beta}{dt} = (-d_0 + r_1 G - r_2 G^2)\beta \tag{3}$$

with the 9 parameters as in the journal article.

Qualitative Analysis of System

The model as a whole can be decomposed into fast (I, G) and slow (β-cell mass) subsystems. We can then combine our qualitative analyses of the subsystems to determine the global behaviour of the system as a whole, as shown in Figure 1:

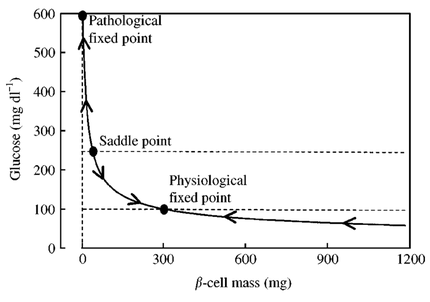

Figure 1: A projection of the slow manifold (solid line) and the β null surfaces (dotted lines) onto the G and β plane. The system has three steady states, indicated by the points above. $\frac{d\beta}{dt}$ is negative in the top and bottom regions separated by the null surfaces, and positive between them. All points above the saddle point are driven towards the pathological fixed point, and all points below towards the physiological one (Topp et al., 2000).

Permanent Neonatal Diabetes Mellitus (PNDM)

PNDM-related mutations in the insulin gene can lead to impaired β-cell proliferation without increasing β-cell apoptosis, which leads to diabetes development [3]. We examine its β-cell mass dynamics next.

Change in Behaviour in Slow Subsystem

To show the change in behaviour of the slow subsystem (equation 3), we split $\frac{d\beta}{dt}$ into replication and death rates as in Topp et al. [2]:

$$\begin{aligned} \frac{d\beta}{dt} &= \text{Replication} - \text{Death} \\ \text{Replication} &= (r_{1r}G - r_{2r}G^2)\beta \\ \text{Death} &= (d_0 - r_{1a}G + r_{2a}G^2)\beta \end{aligned}$$

with parameters as in the journal article. We then modify the replication curve by decreasing r_{1r}, with r_{2r} unchanged. These curves are plotted in Figure 2 using Python:

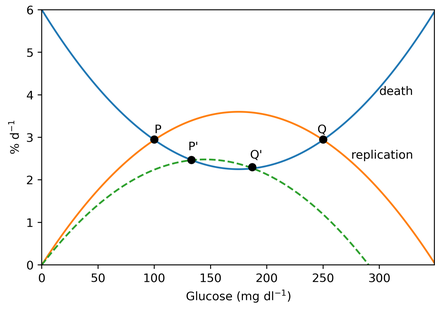

Figure 2: The behaviour of the slow subsystem under normal conditions (solid lines), with the dotted line representing replication rate under PNDM assumptions (i.e. with a decrease in r_{1r}). P and Q are the physiological fixed point and saddle point under normal conditions, respectively, with P' and Q' being those points under PNDM assumptions.

Notably, the 'regulated hyperglycemia' pathway as described in Topp et al. [2] occurs, where the physiological fixed point shifts from the normal level to a hyperglycemic level.

Glucokinase-Maturity-Onset Diabetes of the Young (GCK-MODY)

Glucokinase is an enzyme that acts as a 'glucose sensor' in β-cells in the pancreas. Mutations in the GCK gene, which encodes glucokinase, can cause this sensor to 'activate' at a higher threshold than usual, causing a rise in fasting blood glucose concentration from the typical 100 mg dl^{-1} up to a maximum of 145 mg dl^{-1} [4]. Fasting blood glucose concentration in affected individuals will be taken to be the midpoint of this interval, i.e. 122.5 mg dl^{-1}.

Change in Behaviour in Fast Subsystem

A possible simple interpretation of this description of GCK-MODY is that we can change α, a parameter in equation 2 related to this 'activation level', whilst retaining all other normal parameter values. We examine the fast subsystem by plotting its nullclines ($\frac{dG}{dt} = 0$ and $\frac{dI}{dt} = 0$) and treating β as a parameter, as plotted in Figure 3 using Python:

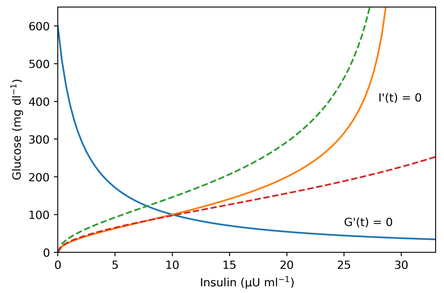

Figure 3: The behaviour of the fast subsystem under normal conditions with $\beta = 300$, with the green dotted line representing $\frac{dI}{dt} = 0$ with α increased such that the nullclines intersect (i.e. there is a fixed point in the system) at G = 122.5 mg dl^{-1}. The red dotted line shows that an increase in β can compensate for this change and bring the fixed point back to normal levels.

It is unknown whether α can actually be manipulated in this way [2]. They further state that this only shifts the physiological fixed point and saddle point to higher β-cell mass values, but doesn't affect glucose or insulin levels at the physiological fixed point. We thus conclude that this may be a subpar interpretation of the GCK-MODY condition.

Discussion

Hyperglycemia in patients with the PNDM and GCK-MODY forms of diabetes was modelled using the βIG model proposed by Topp et al. [2] Using this model, the pathway to diabetes under our interpretation of PNDM resembles the 'regulated hyperglycemia' pathway as outlined in the journal article, whereas our interpretation of GCK-MODY seems to work poorly with this model. As this is quite a simple model, there may be limitations as to what this model can do with limited data. With more research into these niche types of diabetes, there may be scope for a more accurate analysis, with more precise modelling choices and assumptions.

References

[1] NHS England. *NHS to diagnose thousands of people with rare diabetes*;. [Accessed 14th June 2023]. https://www.england.nhs.uk/2021/08/nhs-to-diagnose-thousands-of-people-with-rare-diabetes/.

[2] Topp B, Promislow K, Devries G, Miura RM, Finegood DT. A Model of β-Cell Mass, Insulin, and Glucose Kinetics: Pathways to Diabetes. *Journal of Theoretical Biology*. 2000 July;206(4):605-19.

[3] Balboa D, Saarimäki-Vire J, Borshagovski D, Survila M, Lindholm P, Galli E, et al. Insulin mutations impair beta-cell development in a patient-derived iPSC model of neonatal diabetes. *eLife*. 2018 Nov;7:e38519.

[4] Royal Devon & Exeter NHS Foundation Trust. *What Is Glucokinase (GCK)?*;. [Accessed 15th June 2023]. https://www.diabetesgenes.org/what-is-mody/what-is-glucokinase-gck/.