**A composite computational model of liver glucose homeostasis. Part 2: Exploring system behaviour**

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A composite computational model of liver glucose homeostasis. Part 2: Exploring system behaviour

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1. Abstract

Using a composite model of the glucose homeostasis system, consisting of seven interconnected submodels, we enumerate the possible behaviours of the model in response to variation of liver insulin sensitivity and dietary glucose variability. The model can reproduce published experimental manipulations of the glucose homeostasis system and clearly illustrates several important properties of glucose homeostasis - boundedness in model parameters of the region of efficient homeostasis, existence of an insulin sensitivity that allows effective homeostatic control, and the importance of transient and oscillatory behaviour in characterising homeostatic failure. Bifurcation analysis shows that the appearance of a stable limit cycle can be identified.

2. Introduction

Complex biological systems involve many interacting phenomena which often need to be explored together to understand system behaviour. In a companion paper [1] we presented a composite model of glucose homeostasis using seven distinct validated models combined together in a model management system [2]. The power of this approach is that it permits the use of ordinary differential equation models from a wide range of sources and allows models to be reused and replaced easily to test alternative hypotheses. There have been few comprehensive system level models of physiological systems covering many scales [3]. However the ability to tie biological phenomena to system level behaviour, particularly in clinical applications where most information is obtained from various parts of the system, will be important in the future.

The seven component models for glucose homeostasis which constitute the composite model presented in [1] are as follows: (A) Glucagon Receptor Model for the activation of a G-protein coupled receptor by a hormone stimulus, (B) Calcium Model for the calcium signalling pathway activated by IP3, (C) Cyclic AMP model representing the activation of the G-protein α-subunit of the Glycogen Receptor Model, (D) Insulin Model for the insulin receptor and associated pathway, (E) Blood Model to describe the movements of glucose between the blood, the liver and the pancreas, (F) Glycogenolysis Model representing
glycogen breakdown and synthesis, and (G) Pancreas Model for the production of the hormones glucagon and insulin. The detailed models are given in [1], Appendix A. All models are available at http://www.compbio.org/models.html

The model was validated against data for the homeostatic response to a range of glucose challenges, to demonstrate the existence and correct behaviour of ultradian oscillations under appropriate conditions, and to match observed experimental behaviour in response to a glucagon challenge [4].

Continuous measurement of glucose has demonstrated the presence of ultradian blood glucose oscillations [5,6]. Although originally considered to have their genesis in the pancreas there has been increasing interest in the role of the liver. In the companion paper [1] we used the composite model to confirm that this phenomenon occurs as a result of feedback between pancreas and liver, first identified by Sturis et al. [7]. However it has not been possible until now to undertake a more comprehensive analysis of the oscillatory behaviour of the composite system and this is developed in this paper.

Specifically, here we explore the behaviour of the composite model in response to a range of glucose challenges. We focus on insulin sensitivity because this is the variable that is most susceptible to lifestyle changes and most affected by diet. It therefore has the biggest impact on human health. In particular we seek to ascertain the quantitative behaviour of the expected ultradian oscillations to demonstrate the power of using systems biology models.

3. Exploring System Behaviour

In order to explore the system’s oscillatory behaviour, the qualitative and quantitative behaviour of the blood glucose output was explored in the plane of parameter space described by the external glucose stimulus, $M$, and the threshold value for the Hill function describing the hepatocyte insulin response, $t_I$. $M$ is the glucose input to the Blood Cell Glucose Transport model (Model E of [1]), and $t_I$ models the resistance of action by hepatocytes to insulin in the Insulin model (Model D of [1]). The correct response of the liver to insulin is important in the regulation of blood glucose. In particular, insulin resistance in which the
response of the liver to insulin is below the normal level is a major cause of type 2 diabetes, which accounts for over 90% of diabetes cases globally [8].

In all cases \( M(t) \) is modelled as a step-function describing a sudden-onset, subsequently sustained glucose input. Also a step function is the normal test for dynamic systems to demonstrate significant effects in a consistent manner. Instead of insulin resistance, it is more useful to refer to insulin sensitivity which is given by \( 1 - t_I \) and this value is used in the graphs presented in this paper. Fig 1 shows three example outputs of the model for different values of \( t_I \): stable fixed point solution, oscillatory solution and stable fixed point solution reached via a transient overshoot. Our previous paper [1] gave a series of specific time course results using the model: figure 6 showed the formation of the limit cycle, fig 9 time courses for various values of glucose demand, and fig 10 response to a glucagon challenge.

**FIGURE 1 NEAR HERE**

The parameter \( t_I \) is a derived one so it is instructive to determine how it relates to normal and diabetic states. In most studies insulin resistance was inferred from insulin or peptide measurements and was not directly measured [9]. Weyer et al [9] give the following ranges for insulin: fasting healthy Caucasians 23±9 micro-Unit l\(^{-1}\); fasting diabetic 44±21 micro-Unit l\(^{-1}\); and 2 hours after a meal healthy 100±98 micro-Unit l\(^{-1}\) and diabetic 242±204 micro-Unit l\(^{-1}\). A Unit is 45 µg of insulin. We have assumed that our units of insulin are at the maximum normal levels produced by the pancreas (see [1] supplementary material) and have assumed that the 2 hour data for a diabetic patient would be approximately equal to this. For our model a value of \( t_I = 1 \) would be approximately be 240 micro-Unit l\(^{-1}\) and \( t_I = 0.5 \) approximately 120 micro-Unit l\(^{-1}\) which is somewhat above the normal level.

A bifurcation analysis was undertaken to explore the changes in the behaviour of the composite model as \( M \) and \( t_I \) were varied. The analysis was performed using the bifurcation analysis package, AUTO [10].

**FIGURE 2 NEAR HERE**
The bifurcation diagram in Fig 2 shows the stable solutions of the model with respect to $t_I$ for three values of $M = 0.5, 5$ and $7.5 \, \mu\text{M}$ of blood glucose (as noted above the x-axis shows $(I-t_I)$, such that increasing values indicate increased sensitivity to insulin). For low values of insulin sensitivity there is a stable fixed point of blood glucose, the value of which depends on the value of $M$. As the sensitivity to insulin is increased the blood glucose output undergoes a Hopf bifurcation at which an oscillatory solution (a stable limit cycle) emerges from the stable fixed point. As the insulin sensitivity is increased further the mean blood glucose level (time averaged mean) decreases but with an associated increase in the amplitude of the ultradian oscillations. Insulin sensitivity therefore has a significant effect on the stable blood glucose level resulting from a sustained glucose input, with insulin acting to lower that level. This however, is at the cost of transient glucose (ultradian) oscillations.

The value of insulin sensitivity at which the Hopf bifurcation occurs also varies with the level of the external glucose challenge, $M$. For higher glucose inputs the onset of the limit cycle occurs at lower values of insulin sensitivity. The larger the glucose input the greater the production of insulin by the pancreas and the less sensitive the liver needs to be to observe ultradian oscillations.

FIGURE 3 NEAR HERE

Figure 3 shows that at low insulin sensitivity (high insulin resistance) the level of sustained glucose input has a significant effect on the stable blood glucose level. However at high sensitivities (low resistance) the mean level (time averaged mean) is not significantly affected but transient glucose (ultradian) oscillations occur particularly at the higher sensitivities (Fig 2).

When the glucose input $M$ is driven above $22.5 \, \mu\text{M/s}$, in the model, the blood glucose level increases indefinitely. This does not occur \textit{in vivo} where glucose in excess of that which can be converted into glycogen and stored is broken down to provide substrates for fat metabolism. The inclusion of the way in which excess glucose is handled is perhaps the most obvious extension to the composite model.
The model demonstrates the large transient first excursion in the ultradian oscillation, a feature observed in some of the available experimental studies (e.g. [7]). Most studies, however, concentrate on the long-term behaviour under continuous glucose stimulus. Since the magnitude and duration of the transients vary with the model parameters experimentally observed transients can provide information about the underlying physiology. This is illustrated in figure 4 (A and B). Figure 9 in [1] shows example time courses for $M = 10$ $t_I = 0.8$ (low insulin sensitivity resulting in no oscillations) and $M = 10$ and $t_I = 0.1$ (high sensitivity resulting in oscillations).

The maximum glucose level reached during the transient response to external glucose is controlled by the glucose input, and is largely independent of insulin sensitivity (fig 4A). However the relative amplitude of the initial rise in blood glucose compared to the steady state oscillations (fig 4B) does depend on the sensitivity of the liver to insulin. A high initial transient can therefore be used to identify insulin insensitivity which may have consequences for diagnosis and treatment of disease.

**FIGURE 4 NEAR HERE**

From these results some general findings may be summarised as follows (see figure 5 which gives a schematic representation of the qualitative behaviour of the model with respect to variation in the glucose input parameter $M$ and the insulin sensitivity parameter $t_I$):

Small glucose inputs that do not take blood glucose above the threshold for insulin release from the pancreas can be accommodated by direct glucose control, shown by the light grey region in Fig 5.

For intermediate glucose inputs, even for a liver which is completely resistant to insulin (and hence not subject to pancreatic control), as found in severe Type 2 diabetes or in Type 1 diabetes, where the pancreas fails to release insulin, direct glucose control always results in glycogen synthesis to stabilise blood glucose levels (fig 4A with insulin sensitivity at or near zero). With extreme hyperglycemia it is known that blood glucose levels may be as high as 20mM (see for example [11]). Abnormally high blood glucose levels are diagnosed for blood glucose concentrations greater than 7mM and restoration of a steady state after a glucose bolus is extremely slow in patients. A high, stabilized value of blood glucose characterizes a
situation where the system cannot return to the glucose set point. This result may represent the situation when the liver is completely resistant to insulin, or, alternatively Type 1 diabetes where no insulin is generated by the pancreas. Our model suggests that pancreatic control of blood glucose is possible so long as the sensitivity of the liver insulin receptor is at or above $t_l = 0.8$ ($1 - t_l = 0.2$ as shown on fig 3) when maximum blood glucose is within the range where the pancreas is sensitive.

For large, sustained glucose inputs, the model shows that blood glucose would increase without limit over time if there were no way of eliminating or utilizing the excess. In reality excess glucose is diverted into fat metabolism pathways.

For moderate glucose input and insulin resistance, pancreatic control results in good homeostasis, with low maximum blood glucose (the light grey region in fig 5). Insulin sensitivity above the normal range is characterized by under-damping of blood glucose oscillations.

Increased sensitivity to insulin may occur as a result of an autoimmune reaction, or pituitary or adrenal insufficiency. The onset of oscillations in a glucose tolerance test could provide an early indicator of insulin hypersensitivity. Currently there is no clear consensus over the protocol for a glucose tolerance test. Most practitioners sample only once or twice following the administration of glucose and there is no standard advice over the appropriate timing. In order to reveal the oscillations, it would be necessary to sample several times over two or three hours to reveal the temporal picture. Although individual variation will be considerable, we suggest that sampling for 2 to 3 hours at half hourly intervals would reveal the temporal pattern of the response and indicate whether the response is oscillatory. Oscillations would alert the clinician early to the possibility of a change in insulin sensitivity.

A large transient excursion during the first oscillation, significantly larger than subsequent oscillations, also indicates insulin hypersensitivity. High insulin sensitivity can be a problem for individuals on insulin therapy for diabetes mellitus as a consequence of an autoimmune response. The consequences of insulin hypersensitivity are particularly marked in relation to fat metabolism ([12], [13], [14]).

4. Discussion
The results we obtain from analyzing the composite model suggest that analysis of the relationship between the glucose stimulus and the magnitude of the resultant blood glucose excursion may provide a more effective indicator of homeostatic capability than considering the glucose increase resulting from a single glucose input. In our model effective homeostasis occurs over a region of glucose inputs where increasing glucose input does not result in increased blood glucose level. Further development of the model may reveal potential early clinical indicators of altered insulin resistance. This could be valuable since the model shows that unless insulin resistance increases by more than \( t_I = 0.8 \) (1 - \( t_I = 0.2 \)), direct glucose control will compensate. Increased resistance indicates diabetes, while increased sensitivity may reflect an autoimmune response to insulin or pituitary or adrenal insufficiency. Both conditions benefit from early recognition and therefore treatment. For example, the analysis of transients in glucose tolerance tests may have diagnostic power for the study of pathologies of glucose metabolism (see fig 4B) which reveals that the magnitude of the transient response is determined by insulin sensitivity.

Finally the model supports the proposal that ultradian oscillations result from system level behaviour of feedback between liver and pancreas. Consider a situation in which glucose is fed into the blood at a constant positive rate \( M \). This results in the indefinite growth of blood glucose concentration, other things being equal. However, when blood glucose concentration has reached a threshold level, release of insulin by the pancreas is triggered. This in turn results in an increase in phosphorylated glycogen synthase kinase (GSK), and hence in the increased rate of conversion of blood glucose into glycogen in hepatocytes (Model F of [1], Appendix A.6). The increase in blood glucose concentration is then arrested, resulting in a stable equilibrium concentration, but may be reversed if GSK production is sufficiently sensitive to insulin (i.e. provided \( t_I \) is sufficiently low – Model D of [1], Appendix A.4, equation A.4.1). If this reversal is fast enough, then blood glucose concentration can drop rapidly below the threshold at which insulin is released by the pancreas. In the absence of insulin, GSK then also drops rapidly, and the rate of conversion of glucose into glycogen is therefore reduced. Since glucose is still being ingested at a constant rate, blood glucose concentration may then again increase, and the cycle begins again.
This cycle of events leads to oscillations in blood glucose concentrations. These oscillations may be overdamped, or underdamped [15] or, result in a stable limit cycle as shown in Fig 2 depending on M and other model parameters. For a given M, these outcomes depend essentially on the sensitivity of GSK to insulin. As the control parameter tI decreases the insulin sensitivity increases and there is a sequence of bifurcations through resulting outcome blood glucose concentrations i.e. from stable equilibrium but with high glucose level to overdamped oscillations leading to lower stable equilibrium, to the appearance of a stable limit cycle with lower mean concentration, leading finally to physiologically unsustainable underdamped oscillations. We can demonstrate this computationally using the model.

If we effectively remove the pancreas from the system, by setting the scaling factors between the pancreas and insulin models and pancreas and cAMP models to zero, the system does not produce ultradian oscillations in blood glucose for values of the external glucose input (M) for which oscillations were observed in the complete system. Removing the pancreas from the system is effectively equivalent to setting the insulin sensitivity of the liver to zero. In the first case (no pancreas) no insulin is produced and hence there is no response in the liver. In the second case (insulin sensitivity = 0) insulin may be produced by the pancreas but the liver is unable to respond to the hormone. The bifurcation analysis has shown that under these conditions oscillations do not occur (see figure 2 (bifurcation diagram)).

If we incrementally increase the scaling between the pancreas and insulin models back to its original value we observe the reappearance of oscillatory solutions. The point at which this occurs depends on the glucose input (M) and the sensitivity of the liver to insulin (1 - tI); the higher the insulin sensitivity the lower the scaling value required to produce ultradian oscillations. These results do not depend on the value of the glucagon scaling parameter because for positive glucose inputs the blood glucose level does not fall below the value required to trigger the production of glucagon in the pancreas model.

We can explore the role of the feedback of blood glucose on the pancreas by varying the parameters which govern the response of the pancreas to the changes in blood glucose. The production of hormones by the pancreas is modelled using threshold (or hill) functions. The parameters tIe and tIc determine the level of blood glucose above or below the reference value at which the pancreas releases insulin or glucagon respectively. Increasing these parameters represents the situation in which the pancreas is less sensitive to changes in blood glucose. As tIe is increased for a given M and tI, oscillations cease to exist as the pancreas does not
respond to the initial rise in blood glucose with the release of insulin. The more sensitive the liver is to insulin the greater the range of $t_g$ for which we observe oscillations (see Figure 6); the amount of insulin produced by the pancreas, even with a high glucose response threshold, is sufficient to trigger the regulation of GSK in the liver.

FIGURE 6 NEAR HERE

5. Conclusions

This paper presents an exploration of the behaviour of the composite model of glucose homeostasis described in the companion paper [1]. We have explored the behaviour as a function of a range of glucose input values and also, since oscillatory behaviour is known to occur, we present a bifurcation analysis to provide quantitative information about the occurrence of these oscillations.

Analysis of the composite model and its results in this and the companion paper [1] reveals that direct glucose control, determined by the capacity of the liver to store glucose, plays an important role in the control of glucose homeostasis. Deficiencies in hormonal control generated by, for example, a reduction in insulin sensitivity, can be accommodated through the direct control mechanism over a surprisingly wide range of insulin sensitivities. The analysis suggests that the consequences of reductions in the sensitivity of the insulin receptor do not become significant until receptor sensitivity has fallen below $1 - t_i = 0.2$. The masking of clinically significant alterations in insulin sensitivity by the direct glucose control mechanism has important consequences, because delays in recognizing the early signs of diabetes may have consequences for treatment.

The direct glucose control mechanism depends on the capacity of the liver to store glucose as glycogen, which provides a significant buffer to alterations in blood glucose however they may be generated. Glycogen storage diseases form a significant body of contributory causes to defects in glucose homeostasis, particularly when the defect resides within the liver, rather
than the muscles. Analysis of the part played by direct glucose control in glucose homeostasis should improve understanding of both causes and consequences of glycogen storage disease. The model presented here will provide a relatively simple way of testing the physiological consequences of metabolic defects that underlie glycogen storage disease because there should be directly demonstrable and measurable consequences for glucose homeostasis. Any reduction in the capacity of the liver to store glucose in the form of glycogen will, because of the significant role in glucose homeostasis, exacerbate any consequences of glycogen storage diseases.

The composite model presented here is one step in an ongoing process of developing more complete system models of liver function and enhancing modelling methodology. The current model already yields interesting results and provides a foundation for work including other important elements of liver physiology. An analysis of glycogen storage disease would be valuable. Obvious additions to the core model include: an elaboration of glucose metabolism and storage to represent the physiological transition towards fat metabolism as cellular glucose levels increase, and the representation of multiple hepatocytes with heterogeneous properties and linked to each other by gap junctions, to investigate the role of metabolic zonation in liver function. Our composite model could also be enhanced significantly by the inclusion of a more detailed model of the pancreas.

6. References


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Figure Captions

Figure 1 – Sample model responses showing stable response (M= 7.5, \( t_1 = 0.6 \)), transient with damped oscillations (M= 7.5, \( t_1 = 0.5 \)) and stable limit cycle (M= 7.5, \( t_1 = 0.4 \))

Figure 2. – Bifurcation plot as \( t_1 \) is varied for three values of M showing when Hopf bifurcations occur. Solid line indicates a stable fixed point, filled circles indicate the minimum and maximum values of the limit cycle. Insulin sensitivity is plotted as 1-\( t_1 \)

Figure 3 - Final resting blood glucose concentration as a function of relative insulin resistance. For oscillatory solutions the mean value is shown. The curves represent various glucose inputs, from bottom to top, M = 0, 5, 7.5, 10, 15, 20, 22.5

Figure 4 - Panel A: Maximum glucose value reached as a function of relative insulin resistance. Glucose input values and code for lines as in figure 3. Panel B: Amplitude of initial transient relative to steady state value defined as \( (x_{max}-x_{final})/x_{final} \). M = 7.5 (\( \times \)), 10 (\( \square \)), 15 (\( \ast \)), 20 (\( \Delta \)).

Figure 5 –The qualitative behaviours of the model as a function of insulin resistance and glucose input. When insulin resistance is high, homeostasis can be maintained by direct glucose control. As insulin resistance falls, homeostatic control is increasingly dominated by pancreatic release of insulin and glucagon, oscillations in blood glucose become increasingly prominent, and occur at progressively lower blood glucose levels.

Figure 6 - The y axis shows the value of \( t_{IG} \) at which model oscillations cease. For lower values the system oscillates.
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