Insulin resistance or hypersecretion? The βIG picture revisited

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HIGHLIGHTS

• Over-secretion of insulin may be the central defect underlying type 2 diabetes.
• We construct a mathematical model of this ‘hypersecretion theory’.
• We extend the well-known Topp model by assuming insulin influences beta-cell mass.
• The revised model demonstrates how hypersecretion can lead to diabetes.

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ABSTRACT

Mathematical models of glucose, insulin and pancreatic beta-cell mass dynamics are essential to our understanding of the physiological basis of the development of type 2 diabetes. The classical view of diabetes is that the disease develops due to insulin insufficiency. An alternate viewpoint that has recently staged a revival is that diabetogenesis is a hypersecretion disorder. A prominent model of diabetes progression is the βIG model due to Topp and coworkers. Here we study two new variants of the Topp model, which we name “Topp-IR” and “Topp-HS”. Topp-IR is a model in which increasing insulin resistance is sufficient to drive a system away from health towards hyperglycemia. Topp-HS describes the hypersecretion model in mathematical terms. We thus show that the hypersecretion hypothesis is theoretically sound, and is therefore a potential route to diabetes. On the basis of insights derived from modeling, we clarify several subtleties of that argument, including postulating a central role for transient insulin peaks in driving insulin resistance.

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1. Introduction

The rising rates of type 2 diabetes mellitus over the last couple of decades have brought the re-examination of various theories of diabetogenesis into sharp focus. It is largely accepted that the disease invariably arises from a combination of insulin resistance, primarily in muscle, adipose and liver tissues, and insufficient insulin production. A notable feature of diabetes is that overt hyperglycemia does not develop until secretion failure occurs. At closer examination, the sequence of diabetogenic events is as follows. Insulin resistance typically worsens first in the early phase of the disorder, and islet beta-cells secrete more insulin to compensate and maintain normal plasma glucose. Over a period of time, if failure occurs in the taxed beta-cells it leads to a concomitant increase in glucose, resulting first in “impaired fasting glucose” and then full-blown hyperglycemia. While muscle insulin resistance contributes directly to the elevation in circulating glucose, insulin resistance in the liver exacerbates this disruption away from homeostasis through overproduction of glucose.

There is another theory – one that is sufficiently antithetical of the classical view – that has received much attention recently, largely due to the 2011 Banting Lecture by Corkey (2012). Corkey and coworkers have argued that hypersecretion, not insulin resistance, is the primary defect of the disease. In other words, the various functions that go awry in diabetes can be traced back to a causal dependence on elevated insulin secretion. The dependence of diabetogenic events in this view is as follows (see Fig. 1 in Corkey, 2012). The original insult is that something – some “Factor X” that presumably has roots in changes in our environment – leads to a hypersecretion by beta-cells. This results in hyperinsulinemia; elevated insulin causes insulin resistance, and ultimately hyperglycemia.

The case for hyperinsulinemia is made in two related, though distinct, arguments. First, Corkey et al. noted that oxidative stress is known to stimulate basal insulin secretion (Pi et al., 2007; Corkey, 2012). They postulate that Factor X induces oxidative...
stress and thereby causes hyperinsulinemia. Second, Pories and Dohm (2012) have argued that a theory in which hyperinsulinemia is the primary diabetogenic event is consistent with the reversal of hyperglycemia following Roux-en-Y gastric bypass surgery. While these are both hypersecretion theories, there are some differences between the two as well, especially insofar as the identity of Factor X is concerned. Corkey et al. emphasize the culprit could be food additives, particularly monoacylglycerides and saccharin. Pories and Dohm, on the other hand, argue that a diabetogenic signal from the gut to islets causes hyperinsulinemia.

We remark that the deep introspection that the hypersecretion theory has generated (see for instance, the twin “Diabetes: Have we got it all wrong?” articles Corkey, 2012, Pories and Dohm, 2012 and others Shanik et al., 2008) is not without reason. It is imperative to be able to decide between the two theories not only for theoretical reasons but also the practical, clinical implications. Indeed, one theory posits insufficient secretion as the root cause of the disorder, the other focuses the spotlight on excess secretion. This debate is particularly important for drug design. The hypersecretion theory calls secretagogues (antidiabetic drugs that stimulate insulin secretion) into question.

The origin of the hypersecretion argument presumably arose in trying to reconcile the following central observation: In the early stages of development of the disease glucose does not immediately show elevation, even though IR is putatively higher. It would seem, therefore, whatever initial disruption takes place in homeostasis must be mediated via insulin; that signal is not glucose. In other words, the sequence of events in which IR develops first, following which the beta-cells secrete in compensation, is beset with this problem: How is IR in the peripheral tissue communicated to the pancreas (if not through glucose, the dominant stimulus of beta-cells)? We shall call this the Corkey paradox. Here we use mathematical modeling to resolve this conundrum.

There are few mathematical models that embody the minimal logic of the diabetogenesis theories outlined above (Ajmer et al., 2013). One influential model was introduced by Topp et al. (2000). The Topp model considers the dynamics of the three major variables essential to glucose homeostasis: glucose (G) itself, insulin (I) and beta-cell mass (β). As far as daily changes go, the glucose–insulin couple are in quasi-equilibrium with each other. Glucose changes following a meal cause insulin to rise, which in turns delivers glucose to peripheral tissue; eventually, both glucose and insulin return to basal (or “fasting”) levels. To explain how this basic process can be altered over a period of time – as in the development of diabetes – Topp et al. argue that systematic changes take place in beta-cell mass. That is, the glucose–insulin dynamic couples to a (much) slower-timescale mass dynamic. Mass is assumed to vary in response to glucose in a logistic manner: Small increases in glucose stimulate beta-cell growth (and therefore increased secretion); as glucose increases further it becomes maladaptive and impedes growth. The model has two stable equilibria. One of these corresponds to health, and the other to a high glucose state corresponding to diabetes. The system invariably recovers from small perturbations from the healthy state. Diabetogenic events, on the other hand, can drive the system into the other attractor, viz. hyperglycemia with a severe loss in mass. The Topp model has been used as a template for constructing other models over the years. A pharmacokinetic-pharmacodynamic (PK–PD) model that includes the effect of antidiabetic treatment is considered in Ribbing et al. (2010). Elements of the Topp model are also found in a diabetogenic model of de Gaetano et al. (2008), Palumbo et al. (2013), and Hardy et al. (2012). A recent, comprehensive model that extends the Topp picture is due to Ha and Sherman (to appear; private communication). The basic framework introduced in the Topp class of models is robust; we use it here to study the two competing theories of diabetes described above.

We show below that the Topp model has a simple explanation of the Corkey paradox, viz. that the argument commits a logical fallacy. We hasten to add, however, that even if the Corkey paradox is not itself defensible, the hypersecretion hypothesis is a serious contender for a theory of diabetogenesis. Our main interest in this paper is to show that the Topp model can be modified with very few changes to mathematically describe the hypersecretion theory.

Here we present two adaptations of the Topp model; these will be referred to as the Topp–IR and Topp–HS models respectively. That is, we modify the Topp model in two successive stages. In the Topp–IR model we will first augment the Topp model with a coupling that we think is an essential part of the physiology but was not included in the original version. Namely, we allow β to depend on I, and not on G alone. This has a major consequence: A new route to diabetes emerges in the model that is dependent on changing insulin resistance alone. Topp–IR is thus a mathematical model of IR–dependent diabetogenesis, which Topp was not. In the next stage we construct the Topp–HS model. In this version we arrange for hypersecretion to be the driver of all diabetogenic events: We couple the development of insulin resistance to increases in (basal) secretion. Using insights derived from the Topp–HS model we show that hypersecretion can indeed be

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Fig. 1. The geometry of the Topp model. The slow manifold of the original system is shown as a curve in β – I – G phase space. Fixed points of the model are also shown, in black circles. The healthy, stable glucose state is at $G^* = 100$. The fixed points are alternately stable, unstable and stable, corresponding to $G^* = 250$ and $G^* = 600$ (pathological). The slow manifold for a lower insulin sensitivity, $S_0 = 0.36$, is shifted upward towards a higher $β$ and I. The slow manifold with secretion, $σ$, twice the basal value, 86.4, is pushed out towards lower $β$. 
isolated as the singular locus of all diabetogenic events. We thus
describe a modified Topp model that encapsulates the hypersecre-
tion theory of Corkey et al. in mathematical terms.

2. Models

2.1. The Topp model

The original Topp model is
\[
\frac{dI}{dt} = \sigma \frac{G^2}{\alpha + G^2} - kl
\]  

(1)
\[
\frac{dG}{dt} = R - (E + S_I)l G
\]  

(2)
\[
\frac{d\beta}{dt} = (-d_0 + r_1G - r_2G^2)\beta
\]  

(3)

with parameters as in Topp et al. (2000).

2.2. The Topp-IR model

The Topp model, modified to study dependence on the insulin
resistance parameter, \(S_I\), is
\[
\frac{dI}{dt} = \sigma \frac{G^2}{\alpha + G^2} - kl
\]  

(4)
\[
\frac{dG}{dt} = R - (E + S_I)l G
\]  

(5)
\[
\frac{d\beta}{dt} = (-d_0 + r_1G - r_2G^2 - d_I)\beta
\]  

(6)

The major difference relative to the Topp model is the inclusion
of the \(I\)-dependent term in the \(\beta\) equation. That is, we argue that
just as glucose influences mass in the original Topp equations, so
does insulin. We assume the simplest such interaction between
insulin and mass: an increasingly available plasma insulin sup-
presses increases in mass.

Parameter values that are different from the Topp model are
\(d_0 = 3.93 \times 10^{-2}\), \(d_I = 1.82 \times 10^{-1}\) and \(r_2 = 2.65 \times 10^{-8}\).

2.3. The Topp-HS model

The Topp-HS model extends the Topp-IR model further. It
considers that insulin sensitivity changes in response to secretory
capacity, \(S_I \equiv S_I(\sigma)\):
\[
\frac{dI}{dt} = \sigma \frac{G^2}{\alpha + G^2} - kl
\]  

(7)

\[
\frac{dG}{dt} = R - (E + S_I(\sigma))l G
\]

(8)
\[
\frac{d\beta}{dt} = (-d_0 + r_1G - r_2G^2 - d_I)\beta
\]

(9)

where \(S_I(\sigma) = -8.33 \times 10^{-3} \sigma + 1.079\), while the other parameters
are as in the Topp-IR model above.

3. Results

3.1. The geometry of the Topp model and its implications

In the Topp model perturbations in glucose and insulin relax to
quasi-equilibrium on a timescale of hours that is much faster than
changes in mass, which occur over months or years. That is, the
fast variables, \(G\) and \(I\), evolve according to Eqs. (1) and (2) with \(\beta\)
slowly constant. In other words, the faster \(G-I\) system relaxes
rapidly towards the slow manifold, the curve composed of the fixed
points of the \(G-I\) pair with \(\beta\) held constant. The full system driven
by changes in \(\beta\), Eq. (3), on the slow timescale – with \(G\) and \(I\) in
quasi-equilibrium – evolves close to the slow manifold, given that
the timescale separation is considerable.

Fig. 1 shows the geometry of the Topp model. As described in
Topp et al. (2000), there are three fixed points \((\beta^*, I^*, G^*)\) of the full
system, which are determined as follows. From Eq. (3) we obtain
that either \(\beta^* = 0\) or \(G^*\) satisfies \(-d_0 + r_1G^* - r_2G^{*2} = 0\). The fixed
point corresponding to \(\beta^* = 0\) has \(I^* = 0\) and \(G^* = R/E\); this is the
fixed point corresponding to the disease pathology. With the
parameters used in Topp et al. (2000) the pathological fixed point
is at \((\beta^*, I^*, G^*) = (0, 0, 600)\), and is stable. If \(\beta^* \neq 0\), from Eq. (3) we
obtain two \(G^*\) as the roots of \(-d_0 + r_1G^* - r_2G^{*2} = 0\). \(I^*\) is computed
from Eq. (2) as
\[
I^* = \frac{R}{S_I(G^* - E)}
\]

(10)
and \(\beta^*\) is determined from Eq. (1) as
\[
\beta^* = \frac{kI^*(\alpha + G^{*2})}{\sigma G^{*2}}
\]

(11)

One of these corresponds to a stable fixed point representing a
healthy glucose level, at \((\beta^*, I^*, G^*) = (300, 10, 100)\). The other is an
unstable fixed point, at \((\beta^*, I^*, G^*) = (36.96, 2.8, 250)\).

3.1.1. Insulin sensitivity and hypersecretion in the Topp model

It is significant to note that insulin sensitivity in the original
Topp model does not affect the glucose corresponding to the fixed
points of the model, \(G^*\), or the stability structure. Fixed points are
determined essentially by the \(\beta\) equation, which fixes the glucose
values corresponding to the physiological and saddle points
regardless of \(S_I\).
Decreasing \( S_t \), lifts the slow manifold up towards higher \( I \) and pushes it out towards higher \( \beta \), Fig. 1. That is, a reduced insulin sensitivity forces a greater circulating insulin in the system at healthy glucose. This is effected through an increase in the mass, \( \beta \). Fig. 2 shows, for example, how the healthy state \( G^* \) remains constant with increases in \( S_t \) while the corresponding \( I^* \) and \( \beta^* \) decline.

Next, it is interesting to ask what role does \( \sigma \), the maximal secretory capacity of beta-cells, play in the model. Changes in \( \sigma \) do not change the steady-state glucose or the stability structure of the fixed points. Further, \( I^* \) is also unaffected by \( \sigma \) (see Eq. (10)). Equation (11) shows that \( \sigma \) affects \( \beta^* \). In fact, changes in \( \sigma \) (all other parameters held constant) are “compensated” by changes in \( \beta^* \) that is, the product \( \sigma \beta^* \) is a constant. Fig. 3 shows, for example, the healthy state \( G^* \) and \( I^* \) remain constant with increases in \( \sigma \), while the corresponding \( \beta^* \) declines. That is, if the secretory capacity is increased, the steady-state mass is simply lower.

It is significant to note that in the Topp model changes in the secretory rate alone cannot directly lead to pathogenesis. That is, the healthy fixed point continues to be stable with no change in the resting glucose or insulin. Hypersecretion cannot by itself, lead to pathology.

3.1.2. The \( \beta G \) explanation of the Corkey paradox

As mentioned previously, it is sometimes thought that the Corkey hypersecretion hypothesis can simply be inferred from the observation that a causal signal from insulin resistance to beta-cell secretion is missing. This assumption, however, is non causa pro causa: The required causal signal can, in fact, be glucose. The Topp model can be used to clarify this (also see Topp et al., 2000). Suppose \( S_t \) is decreased abruptly, \( G \) will rise rapidly (because muscle uptake is reduced). This would prompt the beta-cells to secrete in excess and return glucose to normal levels. Note that even though glucose returns to same resting state, a transient change in glucose provides the signal that informs the beta-cells of the increased demand. Were \( S_t \) to change more gradually, the rise in glucose as a stimulus for increased secretion is no longer as obvious, even though the same driving forces are still present.

It cannot therefore be a theoretical argument that increases in insulin resistance cannot drive excess insulin secretion. It is nonetheless plausible that elevated insulin secretion could be a primary cause of the disease. We showed in the previous section that this is not a feature of the Topp model as it stands. It is therefore intriguing to ask if the Topp model can be reasonably modified to provide a mathematical basis of hypersecretion-induced diabetes. We carry out this task below. Models Topp-IR and, in particular, Topp-HS will elucidate various aspects of the corresponding dynamics.

3.1.3. Does hypersecretion imply, or is implied by hyperinsulinemia?

It is important to note that for many authors, such as Pories and Dohm (2012) for example, hyperinsulinemia is synonymous with increased insulin secretion. It is somewhat implicit in their arguments that insulin resistance follows as a natural consequence once basal secretion is elevated. (We note, however, that this reasoning is not strictly necessary for their overall argument: A second consequence of increased basal hyperinsulinemia is increased hepatic gluconeogenesis. Here we will not concern ourselves with this subtlety for the moment, and focus on insulin resistance alone.)

From a theoretical perspective, arguing one from the other is a subtle matter that requires some consideration.

As the Topp model shows, increased basal insulin secretion does not necessarily imply chronic hyperinsulinemia (as in Fig. 3 for example).

Somewhat surprisingly, the converse argument does not hold either. That is, it is not reasonable to infer increased secretion from hyperinsulinemia. Hyperinsulinemia can be explained simply by an increase in insulin resistance, as in Fig. 1; it is not necessary to invoke increased secretion.

In other words, neither hypersecretion nor hyperinsulinemia follow as a direct consequence of each other. A broader context is thus required to correctly identify cause and effect.

3.1.4. The structure of coupling in the Topp model

With a view towards modifying the Topp model below, it is worth reexamining the couplings that are present in the model. The two fast variables, \( G \) and \( I \), are mutually coupled, Fig. 4. The slow variable, \( \beta \), influences \( I \) but not \( G \). The most significant coupling, however, is the dependence of \( \beta \) on \( G \) but not \( I \).

From a purely theoretical point of view, the system is fully coupled, that is, all possible interactions between these three variables are accounted for, except for two: a dependence of \( \beta \) on \( I \), and a dependence of \( G \) on \( \beta \). Including a \( \beta \rightarrow G \) relationship in the model would be tenuous on physical grounds since \( \beta \)-cell mass influences neither gluconeogenesis nor glucose uptake directly, only via insulin.

There are good reasons to explore an extension of the Topp model by examining the implications of including the \( I \rightarrow \beta \) coupling. For one, we are interested in the behavior of the model as we vary the parameters \( S_t \) corresponding to insulin resistance, and \( \sigma \) corresponding to hypersecretion. As described earlier, the \( \beta \) equation shows immediately that the fixed points of the model are determined only by \( G \), and this cannot be influenced either by \( S_t \) or \( \sigma \). This implies that to change the behavior of the Topp model in a nontrivial manner, one needs to allow for \( \beta \) to depend on \( I \).

There is, in fact, considerable evidence that insulin is crucial to the growth response of beta-cells (Okada et al., 2007), and that high insulin may suppress beta-cell mass (Blume et al., 1995). We therefore claim that it is physiologically plausible to assume \( I \) exerts a negative feedback onto \( \beta \)-cells. We will show below that once \( \beta \) is dependent on \( I \) there is a qualitative change in the model behavior relative to the original Topp model.

![Fig. 3.](image-url) \( \sigma \) does not alter the \( G^* \) and \( I^* \) for the healthy steady state in the model, but it does change the corresponding \( \beta^* \).
3.2. The Topp-IR model

In the Topp model insulin sensitivity, $S_I$, changes the equilibrium beta-cell mass and insulin, but does not affect the glucose corresponding to the equilibria (Fig. 1). In this section we construct a modified Topp model in which diabetogenesis arises from changes in insulin sensitivity. We call this the Topp-IR model (see Models, Section 2.2, for the full details).

We make the following changes to the Topp model. We assume that beta-cell mass is controlled not only by glucose levels but also insulin, Eq. (6):

$$\frac{d\beta}{dt} = (-d_0 + r_1 G - r_2 G^2 - d_1 I)\beta.$$

This is a natural modification of the Topp model. In the analysis below we will investigate $S_I$ as the control (bifurcation) parameter. That is, we wish to investigate if changes in $S_I$ can be a route to diabetes in the Topp-IR model.

3.2.1. The transition to IFG and hyperglycemia with increasing $S_I$

Once mass is allowed to depend not only on glucose but also insulin, the fixed points in the model can then also change along the glucose axis. In particular, it is no longer necessary that three fixed points are maintained regardless of $S_I$; we show next that a pair of nodes may now be lost through a saddle-node bifurcation.

Fig. 5 shows the geometry of the Topp-IR model. Parameters have been chosen so the model has a very similar structure as the original Topp model. As $S_I$ is decreased the stable, healthy glucose state and the unstable fixed point grow closer together and eventually coalesce. The Topp-IR model thus has the following significant features:

1. As insulin resistance grows the stable fixed point corresponding to health grows in glucose. That is, insulin resistance causes an increase in resting glucose. There is a concomitant increase in the resting insulin corresponding to elevated glucose. It is useful to note that increased insulin does not restore glucose to the basal levels corresponding to normal sensitivity.
2. The model makes it clear that as insulin resistance increases the unstable fixed point corresponding to the tipping point to hyperglycemia shrinks to lower glucose. Changes along the bold black curve reflect what is clinically described as impaired fasting glucose tolerance (IFG). The model not only explains the elevation in resting glucose that is observed in IFG but also warns that, in fact, the danger of tipping over increases as IFG progresses.
3. Perhaps the most significant departure from the Topp model is in the nature of the transition to IFG and hyperglycemia. In the Topp model a transition from the healthy state to the hyperglycemia fixed point occurs through tipping over the unstable point, regardless of the $S_I$ value. In the Topp-IR model, this is also true so long as the saddle-node bifurcation has not taken place. A mechanism by which hyperglycemia occurs as a result of insulin resistance increasing past the bifurcation point – as opposed to forcing a tipping over – follows as a natural consequence of the dynamics, and may well be one route to diabetogenesis.

4. Once sensitivity is low enough, the bifurcation takes place and the only fixed point that remains in the system is the high glucose one; hence hyperglycemia is inevitable. This feature – that there is SN bifurcation in the system – also explains why people can stay in IFG like states for a long time before developing hyperglycemia: If the loss in sensitivity hovers only a little past the bifurcation point the transition to hyperglycemia would invariably be a slow passage.

In the Topp-IR model fixed points become sensitive to $S_I$. On the other hand, they do not depend on $\sigma$. Similar to analysis described earlier (recall that $\sigma$ and $\beta$ occur as a product in the $f$ equation), changing $\sigma$ changes $\beta^*$ while keeping the same $G^*$ and $I^*$.

Topp-IR is an insulin resistance–first model. In the sense that in Topp-IR decreased insulin sensitivity is the root cause of pathogenesis. We next seek a hypersecretion–first model. To allow for the fixed points of the model to vary with hypersecretion requires additional changes. We develop this line of reasoning in the Topp-HS model.

3.3. The Topp-HS model

In the Topp-IR model, the bifurcation parameter is $S_I$ which leads to a transition to hyperglycemia. However, $\sigma$ cannot induce diabetogenesis in this manner. Hence we study nuances of the Topp-IR model further. The result is the Topp-HS model, so-called because $\sigma$ is the bifurcation parameter and pathogenesis is the result of hypersecretion.

Recall that a central feature of the hypersecretion theory is that hypersecretion leads to hyperinsulinemia, which in turn induces insulin resistance. In other words, insulin sensitivity declines as a function of hypersecretion. We thus modify the Topp-IR model by

\[ G = \frac{r_1 I - r_2 I^2 - d_1 I}{d_0 + r_1 I - r_2 I^2 - d_1 I}. \]
taking the following linear function for \( S_I(\sigma) \):

\[
S_I(\sigma) = -8.33 \times 10^{-7} \sigma + 1.079.
\] (12)

This equation simply express that doubling the \( \sigma \) (from the basal value in the Topp model) halves \( S_I \). The bifurcation parameter now, in the Topp-HS model, is \( \sigma \).

Fig 6 shows the geometry of the Topp-HS model and changes with \( \sigma \). Once again we find there is a saddle-node bifurcation route to diabetes; this time, however, the parameter is \( \sigma \). Increases in the secretory capacity, \( \sigma \), lead not only to increases in basal insulin but also resting glucose, until, finally, the bifurcation takes place and systematic hyperglycemia results. We thus have a model that captures the arguments of the hypersecretion theory.

Before proceeding further, we consider an alternate possibility: It could be argued that it is more ‘realistic’ to allow \( S_I \) to be a function of \( I \) instead of \( \sigma \), since we wish to require that increased \( \sigma \) leads to decreased \( S_I \) because of increased \( I \). It is somewhat subtle to show that this reasoning is naive: Increasing \( \sigma \) in a model in which \( S_I \) is not coupled to \( \sigma \) does not lead to increased insulin (as discussed previously in the discussion of \( \sigma \) in Tipp-IR). That is, if \( S_I \) is fixed and \( \sigma \) is increased, \( \beta \) compensates for the change without altering either \( I \) or \( G \) corresponding to the fixed points. Hypersecretion is, in principle, balanced by a decreased mass – without any residual hyperinsulinemia – and one is left with having to explain how then does increased \( \sigma \) transduce to decreased \( S_I \)?

In Topp-HS both postulates of the hypersecretion theory are satisfied: (i) Hypersecretion as the primary defect, and (ii) Hyperinsulinemia and insulin resistance as its direct consequences. We note, however, that in the model we have assumed \( S_I = S_I(\sigma) \) directly, to emphasize the viewpoint that insulin sensitivity degrades as a function of increased secretion. We are yet to assess the physiological meaning of this relationship, Eq. (12), though. That is, while \( S_I \equiv S_I(\sigma) \) encapsulates the causal dependence of \( S_I \) on \( \sigma \) phenomologically, it says nothing of the mechanism by which such a relation is feasible. The answer lies in noting the difference in timescales between the faster \( G-I \) system, and the much slower beta-cell mass changes. Although \( \beta \) does compensate for increases in \( \sigma \), this takes place slowly; in the interim, the transient insulin peaks are higher, as shown in Fig. 7. We claim that it is these acute insulin elevations that result in decreased sensitivity. That is, although hypersecretion alone cannot generate hyperinsulinemia – because mass would eventually compensate – if hypersecretion develops rapidly, insulin transients encode a signal that can transduce insulin resistance. This justifies our use of the phenomenological model, Eq. (12). Below we comment further on the precise causality of the hypersecretion \( \rightarrow \) insulin resistance transition. In particular, we note that mass never gets a chance to ‘really catch up’ and both hyperinsulinemia and decreased sensitivity become persistent with hypersecretion.

4. Discussion

In the classical view, insulin resistance as well as impaired secretion together contribute to the development of diabetes, although the relative importance of these factors is not generally understood. It has been noted that there may be differences between populations (Raz et al., 2013). For example, beta-cell dysfunction is thought to play a more important role in Asian populations while insulin resistance may be more important in Western populations, where diabetes is often linked to obesity. In either case, the development of insulin resistance is considered the major precursor of diabetogenesis because it precedes beta-cell dysfunction. This conventional, IR-based theory has had a long run, but the “diabetes” (diabetes coupled to obesity) epidemic continues to grow. Disillusioned with this state of affairs, Corkey and colleagues have recently revived the hypersecretion theory, which places over-secretion of insulin by the pancreas at the heart of the development of the disease. If the hypersecretion theory is correct that has enormous implications not only for our understanding of the disease process but also drug development and treatment. Perhaps unsurprisingly, there have been few takers of the theory so far. We argue that this deficit can be addressed, at least in part, by placing the hypersecretion theory on firmer, mathematical ground.

The starting point of our model of the hypersecretion hypothesis is the diabetes model of Topp et al. The Topp model encodes a
glucose–insulin pair of equations that are in quasi-equilibrium. Daily changes, such as the excursions in glucose following meals, are restored rapidly and homeostatically towards a set-point. The Topp model is, however, also capable of exhibiting changes on much slower timescales; these are affected by changes in beta-cell mass. There are three fixed points as a whole in the system relative to this slow mass dynamics: a healthy, normoglycemic state, an unstable, threshold state and a hyperglycemic state. Topp et al. identified five routes by which the healthy stable state can transition to diabetes. Here we are specifically interested in whether changes in insulin resistance can lead to diabetes. Topp et al. argued that changes in $S_0$ – if they are slow – cannot cause diabetes because they do not change the steady-state glucose. However, if the $\beta$-cell mass changes too slowly compared to (fast) changes in $S_0$, the possibility of a transition past the unstable fixed point towards hyperglycemia does arise (the so-called “catch and pass” pathway). Here we focus on changes in insulin resistance that develop over years, that is, they are very slow; whether that can cause pathogenesis. In other words, can the Topp model be extended in a manner that $S_0$ parameterizes the dominant defect of diabetes?

We construct two new models based on extensions to the original Topp model of diabetogenesis. In the first of these, Topp-IR, decreased insulin sensitivity, $S_0$ leads to the transition to diabetes. In the second one, Topp-HS, it arises from an increase in secretion, $\sigma$. Both models are built on the premise that mass is influenced not only by circulating glucose levels – as in the original Topp model – but also insulin. By including a $G$ as well as $l$ dependence in the $\beta$ equation, the healthy and unstable fixed points of the Topp model no longer occur at fixed glucose; the fixed points can move towards each other with increasing $S_0$. This sets the stage for a possible saddle-node bifurcation to occur. Past the bifurcation, the only fixed point that remains is the pathological one; in other words, a transition to diabetes takes place. In Topp-IR the saddle-node bifurcation occurs when $S_0$ is changed directly, while in Topp-HS it is changed indirectly through a change in $\sigma$, which in turn changes $S_0$.

The crucial advance relative to the original Topp model in the variants presented here, Topp-IR as well as Topp-HS, is the inclusion of effects of insulin in the beta-cell mass dynamic. The factors that influence mass are not fully understood, and the mechanisms by which mass adapts are the subject of much investigation. Mass responds to a variety of fuel and neuro-hormonal signals, including nutrient changes (primarily glucose and free fatty acids), incretin hormones such as glucagon-like peptide 1 (GLP-1) and growth factors, including insulin (Prentki and Nolan, 2006). Insulin-like growth factors (IGFs) have much in common with insulin signalling and are important to pancreatic beta-cell development not only during foetal growth but also in the postnatal period and adult life (van Haften and Twickler, 2004). Insulin and insulin-like growth factors 1 and 2 can act through the insulin receptor substrate–2 (IRS-2) pathway, via PKB phosphorylation and inactivation of the forkhead-O transcription factor 1 (FOXO1) to influence the important beta-cell proliferation and apoptosis (Kulkarni et al., 2004; Bouwens and Rooman, 2005) factor, the pancreas/duodenum homeobox gene-1 (Pdx1) (Kitamura et al., 2002; Prentki and Nolan, 2006; van Haften and Twickler, 2004). Downregulation of Pdx1 has been reported, for example, in the deterioration of beta-cell function (the hypothetical phase 2 decompensation associated with mild hyperglycemia) in Weir et al. (2001) and Jonas et al. (1999). It has also been suggested that while IGF-1 exerts an antiapoptotic effect that enables beta-cells to cope with glycemic stress, prolonged hyperglycemia leads to apoptosis and loss of mass (van Haften and Twickler, 2004; Donath et al., 1999). Insulin and IGFs thus exert complex effects on beta-cell mass growth. Here we have shown that assuming a simple negative feedback from insulin onto the mass dynamic is sufficient to develop Topp-type models that engage insulin resistance directly in diabetogenesis.

Another aspect of the model that deserves attention is the absence of an explicit arrow of causality from $\beta$ onto $G$ in the model, see Fig. 4 for example. That is, the model assumes that changes in mass influence glucose only through secretion (but not directly). This assumption, in fact, goes back to the original Topp model; we have retained this here as it is consistent with a “traditional” view of the relationship. Indeed, compartmental models that track glucose–insulin fluxes in detail through the various tissues of the body, such as muscle, liver, fat, gut and the brain, often make this assumption. Of the most prominent of such models is iHOMA2, which adheres to this view as well, see Fig. 1 in Hill et al. (2013) for example. On the other hand, it is intriguing that it is the only missing arrow in an otherwise fully coupled system. There has been considerable progress in understanding the intersection of the nervous and endocrine systems. In particular, there is a growing interest in brain regulation of glucose homeostasis through insulin-dependent as well as insulin-independent pathways (Schwartz et al., 2013). An active line of research into the islet–brain–glucose axis has argued that a $\beta \rightarrow G$ connection is not only physiological plausible, it is the essential reality of glucose homeostasis (Watte, 2013). In light of such evidence as that insulin may act on glucose regulation directly, for example via hormones such as leptin or a mediobasal hypothalamus-directed reduction in hepatic glucose secretion (Benoit et al., 2004), it may prove useful to explore that last remaining causal arrow in future developments of the Topp class of models.

**Insulin resistance or hypersecretion?** It is inherently challenging to reason about the causality of events in diabetes without mathematical models. Each of the three models highlight various subtleties of reasoning. The Topp model teaches, for example, that hyperinsulinism cannot be assumed to arise simply from increased secretion: Increased secretory capacity can be exactly compensated simply by lowering mass. That is, although it is tantalizing at first to speculate that increased secretion raises insulin, that is naive. Topp-IR and Topp-HS are more sophisticated in their dynamics. Their geometries are qualitatively very similar, but the question that distinguishes the two is: What parameter(s) drive the systems to bifurcation? Increased insulin resistance raises $l$ in Topp-IR and drives the healthy and unstable fixed points towards coalescence. To explain how hypersecretion can drive the system to bifurcation – as in Topp-HS – is more involved. Here we have to note that the origin of insulin resistance lies, after all, in insulin increases. The nuance that is needed is that transient insulin pulses are more peaked with increased secretion; we claim this is the signal that drives insulin resistance. That is, Topp-HS encodes the following sequence of events: Hypersecretion leads to higher insulin pulses, which in turn drive insulin resistance. Insulin resistance forms the core that drives diabetogenesis in both Topp-IR and Topp-HS models. However, IR is the causal signal in Topp-IR, while in Topp-HS it is an intermediate signal; hypersecretion is the causal signal in Topp-HS.

Topp-HS is a mathematical model that is consistent with the hypersecretion theory of diabetes. For this pathway to work, we have proposed that although steady-state insulin does increase due to hypersecretion, it is not the signal that links hypersecretion to resistance. The casual sequence of events is not hypersecretion $\rightarrow$ hyperinsulinemia $\rightarrow$ insulin resistance, but hypersecretion $\rightarrow$ transient hyperinsulinemia $\rightarrow$ insulin resistance $\rightarrow$ persistent hyperinsulinemia instead. That is, insulin resistance develops in response to transient, not sustained hyperinsulinemia. If Topp-HS is a good representative of the hypersecretion theory, this highlights a subtlety (in the role of transient insulin peaks) that was not part of the original arguments of Corkey et al. or Pories and Dohm. One way to test Topp-HS experimentally lies in noting the claim that an
increased pulsatility of insulin ought to precede the development of diabetes. It is encouraging that this suggestion is in line with the observation that insulin pulsatility is generally thought to degrade in diabetic patients (Satin et al., 2015).

Finally, we note that it appears difficult to distinguish between the IR and hypersecretion models by inference from observed data alone. Testing these models experimentally will require careful interventions designed to control the pulsatility effects of insulin and insulin resistance, which is perhaps easier done in animal models than human studies.

**Early-warning signals of diabetes.** The Topp variants presented here both encode a transition to hyperglycemia via a saddle-node bifurcation with respect to the dominant bifurcation parameter ($S_1$ in Topp-IR and $a$ in Topp-HS). That is, one possibility for the transition to diabetes is that it can be catastrophic. The other prominent mechanism of a transition to diabetes in these models is by way of crossing over the unstable fixed points that separates the physiological and pathological ones. Indeed, Topp et al. (2000) pointed this out as a pathway to diabetes in their original paper, and it is currently being investigated in greater detail by Sherman and colleagues (private communication).

In principle, it ought to be possible to detect early-warning signals of critical transitions (Scheffer et al., 2009; Li et al., 2014; Trefois et al., 2014) from an analysis of time series data. Typical indicators of a catastrophic shift arising from a fold bifurcation include a significant increase in autocorrelation and variance during a transition across the bifurcation. Investigating early-warning indicators can serve several purposes. For one, early-warning signals of a critical transition from the bifurcation mechanism would be different from those arising from perturbation across the unstable fixed point; an analysis of the data can thus clarify the route taken by the system in reality. Not only would it help in validating theory but, further, it might also help in an early detection of the disease. To carry out such a programme it will be necessary to examine longitudinal data from individuals that are not diabetic to begin with, but acquire hyperglycemia over time. If early-warning indicators were available, perhaps that might better equip physicians to detect the critical point more precisely and prevent the transition.

We note that current thinking in clinical practice appears to point to a catastrophic transition underlying diabetogenesis: Once impaired fasting glucose develops there is an immediate risk for developing hyperglycemia; many patients progress to diabetes in less than three years (Nichols et al., 2007; Meigs et al., 2003). That is, pre-diabetic, impaired glucose states reflect an approach towards the bifurcation point; when a bifurcation does occur, it is not surprising that hyperglycemia follows relatively rapidly (within a decade).

**Oxidative stress and the development of diabetes.** Next, we comment on the role of oxidative stress in diabetes in the context of the Topp family of models. There is, in fact, considerable evidence that oxidative stress (increased, unbalanced ROS) causally generates insulin resistance, which is consistent with the Corkey hypothesis. Corkey et al. have argued for a central role for oxidative stress in their theory in that oxidative stress is a primary insult that drives beta-cells to hyper-secrete (Corkey, 2012). It is significant to note that this is a controversial notion. As an example of the extreme opposite of this view is a hypothesis due to Watson (2014), wherein he argues that diabetes arises from insufficient oxidant stress. There is, therefore, a great need to incorporate oxidative stress in mathematical models of diabetogenesis. Let us examine briefly what shape such a model might take. We note that inasmuch as oxidative stress drives hypersecretion, Topp-HS is essentially a model of oxidative stress-driven diabetogenesis already. It would be straightforward to allow oxidative stress to drive hypersecretion and insulin resistance independently; those effects would simply be additive. On the other hand, such a representation of oxidative stress is rather superficial. There are more complex situations possible. For example, it is also known that high oxidative stress causes apoptosis in beta-cells, which translates into decreased secretion. This effect of oxidative stress on secretion is antagonistic relative to its effect on insulin resistance and hypersecretion. Careful modeling is required to disentangle such issues. We hope to return to these questions in future work.

We have not commented on the mechanisms by which drugs control (reverse?) hyperglycemia. Models of diabetogenesis ought to be useful in addressing such questions as well, but we leave this for future work. We conclude here that the various Topp models demonstrate there is a richer array of scenarios that have a firm basis in theory than thought previously – including diabetes by way of pathologically increased secretion. This is a crucial step in elucidating the variety of routes by which the disease occurs in reality.

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**References**


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