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Insights to the minimal model of insulin secretion through a mean-field beta cell model

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Abstract

The present work introduces an extension of the original minimal model of second phase insulin secretion during the intravenous glucose tolerance test (IVGTT), which can provide both physiological and mathematical insights to the minimal model. The extension is named the mean-field beta cell model since it returns the average response of a large number of nonlinear secretory entities. Several secretion models have been proposed for the IVGTT, and we shall identify two fundamentally different theoretical features of these models. Both features can play a central role during the IVGTT, including the one presented in the mean-field beta cell model.

Keywords: Minimal model; Insulin secretion; Distributed threshold; Mean field

1. Introduction

The intravenous glucose tolerance test (IVGTT) is widely used in order to estimate parameters that constitute the so-called metabolic portrait of the test subject. The insulin sensitivity and glucose effectiveness provide the glucose kinetics part of the metabolic portrait, while the first- and second-phase insulin secretion indices are measures of pancreatic β-cell function. The parameters are embedded in two different minimal models, one describing the glucose kinetics (Bergman et al., 1979) while the other describes the insulin secretion (Toffolo et al., 1980). The minimal models are extensively used and implemented in published computer programs (Pacini and Bergman, 1986) and (Vega-Catalan, 1990). Here we shall concentrate upon the minimal model of insulin secretion (hereafter named MM), as applied e.g. in Pacini and Cobelli (1990), Marchesini et al. (1990), and Piccardo et al. (1994).

MM simply states that during an IVGTT, the second phase insulin secretion into plasma is proportional to the time since the glucose bolus was administrated and to the glucose concentration above some threshold value. MM is based on data, and does not provide any physiological arguments for why the secretion rate rises linearly in time, which subsequently might cast doubt on whether the physiology is satisfactory described by the model. Furthermore, the explicit time dependence causes mathematical problems, specifically when the two minimal models are unified (Gaetano and Arino, 2000).

Based on data analysis, other statistical models have been suggested to replace the minimal model of insulin secretion (Toffolo et al., 1995), (called M1 and M2 in the present paper, just as in the original paper). These models can be argued from theoretically more comprehensive models (Licko and Silvers, 1975), which make them physiologically and mathematically more

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appealing. However, the physiologic assumptions and the theoretical feature behind these models are not the only reasonable ones, which is subject for further elaboration in the following.

The primary goal of the present paper is to introduce a theoretical and mathematical extension of the original MM that clarifies the physiologic background and describes the theoretical feature that has made MM a success. The added structure introduced to clarify the physiology solves the unboundedness of the secretion, which was the more crucial of the mathematical problems.

The theoretical idea behind the suggested model is to describe the collective secretory response of all the beta cells as a single object, a mean-field beta cell. The dynamics of the mean-field beta cell is different from the individual entities it is composed of, but we can give a physiological understanding of the mean-field model based on the behavior described by an appropriate model for the individual entities.

The secondary purpose of the present text is to compare M1 to the mean-field beta cell model in a theoretical context motivated by the distributed threshold model (Grodsky, 1972), which enables us to identify the two separate theoretical model features of the original MM and M1. Finally the models are compared in a short data analysis, to demonstrate that both theoretical features can be seen in the IVGTT experiment. This data analysis deals exclusively with the theoretical features, that could be identified only for a small number of subjects, whereas other complications of a full scale data analysis were completely ignored. The present model is thus not proposed as a competitive model for the IVGTT, but as a tool to illustrate the theoretical features that may be necessary to consider for new insulin secretion models. Especially when more mechanistic models are pursued for a coherent description of different challenges of the beta cell.

All models discussed in the present text are summarized in the appendix, for easy reference.

2. Insulin synthesis and release

Insulin secretion in response to an abrupt increase in blood glucose concentration can to a large extent be described by two phases, a rapid first phase followed by a slowly rising second phase. These phases are related to the pleiotropic effects that glucose induce on the beta cell, ranging over regulation of insulin biosynthesis, movement of insulin within the beta cell, and insulin release.

The duration of the IVGTT is only a few hours, which is a brief period when dealing with insulin synthesis. Over short periods (2 h or less) glucose regulates the proinsulin biosynthesis mainly by increasing the rate of translation of proinsulin mRNA. In vitro studies show that after an abrupt increase in plasma glucose concentration, the amount of translated proinsulin rises approximately linearly in time, see e.g. (Itoh et al., 1978), and approximately linearly with the glucose concentration (Welsh et al., 1986), for time periods and glucose concentrations comparable to the IVGTT. After synthesis, proinsulin is split into insulin and C-peptide, which are packed in equimolar amounts into granules.

The dynamics of intracellular granules, recently reviewed in Rorsman and Renstrom (2003), is an exploding area of research made available by new real-time imaging techniques. Among other things, these studies indicate heterogeneity of the intracellular insulin granules where some move freely within the intracellular space while others are docked in the plasma membrane and only a fraction of the latter are ready to be released, thereby named the readily releasable pool (RRP). Movement of granules from, e.g. the intracellular space to the RRP is included in the concept of redistribution that in the following mathematical models more generally covers changes in the level that insulin released is sensitive to glucose concentration. The RRP is believed to contain the granules contributing to the first phase secretion (Olofsson et al., 2002), while recent experiments with real-time imaging indicate that second phase secretion is due to granules that have just arrived at the plasma membrane (Ohara-Imaizumi et al., 2002). The second phase secretion is seen also when the synthesis of proinsulin is completely inhibited, indicating that recruitment of freely moving intracellular granules are responsible for the provision of new insulin to the membrane. However for other cell types, recent experiments using fluorescent cargo protein that changes color with time demonstrate that newly assembled secretory entities are secreted first (Duncan et al., 2003). For the beta cell, similar experiments might illuminate, whether upregulation of proinsulin does contribute to the second phase secretion after all.

The release of insulin is facilitated by glucose transforming into ATP, stopping the potassium efflux of the sodium–potassium pump, which depolarizes the cell. The depolarization opens voltage-gated calcium channels, and the rise of calcium leads to transport of insulin granules across the cell membrane. The insulin release, ranging over a few minutes, is very fast in the time frame of the IVGTT, and for this reason it is frequently modelled to be instantaneous, but it can also be identified dynamically as described later.

Heterogeneous response of insulin to glucose has been documented, not only at intra-cellular level, but also at the inter-cellular level. These differences exist both in the biosynthesis and in the secretory response, but also different beta cells have been seen to exhibit different thresholds for the glucose-induced insulin release

(Schravendijk et al., 1992). In the following mean-field beta cell model, we model the collective response of the many beta cells as one object, and thus lump together many forms of heterogeneities. The mathematical model will not depend on whether the inhomogeneity is at the level of beta cells or at the level of granules within the cell, and we shall thus simply refer to the secretory entities.

3. The mean-field beta cell model

The first mean-field beta cell model (MFM1 in the following) is a description of the above-basal second phase secretion during the IVGTT. The first phase secretion is not modelled, and could be included either by using a dirac delta function, or simply by letting the plasma insulin concentration start at the maximal insulin concentration I_{max}.

We shall quantify the physiological argument that the second phase secretion must be a combination of the provision of new insulin and the heterogeneity of the secretory entities. The ith entity is described by

$$\mathrm{d}P/\mathrm{d}t = -\alpha(P - H(G-h)),$$

$$SR_i = \beta H(G-h_i)P, \quad P(0)=0,$$

where $H(\cdot)$ is the Heaviside (or step) function, h_i is the individual glucose threshold for the secretion entity, which gives us the heterogeneity in the individual above-basal second phase secretion rate, SR_i, P is the normalized rate of provision of new insulin, similar to what has been used e.g. in Grodsky (1972) and Toffolo et al. (1995), which in the present context is modelled identically for the individual entities. The provision is the combination of recruitment from intracellular granules and from newly synthesized insulin, and like proinsulin it rises slowly starting when glucose concentration rises above some global threshold h. $1/\alpha$ is the characteristic time-scale for the provisionary factor to approach its maximum level, and β is the proportionality factor between the normalized provision and the individual secretion rate.

MFM1 arises through the assumption that the number of secretory entities contributing to the total above-basal secretion is proportional to the glucose concentration above threshold, h. We have MFM1,

$$\mathrm{d}P/\mathrm{d}t = -\alpha(P - H(G-h)),$$

$$SR_{ab} = (\gamma/\alpha)[G-h]^+P, \quad P(0)=0. \qquad \text{(MFM1)}$$

$[G-h]^+$ is the positive part of $(G-h)$, which is modelled to be proportional to the number of contributing secretory entities. SR_{ab} is the total above-basal second phase secretion rate. The parameterization has been changed compared to the model of the individual secretory entities, such that γ is the second phase secretion index (ϕ_2).

We remark that MFM1 respond differently than the individual secretory entities. The individual entities have a sharp threshold above which they begin to secrete, while the mean-field beta cell has a secretion proportional to the glucose concentration above some threshold. This threshold in MFM1 will not represent a typical threshold for the individual packets, but lie in the low end of the individual thresholds, which is in agreement with the typical MM estimation of a threshold near the basal glucose concentration.

Compared to MM, we have used an additional state variable and one extra parameter. The new state variable gives us an interpretation of the linear rise in time, and the extra parameter gives us a glucose-dependent upper bound on the secretion rate.

3.1. Deriving the minimal model from the mean-field beta cell model

In the typical IVGTT, the glucose concentration will not rise above threshold after the first time it has gone below. In this situation, we can derive MM from MFM1 in the limit $\alpha \to 0$. MFM1 can now be written,

$$P = \alpha t + O(\alpha^2) \text{ for } G > h,$$

$$SR_{ab} = (\gamma/\alpha)[G-h]^+P = \gamma[G-h]^+t \qquad \text{(MM)}$$

which is the usual representation of the minimal model.

Since $(1/\alpha)$ is a characteristic time, we can understand the minimal model, as the limit where it takes an infinitely long time before the maximal provision is approached. In this limit the insulin secretion will rise unbounded, just as for the MM.

3.2. Including first phase secretion in the mean-field model

Up until now, we have assumed that the first phase secretion is instantaneous. This is obviously not true, and we might get a better description of the first few measurements by including a state representing the total amount of ready made insulin in the currently secreting entities. This state is named X in the following extended form of the mean-field beta cell model (MFM2 from this point). MFM2 is,

$$P = -\alpha(P - H(G-h)),$$

$$\mathrm{d}X/\mathrm{d}t = (\gamma/\alpha)[G-h]^+P - mH(G-h)X,$$

$$SR_{ab} = mH(G-h)X, \qquad \text{(MFM2)}$$

where $1/m$ is the characteristic time for the first phase secretion, so by taking the limit $m \to \infty$ MFM1 is obtained. The first phase secretion index, ϕ_1 can be derived from the initial amount of readily releasable

insulin in all packets contributing to the first phase secretion.

4. Motivating models for the IVGTT from the distributed threshold hypothesis

The distributed threshold hypothesis (Grodsky, 1972) has played a central role in the development of a suitable model to estimate the secretion indices during an IVGTT. The original experiments on the perfused rat pancreas used to quantify the distributed threshold model was in fact used as motivation for MM (Toffolo et al., 1980). More directly the distributed threshold model has motivated another model for the IVGTT (Licko and Silvers, 1975), which in a slightly altered form has provided an alternative to MM (Toffolo et al., 1995). Also the mean-field beta cell model proposed in this paper can be motivated by the distributed threshold model. We shall present a summary of the distributed threshold model, and then demonstrate the two different approximations corresponding to the two model alternatives.

The fundamental hypothesis is that the readily releasable insulin is stored in small packets, where the different packets have different thresholds, secreting insulin into the plasma only when the glucose concentration has exceeded this threshold. The amount of readily releasable insulin in packets with threshold between θ and $\theta+\mathrm{d}\theta$ is given by $\xi(\theta,t)\,\mathrm{d}\theta$, so the threshold density distribution function ξ can be used to model the total secretion into plasma, i.e.

$$\begin{aligned}\mathrm{d}\xi(\theta,t)/\mathrm{d}t = &-m\xi(\theta,t)H(G-\theta)+\gamma(\theta)P(G,t)\\ &-\Gamma'\xi(\theta,t)+\gamma'(\theta)\int_0^\infty \xi(\theta',t)\,\mathrm{d}\theta',\end{aligned}$$

$$\mathrm{d}P(G,t)/\mathrm{d}t = -\alpha[P(G,t)-P(G,\infty)],$$

$$SR_{tot} = m\int_0^G \xi(\theta,t)\,\mathrm{d}\theta. \qquad \text{(Dist-Thres)}$$

The secretion of insulin into the plasma is realized through the first term $-m\xi H(G-\theta)$, where $H(\cdot)$ is the Heaviside function, P is the provisionary factor, which asymptotically approaches the maximal provision $P(G,\infty)$ at a rate α. The last terms, $\Gamma'\xi$ and $\gamma'\int_0^\infty \xi\mathrm{d}\theta'$ are named redistribution terms corresponding to insulin exchange between the different packets, which can be understood as insulin changing its sensitivity to glucose, and not necessarily its spatial location. Redistribution is necessary in order to return to the initial insulin distribution in steady state after a glucose stimulation. Both γ and γ' are then assumed to be proportional to the threshold density distribution function at constant zero glucose concentration, $\xi(\theta,0)$. SR_{tot} is the total secretion, $SR_{tot}=SR_b+SR_{ab}$, where SR_{ab} is the above-basal secretion as modelled by the IVGTT models described in this paper, and SR_b is the basal secretion rate, which is assumed constant in models of the IVGTT.

Several experiments are needed to identify the different parameters in the distributed threshold model, so it cannot be used directly for the IVGTT. In order to see how the model can motivate MFM1, we present the following approximation of the distributed threshold model: (1) m is taken to infinity, corresponding to an instantaneous first phase secretion, (2) we model only the packets presently secreting, and disregard redistribution, also the important redistribution of insulin from packets not secreting. This approximation gives us,

$$\mathrm{d}P/\mathrm{d}t = -\alpha[P-P(G,\infty)],$$

$$SR_{tot} = fPX(G), \quad X(G)=\int_0^G \xi(\theta,0)\,\mathrm{d}\theta,$$

where f is the proportionality factor between $\gamma(\theta)$ and $\xi(\theta,0)$. The nonlinear functions for the accumulated initial insulin distribution (X) and the maximal provision ($P(G,\infty)$) have been fitted in the original work, see e.g. (O'Connor et al., 1980), to the functions presented in Fig. 1.

MFM1 corresponds to the further approximation,

$$X_{ab}\propto[G-h]^+, \quad P(G,\infty)_{ab}\propto H(G-h),$$

where X_{ab} and $P(G,\infty)_{ab}$ are the part of the functions contributing to the above-basal secretion.

This approximation of the distributed threshold model justifies that the number of secretory entities contributing to the above-basal secretion is proportional to the glucose concentration above threshold, as it is modelled in MFM1.

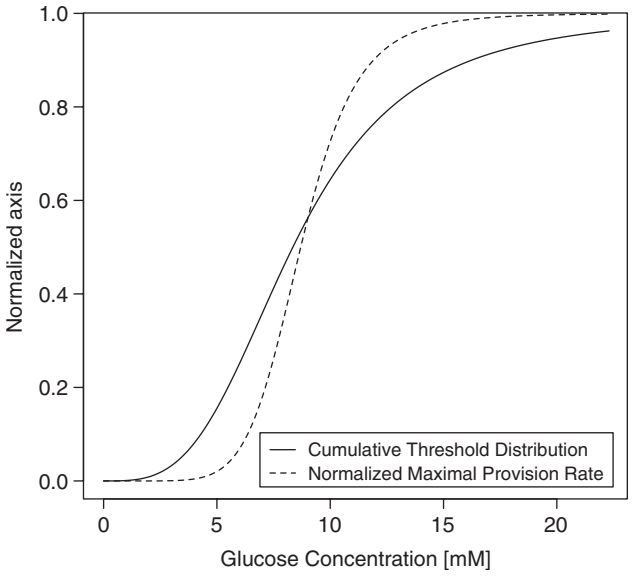

Fig. 1. The normalized cumulative distribution of thresholds, and the normalized maximal rate of provision, as estimated in e.g. O'Connor et al. (1980).

It was chosen to approximate the maximal provision with a piecewise constant function, because a linear approximation would produce a quadratic glucose dependence of the total secretion, while in the distributed threshold model the total glucose dependence of the above-basal secretion is approximately linear. The step function approximation of the maximal provision increases the secretion during the last part of the IVGTT where the glucose concentration is low but still above threshold, which to some extent counter effect that no redistribution has been modelled. This counter effect is perhaps the primary reason that one cannot include an improved description of the maximal provision without also including some form of redistribution.

One can argue that the maximal provision $P(G,\infty)_{ab}$ rather than the threshold distribution X_{ab} should be approximated with a step function. First of all the nonlinear function describing the maximal provision is steeper, hence closer to a step function than the cumulative distribution. Second, changes in the maximal provision influence the secretion only through the provision, while changes in the number of contributing secretory entities affect the secretion directly and immediately. During the IVGTT, the glucose concentration drops quickly, so it might be essential for the secretion model to respond correctly to an immediate decrease.

It is clear that the approximations lead to certain limitations of the model. Since we are modelling only the insulin content in packets presently secreting, the model does not take into account that insulin stored in other packets would secrete directly into plasma if the glucose concentration was to rise. During the IVGTT, this approximation is less important since after the administration of the glucose bolus the plasma glucose concentration is approximately monotonously decreasing. More important is the lack of redistribution that would facilitate an indirect contribution from packets not presently secreting. MFM1 has emphasized modelling of the immediate response of the beta cell, and not the precise form of the total provision, which might be more important for long slowly varying glucose stimulations, since all provisioned insulin is believed to be secreted at some point.

Another approximation of the distributed threshold model emphasizes modelling of the total provision and the total secretion. This approximation is called M1, which is a model for the above-basal second phase secretion. M1 is given by

$$\mathrm{d}P/\mathrm{d}t = -\alpha(P - \beta[G-h]^{+}),$$

$$SR_{ab} = P, \quad P(0) = 0 \qquad \text{(M1)}$$

β is the second phase secretion index, and $1/\alpha$ can again be interpreted as a characteristic time for P to approach the glucose-dependent maximum provision. M1 is a slight variation of the model presented in Licko and Silvers (1975) previously compared to the minimal model in Toffolo et al. (1995). We shall here present the following argument for the model.

For the distributed threshold model, the total provision to all packets is proportional to P, and the redistribution terms makes sure that it will also be secreted at some point. Specifically in steady state, the secretion will be identical to the provision. M1 emphasizes the approximation of the maximal provision in order to precisely account for the total provision, which is then used to approximate the secretion. This approximation is expected to work best for slowly varying glucose stimulations, where the effect of inhomogeneous response from the different secretory entities is diminished by the redistribution of thresholds. The original mathematical approximation in Licko and Silvers (1975) was to disregard the part of the secretion, which is dependent upon variations in glucose concentration. This approximation will thus be exact for a constant glucose stimulation, i.e. the glucose step, and M1 will be very close to the distributed threshold model.

Just as MFM1 was extended to include first phase secretion, a similar extension could be formulated for M1 called M2 (Toffolo et al., 1995), but this provides no further insight in the present context.

5. Analysis

It is important to note that a regular performance comparison of the presented models is not provided and believed to be out of the scope of the present paper. Data has been included merely to illustrate the theoretical point that the inhomogeneity of the individual secretory entities may be an important interpretation for the plasma insulin profiles for some individuals following the IVGTT. As a tool to demonstrate this interpretation, we have provided the least-squares fit of the relevant models to data.

Six out of a group of 30 healthy volunteers completing an IVGTT were selected for the present analysis from a previously published data set (Henriksen et al., 2000). A bolus of 300 mg glucose per kg body weight (up to a maximum of 25 g) was administrated at $t = 0$, and blood samples were collected for measurement of plasma glucose and plasma insulin concentration at times: $-30, -20, -10, -1$, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 26, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 140, 160, 180 min relative to the time of injection. Plasma glucose was measured at the bedside on a Beckman Glucose Analyser (Beckman Instruments, Fullerton, CA, USA) by the glucose oxidase method. Plasma insulin blood samples were immediately centrifuged at 4 °C and stored at −20 °C for later analysis by two-site, time-resolved

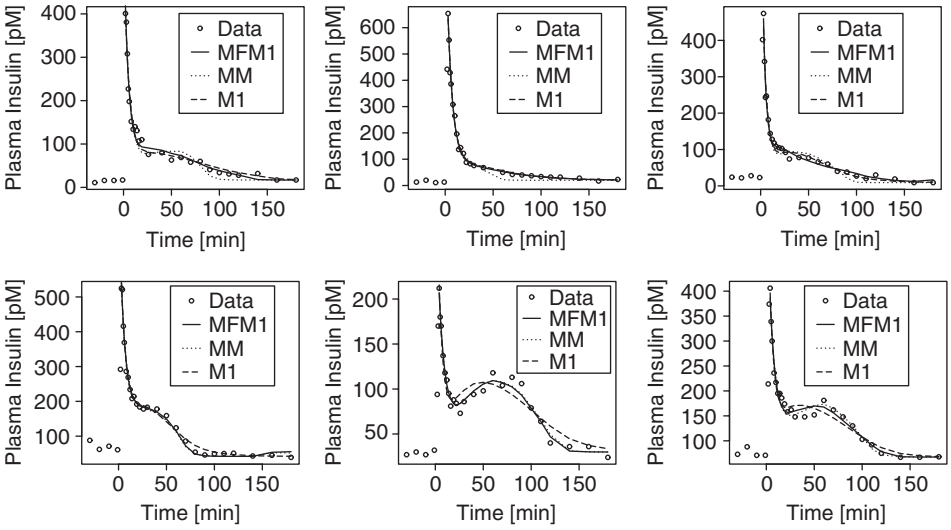

Fig. 2. Plasma insulin concentration and model predictions during an IVGTT for 6 different individuals, where 3 individuals exhibit a vague elongated second phase (top) while the remaining 3 have a more clear and short second phase insulin profile (bottom). The top plots demonstrate similar good predictions of M1 and MFM1, but problems of MM, in the case of elongated second phase where insulin concentrations are elevated also after the glucose concentration has returned towards baseline. In the bottom plots with more clear and short secretion profiles M1 has problems to account for the fast decrease in insulin level when the glucose concentration goes down, while in this case MM and MFM1 give similar good predictions.

immunofluorometric assay (DELFIA) (Hemmila et al., 1984).

The models for second phase secretion were assumed to describe the post-hepatic insulin delivery, and we used the standard first-order elimination

$$\mathrm{d}I/\mathrm{d}t = SR_{ab} - n(I - I_b),$$

where n is the elimination rate and I is the plasma insulin concentration with a basal value I_b.

Parameter estimates and model predictions were obtained by a least-squares fit of the different models to the plasma insulin concentration, assuming a known glucose concentration calculated as the linear interpolation of the measured glucose concentrations. All computations were performed in *R*.

5.1. Comparison of the one compartment models

Of the 6 subjects in the present analysis, 3 individuals were selected for their vague elongated second phase, and the remaining 3 because they exhibit a more clear second phase insulin profile. Many of the remaining unselected individuals, exhibited a more noisy insulin profile, or were in some other way more difficult to characterize into the two types of profiles. An elongated profile is consistent with secretion due to continued provision and redistribution after glucose has returned towards baseline as modelled in the distributed threshold model, but it might also be interpreted as biphasic disposition of insulin. A short second phase profile may indicate inhomogeneity of the secretory entities, where different entities stop secretion at different glucose concentrations during the decrease of glucose in plasma. Here it is investigated to what extent the second phase secretion models MFM1, M1, and MM are able to describe these two fundamentally different features observed in data during an IVGTT.

All models were started at $t = 0$, while the first predictions were at the point of the highest measured insulin concentration where the modelled plasma insulin concentration was set to the parameter I_{max}. It was chosen to estimate all parameters except I_b, which was fixed to the average value of the insulin concentrations measured at 160 and 180 min. For MFM1 the parameters $(\alpha, \gamma, h, I_{max}, n)$ were estimated. For M1 the parameters $(\alpha, \beta, h, I_{max}, n)$ were estimated. For MM the parameters (γ, h, I_{max}, n) were estimated.

The results presented in Fig. 2 demonstrate that for the subjects with a clear second phase both MM and MFM1 are able to describe the rapid decrease of plasma insulin concentration, while M1 gives a more elongated insulin profile. These results indicate that for some individuals the inhomogeneity of the secretory entities included in MM and MFM1 but not in M1, may be necessary to accurately describe the second phase secretion during the IVGTT.

For individuals with a clear second phase the time to reach maximal provision was estimated to be very high indicating that we are close to the MM limit. The higher insulin provision can through the approximation of the distributed threshold model be interpreted as a compensation for the missing redistribution contribution to the active insulin packets.

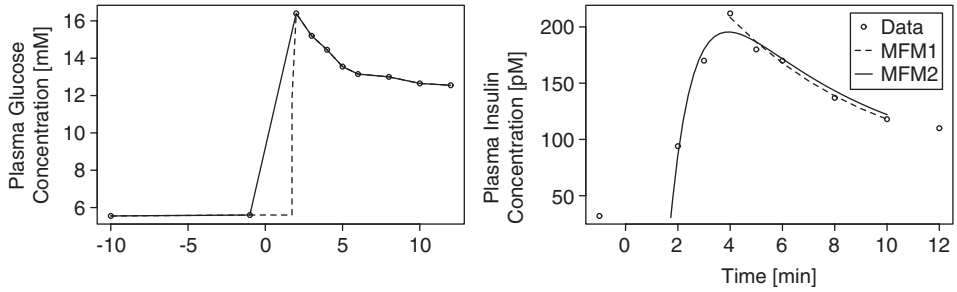

Fig. 3. Plasma glucose (left) and insulin (right) concentrations during the first minutes of the IVGTT. (left plot) A linear interpolation between glucose measurements (solid line) results in an unrealistic elevation of plasma glucose concentration before the IV glucose administration. Instead, it was chosen to estimate the starting point of the model, corresponding to using the glucose concentration profile given by the dashed line. (right plot) The predicted plasma insulin concentrations during first phase secretion are given for model MFM1 (dashed line) and MFM2 (solid line).

Further results demonstrated in Fig. 2 show that M1 and MFM1 are both capable of describing subjects with an elongated insulin profile, while the MM predictions seems to be forced towards baseline when glucose goes down. In this case the estimated time to reach maximal provision was shorter constituting the difference between MM and MFM1.

5.2. Comparing models for the first phase secretion

Two versions of the mean-field beta cell model have been presented, MFM1 and the extension MFM2, which increases the physiological understanding of the secretion by introducing a compartment for the readily releasable insulin. Here we demonstrate that this can be seen in data from an IVGTT.

The initial condition for MFM2 need some attention. X represents the amount of readily releasable insulin in all contributing entities at a given time. So the initial value for X is the amount of readily releasable insulin in all entities contributing to the first phase secretion, namely the active entities during the high glucose concentration right after the glucose bolus is administrated. In principle it does not make sense to use the model to predict insulin secretion before the glucose administration, where a small fluctuation in glucose concentration could be slightly above threshold, which would trigger a first phase spike.

The exact time for the rise in plasma glucose concentration after bolus administration is not known, and the glucose measurements around $t = 0$ are too sparse to obtain a good estimate directly from the glucose concentration profile, see Fig. 3. For MFM2 it was chosen to estimate the optimal starting point along with the other parameters, $(\gamma, h, m, X(0), \alpha, n)$.

The results in Fig. 3 compare MFM1 and MFM2 to demonstrate that the extra compartment for readily releasable insulin included in MFM2 does in fact enable us to describe the first phase secretion.

6. Conclusion

We have presented a physiological interpretable mean-field beta cell model for insulin secretion during the IVGTT, and showed that this model is very close to the original MM. In fact, it was shown that the original MM reappears in some limit of the mean-field model and that we may be close to this limit for some subjects. The model was extended with an extra compartment of readily releasable insulin, which enabled us to understand and describe the first phase secretion.

Theoretical insights of the model was given through the distributed threshold hypothesis, and it is observed that the mean-field model does actually incorporate the inhomogeneity of the different secretory entities. We have further summarized the approximation of a previously published IVGTT secretion model. This enabled us to understand the two fundamentally different approximations of the model, where one crudely approximates the provision and redistribution of newly synthesized insulin, while the other crudely approximates the inhomogeneity of the secretory entities. Investigations shows that both of the theoretical features may be important for data analysis. For some test subjects, in particular those with a clear second phase secretion, the inhomogeneity in the secretory response is essential, while for other subjects, in particular those with a vague elongated secretion, the prolonged secretion along with the redistribution seemed to be superior compared to the minimal model. In both cases the mean-field beta cell model was able to describe the observed profiles.

A comparison between data and model fits was provided to demonstrate that the theoretical features of redistribution and threshold heterogeneity is present in reality. Since MFM1 was able to describe both of these phenomena, it is intriguing to propose MFM1 as the new model to estimate and characterize beta cell function from the IVGTT. However, during data analysis it was found that differences in performance

of the models could be seen clearly only for a small subset of the subjects, and subsequently it was judged that a test of the computational applicability of the model for the would clutter the theoretical findings. Since MFM1 as a model for the IVGTT can provide only a modest improvement if any, it was chosen to keep the focus on the insights provided by the model. These theoretical insights could become important in the pursuit of a more general and physiological correct model that can characterize the beta cell function, not only for the IVGTT, but also for other experiments.

Appendix

All models discussed in the main text are summarized in Table 1 given below.

Table 1
Summary of insulin secretion models

Model		Abbreviation
$\mathrm{d}\xi(\theta,t)/\mathrm{d}t$	$= -m\xi(\theta,t)H(G-\theta)+\gamma(\theta)P(G,t)$ $-\Gamma'\xi(\theta,t)+\gamma'(\theta)\int_0^\infty \xi(\theta',t)\,\mathrm{d}\theta'$	Dist-Thres
$\mathrm{d}P(G,t)/\mathrm{d}t$	$= -\alpha[P(G,t)-P(G,\infty)]$	
SR_{tot}	$= m\int_0^G \xi(\theta,t)\,\mathrm{d}\theta$	
$\mathrm{d}P/\mathrm{d}t$	$= -\alpha(P-H(G-h))$	MFM1
SR_{ab}	$= (\gamma/\alpha)[G-h]^+P, \quad P(0)=0$	
P	$= -\alpha(P-H(G-h))$,	MFM2
$\mathrm{d}X/\mathrm{d}t$	$= (\gamma/\alpha)[G-h]^+P-mH(G-h)X$	
SR_{ab}	$= mH(G-h)X$	
SR_{ab}	$= \gamma[G-h]^+t$	MM
$\mathrm{d}P/\mathrm{d}t$	$= -\alpha(P-\beta[G-h]^+)$	M1
SR_{ab}	$= P, \quad P(0)=0$	

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