



แบบจำลองทางคณิตศาสตร์ของระบบความล้มเหลว  
ของฮอร์โมนอินซูลินและน้ำตาลกลูโคส:  
เครื่องมือสำคัญสำหรับความรู้ความเข้าใจที่ดีขึ้นในเรื่องโรคเบาหวาน  
Mathematical Models of Insulin-Glucose Regulation:  
an Important Tool for a Better Understanding of Diabetes

*Ratchada Viriyapong<sup>1</sup>*

### บทคัดย่อ

แบบจำลองทางคณิตศาสตร์ที่เกี่ยวข้องกับโรคเบาหวาน มีจำนวนเพิ่มมากขึ้นเรื่อยๆ โดยเฉพาะในช่วงทศวรรษล่าสุด นักวิจัยหลายกลุ่มได้มีการขยายแบบจำลองทางคณิตศาสตร์ของโรคเบาหวานโดยเพิ่มปัจจัยที่เกี่ยวข้องอื่นๆ ลงมาในแบบจำลอง จากที่เริ่มต้นแบบจำลองด้วยตัวแปรหลักสองตัวแปร คือ ฮอร์โมนอินซูลินและน้ำตาลกลูโคส ต่อมาก็ได้เพิ่มส่วนอื่นๆ เช่น กรณีมันอิสระ ฮอร์โมนกลูคากอน ฮอร์โมนอัลเดรีนีน มวลของเซลล์เป็นต้นในตับอ่อน และตัวรับฮอร์โมนอินซูลิน เป็นต้น ในบทความฉบับนี้ ผู้เขียนได้รวบรวมแบบจำลองทางคณิตศาสตร์ที่เกี่ยวข้องกับระบบของฮอร์โมนอินซูลินและน้ำตาลกลูโคสในรูปแบบของสมการเชิงอนุพันธ์สามัญ พร้อมทั้งบ่งชี้ลักษณะเด่นและเข้มโภคความสัมพันธ์ของแต่ละแบบจำลองเพื่อให้มองเห็นภาพโดยรวมว่าแบบจำลองใดหรือปัจจัยใดที่ได้ศึกษามาแล้วและแบบจำลองใดหรือปัจจัยใดที่ควรศึกษาต่อไปเพื่อให้เข้าใจเรื่องโรคเบาหวานที่ดีขึ้น

<sup>1</sup>ภาควิชาคณิตศาสตร์ คณะวิทยาศาสตร์ มหาวิทยาลัยนเรศวร สำราญเมือง จังหวัดพิษณุโลก 65000  
E-mail: ratchadapa@nu.ac.th

## ABSTRACT

A number of mathematical models relating to diabetes have grown in complexity during the last decade as new aspects of the disease are discovered and added into each model. Traditional models for diabetes contained only two main factors, being insulin and glucose. Newer models added other related hormones and components such as free fatty acids, glucagon, epinephrine,  $\beta$ -cell mass and insulin receptor. In the present article, the most influential mathematical models of insulin-glucose regulation in the form of ordinary differential equations are compared and discussed. The aim of the article is to bring together the key insights and to understand the relationship between models, in order to evaluate the big picture and to propose further areas of study for better knowledge of diabetes.

**คำสำคัญ:** โรคเบาหวาน ฮอร์โมนอินซูลิน น้ำตาลกลูโคส แบบจำลองทางคณิตศาสตร์ สมการเชิงอนุพันธ์สามัญ

**Keywords:** Diabetes, Insulin, Glucose, Mathematical model, Ordinary differential equation

### 1. Introduction

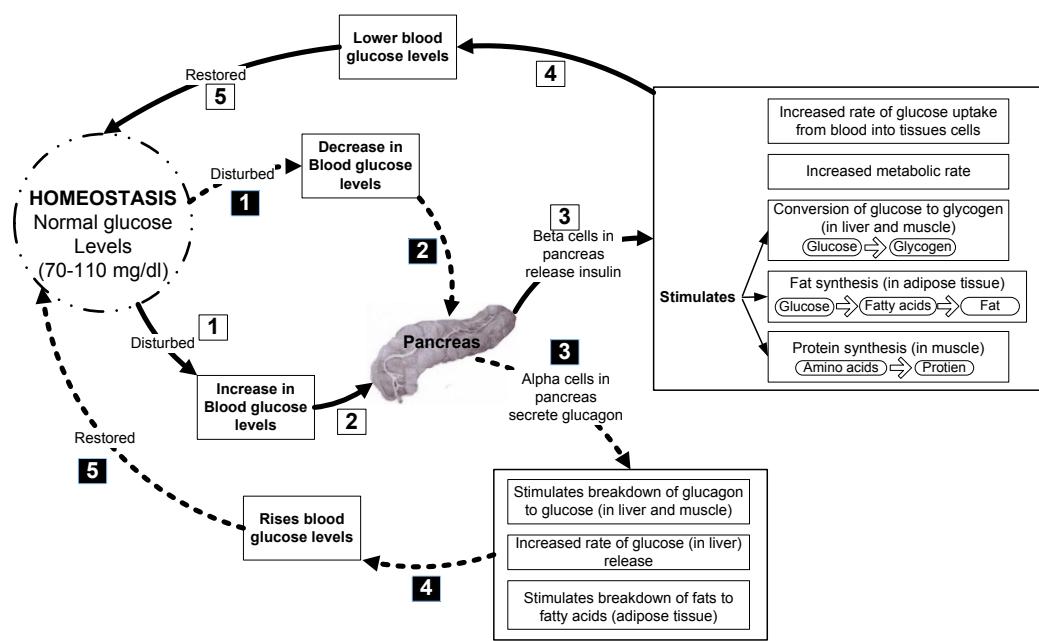
Diabetes Mellitus is a common chronic disease which affects all age groups worldwide especially in the South East Asia. It is characterised by a very high level of plasma glucose (hyperglycemia). According to WHO (World Health Organisation), currently there are about 346 million people who have diabetes and the incidence is increasing dramatically from 171 million diabetics in 2000 to a projected 366 million diabetics in 2030 (Wild et al., 2004). There are two types of diabetes. Type 1 diabetes is an autoimmune condition causing destruction of the pancreatic  $\beta$ -cells leading to an insulin deficiency. It is known as insulin-dependent diabetes. Type 2 diabetes is more common and known as insulin-independent diabetes. It is caused mainly by an insulin resistance, a condition where the normal insulin level is inadequate to lower plasma glucose level. However, the precise cause of this disease remains to be investigated. Together with evidence showing the link between obesity and diabetes (Boden et al., 2004; Trujillo et al., 2006), this shows not only insulin and glucose relationship that leads us to understand diabetes but some other hormones (glucagon, epinephrine, glucocorticoids and thyroxine) might be one of the factors causing this disease. Furthermore, in clinical trials there are often difficulties in measuring the large amount of factors relating to glucose metabolism. Hence, a mathematical model becomes a useful tool to quantify medical applications for the understanding of diseases and perhaps provide future predictions. In this article, most of the

existing mathematical models of insulin-glucose regulation have been brought together with key insights as well as the relationships between models for the researcher to get a picture of what have been studied and what could be further studied. All models are presented in a standard notation (summarised in table 1).

## 2. Insulin-Glucose

### 2.1 Insulin-Glucose regulation

Glucose is an important nutrient which plays a relevant role in the human body. It is essential to keep the plasma glucose concentration within a certain range to maintain normality in the body (Anilkumar et al., 2006). The body maintains the level of plasma glucose concentration mainly through the action of two hormones, insulin and glucagon. Insulin and glucagon are secreted from  $\beta$ -cells and  $\alpha$ -cells which are contained in the Langerhans islets scattered in the pancreas, respectively (Williams et al., 2004; Makroglou et al., 2006). The plasma glucose level, insulin and glucagon relationship is shown in figure 1.



**Figure 1.** Physiological glucose-insulin-glucagon regulatory system. Dash arrows present the process of pancreas performance when the plasma glucose level is low and solid line arrows present the process of pancreas performance when the plasma glucose level is high.

When the plasma glucose concentration level is low, the glucagon from  $\alpha$ -cells is released and acts on liver cells, causing them to release glucose into the plasma thus increasing the plasma glucose level. Glucagon also stimulates the breakdown of fats to fatty acids being ready to convert glycogen into glucose. When the plasma glucose level is high, insulin is released from  $\beta$ -cells, and simultaneously inhibits the hepatic glucose production and induces the uptake of the excess glucose by the liver and other cells, causing the plasma glucose concentration to drop. Insulin also increases the metabolic rate and stimulates the conversion of glucose to glycogen, fat synthesis and protein synthesis.

Despite hyperglycemia and hypoglycemia being increasingly common conditions, there is limited knowledge of them. Hence, more studies are needed to improve our understanding. Over the past thirty years mathematical modelling has played a key role in studying insulin-glucose regulation. One of the goals of this modelling effort is the measurement of the degree to which a given subject is able to accommodate a glucose load, by means of an increase in peripheral tissue glucose uptake driven by an increase in the plasma concentration of insulin. The lack or insufficiency of this normal mechanism is described as insulin resistance, and has a gradually grown in significance in the pathogenesis of conditions like diabetes, cardiovascular and obesity disease (Mukhopadhyay et al., 2004).

### 3. Overview of existing mathematical models of insulin-glucose regulation

There are a number of efforts at building a suitable and exploitable insulin-glucose regulation model indicated in the literature. These models can be mainly classified mathematically as ordinary differential equations (ODEs) for both linear and nonlinear (each state variable (box) in most figures corresponds to a first-order ODE), delay differential equations (DDEs) and integro-differential equations (IDEs). Only ODEs models are going to be reviewed in this article.

#### 3.1 Models in the form of ordinary differential equations (ODEs)

##### 3.1.1 Minimal model

The minimal model is a model approaching to a better understanding the composite effects of insulin secretion and insulin sensitivity on glucose tolerance and risk for type 2 diabetes mellitus. It is the most noticeable model and known as the starting point of all insulin-glucose models, proposed by the group of Bergman and Cobelli in 1980's (Bergman et al., 1981). It contains minimal number of parameters and it is widely used to estimate glucose

effectiveness and insulin sensitivity from intravenous glucose tolerance test (IVGTT) data by sampling over certain periods, in other word, it describes the kinetics of glucose and insulin after glucose injection (Makroglou et al., 2006). This model assumes that there is no insulin produced endogenously and it is shown in the figure below.

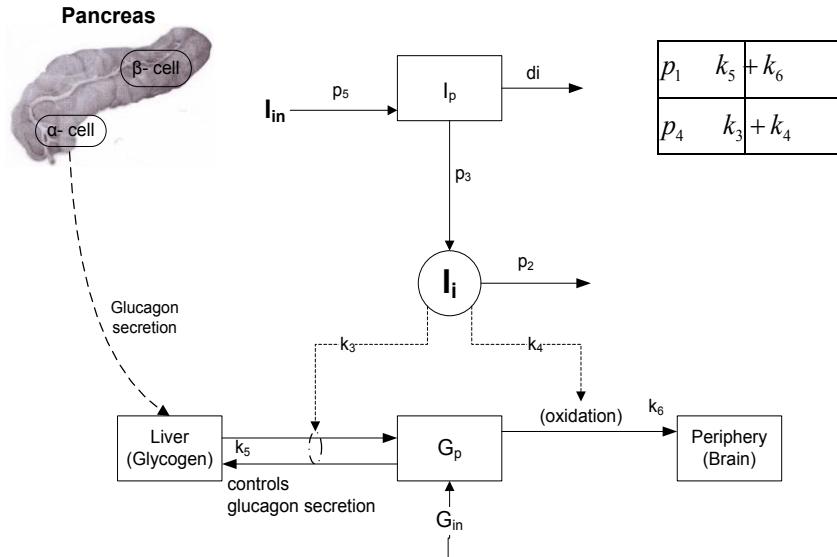


Figure 2. Minimal model

The standard form of the minimal model is as follows:

$$\frac{dI_p}{dt} = -d_i(I_p(t) - I_{pb}) + p_5 I_{in}(t), \quad I_p(0) = I_{pb} \quad (1)$$

$$\frac{dI_i}{dt} = -p_2(I_i(t) - I_{ib}) + p_3(I_p(t) - I_{pb}), \quad I_i(0) = 0 \quad (2)$$

$$\frac{dG_p}{dt} = -p_1(G_p(t) - G_{pb}) - p_4 I_i(t) G_p(t) + \frac{G_{in}(t)}{Vol_G}, \quad G_p(0) = G_{pb} \quad (3)$$

where  $G_p$  is the plasma glucose concentration,  $I_p$  is the plasma insulin concentration and  $I_i$  is the interstitial insulin concentration. Other notations are stated in table 1.

The minimal model consists of two parts; the first part contains equation (1) describing the time course of plasma insulin concentration, accounting for the dynamics of pancreatic insulin release in response to the glucose stimulus. The second part contains equation (2) and (3) describing the time course of plasma glucose concentration, accounting for the dynamics of glucose uptake both dependent on and independent of insulin. However, the simple coupling of the original two parts of the minimal model is not suitable and realistic. This is because for

general observed combinations of parameter values, the coupled model would not admit positive equilibrium and the concentration of active insulin in the interstitial compartment would be predicted to increase without bounds (Gaetano et al., 2000). In addition, the interstitial insulin concentration variable is introduced to cause the delay in the action of insulin (Boutayeb et al., 2006). Therefore, an improved model is needed.

**Table 1.** Summary of notation

Notation	Unit	Meaning
$G_p$	mg/dl	plasma glucose concentration at time $t$ [min]
$I_p$	$\mu$ U/ml	plasma insulin concentration
$I_i$	$\mu$ U/ml	interstitial insulin concentration
$G_{pb}$	mg/dl	the basal plasma glucose concentration, which is measurable. the subject's baseline glycemia
$I_{pb}$	$\mu$ U/ml	the basal plasma insulin concentration, which is measurable the subject's baseline insulinemia
$I_{ib}$	$\mu$ U/ml	the basal interstitial insulin concentration, which is measurable
$G_{in}$	mg/min	dietary absorption or external infusion of glucose
$I_{in}$	mg	the exogenous insulin infusion rate
$Vol_G$	dl	the glucose distribution space
$d_i$	$\text{min}^{-1}$	the rate constant for disappearance of plasma insulin
$p_1$	$\text{min}^{-1}$	the rate at which glucose is removed from the plasma space, independent of insulin influence
$p_2$	$\text{min}^{-1}$	the rate constant expressing the spontaneous decrease of tissue glucose uptake ability
$p_3$	$\text{min}^{-1}$	the insulin-dependent increase in tissue glucose uptake ability, per unit of insulin concentration excess over baseline insulin
$p_4$	ml/min/ $\mu$ U	the combined rate of glucose uptake under the influence of insulin
$p_5$	$\text{min}^{-1}$	the appearance rate of plasma insulin

### 3.1.2 The Insulin-Glucose feedback model

This model was originally developed by Sturis et al. (1991) and aimed to present a possible mechanism for the origin of the slow (ultradian) oscillations. Its structure looks similar to the minimal model. The main characters of this model are the feedback loops, which are glucose stimulates pancreatic insulin secretion, insulin stimulates glucose uptake and inhibits hepatic glucose production, and glucose enhances its own uptake. A special feature of this model is to have two significant delays (Tolic et al., 2000). One delay is related to the fact that

the physiological action of insulin on the utilisation of glucose is correlated with the concentration of insulin in a slowly equilibrating interstitial compartment rather than with the concentration of insulin in the plasma. Another delay is correlated to the time lag between the appearance of insulin in the plasma and its inhibitory effect on the hepatic glucose production. The equations describing this model are as follow:

$$\frac{dI_p}{dt} = f_1(G) - E(I_p - I_i) - \frac{I_p}{t_p} \quad (4)$$

$$\frac{dI_i}{dt} = E(I_p - I_i) - \frac{I_i}{t_i} \quad (5)$$

$$\frac{dG}{dt} = G_{in} - f_2(G) - f_3(G)f_4(I_i) + f_5(x_3) \quad (6)$$

$$\frac{dx_1}{dt} = \frac{3}{t_d}(I_p - x_1) \quad (7)$$

$$\frac{dx_2}{dt} = \frac{3}{t_d}(x_1 - x_2) \quad (8)$$

$$\frac{dx_3}{dt} = \frac{3}{t_d}(x_2 - x_3) \quad (9)$$

where  $G$  is the concentration of glucose in plasma and interstitial compartment,  $G_{in}$  is the rate at which glucose is supplied to the plasma at an exogenously controlled,  $E$  is the transfer rate of the transportation of insulin between plasma and interstitial compartment.  $t_d$  denotes a time delay responding to the delay of hepatic glucose production response to changes in the plasma insulin concentration. Auxiliary state variables,  $x_1$ ,  $x_2$ , and  $x_3$  are associated with certain delays of the insulin effect on the hepatic glucose production with total time delay  $t_d$ . Moreover, insulin degradation is assumed to be exponential with time constant  $t_p$  [min] in plasma and  $t_i$  [min] for insulin in the interstitial compartment. The expression of functions  $f_1$ ,  $f_2$ ,  $f_3$ ,  $f_4$ , and  $f_5$  are provided in Tolic et al. (2000). The function  $f_1(G)$  is a pancreatic insulin production function which is controlled by the glucose concentration. The function  $f_2(G)$  is insulin-independent glucose utilisation (glucose uptake by the brain and nerve cells), while  $f_3(G)$  and  $f_4(I_i)$  are the glucose-dependent terms in the function expressing glucose utilisation by muscle and fat cells.

The function  $f_5(x_3)$  is modelling hepatic glucose production with time delay  $t_d$  associated with auxiliary variables  $x_1$ ,  $x_2$ , and  $x_3$ . Their simulated results (insulin-glucose dynamics) corresponded well with most of the experimental results from the literature and therefore their model simulates ultradian insulin secretion oscillations numerically. In addition, a greater hypoglycemic effect occurred during oscillatory insulin infusion compared to a constant infusion. The primary reason for this is because of the higher inhibition of the hepatic glucose production, which could be by both direct and indirect mechanisms (e.g. effects of insulin on the pancreatic  $\alpha$ -cells, adipocytes and muscles). Hence, some additional state variables like free fatty acid,  $\beta$ -cell mass and glucagon hormones could be influencing factors for the insulin-glucose dynamics and are worth including in further models.

Recently, Wang's group have modified the model (Wang et al., 2012) by adding the mass of  $\beta$ -cells. This is to explore whether  $\beta$ -cells mass plays an important role in diabetes. Equations (5) and (7)-(9) remained the same whereas equations (4) and (6) were changed and  $\beta$ -cells mass equation was added as follows:

$$\frac{dI_p}{dt} = \beta f_1(G) - E(I_p - I_i) - \frac{I_p}{t_p} \quad (10)$$

$$\frac{dI_i}{dt} = E(I_p - I_i) - \frac{I_i}{t_i} \quad (11)$$

$$\frac{dG}{dt} = G_{in} - f_2(G) - f_3(G)f_4(I_i) + f_5(x_3) - f_6(G) \quad (12)$$

$$\frac{dx_1}{dt} = \frac{3}{t_d}(I_p - x_1) \quad (13)$$

$$\frac{dx_2}{dt} = \frac{3}{t_d}(x_1 - x_2) \quad (14)$$

$$\frac{dx_3}{dt} = \frac{3}{t_d}(x_2 - x_3) \quad (15)$$

$$\frac{d\beta}{dt} = (\rho(I_p) - \mu(G))\beta(t) + f_7(G) \quad (16)$$

where all notations used are the same as in Tolic's model.  $\beta$  is  $\beta$ -cell mass,  $f_\delta(G)$  is the function where the kidneys begin to excrete glucose,  $f_\gamma(G)$  is a function of  $\beta$ -cell neogenesis flux. The rate constant of  $\beta$ -cell proliferation and death are  $\rho$  and  $\mu$ , respectively. The analysis is divided into two parts: with and without  $\beta$ -cell neogenesis. Without  $\beta$ -cell neogenesis, the dynamic of  $\beta$ -cell mass contained two fixed points; a higher stable point and a lower unstable point which is referred to as a "pathological" fixed point. The latter point could lead to the loss of  $\beta$ -cells causing further hyperglycemia and may finally underlie non-autoimmune diabetes. Furthermore, the results showed that once the majority of  $\beta$ -cell mass was destroyed by glycemic load, it takes about 50 years to recover, i.e. the subject will have diabetes for as long as her life time. On the other hand, in the model with  $\beta$ -cell neogenesis, recovery of  $\beta$ -cell mass was much more rapid which corresponds to results in the literature. Once the majority of  $\beta$ -cell mass was destroyed by glycemic load, recovery takes about a year indicating that the subject would have diabetes for a number of months until it recovers. Hence, Wang's group has shown the importance of  $\beta$ -cell neogenesis in the study of diabetes.

### 3.1.3 Dynamic modeling of free fatty acid, glucose, and insulin: an extended "minimal model"

Due to the fact that when the body is at rest, there is approximately 90% of the muscle energy derived from free fatty acid (FFA) metabolism (Felig et al., 1975; Marliss et al., 2002). Anirban Roy and the group proposed this model which included the contribution of FFA metabolism in the body including the interactions among FFA, insulin and glucose. This model is another extension model from Bergman's minimal model. The schematic of this model is shown in figure 3.

Hence, the model takes a form as follows:

$$\frac{dI_p}{dt} = -d_i(I_p(t) - I_{pb}) + p_5 I_{in}(t), \quad (17)$$

$$\frac{dI_i}{dt} = -p_2(I_i(t) - I_{ib}) + p_3(I_p(t) - I_{pb}), \quad I_i(0) = 0 \quad (18)$$

$$\frac{dG_p}{dt} = -p_1(G_p(t) - G_{pb}) + p_6(G_p(t)F_i(t) - G_{pb}F_{ib}) - p_4 I_i(t)G_p(t) + \frac{G_{in}(t)}{Vol_G} \quad (19)$$

$$\frac{dI_{ii}}{dt} = -p_{F2}(I_{ii}(t) - I_{iib}) + p_{F3}(I_p(t) - I_{pb}) \quad (20)$$

$$\frac{dF_p}{dt} = -p_7(F_p(t) - F_{pb}) + p_9(G_p)(F_p(t)G_p(t) - F_{pb}G_{pb}) - p_8I_{ii}(t)F_p(t) + \frac{F_{in}(t)}{Vol_F} \quad (21)$$

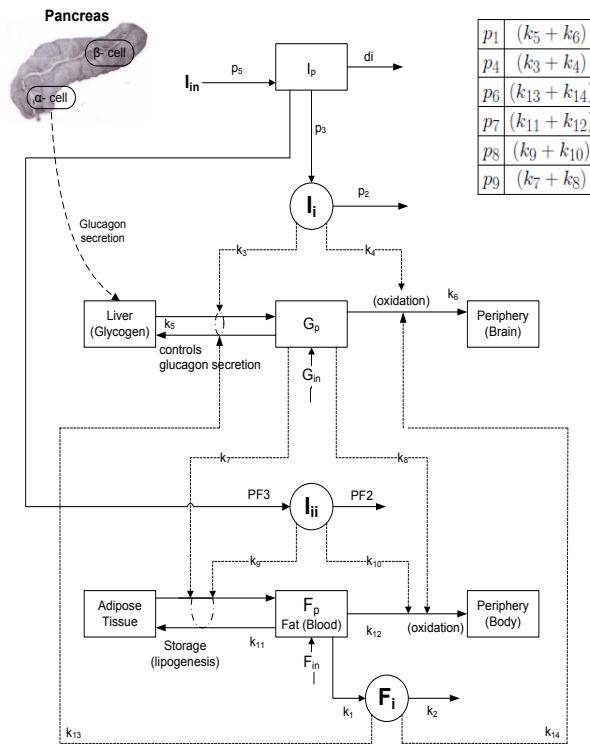
$$\frac{dF_i}{dt} = -k_2(F_i(t) - F_{ib}) + k_1(F_p(t) - F_{pb}) \quad (22)$$

where  $I_{ii}$  and  $I_{iib}$  denotes the second interstitial insulin compartment and its basal one respectively, adding to slow down the insulin-mediated FFA uptake from the circulatory system into the adipose tissue.  $F_p$  and  $F_{pb}$  denotes plasma and basal FFA concentration and  $F_i$  and  $F_{ib}$  is an interstitial and basal interstitial FFA compartment adding to slow down the impairing effect of FFA on glucose uptake.  $F_{in}$  represents external lipid infusion where  $Vol_F$  is FFA distribution space.  $p_6$  is the impairing action of plasma FFA on glucose uptake.  $p_7$  and  $p_8$  are the combined rate at which plasma FFA disappears without and with insulin influence, respectively and  $p_9$  is the lipolytic effect of plasma glucose concentration level.  $p_{F2}$  and  $p_{F3}$  are the rate of clearance and entering of insulin from and into  $I_{ii}$ .  $k_1$  and  $k_2$  denotes the rate of appearance and disappearance of FFA from  $I_{ii}$ . The results showed that they can predict a better glucose dynamics after a mixed meal (containing carbohydrates and fat) and due to the meal intake, it could also predict the variation in FFA level. Furthermore, by combining this model with a mixed model, it can describe the dynamics of glucose and FFA absorption including their circulating plasma levels (Anirban Roy et al., 2006). This is a good starting point for further investigating the effect of FFA on glucose and insulin dynamics.

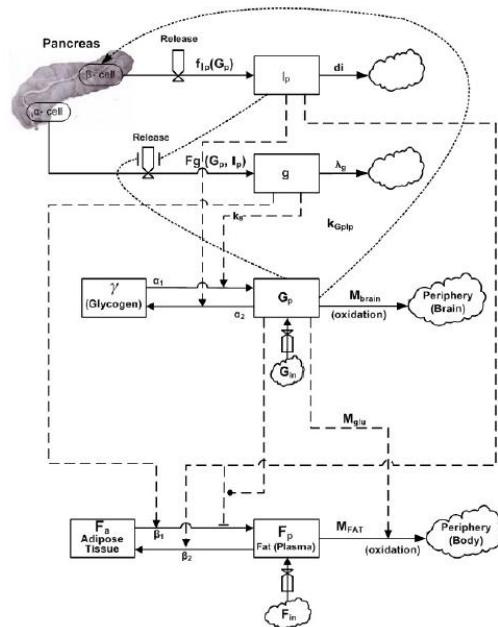
### 3.1.4 Modelling adipose tissue production and the development of obesity

A similar thought to combine fatty acids in the model also arose in the same year. Jim Mass (Mass et al., 2006) and his group's model concentrated on development of obesity i.e. their ultimate goal is to integrate the model of short-time and long-time dynamics of insulin, glucose and glucagon. This model accounted for the inefficiencies in energy conversion from glucose to fat and glycogen and also predicted the body fat mass variation over a period of years (Mass et al., 2006).

According to the fact that food supplies the body energy in three different forms which are fat, protein and carbohydrate, Mass would take these forms into account in the model, where protein metabolism is excluded as it indirectly affects the body energy supply. Hence, the pathway that they covered in their model is shown in figure 4.



**Figure 3.** The extended minimal model. (Adaptation from the extended minimal model Anirban Roy et al., 2006)



**Figure 4.** Metabolic pathways involving the storage and utilisation of ingested carbohydrates and fat included in this model.

This model is based on the following effects:

- (i) Insulin catalyses the conversion of glucose into fatty acids in the blood, and converts fatty acids in the blood into fat stored in adipocytes.
- (ii) Glucagon stimulates some fat from adipocytes into the blood and enhances the conversion of glycogen into glucose.

The function  $I_p$  and  $G_p$  denote the concentration of plasma insulin and glucose, respectively. In addition, the concentration of glucagon, glycogen, fatty acids in the blood and in the fat stored in adipocytes were denoted as  $g$ ,  $\gamma$ ,  $F_p$ , and  $F_a$ , respectively. Both insulin and glucagon are degraded at decay rate  $d_i$  and  $\lambda_g$ .

The model of metabolism over short timescales is shown as follows:

$$\frac{dI_p}{dt} = f_{I_p}(G_p) - d_i I_p \quad (23)$$

$$\frac{dg}{dt} = f_g(G_p) - \lambda_g g - k_{I_p g} I_p g \quad (24)$$

where  $k_{I_p g}$  models the inhibitory effect of insulin on glucagon secretion.

The function  $f_{I_p}$  and  $f_g$  represent the production rate of plasma insulin and glucagon, respectively. The expressions of them are given by the Hill functions which may be seen in Mass et al. (2006).

Another four differential equations relating to glucose, glycogen, fatty acids in the blood and in the fat stored in adipocytes in this model are as follows:

$$\frac{dG_p}{dt} = G_{in} - M_{brain}(t) - M_{glu}(G_p, F_p, t) - \alpha_2 I_p G_p (\gamma_0 - \gamma) - k_{G_p I_p} G_p I_p + \alpha_1 g \gamma \quad (25)$$

$$\frac{d\gamma}{dt} = -\alpha_1 g \gamma + \alpha_2 I_p G_p (\gamma_0 - \gamma) \quad (26)$$

$$\frac{dF_p}{dt} = F_{in} - M_{fat}(G_p, F_p, t) + \theta k_{G_p I_p} G_p I_p + \beta_1 g F_a - \beta_2 I_p F_p \quad (27)$$

$$\frac{dF_a}{dt} = \beta_2 I_p F_p - \beta_1 g F_a \quad (28)$$

where  $M_{brain}(t)$  represents the energy used by the brain and assumed to be constant. The function  $G_{in}$  and  $F_{in}$  are glucose and fatty acids which are supplied to the plasma through the

diet. Moreover,  $\alpha_1, \alpha_2, \beta_1, \beta_2$  are defined as rate constants.  $M_{glu}(G_p, F_p, t)$  and  $M_{fat}(G_p, F_p, t)$  denotes the utilisation of plasma glucose and fatty acids, respectively. Their expression could be seen in Mass et al. (2006). Finally, the constant  $\theta$  (with  $0 < \theta < 1$ ) represents the efficiency of the process which converts glucose into fat.

By integrating the short-time and long-time dynamics model, they finally had suggested the growth function. Their numerical results are also interesting as they simulated it in different conditions, such as, fixed daily diet, drip feed diet and diet dependent on metabolism to study the dynamics of insulin, glucagon, glycogen, fatty acids in the blood and in the fat stored in adipocytes (Mass et al., 2006). After all, this is another model which does improve the obesity understanding and provides us not only the dynamics of insulin and glucose, but also the lean body mass in a growth function over decades. However, some calibrations for parameter values in the model remain to be addressed and this model could also be extended by including others factors e.g. appetite and insulin resistance for further improvement.

### 3.1.5 A Model of $\beta$ -cell mass, insulin, and glucose kinetics: pathways to diabetes

Diabetes not only relates to insulin and glucose, but  $\beta$ -cells are another factor that could cause diabetes. Topp's group (Topp et al., 2000) developed a novel model of  $\beta$ -cell mass, insulin and glucose dynamics, where glucose and insulin dynamics is fast relative to  $\beta$ -cell mass dynamics. Their model was written as follows:

$$\frac{dG}{dt} = a - (b + cI_p)G \quad (29)$$

$$\frac{dI_p}{dt} = \frac{\beta dG^2}{(e + G^2)} - fI_p \quad (30)$$

where  $a$  [ $\text{mgdl}^{-1}\text{t}^{-1}$ ] denotes the net rate of production at zero glucose,  $b$  [ $\text{t}^{-1}$ ] is the total glucose effectiveness at zero insulin and  $c$  [ $\mu\text{U}^{-1}\text{mlt}^{-1}$ ] is the total insulin sensitivity.  $\beta$  [mg] represents the mass of pancreatic  $\beta$ -cells and  $d$  [ $\mu\text{Uml}^{-1}\text{t}^{-1}$ ] is the maximal rate at which all  $\beta$ -cells are assumed to secrete insulin.

$$\frac{G^2}{(e + G^2)}$$

The expression  $\frac{G^2}{(e + G^2)}$  is a Hill function with coefficient 2 that describe a sigmoid ranging from 0 to 1 which reaches half its maximum at  $G = e^{1/2}$ . Moreover,  $fI_p$  is the insulin

clearance rate where  $f$  [ $t^{-1}$ ] is the clearance constant which represents the combined insulin uptake at the livers, kidneys, and insulin receptors.

In addition, for  $\beta$ -cell mass dynamic, the replication rates for  $\beta$ -cells increase with increasing glucose level. Nevertheless,  $\beta$ -cell replication might be reduced at extreme hyperglycemia. Therefore, Topp's group modelled this behaviour with a simple second-degree polynomial which is the patterned after logistic growth. The  $\beta$ -cell mass dynamics is as the following:

$$\frac{d\beta}{dt} = (-g + hG - iG^2)\beta \quad (31)$$

where  $g$  [ $t^{-1}$ ] is the death rate of  $\beta$ -cell mass at zero glucose,  $h$  [ $mg^{-1} dl t^{-1}$ ] and  $i$  [ $mg^{-2} dl^2 t^{-1}$ ] are rate constants that determine the  $\beta$ -cell glucose tolerance range.

The analysis of this model as a whole is computed from two subsystems; fast ( $G, I$ ) and slow ( $\beta$ ) subsystems which lead to three steady-stable solutions: the physiological fixed point, the saddle point, and the pathological fixed point of the slow subsystem. When the blood glucose levels are larger than  $250 mgdl^{-1}$ , this condition makes  $\beta$ -cell death rates exceed replication rates and then drives the system towards a pathological steady state. Moreover, Topp and his group revealed that this model also predicts three different pathways to diabetes, which are regulated hyperglycemia, bifurcation, and dynamical hyperglycemia (catch and pass). However, they still have difficulty in quantifying which one would correspond to the behaviour of the real system.

### 3.1.6 A Model of $\beta$ -cell mass, insulin, glucose and insulin receptor dynamics

In 2001, the model of Topp et al. (2000) was modified by Hernandez's group. They had raised the importance of the insulin receptor according to the fact that the insulin resistance, which is the main cause of Type 2 diabetes, is associated with the down-regulation of these receptors at the surface of muscle cells. In addition, in insulin resistant people, the resistance has been revealed in both skeletal muscle and adipose tissue. Insulin receptor was then added to the Topp et al.'s model as the fourth component of nonlinear ODE. Their model is as follows:

$$\frac{dG}{dt} = a - (b + cRI_p)G \quad (32)$$

$$\frac{dI_p}{dt} = \frac{d\beta G^2}{(1+R)(e+G^2)} - fI_p - fRI_P \quad (33)$$

$$\frac{d\beta}{dt} = (-g + hG - iG^2)\beta \quad (34)$$

$$\frac{dR}{dt} = j(1-R) - kIR - lR \quad (35)$$

where  $R$  denotes the fraction of insulin receptors on the surface of the muscle cells,  $\frac{d}{1+R}$  is

the rate at which a single  $\beta$ -cell will secrete insulin. The term  $fRI_P$  represents the insulin clearance by muscle cell receptor. The rate  $j$  denotes the recycling rate of internalised receptors,  $k$  is the insulin induced down-regulation rate of the surface receptors and  $l$  is the natural endocytosis rate of the surface receptors.

Analytical calculations and numerical simulations showed that this model improved quantitative results in describing the  $\beta$ -cell mass and provided a theoretical justification for experimentally observed receptor behaviour that is they obtained  $R = 0.84$  matching the fact that there are approximately 85% of insulin receptors on the surface of muscle cells (Hernandez R.D. et al., 2001).

Recently Kwach and his group (Kwach B et al., 2011) have raised the importance of epinephrine in insulin-glucose kinetics. Epinephrine is a hormone secreted by the adrenal medulla in response to acute stress participating in the fight or flight response (Duff and Jason 2000). Research showed that it increased glucose production from lactate, amino acids and glycogen breakdown and increased fat mobilisation by the stimulation of hormone sensitive lipase. With the assumption that there is no recent digestion, the model is then written as follows (Ackerman et al., 1969):

$$\frac{dG}{dt} = -aG - bI_p + fE \quad (36)$$

$$\frac{dI_p}{dt} = cG - dI_p + kE \quad (37)$$

$$\frac{dE}{dt} = -lG - mI_p + nE \quad (38)$$

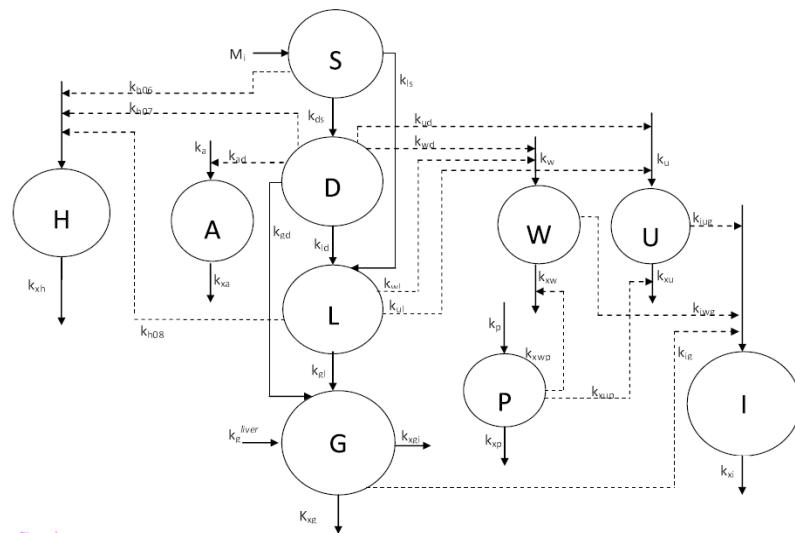
where  $E$  represents epinephrine and the letter  $a - n$  are constants. The results from this model showed that this third variable lies in its ability to help in conducting a reliable test for detecting diabetes in the blood. In addition, results showed a shorter period of time in which glucose concentration returns to the normal level and the model is asymptotically stable. It is worth noting here that only an internal rate is taken into account in this model, hence, an external rate still needs to be further studied.

### 3.1.7 Bariatric surgery and T2DM improvement mechanism: a mathematical model

Recently, there have been a number of relevant findings about obesity, which is also one of the major problems worldwide. One of the main diseases that is linked to obesity is type 2 diabetes mellitus (T2DM) (Boden et al., 2004; Bose et al., 2009; Trujillo et al., 2006). One of the obesity treatments is bariatric surgery and evidence has shown that this is related to diabetes. An interesting side-effect of surgery has been observed since 1970's that it can lead to type 2 diabetes mellitus remission. Much research has been explored what could make this happen. Possible mechanisms which could affect this remission included incretin, ghrelin and some intestinal factors due to intestinal bypass (Mingrone, 2008; Mingrone et al., 2006; Salinari et al., 2009).

Ghrelin is a hormone secreted by the stomach, which it increases appetite. Within the lower intestine, there is an incretin which is a peptide called Glucagon-like peptide-1 (GLP-1), secreting from enteroendocrine L-cells. GLP-1 increases insulin secretion and  $\beta$ -cell proliferation and decreases  $\beta$ -cell apoptosis. And for the upper intestine, duodenum has shown to influence glucose homeostasis (Cummings DE 2009). Therefore, Toghaw's group (Toghaw et al., 2012) has added ghrelin, lower intestine and upper intestine in their models to explore the glucose-insulin-incretin system as a model diagram in Figure 5. All symbols in this model are kept as original paper for convenience.

$M_i$  is the path of ingested glucose from the stomach ( $S$ ) through duodenum ( $D$ ) and ileum ( $L$ ) and absorption in the plasma glucose concentration compartment ( $G$ ).  $I$  represents insulin compartment,  $W$  and  $U$  are incretins,  $P$  is Dipeptidyl-peptidase IV (DPP4), it is a serine protease degrading glucose-dependent insulinotropic polypeptide (GIP) and GLP-1. Finally,  $A$  and  $H$  indicate anti-incretin and ghrelin, respectively.



**Figure 5.** Dynamics chart of insulin-glucose regulation involved with incretin system. State variables are shown as circles; solid arrows represent mass transfer and dashed arrows represent stimulations. All the letters are explained in the text. (This figure is taken from Toghaw et al., 2012).

This model can be written as differential equations as follows:

$$\frac{dS(t)}{dt} = -k_{ds}S(t) - k_{ls}S(t) + \sum_{i=1}^{N_{meals}} M_i \delta(t - t_i), \quad S(T_{\min}) = S_{T \min} \quad (39)$$

$$\frac{dD(t)}{dt} = k_{ds}S(t) - k_{ld}D(t) - k_{gd}D(t), \quad D(T_{\min}) = D_{T_{\min}} \quad (40)$$

$$\frac{dL(t)}{dt} = k_{ld} D(t) + k_{ls} S(t) - k_{gl} L(t), \quad L(T_{\min}) = 0 \quad (41)$$

$$\frac{dG(t)}{dt} = -k_{xg} G(t) - k_{xgi} I(t)G(t) + f \frac{k_{gd} D(t) + k_{gl} L(t)}{V_e} + k_g^{liver}, \quad G(T_{\min}) = G_{T \min} \quad (42)$$

$$\frac{dI(t)}{dt} = (k_{ig}G(t)) + k_{iwg}G(t)W(t)e^{-\lambda_{01a}A(t)} + k_{iug}G(t)U(t)e^{-\lambda_{02a}A(t)}e^{-\lambda_{03a}H(t)} - k_{xi}I(t), I(T_{\min}) = I_{T_{\min}} \quad (43)$$

$$\frac{dW(t)}{dt} = k_{wd} D(t) e^{-\lambda_{w_{\text{in}}} A(t)} + k_{wl} L(t) - k_{xwp} P(t) W(t) - k_{xw} W(t) + k_w, W(T_{\min}) = W_{T_{\min}} \quad (44)$$

$$\frac{dU(t)}{dt} = k_{ud} D(t) e^{-\lambda_{ud} A(t)} + k_{ul} L(t) - k_{sup} P(t) U(t) - k_{xu} U(t) + k_u U(T_{\min}) = U_{T \min} \quad (45)$$

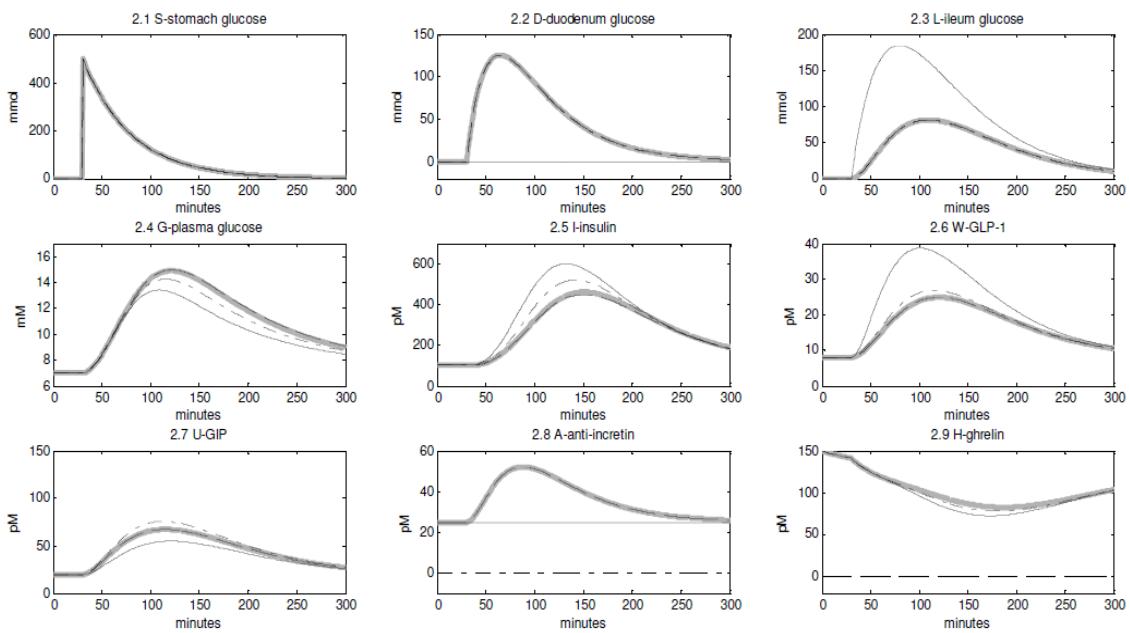
$$\frac{dP(t)}{dt} = k_p - k_{xp} P(t), \quad P(T_{\min}) = P_{T_{\min}} \quad (46)$$

$$\frac{dA(t)}{dt} = k_{ad} D(t) - k_{xa} A(t) + k_a, \quad A(T_{\min}) = A_{T_{\min}} \quad (47)$$

$$\frac{dH(t)}{dt} = (k_{h06} e^{-\lambda_{06,i} S(t)} + k_{h07} e^{-\lambda_{07,d} D(t)} + k_{h08} e^{-\lambda_{08,L} L(t)}) e^{-\lambda_{09,I} I(t)} - k_{xh} H(t), \quad H(T_{\min}) = H_{T_{\min}} \quad (48)$$

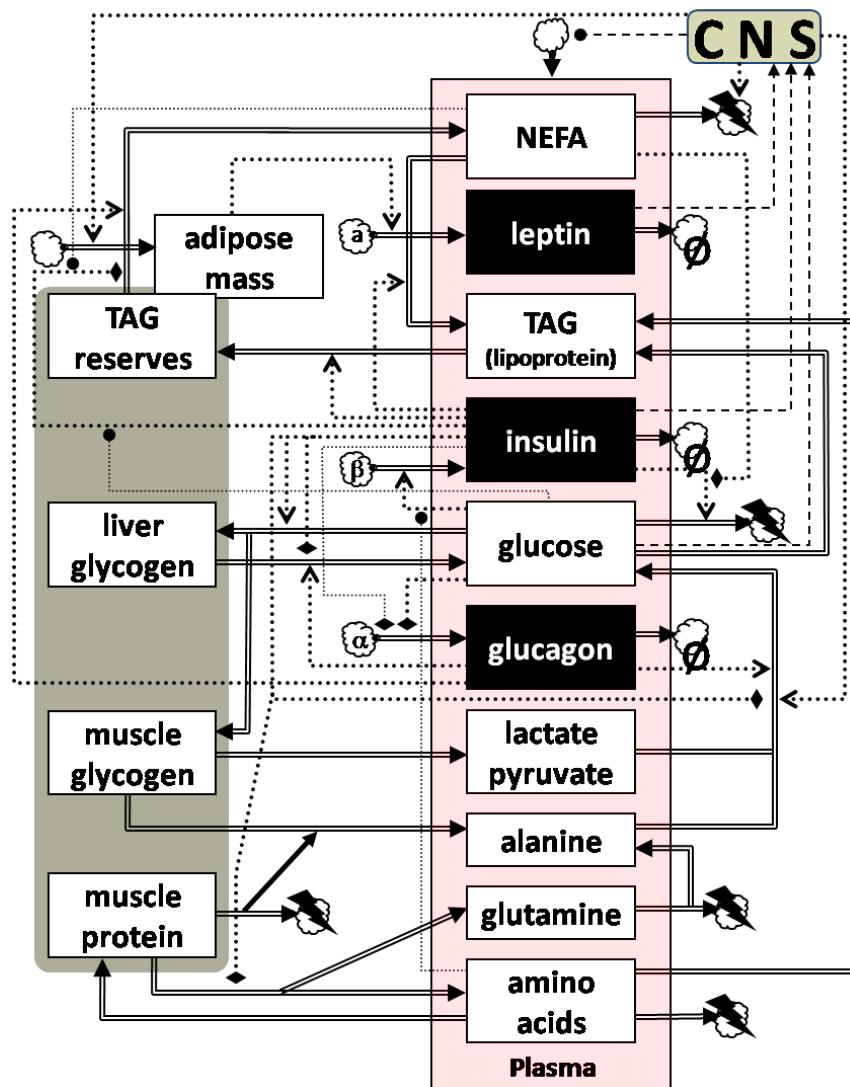
With some assumptions and data from patients, the simulation has been studied in four different cases: (i) pre-surgery (baseline) (ii) duodenum (lower intestine) exclusion (iii) anti-incretin exclusion and (iv) ghrelin exclusion. The results are shown in Figure 6, indicating that the ghrelin levels are unchanged after bariatric surgery compared to the pre-surgery curve, whereas case (ii) and (iii) give higher plasma insulin concentration peaks. In the anti-incretin exclusion case, the study reports an increase in both GLP-1 and GIP level, while in the duodenum exclusion case, it shows an dramatic increase in GLP-1 level and a decrease in GIP level. Interestingly, in the case of ghrelin exclusion, the level of all state variables are at the same level to pre-surgery case, indicating that the hypothesis that ghrelin could be a factor for the remission of T2DM post-surgery is not convincing.

All in all, there are still several limitations and some assumptions have been made within this model which could affect the results. In addition, the meal intake for the patient contained not only glucose but fat and proteins which could drive to several involving mechanisms into this model. However, it looks promising to further develop the model to explore factors of T2DM remission in order to help diabetic obese people.



**Figure 6.** Model simulation result: thick gray line: pre-surgery case; solid line: duodenum exclusion case; dash-dot line: anti-incretin exclusion case; dashed line: ghrelin exclusion. All parameters used in this simulation can be seen from Toghaw et al. (2012).

To sum up, a variety of mathematical models of the regulation of insulin and glucose have been published in the past decade in order to obtain a better understanding of diabetes. The modellers have tried to extend the minimal model which contains the least parameters by adding related hormones and components in their models to make them more realistic. In reality, many more hormones, fat, protein, substrate and the central nervous system get involved in this regulation. Figure 7 shows how several models published in the literature fit together, this figure is adapted from Pattaranit R. and van den Berg H.A. (2008). Furthermore, recent work by Toghaw et al. (2012) has also shown the importance of lower and upper intestine which could be another factor affecting glucose homeostasis and can be added in the model.



**Figure 7.** Dynamics chart of insulin-glucose regulation involved with hormones, fat, protein, liver, muscle and the central nervous system (CNS). State variables are shown as boxes; those in the box marked plasma represent plasma concentrations. Boxes on the left-hand side represent internal stores, double arrows denote all the fluxes, whereas the flows of information are represented by dotted arrows and sources and sinks are shown as clouds.

#### 4. Concluding remarks

During the last few decades, diabetes has become one of the most urgent global health threats, especially in the South East Asia region. A clearer understanding of the disease, its

causes and effects is a significant factor in improving this situation. Insulin-glucose dynamics is one of the studies which give a better understanding. Mathematical models are useful tools to study biomedical problems, as they can simulate the simple and complex phenomena and provide future predictions, and many mathematical models have demonstrated value in understanding the insulin-glucose regulation. This review has shown models explaining insulin-glucose regulation only in ordinary differential equations (ODEs) form. The review starts from a look at the minimal model consisting of only insulin and glucose as state variables, then continues with several models extended with additional components, for example, FFA, glucagon,  $\beta$ -cell mass, insulin receptor, epinephrine and recently ghrelin, incretin and intestine. Nevertheless, the dynamics of diabetes are relatively complex due to some hormones and/or components being inter-dependent to one another including the connection to the brain (Friedman and Halaas, 1998; Gaohua and Kimura, 2009; Pattaranit and van den Berg, 2008). Hence, some of the important aspects relating to insulin-glucose dynamics and other forms of mathematics model (e.g. delay differential equations and some programming tools to compute algorithms) have not been emphasised in this review. In order to observe the big picture of this kinetic and to make it more realistic, further variables involved in regulating glucose and insulin are needed as shown in Figure 7. However, taking all variables mentioned into the model is non-trivial due to the difficulty of estimating all parameters. Therefore, modellers have to be careful weighting between realistic and accuracy. In conclusion, mathematical models have shown to be an important tool to at least verify whether some hormones or components do affect glucose homeostasis or not, this is to do by running different cases of simulation in each model.

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