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Mathematical models and software tools for the glucose-insulin regulatory system and diabetes: an overview

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Abstract

An overview of some of the mathematical models appearing in the literature for use in the glucose-insulin regulatory system in relation to diabetes is given, enhanced with a survey on available software. The models are in the form of ordinary differential, partial differential, delay differential and integro-differential equations. Some computational results are also presented.

Keywords: Glucose-insulin; Diabetes; Mathematical models; Software tools; Overview

1. Introduction

The normal blood glucose concentration level in humans is in a narrow range (70–110 mg/dl) (cf. [32]). Exogenous factors that affect the blood glucose concentration level include food intake, rate of digestion, exercise, reproductive state. The pancreatic endocrine hormones insulin and glucagon are responsible for keeping the glucose concentration level in check. Roughly speaking, insulin and glucagon are secreted from β-cells and α-cells respectively, which are contained in the so-called Langerhans islets scattered in the pancreas. When the blood glucose concentration level is high, the β-cells release insulin

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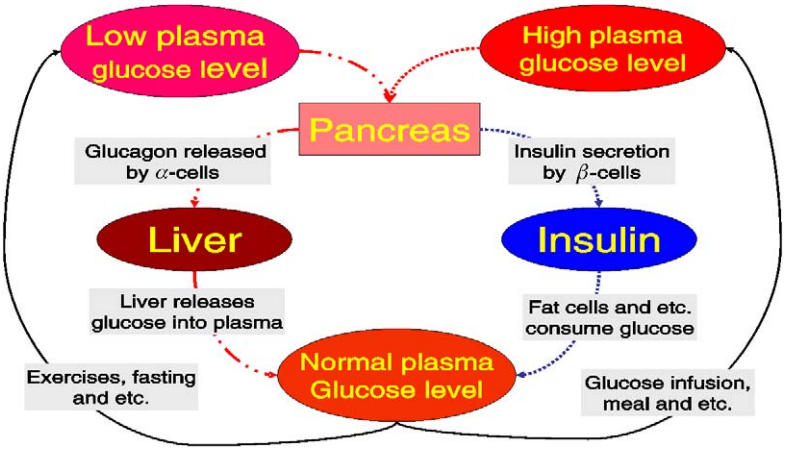

Fig. 1. Physiological glucose-insulin regulatory system.

which results in lowering the blood glucose concentration level by inducing the uptake of the excess glucose by the liver and other cells (e.g., muscles) and by inhibiting hepatic glucose production. When the blood glucose level is low, the α-cells release glucagon, which results in increasing the blood glucose level by acting on liver cells and causing them to release glucose into the blood (cf. [41,60]).

If one's glucose concentration level is constantly out of the range (70–110 mg/dl), this person is considered to have blood glucose problems known as hyperglycemia or hypoglycemia. Diabetes mellitus is a disease of the glucose-insulin regulatory system [13,65], which is referred to as hyperglycemia. (See Fig. 1 for plasma glucose-insulin interaction loops.)

Diabetes is classified into two main categories: Type 1 diabetes, juvenile onset and insulin-dependent, and type 2 diabetes, adult onset and insulin-independent. The relative interaction and contribution in the pathogenesis of this disease of various defects of the glucose-insulin regulatory system associated for example with β-cells mass, the responsiveness level of β-cells to glucose and the sensitivity of tissues to insulin, remains to be clarified [24]. Complications of the disease include retinopathy, nephropathy, peripheral neuropathy and blindness [28]. There are many diabetic patients in the world and diabetes mellitus is becoming one of the worst diseases with respect to the size of the affected population. This motivates many researchers to study the glucose-insulin endocrine regulatory system.

Various *in-vivo* and *in-vitro* experiments have shown that the insulin secretion rate (ISR) from pancreatic islets, oscillates in a number of different time scales: The *fastest* oscillations have a period of tens of seconds and they have been shown to be in phase with oscillations in the free Ca^{2+} concentration of β-cells; the *second fast* or *rapid* oscillations have a period of 5–15 minutes and the *slow* oscillations referred to usually as *ultradian* oscillations, have a period within the range of 50–120 minutes [57,60,17]. In addition to these types of oscillations, circadian rhythms have been also observed (cf. [17], originally Peschke and Peschke (1998) [55]).

The *rapid* oscillations are caused by *coordinate* periodic secretory insulin bursting from the β-cells. These bursts are the dominant mechanism of insulin release at basal states [57]. According to Bertram et al. (2004) [17], in some cases *compound bursting* occurs, the term referred to episodic bursts clustered together and they propose that the compound bursting is responsible for insulin oscillations with a period of approximately 5 minutes.

The *ultradian* oscillations of insulin concentration are associated to similar oscillations of the plasma glucose concentration, and they are best seen after meal ingestion, oral glucose intake, continuous enteral nutrition or intravenous glucose infusion [60,62].

Many mathematical models have been developed to better understand the mechanisms of the glucose-insulin regulatory system. The most noticeable model is the so-called "minimal model" which contains minimal number of parameters [15,14] and it is widely used in physiological research work to estimate glucose effectiveness (S_G) and insulin sensitivity (S_I) from intravenous glucose tolerance test (IVGTT) data by sampling over certain periods. The IVGTT focuses on the metabolism of glucose in a short time period starting from the infusion of a big bolus (0.33 g/kg) of glucose at time $t = 0$. Models addressing insulin secretion oscillations include these presented in the papers [43,62,63,33,7,47,17]. A few models are based on the control through meals and exercise (cf. [28]). See also a review paper by Mari [50] for a classification of models.

Types of models which have been used in the literature can be classified mathematically as: ordinary differential equations (ODEs), delay differential equations (DDEs), partial differential equations (PDES), Fredholm integral equations (FIES) (in the estimation of parameters problem), stochastic differential equations (SDEs) and integro-differential equations (IDEs). Different software packages can be used for different types of models for numerical analysis and simulations.

In this paper an overview of some mathematical models in the form of ODEs, DDEs, PDEs and IDEs is given. In addition, a survey of software packages available for analysis and simulation of such models is presented. The organisation of the paper is as follows: Sections 2–5 contain examples of models in the form of ODEs, DDEs, IDEs and PDEs respectively. Some references to other approaches are given in Section 6. A short introduction to methods of parameter estimation is given in Section 7. Software packages are introduced in Section 8. Section 9 contains some simulation results.

2. Ordinary differential equation models

According to Bergman (2002) [12], ODE modeling started with the so-called *minimal model* [15,63, 14], motivated to modeling the intravenous glucose tolerance test. There are now approximately 50 major studies published per year and more than 500 can be found in the literature, according to the same author, which involve the minimal model. For a history of the model see Bergman (1997, 2001) [10,11] (Ref. in Bergman (2002) [12]), Godsland (2003) [36]. One of the pioneering papers in this field is Bolie (1961) [19] according to Derouich and Boutayeb (2002, p. 912) [28] for example.

The form of the IVGTT *minimal model* is (cf. [25]):

$$\begin{aligned}
\frac{\mathrm{d}G(t)}{\mathrm{d}t} &= -\big[b_1 + X(t)\big]G(t) + b_1 G_b,\\
\frac{\mathrm{d}X(t)}{\mathrm{d}t} &= -b_2 X(t) + b_3\big[I(t) - I_b\big],\\
\frac{\mathrm{d}I(t)}{\mathrm{d}t} &= b_4\big[G(t) - b_5\big]^+ t - b_6\big[I(t) - I_b\big],
\end{aligned} \tag{2.1}$$

where $G(0) = b_0$, $X(0) = 0$, $I(0) = b_7 + I_b$, $[G(t) - b_5]^+ = G(t) - b_5$ if $G(t) > b_5$ and 0 otherwise, $G(t)$ denotes blood glucose concentration at time t, $I(t)$ insulin blood concentration, $X(t)$ is an auxiliary function representing insulin-excitable tissue glucose uptake activity, G_b is the subject's baseline

glycemia, I_b the subject's baseline insulemia, b_1–b_6 are various rate constants, and b_0, b_7 are constants. The auxiliary variable $X(t)$ mimics the time delay of the insulin consumption on glucose. See Section 4 for delay integro-differential equation models. As pointed out in [25, Section 3, pp. 143–144], the minimal model is structurally incorrect in mathematics. For example, if the target glycemia $b_5 < G_b$, the system even does not assume a steady state, although insulin secretion tries to attain the target. In this case, the auxiliary variable $\limsup_{t\to\infty} X(t) = \infty$ [25, Proposition I.1]. More formal mathematical analysis on the minimal model are given in [25].

Nucci and Cobelli (2000) [52] review 6 models in detail for the subcutaneous (sc) insulin kinetics, four of them are ODE models, one is a PDE and the other one is a DDE model.

These sc insulin absorption models (e.g., [45,58]) and the critical review in [52] on the available models, are primarily motivated [52] by the usefulness of a quantitative description of insulin absorption after a sc injection for the management of type 1 diabetic patients and the creation of decision support systems.

Two of these ODE models (Kraegen and Chisholm (1984) [45], and Puckett and Lightfoot (1995) [58]) were also examined in Kalmoukou (2003) [42]. See Parker et al. (2001) [54] and Bellazzi et al. (2001) [6] for two more review papers for intravenous and subcutaneous insulin kinetics respectively.

Based on two negative feedback loops describing the effects of insulin on glucose utilization and production and the effect of glucose on insulin secretion, the authors, Sturis et al. (1991) [62], developed a six-dimensional ODE model. Tolić et al. (2000) [64] simplified this model a little bit. This model has been the basis of several DDE models [31,33,7,47]. It has the following form (cf. [64, p. 363])

$$
\begin{aligned}
\frac{\mathrm{d}G(t)}{\mathrm{d}t} &= G_{\mathrm{in}} - f_2\big(G(t)\big) - f_3\big(G(t)\big) f_4\big(I_i(t)\big) + f_5\big(x_3(t)\big),\\
\frac{\mathrm{d}I_p(t)}{\mathrm{d}t} &= f_1\big(G(t)\big) - E\left(\frac{I_p(t)}{V_p} - \frac{I_i(t)}{V_i}\right) - \frac{I_p(t)}{t_p},\\
\frac{\mathrm{d}I_i(t)}{\mathrm{d}t} &= E\left(\frac{I_p(t)}{V_p} - \frac{I_i(t)}{V_i}\right) - \frac{I_p(t)}{t_i},\\
\frac{\mathrm{d}x_1(t)}{\mathrm{d}t} &= \frac{3}{t_d}\big(I_p(t) - x_1(t)\big),\\
\frac{\mathrm{d}x_2(t)}{\mathrm{d}t} &= \frac{3}{t_d}\big(x_1(t) - x_2(t)\big),\\
\frac{\mathrm{d}x_3(t)}{\mathrm{d}t} &= \frac{3}{t_d}\big(x_2(t) - x_3(t)\big),
\end{aligned}
\tag{2.2}
$$

where $G(t)$ is the mass of glucose, $I_p(t), I_i(t)$ the mass of insulin in the plasma and the intercellular space, respectively, V_p is the plasma insulin distribution volume, V_i is the effective volume of the intercellular space, E is the diffusion transfer rate, t_p, t_i are insulin degradation time constants in the plasma and intercellular space, respectively, G_{in} indicates (exogenous) glucose supply rate to plasma, and $x_1(t), x_2(t), x_3(t)$ are three additional variables associated with certain delays of the insulin effect on the hepatic glucose production with total time t_d. $f_1(G)$ is a function modeling the pancreatic insulin production as controlled by the glucose concentration, f_2, f_3, f_4 are functions for glucose utilization by various body parts (brain and nerves (f_2), muscle and fat cells (f_3, f_4)) and f_5 is a function modeling hepatic glucose production. The forms of the functions $f_1, \ldots, f_5$ are given in [64].

There are two time delays in the system. One is glucose triggered insulin production delay that is reflected by breaking the insulin in two separate compartments, and the other one is hepatic glucose production delay which is fulfilled by the three auxiliary variables, x_1, x_2 and x_3. This model simulated ultradian insulin secretion oscillations. For conclusions drawn from the simulations we refer to [62].

3. Models in the form of delay differential equations

To analyze the ultradian insulin secretion oscillations, several models in the form of DDEs based on the model by Sturis et al. (1991) [62] have been introduced in the literature. They include: Drozdov and Khanina (1995) [31], Engelborghs et al. (2001) [33], Bennett and Gourley (2004) [7], Li et al. (2005) [47]. They are modifications of the Sturis model (Sturis et al. (1991) [62] and Tolić et al. (2000) [64]).

Two models in DDE form are introduced in [33]. One [33, p. 363], is for ultradian insulin oscillation but in which glucose triggered insulin production delay is missing:

$$\begin{aligned}
\frac{\mathrm{d}G(t)}{\mathrm{d}t} &= G_{\mathrm{in}} - f_2\big(G(t)\big) - f_3\big(G(t)\big) f_4\big(I(t)\big) + f_5\big(I(t-\tau_2)\big),\\
\frac{\mathrm{d}I(t)}{\mathrm{d}t} &= f_1\big(G(t)\big) - \frac{I(t)}{t_1}.
\end{aligned} \tag{3.1}$$

The other one [33, p. 364], is trying to model the exogenous insulin infusion but the authors assumed that the exogenous insulin infusion function takes the same form as the internal insulin production, which, as the authors admitted, is too artificial:

$$\begin{aligned}
\frac{\mathrm{d}G(t)}{\mathrm{d}t} &= G_{\mathrm{in}} - f_2\big(G(t)\big) - f_3\big(G(t)\big) f_4\big(I(t)\big) + f_5\big(I(t-\tau_2)\big),\\
\frac{\mathrm{d}I(t)}{\mathrm{d}t} &= \alpha f_1\big(G(t)\big) - \frac{I(t)}{t_1} + (1-\alpha) f_1\big(G(t-\tau_1)\big).
\end{aligned} \tag{3.2}$$

A noticeable addition to the work of this paper is the usage of DDE-BifTool software package to analyze and simulate the bifurcation diagram and other numerical analysis.

Some analytical work can be seen in Bennett and Gourley (2004) [7, p. 190] in which they introduced the following model:

$$\begin{aligned}
\frac{\mathrm{d}I_p(t)}{\mathrm{d}t} &= f_1\big(G(t)\big) - E\left(\frac{I_p(t)}{V_p} - \frac{I_i(t)}{V_i}\right) - \frac{I_p(t)}{t_p},\\
\frac{\mathrm{d}I_i(t)}{\mathrm{d}t} &= E\left(\frac{I_p(t)}{V_p} - \frac{I_i(t)}{V_i}\right) - \frac{I_i(t)}{t_i},\\
\frac{\mathrm{d}G(t)}{\mathrm{d}t} &= G_{\mathrm{in}} - f_2\big(G(t)\big) - qG(t) f_4\big(I_i(t)\big) + f_5\big(I_p(t-\tau)\big),
\end{aligned} \tag{3.3}$$

where $I_p(s) = I_p^0(s) \geqslant 0$, $s \in [-\tau, 0]$, $I_p^0(0) > 0$, $\tau \geqslant 0$, $q > 0$ are constants, $I_i(0) = I_i^0 > 0$, $G(0) = G^0 > 0$. Specific forms of the functions $f_1(G)$, $f_2(G)$, $f_4(I)$, $f_5(I)$ are the same as in [62].

The main analytical result in this paper is some sufficient conditions for global stability, or in other words, the nonexistence of long term oscillation, which is not in the physiological sense.

Observing the time delay of glucose triggered insulin production, Li et al. (2005) [47] recently applied time delay in the insulin response to the glucose stimulation and presented the following model.

$$\frac{\mathrm{d}G(t)}{\mathrm{d}t} = G_{\mathrm{in}} - f_2\big(G(t)\big) - f_3\big(G(t)\big) f_4\big(I(t)\big) + f_5\big(I(t-\tau_2)\big),$$
$$\frac{\mathrm{d}I(t)}{\mathrm{d}t} = f_1\big(G(t-\tau_1)\big) - d_i I(t), \tag{3.4}$$

with initial conditions $I(0) = I_0 > 0$, $G(0) = G_0 > 0$, $G(t) \equiv G_0$ for all $t \in [-\tau_1, 0]$ and $I(t) \equiv I_0$ for $t \in [-\tau_2, 0]$, where $\tau_1, \tau_2 > 0$. τ_1 is the time delay of insulin production stimulated by glucose, τ_2 is the time delay of hepatic glucose production and d_i is the insulin degradation rate. The other parameters and functions have the same meaning as in the model in [62]. The purpose of this model is to provide a possible mechanism for the origin of ultradian oscillations in pancreatic insulin secretion with appropriate analysis and numerical simulations with suitable software packages.

4. Models in the form of integro-differential equations

Papers with models in the form of IDEs include: Grodsky (1972) [37] and a modification by Hagander et al. (1978) [39], De Gaetano and Arino (2000a), (2000b) [25,26], Li et al. (2001) [48], Mukhopadhyay et al. (2004) [51].

Here we give the forms of the De Gaetano and Arino (2000a) [25], Li et al. (2001) [48] and Mukhopadhyay et al. (2004) [51].

All these models are modeling glucose-insulin dynamics in IVGTT. The motivation to introduce these models is due to the fact that the widely used *minimal model* [15,14] is considered improper in qualitative behavior as it requires the parameter b_5 to equal the basal glucose level G_b. De Gaetano and Arino [25] did formal mathematical analysis on the *minimal model* and introduced a more realistic delay integro-differential equation model [25,26], a *dynamic model*, as the authors called it [25, p. 141]:

$$\frac{\mathrm{d}G}{\mathrm{d}t} = -b_1 G(t) - b_4 I(t) G(t) + b_7,$$
$$\frac{I(t)}{\mathrm{d}t} = -b_2 I(t) + \frac{b_6}{b_5} \int_{t-b_5}^{t} G(s)\,\mathrm{d}s, \tag{4.1}$$

where $G(t) = G_b$, $t \in [-b_5, 0]$, $G(0) = G_b + b_0$, $I(0) = I_b + b_3 b_0$.

Li et al. (2001) [48, p. 106] introduced a more generic model as follows:

$$\frac{\mathrm{d}G(t)}{\mathrm{d}t} = -f\big(G(t)\big) - g\big(G(t), I(t)\big) + b_7,$$
$$\frac{\mathrm{d}I(t)}{\mathrm{d}t} = -p\big(I(t)\big) + q\big(L(G_t)\big), \tag{4.2}$$

where $G(0) = G_b + b_0$, $I(0) = I_b + b_3 b_0$, $G(t) = G_b$, $t \in [-b_5, 0]$, $G_t(\theta) = G(t+\theta)$, $t > 0$, $\theta \in [-b_5, 0]$, $L(\phi) = \int_{-b_5}^{0} \phi(s)\,\mathrm{d}(\mu(s))$ and $\mu(s)$ is nondecreasing with $\int_{-b_5}^{0} \mathrm{d}(\mu(s)) = 1$. This model is generic so that, for example, the following two special cases for $L(G_t)$ were considered:

$$L(G_t) = G(t - b_5) \quad \text{and} \quad L(G_t) = \frac{1}{b_5} \int_{-b_5}^{0} G(t+\theta)\,\mathrm{d}\theta.$$

Both analysis and numerical simulations are performed, especially, when insulin dependent net glucose tissue uptake is assumed to follow Michaelis–Menten dynamics with $1/\alpha$ as the half-saturation constant. The models in these two special cases are as follows [48, p. 107]:

Case I:

$$\frac{\mathrm{d}G(t)}{\mathrm{d}t} = -b_1 G(t) - \frac{b_4 I(t) G(t)}{\alpha G(t) + 1} + b_7,$$
$$\frac{\mathrm{d}I(t)}{\mathrm{d}t} = -b_2 I(t) + b_6 G(t - b_5). \tag{4.3}$$

Case II:

$$\frac{\mathrm{d}G(t)}{\mathrm{d}t} = -b_1 G(t) - \frac{b_4 I(t) G(t)}{\alpha G(t) + 1} + b_7,$$
$$\frac{\mathrm{d}I(t)}{\mathrm{d}t} = -b_2 I(t) + \frac{b_6}{b_5} \int_{-b_5}^{0} G(t + \theta)\, \mathrm{d}\theta. \tag{4.4}$$

The reason of assuming that the insulin-dependent glucose uptake takes a Michaelis–Menten form is that in a unit of time, a unit of insulin can only process a limited amount of glucose. The mass action law in this situation is not quite realistic.

The Mukhopadhyay et al. (2004) [51, p. 408] model (for IVGGT):

$$\frac{\mathrm{d}G(t)}{\mathrm{d}t} = -b_1 G(t) - b_4 I(t) G(t) + b_7,$$
$$\frac{\mathrm{d}I(t)}{\mathrm{d}t} = -b_2 I(t) + b_6 \int_{0}^{\infty} w(s) G(t - s)\, \mathrm{d}s, \tag{4.5}$$

where $G(t) = G_b$, $t \in (-\infty, 0)$, $G(0) = G_b + b_0$, $I(0) = I_b + b_3 b_0$. A $w(s)$ example: $w(s) = \alpha^2 s e^{-\alpha s}$ [51, p. 413]. The model is a subfamily of models by Li et al. (2001) [48].

5. Models in the form of partial differential equations

Papers presenting models in the form of PDEs include: Boutayeb and Derouich (2002) [20], Boutayeb and Twizell (2004) [21] (age structured models), Aslanidi et al. (2002) [4], Bertram and Pernarowski (1998) [16] (reaction–diffusion type related to the Langerhans islets), Wach et al. (1995) [69] (a model for the absorption of subcutaneously injected insulin), Keener (2001) [44] (a model for the infusion induced oscillatory insulin secretion from β-cells in pancreas). Two models are outlined here, the models by [69,44].

The Wach et al. (1995) [69] PDE model:

Assumptions: Injected soluble insulin is present in the sc tissue in hexameric and dimeric form; only dimeric molecules can penetrate the capillary membrane:

$$\frac{\partial h}{\partial t} = P\left(Qd^3 - h\right) + D\nabla^2 h, \qquad \frac{\partial d}{\partial t} = -P\left(Qd^3 - h\right) + D\nabla^2 d - Bd, \tag{5.1}$$

where h, d are concentrations of hexameric and dimeric insulin, P is a rate constant, Q is a chemical equilibrium constant, D is a diffusion constant, and B is an absorption rate constant. The authors solve numerically by dividing the sc region into spherical shells for the space discretization. The PDE model by Wach et al. (1995) [69] has also been extended by the authors for use with monomeric insulin.

Keener [44] introduced two models to address the oscillatory nature of the *in vitro* insulin secretion by the β-cells. One model [44, Section 2] assumes the situation of a one-dimensional reactor (no diffusion) assuming a mechanism of insulin secretion identical to that assumed by Maki and Keizer (1995) [49]. It was then shown that for certain large values of the ratio of the flow rate to the volume of the reaction islet bed, there are no oscillations. Keener's second model [44, Section 4] introduces diffusion. The model predicts that oscillations occur if there is sufficient diffusion (values of a scaled diffusion parameter $\delta > 0.1$) to create adequate concentrations mixing in the reacting layers of the cells. With insufficient such mixing, the oscillations are inhibited. An 'unsolved dilemma' having to do with difficulty to produce large enough δ values ($\delta > 0.1$) from experimental values of the scaling parameters V, L_{bed}, where L_{bed} is the length of the islet bed and V is the velocity of the steady flow of the solution along the 1-dimensional reactor, and large physical diffusion (large D_I coefficient) which is needed for the model to predict oscillations, is mentioned at the end of the paper. The software package AUTO97 was used for the simulations [30].

6. Other approaches

The blood glucose control problem has also been seen as a *control problem* (cf. Faria (2003) [35]—optimal control for a utility function involving a medical treatment, diet and exercise routines, Candas and Radziuk (1994) [22]—adaptive plasma glucose controller, Ruiz-Velázquez et al. [59]—blood glucose control for type 1 diabetes mellitus seen as an H_∞ control problem.

Other types of equations: *Stochastic differential equations* (cf. Bleckert et al. (1998) [18], De Vries and Sherman (2000) [29]).

7. Parameter estimation techniques

Parameter estimation techniques include:

- *Fisherian type* parameter estimation techniques (ML (maximum likelihood), nonlinear least squares), cf. Pacini and Bergman (1986) [53], Barrett et al. (1998) [5].
- *Bayesian type* parameter estimation (cf. Andersen and Højbjerre [3] for a stochastic minimal model. The method uses also the so-called *graphical* models (based on directed acyclic graphs). See also: Andersen et al. (2003) [1,2]—applied to the IDE method of De Gaetano and Arino (2000a) [25] too, Bleckert et al. (1998) [18], Pillonetto et al. (2003) [56].
- *Stochastic nonparametric deconvolution* for estimation of EGP (endogenous glucose production) during an IVGTT test (Vicini et al. (1997), [68]). The problem of the EGP estimation is formulated as an input estimation problem solvable as a *Fredholm integral equation (FIE) of the first kind* (Caumo and Cobelli (1993) [23], De Nicolao et al. (1997) [27]). Its solution is using regularization (deconvolution) algorithms like Phillips and Tikhonov (nonparametric deconvolution approach).

Other nonparametric methods use truncated *singular value decomposition*, and the *maximum entropy principle*.

- Other methods: control theory based, using techniques like *Kalman filters and fuzzy filters* (cf. Trajanoski and Wach (1996), [66]).

8. Software packages for analysis and simulations

Several packages exist, some freely available, some commercial. Several are mentioned in the review paper by Lehmann and Deutsch (1995) [46].

Here is a partial list: (The URLs were last accessed on 6 December 2004).

- *AIDA*: By E.D. Lehmann and T. Deutsch. Freely available from: *http://www.2aida.org/aida/technical.htm*. It is suitable for patient and medical staff education for glucose-insulin interaction in insulin-dependent (type 1) diabetes mellitus. It is based on models presented in Guyton et al. (1978) [38] and by Berger and Rodbard (1989) [9].
- *WINSTODEC*. Aimed at allowing the clinical investigator to easily obtain the solution of a deconvolution problem. MATLAB environment. By Sparacino et al. (2001) [61]. Implements the stochastic deconvolution algorithm of De Nicolao et al. (1997) [27].
- A *Matlab suit of routines* for a FSIGTT (frequently sampled intravenous glucose tolerance test) with minimal models. By Van Riel (2004) [67]. Downloadable from: *ftp://ftp.mbs.ele.tue.nl/CS/Riel/*.
- *DIAS*—the diabetes advisory system. By Hejlesen et al. (1997) [40] (*http://www.mi.auc.dk/~okh/dias.htm*). It is a decision support system for insulin dependent diabetes. It uses compartmental model of human carbohydrate metabolism. The method it applies is the so-called causal probabilistic network.
- *SAAM II* (*http://www.saam.com*). By the SAAM Institute Inc. Available for a 'small' fee on a CD.
- *WinSAAM*. The Simulation, Analysis and Modeling Software, freely available from *http://www.winsaam.com/contact.htm*. Its use is described also in the book [70].
- *COMKAT* (Compartmental Model Kinetic Analysis Tool). It is Matlab based and available on request from *http://www.nuclear.uhrad.com/comkat/*.
- *Mathematica based*. Mentioned in Benyó et al. (preprint) [8] for: 'blood glucose control of diabetic patients in intensive care'. It is based on a modified 2-compartment model of Bergman et al. (1979) [15].
- *Mlab* (Mathematical Modeling Software), from *http://www.civilized.com* (commercial).
- *Glucosim* (*http://216.47.139.198/glucosim/index.html*). A Web-based educational simulation package for glucose-insulin levels in the human body, by the Process Modeling, Monitoring and Control Research Group of Dept. of the Chemical and Environmental Engineering of the Illinois Institute of Technology (downloadable version freely available on request). The simulator is written in C and uses the *Netlib* routine *CVODE*.
- *DDE-BIFTOOL*. Available on request from *http://www.cs.kuleuven.ac.be/~twr/research/software/delay/ddebiftool.shtml*. It is referenced in the paper Engelborghs et al. (2001) [33].
- *AUTO*. Continuation and Bifurcation Software for Ordinary Differential Equations (with HomCont), (*http://indy.cs.concordia.ca/auto/*). AUTO2000 User's manual available from: *http://prdownloads.sourceforge.net/auto2000/auto2000-0.9.6.ps.gz*.

- *XPPAUT*. Available from: *http://www.math.pitt.edu/~bard/xpp/xpp.html*. It is suitable for solving differential equations, difference equations, delay equations, functional equations, boundary value problems, and stochastic equations. Its use is now explained in the book Ermentrout (2002) [34].
- *DDE23* by L.F. Shampine and S. Thompson. It has been included in Matlab 6.5. DDE23 can be used to solve delay differential equations and thus draw 2D or 3D solution curves or orbits (*http://www.radford.edu/~thompson/*, see also *http://www.mathworks.com/matlabcentral/fileexchange/loadFile.do?objectId=3899*).
- *Time-Delay System Toolbox* (*http://matlab.fde.uran.ru/*) by the Functional Differential Equation Laboratory of the Institute of Mathematics and Mechanics, Ural Branch of the Russian Academy of Sciences. On-line simulations are possible. See also the page (*http://fde.uran.ru/default.en.htm*) of the FDE Virtual System Center on Functional Differential Equations of the Dept. of Numerical Mathematics of the Ural State University for other collaborators.
- *MatCont*. MatCont is a user friendly software to solve ODEs numerically. It provides graphical user interface and handles bifurcations. Downloadable from: *http://allserv.rug.ac.be/~ajdhooge/research.html*.

9. Some computational results

Most of the papers introducing different models include also results for computational simulations. The great majority of the models that appear in the literature involve ODEs linear or nonlinear. To test and compare all of them in one paper is a difficult or probably an impossible task. Review papers that have been published concentrate on a specific process/problem, like for example the review paper by Nucci and Cobelli (2000) [52], which reviewed some ODE and PDE models for subcutaneous insulin kinetics (see also Kalmoukou (2003) [42]).

Simulation results are presented here for the following models.

Considering the Generic IVGTT model [48], take the data from subject 6 for example, using DDE-BifTool, starting a guessed steady state $(G^{*\prime}, I^{*\prime}) = (150, 90)$, the starting point can be corrected to steady state $(G^*, I^*) = (133.8791, 104.6922)$:

Further, using DDE-BifTool to Generic IVGTT model [48], a Hopf bifurcation point $\tau = 457.7210$ is detected (see Fig. 2: left).

hopf.parameter ...
ans = 0.0002 0.0001 0.0100 0.6800 0.0422 0.0330 457.7210.

Letting $\tau = 457.7200$, the DDE-BifTool shows that all characteristic roots of the characteristic equation of the Generic IVGTT model have negative real parts (see Fig. 2: right).

With another easy to use software tool, DDE23, it is verified that the steady state $(G^*, I^*) = (133.8791, 104.6922)$ of the Generic IVGTT model [48] is stable when $\tau = 455.00$ (see Fig. 3: left) and unstable and thus oscillating when $\tau = 460.00$ (see Fig. 3: right.)

MATCONT is a graphical MATLAB package for the interactive numerical study of ODE dynamical systems, while CL MATCONT provides the same functionalities in command line. Both MATCONT and CL MATCONT allow to compute curves of steady states, limit points, Hopf bifurcation points, limit cycles and period doubling bifurcation points of limit cycles.

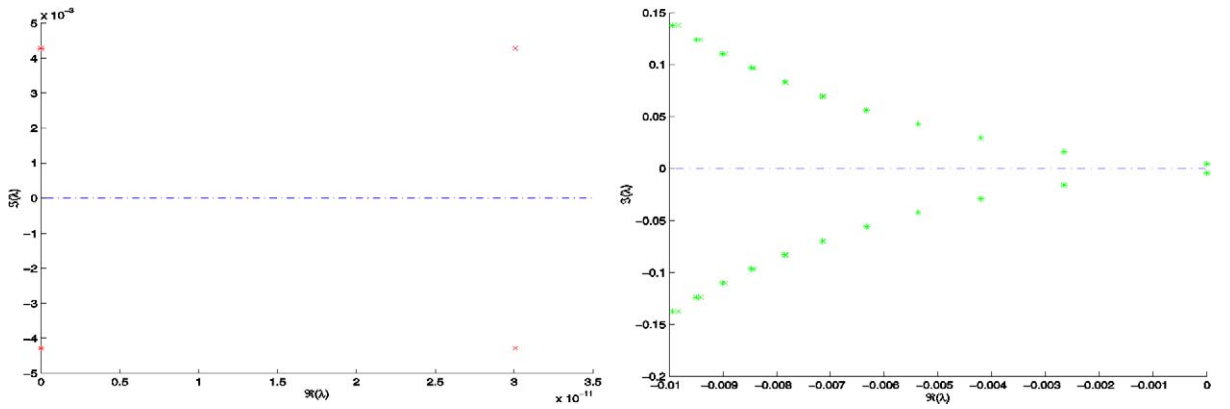

Fig. 2. Left: DDE-BifTool detected Hopf bifurcation point at $\tau = 457.7210$ in Generic IVGTT model [48]. The sign '$\times$' indicates guessed roots. Right: DDE-BifTool shows that all characteristic roots have negative real parts in Generic IVGTT model [48] at $\tau = 457.7200$. The sign '$\times$' indicates guessed roots.

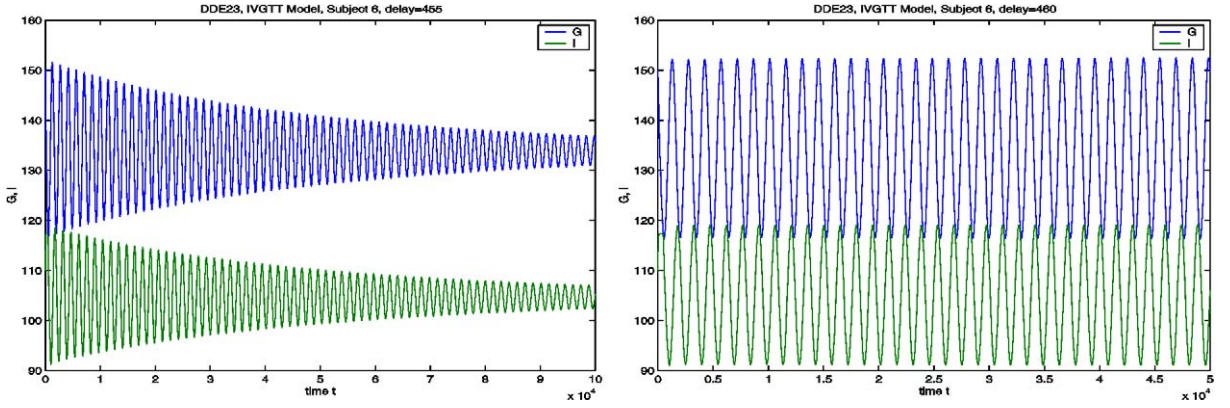

Fig. 3. Left: DDE23 shows that the steady state of the Generic IVGTT model [48] is stable at $\tau = 455.00$. Right: DDE23 shows that the steady state of the Generic IVGTT model [48] is unstable at $\tau = 460$.

MATCONT makes the MATLAB ODE suite for time integration interactively available and can use the MATLAB Symbolic Toolbox for computing derivatives whenever it is installed. In handling limit cycles and their bifurcations it uses the MATLAB sparse matrix routines to exploit the sparsity of the resulting linear systems.

Applying MatCont to the Sturis Model [62,64], the unique steady state is calculated at $(G^*, I_p^*, I_i^*, x_1^*, x_2^*, x_3^*) = (19365.124713, 493.535565, 1167.503488, 493.535565, 493.535565, 493.535565)$. Letting t_d vary, MatCont finds that there exist a branching point at $t_d = 787.905332$ and a Hopf bifurcation point at $t_d = -12.507219$ (see also Fig. 4).

start computing extended curve
using user locator
label = BP, $x = (19365.124713 \quad 493.535565 \quad 1167.503488 \quad 493.535565 \quad 493.535565$
$493.535565 \quad 787.905332)$

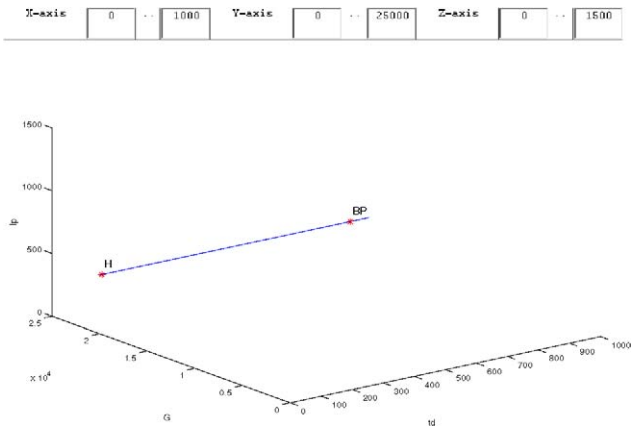

Fig. 4. Varying parameter t_d, MatCont detects a branching point BP at $t_d = 787.905332$ and a Hopf point H at $t_d = -12.507219$ of the ultradian oscillation model given in [62] and [64]. Both points are in nonmeaningful zones.

label = H, $x = (19365.124713 \quad 493.535565 \quad 1167.503488 \quad 493.535565 \quad 493.535565 \quad 493.535565 \quad -12.507219)$

Neutral saddle

Since the delay of hepatic glucose production is usually between 25 min to 50 min, these two bifurcation points do not need to be considered.

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