DELAY DIFFERENTIAL EQUATION MODELS IN DIABETES MODELING: A REVIEW

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Contents

Summary

Delay differential equation models can generate rich dynamics using minimum number of parameters. This characteristic enables such models to play important roles in a growing number of areas of diabetes studies. Such areas include the insulin/glucose regulatory system, intravenous glucose tolerance test (IVGTT), and insulin therapies. In this paper, a review of such models is presented together with some computational results and brief summaries of theoretical results for the cases of models for ultradian oscillations of insulin and models for diagnostic tests.

1. Introduction

Diabetes mellitus is a disease of the glucose-insulin regulatory system. It is classified into two main categories. Type 1 diabetes which is juvenile onset and insulin-dependent and Type 2 diabetes which is adult onset and insulin-independent. Complications of the disease include retinopathy, nephropathy, peripheral neuropathy, blindness. The disease is affecting hundreds millions of people worldwide (type 2 diabetes mellitus had an

estimated incidence of 151 million in the year 2000), which has motivated many researchers to study the mathematical, computational and medical problems associated with it. Articles about the prevalence and the problems of diabetes appear frequently in various media outlets.

Type 1 diabetes is considered to be the result of an immunological destruction of the insulin-producing β-cells. According to Lupi and Del Prato (2008), p. 560, the normal pancreas contains approximately 1 million islets of Langerhans and each islet includes β-cells $(60-80\%)$,α-cells $(20-30\%)$, somatostatin (δ-cells) $(5-15\%)$ and pancreatic polypeptide (PP-cells).

Type 2 diabetes is the result of insulin resistance. The term insulin resistance usually connotes resistance to the effects of insulin on glucose uptake, metabolism, or storage, due to excessive hepatic glucose production and defective β-cell function (cf. Lupi and Del Prato (2008), p. 556).

For more information about the pathogenesis of diabetes we refer for example to Jaïdane and Hober (2008) (type 1 diabetes), and to Lupi and Del Prato (2008) (type 2 diabetes).

Treatment of type 1 diabetes is based on the administration of insulin of various types in a number of ways. Insulin was discovered in 1921 by Bantig, Best, Collip and Macleod. Such insulin administration ways include subcutaneous injections and use of pumps. Cure of type 1 diabetes involves pancreas transplantation and islet transplantation.

Many mathematical models have been developed for studying problems related to diabetes. These include 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). We refer for example to the review papers Makroglou, Li, Kuang (2006), Pattaranit and van den Berg (2008), for more details about several such models and corresponding bibliography.

For information about numerical methods for solving delay differential equations we refer for example to Bellen and Zennaro (2003), see also the web page http://www.scholarpedia.org/article/Delay-differential_equations.

Recently, several papers have appeared in the literature which show renewed interest in the models of insulin secretion introduced by G. H. Grodsky and his co-workers in the late 1960s, 1970s and 1980s. Grodsky introduced the so called threshold hypothesis for the pancreatic granules according to which each granule secrets its insulin contents if glucose is above a certain threshold level. Such recent papers (revisiting, modifying, extending this work but using ODEs mainly) include: Pedersen, Corradin, Toffolo, Cobelli (2008), (the paper describes also the current state of the art accompanied by rich bibliographical information. Their model includes the notion of distinct pools of granules as well as various mechanisms, like priming, exocytosis etc, and it is claimed to be the first physiology-based one to reproduce the staircase experiment, which underlies derivative control, that is the pancreatic capacity of measuring the rate of

change of the glucose concentration).Mari and Ferrannini (2008) (the paper includes an interesting historical background presentation too).

In this chapter a review of some mathematical models in the form of delay differential equations is given, accompanied by some computational results using Matlab and elements of their theoretical analysis. The organization of the chapter is as follows: Section 2 contains the description of the models and some computational results and brief summaries of theoretical results. Two cases are covered here, the case of models for ultradian oscillations of insulin (Section 2.1) and the case of models used in diagnostic tests (Section 2.2). Concluding remarks are in Section 3. The notation is kept as in the original papers for easy reference. The Matlab function DDE23 was used for obtaining graphs of models in the form of DDE systems, see for example the tutorial http://www.runet.edu/~thompson/webddes/tutorial.html for help with its use.

2. Models in the Form of Delay Differential Equations

Delay differential equations (DDEs) have been used as mathematical models in many areas of Biology and Medicine. Such areas include Epidemiology, Population Biology, Immunology, Physiology, Cell mobility.

Delayed effects often exist in the glucose-insulin regulatory system, for example, the insulin secretion stimulated by elevated glucose concentration level and hepatic glucose production. Therefore the delays need to be taken into account when modeling the systems. General approaches include the technique of compartment-split by introducing of auxiliary variables in ordinary differential equations (ODEs), and modeling in delay differential equations (DDEs) by using explicit time delays in either discrete or distributed forms.

The delays in the compartment-split approach are classified as "soft delays" by using γ kernel that is an approximation of the Dirac kernel, while the explicit delays in models as "hard delays". Apparently, modeling by explicit delays is more natural and accurate, although the analysis is usually harder.

Models in the form of delay differential equations grouped according to their functions/purposes include:

- Models used to analyze the ultradian insulin secretion oscillations,
- Models used with diagnostic tests,
- Models related to insulin therapies,
- Models taking intracellular activity of β-cells into account.

Due to limitations with respect to the number of references and the number of pages, models of the first and 2nd category are going to be presented here.

2.1 Ultradian Insulin Secretion Related Models

Insulin is released in a biphasic manner when the glucose concentration is raised from subthreshold to stimulatory levels, with a rapid peak at 2-4 min (first phase), a decrease lasting 10-15 min (pulsatile insulin secretion) followed by a gradual increase within the

next couple of hours (50-120 minutes), cf. Chew et al (2009), (second phase, ultradian insulin secretion).

As mentioned in Chew et al (2009), ultradian oscillations have been seen after meal ingestion, during continuous enteral nutrition, and during intravenous glucose infusion.

Historically, it was in 1923 when rapid and slower oscillations in the peripheral concentrations of glucose were reported by Karen Hansen and half a century later rapid oscillations in the peripheral insulin concentrations were demonstrated.

As several authors mention, the precise mechanisms generating ultradian oscillations are not fully understood yet and the two most common mechanisms mentioned are:

- Instability of the glucose-insulin feedback loop, where the insulin oscillations entrain these of the glucose
- Existence of an intrapancreatic pacemaker.

Entrainment means the ability of a self-oscillating system when perturbed exogenously with a periodic stimulus, to adjust its period of oscillation to that of the stimulus. The entrainment ability seems to have been lost in diabetic patients with type 2 diabetes.

Two time delays exist in the glucose-insulin regulatory system, (cf. Sturis, Polonsky, Mosekilde, Van Cauter (1991)). To model the ultradian insulin secretion oscillations in the regulation with time lags, Sturis et al (1991) proposed a model in ODE utilizing the compartment-split technique. This model was later simplified by Tolić et al (2000). Several models based on this model were proposed consequently. Examples of such models are (see also Makroglou, Li, Kuang (2006)), Drozdov and Khanina (1995), Li, Kuang, Maison (2006), Li and Kuang (2007).

The model in Sturis, Polonsky, Mosekilde, Van Cauter (1991) and models in papers presenting extensions of it, like the models in Li, Kuang and Mason (2006), Tolić, Mosekilde and Sturis (2007), make use of certain functions (f_1, f_2,…, f_5) given below with plasma glucose is denoted by G and plasma insulin or interstitial insulin by I:

$$f_1(G) = R_{\mathrm{m}} \Big/ (1+\exp((C_1 - G/V_{\mathrm{g}})/a_1)), \tag{1}$$

$$f_2(G) = U_{\mathrm{b}}(1-\exp(-G/(C_2 V_{\mathrm{g}}))), \tag{2}$$

$$f_3(G) = G \Big/ (C_3 V_{\mathrm{g}}), \tag{3}$$

$$f_4(I) = U_0 + (U_{\mathrm{m}} - U_0) \Bigg/ \left(1+\exp\left(-\beta \ln \frac{I\left(1/V_{\mathrm{i}} + 1/(Et_{\mathrm{i}})\right)}{C_4}\right)\right), \tag{4}$$

$$f_5(I) = R_{\mathrm{g}} \Big/ \left(1+\exp\left(\hat{\alpha}(I/V_{\mathrm{p}} - C_5)\right)\right). \tag{5}$$

$f_1(G)$: insulin production stimulated by glucose production,

$f_2(G)$: insulin-independent glucose utilization,
$f_3(G)\,f_4(I)$: insulin-dependent glucose uptake (mostly due to fat and muscle cells),
$f_5(I)$: glucose production controlled by insulin concentration.

The values of the parameters may be found for example in Tolić, Mosekilde and Sturis (2000).
The functions $f_1, f_2, \ldots, f_5$ are assumed to satisfy certain general assumptions by Li and Kuang (2007).

Here we present the DDE models by Drozdov and Khanina (1995), Li, Kuang and Mason (2006) model, Chen and Tsai (2010), plus the Sturis et al (1991) and Tolić et al (2000) models that formed the basis of the DDE models.

Some more such models may be found in Makroglou, Li and Kuang (2006).

2.1.1 Compartment-Split ODE Model Proposed by Sturis et al (1991)

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, Polonsky, Mosekilde and Van Cauter (1991), developed a six dimensional ODE model. Tolić, Mosekilde and Sturis (2000) simplified this model a little bit. This model has been the basis of several DDE models. It has the following form (cf. Tolić, Mosekilde and Sturis (2000), p. 363)

$$
\begin{aligned}
&\frac{dG}{dt}(t) = G_{\text{in}} - f_2(G(t)) - f_3(G(t))\,f_4(I_i(t)) + f_5(x_3(t)),\\
&\frac{dI_{\text{p}}}{dt}(t) = f_1(G(t)) - E\left(\frac{I_{\text{p}}(t)}{V_{\text{p}}} - \frac{I_{\text{i}}(t)}{V_{\text{i}}}\right) - \frac{I_{\text{p}}(t)}{t_{\text{p}}},\\
&\frac{dI_{\text{i}}}{dt}(t) = E\left(\frac{I_{\text{p}}(t)}{V_{\text{p}}} - \frac{I_{\text{i}}(t)}{V_{\text{i}}}\right) - \frac{I_{\text{p}}(t)}{t_{\text{i}}},\\
&\frac{dx_1}{dt}(t) = \frac{3}{t_{\text{d}}}(I_{\text{p}}(t) - x_1(t)), \quad \frac{dx_2}{dt}(t) = \frac{3}{t_{\text{d}}}(x_1(t) - x_2(t)), \quad \frac{dx_3}{dt}(t) = \frac{3}{t_{\text{d}}}(x_2(t) - x_3(t)),
\end{aligned}
\tag{6}
$$

where $G(t)$ is the mass of glucose, $I_{\text{p}}(t), I_{\text{i}}(t)$ 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 by (1)-(5).

For the two time delays, 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 numerically. For conclusions drawn from the simulations we refer to Sturis, Polonsky, Mosekilde, Van Cauter (1991).

2.1.2 Single-Delay DDE Model Proposed by Drozdov and Khanina (1995)

A single-delay DDE model is introduced by Drozdov and Khanina (1995) for the description of ultradian oscillations in human insulin secretion. The model equations are (paper, p.27)

$$\begin{aligned}
\frac{dx}{dt}(t) &= f_1\left(\frac{0.1z(t)}{V_3}\right)-\left(\frac{E}{V_1}+\frac{1}{T_1}\right)x(t)+\frac{E}{V_2}y(t),\\
\frac{dy}{dt}(t) &= \frac{E}{V_1}x(t)-\left(\frac{E}{V_2}+\frac{1}{T_2}\right)y(t),\\
\frac{dz}{dt}(t) &= f_3\left(\frac{x(t-T)}{V_1}\right)-\frac{0.1z(t)}{V_3}f_2\left(\frac{y(t)}{V_2}\right)+(L-p_0),
\end{aligned} \tag{7}$$

where $x(t)$ (mU) is the amount of insulin in the plasma, $y(t)$ (mU) is the amount of insulin in the interstitial fluid and $z(t)$ (mg) is the amount of glucose treated as occupying one compartment; $V_1(l), V_2(l), V_3(l)$ are the volumes (in liter) of the plasma, interstitial fluid and the glucose compartment respectively, with values $V_1 = 3$ l, $V_2 = 11$ l, $V_3 = 10$ l, and $T_1 = 3$ min, $T_2 = 100$ min, are given parameters, L (mg min^{-1}) is the rate of glucose delivery from the environment ($L = 100$ (mg min^{-1}) paper, p.28, corresponds to the normal delivery of glucose in 150 g day^{-1}), $p_0 = 72$ is a constant, $E = 0.2$ min^{-1}, T is the delay in glucose production.

The form of the functions $f_1 - f_3$ is (note that there is a small typo in the paper's f_2 formula in Eq. (9) which was easy to recover from the preceding calculations)

$$\begin{aligned}
f_1(c_z) &= \frac{210}{1+\exp(a+bc_z)}, \quad a = 5.21, \quad b = -0.03,\\
f_2(c_y) &= \frac{9}{1+\exp(7.76-1.772\ln(c_y(1+V_2/(ET_2))))}+0.4,\\
f_3(c_x) &= \frac{160}{1+\exp(0.29c_x-7.5)},
\end{aligned} \tag{8}$$

where c_x is the plasma concentration of insulin, $c_x = \frac{x}{V_1}$ (μU ml^{-1}), c_y is the remote compartment insulin concentration, $c_y = \frac{y}{V_2}$ (μU ml^{-1}), and c_z is the glucose concentration $c_z = \frac{0.1z}{V_3}$ (mg dl^{-1}). The authors mention that the form of the functions $f_1 - f_3$ is similar to that proposed in Sturis, Polonsky, Mosekilde, Van Cauter (1991), but with different parameter values which they obtained by least squares fitting to published data. Initial conditions used in the numerical simulations are, paper, p. 28, $c_x(\theta) = 30,\ -T \le \theta \le 0,\ c_y(0) = 20,\ c_z(0) = 120.$

Numerical results were obtained for a number of L and T values. Stability analysis is also presented in the paper for a linearized system of DDEs. The claim is (paper, p. 31) that for very small and very large L values the steady state solution is stable and ultradian oscillations do not arise, but for moderate L values, the steady state solutions become unstable and periodic oscillations of insulin and glucose occur.

Figures 1, 2 for plasma insulin and glucose concentrations correspond to Figure 6 of the chapter.

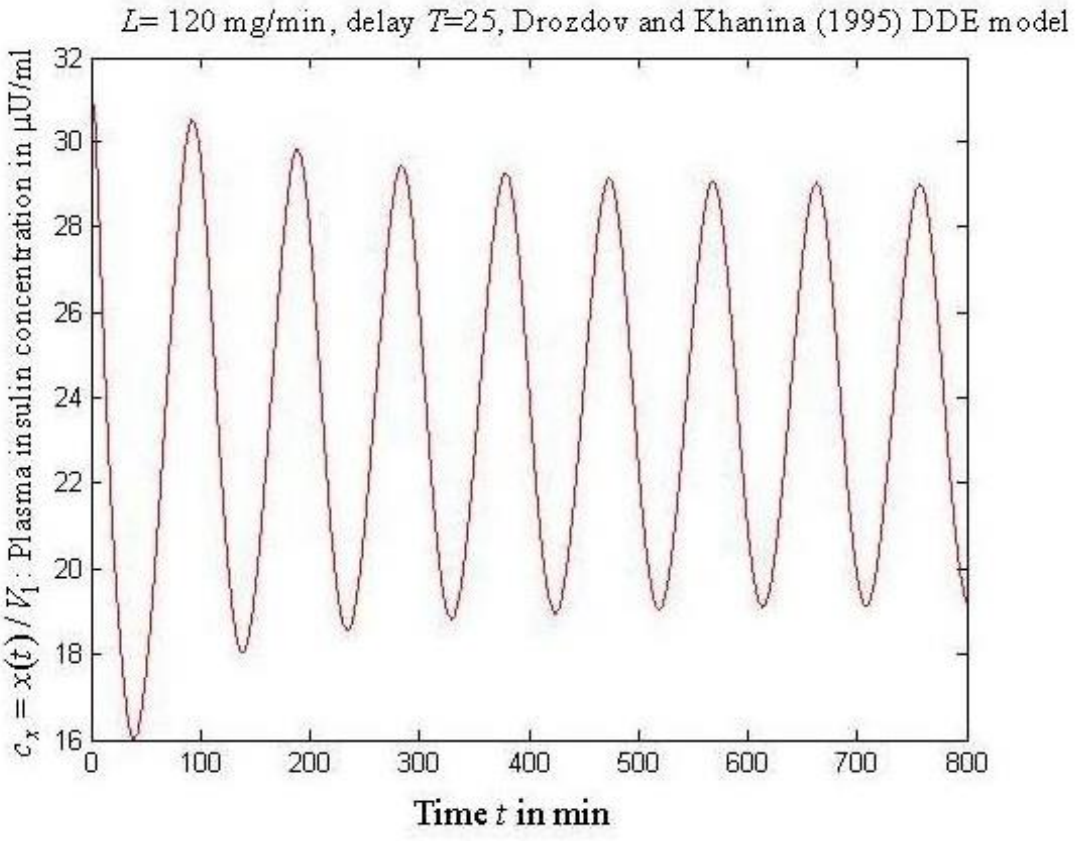

Figure 1. Plasma insulin concentration in μU ml^{-1}, Drozdov and Khanina (1995) DDE model

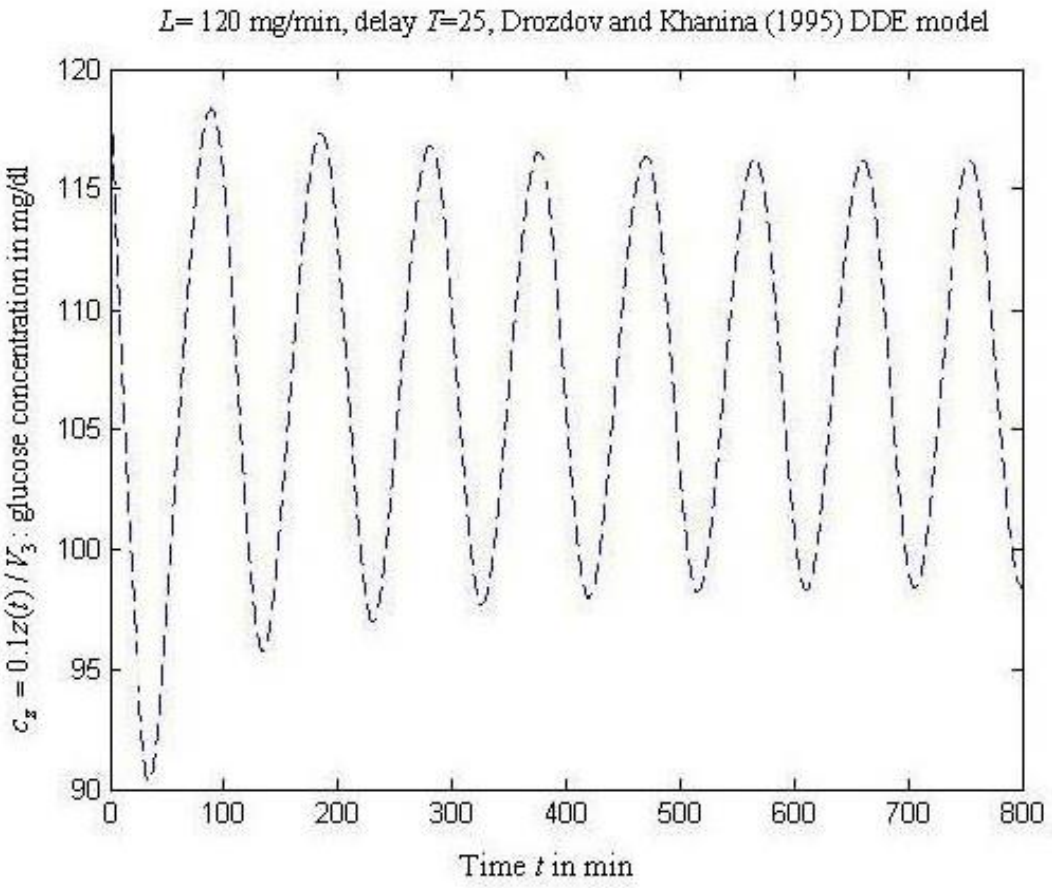

Figure 2. Glucose concentration in mg dl^{-1}, Drozdov and Khanina (1995) DDE model

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Biographical Sketches

Dr. Athena Makroglou, was born in Karlovassi, Samos island, Greece. She obtained a B.Sc. degree in Mathematics from the University of Athens, Athens, Greece in 1972, an M.Sc. degree in Numerical Analysis and Computing, and a Ph.D. degree on the Numerical solution of Volterra Integro-Differential Equations from the University of Manchester, Manchester, UK, in 1974 and 1977 respectively.

Her work experience includes work as a faculty or visiting member at Universities in Greece, USA, and UK, and work as an Analyst/Programmer at the Greek Ministry of Agriculture, Athens, Greece. Her current post is that of a senior lecturer at the Department of Mathematics of the University of Portsmouth, UK.

Her publications are in the area of numerical solution of integral equations/integro-differential equations and their applications in Actuarial Science, Biology and Medicine which is also her current research area.

Two recent publications of hers are:

A. Makroglou, J. Li, Y. Kuang (2006), Mathematical models and software tools for the glucose-insulin regulatory system and diabetes: an overview, Applied Numerical Mathematics, 56, 559-573.

A. Makroglou, D. Konstantinides (2006), Numerical solution of a system of two first order Volterra integro-differential equations arising in ultimate ruin theory, HERMIS Journal, 7, 123-143.

She has participated to many International and National Conferences, with some of the talks invited, and has co-organized special sessions and mini-symposia at several international professional meetings and in addition two Workshops (IWANASP06, Aegean University, Karlovassi, Samos, Greece, 6-8 September 2006, and DIEBM2010, http://www.icsd.aegean.gr/diebm2010, Aegean University, Karlovassi, Samos, Greece, 7-10 September 2010).

Dr. Makroglou is a member of SIAM (Society for Industrial and Applied Mathematics), AMS (American

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Iordanis Karaoustas was born in Komotini, Greece, in 1980. At the age of 16 he took part for the first time in the Pan-Hellenic Contest of Computing, and was one of the best 30 students of Greece. He obtained a B.Sc. degree in Mathematics from the Aristotle University of Thessaloniki, Greece in 2002, and a M.Sc. degree in Mathematical Sciences from the University of Portsmouth, UK in 2004. He is currently a part-time Ph.D. student at the University of Portsmouth, UK under the supervision of Dr Athena Makroglou. His area of research is on the numerical solution of Volterra integro-differential equations with applications to diabetes modelling. Furthermore he is a teacher of mathematics at the Secondary Education Level of Greece.
Iordanis Karaoustas is also a member of the Hellenic Mathematic Society, of Friends of C. Caratheodory association and of the Parents of Children with Learning Disabilities of Northern Greece association.
He has participated to two meetings with contributed talks:
I. Karaoustas and A. Makroglou, ODE methods for the numerical solution of Volterra integral equations, The Second International Workshop on Analysis and Numerical Approximation of Singular Problems , 6-8 September 2006, Samos, Greece.
A. Makroglou and I. Karaoustas, Numerical solution of some integro-differential equation models for diabetes, ECMTB 2008, European Conference on Mathematical and Theoretical Biology, Edinburgh, 29th June - 4th July, 2008, Minisymposium: Modelling the glucose/insulin/energy system.
The talks were presented by Iordanis Karaoustas.

Dr. Jiaxu Li was born in Tongliao, Inner Mongolia, China. He obtained his B.Sc. degree from Jilin University in 1982, M.Sc. degree from Dalian University of Technology in 1988, Master in Computer Science degree in 1996, and Ph.D. degree in Applied Mathematics in 2004 from Arizona State University under Dr. Yang Kuang's guidance.
He joined the faculty of University of Louisville as an assistant professor in 2007 after working in industry as a Senior Staff Engineer for eleven years. He was a Lecturer at Heilongjiang University, China, from 1988 to 1991. With his colleagues, Li has proposed and studied several models in the relevant area, e.g.,
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