A review on delay differential equation models in diabetes modeling, II: the insulin therapies and the intracellular activities of β-cells case

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[1]Work is partially supported by NIH Grant R01-DE019243, P30ES01443 and DOE Grant DE-EM0000197.

[2]Work is partially supported by the grants DMS-0436341 and DMS-0920744.

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Abstract

This is a sequel to the paper by Makroglou et al (2010) which gave a review of diabetes modeling in the form of delay differential equations associated with ultradian oscillations and the intravenous glucose tolerance test (IVGTT). This sequel includes a review of diabetes modeling in the form of delay differential equations associated with insulin therapies and models involving intracellular activities of β-cells. The statement of the models is accompanied with some computational results and brief summaries of theoretical results.

1. Introduction

Diabetes mellitus is a disease of the glucose-insulin regulatory system (see for example Fig. 1.1 in Makroglou, Li, Kuang [47] for a picture of the plasma glucose-insulin interaction loops). 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 (cf. Derouich, Boutayeb [25]). The disease is affecting hundreds millions of people worldwide (type 2 diabetes mellitus

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[2]Work is partially supported by the grants DMS-0436341 and DMS-0920744.

had an estimated incidence of 151 million in the year 2000, (cf. Nugent, Smith, Jones [55], p. 529).

Type 1 diabetes is considered to be the result of an immunological destruction of the insulin-producing β-cells of the pancreas (cf. Atkinson, Eisenbarth [1], p. 221). Type 2 diabetes is the result of resistance to the effects of insulin on glucose uptake, metabolism or storage (cf. Kahn, Flier [35], p. 473), due to excessive hepatic glucose production (cf. Burcelin, Knauf, Cani [19]) and defective β-cell function (cf. Lupi, Del Prato [45], p. 556). For more information about the pathogenesis of diabetes we refer for example to Atkinson, Eisenbarth [1], Jaïdane, Hober [34] (type 1 diabetes), Lupi, Del Prato [45], Virally et al [79] (type 2 diabetes). Treatment of type 1 diabetes is based on the administration of insulin of various types (cf. Owens, Zinman, Bolli [58]) in a number of ways. For information about treatment of type 2 diabetes we refer for example to Virally et al [79], p. 237, Raccah [65], Tibaldi [77].

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 to the review papers Parker, Doyle III, Peppas [61], Bellazi, Nucci, Cobelli [3], Mari [49], Makroglou, Li, Kuang [47], Boutayeb, Chetouani [18], Pattaranit, van den Berg [62], Landersdorfer, Jusko [38], Kansal [36], 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 Baker, Paul, Will [2], Bellen, Zennaro [4], Shampine, Thompson [67], 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 [30], Cerasi, Fick, Rudemo [20], O'Connor, Landahl, Grodsky [56]). 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 et al [64], Mari, Ferrannini [50], Overgaard, et al [57].

In this paper 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. It is a sequel to the paper by Makroglou et al [48] and it contains models that involve (i) insulin therapies and (ii) intracellular activities of β-cells.

The organisation of the paper is as follows: Section 2 contains the description of the models and some computational results and brief summaries of theoretical results. 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 Shampine, Thompson [67] and 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, see for example Bocharov, Rihan [17] and the references therein.

Delayed effects often exist in the glucose-insulin regulatory system, for example, the insulin secretion stimulated by elevated glucose concentration level, hepatic glucose production (Li, Kuang, Mason [44], Simon, Brandenberger [69], Sturis et al [71]). 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 (ODE) (Bergman et al [7], Sturis et al [71]), and modeling in delay differential equations (DDE) by using explicit time delays in either discrete or distributed forms (Engelborghs et al [27], Li, Kuang, Mason [44], Li, Kuang [41], Li, Kuang [42], Li, Kuang, Li [43], Mosekilde et al [52], Palumbo, Panunzi, De Gaetano [59], Panunzi, Palumbo, De Gaetano [60]). Pattaranit and van den Berg (Pattaranit, van den Berg [62], Tarín et al [75]) classified that the delays in the compartment-split approach 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 (De Gaetano, Arino [24], Li, Kuang [41], Li, Kuang, Li [43], Mukhopadhyay, De Gaetano, Arino [54], Palumbo, Panunzi, De Gaetano [59]).

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.

Models falling into the first two categories have been the subject of the paper by Makroglou et al [48] whilst models falling in categories three and four will be described here.

Other DDE models include ones using control theory, see for example the review paper by Takahashi, Xiao, Hu [74].

The model in [71] and models in papers presenting extensions of it, like the models

in [44], [78], make use of certain functions $(f_1 - f_5)$ given below:

$$
\begin{aligned}
f_1(G) &= R_m/(1 + exp((C_1 - G/V_g)/a_1)), && (2.1)\\
f_2(G) &= U_b(1 - exp(-G/(C_2V_g))), && (2.2)\\
f_3(G) &= G/(C_3V_g), && (2.3)\\
f_4(I) &= U_0 + (U_m - U_0)/(1 + exp(-\beta \ln \frac{I(1/V_i + 1/(Et_i))}{C_4})), && (2.4)\\
f_5(I) &= R_g/(1 + exp(\hat{\alpha}(I/V_p - C_5))). && (2.5)
\end{aligned}
$$

$f_1(G)$: 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 [78].

The functions $f_1 - f_5$ are assumed to satisfy certain general assumptions by [41].

2.1. Insulin therapies related models

Insulin therapies including mainly multiple daily insulin injections and subcutaneous insulin infusion are available for diabetic patients with the role to keep their glucose-insulin regulatory system as close as possible to that of a healthy subject. In type 1 diabetics, the pancreatic β-cells do not secrete insulin. In type 2 diabetics, insulin secreted from the β-cells is not enough to help the body cells to utilize the glucose. This is mainly due to the dysfunction of the glucose-insulin regulatory system, (cf. Wang, Li, Kuang [80]). The glucose needs of a human are mainly obtained by meal ingestions. For a healthy subject, the increase of the glucose concentration in the plasma can trigger the pancreatic β-cells to secrete insulin in oscillatory modes. Therefore the task of insulin therapies is to mimic the oscillation modes of insulin secretion of the pancreatic β-cells. This oscillation can be considered as the oscillation forced by the periodic exogenous glucose inputs (Toli, Mosekilde, Sturis [78]). Such a forced oscillation has been modeled by Sturis et al [71], Toli, Mosekilde, Sturis [78] with an ordinary differential equation model, and by Wang, Li, Kuang [80], Wang, Li, Kuang [80] with a delay differential equation model.

In this section, we introduce the DDE models in Wang, Li, Kuang [80] and in Wang, Li, Kuang [81] that theoretically confirm the clinical insulin administration for type 1 diabetes, in which the oscillations entrained by exogenous meal ingestion (Toli, Mosekilde, Sturis [78]) are stimulated by a periodic function.

ODE models have been considered in Doran et al [26], Wilinska et al [82]. We refer to the review article by Takahashi, Xiao, Lewis [72] and erratum (Takahashi, Xiao, Lewis [73]), for more information.

An ODE model is also introduced in Li, Kuang [42] that models the long-acting insulin analogue injection with an auxiliary bound state mimicking the delayed dissolution in the injection depot. An equivalent DDE model is proposed in Li, Johnson [40]. These models were formulated in view of the molecular events in insulin analogues after subcutaneous injection. These models have been compared with the models proposed by Wilinska et al [82] in Li, Johnson [40]. The role of such kind

of models can be a piece in the algorithms for insulin delivery in artificial pancreas, which was discussed in detail by Hovorka et al [33].

Current information about different type of insulin and other therapies for diabetics, may be found for example in Mirbolooki et al [51]. More references for diabetes treatment have been given in the Introduction of this.

2.1.1. The model proposed by Wang, Li, Kuang (2007)

This is a two-delay DDE model for the simulation of the dynamics of insulin therapies for type 1 diabetic patients. The model equations are, Wang, Li, Kuang [80], p. 20,

$$\begin{aligned} \frac{dG}{dt}(t) &= G_{in}(t) - f_2(G(t)) - f_3(G(t))f_4 I(t-\tau_3) + f_5(I(t-\tau_2)), \\ \frac{dI}{dt}(t) &= I_{in} - d_i I(t), \end{aligned} \tag{2.6}$$

$$I(0) > 0, G(0) > 0, I(t) \equiv I(0), t \in [-\max[\tau_2, \tau_3], 0], \tau_2, \tau_3 > 0.$$

$I_{in}(t)$ represents the exogenous insulin infusion rate profile and $G_{in}(t)$ is the glucose intake rate function. The form of the functions $f_1 - f_5$ is as in 2.1-2.5. The form of $I_{in}(t)$ is given in Wang, Li, Kuang [80], p. 26, for two choices of insulin, lispro and regular insulin, see also Geraghty [28].

Numerical simulations and theoretical results are presented in the paper. The theoretical results concern the existence of a positive bounded ω-periodic solution (G^*, I^*) to 2.6 (i.e. such that $G^*(t+\omega) = G^*(t), I^*(t+\omega) = I^*(t)$), which (Wang, Li, Kuang [80], Theorem 3.5) is globally asymptotically stable and unique.

Figures 2.1, 2.2 show the glucose and insulin concentrations after injections of lispro insulin, with $\tau_2 = 15$ min, $\tau_3 = 5$ min, $d_i = 0.0076$ (min^{-1}) with $\omega = 240$ min over 24 hours (see also Geraghty [28]).

Figure 2.1: Glucose Concentration over 24 hours, Wang, Li, Kuang (2007) DDE model

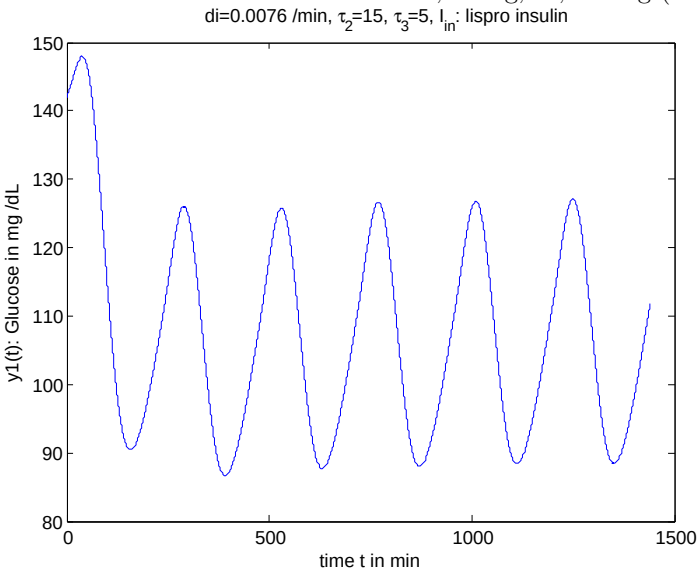
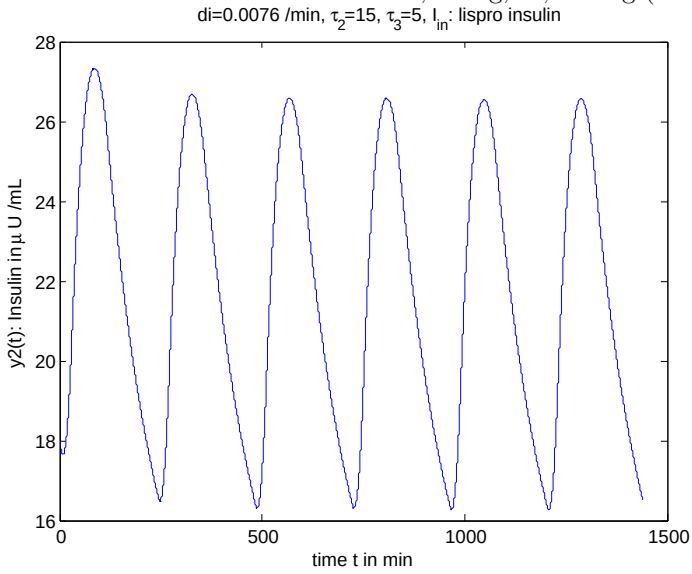


Figure 2.2: Insulin Concentration over 24 hours, Wang, Li, Kuang (2007) DDE model



Figures 2.3 and 2.4 show the glucose and insulin concentration after injections of regular insulin, with $\tau_2 = 15$ min, $\tau_3 = 5$ min, $d_i = 0.0107$ (min^{-1}) with $\omega = 480$ min over 32 hours.

Figure 2.3: Glucose Concentration over 32 hours, Wang, Li, Kuang (2007) DDE model

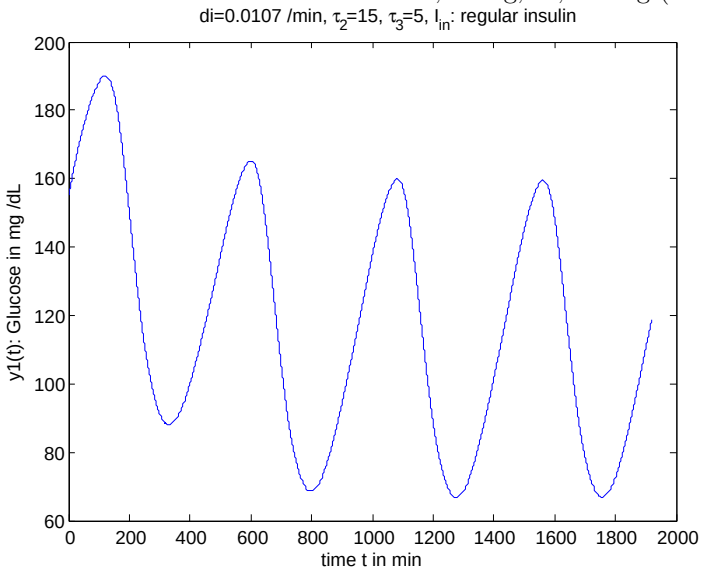
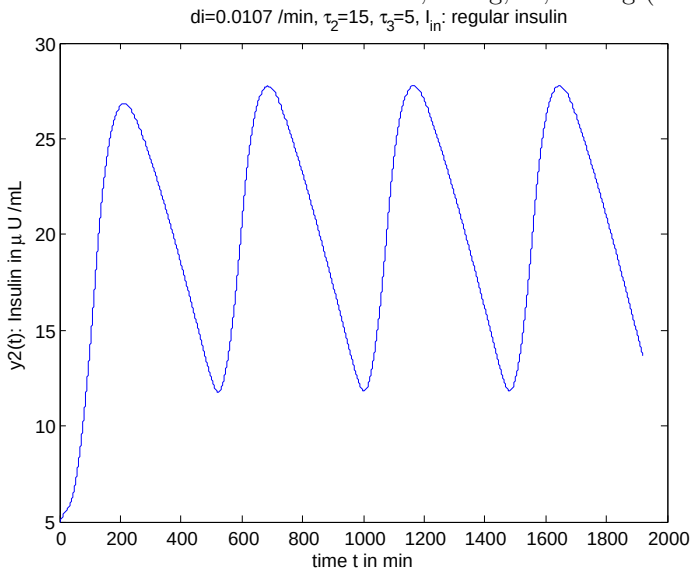


Figure 2.4: Insulin Concentration over 32 hours, Wang, Li, Kuang (2007) DDE model



2.1.2. The model proposed by Wang, Li and Kuang (2009)

This is a single-delay DDE model used for insulin therapies for both type 1 and type 2 diabetes mellitus and the insulin degradation rate assumes Michaelis-Menten

kinetics. The model equations are (Wang, Li, Kuang [81], p. 23)

$$\begin{aligned} \frac{dG}{dt}(t) &= G_{in}(t) - f_2(G(t)) - f_3(G(t))f_4(I(t)) + f_5(I(t)), \\ \frac{dI}{dt}(t) &= \alpha I_{in}(t) + bf_1(G(t-\tau_1)) - \frac{d_1 I(t)}{d_2 + I(t))}. \end{aligned} \tag{2.7}$$

$$I(0) > 0, G(0) > 0, G(t) \equiv G(0), t \in [-\tau_1, 0], \tau_1 > 0, \alpha > 0, \beta \in [0, 1].$$

For type 1 diabetes, $b = 0$ (no insulin is secreted from the pancreas). For type 2 diabetes, $0 < b \leq 1$.

The functions $f_1 - f_5$ are as in 2.1-2.5.

$$I_{in}(t) = I_{inGlargine}(t) + I_{inLispro}(t).$$

The forms of $I_{inGlargine}(t), I_{inLispro}(t)$ and $G_{in}(t)$ are given in Wang, Li, Kuang [81], p. 29.

Simulations and theoretical results are presented. The authors prove that the solution of 2.7 is positive and bounded from above and also uniformly persistent. They also prove existence of a positive periodic solution which is (Wang, Li, Kuang [81], Theorem 2.5) locally asymptotically stable under certain conditions.

For parameter values see Table 2, p. 28 of Wang, Li, Kuang [81].

Figures 2.5, 2.6 correspond to the graphs of Figure 4 of the paper.

Figure 2.5: Glucose Concentration, Wang, Li, Kuang (2009) DDE model

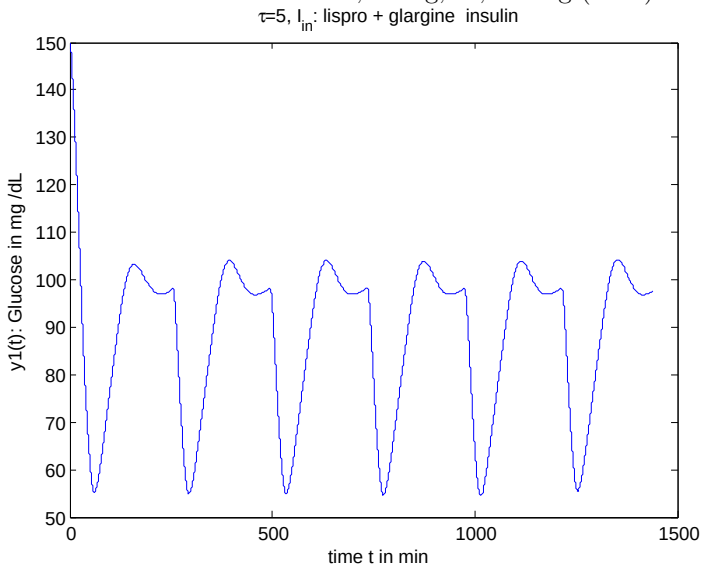
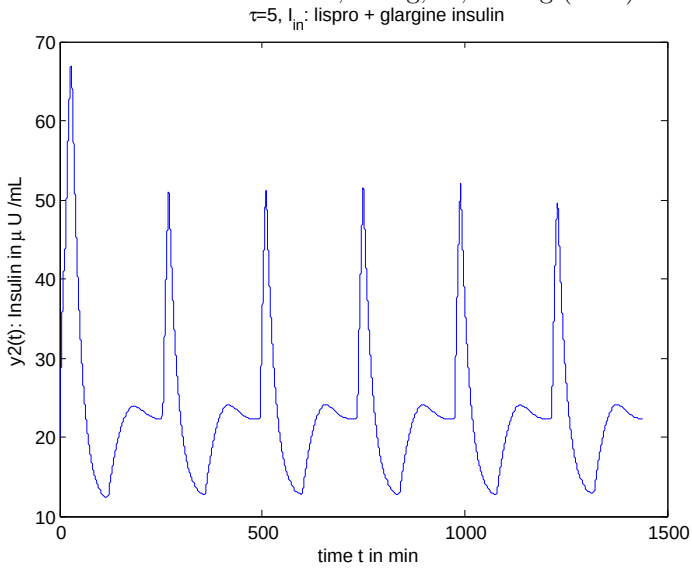


Figure 2.6: Insulin Concentration, Wang, Li, Kuang (2009) DDE model



2.1.3. A systemic model of pharmacokinetical process of long-acting insulin analogous

To model the delayed effects in processes of chemical reactions, auxiliary states are often added in ODE models. For example, the minimal model (Bergman [6], Bergman, Cobelli [8], Bergman et al [7]), ultradian oscillation models (Sturis et al [71], Toli, Mosekilde, Sturis [78]), and pharmacokinetical models of long-acting insulin analogues (Li, Kuang [42], Mosekilde et al [52], Tarín et al [75]). Such auxiliary states can be replaced by explicit time delays (De Gaetano, Arino [24], Li, Kuang, Li [43], Bennett, Gourley [5], Li, Johnson [40], Li, Kuang [41], Li, Kuang, Mason [44], Mukhopadhyay, De Gaetano, Arino [54], Palumbo, Panunzi, De Gaetano [59] and also Pattaranit, van den Berg [62] and Landersdorfer, Jusko [38]).

To mimic the delayed process of the absorption by adding the zinc ions in long-acting insulin analogues, for example, Glargine and Ultralante, an imaginary state B was added in modeling (Li, Kuang [42], Mosekilde et al [52], Tarín et al [75]). The most recent model is given by Li, Kuang [42] as follows

$$\begin{cases} B'(t) = -kB(t)\dfrac{C_{max}}{1+H(t)} \\ H'(t) = -p(H(t) - qD^3(t)) + kB(t)\dfrac{C_{max}}{1+H(t)} \\ D'(t) = p(H(t) - qD^3(t)) - \dfrac{bD(t)}{1+I(t)} \\ I'(t) = \dfrac{rbD(t)}{1+I(t)} - d_iI(t) \end{cases} \tag{2.8}$$

with initial condition $B(0) = B_0 > 0, H(0) = 0, D(0) = 0$, and $I(0) = I_0 \geq 0$, where $B(t)$ (U/ml) is the concentration the insulin analogue in hexameric form at the imaginary bound state, $H(t)$ (U/ml) is the concentration of insulin analogue in hexameric form other than the auxiliary state, $D(t)$ (U/ml) is the concentration of the dimers, and $I(t)$ (U/ml) for plasma insulin concentration at time $t \geq 0$. Constant C_{max} in the term $kB(t)C_{max}/(1 + H(t))$ is the maximum transformation capacity from auxiliary state B to hexameric state H (Mosekilde et al [52], Tarín et al [75]), where constant k (min^{-1}) is the absorption rate. For other rate constants, we refer to Li, Kuang [42]. Li, Johnson [40] substituted the auxiliary state B in the model (2.8) by an explicit delay τ for the delayed process and proposed a DDE model

$$\begin{cases} H'(t) = -p(H(t) - qD^3(t)) \\ D'(t) = p(H(t-\tau) - qD^3(t)) - \dfrac{bD(t)}{1+I(t)} \\ I'(t) = \dfrac{rbD(t)}{1+I(t)} - d_iI(t) \end{cases} \tag{2.9}$$

Using the same approach as in the proof of Theorem 4.1 in Li, Kuang [42], we can prove that the unique steady state $(0, 0, 0)$ of the model (2.9) is globally asymptotically

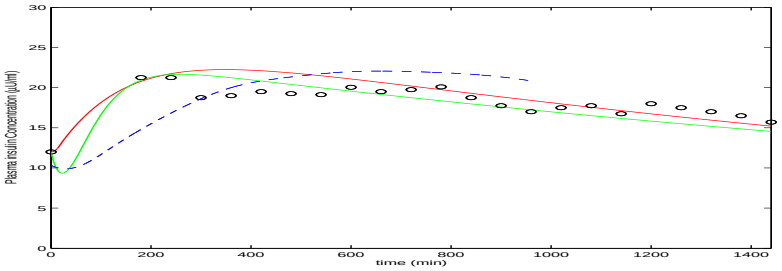


Figure 2.7: Simulation result of the plasma insulin concentration by the model (2.8) (lower/green solid curve), the model (2.9) (upper/red solid curve) ($p = 0.5$, $q = 3.04$, $r = 0.2143$, $c = 15$, $b = 0.025$, $k = 2.35 \times 10^{-5}$ and $d_i = 0.0215$), and the model by Tarín et al [75] (dotted curve) with experimental data (circle $\circ$) given by Lepore et al [39].

stable independent of the delay. Figure 2.7 shows the profiles generated by the models (2.8), (2.9), and the model in Tarín et al [75] for a comparison.

2.2. Models taking intracellular activity of β-cells into account

Insulin secreting β-cells located within the pancreatic islets of Langerhans are excitable cells that produce regular bursts of action potentials when stimulated by glucose (Bertram, Sherman [14]). The islets of Langerhans are roughly spherical structures of radius 50-250 μm in which the β-cells and other secretory cells are densely packed. Within the pancreas there are on the order of 10^6 islets and within each islet there exist $10^3 - 10^4$ β-cells and 100-200 secretory cells of other types (Bertram, Pernarowski [10], p. 1722).

There are many experimental and theoretical studies for the pancreatic β-cell and its association to insulin secretion. The consensus model for glucose stimulated insulin secretion (GSIS) from pancreatic β-cells, can be outlined as follows (Bertram, Sherman, Satin [15]):

• Glucose enters the cell through the GLUT2 glucose transporters.

• It is metabolized to increase the ATP/ADP ratio, where (Bertram et al [13], p. 3074), ATP means the adenosine triphosphate and ADP the adenosine disphosphate.

• Increased ATP/ADP ratio closes the ATP-sensitive K^+ K(ATP) channels.

• 'Closed K(ATP) channels' depolarizes the membrane, opens L-type Ca^{2+} channels which is followed by an influx of Ca^{2+}.

• Increase in the cytosolic Ca^{2+} concentration results in exocytosis of insulin granules.

The exocytosis of insulin containing granules is believed to include (Chen, Wang, Sherman [22]) a cascade of steps (granule docking, priming, Ca^{2+}-triggered granule

fusion and insulin release). Although many of the molecules have been identified (SNARE, Rab, Munc), the detailed kinetic mechanism of the exocytosis cascade, is still not well understood.

Most of the mathematical models introduced are in the form of systems of ODEs, see for example the didactic encyclopaedia paper by Sherman, Bertram [68] for the description for three examples of such models, one of which is the Chay-Keizer (Chay, Keizer [21]) model, together with its bibliographical evolution over 20 years. We also refer to the recent papers Bertram et al [11], Bertram, Sherman, Satin [15], Bertram [12], Zhang et al [83], Chen, Wang, Sherman [22], Bertram, Arceo II [9] and to the invited review paper by Pedersen [63], and the references therein for more recent theories and bibliography.

To our knowledge there are not many mathematical models taking into account β-cell activity in the form of DDEs. In next section a short presentation of three of them is given, namely, the models proposed by Morris, O'Reilly, Streja [53]), Sarika et al [66], and by Bertuzzi, Salinari, Mingrone [16].

2.2.1. The model proposed by Morris, O'Reilly and Streja (2004)

This is a single-delay DDE model which the authors present as an extension of the BMM (Bergman minimal model) taking also into account the bursting activity of the β-cells.

The first 3 model equations are (Morris, O'Reilly, Streja [53], p. 784) are

$$\begin{aligned} \frac{dG}{dt}(t) &= -s_1(G(t)-G_b) - X(t)G(t) + R_{ext}, \\ \frac{dX}{dt}(t) &= p_3(I_p(t)-I_b) - p_2X(t), \\ \frac{dI_p}{dt}(t) &= \gamma v_{exo}(G(t-\tau)) - n(I_p(t)-I_b). \end{aligned} \tag{2.10}$$

The 'exocytosis rate' $v_{exo}(G)$ is determined by an additional set of equations (not given in the paper). $G(t)$ is the plasma glucose concentration, $X(t)$ is the insulin-dependent fractional transfer rate, $I_p(t)$ is the plasma insulin concentration, G_b and I_b are basal glucose and insulin concentrations.

The paper contains also a good description of the 'mechanisms that link glucose metabolism to changes in the electrical activity of β-cells that induce insulin secretion', (Morris, O'Reilly, Streja [53], section II), with reference to Thévenod [76].

No simulations were done for this model, due to difficulty in obtaining full details of the model.

2.2.2. The model proposed by Sarika et al (2008)

It is a two-delay DDE model describing the dynamics of the glucose-insulin feedback system which involves an equation for the number of β-cells. The model equa-

tions are, (Sarika et al [66], p. 80),

$$\begin{aligned}
\frac{dx}{dt}(t) &= z(t-\tau_g)[r_1 y(t-\tau_g) - r_2 x + c_1], \\
\frac{dy}{dt}(t) &= \frac{R_3 N}{z} - R_4 x(t-\tau_i) + C_2 + w, \\
\frac{dz}{dt}(t) &= R_5(y-\hat{y})(T-z) + R_6 z(T-z) - R_7 z, \\
\frac{dw}{dt}(t) &= -aw + aw^2,
\end{aligned} \tag{2.11}$$

where $x(t), y(t)$ are the insulin and glucose concentrations above their basal levels respectively, $w(t)$ is the gastrointestinal absorption term, $\hat{y}$ is the glucose fasting level above the basal level, $z(t)$ is the number of β-cells in the proliferative phase, N is the normal number of β-cells, T is the total number of dividing and non-dividing β-cells that is assumed to be constant.

The paper is concerned with proofs of theoretical results and numerical simulations; in addition a review of previous models is included.

The authors note that the last equation of the model can be solved in $w(t)$, and they find that $w(t) \to 0$ as $t \to \infty$. With $w(t) = 0$ the above DDE system reduces to the following 3 equations one.

$$\begin{aligned}
\frac{dx}{dt}(t) &= z(t-\tau_g)[r_1 y(t-\tau_g) - r_2 x(t) + c_1], \\
\frac{dy}{dt}(t) &= \frac{R_3 N}{z(t)} - R_4 x(t-\tau_i) + C_2, \\
\frac{dz}{dt}(t) &= R_5(y-\hat{y})(T-z(t)) + R_6 z(t)(T-z(t)) - R_7 z(t),
\end{aligned} \tag{2.12}$$

The theoretical results concern existence and uniqueness of the steady state solution of 2.12 provided $R_7 - R_6 T > 0$ (Sarika et al [66], Lemma 1, p. 80). Considering a linearized version of the system 2.12 the authors arrive at Theorem 3 (Sarika et al [66], p. 83) which states that under certain conditions a Hopf bifurcation occurs for a positive composite delay $\tau = \tau_i + \tau_g \in [0, \tau_0)$, where $\tau_0 = \min_{1 \le k \le 3, j \ge 1}(\tau_k^{(j)}, \tau_k^{(j)} > 0)$ and $\tau_k^{(j)}$ is an expression that involves coefficients of the characteristic equation and its roots.

The following two graphs (2.8, 2.9) use parameter values as given in Fig. 2, p. 83 of the paper, starting values the steady state ones perturbed by 1, $\tau_g = 2.0, \tau_i = 0.4$ (paper p. 85) to compute glucose and insulin concentrations above basal levels. (Compare with Fig. 3 of the paper, but for different initial values).

Figure 2.8: Plasma insulin concentration, Sarika et al (2008) DDE model

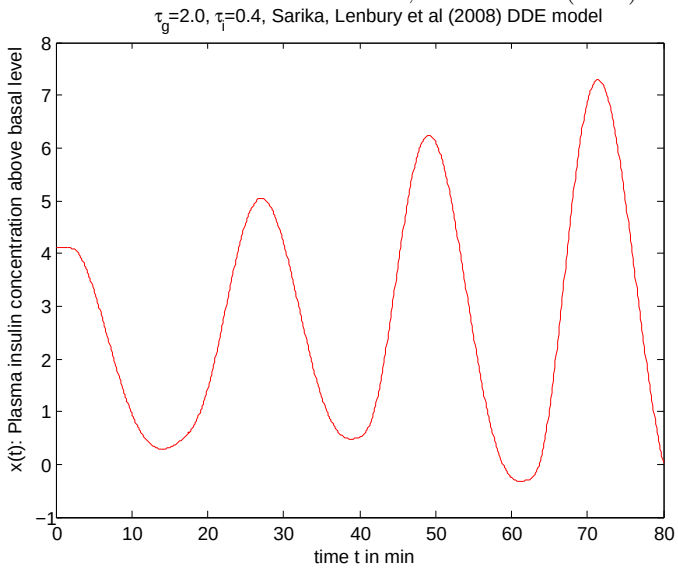
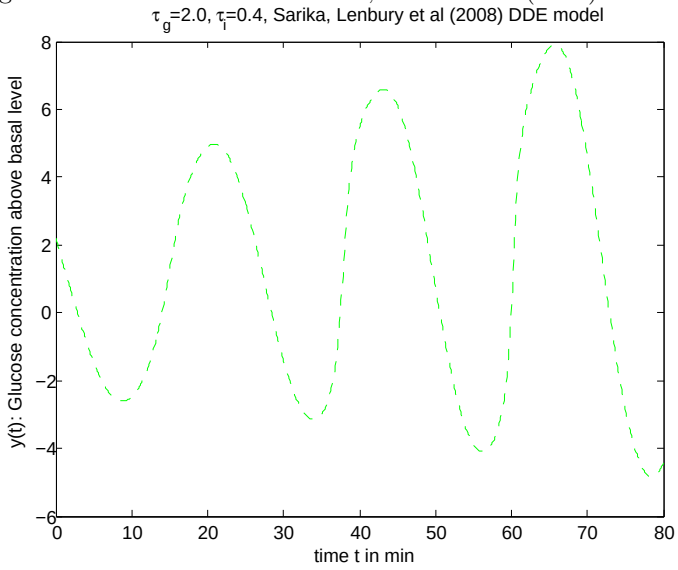


Figure 2.9: Glucose concentration, Sarika et al (2008) DDE model



2.2.3. The model proposed by Bertuzzi, Salinari and Mingrone (2007)

The authors proposed a mathematical model that represents the dynamics of intracellular insulin granules in β-cells. It focuses on the dynamics of formation, translocation to cell membrane, and exocytosis of insulin granules in β-cells (Bertuzzi, Salinari, Mingrone [16], p. E396).

The model equations are (Bertuzzi, Salinari, Mingrone [16], p. E398),

$$\begin{aligned}
\frac{dI}{dt}(t) &= -kI(t)V(t) - \alpha_I I(t) + b_I \\
\frac{dV}{dt}(t) &= -kI(t)V(t) - \alpha_V V(t) + b_V + \sigma F(t-\tau_V) \\
\frac{dR}{dt}(t) &= kI(t)V(t) - \gamma(t)R(t) \\
\frac{dD}{dt}(t) &= \gamma(t)R(t) - k_1^+[C_T - D_{IR}(t)]D(t) + k_1^- D_{IR}(t) \\
\frac{dD_{IR}}{dt}(t) &= k_1^+[C_T - D_{IR}(t)]D(t) - k_1^- D_{IR}(t) - \rho(t)D_{IR}(t) \\
\frac{dF}{dt}(t) &= \rho(t)D_{IR}(t) - \sigma F(t),
\end{aligned} \tag{2.13}$$

where $I(t)$ is the pool of 'free' (i.e. not yet segregated into granule membranes) proinsulin aggregates, $V(t)$ is the pool of available free granule membrane material not yet enclosing proinsulin, at time t, $R(t)$ is the number of insulin granules in the reserve pool at time t, $D(t)$ is the pool of docked and primed granules, $D_{IR}(t)$ is the pool of immediately releasable granules, and $F(t)$ is the number of granules that are fused with cell membranes.

The above model is complemented with the following equations (Bertuzzi, Salinari, Mingrone [16], p. E399, E400, E407) that 'relate the glucose stimulus to the quantities that govern the machinery of granule trafficking'.

$$\begin{aligned}
\frac{d\gamma}{dt}(t) &= \eta\{-\gamma(t) + \gamma_b + \psi(t) + h_\gamma[G(t-\tau_G)]\} \\
\frac{d\rho}{dt}(t) &= \zeta\{-\rho(t) + \rho_b + h_\rho[\gamma(t)]\}
\end{aligned} \tag{2.14}$$

$$\tag{2.15}$$

and

$$ISR(t) = I_0 \sigma F(t) f(G(t-\tau_G)) N_c N_i,$$

$$h_\gamma(G) = \begin{cases} 0 & \text{if } G \le G^* \\ \frac{\hat{h}(G-G^*)}{\hat{G}-G^*} & \text{if } G^* < G \le \hat{G} \\ \hat{h} & \text{if } G > \hat{G} \end{cases}$$

$$h_\rho(\gamma) = \begin{cases} 0 & \text{if } \gamma < \gamma_b \\ k_\rho(\gamma - \gamma_b) & \text{if } \gamma \ge \gamma_b \end{cases}$$

$$f(G) = \begin{cases} f_b & \text{if } G < G^* \\ f_b + (1-f_b)\frac{G-G*}{K_f+G-G^*} & \text{if } G \ge G^* \end{cases}$$

where ψ is an oscillatory forcing function that represents the events inducing [ATP] oscillations, ISR is the insulin secretion rate, τ_G is the time delay required by glucose metabolism, G denotes glucose concentration assumed in the range $(G^*, \hat{G})$, N_c is the average number of β-cells per islet, N_i the number of islets, N is the total number of β-cells, $f(t) = f[G(t - \tau_G)]$ is a fraction of the total cell population that responds to glucose. The meaning of all variables and parameters is given in the paper's glossary (Bertuzzi, Salinari, Mingrone [16], p. E396-E397). Many computational results (graphs) are presented in the paper.

The following two graphs use parameter values as given in Fig. 5 and Fig. 3, p. E403, E402 of the paper respectively, and starting values as given in p. E401 (baseline values); The first one shows the graphs of $D(t)/50$ and $D_{IR}(t)$, and the second one the graph of $ISR(t)$ in $\mu g/min$, for $0 \leq t \leq 60$ when G varies from 1 to 16.7 mmol/l. $\psi(t)$ was taken equal to zero. They are in agreement with the graphs of Fig. 5A, 5B, p. E403 of the paper (Bertuzzi, Salinari, Mingrone [16]).

Figure 2.10: D(t) and $D_{IR}(t)$, Bertuzzi et al (2007) DDE model

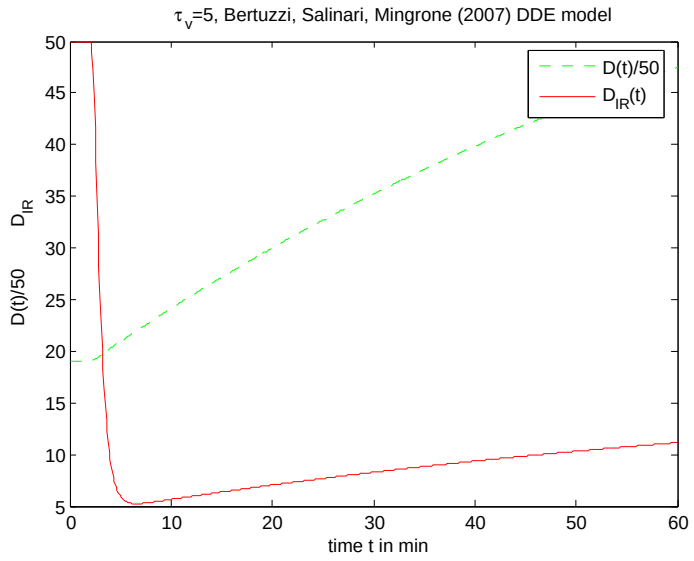
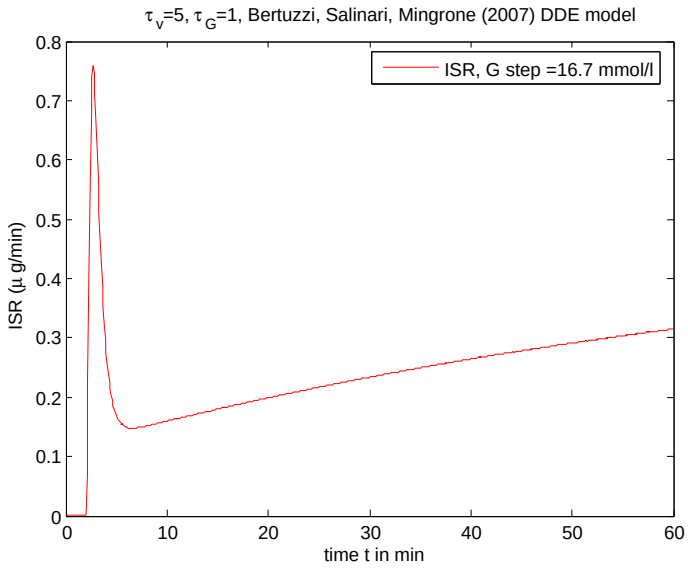


Figure 2.11: ISR (t): insulin secretion rate, Bertuzzi et al (2007) DDE model



3. Concluding remarks

The time delays exist in the glucose-insulin regulatory system and other interactions of the real world including life sciences and control theory. It is natural to include explicitly the delays in mathematical modeling. Although the delayed effects can be simulated by introducing the auxiliary states in ordinary differential equation systems, as we have seen earlier, it is an approximation by using different kernels and also the number of equations in the system is larger. Modeling by delay differential equations can not only more accurately simulate the real life problems, but also reduce the number of equations. Comparing to ODE models, it is more challenging to analyze DDE models. However, a handful of existing books documents the theory of functional differential equations and their applications in biology and engineering. Interested readers can refer to Hale [31], Cushing [23], MacDonald [46], Gopalsamy [29], Hale, Verduyn Lunel [32], Kuang [37], and Smith [70].

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