A new approach to diabetic control – human glucose metabolism using interval arithmetic

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Abstract: The paper presents parameter identification for the model of human glucose metabolism on the basis of interval arithmetic. The model parameters to be identified are uncertain and represented by intervals. The process of identification considers uncertain parameters using the RDM method (Relative Distance Measure arithmetic), which uses a new representation of intervals. General characteristics of the RDM method are described and the outline of decision analysis is presented, including its orientation and model for the inflow of glucose into the blood. The paper determines the influence of each uncertain parameter on the variation of the overall biomedical model output and shows the applicability of the RDM method.

1. Introduction

Decision-making under uncertainty is of perennial interest because of its direct relevance to modeling of real-world processes including finance (Bandemer, 2005), economy (Machina, 1987), mechanics and medicine (Karni, 2009). Solving problems with uncertain variables or parameters requires appropriate, subtle and multi-dimensional methods. Among these methods the interval arithmetic can be mentioned. It was introduced by Moore (1966) and has been developed by many scientists till now. The main focus in the interval arithmetic is on the simplest way to calculate upper and lower endpoints for the range of values of a function in one or more variables. One of the new representations of interval arithmetic is the RDM method introduced by Piegat and Landowski (2013*a*), described in next section and applied as a method for the improvement of parameter identification for biomedical models. Modeling of biomedical systems turns out to be a non-trivial problem since the models are usually rather complex, nonlinear and characterized by many parameters which have to be identified for each single patient. Diabetes, which has been of interest in recent years, is a good example of a complex biomedical problem considered in the paper. The diabetics have many difficulties starting from regular medication with injections up to being imperiled by bad risk of heart attacks. In order to improve therapy and to develop optimal medication for diabetes, the main characteristics of human glucose

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metabolism need to be studied. The first step of this analysis is to find appropriate mathematical models and make simulations. There are some practical models for the human glucose metabolism, which are described in many papers and books. Among them the models of Cobelli et al. (1982); Glockle (1983); Puckett (1992) can be mentioned. Some scientists have tried to make simulations of these models using different methods, for example fuzzy arithmetic or transformation method (Hanss and Nehls, 2000). However, considering the fact that biomedical models are exceedingly subjected to uncertainties, the new methods still have to be tested to facilitate the process of analysis and assist treatment. These methods have to take into account that the parameters of the models exhibit a large range of imprecision and variability. What affects the parameters is for example the individual physique of the patient, as well as the duration of the disease.

What is more, some of the initial values of the models, such as the nutritional content of the ingested food, can only be quantified with a high degree of uncertainty. To overcome these limitations the RDM-method is applied to the human glucose metabolism problem.

2. Interval arithmetic – the RDM-method

In many decision problems some variables are uncertain and the only knowledge is the maximum and minimum possible value of the variable. On the basis of this information, interval arithmetic is often used. Unfortunately, the arithmetic on intervals introduced by R.E. Moore has many faults. Some of them concern the width effect problem or the dependency problem, which is described in many papers (Dymova, 2011; Piegat and Tomaszewska, 2013). To eliminate these defects and use intervals in complex mathematical equations, a new approach to interval arithmetic was introduced. It is called Relative Distance Measure method, but its abbreviation, the RDM-method, is used more often. The method gives a new representation of an interval, where an information granule given as a variable x can be described with the formula (Piegat and Landowski, 2013*b*):

$$x \in [\underline{x}, \overline{x}] : x = \underline{x} + \alpha_x (\overline{x} - \underline{x}), \qquad \alpha_x \in [0, 1] \tag{1}$$

where $\underline{x}$ is the lower limit and $\overline{x}$ is the upper limit of the interval and α_x is the relative distance measure.

Formula (1) gives the possibility to make different operations on many intervals easily. To illustrate it, let us consider the addition and subtraction of two intervals:

$$[\underline{a}, \overline{a}] + [\underline{b}, \overline{b}] = [\underline{x}, \overline{x}]$$

$$\underline{a} + \alpha_a (\overline{a} - \underline{a}) + \underline{b} + \alpha_b (\overline{b} - \underline{b}) = x, \quad \alpha_a \in [0, 1] \quad \alpha_b \in [0, 1] \tag{2}$$

$$[\underline{a}, \overline{a}] - [\underline{b}, \overline{b}] = [\underline{x}, \overline{x}]$$

$$\underline{a} + \alpha_a (\overline{a} - \underline{a}) - \underline{b} - \alpha_b (\overline{b} - \underline{b}) = x, \quad \alpha_a \in [0, 1] \quad \alpha_b \in [0, 1] \tag{3}$$

Depending on the values of variables α_a and α_b the resulting variable x assumes various values. It should be noted that the operations on the two intervals are 3-dimensional: the result depends on two variables α_a and α_b. Tab. 1 shows values of x for border values of RDM-variables α_a and α_b.

Tab. 1. The resulting values for formula (2) and (3) for border values of the RDM-variables.

α_a, α_b	0, 0	0, 1	1, 0	1, 1
addition	$(\underline{a}+\underline{b})$	$(\underline{a}+\overline{b})$	$(\overline{a}+\underline{b})$	$(\overline{a}+\overline{b})$
subtraction	$(\underline{a}-\underline{b})$	$(\underline{a}-\overline{b})$	$(\overline{a}-\underline{b})$	$(\overline{a}-\overline{b})$

The RDM- method can be used to all arithmetic operations and for more than two uncertain variables, but it makes the problem more multidimensional. It is worth mentioning that the RDM-method can also produce distributions of possibility and distributions of probability density, which can have a great meaning in the case of complex problems and can be used in probabilistic arithmetic (Piegat and Landowski, 2013*b*).

3. Model for the inflow of glucose into the blood

The problem described in this paper concerns human glucose metabolism. Cells inside the human body mostly need glucose for proper functioning. By metabolizing glucose, the body is technically able to supply the cells with the much-needed fuel. Glucose is usually derived from carbohydrates. Many food products which are rich in carbohydrates have high starch and sugar content. After meals, carbohydrate metabolism takes place in the digestive tract where carbohydrates are converted into glucose. Then glucose is absorbed in the blood and distributed by the bloodstream to all cells in the body. The disease that affects body's ability to use glucose is diabetes. Diabetes is classified into three types: Type 1, Type 2 and gestational diabetes (Dorner and Pinget, 1977). In this paper Type 1 is considered. Diabetics with Type 1 have an abnormal glucose tolerance and little or no insulin in their blood. The lack of insulin or insulin resistance directly causes high blood-glucose levels during fasting and after a meal (reduced glucose tolerance). High levels of glucose present in the blood over a sustained period of time end up damaging the blood vessels and causing other complications. The full model for the inflow of exogenic glucose into the blood consists of two submodels: one for the concentration of carbohydrates in the stomach and one for the concentration of carbohydrates in the intestine (Cobelli et al., 1982; Hanss and Nehls, 2000). Whereas the stomach is modeled as a system with concentrated parameters, the intestine is considered as a pipe with the coordinate z and is thus modeled as a system with distributed parameters. The paper focuses only on the model for the concentration of carbohydrates in the stomach.

The governing model equations for the concentration $c_c^S(t)$ of carbohydrates in the stomach of volume $V(t)$ are:

$$\frac{d}{dt}\left[c_c^S(t)\,V(t)\right] = -\alpha V c_c^S, \tag{4}$$

$$\frac{dV(t)}{dt} = -\alpha V + q^* = -q(t) + q^* \tag{5}$$

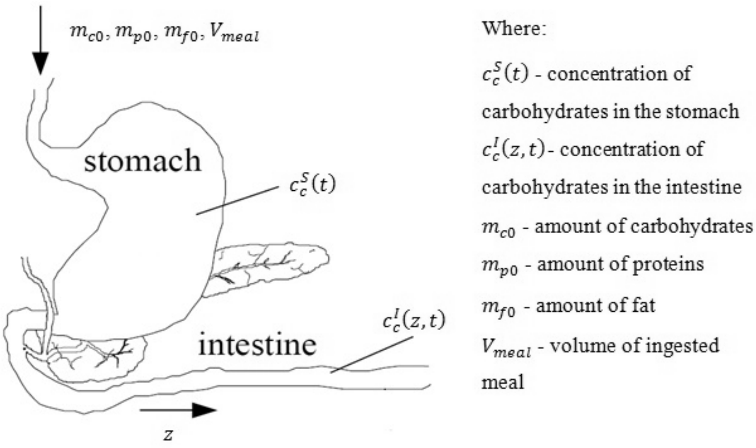

Fig. 1. The apparatus of digestion.

With the initial conditions:

$$c_c^S(0) = \frac{m_{c0}}{V(0)} \tag{6}$$

$$V(0) = V_{empty} + (1 + f_{sec})\, V_{meal} \tag{7}$$

and the parameters

$$\alpha = \frac{f_{gas} \ln 2}{V_{meal}\left[\theta_1 - \theta_2 \exp(-\tau k)\ \right]} \tag{8}$$

$$k = \frac{1}{V_{meal}} (\beta_c m_{c0} + \beta_p m_{p0} + \beta_f m_{f0}) \tag{9}$$

The parameter α denotes the evacuation rate of the stomach, which can individually be adopted by the patient-specific gastroparesis factor f_{gas} and k – the energy density of the ingested food.

To solve the model differential equations (4) and (5) a MATLAB tools was used. One of its most common solvers, *ode45*, which implements a version of the Runge-Kutta 4^{th} order algorithm was adapted.

4. Analysis of the uncertain model using the RDM-method

In order to analyze the model for the concentration $c_c^S(t)$ of carbohydrates in the stomach of volume $V(t)$ (4) and (5) some certain assumptions have to be specified. There are two uncertain parameters in the model: the gastroparesis factor f_{gas} and the amount of carbohydrates m_{c0}. The gastroparesis factor in the glucose model has a rather high degree of uncertainty, inasmuch as it depends on the patients' individual physique. Additionally, it is fairly difficult to determine the amount of carbohydrates in the ingested food precisely. For these reasons, the parameters are considered as uncertain and they are represented by RDM-method numbers, defined by:

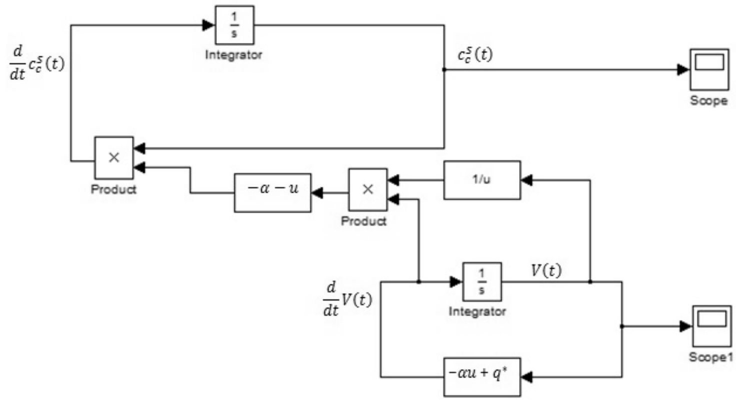

Fig. 2. Simulink's model for the concentration $c_c^S(t)$ of carbohydrates in a stomach volume $V(t)$.

$$f_{gas} = 0.6 + 0.1 \cdot \alpha_f,\ \alpha_f \in [0,1] \tag{10}$$

$$m_{c0} = 68 + 32 \cdot \alpha_c,\ \alpha_c \in [0,1] \tag{11}$$

Other parameters (Höfig, 1998): $\theta_1 = 0.1797$ min ml^{-1}$\tau = 0.2389$ ml kJ^{-1}, θ_2= 0.1670 min ml^{-1}V_{empty}= 50 ml, $\beta_c = 0.0167$ kJ mg^{-1}$f_{sec} = 1.0$, $\beta_p = 0.0167$ kJ mg^{-1}$q^* =$ 0.4861 ml min^{-1}, $\beta_f = 0.0377$ kJ mg^{-1}.

The food specific parameters m_{c0}, m_{f0} and m_{p0} can be determined by food labels, reference books or software. In this problem the nutritional content of carbohydrates, fat and proteins in a specific product are considered. Their values were estimated on the basis of product labels. Because the labels give the information about the amount of nutrients as a weight in grams, they had to be converted to volume: $m_{p0} = 18$ ml, $m_{f0} = 10$ ml, V_{meal}= 674 ml.

The uncertain biomedical model can be simulated by the use of simulink's model including uncertain parameters in a form of RDM-variables. The evacuation rate of the stomach (α) depends on these two uncertain parameters. Tab. 2 presents possible values of α for the minimum, medium and maximum values of RDM-variables.

Tab. 2. Possible values of α for different values of RDM-variables.

α_f	0	0	0	0.5	0.5	0.5	1	1	1
α_c	0	0.5	1	0	0.5	1	0	0.5	1
α	0.04818	0.04812	0.04806	0.05220	0.05213	0.05206	0.05621	0.05614	0.05607

It can be seen in Tab. 2 and Fig. 3 that different values of parameter α_f have a greater impact on the value of the evacuation rate of the stomach than different values of α_c.

Parameter α has a strong influence on concentration $c_c^S(t)$ of carbohydrates in the stomach. The problem is multidimensional, $c_c^S(t)$ depends on time and other

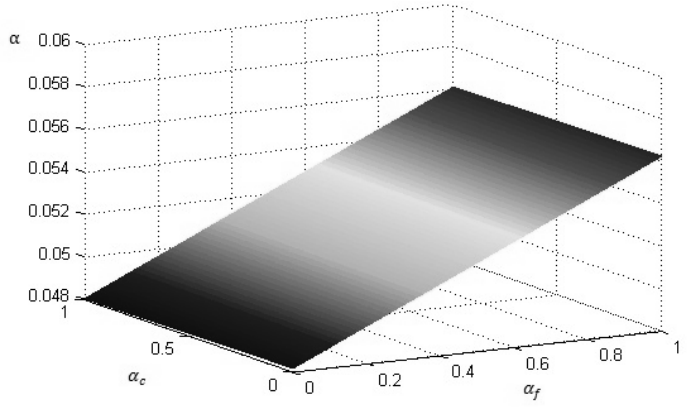

Fig. 3. The granule of the evacuation rate of the stomach.

variables, so it is difficult to illustrate the entire solution in a figure. For this reason, the result of the concentration of carbohydrates in the stomach is simplified to a 2D-space and presented in Fig. 4.

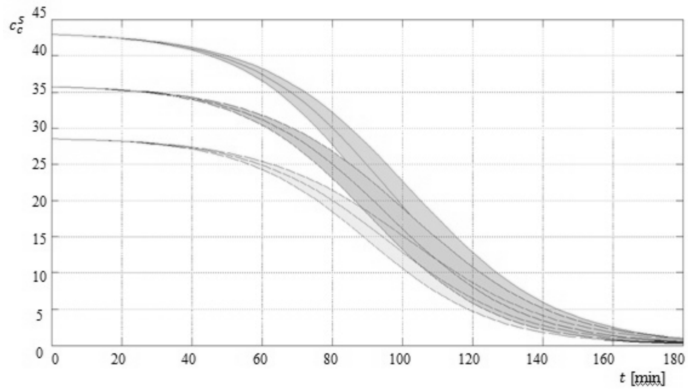

Fig. 4. The concentration $c_c^S(t)$ of carbohydrates in the stomach.

In Fig. 4. three surfaces for different initial conditions ($c_c^S(0)$) are marked. The green surface is for $\alpha_c = 0$, the blue one for $\alpha_c = 0.5$ and the red one for $\alpha_c = 1$. All surfaces include various values of $\alpha_f \in [0, 1]$. For the first 40 min they remain more or less constant (the value of c_c^S), which depends on the value of initial conditions including different values of m_{c0}. The difference in the value of c_c^S ranges in 20 min for these three cases. After 3 h each case comes close to achieve 0. The conclusion is that the concentration of carbohydrates in the stomach is affected by patient specific gastroparesis factor much more than by uncertainties in the parameter of the ingested food. The parameter of the ingested food has a huge influence only in the first 40 min after eating. The future research can be expanded by a model for the inflow of insulin into the blood and a model for the concentration of carbohydrates in the intestine.

5. Conclusions

Problems of decision making very often have a high degree of uncertainty. One of these problems is presented in the paper. The approach to improve the parameter identification of a complex biomedical model has turned out to be very promising and successful. Using the RDM method, the model can be analyzed with the intention of determining the influence of each parameter on the variation of the overall model output.

Moreover, considering the fact that biomedical systems are extremely hard to model and identify, the presented method can cope with all these difficulties. The RDM-method facilitates the calculations of complex equations with uncertain variables shown in this problem and gives satisfactory results. The author believes that this approach gives basis to conduct further research on human glucose metabolism, which can improve therapy and develop optimal medication for diabetes.

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