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# Mathematical Modeling of Blood Glucose Concentration Dynamics

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*In this work, the main models of the blood glucose concentration (BGC) dynamics are considered. The food intake function is introduced as a factor to be to taken into account in BGC dynamics modeling. Three forms of food intake are considered. Mean-square deviation (MSD) is estimated for the modified models of Sturis, Engelborghs, Bennett–Gourley, and sigma model for individual tracks of the DirecNet database. The MSD values for these models are 64.5, 45.3, 50.0, and 15.7 mg/dl, respectively.*

## Introduction

Dynamics of diabetes mellitus is a serious problem worldwide: according to the International Diabetes Federation, the number of patients with diabetes mellitus in 2013 was 382 millions (5% of the world population). By 2035, this number is predicted to increase 1.5-fold [1]. Diabetes mellitus is the most widespread disease after cardiovascular and oncological diseases [2].

Insulin should be injected subcutaneously to patients with diabetes mellitus I. The injection is mediated by special syringes, pen-syringes, or insulin pumps. In modern medical systems, the amount of injected insulin is determined by the patient. The automation of the procedure requires short-term prognosis of blood glucose concentration (BGC). Occasional and systematic mistakes in BGC monitoring should be also predicted.

BGC prognosis can be estimated in a mathematical model of BGC dynamics with respect to various factors [3] and the patient's individual specificity.

The goal of this work is to review mathematical models of BGC dynamics.

## Materials and Methods

Mathematical models of BGC dynamics and blood insulin concentration (BIC) have been extensively studied since the1970s. The Bergman model (minimal model) is the most popular [4]. This model is based on a set of simultaneous ordinary differential equations (ODE):

$$\begin{cases} \dfrac{dg(t)}{dt} = -\left[b_1 + x(t)\right] g(t) + b_1 g_b; \\ \dfrac{dx(t)}{dt} = -b_2 x(t) + b_3 \left[i(t) - i_b\right]; \\ \dfrac{di(t)}{dt} = b_4 \left[g(t) - b_5\right]^+ t - b_6 \left[i(t) - i_b\right], \end{cases} \quad (1)$$

where $t \geqslant 0$ is time; $g(t)$ is BGC; $i(t)$ is BIC; $x(t)$ is dependence of BIC on glucose consumed; $g_b$ is glucose consumed by insulin-independent cells; $i_b$ is basal BIC; $b_1$ is insulin-independent rate constant of glucose uptake in liver, fat, and muscles; $b_2$ is rate of change in glucose uptake; $b_3$ is insulin-dependent rate of glucose uptake per insulin concentration higher than $i_b$; $b_4$ is insulin release rate in pancreas after glucose injection for glucose concentration higher than $b_5$ (glucose threshold for insulin generation); $b_6$ is insulin decay rate in plasma. The Bergman model is valid only in healthy subjects.

This model was one of the first models of interaction of glucose and insulin. It was suggested to describe patient's body reaction to the glucose tolerance test. This model is not mathematically optimal: for some parameters, the model is not physiologically sensible. Despite the disadvantages of the model, it provided the basis for further research; about 50 works are published annually based on this model.

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The Sturis model [5] contains two negative feedback loops for describing glucose consumption and insulin release in the pancreas. The Sturis model is based on six simultaneous ordinary differential equations (ODE) of the first order:

$$\begin{cases} \dfrac{dg(t)}{dt} = g_{im} - f_2\left[g(t)\right] - f_3\left[g(t)\right] f_4\left[i_i(t)\right] + f_5\left[x_3(t)\right]; \\ \dfrac{di_p(t)}{dt} = f_1\left[g(t)\right] - e\left[\dfrac{i_p(t)}{v_p} - \dfrac{i_i(t)}{v_i}\right] - \dfrac{i_p(t)}{t_p}; \\ \dfrac{di_i(t)}{dt} = E\left[\dfrac{i_p(t)}{v_p} - \dfrac{i_i(t)}{v_i}\right] - \dfrac{i_p(t)}{t_i}; \\ \dfrac{dx_1(t)}{dt} = \dfrac{3}{t_d}\left[i_p(t) - x_1(t)\right]; \\ \dfrac{dx_2(t)}{dt} = \dfrac{3}{t_d}\left[x_1(t) - x_2(t)\right]; \\ \dfrac{dx_3(t)}{dt} = \dfrac{3}{t_d}\left[x_2(t) - x_3(t)\right], \end{cases} \quad (2)$$

where $g(t)$ is blood glucose mass; $i_p(t)$, $i_i(t)$ are blood insulin mass and intercellular space mass, respectively; $v_p$, $v_i$ are rates of insulin diffusion in plasma and intercellular space, respectively; $e$ is parameter of diffusion rate; $t_p$, $t_i$ are time constants characterizing decrease in insulin concentration in blood and in intercellular space, respectively; $x_1(t)$, $x_2(t)$, $x_3(t)$ are parameters of insulin propagation decay; $f_1(g)$ is insulin release in pancreas; $f_2, f_3, f_4$ are glucose uptake values in different segments of patient body ($f_2$ – neurons and brain cells, $f_3$ – muscular cells, $f_4$ – fat cells); $f_5$ is glucose decay in liver cells; $t_d$ is time of glucose decay. Here and further, $g_{\text{in}}$ is initial BGC.

Parameters of Eq. (2) are as follows:

$$f_1(g) = \frac{R_m}{1 + \exp\left(\dfrac{C_1 \cdot V_g - g}{a_1 \cdot V_g}\right)}; \quad (3)$$

$$f_2(g) = U_b \cdot \left[1 - \exp\left(-\frac{g}{C_2 \cdot V_g}\right)\right]; \quad (4)$$

$$f_3(g) = \frac{g}{C_3 \cdot V_g}; \quad (5)$$

$$f_4(i) = U_0 + \frac{U_m - U_0}{1 + \exp\left(-\beta \cdot \ln\left\{\dfrac{i}{C_4} \cdot \left[V_i^{-1} + (E \cdot t_i)^{-1}\right]\right\}\right)}; \quad (6)$$

$$f_5(i) = \frac{R_g}{1 + \exp\left[\alpha \cdot \left(i \cdot V_p^{-1} - C_5\right)\right]}. \quad (7)$$

The Engelborghs model [6] is a modification of the Sturis model. This model takes into account the time delay between insulin generation and glucose decay:

$$\begin{cases} \dfrac{dg(t)}{dt} = g_{in} - f_2\left[g(t)\right] - f_3\left[g(t)\right] f_4\left[i(t)\right] + f_5\left[i(t-\tau_2)\right]; \\ \dfrac{di(t)}{dt} = f_1\left[g(t)\right] - \dfrac{i(t)}{t_1}, \end{cases} \quad (8)$$

where $\tau_2$ is time delay between insulin generation and glucose decay; $t_1$ is inverse rate of BIC decrease. The main advantage of the model is its stability.

The model of Bennett and Gourley [7] is another modification of the Sturis model. Like in the Engelborghs model, the Bennett–Gourley model is based on a set of simultaneous ordinary differential equations with retarded argument. The time delay between insulin generation and glucose supply in blood is also taken into account:

$$\begin{cases} \dfrac{dg(t)}{dt} = g_{in} - f_2\left[g(t)\right] - f_3\left[g(t)\right] f_4\left[i(t)\right] + f_5\left[i(t-\tau_2)\right]; \\ \dfrac{di(t)}{dt} = f_1\left[g(t-\tau_1)\right] - d_i i(t), \end{cases} \quad (9)$$

where $\tau_1$ is time delay of insulin generation; $d_i$ is BIC decay rate.

The sigma model is based on the Verhulst law [8] characterizing BGC upon intake of food and insulin injection.

In the case of food intake, BGC is:

$$G = G_0 + \frac{m_c GI}{k m_T} \cdot \left\{\frac{1}{1 + \exp\left[-\alpha\left(t - t_M - \tau\right)/\tau\right]}\right\}, \quad (10)$$

where $m_c$ is consumed carbohydrate mass; $GI$ is glycemic food index; $k$ is coefficient of correlation between body mass and liquid volume (7 dl/kg); $m_T$ is body mass; $t_M$ is time of food intake; $\tau$ is time interval before BGC maximum; $\alpha$ is scaling factor of glucose consumption.

In the case of insulin injection, the amplitude of the sigma function is the amount of insulin, insulin index, and coefficient of glucose consumption. The effect of insulin injection on BGC is:

$$G = G_0 - \frac{m_i hII}{k m_T} \cdot \left\{\frac{1}{1 + \exp\left[-\beta\left(t - t_i - \tau\right)/\tau\right]}\right\}, \quad (11)$$

**TABLE 1.** Model Parameters

| Designation | Value | Dimension |
|---|---|---|
| $V_g$ | 10 | liters |
| $R_m$ | 210 | mmol/min |
| $a_1$ | 300 | mg/liter |
| $C_1$ | 2000 | mg/liter |
| $U_b$ | 72 | mg/min |
| $C_2$ | 144 | mg/liter |
| $C_3$ | 1000 | mg/liter |
| $V_p$ | 3 | liters |
| $V_i$ | 11 | liters |
| $E$ | 0.2 | liters/min |
| $U_0$ | 40 | mg/min |
| $U_m$ | 940 | mg/min |
| β | 1.77 | – |
| $C_4$ | 80 | mole/liter |
| $R_g$ | 180 | mg/min |
| α | 0.29 | liters/mole |
| $C_5$ | 26 | mole/liter |
| $t_i$ | 100 | min |
| $t_p$ | 6 | min |
| $t_d$ | 36 | min |
| $\tau_1$ | 30 | min |
| $\tau_2$ | 5 | min |

where $m_i$ is injection dose; $II$ is insulin food index; $k$ is coefficient of correlation between body mass and liquid volume; $h$ is carbohydrate consumption per insulin unit; $m_T$ is body mass; $t_i$ is time of insulin injection; τ is time interval of insulin action; β is scaling factor of insulin consumption.

The sigma model is a superposition of the functions of food intake (Eq. (10)) and insulin injection (Eq. (11)):

$$G = G_0 + \sum_i \frac{m_c GI_i}{km_T} \cdot \left\{ \frac{1}{1+\exp\left[-4.4\left(t-t_i-\tau\right)/\tau\right]} \right\} - \\ - \sum_j \frac{m_i hII_j}{km_T} \cdot \left\{ \frac{1}{1+\exp\left[-4.4\left(t-t_j-\tau\right)/\tau\right]} \right\}, \qquad (12)$$

where $i$ is number of food intake events; $j$ is insulin injection number.

The models of Sturis, Engelborghs, and Bennett–Gourley were compared using the parameters listed in Table 1. Time delay parameters for models with retarded argument were estimated using MSD minimization between them and initial Sturis model.

## Results and Discussion

Results of comparison between models of Sturis, Engelborghs, and Bennett–Gourley are shown in Fig. 1. Note that the models of Engelborghs and Bennett–Gourley demonstrate normal BGC level within 100 min and insignificantly differ in slope. The model of Sturis demonstrates larger slope angle (different BGC level). The time of the BGC change is 20 h, which is physiologically unreasonable.

In the models of Sturis, Engelborghs, and Bennett–Gourley, food intake and insulin injection are not regarded. Thus, these models are not suitable for BGC prognosis. On the other hand, the functions describing the dynamics of BGC and BIC can be added to the corresponding equations. The form of the function determines the response to food intake.

Various food intake curves were compared: rectangular, triangular, and trapezoid. The results of the comparison demonstrated that a trapezoid food intake curve was the closest to the physiological curve.

Modified Sturis, Engelborghs, and Bennett–Gourley models, as well as the sigma model, were also tested for food intake efficiency (Fig. 2).

Models of Sturis, Engelborghs, and Bennett–Gourley describe BGC dynamics in healthy subjects, whereas the sigma model describes the BGC dynamics in patients with suppressed insulin synthesis. For this purpose, the sigma model was supplemented with insulin compensating the BGC level. Figure 2 shows that the models of Engelborghs, Bennett–Gourley, and the sigma model provide virtually the same response, whereas oscillating Sturis model demonstrates small response, lower than the oscillation amplitude.

At the next stage of the test, the actual track of BGC was simulated. Comparison was made in tracks from the DirecNet database [9], which contains complete data on patient, food intake, and insulin injection. The results of the comparison between BGC tracks are shown in Fig. 3.

The mean-square deviations are 64.5 mg/dl (Sturis model), 45.3 mg/dl (Engelborghs model), 50 mg/dl (Bennett–Gourley model), and 15.7 mg/dl (sigma model).

## Conclusion

The models adequately describe the food-induced peaks of BGC dynamics. The track based on the Sturis

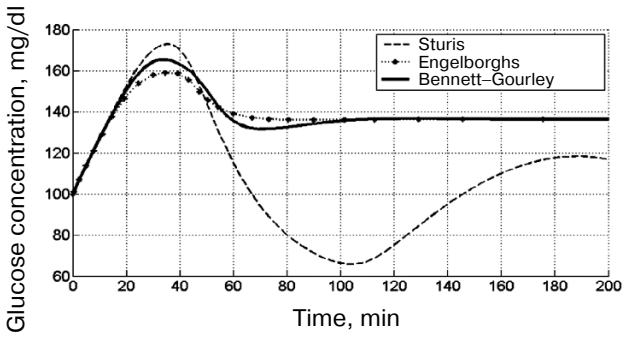


**Fig. 1.** Comparison between models of Sturis, Engelborghs, and Bennett–Gourley.

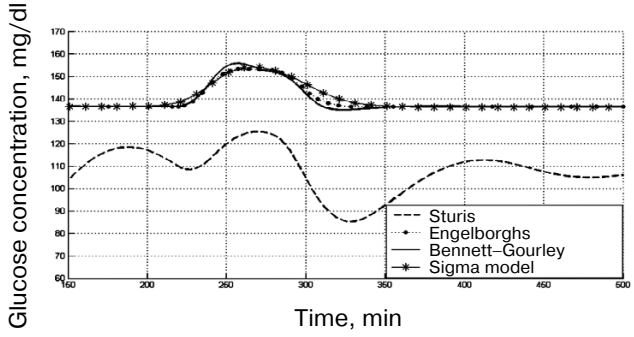


**Fig. 2.** Comparison of the intake of 10 g of glucose in the models of Sturis, Engelborghs, and Bennett–Gourley.

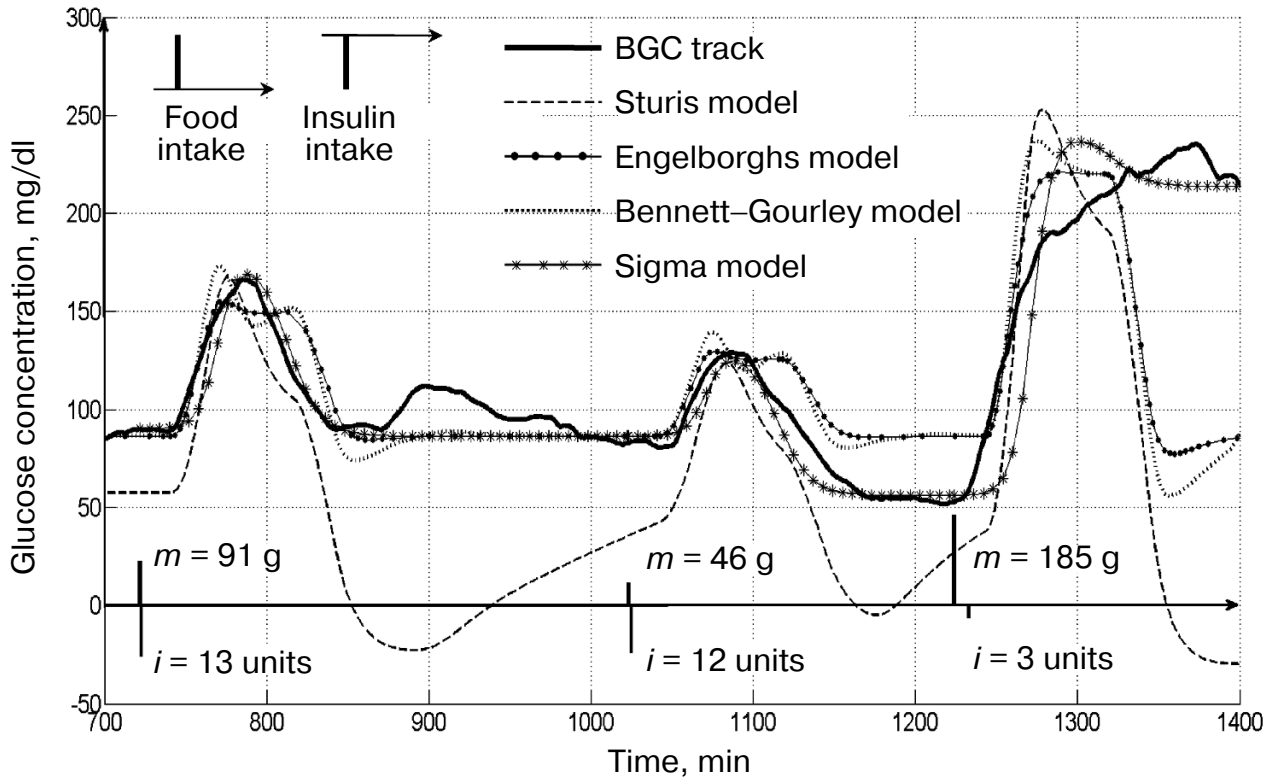


**Fig. 3.** Comparison between BGC tracks based on experimental data and model.

model is inadequate. The tracks reported from the food-intake and insulin-injection-modified models of Bennett–Gourley and Engelborghs are adequate, but demonstrate disadvantages because these models are mainly intended for healthy subjects. The disadvantage caused by the trend toward a constant level of BGC prevents the models from transition to a different constant level of BGC. Even in healthy subjects, the glycemia can be at different levels.

The results of simulation of the sigma model show low MSD, which allows this model to be used for automatic BGC prognosis.

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