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# A MATHEMATICAL MODEL OF GLUCOSE HOMEOSTASIS IN CHAD CONTEXT

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**Abstract:** During these decades, mathematical modeling has become a key domain in science, especially in biomedical sciences. It allows for an experimental and rigorous approach. Thanks to mathematical modeling, the glucose-insulin system could be materialized, which is also theoretical, in order to analyze and interpret it and to predict the results. Many of the mathematical models of the glucose-insulin system have emerged in recent years. In literature, there are models that show the role of physical activity and response of mathematical model to glucose-insulin system dynamics. We propose the mathematical model of ordinary differential equations to investigate simple homeostasis generated by the dynamics of physiological parameters of the glucose-insulin system during physical activity for a healthy subject. Model parameters are estimated using a nonlinear optimization

method generally based on inverse problems. The numerical simulations show that the proposed model is adaptable to the data collected in Chad and can be used to test glucose homeostasis for glucose-insulin system.

**Keywords and Phrases:** Glucose, Insulin, Glucagon, Mathematical model, Homeostasis, Numerical simulation, Chad.

**2020 Mathematics Subject Classification:** 034A34, 37M05, 65P40 65K05.

## 1. Introduction

Diabetes is a progressive, chronic non-communicable disease that is characterized by high levels of blood sugar. It occurs when the human body is unable to produce enough insulin or use it effectively [6]. It is also defined by fasting blood sugar (blood sugar) above 126mg/dl [18]. It is a real public health problem both nationally and internationally, which does not spare the developing countries. This disease existed for a long time and is growing in the world and according to a report from the International Diabetes Federation (IDF) the number of patients with diabetes was estimated at 231,290 in Chad in 2013 for total population of 13,130,000 million [9]. It is a serious disease in the sense that it often progresses silently, without developing symptoms. Nearly one-third of cases may not be detected at all [10]. Furthermore, a patient can suffer from diabetes for years without knowing as much and what causes gravity. More than 5 million deaths a year, or more than 13,000 deaths per day, or more than 570 deaths per hour, one leg cut every 30 seconds [1]. Diabetes is also a direct consequence of certain pathologies such as: cardiovascular diseases, ocular disorders, neuropathies, susceptibility to infections. The consequences of this disease are enormous, and this is what prompted researchers to find techniques to diagnose and treat this disease. On the other hand, the specialists in mathematical modeling developed different approaches to help the understanding of processes. They describe the glucose-insulin system dynamics [2, 5, 8, 19]. Mathematical modeling has, on the one hand, enabled a better understanding of the phenomenon of diabetes, and on the other hand a proposal of solutions that prevent diabetes and help to avoid its complications. Several studies have been conducted to simulate and analyze the dynamics of glucose and insulin leading to diabetes over the last two decades. A number of mathematical models of insulin glucose dynamics have been reported in the literature [12, 13, 15]. The homeostasis is process of maintaining blood glucose at a steady-state. This process is very important for two reasons: firstly low blood concentrations of glucose can causes seizures, loss of consciousness, and death and secondly long lasting elevation of blood glucose concentrations. It can result in blindness, renal failure, vascular disease, and neuropathy. The homeostasis is achieved throughout several factors.

These factors include the rate of consumption and intestinal absorption of dietary carbohydrate, the rate of utilization of glucose by peripheral tissues and the loss of glucose through the kidney tubule, and the rate of removal or release of glucose by the liver and kidney. Clearly, in the control of glucose homeostasis pancreatic islets play a central role. After a meal, when plasma glucose levels rise, the glucose becomes low by effect of the associated increase of insulin secretion and action on key target tissues. This process is done by inhibiting hepatic glucose production and by increasing tissue glucose uptake. When food is unavailable, islet hormones again play a critical role to defend glucose homeostasis: falling plasma glucose levels inhibit insulin secretion while enhancing the release of glucagon, a combination that increases hepatic glucose production and prevents plasma glucose levels from dropping out of the normal range [14]. The exercises play also a role in maintaining blood glucose homeostasis. Indeed, during the prolonged exercise the increased demand for glucose by contracting muscle causes the increase of glucose uptake to working skeletal muscle. Increase in glucose uptake by working skeletal muscle during prolonged exercise is due to an increase in the translocation of insulin and contraction sensitive glucose transporter-4 (GLUT4) proteins to the plasma membrane [4, 16]. In this paper, we propose a mathematical model for glucose homeostasis adapted to people without diabetes. In other words a model after an increase in blood glucose level, it can return to normal due to the response of physical activity. As a result, the estimation of model parameters is carried out using the data collected in Chad. This paper is organised as follows. In this Section 2 we present material and methods. It deals with data sources, mathematical model equations. The Section 3 focuses on estimation of parameters of model. The numerical tests are given in Section 4 while concluding remarks in the last section are presented in section 5.

## 2. Material and methods

The data collection for diabetic patients started on 23, January 2019 and ended on 23, February 2019 at laboratory of hematology department of regional Abéché hospital, Chad. More three cases have been taken into consideration : diabetes type 1, diabetes type 2 and healthy subjects. Furthermore, 10 participants are received in each category during 30 days. This makes in total 900 exams for the better simulations. But, all expected data are not collected due to certain number of difficulties such as lack of material, lower number of enumerators and financial means. Mainly, we did not have enough equipment to measure glucose, the one was available for the laboratory, some patients lived far from the hospital so that they should come to the hospital very early in the morning (fasting) or we might organize the visit to their living home. That is why only a sample of 96 patients has been

taken into account and the fasting blood sugar levels were recorded every morning in a period of one month. The average of blood sugar level is taken daily. The insulin was not measured but using the collected data of glucose and Bergman's insulin minimal model [3] the data of insulin are calculated as follows.

$$\frac{dI(t)}{dt} = \begin{cases} k_1\left(G(t) - G_b\right)t - k_2 I(t), & \text{if } G(t) > G_T \\ -k_2 I(t) & \text{otherwise} \end{cases} \quad \text{with } I(0) = I_0, \qquad (1)$$

where $k_1$ and $k_2$ are parameter of mathematical model, and $G_T$ denotes the threshold for blood glucose concentration. Solving (1) we get

$$I(t) = \begin{cases} e^{-k_2 t}\left[\frac{k_{1(G(t)-G_b)}}{k_2}\left(1 + \left(t - \frac{1}{k_2}\right)e^{k_2 t}\right) + I_0\right], & \text{if } G(t) > G_T \\ I_0 e^{-k_2 t}, & \text{otherwise} \end{cases} \qquad (2)$$

The values of $k_1$, $k_2$, and $G_b$ are 0.0055, 0.29, and 92.5, respectively.

## 3. Model equations

The mathematical model is governed by 5 ordinary differential equations with 19 parameters to be estimated and 6 parameters obtained from literature. The variables and parameters of mathematical model are described as follows.

### Model variables

- $\Gamma$ $(pg/ml)$: Glucagon concentration to release glucose stored in the liver for a balanced system
- $I_P$ $(\mu U/dl)$: Concentration of insulin secreted by the beta cells
- $G_T$ $(mg/dl)$: Concentration of glucose in the tissues transported and stored as fat by insulin if the the liver can not store it. Otherwise it will be stored in the liver,
- $G_H$ $(mg/dl)$: Blood glucose concentration,
- $G_L(mg/dl)$: Concentration of glucose if the liver.

### Parameter to be estimated

- $p_1(dl/min)$: Rate of glucose from the liver to the blood,
- $p_2(dl/min)$: Rate of glucose from the blood to the liver,
- $p_3(dl/min)$: Rate of glucose from the tissues to the blood,

- $k_1(dl/\text{min})$, $k_2(dl/\text{min})$: Rate of glucose coming in the pancreas indirectly,
- $k_3(mg/\mu U.\text{min})$: Quantity of glucose from the pancreas to blood,
- $k_7(mg/\mu U.\text{min})$: Quantity of glucose from the pancreas to the tissues ,
- $Q_P$ $(dl/\text{ min})$: Rate of glucose from pancreas to the tissues,
- $R_{G_T}(mg/\text{ min})$: Rate of glucose in the tissues in fat due to effect of insulin,
- $R_{meal}(mg/\text{ min})$: Rate of glucose in the blood due the meals.

**Constants**

- $\alpha, \beta$, $k_4$, $k_5$ and $k_6$

**Constant from literature [15]**

- $V^{\Gamma}(dl)$: Volume of glucagon in the pancreas compartment,
- $V^{I_P}(dl)$: Volume of insulin in the pancreas compartment,
- $V^{G_T}(dl)$: Volume of glucose in the tissues compartment,
- $V^{G_H}(dl)$: Volume of glucose in the heart compartment,
- $V^{G_L}(dl)$: Volume of glucose in the liver compartment,
- $Q_L(dl/\text{ min})$: Left cardiac output,
- $Q_R(dl/\text{ min})$: Right cardiac output.

The glucose homeostasis is due to the following physiological mechanism. During physical activity or fasting, the glucose level in the body decreases, the pancreas secretes glucagons. Moreover, the glucagons are secreted by the alpha cells of Langerhan's islets in the pancreas [20] to release glucose stored in the liver so that we have glucose homeostasis. In addition, after eating, the rate of glucose increases. Furthermore, insulin is secreted by beta cells of Langerhan's islets in the pancreas to enter in the blood and poured into blood. Its main role is to facilitate the storage of the surplus of the blood glucose in the liver. The diagram of mathematical model is illustrated in the Figure 1. The following mathematical model is governed by 5 ordinary differential equations with 19 parameters to be estimated and 6 parameters obtained from literature.

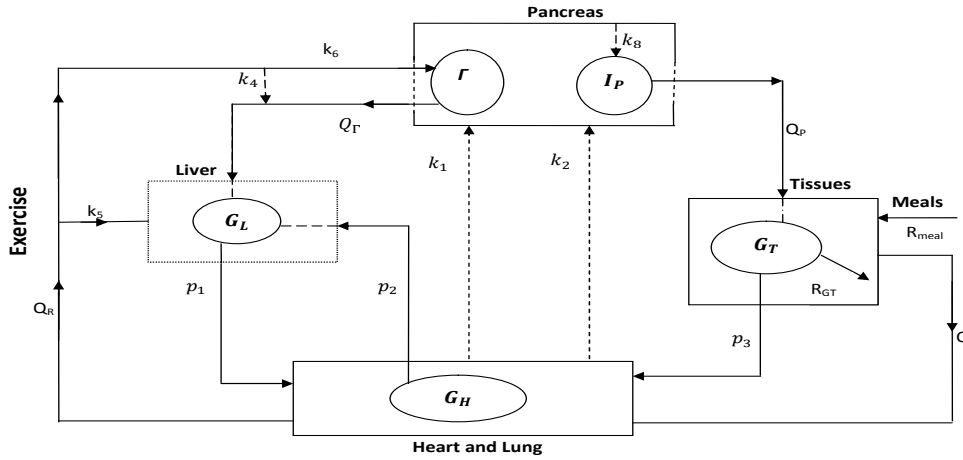


Figure 1: Diagram of mathematical model

$$\begin{cases} \dfrac{d\Gamma(t)}{dt} = \dfrac{1}{V^{G_\Gamma}}\left[(k_1 + k_6 Q_R)G_H - Q_\Gamma \Gamma\right]; \\ \dfrac{dI_p(t)}{dt} = \dfrac{1}{V^{I_p}}\left[k_2 I_p^{\alpha} + k_8 Q_R G_H - Q_p I_p\right] + \sigma_1 PVO_2^{max}; \\ \dfrac{dG_T(t)}{dt} = \dfrac{1}{V^{G_T}}\left[k_7 Q_p I_p - (p_3 + Q_L)G_H - R_{G_T} + R_{meal}\right]; \\ \dfrac{dG_H(t)}{dt} = \dfrac{1}{V^{G_H}}\left[(p_3 + Q_L)G_T - (p_2 + Q_R)G_H + k_3 Q_L I_p^{\beta}\right]; \\ \dfrac{dG_L(t)}{dt} = \dfrac{1}{V^{G_L}}\left[k_4 Q_\Gamma \Gamma + (p_2 + k_5 Q_R)G_H - p_1 G_L\right] + \sigma_2 PVO_2^{max}. \end{cases} \tag{3}$$

The percentage of maximum uptake of oxygen during a upgraded exercise ($PVO_2^{max}$) is calculated using the following ordinary differential equation.

$$\frac{dPVO_2^{max}(t)}{dt} = -0.8PVO_2^{max}(t) + 0,8u(t),$$

where 0.8 (1/min) is selected to achieve a $PVO_2^{max}(t)$ settling time of approximately 5 minutes [1]. The function $u(t)$ is the model input representing the target value of the exercise intensity above the basal level. It is defined by

$$u(t) = \begin{cases} 0, & 0 < t < t_{ex}^{start} \\ T_v, & t_{ex}^{start} < t < t_{ex}^{end} \\ 0, & t > t_{ex}^{end}. \end{cases}$$

The target value $T_v$ ranges from 0 to 92% according to the basal consumption equals to 8% of the maximum value [11]. In [11] the value of $Tv = 67$ for exercise

duration of 150 *min*. In our numerical simulation, we consider the same value.

## 4. Convergence of the Numerical Blow-up Time

The Table 1 shows the values of the volumes of the mathematical model (3). They are collected from the global mathematical model developed by John Thomas Sorensen [15].

| **Paramete** | **Unit** | **The used value** | **Range** | **Source** |
|---|---|---|---|---|
| $V^{G_H}$ | $dl$ | 3.5 | $[2.5, 4.5]$ | [15] |
| $V^{G_L}$ | $dl$ | 25.1 | $[17.2, 30]$ | [15] |
| $V^{G_T}$ | $dl$ | 9.5 | $[7, 12]$ | [15] |
| $V^{G_\Gamma}$ | $dl$ | 113.1 | $[90, 125]$ | [15] |
| $V^{I_P}$ | $dl$ | 67.4 | $[55, 75]$ | [15] |
| $Q_L = Q_R$ | $dl/min$ | 60 | $[40, 80]$ | [17] |

Table 1: Parameters from literature

Note that the last equation of the mathematical model (3) depends on five other equations. Let $X_1 = (\Gamma, I_p, G_T, G_H, G_L)^t$ and $X_2 = PVO_2^{max}$ be vector states of the mathematical model. Setting

$$F_1 = \frac{1}{V^\Gamma}[(k_1 + k_6 Q_R)G_H - Q_\Gamma \Gamma];$$

$$F_2 = \frac{1}{V^{I_p}}[k_2 I_p^\alpha + k_6 Q_R G_H - Q_p I_p];$$

$$F_3 = \frac{1}{V^{G_T}}[k_7 Q_p I_p - (p_3 + Q_L)G_H - R_{G_T} + R_{meal}];$$

$$F_4 = \frac{1}{V^{G_H}}[(p_3 + Q_L)G_T - (p_2 + Q_R)G_H + k_3 Q_R I_p^\beta];$$

$$F_5 = \frac{1}{V^{G_L}}[k_4 Q_\Gamma \Gamma + (p_2 + k_5 Q_R)G_H - p_1 G_L];$$

$$F_6 = -0,8 PVO_2^{max}(t) + 0,8u(t)$$

the compact form of the system (3) becomes

$$\frac{dX_1}{dt} = F(X_1) \text{ and } \frac{dX_2}{dt} = F_6(X_2)$$

where

$$F = (F_1, F_2, F_3, F_4, F_1, F_5)^t.$$

The mathematical model (3) has parameters which can be adjusted to physical activity. A nonlinear optimization problem can be used to identify those parameters. Furthermore, the mathematical model can be represented in the following compact form

$$\dot{X}(t) = f(X(t), \mu), \tag{4}$$

where $\mu$ is the vector of parameters to be estimated. That is

$$\mu = (Q_\Gamma, \alpha, \beta, p_1, p_2, p_3, k_1, k_2, k_3, k_4, k_5, k_6, k_7, Q_P, R_{G_T}, R_{meal})'.$$

For computational purposes we discretize the system using $N$ linear B-splines. Let us consider

$$\mathcal{B}^N = \left\{\psi_j^N,\ j = 1, ..., N\right\}, \tag{5}$$

a linear B-splines basis functions on the uniform grid

$$\Omega_N = \left\{t_k = \frac{kT_{\max}}{N},\quad k = 0, ..., N\right\}, \tag{6}$$

such that

$$\psi_i^N(t_k) = \delta_{ik},$$

where $\delta_{ik}$ is Kronecker symbol. Let us introduce the vector space $W^N$ whose the basis is $\mathcal{B}^N$. It follows that $\dim W^N = N$ and $W^n \subset W^{n+1}$, $n = 1, ..., N$. We assume that functions appearing in the system (4) are continuous on $[0, T_{\max}]$ . Let us denote $W = C^0(0, T_{\max})$ and consider the interpolation operator

$$\Pi^N \ : \ W \ \longrightarrow \ W^N,$$

satisfying $\forall \phi \in W$

$$\Pi^N \phi(t_k) = \phi(t_k), \qquad k = 1, \cdots, N.$$

Therefore, we determine the solution $X^N \in W^N$ of the following discrete problem

$$\dot{X}^N(t) = f(X^N(t), \mu^N), \text{ such that } X^N(0) = X_0^N, \tag{7}$$

where the control is

$$\mu^N = \left(Q_\Gamma^N, \alpha^N, \beta^N, p_1^N, p_2^N, p_3^N, k_1^N, k_2^N, k_3^N, k_4^N, k_5^N, k_6^N, k_7^N, Q_P^N, R_{G_T}^N, R_{meal}^N\right) \in (W^N)^{16}.$$

The cost function corresponding to optimal control problem is as follows.

$$\begin{aligned}\sum_{k=1}^{N} \quad & \Big(q_G \left(G_T^N(t_k) - G_T^{obs}\right)^2 + q_I \left(I_p^N(t_k) - I_p^{obs}\right)^2 \\ & + q_H \left(G_H^N(t_k) - G_H^b\right)^2 + q_L \left(G_L^N(t_k) - G_L^b\right)^2\Big) h,\end{aligned} \tag{8}$$

with respect to (7) and $h = \frac{T}{N}$. Superscript "*obs*" refers to the observed data of glucose and insulin concentrations while "*b*" denotes basal glucose. The positive scalar coefficients $q_G$, $q_I$, $q_H$ and $q_L$ determine how much weight is associated to each term in the integrand. In compact form the problem (8) can be rewritten as follows

$$\min_{\mu^N} J^N(\mu^N) = \sum_{k=1}^{N} h Y_k^T R Y_k \tag{9}$$

subject to

$$\begin{cases} \dot{X}^N(t) = f(X^N(t), \mu^N) \\ X^N(0) = X_0^N \end{cases}, \tag{10}$$

where $Y_k$ $k = 1, ..., N$ is the following matrix

$$\left(\left(G_T^N(t_k) - G_T^{obs}\right), \left(I_p^N(t_k) - I_p^{obs}\right), \left(G_H^N(t_k) - G_H^b\right), \left(G_L^N(t_k) - G_L^b\right)\right)',$$

and $R$ is the matrix defined by

$$R = diag(v) \text{ with } v = (q_G, q_I, q_H, q_L)'.$$

The Table 2 shows those weights used in numerical computation.

| Weight | $q_G$ | $q_I$ | $q_H$ | $q_L$ |
|---|---|---|---|---|
| Value | 20 | 10 | 2 | 1 |

Table 2: Values of weight used in numerical simulation

The estimated parameters of mathematical model are shown in Table 3.

| Parameter | Value | Parameter | Value |
|---|---|---|---|
| $Q_\Gamma$ | 37.0292 | $k_4$ | 11.5612 |
| $\alpha$ | 0.1201 | $k_5$ | 0.1696 |
| $\beta$ | 0.0308 | $k_6$ | 0.0105 |
| $p_1$ | 90.0305 | $k_7$ | 8.0504 |
| $p_2$ | 61.1903 | $k_8$ | 0.0968 |
| $p_3$ | 82.6098 | $Q_P$ | 74.1223 |
| $k_1$ | 0.5754 | $R_{G_T}$ | 43.5262 |
| $k_2$ | 0.2230 | $R_{meal}$ | 137.7010 |
| $k_3$ | 0.1041 | $\sigma_1$ | 0.2093 |
| | | $\sigma_2$ | 0.01756 |

Table 3: Estimated model parameters

## 5. Numerical simulations

We investigate the plasma glucose, the plasma insulin dynamics during exercise, the rates of glucose uptake and the hepatic glucose production induced by exercise for both female and male healthy subjects performing the continuous walking or gym tonic as physical activity during 40 minutes. For validation of the mathematical model (3), a separate simulation study was implemented using a different exercise intensity: mild exercise ($PVO_2^{max} = 30$) and moderate exercise ($PVO_2^{max} = 60$) [2]. Test results for female are plotted in Figures 2, 3, 4, 5 and 6, respectively.

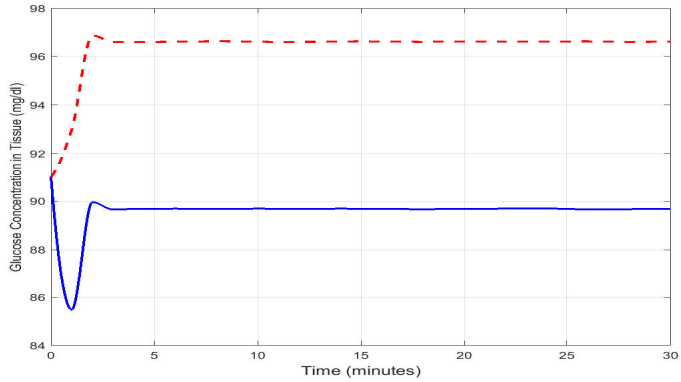


Figure 2: Response of $PVO_2^{max} = 30$ (Solid line) and $PVO_2^{max} = 60$ (Dash line) to glucose concentration in tissues.

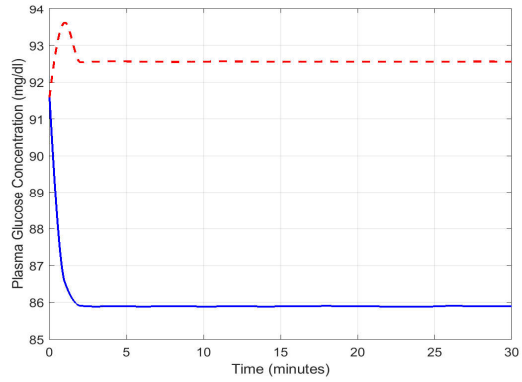


Figure 3: Response of $PVO_2^{max} = 30$ (Solid line) and $PVO_2^{max} = 60$ (Dash line) to blood glucose concentration.

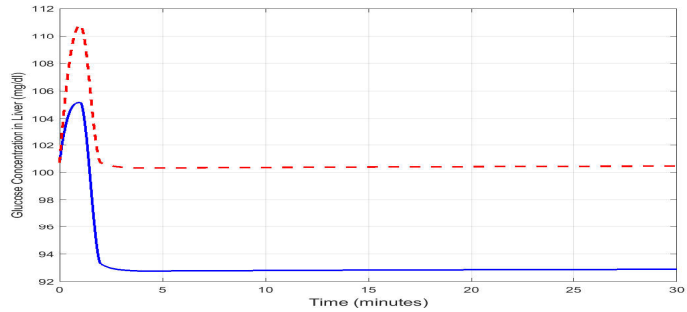


Figure 4: Response of $PVO_2^{max} = 30$ (Solid line) and $PVO_2^{max} = 60$ (Dash line) to glucose concentration in liver.

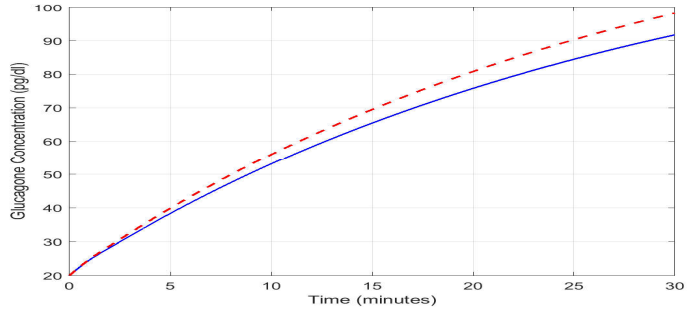


Figure 5: Response of $PVO_2^{max} = 30$ (Solid line) and $PVO_2^{max} = 60$ (Dash line) to **glucagon** concentration

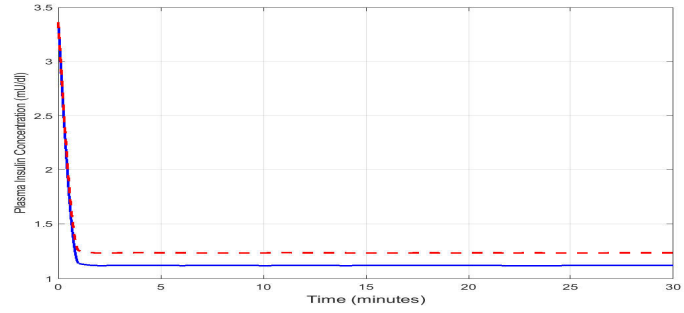


Figure 6: Response of $PVO_2^{max} = 30$ (Solid line) and $PVO_2^{max} = 60$ (Dash line) to insulin concentration

The glucose level of a non-diabetic (healthy) person varies between 70mg /dl and 110mg/dl [16]. Glucagon and insulin are hormones secreted by alpha and beta cells respectively. They play two antagonistic roles. Moreover, glucagon under its action, increases the blood glucose level, while insulin decreases the blood glucose levels. For the mathematical model we developed, this is the effect of physical activity on the dynamic of glucose dynamics for a subject. The numerical results illustrate glucose homeostasis in the tissues (See Figure 2), in the blood (See Figure 3) and in the liver (See Figure 4). They show that response of physical activity to concentration of determinants parameters (glucose and insulin) of glucose-insulin system does not change their expected values. However they are rather high for moderate exercise compared with mild exercise. This is due to the fact that different organs of human body demand an increase in glucose during exercise intensity.

## 6. Concluding remarks

In this work, we have proposed the mathematical model of ordinary differential equations describing the dynamics of physiological parameters of the glucose-insulin system during physical activity for a healthy subject. The results show that exercise plays a very important role. It is a very effective factor to maintain glucose homeostasis. During physical activity, the glucagons are secreted and they stabilize the system when the glucose is at high level. If the regular physical activity is performed then the peripheral tissues needs the glucose. This results in a decrease in blood glucose levels. Finally, we have shown by numerical simulations that the proposed model is adaptable to healthy subject. It can be used by experts to test performance glucose-insulin system generally for glucose homeostasis.

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