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グルコース, インスリンとC-ペプチドのダイナミクスを記述するコンパートメント体循環モデルのパラメータ推定

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In recent years, the number of diabetic patients has been rapidly increasing along with changes in lifestyle and social environment. Once the diabetes is developed, it is difficult to return back to the healthy state, and thus the establishment of a mathematical understanding of human glucose metabolism, so as to prevent the diabetes from developing, has become an important and urgent issue. In this study, we aim at contructing mathematical modeling for the human glucose metabolism system to attain a mathematical understanding of the mechanism of blood glucose homeostasis.

In this presentation, we first present the construction of a compartmental model of systemic circulation describing Glucose, Insulin, and C-peptide dynamics. Then, by using Oral Glucose Tolerance Test (OGTT) data from healthy subjects,and the Markov Chain Monte-Carlo method we perform the parameter estimation for this compartmental model. The results obtained from the model are validated by the medical facts, such as the halflife times and the insulin hepatic rate. And we finally discuss some future directions, such as using the data of the mouse of different diets.

Key Words : *Glucose metabolism, Mathematical modeling, Parameter estimation*

1. INTRODUCTION

Many mathematical models have been developed to better understand the mechanisms of the glucose-insulin regulatory system. [1] gives an overview of some of the mathematical models for the glucose-insulin regulatory system in relation to diabetes. In 2021, Kurata [2] proposed the most comprehensive, largest, and highly predictive model of the whole-body metabolism. The model consists of 202 ordinary differential equations with 217 reaction rates and 1140 kinetic parameter constants which makes it laborious for parameter estimation. [3] presents Bayesian analysis of a model for glucose insulin dynamics during OGTT, however the model does not consider the detail functions of different organs ni contain the dynamic of C-peptide and they have not considered the medical validations such as insulin and C-peptide's half-life times.

In our work, we consider the blood circulation among 9 organs: Heart, Hepatic, Pancreas, Mesentery, Renal, Upper arm, Lower limbs, Brain and Stomach. And we use the letters T, H, P, M, R, U, L, B and S to represent them respectively. The blood flux goes out from the heart and transport glucose, insulin and C-peptide into hepatic, pancreas, mesentery, renal, upper arm, lower limbs, brain and stomach through artery. The blood then flows out of each organ and transport the 3 sustances back towards the heart through the vein. The blood flows out of renal, upper arms, lower limbs and brain will flow back directly to the heart; meanwhile the blood flowing out of pancreas, mesentery and stomach will first gather together at the portal vein, then flow into the hepatic, and flow out of hepatic to go back to the heart.

In each organ, we apply the following conservation principle for the moles of Glucose, Insulin and C-peptide respectively:

$$\begin{aligned} &\text{change of the moles per unite time} \\ &= \text{the moles taken in by inflow} \\ &\quad - \text{the moles taken away by outflow} \\ &\quad + \text{secretion or digestion} \\ &\quad - \text{consumption or excretion.} \end{aligned} \tag{1}$$

The secretion/digestion and consumption/excretion are based on the following facts.

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1. The C-peptide is excreted from the renal.
2. The insulin is cleared in hepatic and in the upper and lower limbs.
3. The secretion of C-peptide and of insulin is at the ratio 1:1 with respect to the moles in pancreas; and is intrigued by the nerves and by the increment of the glucose in pancreas.
4. The glucose is taken from the mouth, absorbed from the mesentery and consumed in hepatic, pancreas and brain.
5. When the concentration of glucose in blood vessels is high, the glucose will be stored in the heptocyte in the form of glycogen; and when the concentration is low in blood vessels of the hepatic, the hepatocyte will transfer glycogen to glucose into the blood vessels.
6. In upper arms and lower limbs, the consumed insulin stimulates the protein GLUT4 who transports glucose across the plasma membrane, which results in the decrease of the concentration of the glucose in the blood.

2. The mathematical model

Based on the blood circulation and the upper facts, we construct the mathematical model. We denote by C_{i}, the concentration of the C-peptide in the blood vessels of the organ i, where $\mathrm{i} \in \{\mathrm{T,H,P,M,R,U,L,B,S}\}$, and we denote by I_{i} and G_{i} for the concentrations of insulin and glucose respectively. Let $|V_{\mathrm{i}}|$ to be the volume of the blood vessels and Q_{i} to be flux through the organ i, we denote by C_{PV} the concentration of the C-peptide at the portal vein. We then compute the concentration of C-peptide at the heart at the portal vein by the following formula

$$C_{\mathrm{T}} = \frac{(Q_{\mathrm{P}} + Q_{\mathrm{M}} + Q_{\mathrm{S}} + Q_{\mathrm{H}})C_{\mathrm{H}} + \sum_{i=\{U,B,L,R\}} Q_{\mathrm{i}}C_{\mathrm{i}}}{Q_{\mathrm{U}} + Q_{\mathrm{B}} + Q_{\mathrm{L}} + Q_{\mathrm{R}} + Q_{\mathrm{P}} + Q_{\mathrm{M}} + Q_{\mathrm{S}} + Q_{\mathrm{H}}}$$

and

$$C_{\mathrm{PV}} = \frac{Q_{\mathrm{P}}C_{\mathrm{P}} + Q_{\mathrm{M}}C_{\mathrm{M}} + Q_{\mathrm{S}}C_{\mathrm{S}}}{Q_{\mathrm{P}} + Q_{\mathrm{M}} + Q_{\mathrm{S}}}.$$

I_{T}, G_{T} and I_{PV}, G_{PV} are computed in a similar way.

$$I_{\mathrm{T}} = \frac{(Q_{\mathrm{P}} + Q_{\mathrm{M}} + Q_{\mathrm{S}} + Q_{\mathrm{H}})I_{\mathrm{H}} + \sum_{i=\{U,B,L,R\}} Q_{\mathrm{i}}I_{\mathrm{i}}}{Q_{\mathrm{U}} + Q_{\mathrm{B}} + Q_{\mathrm{L}} + Q_{\mathrm{R}} + Q_{\mathrm{P}} + Q_{\mathrm{M}} + Q_{\mathrm{S}} + Q_{\mathrm{H}}}$$

and

$$I_{\mathrm{PV}} = \frac{Q_{\mathrm{P}}I_{\mathrm{P}} + Q_{\mathrm{M}}I_{\mathrm{M}} + Q_{\mathrm{S}}I_{\mathrm{S}}}{Q_{\mathrm{P}} + Q_{\mathrm{M}} + Q_{\mathrm{S}}}.$$

And

$$G_{\mathrm{T}} = \frac{(Q_{\mathrm{P}} + Q_{\mathrm{M}} + Q_{\mathrm{S}} + Q_{\mathrm{H}})G_{\mathrm{H}} + \sum_{i=\{U,B,L,R\}} Q_{\mathrm{i}}G_{\mathrm{i}}}{Q_{\mathrm{U}} + Q_{\mathrm{B}} + Q_{\mathrm{L}} + Q_{\mathrm{R}} + Q_{\mathrm{P}} + Q_{\mathrm{M}} + Q_{\mathrm{S}} + Q_{\mathrm{H}}}$$

and

$$G_{\mathrm{PV}} = \frac{Q_{\mathrm{P}}C_{\mathrm{P}} + Q_{\mathrm{M}}G_{\mathrm{M}} + Q_{\mathrm{S}}G_{\mathrm{S}}}{Q_{\mathrm{P}} + Q_{\mathrm{M}} + Q_{\mathrm{S}}}.$$

I_{T}, G_{T} and I_{PV} We present the model on the dynamics of C-peptide.

$$\begin{cases} |V_{\mathrm{H}}|\dfrac{\mathrm{d}C_{\mathrm{H}}}{\mathrm{d}t} = Q_{\mathrm{H}}C_{\mathrm{T}} + Q_{\mathrm{PV}}C_{\mathrm{PV}} - Q_{\mathrm{V}}C_{\mathrm{H}} \\ |V_{\mathrm{P}}|\dfrac{\mathrm{d}C_{\mathrm{P}}}{\mathrm{d}t} = Q_{\mathrm{P}}C_{\mathrm{T}} - Q_{\mathrm{P}}C_{\mathrm{P}} + |V_{\mathrm{P}}|F_{\mathrm{Insulin}}(S_{\mathrm{in}}, G_{\mathrm{P}})C_{\mathrm{PC}} \\ |V_{\mathrm{M}}|\dfrac{\mathrm{d}C_{\mathrm{M}}}{\mathrm{d}t} = Q_{\mathrm{M}}C_{\mathrm{T}} - Q_{\mathrm{M}}C_{\mathrm{M}} \\ |V_{\mathrm{R}}|\dfrac{\mathrm{d}C_{\mathrm{R}}}{\mathrm{d}t} = Q_{\mathrm{R}}C_{\mathrm{T}} - Q_{\mathrm{R}}C_{\mathrm{R}} - |V_{\mathrm{R}}|k_{\mathrm{CR3}}\dfrac{C_{\mathrm{R}}^{m_{c1}}}{\gamma_{c1}^{m_{c1}} + C_{\mathrm{R}}^{m_{c1}}} \\ |V_{\mathrm{U}}|\dfrac{\mathrm{d}C_{\mathrm{U}}}{\mathrm{d}t} = Q_{\mathrm{U}}C_{\mathrm{T}} - Q_{\mathrm{U}}C_{\mathrm{U}} \\ |V_{\mathrm{L}}|\dfrac{\mathrm{d}C_{\mathrm{L}}}{\mathrm{d}t} = Q_{\mathrm{L}}C_{\mathrm{T}} - Q_{\mathrm{L}}C_{\mathrm{L}} \\ |V_{\mathrm{B}}|\dfrac{\mathrm{d}C_{\mathrm{B}}}{\mathrm{d}t} = Q_{\mathrm{B}}C_{\mathrm{T}} - Q_{\mathrm{B}}C_{\mathrm{B}} \\ |V_{\mathrm{S}}|\dfrac{\mathrm{d}C_{\mathrm{S}}}{\mathrm{d}t} = Q_{\mathrm{S}}C_{\mathrm{T}} - Q_{\mathrm{S}}C_{\mathrm{S}}. \end{cases} \tag{2}$$

where, the secretion of C peptide is given as

$$\frac{d}{dt}C_{\mathrm{PC}} = -F_{\mathrm{Insulin}}(S_{\mathrm{in}}, G_{\mathrm{P}})C_{\mathrm{PC}} + k_{\beta}C_{\mathrm{PC}}^{0}, \tag{3}$$

where $F_{\mathrm{Insulin}}(S_{\mathrm{in}}, G_{\mathrm{P}}) = k_{\mathrm{E}}\frac{S_{\mathrm{in}}}{(\gamma_{\mathrm{S}})+S_{\mathrm{in}}} + k_{\mathrm{GIP}}\frac{G_{\mathrm{P}}}{\gamma_{\mathrm{G}}+G_{\mathrm{P}}} + k_{\mathrm{out}}$. The first term represents the secretion rate stimulated when the absorptive epithelial cell of mesentery sense the intake of glucose; the second term represents the secretion rate stimulated by the increasement of glucose concentration in pancreas' blood vessels; and the third term is the basic secretion rate. Using the same idea, we construct the model on the dynamics of insulin

$$\begin{cases} |V_{\mathrm{H}}|\dfrac{\mathrm{d}I_{\mathrm{H}}}{\mathrm{d}t} = Q_{\mathrm{H}}I_{\mathrm{T}} + Q_{\mathrm{PV}}I_{\mathrm{PV}} - Q_{\mathrm{V}}I_{\mathrm{H}} \\ \qquad\qquad - |V_{\mathrm{H}}|k_{\mathrm{IH1}}\dfrac{I_{\mathrm{H}}^{m_{i1}}}{\gamma_{i1}^{m_{i1}} + I_{\mathrm{H}}^{m_{i1}}} \\ |V_{\mathrm{P}}|\dfrac{\mathrm{d}I_{\mathrm{P}}}{\mathrm{d}t} = Q_{\mathrm{P}}I_{\mathrm{T}} - Q_{\mathrm{P}}I_{\mathrm{P}} + |V_{\mathrm{P}}|F_{\mathrm{Insulin}}(S_{\mathrm{in}}, G_{\mathrm{P}})I_{\mathrm{PC}} \\ |V_{\mathrm{M}}|\dfrac{\mathrm{d}I_{\mathrm{M}}}{\mathrm{d}t} = Q_{\mathrm{M}}I_{\mathrm{T}} - Q_{\mathrm{M}}I_{\mathrm{M}} \\ |V_{\mathrm{R}}|\dfrac{\mathrm{d}I_{\mathrm{R}}}{\mathrm{d}t} = Q_{\mathrm{R}}I_{\mathrm{T}} - Q_{\mathrm{R}}I_{\mathrm{R}} \\ |V_{\mathrm{U}}|\dfrac{\mathrm{d}I_{\mathrm{U}}}{\mathrm{d}t} = Q_{\mathrm{U}}I_{\mathrm{T}} - Q_{\mathrm{U}}I_{\mathrm{U}} - |V_{\mathrm{U}}|k_{\mathrm{IU}}\dfrac{I_{\mathrm{U}}^{m_{i2}}}{\gamma_{i2}^{m_{i2}} + I_{\mathrm{U}}^{m_{i2}}} \\ |V_{\mathrm{L}}|\dfrac{\mathrm{d}I_{\mathrm{L}}}{\mathrm{d}t} = Q_{\mathrm{L}}I_{\mathrm{T}} - Q_{\mathrm{L}}I_{\mathrm{L}} - |V_{\mathrm{L}}|k_{\mathrm{IL}}\dfrac{I_{\mathrm{L}}^{m_{i3}}}{\gamma_{i3}^{m_{i3}} + I_{\mathrm{L}}^{m_{i3}}} \\ |V_{\mathrm{B}}|\dfrac{\mathrm{d}I_{\mathrm{B}}}{\mathrm{d}t} = Q_{\mathrm{B}}I_{\mathrm{T}} - Q_{\mathrm{B}}I_{\mathrm{B}} \\ |V_{\mathrm{S}}|\dfrac{\mathrm{d}I_{\mathrm{S}}}{\mathrm{d}t} = Q_{\mathrm{S}}I_{\mathrm{T}} - Q_{\mathrm{S}}I_{\mathrm{S}}. \end{cases} \tag{4}$$

We remark that following the fact 3, we have $C_{\mathrm{PC}} = I_{\mathrm{PC}}$.

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Next, we present the model for the glucose

$$\begin{cases} |V_{\mathrm{H}}|\dfrac{\mathrm{d}G_{\mathrm{H}}}{\mathrm{d}t} = Q_{\mathrm{H}}G_{\mathrm{T}} + Q_{\mathrm{PV}}G_{\mathrm{PV}} - Q_{\mathrm{V}}G_{\mathrm{H}} \\ -|V_{\mathrm{H}}|k_{\mathrm{GH1}}\dfrac{G_{\mathrm{H}}^{m_{g1}}}{\gamma_{g1}^{m_{g1}} + G_{\mathrm{H}}^{m_{g1}}} + |V_{\mathrm{H}}|k_{\mathrm{GH2}}\dfrac{G_{\mathrm{HC}}^{m_{hc1}}}{\gamma_{hc1}^{m_{hc1}} + G_{\mathrm{HC}}^{m_{hc1}}} \\ |V_{\mathrm{P}}|\dfrac{\mathrm{d}G_{\mathrm{P}}}{\mathrm{d}t} = Q_{\mathrm{P}}G_{\mathrm{T}} - Q_{\mathrm{P}}G_{\mathrm{P}} - |V_{\mathrm{P}}|k_{\mathrm{GLUT2}}\dfrac{G_{\mathrm{P}}}{\gamma_{\mathrm{GP}} + G_{\mathrm{P}}} \\ |V_{\mathrm{M}}|\dfrac{\mathrm{d}G_{\mathrm{M}}}{\mathrm{d}t} = Q_{\mathrm{M}}G_{\mathrm{T}} - Q_{\mathrm{M}}G_{\mathrm{M}} + k_{\mathrm{gm}}|V_{\mathrm{M}}|\dfrac{g_{\mathrm{m}}^2}{\gamma_{\mathrm{g}}^2 + g_{\mathrm{m}}^2} \\ |V_{\mathrm{R}}|\dfrac{\mathrm{d}G_{\mathrm{R}}}{\mathrm{d}t} = Q_{\mathrm{R}}G_{\mathrm{T}} - Q_{\mathrm{R}}G_{\mathrm{R}} \\ |V_{\mathrm{U}}|\dfrac{\mathrm{d}G_{\mathrm{U}}}{\mathrm{d}t} = Q_{\mathrm{U}}G_{\mathrm{T}} - Q_{\mathrm{U}}G_{\mathrm{U}} - k_{\mathrm{GU}}G_{4\mathrm{U}}|V_{\mathrm{U}}|G_{\mathrm{U}} \\ |V_{\mathrm{L}}|\dfrac{\mathrm{d}G_{\mathrm{L}}}{\mathrm{d}t} = Q_{\mathrm{L}}G_{\mathrm{T}} - Q_{\mathrm{L}}G_{\mathrm{L}} - k_{\mathrm{GL}}G_{4\mathrm{L}}|V_{\mathrm{L}}|G_{\mathrm{L}} \\ |V_{\mathrm{B}}|\dfrac{\mathrm{d}G_{\mathrm{B}}}{\mathrm{d}t} = Q_{\mathrm{B}}G_{\mathrm{T}} - Q_{\mathrm{B}}G_{\mathrm{B}} - k_{\mathrm{GB}}|V_{\mathrm{B}}|G_{\mathrm{B}} \\ |V_{\mathrm{S}}|\dfrac{\mathrm{d}G_{\mathrm{S}}}{\mathrm{d}t} = Q_{\mathrm{S}}G_{\mathrm{T}} - Q_{\mathrm{S}}G_{\mathrm{S}}. \end{cases} \tag{5}$$

We then present the model describing the glucose digestion, fact 4, which is given as follows,

$$\begin{cases} f(t) = \dfrac{1}{1+\exp\left(-2\frac{t-T_1}{\delta}\right)}\dfrac{1}{1+\exp\left(-2\frac{T_2-t}{\delta}\right)} \\ S(t) = f(t) \times \dfrac{\text{Mass of glucose[g]}}{\text{Water volume[dL]}} \times 55.5\text{[mmol/L]} \\ |V_{\mathrm{in}}|\dfrac{d}{dt}S_{\mathrm{in}} = Q_{\mathrm{in}}S(t) - Q_{\mathrm{SM}}S_{\mathrm{in}} \\ |V_{\mathrm{M}}|\dfrac{d}{dt}g_{\mathrm{m}} = Q_{\mathrm{SM}}S_{\mathrm{in}} - k_{\mathrm{gm}}|V_{\mathrm{M}}|\dfrac{g_{\mathrm{m}}^2}{\gamma_{\mathrm{g}}^2 + g_{\mathrm{m}}^2}, \end{cases} \tag{6}$$

where T_1 is the time moment the testee starts to drink the water, which will be set to 0, and T_2 is the time finish drinking. Q_{in} is the water flux from mouth to the mesentery, $S(t)$ is the concentration of glucose at time t in to the mouth; S_{in} is the concentration of glucose absorbed by the absorptive epithelial cell; g_{m} is the glucose in the blood vessels of the mesentery and $k_{\mathrm{gm}}|V_{\mathrm{M}}|\frac{g_{\mathrm{m}}^2}{\gamma_{\mathrm{g}}^2+g_{\mathrm{m}}^2}$ is the glucose in the blood vessel of the mesentery which participated in the circulation.

The glucose dynamics in the hepatocyte considering the phosphorylation and the tricarboxylic acid cycle are given by

$$\begin{cases} \dfrac{\mathrm{d}G_{\mathrm{HC}}}{\mathrm{d}t} = k_{\mathrm{GH1}}\dfrac{G_{\mathrm{H}}^{m_{g1}}}{\gamma_{g1}^{m_{g1}} + G_{\mathrm{H}}^{m_{g1}}} - k_{\mathrm{GH2}}\dfrac{G_{\mathrm{HC}}^{m_{hc1}}}{\gamma_{hc1}^{m_{hc1}} + G_{\mathrm{HC}}^{m_{hc1}}} \\ \qquad - k_{\mathrm{HC1}}\dfrac{G_{\mathrm{HC}}}{\gamma_{hc2} + G_{\mathrm{HC}}}I_{\mathrm{HC}} \\ \qquad + k_{\mathrm{HC2}}\dfrac{G_{6\mathrm{P}}}{\gamma_{hc3} + G_{6\mathrm{P}}}\dfrac{\gamma_{he2}^2}{\gamma_{he2}^2 + G_{\mathrm{H}}^2} \\ \dfrac{\mathrm{d}G_{6\mathrm{P}}}{\mathrm{d}t} = k_{\mathrm{HC1}}\dfrac{G_{\mathrm{HC}}}{\gamma_{hc2} + G_{\mathrm{HC}}}I_{\mathrm{HC}} \\ \qquad - k_{\mathrm{HC2}}\dfrac{G_{6\mathrm{P}}}{\gamma_{hc3} + G_{6\mathrm{P}}}\dfrac{\gamma_{he2}^2}{\gamma_{he2}^2 + G_{\mathrm{H}}^2} \\ \qquad - k_{\mathrm{TCA}}\dfrac{G_{6\mathrm{P}}}{\gamma_{\mathrm{TCA}} + G_{6\mathrm{P}}} + k_{\mathrm{gly}}(G_{\mathrm{LY}}^* - G_{6\mathrm{P}}), \end{cases} \tag{7}$$

where I_{HC} satisfies

$$\frac{\mathrm{d}I_{\mathrm{HC}}}{\mathrm{d}t} = k_{\mathrm{IH1}}\frac{I_{\mathrm{H}}^{m_{i1}}}{\gamma^{m_{i1}} + I_{\mathrm{H}}^{m_{i1}}} - k_{\mathrm{h3}}I_{\mathrm{HC}}. \tag{8}$$

The glucose and insulin dynamics, including the glucose transporter 4, in the upper and lower limbs for the fact 6 are given as

$$\begin{cases} \dfrac{dG_{4\mathrm{U}}}{dt} = k_{\mathrm{G4U}}(G_{4\mathrm{U}}^{\max} - G_{4\mathrm{U}})I_{\mathrm{UC}} - k_{d\mathrm{U}}G_{4\mathrm{U}} \\ \dfrac{dG_{4\mathrm{L}}}{dt} = k_{\mathrm{G4L}}(G_{4\mathrm{L}}^{\max} - G_{4\mathrm{L}})I_{\mathrm{LC}} - k_{d\mathrm{L}}G_{4\mathrm{L}} \end{cases} \tag{9}$$

where I_{UC} and I_{LC} satisfy

$$\begin{cases} \dfrac{d}{dt}I_{\mathrm{UC}} = k_{\mathrm{IU}}\dfrac{I_{\mathrm{U}}^2}{\gamma_{u2}^2 + I_{\mathrm{U}}^2} - k_{u2}I_{\mathrm{UC}} \\ \dfrac{d}{dt}I_{\mathrm{LC}} = k_{\mathrm{IL}}\dfrac{I_{\mathrm{L}}^2}{\gamma_{l2}^2 + I_{\mathrm{L}}^2} - k_{l2}I_{\mathrm{LC}}. \end{cases} \tag{10}$$

(1) The parameter estimation

We apply clinical data of the oral glucose tolerance test (OGTT) to perform the parameter estimation for the total system consists of the models (2) – (10).

In the OGTT, the healthy testee is asked to take 15.1 grams of glucose dissolved in 100 mL water within 3 minutes; and the concentration of glucose, insulin, and C-peptide concentrations in blood vessel of upper arm vein for every 15 minutes till time length of two hours will be taken as data.

The model contains 34 equations and about 40 parameters, and we apply Markov Chain Monte-Carlo (MCMC) method [5] to search for the parameters which minimize the error between the simulation results and the data.

(2) The medical validations

Once we obtained the estimated values parameters, we will computed the half-life time of insulin and of C-peptide and the hepatic insulin clearance rate to give the validation of the model in the medical sense.

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The half-life time

We compute the total moles of insulin and of C-peptide respectively, such that

$$I_{\mathrm{all}}(t) = \sum_{\mathrm{i}} |V_{\mathrm{i}}| I_{\mathrm{i}}(t), \text{ and } C_{\mathrm{all}}(t) = \sum_{\mathrm{i}} |V_{\mathrm{i}}| C_{\mathrm{i}}(t),$$

where $\mathrm{i} \in \{\mathrm{H}, \mathrm{P}, \mathrm{M}, \mathrm{R}, \mathrm{U}, \mathrm{L}, \mathrm{B}, \mathrm{S}\}$, and $I_{\mathrm{all}}(0)$ and $C_{\mathrm{all}}(0)$ is the value of insulin and C-peptide data at time $t = 0$ respectively. The half-life time $t_{1/2}$ of insulin is the time that $I_{\mathrm{all}}(t_{1/2}) = 0.5 \times I_{\mathrm{all}}(0)$ under the assumption that there is no secretion of insulin. And we define the half-life time of C-peptide correspondingly. We recall that as a medical fact, $t_{1/2}$ is about 4 to 10 minutes for insulin and $t_{1/2} \approx 30$ minutes for C-peptide.

The insulin hepatic clearance

While circulating in the body, the insulin will be cleared by hepatic and also by the upper arm and lower limbs. The ratio of the hepatic clearance is an important index of reflecting the hepatic function.

$$\begin{aligned}
&\text{Insulin Hepatic Clearance rate } (\%) \\
&= \frac{\text{Insulin cleared by hepatic}}{\text{Insulin cleared by hepatic and by upper and lower limbs}} \\
&= \frac{k_{\mathrm{IH1}} \dfrac{I_{\mathrm{H}}^{m_{\mathrm{i1}}}}{\gamma_{\mathrm{i1}}^{m_{\mathrm{i1}}} + I_{\mathrm{H}}^{m_{\mathrm{h1}}}}}{k_{\mathrm{IH1}} \dfrac{I_{\mathrm{H}}^{m_{\mathrm{i1}}}}{\gamma_{\mathrm{i1}}^{m_{\mathrm{i1}}} + I_{\mathrm{H}}^{m_{\mathrm{i1}}}} + k_{\mathrm{IU}} \dfrac{I_{\mathrm{U}}^{m_{\mathrm{i2}}}}{\gamma_{\mathrm{i2}}^{m_{\mathrm{i2}}} + I_{\mathrm{U}}^{m_{\mathrm{i2}}}} + k_{\mathrm{IL}} \dfrac{I_{\mathrm{L}}^{m_{\mathrm{i3}}}}{\gamma_{\mathrm{i3}}^{m_{\mathrm{i3}}} + I_{\mathrm{L}}^{m_{\mathrm{i3}}}}}.
\end{aligned}$$

As a medical fact, this rate shall be within $30\% \sim 80\%$.

3. Numerical results

We present the volume size of the blood vessels and the flux of blood through each organ. We apply the values in Table 1 [4].

Table 1 Values concerning the blood flux

Organ	Volume of blood vessels	Flux ratio
Hepatic	$\lvert V_{\mathrm{H}}\rvert = 1.14$	$\alpha_{\mathrm{H}} = 0.05$
Pancreas	$\lvert V_{\mathrm{P}}\rvert = 1.14$	$\alpha_{\mathrm{P}} = 0.05$
Mesentery	$\lvert V_{\mathrm{M}}\rvert = 0.94 \times \frac{\alpha_{\mathrm{S}}}{\alpha_{\mathrm{M}}+\alpha_{\mathrm{S}}}$	$\alpha_{\mathrm{M}} = 0.1$
Renal	$\lvert V_{\mathrm{R}}\rvert = 0.51$	$\alpha_{\mathrm{R}} = 0.2$
Upper arm	$\lvert V_{\mathrm{U}}\rvert = 0.74 \times \frac{\alpha_{\mathrm{U}}}{\alpha_{\mathrm{U}}+\alpha_{\mathrm{L}}}$	$\alpha_{\mathrm{U}} = 0.15$
Lower limbs	$\lvert V_{\mathrm{L}}\rvert = 0.74 \times \frac{\alpha_{\mathrm{L}}}{\alpha_{\mathrm{U}}+\alpha_{\mathrm{L}}}$	$\alpha_{\mathrm{L}} = 0.25$
Brain	$\lvert V_{\mathrm{B}}\rvert = 0.26$	$\alpha_{\mathrm{B}} = 0.15$
Stomach	$\lvert V_{\mathrm{S}}\rvert = 0.94 \times \frac{\alpha_{\mathrm{S}}}{\alpha_{\mathrm{M}}+\alpha_{\mathrm{S}}}$	$\alpha_{\mathrm{S}} = 0.05$

And there holds

$$\begin{aligned}
Q_{\mathrm{T}} &= \sum_{\mathrm{i}} Q_{\mathrm{i}} \\
Q_{\mathrm{i}} &= \alpha_{\mathrm{i}} Q_{\mathrm{T}},
\end{aligned} \tag{11}$$

where $\mathrm{i} \in \{\mathrm{H}, \mathrm{P}, \mathrm{M}, \mathrm{R}, \mathrm{U}, \mathrm{L}, \mathrm{B}, \mathrm{S}\}$, $Q_{\mathrm{T}} = 3.6$ [L/min], which is the total flux goes in and out of the heart. We set all the power in the Hill's function to be 2 and we perform estimation and present one estimated results as follows in Jupyter widgets.

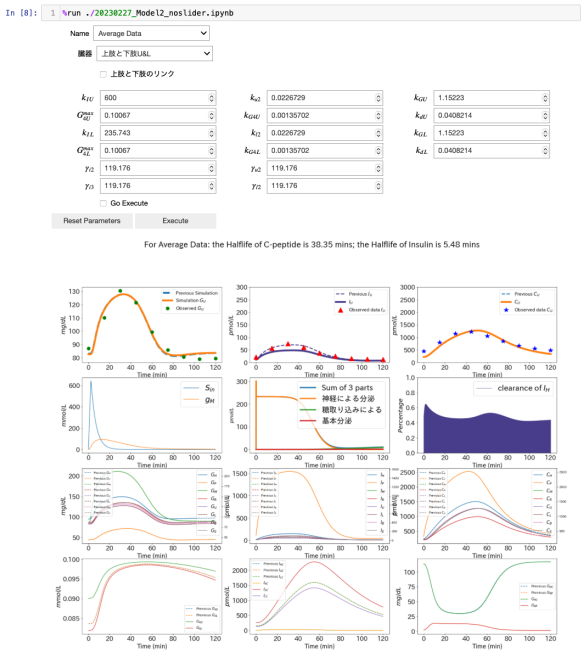

Fig. 1 Numerical results

From the simulation results, we observe that the insulin hepatic clearance varies within the region from 30% to 80%. With the estimated parameters, we simulate the total moles of insulin I_{all} and of C-peptide C_{all}, and compute the half-life times which turn out to be 6.07 minutes for insulin and 38.35 minutes for C-peptide.

4. Conclusion

In this work, we present a compartmental model of systemic circulation which describes the glucose, insulin and C-peptide dynamics. The model is constructed based on the principle of conservation of moles, and has taken the blood circulation and the dynamics of all the organs concerning with glucose, insulin and C-peptide into account. We apply Markov Chain Monte-Carlo method to estimate the parameters' values which minimize the error between the model results and the data. We apply the estimated parameters and compute the half-life times of insulin and of C-peptide, as well as the insulin hepatic clearance, and the results are validated by the medical facts.

Our results obtained the medical validation for the model. As the aim of this research is to find the early signals of the diabetes so to prevent the diabetes from developing, and the data we have used in this presentation is from the healthy people, a next step is to use the data of the mouse with different diet. High fat diet treated mouse is widely used as experimental animal model for hyperglycemia study. We plan to determine the parameters which are different between the healthy mouse and the hyperglycemia mouse, and we expect the results to lead to the clarification of healthy and unhealthy mouse, and then to the definition of healthy, pre-disease, and disease states

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of diabetes by the mathematical model.

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APPENDIX : The parameters to be estimated.

Table 2 Parameters to be estimated

Parameters	Explanation
$k_{\mathrm{CR3}}, \gamma_{\mathrm{c1}}$	Excretion of C-petide
$k_{\mathrm{IU}}, \gamma_{\mathrm{i2}}$	Insulin upper arm clearance
$k_{\mathrm{IH}}, \gamma_{\mathrm{i1}}$	Insulin hepatic clearance
$k_{\mathrm{IL}}, \gamma_{\mathrm{i3}}$	Insulin lower limbs clearance
$k_{\beta}, I^{0}_{\mathrm{PC}}$	Insulin basic production
$k_{\mathrm{E}}, \gamma_{\mathrm{S}}$	Insulin secretion (intake of glucose)
$k_{\mathrm{GIP}}, \gamma_{\mathrm{G}}$	Insulin secretion (increasement of G_{P})
k_{out}	Basic Insulin secretion
$k_{\mathrm{GH2}}, \gamma_{\mathrm{hc1}}$	Glucose from hepatocyte to blood
$k_{\mathrm{GH1}}, \gamma_{\mathrm{g1}}$	Glucose from blood to heptocyte
Q_{sm}, T_2	Glucose intake
$k_{\mathrm{gm}}, \gamma_{\mathrm{g}}$	Glucose absorption
$k_{\mathrm{GLUT}}, \gamma_{\mathrm{GP}}$	Glucose in pancreas
$k_{\mathrm{HC1}}, k_{\mathrm{HC2}}$	Dynamics in hepatocyte
$\gamma_{\mathrm{hc2}}, \gamma_{\mathrm{hc3}}$	Dynamics in hepatocyte
$\gamma_{\mathrm{he2}}, k_{\mathrm{h3}}$	Dynamics in hepatocyte
$k_{\mathrm{TCA}}, \gamma_{\mathrm{TCA}}$	Dynamics in hepatocyte
$k_{\mathrm{gly}}, G^{*}_{\mathrm{LY}}$	Dynamics in hepatocyte
$k_{\mathrm{G4U}}, G^{\max}_{\mathrm{4U}}$	GLUT4 dynamics
k_{dU}	GLUT4 dynamics
$k_{\mathrm{u2}}, \gamma_{\mathrm{u2}}$	Insulin dynamics in upper arms
$k_{\mathrm{l2}}, \gamma_{\mathrm{l2}}$	Insulin dynamics in lower limbs

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