Effect of physiological parameters on glucose microcirculation compartmental model in glucose monitoring

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ABSTRACT

A glucose microcirculation compartmental model (GMCM) for predicting blood glucose concentrations from the reference interstitial fluid (ISF) glucose concentrations was proposed before. It was used to compensate the delay error in ISF in order to improve the prediction accuracy and to facilitate the clinical application of continuous blood glucose monitoring. In this paper, many physiological parameters in GMCM reflecting delay and transport properties were discussed in details. The significance and influence of the parameters, diffusion distance (x), pressure gradient-driven transport ratio ($R_{Starling}$), blood flow velocity ($F$), glucose capillary permeability ($P$), glucose diffusion coefficient ($D$), on the model were simulated and analysed. One group of blood (ISF) glucose values was set as input for the model with one varied parameter and other fixed parameters to predict ISF (blood) glucose concentrations. The results verified that $F$ and $P$ have much influence on the model and others play more minor roles. And some have positive influence on the model, like $P$, while others have a reverse effect, like $F$. All parameters can be modulated for different species or different physiological status during the model application.

Introduction

Most continuous blood glucose monitoring (CBGM) methods are based on detecting interstitial fluid (ISF) glucose concentrations continuously [1,2]. There is a delayed relationship between blood and ISF glucose concentrations, especially when glucose levels are rapidly changing [3]. The clinical diagnosis and treatment criteria for diabetes are still blood glucose concentrations. Therefore, the quality of ISF-derived CBGM data consequently depends on the degree of precision and accuracy of the ISF glucose measurements, and the accurate calculation of blood glucose concentrations from ISF glucose measurements. It remains challenging to establish an accurate mathematical model to reflect the delayed relationship and convert ISF to blood glucose concentrations.

At present, some mathematical models reflecting the blood and ISF glucose delay relationship with normal and physiological parameters have been established by different research institutions. Schmidtke et al. [4] proposed a two-compartmental model based on vessel and tissue compartments, with one parameter of the rate of glucose movement from blood to tissue or from tissue to blood. Rebrin et al. [5] and Steil et al. [6,7] simplified the compartmental model to a mass transfer model including the parameters of the volume of ISF, the mass transfer coefficient and the uptake and utilization rate of glucose by cells etc. Barman et al. [8,9] proposed pre-calibration dynamic concentration correction and post-prediction dynamic concentration correction models with one-parameter, delay coefficient reflecting all potential changes in the model. Koutny [10–13] utilized a differential method to change the mass transfer model into a new one including the parameters of glucose permeability, glucose uptake rate, blood flow etc. Our glucose microcirculation compartmental model (GMCM) proposed before [3] also introduced many parameters to reflect the glucose dynamic properties between blood and ISF, like glucose permeability, blood flow and glucose diffusion coefficient etc. And some in vivo experiments related to the physiological parameters have been discussed by some researchers [14]. As shown in the above-mentioned models, if the models are to be applied to the CBGM detection methods or the clinical diagnosis and treatment, the parameters, normal or physiological ones, should be analysed and fixed first, otherwise the models would just stop with theoretical analysis.
The purpose of the present work was to simulate the variations of parameters in the model by the computer MATLAB language, analyse the influence of these parameters on the model and discuss the biological significance and the correspondence relationship between physiological parameters and status in the living body. The theoretical model (GMCM) was verified by simulating glucose kinetics based on model formulae, and fitting given glucose concentrations into the model with fixed parameters.

### Simulation methods of physiological parameters

In the following established GMCM (Equation (1)), many parameters, reflecting kinetics characteristics and delay properties, were introduced into the equations. Where \( C_{\text{blood}} \) is the blood glucose concentration, \( C_{\text{isf}} \) is the ISF glucose concentration, \( C_{\text{blood-isf}} \) is the ISF glucose concentration close to the capillary walls, \( P \) is the permeability coefficient, \( F \) is the blood flow, \( erf \) is the error function, \( D \) is the glucose diffusion coefficient, \( A \) is the surface area, \( x \) is the diffusion distance, \( t \) is time, \( R_{\text{Fick}} \) and \( R_{\text{Starling}} \) are the ratios of concentration and pressure gradient-driven transport, \( C_{\text{isf-Fick}} \) and \( C_{\text{isf-Starling}} \) are ISF glucose concentrations by concentration and pressure gradient-driven transport, \( J_{V-\text{gain}} \) and \( J_{V-\text{loss}} \) are the flux tissue got or lost. The model includes the capillary hydrostatic pressure \( P_{\text{c}} \), the interstitial hydrostatic pressure \( P_{\text{v}} \), the capillary oncotic pressure \( \pi_{\text{c}} \) and the interstitial oncotic pressure \( \pi_{\text{v}} \). They are related to the pressure gradient-driven transport, which describes the liquid exchange between blood and tissues. Unless there are physiological pathological changes such as oedema, liquid exchange, pressure gradient-driven transport will eventually achieve a dynamic balance state with constant pressure values. Both the filtration \( K_{f} \) and the reflection coefficient \( \sigma \) are proportionality constant. The capillary pressure approximations are \( P_{\text{a}} = 35 \text{ mmHg} \), \( P_{\text{v}} = 15 \text{ mmHg} \), \( \sigma_{\text{c}} = 25 \text{ mmHg} \), and \( K_{v} \) a proportionality constant, is set as \( K_{f} = 0.978 \text{ mL/min/mmHg} \) [15]. The surface area \( A \) is set as 1 unit:

\[
\begin{align*}
C_{\text{blood-isf}}(t) &= R_{\text{Fick}} \times C_{\text{isf-Fick}}(t) + R_{\text{Starling}} \times C_{\text{isf-Starling}}(t) \\
C_{\text{isf-Fick}}(t) &= C_{\text{blood}}(t) - \left( \frac{1 - e^{-PA/F}}{P} \right) \times F \times C_{\text{blood}}(t) \\
C_{\text{isf-Starling}}(t) &= \frac{J_{V-\text{gain}}}{J_{V-\text{gain}} + J_{V-\text{loss}}} \times C_{\text{blood}}(t) + \frac{J_{V-\text{loss}}}{J_{V-\text{gain}} + J_{V-\text{loss}}} \times C_{\text{isf}}(t) \\
J_{V-\text{gain}} &= K_{f} \left( \int_{P_{\text{a}}}^{P_{\text{c}}} P_{\text{c}} - P_{\text{a}} \times dP_{c} \right) \\
J_{V-\text{loss}} &= K_{f} \left( \int_{P_{\text{a}}}^{P_{\text{c}}} P_{\text{v}} - P_{\text{a}} \times dP_{c} \right)
\end{align*}
\]

To discuss the parameters’ variation and significance on the model, the equations were simulated through a computer program. One group of glucose concentrations (in blood or ISF) need to be set as the input of the model. Therefore, we made a group of represented blood glucose concentrations as the input data (Table 1), which could reflect the glucose variation in glucose tolerance condition. The given group of blood glucose concentrations with linear interpolation, under a glucose tolerance test, was used as the input to simulate the reference ISF glucose concentration using GMCM. The following parameters, the ratio of pressure gradient-driven transport, blood flow velocity, glucose membrane permeability and diffusion coefficient, in GMCM would be simulated and discussed respectively. According to the physiological knowledge, the ratio of pressure gradient-driven transport (\( R_{\text{Starling}} \)) is very small, so its effective range is assumed to be \( 0 \sim 0.2 \) [16]. The blood flow velocity (\( F \)) of skin tissue is \( 1 \sim 3 \text{ mL}/100 \text{ g/min} \) at rest and \( 5 \sim 15 \text{ mL}/100 \text{ g/min} \) in motion [16]. The values of the glucose membrane permeability (\( P \)) range from 15 to 30 \text{ mL}/100 \text{ g/min}/\text{m}^2 [17]. The effective range of the diffusion coefficient \( D \) is \( 1 \sim 3 \times 10^{-10} \text{ m}^2/\text{s} \) [18].

### Results and discussion

#### Diffusion distance of glucose molecule

In muscle and adipose tissue, the longest inter-capillary diffusion distance is \( 30 \sim 50 \ \mu \text{m} \) [19]. Therefore, we assumed a diffusion distance \( x \) of 0, 5, 10, 15, 20 and 25 \( \mu \text{m} \) to discuss the model variation. The physiological parameters in GMCM were fixed based on theoretical values, \( R_{\text{Starling}} = 0.05 \), \( R_{\text{Fick}} = 0.95 \), \( F = 3 \text{ mL}/100 \text{ g/min} \), \( P = 30 \text{ mL}/100 \text{ g/min}/\text{m}^2 \) and \( D = 2 \times 10^{-10} \text{ m}^2/\text{s} \). The simulation results are presented in Figure 1. ISFG
represent ISF glucose concentrations. The results showed that there are no obvious differences in the glucose concentrations in the tissue at a distance of 0, 5, 10, 15, 20 and 25 \( \mu m \) from the capillary wall. This may be because the glucose diffusion over such a small distance is rapid and occurs within a few seconds. Our findings are in agreement with a previous study [11], in which ISF glucose concentrations in different tissues, e.g. the subcutaneous tissue, the skeletal muscle tissue and the visceral fat, were found to be approximately equal.

**Pressure gradient-driven transport ratio**

The glucose molecules movements between blood and tissues include two forms: one is pressure gradient-driven transport and the other is diffusion transport through capillary walls. \( R_{\text{Starling}} \) is the ratio of the pressure gradient-driven transport. \( R_{\text{Fick}} \) is the ratio of the diffusion transport through the capillary walls. The sum of \( R_{\text{Starling}} \) and \( R_{\text{Fick}} \) is 1. According to the physiological knowledge, the ratio of the glucose pressure gradient-driven transport is very small. Therefore, the effective range of \( R_{\text{Starling}} \) is assumed to be between 0 and 0.2. When it was fixed at 0, 0.05, 0.1, 0.15, 0.2, the relationship of glucose concentrations in blood and ISF in GMCM was simulated by computer, and the other physical parameter values were fixed in their effective range, \( P = 30 \text{ mL/100 g/min/m}^2 \), \( F = 3 \text{ mL/100 g/min} \), \( D = 2 \times 10^{-10} \text{ m}^2/\text{s} \). In short, after the other parameters are fixed, the corresponding changes of glucose concentration in the tissue are discussed by substituting the interpolation blood glucose concentration into the model.

The simulation results are shown in Figure 2. The blood and ISF glucose concentrations had the same variation trend. When blood glucose levels rise, ISF glucose levels rise, and vice versa. However, the blood and ISF glucose concentrations are not equal at each time point, and exhibit delayed changes when glucose levels rapidly change. When \( R_{\text{Starling}} \) was 0, the concentration of glucose in the tissue fluid was closest to the blood glucose levels. With the increase of the ratio value, the difference among the ISF glucose concentrations corresponding to different ratio values was small, indicating that the variation of the pressure gradient-driven transport ratio had little effect on the model. Therefore, the pressure gradient-driven transport is not the main transport of glucose molecules through capillary walls, but diffusion transport.
is. Though the pressure gradient-driven transport is secondary, this kind of movement really exists in glucose exchange between blood and ISF. Within the effective range of 0~0.2, all can be considered to be the best parameter values of this ratio. This is in agreement with other reports that the mass of glucose transferred increases with an increase in the concentration gradient.

**Blood flow velocity**

$F$ is the blood flow velocity; this physiological parameter can be influenced by many factors, like the neuromodulation system, temperature, changes in hormone levels and some chemicals in the organism. The blood flow velocity of skin tissue, at rest is 1~3 mL/100 g/min and in motion, 5~15 mL/100 g/min [16]. Blood glucose molecules are not static; blood glucose concentration changes with the flow of blood through the microcirculation system of capillary blood vessels. The blood flow velocity can reflect the physiological state of the organism because of the association with the temperature of living organisms. When the body is in a state of motion or exuberant life activities, the body temperature rises and the blood flow velocity will be faster. When the body is in a state of rest or sleep, the body temperature drops and the blood flow rate will be slower. Therefore, the GMCM proposed in this paper is closely related to the organism physiological state, such as motion, rest and sleep. According to different physiological states, the glucose concentration physiological parameters in the model can be adjusted to improve and enhance the model accuracy for CBGM, and finally design a personalized treatment plan. When using a computer to simulate the blood flow velocity, the other parameters were fixed within the effective range, $P = 30$ mL/100 g/min/m², $R_{Starling} = 0.1$, $D = 2 \times 10^{-10}$ m²/s; the blood glucose concentrations were substituted into the model as the input value to discuss ISF glucose with a blood flow velocity of 1, 3, 5, 10 and 15 mL/100 g/min.

The simulation results are shown in Figure 3. When the blood flow velocity is smaller, the ISF glucose is much closer to the blood glucose concentration, which suggests that there is enough time for exchange of glucose molecules between capillaries and the surrounding tissue in slow blood flow. On the contrary, when the blood flow velocity is greater, the ISF glucose concentration diverges far from the blood glucose concentration, indicating that there is less time for exchange of glucose molecules between the two compartments in such a fast blood flow. Consequently, the difference between the glucose concentration in the blood and ISF is larger. These results suggest that the blood flow has a great influence on the model and the delay relationship of ISF glucose changes. There is an inversely proportional relationship between blood flow and ISF glucose concentrations, which means that the higher the blood flow rate is, the lower the ISF glucose concentrations become and vice versa. However, both high correlation and delay relationship exist between blood and ISF glucose concentrations. Koutny [13] proposed that greater volume of the ISF results into a lower speed of flow, which increases the glucose molecules travel time. This was supported to a certain extent by our findings.

**Glucose capillary permeability**

$P$ is the glucose capillary permeability, determined by the capillary wall structure, the gap and the size of molecular exchange. It is usually constant for one particular molecule, which reflects the ability of the molecule to pass through the capillary walls. The permeability of glucose molecules through the capillary is in the range of 15~30 mL/100 g/min/m² [17,20]. The choice of parameters was done by analogy to that above: the glucose permeability was set at 15, 20, 25, 30 and 35 mL/100 g/min/m² and the other parameters were fixed at $F = 3$ mL/100 g/min, $R_{Starling} = 0.1$, $D = 2 \times 10^{-10}$ m²/s. As shown in Figure 4, when the value of permeability is large, the ISF glucose concentrations are much closer to the blood glucose concentrations, as much more glucose molecules pass through the capillary wall. When the permeability value becomes smaller, less glucose molecules pass through the capillary wall, so the difference between blood and ISF glucose concentrations becomes larger. From the simulation, it can be seen that the model is influenced to a large extent by the parameter glucose permeability. The computer simulation results are consistent with the theory. The results...
obtained in this study are in accordance with recent observations that the verified capillaries permeability in different compartments is different, which results in different ISF glucose concentrations [13].

**Glucose diffusion coefficient**

$D$ is the glucose molecules diffusion coefficient in the tissue, reflecting the character of the glucose molecules’ diffusion rate, which is usually constant. It is associated with the diffusion medium environment and diffusion medium density. The range of the glucose diffusion coefficient values [18] is within $1 \times 10^{-10} \text{ m}^2/\text{s}$. The above three physical parameters are related to the glucose transport between capillaries and the surrounding tissue through the capillary wall and the parameter $D$ is associated with glucose diffusion movement. By analogy to the considerations discussed above, within the effective range, $D$ was taken to be $1, 1.5, 2, 2.5, 3 \times 10^{-10} \text{ m}^2/\text{s}$ and the other parameters were fixed at $F = 3 \text{ mL}/100 \text{ g/min}$, $R_{\text{Starling}} = 0.1$ and $P = 30 \text{ mL}/100 \text{ g/min}/\text{m}^2$.

The blood glucose concentrations under the tolerance test with interpolation were set as the model input values for predicting the change of the glucose concentrations in ISF through computer simulation.

As shown in Figure 5, the ISF glucose level changes were shown to be closer to the variation in the blood glucose concentration with the larger diffusion coefficient; on the contrary, the ISF glucose concentration was only a little different from the blood glucose concentration at the corresponding time with a smaller diffusion coefficient. These results show that the larger the diffusion coefficient is, the faster the glucose molecules diffuse, and the smaller the coefficient is, the slower the glucose molecules diffuse. However, the difference among the ISF glucose concentrations simulated with different diffusion values was small, indicating that the diffusion coefficient has little influence on the model. This is in accordance with different tissue position with similar ISF glucose concentrations [11].

**Conclusions**

The GMCM reflecting the delay relationship between blood and ISF glucose was verified and discussed by simulation. The results revealed that the ISF glucose concentrations are lower than the blood glucose concentrations in most conditions. The inter-capillary distance in the tissue is very short. The glucose diffusion over such a small distance is rapid and occurs within a few seconds. Blood flow velocity and glucose capillary permeability were shown to have much influence on this model, whereas other parameters had less influence on it. Comparing to pressure gradient-driven transport, concentration gradient-driven transport is the main form of glucose transport between capillaries and the surrounding tissue. The glucose diffusion coefficient largely depends on the tissue structure, so it is much stabilized. The blood flow is easily changed by the physiological activities, while the permeability can be influenced by physiological disorders. The analysis and discussion of GMCM’s parameters are very important for compensating the delay in ISF glucose variation, improving the prediction accuracy and facilitating the clinical application of CBGM.

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