Two Compartment Model: FDG method for measuring regional cerebral glucose metabolism rate

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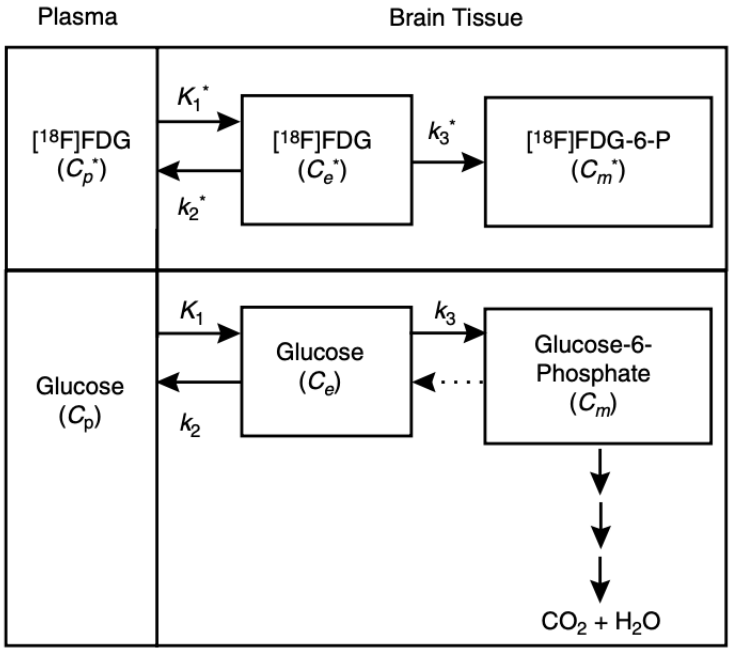

Figure 1: Model for the measurement of cerebral glucose use with [18F]FDG. Taken from [1].

1 Model and operational calculation

Physiolocal and biochemical processes: Glucose is transported between arterial blood and tissue by a saturable carrier. Once it enters the tissue, it undergoes phosphorylation by hexokinase

(an enzyme) and produces glucose-6-phosphate, which continues down the metabolism pathway to produce water and CO2. FDG competes with glucose for the same blood-tissue transport carrier and hexokinase. The difference is that, after phosphorylation FDG becomes FDG-6-P, which cannot continue the metabolism path and is essentially trapped in the tissue over the time course of the measurements. (Key words: blood-tissue carrier-mediated transport, phosphorylation with hexokinase, competing substrates.)

- C_p^* and C_p: concentration of [18F]FDG and glucose in arterial plasma, respectively.
- C_e^* and C_e: concentration of free [18F]FDG and glucose in the exchange/precursor pool in tissue, respectively.
- C_m^* and C_m: concentration of [18F]FDG-6-P and Glucose-6-Phosphate in the tissue, respectively.
- K_1^* and K_1: rate constant of the carrier-mediated transport from blood to tissue of [18F]FDG and glucose, respectively.
- k_2^* and k_2: rate constant of the carrier-mediated transport from tissue to blood of [18F]FDG and glucose, respectively.
- k_3^* and k_3: rate constant for phosphorylation by hexokinase of [18F]FDG and glucose in tissue, respectively.

The dashed line represents the possibility of glucose-6-phosphate hydrolysis by glucose-6-phosphatase, a process that reverses the phosphorylation process and produces glucose.

The quantity we are interested in is the *regional cerebral metabolism rate of glucose*, abbreviated as $\mathrm{rCMR_{glc}}$ in [1]. For simplicity in this note we use the symbol R. The unit of R is concentration of glucose per unit time, i.e. amount of glucose per mass of tissue per unit time, e.g. mg/100 g brain tissue/min.

The operational equation to calculate R is

$$R = \frac{C_t^*(T) - K_1^* \displaystyle\int_0^T C_p^*(t) e^{-(k_2^*+k_3^*)(T-t))}\,\mathrm{d}t}{\left(\frac{\lambda}{\Phi}\frac{V_m^* K_m}{V_m K_m^*}\right)\left(\displaystyle\int_0^T \frac{C_p^*(t)}{C_p}\mathrm{d}t - \int_0^T \frac{C_p^*(t)}{C_p} e^{-(k_2^*+k_3^*)(T-t)}\mathrm{d}t\right)}, \tag{1}$$

where

- T is the end time point of measurements.
- $C_t^*(t)$ is the total concentration of 18F in *tissue* measured by the scanner at time t. This activity may come from both [18]FDG and [18F]FDG-6-P. Note that the value of $C_t^*(t)$ obtained through a scanner measurement by an ROI analysis may contain activity from blood as well, although it is a small fraction. In the original Sokoloff paper [2], this is denoted as $C_i^*(t)$.
- $C_p^*(t)$ is the concentration of [18F]FDG in the arterial plasma at time t, to be measured.
- C_p is the concentration of glucose in the arterial plasma, assumed to be a constant and measured. (ZEYU: how to determine this value?)

- V_m^*, K_m^*, V_m, K_m are the maximal velocity and Michaelis-Menten constant of the hexokinase reaction for [18F]FDG and glucose phosphorylation, respectively.
- $\lambda = \frac{K_1^*/(k_2^*+k_3^*)}{K_1/(k_2+k_3)}$ is the ratio of the distribution volume for [18F]FDG and glucose in the tissue.
- Φ is a constant between 0 and 1 that represents the fraction of glucose that once phosphorylated is metabolized further. Φ is close to 1, because there is little glucose-6-phosphanase in the brain to facilitate the hydrolysis process. Thus $R = \Phi v$, the *net* glucose use rate, where v is the glucose phosphorylation rate.
- $\frac{\lambda}{\Phi}\frac{V_m^* K_m}{V_m K_m^*}$ is the *lumped constant* to be measured/estimated.

2 Interpretation

Recall that R is the metabolism rate of glucose. Whenever one talks about rate, it is some physical quantity per unit time. In this case, this is the glucose usage (in terms of concentration) per time. Therefore the numerator of R must be some kind of concentration, and the denominator of R must be some kind of time, with some appropriate scaling.

As can be shown in the derivation below, the numerator is $C_e^*(T) - C_e^*(T)$, the difference between the concentration of [18F]FDG in blood and in tissue precursor pool at the end of measurement T, i.e. it is $C_m^*(T)$, the concentration of [18F]FDG-6-P, the product of [18F]FDG phosphorylation, in tissue at time T.

Now, take a look at the denominator. The scaling constants convert rates for [18F]FDG to rates for glucose. Now, think about the difference between the two integrals. Take $\frac{1}{C_p}$ out first. The integral

$$\int_0^T C_p^*(t)\,\mathrm{d}t$$

is the area of the curve $C_p^*(t)$ over time from time zero to T. Physically, it is the *total/integrated concentration* (alternatively, total/integrated activity) of [18F]FDG in plasma from time zero to T, and its unit is *concentration* $\cdot$ *minutes*. The second integral

$$\int_0^T C_p^*(t) e^{-(k_2^*+k_3^*)(T-t)}\,\mathrm{d}t\,,$$

according to [1], is a correction term that corrects for the lag in equilibrium of the tissue precursor pool behind the plasma (ZEYU: I don't understand this sentence.). It follows that, this corrected integrated concentration or activity of [18F]FDG is divided by C_p to produce a *scaled time*. To summarize,

$$\text{rate} = \frac{\text{concentration of produced [18F]FDG-6-P}}{\text{scaled time}}\,.$$

3 Derivation

This derivation is adapted from the calculation of R using [14C]deoxyglucose in [2]. [14C]deoxyglucose and [18F]FDG share similar biochemical properties, as far as the processes considered in the compartment model.

Step 1: link the glucose process to the FDG process.

Recall that we want to calculate R, the net metabolism rate of glucose. However, because glucose is not labeled, it cannot be detected or measured directly. So we need to link R to some reaction rates related to FDG which can be measured.

We start with applying the Fick's principle to the glucose extraction from blood to tissue:

$$F(C_a - C_v) = R\,, \tag{2}$$

where F is the blood flow (perfusion) in volume per unit time per mass of tissue (e.g. ml/min/g), C_a and C_v are the concentrations of glucose in the arterial and venous blood, respectively, with units in e.g. mg/ml. The equation says, the net rate of glucose uptake in the blood is equal to the net rate of glucose utilization/use in the tissue. **The implicit assumption here is that, the glucose metabolism of the tissue is in steady state, i.e. R is a constant.**

Applying Fick's principle again to [18F]FDG, we get

$$F(C_a^* - C_v^*) = \frac{\mathrm{d}C_i^*(t)}{\mathrm{d}t}\,, \tag{3}$$

where C_a^* and C_v^* are the concentrations of 18F in the arterial and venous blood, respectively, and $C_i^*(t)$ is the total concentration of 18F in the tissue at time t. The source of $C_i^*(t)$ could be either [18F]FDG or [18F]FDG-6-P, therefore

$$C_i^*(t) = C_e^*(t) + C_m^*(t)\,, \tag{4}$$

and it follows that

$$\frac{\mathrm{d}C_i^*(t)}{\mathrm{d}t} = \frac{\mathrm{d}C_e^*(t)}{\mathrm{d}t} + \frac{\mathrm{d}C_m^*(t)}{\mathrm{d}t}\,. \tag{5}$$

By definition, $\frac{\mathrm{d}C_m^*(t)}{\mathrm{d}t}$ is the rate of [18F]FDG phosphorylation, the rate at which [18F]FDG-6-P accumulates. We denote this by v^*, thus

$$\frac{\mathrm{d}C_i^*(t)}{\mathrm{d}t} = \frac{\mathrm{d}C_e^*(t)}{\mathrm{d}t} + v^*\,. \tag{6}$$

Dividing both sides by R, we get

$$\frac{\mathrm{d}C_i^*(t)/\mathrm{d}t}{R} = \frac{\mathrm{d}C_e^*(t)/\mathrm{d}t}{R} + \frac{v^*}{R}\,. \tag{7}$$

(ZEYU: it seems like we didn't use Eq. (2) and Eq. (3). Turns out that they are useful in deriving an equation for the empirical estimate of the lumped constant. For now, we don't use them.)

Next, we relate R to v by $R = \Phi v$. Recall that v is the glucose phosphorylation rate. According to the model, not all phosphorylated glucose will continue down the metabolism path. Some of the produced glucose-6-phosphate go through the reverse process called hydrolysis to bring back some glucose. Φ is the fraction of glucose that once phophorylated is metabolized further, a value between 0 and 1. According to [2], Φ is very close to one. Thus,

$$\frac{\mathrm{d}C_i^*(t)/\mathrm{d}t}{R} = \frac{\mathrm{d}C_e^*(t)/\mathrm{d}t}{R} + \frac{v^*}{\Phi v}\,. \tag{8}$$

We can re-arrange the above to obtain

$$R = \frac{\mathrm{d}C_i^*(t)/\mathrm{d}t - \mathrm{d}C_e^*(t)/\mathrm{d}t}{\frac{1}{\Phi}\frac{v^*}{v}}\,. \tag{9}$$

This is not the operational equation used by Sokoloff et. al., but this provides much **insight: the glucose metabolism rate R is proportional to the glucose phosphorylation rate v, which is proportional to the [18]FDG phosphorylation rate v^* through enzyme competition, which is equal to** $\frac{\mathrm{d}C_m^*(t)}{\mathrm{d}t} = \frac{\mathrm{d}C_i^*(t)}{\mathrm{d}t} - \frac{\mathrm{d}C_e^*(t)}{\mathrm{d}t}$. This insight can be briefly summarized in the following math:

$$R \propto v \propto v^* = \frac{\mathrm{d}C_m^*(t)}{\mathrm{d}t} = \frac{\mathrm{d}C_i^*(t)}{\mathrm{d}t} - \frac{\mathrm{d}C_e^*(t)}{\mathrm{d}t}\,. \tag{10}$$

However, Eq. (9) is not used by Sokoloff et. al. as the operational equation, because this calculation is essentially based on a time instant t. It should be noted that the term $\frac{v^*}{v}$ is actually time-dependent, because v^* is time-dependent and v is assumed to be constant (more on this later). A more robust way is to calculate an average R over the course of the measurement. Sokoloff et. al. take the integration on both sides of Eq. (8) from time zero to T, then re-arrange to get

$$R = \frac{C_i^*(T) - C_e^*(T)}{\frac{1}{\Phi}\displaystyle\int_0^T \frac{v^*}{v}\,\mathrm{d}t}\,. \tag{11}$$

At this point, we have shown where the first term $C_t^*(T)$ (or $C_i^*(T)$) in the numerator in Eq. (1) comes from. The coefficient $\frac{1}{\Phi}$ in the denominator also appears.

Step 2: Calculate $C_e^*(T)$ by standard convolution.

Consider the precursor compartment for [18F]FDG, the following first-order DE can be obtained for [18F]FDG kinetics:

$$\frac{\mathrm{d}C_e^*(t)}{\mathrm{d}t} = K_1^* C_p^* - k_2^* C_e^* - k_3^* C_e^*\,. \tag{12}$$

The solution is

$$C_e^*(t) = K_1^* C_p^*(t) \otimes e^{-(k_2^*+k_3^*)t} = K_1^* \int_0^t C_p^*(\tau) e^{-(k_2^*+k_3^*)(t-\tau)}\,\mathrm{d}\tau\,. \tag{13}$$

Replacing t with T, we obtain the second term in the numerator in Eq. (1).

Step 3: Find $\frac{v^*}{v}$ by Michaelis-Menten kinetics for two competing substrates.

The phosphorylation of glucose and [18F]FDG are both activated by the same enzyme called hexokinase. Therefore glucose and [18F]FDG are two competing substrates. By Michaelis-Menten kinetics (see a previous note by Zeyu), the phosphorylation rates of [18F]FDG and glucose are, respectively:

$$v^* = \frac{\frac{V_m^*}{K_m^*} C_e^*(t)}{1 + \frac{C_e^*(t)}{K_m^*} + \frac{C_e}{K_m}} \quad \text{and} \quad v = \frac{\frac{V_m}{K_m} C_e}{1 + \frac{C_e^*(t)}{K_m^*} + \frac{C_e}{K_m}}\,, \tag{14}$$

where V_m^* and V_m are the maximal reaction rates of [18F]FDG and glucose, respectively, K_m^* and K_m are the Michaelis-Menten constants of the hexokinase reaction for [18F]FDG and glucose, respectively. Note that because of the steady state assumption of glucose metabolism, we write C_e as a constant. The free [18F]FDG concentration $C_e^*(t)$, however, is time varying. We obtain

$$\frac{v^*}{v} = \frac{C_e^*(t)}{C_e} \frac{V_m^* K_m}{V_m K_m^*}\,. \tag{15}$$

At this point, the denominator of Eq. (11) becomes

$$\text{denominator} = \frac{1}{\Phi} \frac{V_m^* K_m}{V_m K_m^*} \int_0^T \frac{C_e^*(t)}{C_e}\,\mathrm{d}t\,. \tag{16}$$

Next, we address the term C_e and then the integral.

Step 4: relate C_e to C_p by steady state assumption of glucose.

Due to the steady state assumption of glucose metabolism, the net flux of glucose between blood and tissue is zero. Thus

$$0 = \frac{\mathrm{d}C_e}{\mathrm{d}t} = K_1 C_p - k_2 C_e - k_3 C_e \,., \tag{17}$$

which leads to

$$C_e = \frac{K_1}{k_2 + k_3} C_p \,. \tag{18}$$

Step 5: Simplify the integral $\int_0^T C_e^*(t)\,\mathrm{d}t$.

Using Eq. (13), we have

$$I \triangleq \int_0^T C_e^*(t)\,\mathrm{d}t = K_1^* \int_0^T \left(\int_0^t C_p^*(\tau) e^{-(k_2^*+k_3^*)(t-\tau)} \mathrm{d}\tau \right) \mathrm{d}t \,. \tag{19}$$

In the rest of this step, we try to simplify this integral. First, we pull the $e^{-(k_2^*+k_3^*)t}$ term out of the inner integral:

$$I = K_1^* \int_0^T e^{-(k_2^*+k_3^*)t} \left(\int_0^t C_p^*(\tau) e^{(k_2^*+k_3^*)\tau}\,\mathrm{d}\tau \right) \mathrm{d}t \,. \tag{20}$$

Write $u'(t) = e^{-(k_2^*+k_3^*)t}$ and $v(t) = \int_0^t C_p^*(\tau) e^{(k_2^*+k_3^*)\tau}\,\mathrm{d}\tau$. Then $u(t) = -\frac{1}{k_2^*+k_3^*} e^{-(k_2^*+k_3^*)t}$ and $v'(t) = C_p^*(t) e^{(k_2^*+k_3^*)t}$. Using integral by parts, we have

$$\begin{aligned} I &= K_1^* \int_0^T u'(t) v(t)\,\mathrm{d}t \\ &= K_1^* \left\{ [u(t)v(t)]_{t=0}^T - \int_0^T u(t) v'(t)\,\mathrm{d}t \right\} . \end{aligned} \tag{21}$$

But

$$u(T)v(T) = -\frac{1}{k_2^*+k_3^*} e^{-(k_2^*+k_3^*)T} \int_0^T C_p^*(\tau) e^{(k_2^*+k_3^*)\tau}\,\mathrm{d}\tau \quad \text{and} \quad u(0)v(0) = 0 \,,$$

and

$$\int_0^T u(t)v'(t)\,\mathrm{d}t = \int_0^T -\frac{1}{k_2^*+k_3^*} e^{-(k_2^*+k_3^*)t} C_p^*(t) e^{(k_2^*+k_3^*)t}\,\mathrm{d}t = -\frac{1}{k_2^*+k_3^*} \int_0^T C_p^*(t)\,\mathrm{d}t \,.$$

Putting everything together, we get

$$I = \frac{K_1^*}{k_2^*+k_3^*} \left(\int_0^T C_p^*(t)\,\mathrm{d}t - \int_0^T C_p^*(t) e^{-(k_2^*+k_3^*)(T-t)}\,\mathrm{d}t \right) \tag{22}$$

Step 6: Introduce λ.

Combining Equations (16), (18) and (22), along with the definition

$$\lambda = \frac{K_1^*/(k_2^*+k_3^*)}{K_1/(k_2+k_3)} \,, \tag{23}$$

we obtain the operational Equation (1) .

Recall that $\frac{K_1^*}{k_2^*+k_3^*} = \frac{C_e^*}{C_p^*}$ is the distribution volume for [18F]FDG, and $\frac{K_1}{k_2+k_3}$ for glucose, λ is the ratio of the distribution volumes for [18F]FDG and glucose in the tissue.

4 Other issues

- Assumptions: constant arterial plasma concentration for glucose, steady state for glucose metabolism, tracer amount (necessary for defining first-order DEs).
- The choice of T? For larger T, better accuracy?
- How is the constant C_p determined? Is the full course of C_p measured and the average used?
- Determination of K_1^*, k_2^* and k_3^*.
- Determination of the lumped constant.

References

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