

# Quantitation in PET Imaging

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## Introduction

PET is the technology used for measuring the biochemical and physiologic functions of a living object. Biochemical processes are the basis of the body's function and their alteration results in abnormal function frequently equated with disease. Since these early biochemical changes always precede anatomical alterations, the information provided by PET will increase our knowledge of the biochemical basis of human disease and increase our abilities for more specific and improved therapies.

## What is PET?

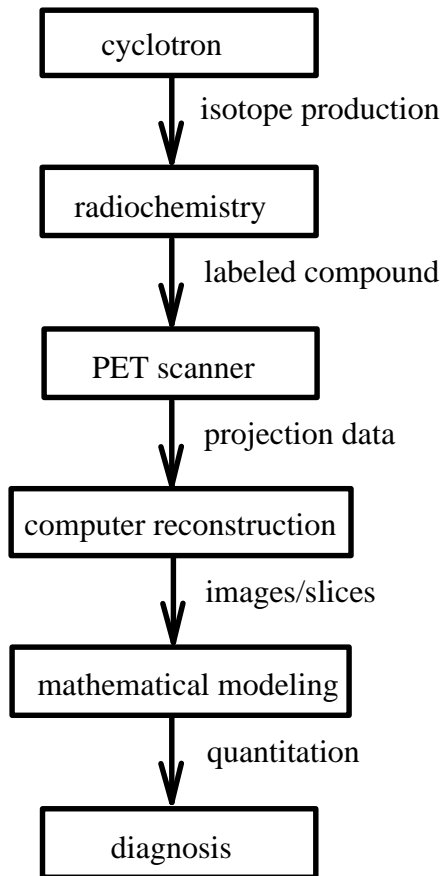
Positron Emission Tomography

Coincidence detection of positron decay

## Physical properties of positron decay

- } An unstable proton rich nucleus can release energy and excess charge by emitting a positron. The positron is an anti-electron, identical to the electron in every respect except charge.
- } When a positron comes in contact with an electron, the two particles annihilate turning the mass of both particles into two 511 keV gamma-rays that are emitted at 180 degrees to each other.

### Flow of PET Studies



### Scanditronix PET PC4096-15WB

- } 4 detector rings      15 slices
- } axial FOV (field of view) 10.3 cm      slice thickness 7mm
- } BGO (Bismuth Germanate) crystals/ring      4096 crystals totally
- } crystal assembly = 4x4 BGO crystals + 2 photomultiplier tubes
- } cassette = 4 assemblies
- } 2x32 cassettes      4096 crystals
- } gantry tilt and slew:  $\pm 20$  degrees
- } maximal wobble speed: 1 cycle per second
- } patient alignment by orthogonal cross-hair lasers

### PET Image Analysis

The process of taking PET images and using tracer kinetic modeling to extract useful information is termed PET image analysis.

In general, a dynamic imaging sequence with simultaneous arterial/venous blood sampling is necessary for a true quantitative study. Such a process is impractical for clinical studies. Therefore, a simple semiquantitative index called standardized

uptake value (SUV) or differential uptake rate (DUR) is generally used. It serves as a sensitive tumor index. The method is essentially model independent. It can be conceptualized as the concentration of radiotracer in the tumor divided by the concentration of injected dose distributed throughout the mass of the body.

$$\text{SUV} = \frac{\text{average activity in ROI (mCi/cc)}}{\text{injected dose (mCi)/patient weight (gm)}}$$

or using body surface area,  $\text{BSA} = (\text{weight in Kg})^{0.425} \times (\text{height in cm})^{0.725} \times 0.007184$ .

### **Factors Affecting the Quantitation Process**

- } attenuation of photons by tissue
- } transaxial spatial resolution and effective slice thickness of the PET scanner
- } input function
- } plasma glucose level
- } definition of anatomical regions and image registration

### **Attenuation Correction**

Gamma rays originating from the inner structure is generally attenuated by the surrounding tissue and bone. The magnitude of attenuation depends on the attenuation coefficient of the tissue and the thickness of the tissue transversed. Since the tissue is nonhomogeneous, this coefficient varies in different locations. Therefore assuming a constant attenuation coefficient makes the attenuation correction of the image inaccurate.

In PET scanning, correcting the emission image for the attenuation effects can be done in an exact manner because two back-to-back gamma rays are involved. By measuring the total attenuation along the line that these gamma rays travel the attenuation effect can be corrected from the emission image. It can be described as follows:

- } A source of 511 keV gamma radiation of Ge-68 is placed in the patient gantry, without the patient, and a "blank scan" is collected for 30 min.
- } Before administering any radioactivity, a "transmission scan" is acquired for 15 min by placing the patient in the scanner while external source is still there. The exact information about the photon attenuation across each line of response can be obtained.
- } The external source is removed before the radioactivity is administered to the patient to start the emission scan. Using the blank scan as a reference and the attenuation information provided by transmission scan, the emission can be corrected for attenuation.

## Input Function

- } Different input function will introduce different response function for the same clearance/flow rate. The true clearance rate can be obtained by deconvolving the input function from the observed time-activity curve. The measurement of input function can be divided into 4 categories: arterial sampling, venous sampling after warming the hand to shunt arterial blood to the venous drainage, dynamic images, and constant infusion.
- } In a number of procedures only one component of the blood is involved in the input function. For example, in the LCMRGlc (local cerebral metabolic rate of glucose) determination with FDG, only the plasma concentration of FDG is used, and in the  $LCMRO_2$  (local cerebral metabolic rate of oxygen) determination with O-15 molecular oxygen, labeled oxygen must be separated from labeled water. In each case the blood sample must be centrifuged and the components separated. In the case of O-15 it must be done very rapidly.
- } When the input function requires only measurements of whole blood activity, automatic blood sampling machine can provide a much more accurate input function. The primary application of this technique is in LCBF (local cerebral blood flow) measurements with bolus injection of O-15 labeled water.
- } Two methods have been developed to avoid arterial puncture in the measurement of the input function. The first one is so called arterialization method by heating the hand in a 43 degrees water bath and the blood samples are drawn from a hand vein. It takes advantage of the fact that, when the temperature of the hand is raised, there is dilation of the blood vessels and the blood in the surface veins is effectively arterialized. This produces a very high blood flow in the hand without an increase in metabolic function, and the extraction of the substrate in the hand is typically small.
- } Two physical problems should be undertaken for the arterialization method: time delay and curve shape.
- } The input function can be measured from the activity in the left ventricle, aorta, or other large artery as a function of time (i.e., time-activity curves). This method requires that the PET system be capable of acquiring data rapidly enough to satisfy the temporal sampling requirements of the particular input function. Of course this method is also limited to those cases in which the left ventricle or an adequately large artery locates in the imaging planes.

### **Tracer Kinetic Modeling**

- } Modeling is a very commonly used scientific tool for investigating, understanding, or predicting various phenomena in science or engineering. The models used in PET studies are generally called tracer kinetic models.
- } The tracer method is a simple, rapid, convenient, and sensitive measurement technique for volume, flow and the rate/flux of dynamic processes. A tracer is a labeled molecule or compound that follows the transport of biological substances in a biological/physiological process in the body. The tracer should have the same transport characteristics as the natural substance it traces. The mass of a tracer should be small so that its introduction does not affect the biological process being studied.

### **Principle of Tracer Kinetics**

The principle of tracer study is based on the phenomenon that the amount of tracer delivered to tissue is proportional to the blood flow/perfusion to the tissue, i.e.,

$$\frac{\text{amount of tracer in tissue A}}{\text{amount of tracer in tissue B}} = \frac{\text{blood flow to tissue A}}{\text{blood flow to tissue B}}$$

If tissue B is a reference with known blood flow, then blood flow to tissue A can be determined by the measurement of the amount of tracer in tissue A relative to that in tissue B. The use of N-13 ammonia for imaging the relative myocardial blood flow is based on the same principle.

### **Conservation of Mass**

Another basic principle is based on conservation of mass. It is frequently called the dilution-principle. For example, for measurement of fluid volume in a static system, the amount of tracer introduced (Q) is equal to the concentration (C) of the tracer times the volume (V) of the fluid. That is,

$$Q = CV .$$

For a dynamic system having a flow F, after an amount Q of tracer has been introduced into the system, the amount of tracer leaving the system within a small time interval (dt) at time t is FC(t)dt, where C(t) is the concentration of tracer in the fluid that is leaving the system at time t, and is commonly called a TAC. Using the principle of conservation of mass, one can establish

$$Q = F \int_0^{\infty} C(t) dt .$$

Since C(t) is measurable and Q is known, the flow F through the system can be calculated.

### Central Volume Principle

In a simple tubing system with fluid flowing steadily inside. Tracer is introduced at point A as a bolus. Tracer concentration detected at point B will be delayed and spread out. The mean transit time of the tracer through the system is equal to the volume  $V$  of the system divided by the flow  $F$  through the system.

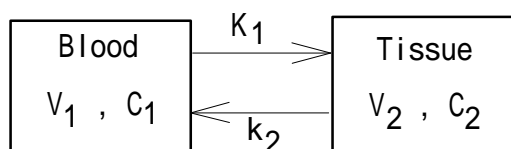
$$t = V / F$$

If flow per volume is desired, then one only needs to determine  $1/t$ .

### Basic Assumptions of Tracer Kinetic Techniques

- } A tracer must either be structurally related to the natural substance involved in the dynamic process (i.e., metabolic processes) or have similar transport properties (i.e., flow systems).
- } The process being measured should not be perturbed by the introduction of the tracer.
- } The dynamic process being evaluated is assumed to be in a steady state.

### Compartmental Models



A compartmental model is represented by a number of compartments linked by arrows indicating transport between compartments. A compartment is defined as a space in which the tracer is distributed uniformly. The symbol next to the arrow is called the rate constant which denotes the fraction of the total tracer leaving the compartment per unit time.

Fig. 7.4

Fig. 7.6

### Choices of Tracer

There are two general categories of tracers, namely, chemical analogs and natural substrates.

Chemical analogs are compounds that have chemical structures similar to the natural substrates, except that at some key positions the molecules are modified. The limitation on the use of analogs is that the relationships between the analogs and their

natural substrates in terms of their transport or reaction rates in all the related steps need to be understood and carefully verified.

Unlike the analog tracer, labeled natural substrates usually cannot be used to isolate specific reaction steps, and thus adequate description of their kinetics would require more complicated models.

Fig. 7.8

### Comprehensive Models

Fig.7.13

### Workable Models

Model reduction by merging compartments

Model reduction by fixing rate constants

### Validation of Models

Kinetic validation

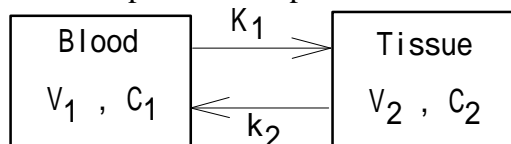
Biochemical validation

Fig.7.23

Good fitting alone does not verify that the model is adequate for the data.

Examination of the speed of convergence, the range of the estimated parameter values, the residual functions, and the standard errors of the estimates provides more information about the adequacy of the model.

For a simple two-compartment model as follows:



The net gain of tracer in compartment 2 can be expressed as

$$\frac{dM_2}{dt} = k_1 V_1 C_1 - k_2 V_2 C_2$$

The product of  $k_1$  and  $V_1$  defines a clearance  $K_1$ , which reflects perfusion when there are no barriers to diffusion of the tracer between the circulation and the compartment.

The above equation becomes

$$\frac{dM_2}{dt} = K_1 C_1 - k_2 M_2$$

The general solution is

$$M_2 = e^{-k_2 T} \{M_2(0) + K_1 \int_0^T C_1 e^{-k_2 t} dt\}$$

The above equation can be solved by regression analysis using a suitable optimization program.

For PET studies, we can only measure M, the sum of  $M_1$  and  $M_2$ , therefore the equation is

$$M_1 = V_a C_a$$

$$M_2 = K_1 \int_0^T C_a dt - k_2 \int_0^T M_2 dt$$

$$M = V_a C_a + (K_1 + k_2 V_a) \int_0^T C_a dt - k_2 \int_0^T M dt$$

The coefficients of the above equation can be obtained by 4-D linear regression including 3 independent variables (i.e.,  $C_a$  and two integrals) and one dependent variable M:

$$y = p_1 x_1 + p_2 x_2 + p_3 x_3$$

Autoradiographic solution

$$K_1 = \frac{M + k_2 \int_0^T M_e dt - V_a C_a}{\int_0^T C_a dt}$$

where  $M_e$  is the total mass of tracer in the extravascular water volume, equal to  $V_2 C_2$ . With a single measurement of M, the calculation of  $K_1$  requires both negligible backflux and a known  $V_a C_a$ .

Patlak plot

$$V = \frac{M}{C_a} = V_a + K_1 \Theta - k_2 \frac{\int_0^T M_e dt}{C_a}$$

$$\Theta = \frac{\int_0^T C_a dt}{C_a}$$

The 3-compartment model



The differential equations are as follows:

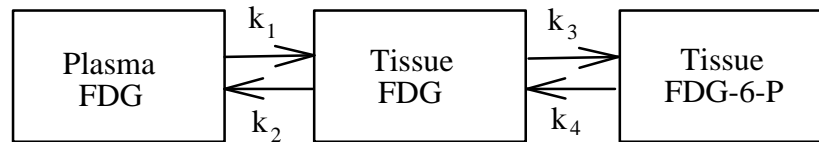
$$\frac{dM_2}{dt} = K_1 C_1 - (k_2 + k_3)M_2 + k_4 M_3$$

$$\frac{dM_3}{dt} = k_3 M_2 - k_4 M_3$$

where  $M_2$  and  $M_3$  represent the exchangeable and trapped quantities of tracer, respectively.

### FDG Model

A variety of radiopharmaceuticals have been used for PET tumor imaging. The most commonly used one is FDG. FDG is an analog of glucose. It can be transported to tissue and be phosphorylated to its phosphorylated form like glucose does, but the phosphorylated FDG (FDG-6-P) is not a substrate for further glycolysis. FDG-6-P does not leave tissue except through a slow hydrolysis back to free FDG. The transport and biochemical behavior of FDG can be summarized by the following compartmental model described by Sokoloff in the rat brain study.



Since FDG has similar properties as glucose in the transport and the phosphorylation reaction, the flux of FDG from the middle compartment to the one on the right is proportional to the flux of glucose utilized by the tissue. In general,  $k_1$  and  $k_2$  refer to the forward and reverse capillary transport of FDG, while  $k_3$  and  $k_4$  refer to the phosphorylation of FDG and the dephosphorylation of FDG-6-P, respectively. Based on this model, the utilization rate of glucose in tissue can be calculated by

$$\text{MRGlc} = \frac{C_p}{\text{LC}} \frac{k_1 k_3}{(k_2 + k_3)}$$

where  $C_p$  is the plasma glucose concentration, and LC is the so-called lumped constant that accounts for the relative rates of FDG and glucose in their transport and phosphorylation.  $C_p$  can be measured from blood samples and the value of LC has been found to be constant for normal subjects. The values of the k's can be obtained by curve fitting the tissue TAC with the model equation.

An approach, originally used in autoradiography for measuring MRGlc with deoxyglucose in rats by Sokoloff, can be applied to simplify the above procedure. MRGlc can be calculated with an operational equation as

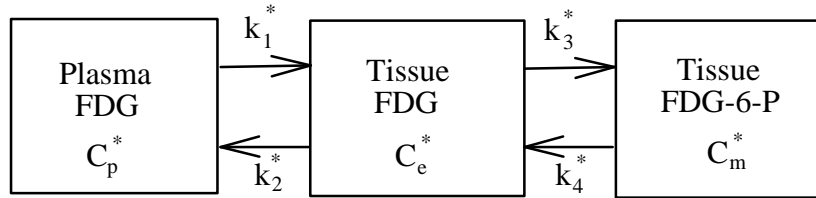
$$MRGlc = \frac{C_p}{LC} \frac{(\text{tissue F-18 activity at T}) - (\text{free tissue FDG activity at T})}{(\text{total amount of FDG delivered to tissue of phosphorylation})}$$

The time T for measurement of tissue radioactivity can be between 40 to 120 min.

### Parameter Estimation Techniques

The parameter estimation techniques used in PET modeling consist of the nonlinear least squares method (NLS), weighted integration projection method (WIP), autoradiographic approach (AR), Patlak graphic approach (PGA), and linear least squares method (LLS).

The tracer concentrations in the 3 compartments are represented by  $c_p^*(t)$  (for plasma FDG concentration),  $c_e^*(t)$  (for tissue FDG concentration), and  $c_m^*(t)$  (for tissue FDG-6-P) respectively.  $c_p^*(t)$  represents the input function that can be measured from blood samples. The sum of the activity in the tissue,  $c_e^*(t) + c_m^*(t)$ , is obtained from PET images.



The set of differential equation of the above model can be given as follows:

$$\frac{dc_e^*(t)}{dt} = k_1^* c_p^*(t) - (k_2^* + k_3^*) c_e^*(t) + k_4^* c_m^*(t)$$

$$\frac{dc_m^*(t)}{dt} = k_3^* c_e^*(t) - k_4^* c_m^*(t)$$

where  $k_1^* - k_4^*$  are the rate constants to be estimated. The asterisks' notation means that these rate constants are the radioactive FDG instead of those of the endogenous glucose. The physiological parameter rCMRGlC (regional cerebral metabolic rate of glucose) can then be calculated by the following equation:

$$rCMRGlC = \frac{1}{LC} \frac{k_1^* k_3^*}{k_2^* + k_3^*} c_p^*(t)$$

where LC is the lumped constant which summarizes the difference between FDG and glucose in transportation and phosphorylation.  $c_p^*(t)$  is the glucose concentration in the plasma.

### Nonlinear Least Squares Method

The operational equations of NLS can be obtained by using the Laplace transform of the differential equations in the model. They are illustrated as follows:

$$c_e^*(t) = \frac{k_1^*}{r_2 - r_1} [(k_4^* - r_1)e^{r_1 t} + (r_2 - k_4^*)e^{r_2 t}] \otimes c_p^*(t)$$

$$c_m^*(t) = \frac{k_1^* k_3^*}{r_2 - r_1} [e^{r_1 t} - e^{r_2 t}] \otimes c_p^*(t)$$

where  $\otimes$  means the convolution operator.  $r_1$  and  $r_2$  are defined as follows:

$$r_1 = \frac{1}{2} \left[ (k_2^* + k_3^* + k_4^*) - \sqrt{(k_2^* + k_3^* + k_4^*)^2 - 4k_2^* k_4^*} \right]$$

$$r_2 = \frac{1}{2} \left[ (k_2^* + k_3^* + k_4^*) + \sqrt{(k_2^* + k_3^* + k_4^*)^2 - 4k_2^* k_4^*} \right]$$

The F-18 activity in the tissue  $c_i^*(t)$  is defined by

$$c_i^* = c_e^* + c_m^*$$

$$= \frac{k_1^*}{r_2 - r_1} [(k_3^* + k_4^* - r_1)e^{r_1 t} + (r_2 - k_3^* - k_4^*)e^{r_2 t}] \otimes c_p^*(t)$$

A nonlinear regression analysis is required to solve the micro-parameters  $k_1^* - k_4^*$ . Optimization algorithm such as Newton-Gaussian method is used to solve the problem iteratively.

### **Autoradiographic Method**

AR provides an operational equation to determine rCMRGlc utilizing only one PET scan measurement, the arterial blood sample, and a set of predefined rate constants [1,2]. The operational equation of AR is as follows:

$$rCMRGlc = \frac{c_p(t) \left\{ c_i^*(T) - \frac{k_1^*}{r_2 - r_1} [(k_4^* - r_1)e^{-r_1 T} + (r_2 - k_4^*)e^{-r_2 T}] \otimes c_p^*(t) \right\}}{(LC) \frac{k_2^* + k_3^*}{r_2 - r_1} [e^{-r_1 T} - e^{-r_2 T}] \otimes c_p^*(t)}$$

where  $c_i^*(T)$  corresponds to a single measurement of the tissue concentration obtained from PET scanner,  $k_1^* - k_4^*$  the assumed set of average rate constants, and  $c_p^*(T)$  the measured input function.  $\otimes$  means the convolution operator.  $r_1$  and  $r_2$  are defined as those used in NLS.

### **Patlak Graphic Approach**

The PGA method proposed by Patlak et al. [4], assumes linear transfer kinetics in estimating rCMRGlc with  $k_4^*$  being equal to zero. The differential equation can be stated as follows:

$$\frac{dc_e^*(t)}{dt} = k_1^* c_p^*(t) - (k_2^* + k_3^*) c_e^*(t)$$

$$\frac{dc_m^*(t)}{dt} = k_3^* c_e^*(t)$$

Solving the above equations, we can obtain the following solution [4,5]:

$$\frac{c_i^*(t)}{c_p^*(t)} = K \frac{\int_0^t c_p^*(\tau) d\tau}{c_p^*(t)} + \frac{k_1^* k_2^*}{(k_2^* + k_3^*)^2}$$

where  $c_i^*(t)$  and  $c_p^*(t)$  are the tissue and blood measurements respectively,  $K = k_1^* k_2^* / (k_2^* + k_3^*)$ . The parameter K can be obtained by plotting  $c_i^*(t) / c_p^*(t)$  versus  $\int_0^t c_p^*(\tau) d\tau / c_p^*(t)$  at different time and fitting to slope of a line. rCMRGlc is equal to  $K c_p^*(t) / LC$ .

### Weighted Integration Projection Method

WIP is a generalization of the integrated projection method of Huang et al. [6] by incorporating the concept of weighted integrals [7]. The operational equation of the 3-compartment model is as follows:

$$c_i^*(t) = P_1 \int_0^t c_p^*(\tau) d\tau + P_2 \iint c_p^*(\tau) d\tau dt + P_3 \int_0^t c_i^*(\tau) d\tau$$

where the macro-parameters P are related the micro-parameters of the Sokoloff model by  $P_1 = k_1^*$ ,  $P_2 = k_1^* k_3^*$ , and  $P_3 = -(k_2^* + k_3^*)$ . Multiplying the above equation by the weighting function W, and integrating over the scan duration T, a set of equations can be obtained and shown in matrix form:

$$A = B \mu + \sim$$

where

$$A = \begin{bmatrix} \int_0^T w_1(t) c_i^*(t) dt \\ \int_0^T w_2(t) c_i^*(t) dt \\ \int_0^T w_3(t) c_i^*(t) dt \end{bmatrix}, \mu = \begin{bmatrix} P_1 \\ P_2 \\ P_3 \end{bmatrix}, \sim = \begin{bmatrix} \sim_1 \\ \sim_2 \\ \sim_3 \end{bmatrix},$$

$$B = \begin{bmatrix} \int_0^T w_1(t) \int_0^t c_p^*(\tau) d\tau dt & \int_0^T w_1(t) \int_0^t \int_0^t c_p^*(\tau) d\tau dt dt & \int_0^T w_1(t) \int_0^t c_i^*(\tau) d\tau dt \\ \int_0^T w_2(t) \int_0^t c_p^*(\tau) d\tau dt & \int_0^T w_2(t) \int_0^t \int_0^t c_p^*(\tau) d\tau dt dt & \int_0^T w_2(t) \int_0^t c_i^*(\tau) d\tau dt \\ \int_0^T w_3(t) \int_0^t c_p^*(\tau) d\tau dt & \int_0^T w_3(t) \int_0^t \int_0^t c_p^*(\tau) d\tau dt dt & \int_0^T w_3(t) \int_0^t c_i^*(\tau) d\tau dt \end{bmatrix}$$

Solving for  $\mu$  yields  $\mu = B^{-1} A$ . The micro-parameters can then be calculated from the macro-parameters.

### Linear Least Squares Method

The LLS method derived by Feng et al. [8] defines the operational equations as follows:

$$c_i^*(t_1) = P_1 \int_0^{t_1} c_p^*(\tau) d\tau + P_2 \iint c_p^*(\tau) d\tau dt + P_3 \int_0^{t_1} c_i^*(\tau) d\tau + P_4 \iint c_i^*(\tau) d\tau dt + \epsilon_1$$

$$c_i^*(t_2) = P_1 \int_0^{t_2} c_p^*(\tau) d\tau + P_2 \iint c_p^*(\tau) d\tau dt + P_3 \int_0^{t_2} c_i^*(\tau) d\tau + P_4 \iint c_i^*(\tau) d\tau dt + \epsilon_2$$

$$c_i^*(t_m) = P_1 \int_0^{t_m} c_p^*(t) dt + P_2 \iint c_p^*(t) dt dt + P_3 \int_0^{t_m} c_i^*(t) dt + P_4 \iint c_i^*(t) dt dt + \epsilon_m$$

Using matrix notation, the above equations can be expressed as

$$Y = X\beta + \epsilon$$

The LLS estimator of  $\beta$  is

$$\hat{\beta} = (X^T X)^{-1} X^T Y$$

The micro-parameters can be calculated as follows:

$$\begin{aligned} k_1^* &= P_1 \\ k_2^* &= -P_2 / P_1 - P_3 \\ k_3^* &= -P_3 - k_2^* - k_4^* \\ k_4^* &= -P_4 / k_2^* \end{aligned}$$

Because the error terms in LLS are not independent to each other due to the overlapping of the integration period. These biased estimates can be eliminated with the introduction of generalized linear least squares method (GLLS) [8, 9]. The GLLS estimator is given by

$$\hat{\beta} = (Z^T Z)^{-1} Z^T R$$

where

$$\hat{\beta} = \begin{bmatrix} P_1 \\ P_2 \\ P_3 \\ P_4 \end{bmatrix}, R = \begin{bmatrix} c_i^*(t_1) + P_3 \mathcal{E}_1(t_1) \otimes c_i^*(t) + P_4 \mathcal{E}_2(t_1) \otimes c_i^*(t) \\ c_i^*(t_2) + P_3 \mathcal{E}_1(t_2) \otimes c_i^*(t) + P_4 \mathcal{E}_2(t_2) \otimes c_i^*(t) \\ \dots \\ c_i^*(t_m) + P_3 \mathcal{E}_1(t_m) \otimes c_i^*(t) + P_4 \mathcal{E}_2(t_m) \otimes c_i^*(t) \end{bmatrix}$$

$$Z = \begin{bmatrix} \mathcal{E}_1(t_1) \otimes c_p^*(t) & \mathcal{E}_2(t_1) \otimes c_p^*(t) & \mathcal{E}_1(t_1) \otimes c_i^*(t) & \mathcal{E}_2(t_1) \otimes c_i^*(t) \\ \mathcal{E}_1(t_2) \otimes c_p^*(t) & \mathcal{E}_2(t_2) \otimes c_p^*(t) & \mathcal{E}_1(t_2) \otimes c_i^*(t) & \mathcal{E}_2(t_2) \otimes c_i^*(t) \\ \dots & \dots & \dots & \dots \\ \mathcal{E}_1(t_m) \otimes c_p^*(t) & \mathcal{E}_2(t_m) \otimes c_p^*(t) & \mathcal{E}_1(t_m) \otimes c_i^*(t) & \mathcal{E}_2(t_m) \otimes c_i^*(t) \end{bmatrix}$$

with

$$\mathcal{E}_1(t) = \frac{1}{\lambda_2 - \lambda_1} \{ \lambda_2 e^{-\lambda_2 t} - \lambda_1 e^{-\lambda_1 t} \}, \quad \mathcal{E}_2(t) = \frac{1}{\lambda_2 - \lambda_1} \{ e^{-\lambda_1 t} - e^{-\lambda_2 t} \},$$

$$\lambda_1 = -\frac{P_3 + \sqrt{P_3^2 + 4P_4}}{2}, \quad \text{and} \quad \lambda_2 = -\frac{P_3 - \sqrt{P_3^2 + 4P_4}}{2}$$

## Conclusion

PET is an ideal tool for in vivo quantitation of biochemical or physiological processes. One of its promising future is in the area of therapeutic monitoring, since it is expected that biochemical changes in a tumor will occur before morphological or anatomical changes. Using PET, the oncologist can maximize the proper therapeutic regimen by quantifying and predicting a tumor's specific biologic response to a

chemotherapeutic agent in each patient. However, the true quantitative studies have some critical requirement that may be impractical to the clinical application. Therefore a semiquantitative study is preferred in the clinical studies. In the future, accurate and concise quantitative procedures should be investigated so that the full power of PET can be applied to clinical studies.