Journal of Theoretical Biology 295 (2012) 1–8

Contents lists available at SciVerse ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Model-independent plot of dynamic PET data facilitates data interpretation and model selection

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ARTICLE INFO

Article history:
Received 16 May 2011
Received in revised form
5 September 2011
Accepted 3 November 2011
Available online 11 November 2011

Keywords:
Radiotracer
Logan plot
Patlak plot
Kinetic model
Steady state

ABSTRACT

When testing new PET radiotracers or new applications of existing tracers, the blood–tissue exchange and the metabolism need to be examined. However, conventional plots of measured time–activity curves from dynamic PET do not reveal the inherent kinetic information. A novel model-independent volume–influx plot (*vi*-plot) was developed and validated. The new *vi*-plot shows the time course of the instantaneous distribution volume and the instantaneous influx rate. The *vi*-plot visualises physiological information that facilitates model selection and it reveals when a quasi-steady state is reached, which is a prerequisite for the use of the graphical analyses by Logan and Gjedde–Patlak. Both axes of the *vi*-plot have direct physiological interpretation, and the plot shows kinetic parameter in close agreement with estimates obtained by non-linear kinetic modelling. The *vi*-plot is equally useful for analyses of PET data based on a plasma input function or a reference region input function. The *vi*-plot is a model-independent and informative plot for data exploration that facilitates the selection of an appropriate method for data analysis.

1. Introduction

In dynamic PET studies, metabolic processes can be quantified using kinetic models that relate the time course of the tracer concentration in the tissue, $M(t)$, to that in the plasma supplying the tissue, $C_i(t)$, or to that in a reference region. In order to obtain physiologically relevant information, the kinetic model has to closely reflect both the blood–tissue exchange and the metabolism of the tracer. At the same time, though, its complexity must be limited depending on the duration of the experiment and the temporal resolution and statistical noise of the PET data. A compromise is to use a simpler model, e.g. a compartmental model, which allows physiologically reasonable parameter estimates without unfolding the entire behaviour of the tracer.

PET data are often quantified by linearisations of compartmental model equations using the Logan linearisation for reversible metabolism (Logan et al., 1990) and the Gjedde–Patlak linearisation for irreversible metabolism (Gjedde, 1982; Patlak et al., 1983). These graphical analyses only include a few, mathematically identifiable parameters. In addition, they make no assumptions about the number of compartments and their configuration other than whether or not all the compartments are reversible. The linearisations utilise transformed variables that exhibit an asymptotic linear relationship when rapidly reversible components of the tissue kinetics approach a quasi-steady state in which net fluxes between the compartments are small. The slope of the late, linear part of the graphs can be used to estimate the total distribution volume for reversible compartments (Logan et al., 1990) or the influx rate constant for irreversible compartments (Gjedde, 1982; Patlak et al., 1983).

The choice of graphical analysis approach depends on whether metabolism of the tracer is reversible or irreversible and how much of the initial data to disregard when fitting the slope. For new radiotracers or for new applications of existing tracers, these decisions are not always straightforward. Tracers rarely behave in a truly irreversible manner, even though they may appear to be irreversible during the finite period of data acquisition. We thus need to wait long enough for the fast components to reach quasi-steady state, but if we wait too long, many tracers will start to leave the tissue again, i.e. exhibit reversible behaviour. On the other hand, though, no tracers act in a truly reversible manner before a quasi-steady state has been reached, which may not occur during the data acquisition period. In either case, conventional plots of the measured data, i.e. $M(t)$ and $C_i(t)$, do not reveal the required information.

This paper introduces a novel way of graphically representing dynamic PET data in a manner that directly reveals inherent kinetic information while concomitantly revealing whether a quasi-steady state has been reached within a tolerance allowing linear graphical analysis. The new plot is based on the time course

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doi:10.1016/j.jtbi.2011.11.004

of the instantaneous distribution volume and the instantaneous influx rate of the tracer and is hence denoted as the volume–influx plot (*vi*-plot). The plot is model-independent and provides physiological information that facilitates the selection of linear/non-linear kinetic models. The *vi*-plot is introduced using simulated brain kinetics data for a glucose analogue using a compartment model. The versatility of the *vi*-plot is then demonstrated by applying it to measured data from two dynamic PET studies: a study of glucose analogues in the liver using plasma input functions (Munk et al., 2001), and ligand studies in brain regions using a reference region input function (Moller et al., 2007).

2. Methods

2.1. Graphical analysis of reversible metabolism

The Logan linearisation (Logan et al., 1990) is used to evaluate reversible metabolism by considering kinetic model configurations with one or more reversible tissue components. When the fast reversible component has reached quasi-steady state, the total distribution volume, V_d, can be estimated as the asymptotic slope of the transformed data

$$\frac{\int_0^t M(t)dt}{M(t)} = V_d \frac{\int_0^t C_i(t)dt}{M(t)} + i.c. \quad (1)$$

The second parameter, the intercept (*i.c.*), is not used in the new *vi*-plot presented in this paper. Eq. (1) is used here to calculate the time-dependent tangent, $v(t)$, of the non-linear Logan plot at all times, including before a quasi-steady state is reached.

2.2. Graphical analysis of irreversible metabolism

The Gjedde–Patlak linearisation (Gjedde, 1982; Patlak et al., 1983) is widely used to evaluate irreversible metabolism. It reduces the kinetic model configuration into reversible and irreversible tissue components. When the reversible component has reached quasi-steady state, the rate constant for influx into the irreversible component, K, can be estimated as the asymptotic slope of the transformed data

$$\frac{M(t)}{C_i(t)} = K \frac{\int_0^t C_i(t)dt}{C_i(t)} + i.c. \quad (2)$$

The second parameter, the intercept (*i.c.*), is not used in the new *vi*-plot. Eq. (2) is used here to calculate the time-dependent tangent, $i(t)$, of the non-linear Gjedde–Patlak plot at all times, including before a quasi-steady state is reached.

2.3. Volume–influx plot (vi-plot)

The Logan and Gjedde–Patlak graphical analyses are used to estimate the distribution volume, V_d, and influx rate constant, K, during quasi-steady conditions. The estimated parameters are constants, but their interpretation is obscured during non-steady conditions, particularly if quasi-steady state conditions are not reached during data acquisition. In contrast, the *vi*-plot is not confined to quasi-steady state conditions. Instead, instantaneous estimates of the slopes (tangents) are calculated as a function of time. This is an important conceptual difference compared to conventional kinetic modelling, where parameters are treated as constants. The instantaneous slope estimates must be interpreted *time-dependently* as *instantaneous distribution volumes*, $v(t)$, and *instantaneous influx rates*, $i(t)$. Fig. 1 shows an example of the time course of $v(t)$ and $i(t)$ (see the Section 3 for details). The purpose of a dynamic PET experiment is to estimate physiological parameters such as distribution volumes and influx rates. This information may be condensed as a two-dimensional projection by plotting $i(t)$ as a function of $v(t)$ using the instantaneous slope estimates from Eqs. (1) and (2). The *vi*-plot unifies – at all times – the information from Logan and Gjedde–Patlak linearisations. Thus, a *vi*-plot visualises the entire tracer kinetics, and at quasi-steady state it is as independent of the underlying model configuration as

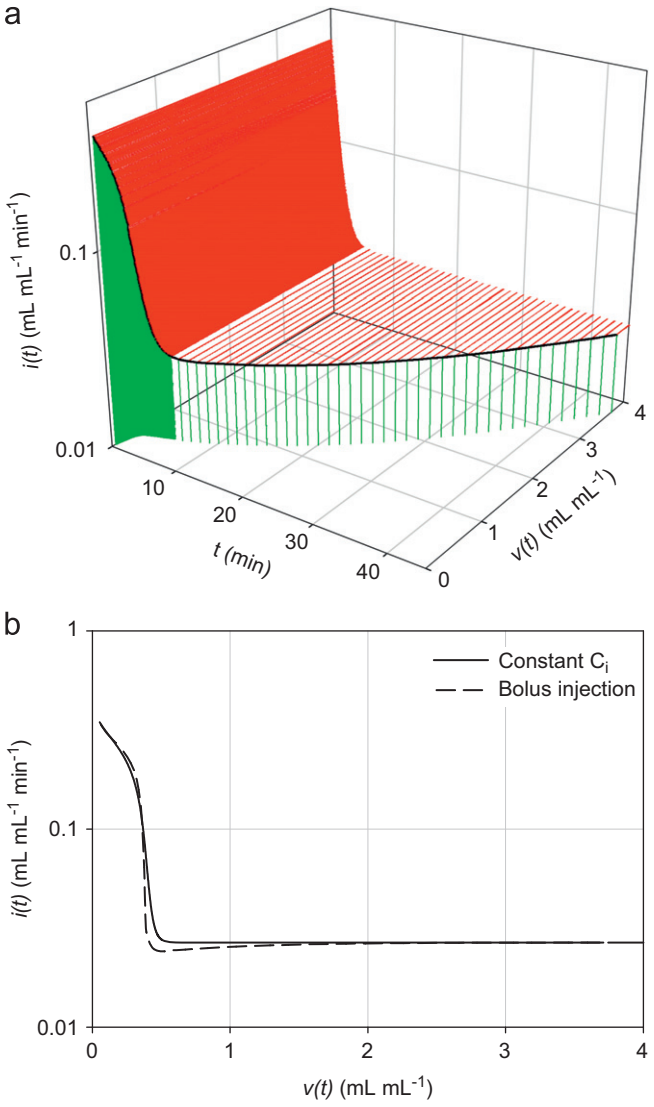

Fig. 1. A simulated time–activity curve was generated with the irreversible two-tissue compartmental model using the parameters: K_1=0.35 mL mL^{-1} min^{-1}, k_2=1.09 min^{-1}, k_3=0.09 min^{-1}, V_b=0.05 mL mL^{-1}, and a 45-min constant input function. The rate constants correspond to the brain kinetics of 2-deoxy-D-glucose using a 5% blood volume (Gjedde, 1982). $i(t)$ and $v(t)$ were calculated as a function of time. Three projections can be made from the curve: (i,t), (v,t), and (v,i). The (i,t) and (v,t) projections are shown in Fig. 1a as drop lines, while the (v,i) projection is shown in Fig. 1b. (a) Three-dimensional plot of time t, $i(t)$, and $v(t)$. The projection onto the two-dimensional plot of $i(t)$ as a function of time is shown by red drop lines, while the projection onto the two-dimensional plot of $v(t)$ as a function of time is shown by green drop lines. $i(t)$ decreases monotonically as a function of time, and $v(t)$ increases monotonically as a function of time. (b) The third projection shows $v(t)$ as a function of $i(t)$ (solid line). In this volume–influx plot, *vi*-plot, time increases as $v(t)$ increases. The *vi*-plot allows detailed visual inspection of the kinetics obtained by kinetic analyses. For comparison, the time–activity curve was also simulated using a bolus injection input function (broken line) instead of a constant input function. Note the logarithmic axis of $i(t)$ is useful when the delivery of tracer by flow is orders of magnitude faster than the metabolic processes in the organ. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)