

BIOLOGICAL INTERPRETATION OF QUANTITATIVE PET BRAIN DATA

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The variety of available positron emission tomography (PET) radiotracers and the ability of providing quantitative estimates of radiotracer concentrations make PET an invaluable tool in the in-vivo investigation of biological processes. Mathematical descriptions of the processes under investigation are used to extract relevant kinetic parameters from the time course of radioactivity concentrations. Such kinetic parameters can provide a quantitative description of both, the characteristics of a particular process, and its changes due to various disease states.

1 Introduction

Positron Emission Tomography (PET) is a functional imaging modality used in brain research to map in vivo neurotransmitter and receptor activity and to investigate glucose utilization or blood flow patterns both in healthy and disease states. Such research is made possible by the wealth of radiotracers available for PET and by the fact that metabolic and kinetic parameters of particular processes can be extracted from PET data. The minute tracer amounts, the quantitative aspect of the PET images, and the biological modeling of the processes under investigation are required for a quantitative description of the biological processes. Such quantitative description then allows the investigators to not only use PET to separate disease state from health, but to proceed to more detailed investigations, such as the understanding of a particular disease mechanism, the ability of the brain to react to insults, or to link personality traits to the neurochemical structure of the brain. This paper will describe the steps necessary to obtain a quantitative description of the neurochemical processes with PET with specific examples taken from the investigation of Parkinson's disease.

2 The tracer principle in PET

The tracer principle requires that the amount of the tracer substance administered is so small that it does not perturb the system. If this condition is satisfied, then by tracking the tracer distribution it is possible to infer direct information on the behavior of the system itself. The tracer principle is certainly

satisfied in most PET studies: picomolar tracer concentrations are generally sufficient to produce a good PET signal.

PET tracers are typically analogues of endogenously present substances or compounds that are very selective for a particular site of interest. A good example of the first category is ^{18}F -fluorodeoxyglucose (FDG), which is a glucose analogue, while examples of the second group are tracers that bind to specific neuroreceptor sites. The two most commonly used radioisotopes in PET are ^{18}F ($\lambda_{1/2} = 109.8$ min) and ^{11}C ($\lambda_{1/2} = 20.4$ min). ^{11}C is a natural choice, since it is an isotope of an atom that is present in organic molecules, while many of the ^{18}F characteristics are similar to those of H. Their $\lambda_{1/2}$ also matches reasonably well the biological $\lambda_{1/2}$ of many processes of interest.

3 Quantitative aspect of PET data

In PET the basic event is the simultaneous detection of the two γ rays that originate from a positron annihilation. Quantification in PET means that proportionality between tomograph count density in any region of the image and radiotracer concentration in the corresponding location of the object being imaged is preserved. A fundamental limit to quantification is posed by the finite tomograph resolution that leads to partial volume effects when the size of the imaged object is smaller or approximately equal to the tomograph resolution element [1]. For structures larger than the tomograph resolution element quantification is preserved when the tomograph is appropriately calibrated. This involves correcting for system dead time, detector non-uniformity, the presence of events where the γ rays undergo Compton scattering, the presence of random coincidence events and the loss of those events where one (or both) of the two γ rays remains undetected (loosely referred to as attenuation). In the case of brain scanning the quantification accuracy can be accurate to approximately 5% [2]. The tomograph sensitivity calibration procedure provides the conversion factors from count density to effective concentration values.

A series of sequential scans (dynamic scanning) can provide information on the radioactivity distribution as a function of time for any brain region (figure 1) Mathematical kinetic modeling is then used to convert a process observed in terms of radioactivity distribution into biologically meaningful variables.

4 Mathematical modeling

The basic idea of mathematical modeling is to describe the biological system under investigation with a set of linear differential equations, where each form that the radiotracer can assume, is assigned a different compartment. The free parameters of the differential equations are typically the rate constants of the

process of interest. An example of such system is shown in figure 2, which shows the model appropriate for the D2 dopamine antagonist ^{11}C -Raclopride (RAC) used to study the dopaminergic system. Since PET can only measure radioactivity distributions and can not distinguish amongst compartments, the number of direct observables in a PET study is generally much smaller than the number of compartments and/or rate constants that appropriately model the system: generally it is possible to only measure the overall radioactivity concentrations in different areas of the brain tissue and the tracer concentration in the plasma. A typical time radioactivity curve obtained by PET for a specific brain region is shown in figure 1 together with a plasma time activity curve (TAC). It is immediately obvious that only a limited number of parameters can be extracted from the knowledge of these two curves. It is therefore necessary to proceed to model simplifications: the challenge is to introduce enough simplifications to make the parameter estimate robust while still preserving biological accuracy and utility in quantifying the effects of various diseases on the system. Some models developed to describe RAC kinetics will be used as examples.

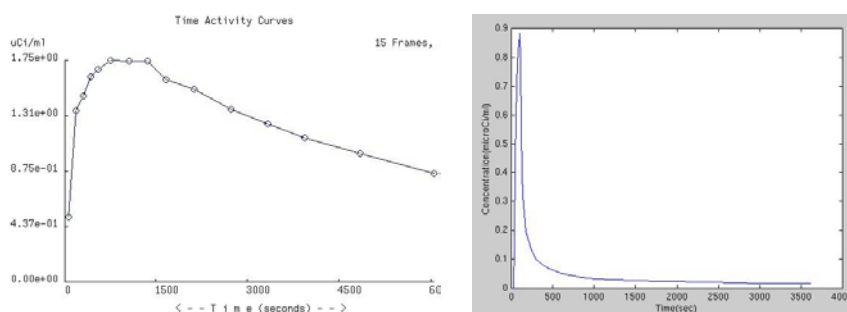


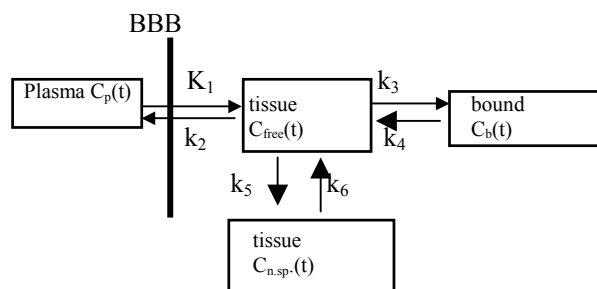
Figure 1. Time activity obtained for RAC in a region of interest placed on a subsection of the striatal image (left). Typical plasma tracer TAC (right). The line connects the measured points.

4.1 Compartmental model approach

The compartmental description for RAC is described in figure 2. In order to obtain a full description of the system six parameters should be extracted from the data. Since the measured data do not support a robust estimate of six parameters, approximations must be introduced into the model. A first possible approximation is that the compartments C_{free} and $C_{\text{n.sp.}}$ are kinetically indistinguishable and can therefore be merged into a single compartment. Since RAC studies are mostly aimed at determining characteristics related to D2 receptors, the quantity of greatest interest is the tracer(ligand)- receptor binding potential (BP), defined as the ratio between B_{max} , (the maximum free receptor density) and K_D (the ligand-receptor

affinity). Under a three compartment assumption it can be shown that $BP = k_3/k_4$ [3].

It has been experimentally found that even a three compartment model for RAC produces fairly noisy estimates for k_3 and k_4 [4]. Further simplifications are therefore desirable. Several approaches have been developed to this extent [5],[6]. Of particular interest are the graphical approaches [3,7,8,9]



$$dC_{free}(t)/dt = K_1 C_p(t) - (k_2 + k_3 + k_5) C_{free}(t) + k_6 C_{n.sp.}(t) + k_4 C_b(t)$$

Figure 2. Full model for the radiotracer RAC. The tracer is injected into the plasma (C_p), it then crossed the blood brain barrier (BBB). In tissue it can exist either in a free form (C_{free}) or non specifically bound ($C_{n.sp.}$). It can also be specifically bound to the sites of interest (C_b), in our example to the D2 dopamine receptors. The equation is an example of the types of equations used to describe the system. [K_1]=ml g⁻¹ min⁻¹, [k_2](and others)= min⁻¹

4.2 Graphical model approach

The models belonging to this category are called graphical because the parameters of interest are determined as the slope of a line fitted to a combination of the measured data. In order for such a model to be applicable steady state between the compartments and the plasma must be reached during the course of the study. If this condition is satisfied than the following equation can be applied to the data:

$$\int_0^T C_{TOT}(t') dt' / C_{TOT}(T) = \text{slope} \int_0^T C_p(t') dt' / C_{TOT}(T) + \text{intercept} \quad (1)$$

where C_{TOT} is the sum of the radioactivity in all tissue compartments and C_p is the tracer concentration in the plasma. The slope can be interpreted as the tissue distribution volume (DV), which is the volume that the tracer would occupy in the tissue, if the tracer concentration in the tissue were the same as that in the plasma. DV is therefore an index of the tissue storage capacity for the tracer [9].

It can be shown that in the case of a three compartmental model the slope equals to $k_1/k_2(1+k_3/k_4)$ [3]. A simplification of the data analysis is thus obtained at the cost of a loss of detailed information, since no separate determination of the rate constants is now possible. An interesting feature of these models is the fact that they provide a self-consistency check: if the process does not satisfy the assumptions

required by the model, a straight line segment in the graphical plot will not be found.

A region with no specific binding can be described with a two compartmental approach and the expression of the slope in this case corresponds to k'_1/k'_2 . If $k_1/k_2 = k'_1/k'_2$ then the BP, which is the primary parameter of interest, can be determined from the ratio of the two slopes [3]. If such a region exists, it is called the reference region and its time activity course together with the time activity course of the primary region can be used to define the binding potential. Data from three measured curves are now used to determine a single final parameter and the result is more stable. There is however an increased risk of biasing the data: results will be altered if the reference region is not entirely free of specific binding.

4.3 Tissue input graphical model approach

Very often it is difficult and sometimes impossible to obtain plasma samples. It is therefore desirable to develop methods that do not require a plasma input function. The graphical approach offers this possibility under the condition that a predetermined k'_2 value can be used, which implies that there is no significant k'_2 intersubject variability. In this case the expression analogue to eq. 1 is:

$$\int_0^T C_{TOT}(t') dt' / C_{TOT}(T) = \text{slope} [\int_0^T C_{ref}(t') dt' + C_{ref}(T)/k'_2] / C_{TOT}(T) + \text{inter.} \quad (2)$$

The slope now equals to the distribution volume ratio ($DVR = 1+k_3/k_4$) and the BP can be directly determined from the data [9]. The tissue input method provides generally very robust data. However this occurs at the expense of additional assumptions on the tracer behavior, at the expense of an even greater loss of information (two brain regions are used to determine a single parameter) and at an increased risk of bias introduced if the assumptions are not fully satisfied.

4.4 Other approaches

The compartmental and the graphical approaches are some of the most commonly used methods. Sometimes the scanning protocol does not allow for the acquisition of a dynamic sequence of the data. Depending on the particular tracer kinetics, further simplifications might be possible such as simply calculating the ratio between the radioactivity concentration in the target region and that in the reference region [6]. Although simple and often effective at separating health from disease, these methods might be harder to interpret from the biological aspect [9].

Generally the introduction of an increased number of assumption leads to simplified models, a more statistically robust determination of the unknown parameters, while decreasing the ability to obtain detailed information and increasing the risk of systematic bias in the data and possibly hampering the biological interpretation of the fitted parameters.

5 Choice of a model

The validity of a model must be tested for each tracer separately. Since tracers are designed to investigate different processes, it is reasonable to expect that not all of the assumption required for a particular model are satisfied by each tracer. The first test is to verify if reasonable parameter values are obtained with the model being tested: this implies the ability to fit the time activity curve in the case of compartmental model approaches or existence of a straight line portion in the data arranged according to eq 1 or eq. 2. Criteria such as ability to distinguish a healthy from a diseased state or reliability calculations [10] are then used to assess the statistical characteristics of the parameters. Often a combination of measured and simulated data are used to explore model sensitivity to bias. If more models are proven to yield similar information with similar accuracy and precision, the simplest one that provides the required information is generally chosen.

6 Discussion and conclusion

The process of extracting quantitative biologically relevant parameters from the PET data has been presented. The ability to quantify parameters related to various processes under investigation allows not only to quantitatively follow disease progression but also to explore specific disease mechanisms. An interesting example is the investigation of compensatory mechanism in Parkinson's disease [11], which is characterized by a lack of neurotransmitter dopamine due to death of dopamine producing neurons. By using three different tracers and determining the relative rate constants and binding potentials it was found that the dopaminergic system attempts to compensate for dopamine loss. In the surviving neurons there is an increased dopamine production compared to healthy tissue, and the dopamine receptors undergo a transformation aimed at maximizing the probability of the signal being transmitter from one neuron to the next (synaptic transmission). Likewise a neurochemical change associated to the placebo effect has been demonstrated using the quantitative capabilities of PET [12].

The findings used as examples in the previous paragraph would not have been possible without PET and without the ability to extract quantitative information. When performing such research it is however also important to keep in mind the limitations to the quantitative accuracy of the PET data: partial volume effect, patient motion, potential low number of acquired counts being some of them. In order to improve on these limitations there is continuous research in detector technology to improve scanner performance, in new tracer development to develop specific and highly sensitive tracers and in the field of quantification, reconstruction and modeling algorithms to maximize the information that can be extracted from the data. The need for such a broad range of expertise makes PET a truly inter- and trans- disciplinary research field.

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