Postprocessing and Cross Validation

Modeling and Quantification

Linearised Models and Parametric Imaging

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Learning Objectives:

- Understand the advantages of linearised models
- Understand the limitations of linearised models
- Obtain an overview of the various linearized methods available
- Understand why linearized models are needed for parametric imaging

Molecular in vivo imaging techniques provide non-invasive measurements of regional tissue uptake and clearance of selected molecules. The kinetic behaviour of these molecules (tracers, probes) depends on several underlying physiological and/or biochemical processes. Tracer kinetic modelling is required to extract quantitative information on the specific molecular process under study.

PET provides for accurate measurements of regional tissue concentrations of tracers labelled with a positron emitter. Tracer kinetic models are needed to extract quantitative values of an underlying molecular process from these measurements. In practice, essentially all models are compartment models and physiological or biochemical parameters are obtained by fitting measured time-activity curves to the non-linear operational (model) equation. The most common parameters of interest are volume of distribution (V_T) and non-displaceable binding potential (BP_{ND}), providing measures of total and specific uptake in tissue, respectively, normalized to activity delivered (input function).

In general, data are fitted using standard non-linear regression algorithms. Non-linear regression, however, is rather slow and sensitive to noise, and therefore it usually is applied only to region of interest data (low noise level). Ideally, fits should be performed at the voxel level, thereby enabling the generation of parametric images (i.e. images of the parameter under study). Although, in theory, it is possible to fit individual voxel data, in practice this is not feasible. Apart from being too slow, non-linear regression would result in very noisy images with (many) outliers. To generate parametric images, linearization of the model equations is required. Several methods have been developed using either graphical or multi-linear regression approaches: Patlak plot- direct integration of model equations and Logan plot- multi-linear regression analysis. As these methods involve some sort of transformation of variables, they are “approximations” of the full compartmental equations and require validation for specific applications.

Another approach is the basis function method, which in theory can be used for all compartment models. The method is especially known for its implementation of the simplified reference tissue method. The basic principle of the basis function method is to pre-calculate any convolution in the model equation for a set of “basis” functions that cover the entire range of physiological values. For each pre-calculated convolution, the model equation becomes linear and its coefficients can be obtained by linear regression. The final parameters are then obtained by selecting the linear fit with the lowest residual sum of squares. The main advantage of parametric methods is that they allow for

parameter estimations at the highest possible (scanner) resolution. Nevertheless, as they are linearizations, parametric methods need to be validated against their full compartmental counterparts. For each tracer, several parametric methods should be investigated, as no single method is ideal for all applications.

Relevant Publications:

1. Blomqvist G (1984) On the construction of functional maps in positron emission tomography. J Cereb Blood Flow Metab 4:629-632
2. Gunn RN, Lammertsma AA, Hume SP et al (1997) Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. NeuroImage 6:279-287
3. Ichise M, Toyama H, Innis RB et al (2002) Strategies to improve neuroreceptor parameter estimation by linear regression analysis. J Cereb Blood Flow Metab 22:1271-1281
4. Ichise M, Liow JS, Lu JQ et al (2003) Linearized reference tissue parametric imaging methods: application to [11C]DASB positron emission tomography studies of the serotonin transporter in human brain. J Cereb Blood Flow Metab 23:1096-1112
5. Logan J, Fowler JS, Volkow ND et al (1990) Graphical analysis of reversible radio-ligand binding from time-activity measurements applied to [N-11C-methyl]-(-)-cocaine PET studies in human subjects. J Cereb Blood Flow Metab 10:740−747
6. Logan J, Fowler JS, Volkow ND et al (1996) Distribution volume ratios without blood sampling from graphical analysis of PET data. J Cereb Blood Flow Metab 16:834–840
7. Patlak CS, Blasberg RG, Fenstermacher JD (1983) Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. J Cereb Blood Flow Metab 3: 1-7