RPM STATISTICS - A Statistical Tool for Receptor Parametric Mapping
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Introduction
Neuroreceptor Imaging studies using Positron Emission Tomography (PET) allow for the in-vivo assessment of neurotransmission [5]. 4-dimensional spatio-temporal datasets are acquired for a radioligand of interest from each subject during the PET scanning procedure. Subsequent analyses of these data using an appropriate mathematical model produces parametric images of receptor related parameters. Statistical inferences about these parameters across individuals can then be made, after transformation into stereotactic space.

Methods for image-wide statistical analysis are often less sophisticated than those used in other branches of Neuroimaging, especially those of fMRI and SPM. Although these methods are not directly applicable to neuroreceptor imaging studies, analogous methods can be implemented to allow for a comparable level of statistical analysis.

Receptor Parametric Mapping (RPM) software has been developed for the analysis of neuroreceptor studies. This incorporates both parameter and error estimation from a compartmental description of the radioligand, as well as error estimation of population effects (random effects). This allows inferences about single or multiple subject studies, and thus general inferences can be made about the population.

Methods
There are two distinct components to the analysis. The first component estimates the intra subject or measurement variance component, and the second estimates the inter subject or random effect component using the estimate of the first component. These two methods have been introduced previously [1], [6], [7] and are now integrated to form a comprehensive analysis tool for neuroreceptor imaging data.

The intra-subject error has been assessed [1] for the simplified reference tissue model (SRTM [4]) and is the effect vector and

\[ \sigma^2_{\text{intra}} = \sigma^2_{\beta} + \sigma^2_{\text{residual}} \]

where \( \sigma^2_{\beta} \) is the estimate of the operational equation at the \( \theta \)th time point and

\[ j(\beta) = \frac{1}{\theta} \sum_{i=1}^{\theta} (Y_i - X_i \beta) \]

This gives estimates for the variance of the parameter estimates, which typically have large degrees of freedom (df), due to the use of all the available temporal information contained in the dynamic scan.

The inter-subject error is derived from the linear model [8]. Maximum allows for a compromise between a full random effects analysis and a purely fixed effects analysis (one where only measurement error is considered). This is achieved by smoothing the variance ratio image of the fixed to the random effect and thus, in reality, a mixed effects model. The inter-subject error estimate (\( \sigma^2_{\text{subject}} \)) is calculated using the REML (Restricted Maximum Likelihood) estimator with an expectation maximization algorithm:

\[ \begin{align*}
\sigma^2_{\text{subject}} & = \left( \sigma^2_{\text{subject}} \right) \mathcal{L}(Y | X \beta) + \sigma^2_{\text{residual}} \mathcal{L}(Y | X \beta)
\end{align*} \]

where \( \mathcal{L}(Y | X \beta) \) is the likelihood of the model matrix, \( X \) and \( \mathcal{L}(Y | X \beta) \) is the log-likelihood of the model matrix, \( X \) and

\[ \sigma^2_{\text{subject}} = \frac{\text{var}(\beta)^2}{(n-1) \text{var}(\beta)^2 + \text{var}(\beta)^2} \]

This analysis provides a compromise between a pure random effects analysis where the df are low, and a pure fixed effects analysis which whilst having a large number of df, does not take account of subject or population effects.

Implementation
These components have been incorporated as part of the RPM software package [3], http://www.bic.mni.mcgill.ca/users/jastonrpm_statistics.html. The fixed effects model using residual statistics has been incorporated into the main RPM basis function fitting techniques. This incorporates the computation of the voxel by voxel errors associated with the parameters into the fitting procedure. In terms of computational speed, this is superior to a subsequent error computation. The algorithm calculates the partial derivatives from explicit algebraic forms as opposed to numerical approximations.

The parametric images and their associated errors from individual scans are then combined to produce statistical parametric images. This allows the estimation of fixed and random effect statistics based on the models determined in [6]. Residual error images are only required for a fixed or mixed effects analysis. In such cases, the degrees of freedom of the mixed effects model can be increased if assumptions about the spatial correlation of the variance ratio are satisfied. The software also allows for a pure random effects analysis, based solely on the parameter estimates themselves.

Case Study
There are many ways to analyze any given dataset. Each method contains its own set of assumptions and it is decisions about the appropriateness of these which should lead to the selection of the analysis method. The three types of analysis available here, are fixed, random or mixed effects models. These were considered for analysis of control data from a \([4]^{11}C\text{SCH23390} \) study [2] where there should be no detectable change. The control data contained temporal information, so a random effects analysis was discounted immediately, and due to the multiple subjects in the data, so was the fixed effects analysis. Thus the choice was whether to smooth the variance ratio for a mixed effects model. Smoothing increases the power of the analysis, but requires additional assumptions to be satisfied. Smoothing is only valid if there is no sign of anatomical structure in the variance ratio image. It has been previously shown [1] that there is a large amount of anatomical structure in the parameter error images, in the same way as SPM, but this problem was addressed in SPM by using the variance ratio (fixed : random) as opposed to the variance itself. It was expected that the variance ratio would show little anatomical structure in PET neuroreceptor ligand data, and this was indeed the case for the \([4]^{11}C\text{SCH23390} \) study. Had there been anatomical structure in the variance ratio, a mixed effects model with no variance ratio smoothing would be the most appropriate method of analysis.

Conclusion
This statistical tool provides a comprehensive framework for the analysis of neuroreceptor ligand data on a voxel basis. Fixed effects (for single subject studies), random effects (where there are no associated error images), or mixed effects (with or without smoothing) analyses may be performed. The spatial smoothing of the variance ratio allows for increased statistical power. These techniques are generalizable to other neuroimaging modalities given appropriate physiological models.

References
2. Dagher, A et al. Reduced dopamine D1 receptor binding in the ventral striatum of cigarette smokers. Synapse, in press (2001)