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Tutoral: Functional MRI Analysis.

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1 Functional MRI Analysis

The importance of accurate measurement of cerebral function in clinical practice cannot be overestimated. Changes in blood flow occur in all cerebral diseases and can provide valuable diagnostic and prognostic data for patient management. Also important is the ability to measure reductions in blood flow which may produce ischaemic cell death either due to ischaemic apoptosis or stroke. In addition, the growth of tumours over a certain size is dependant upon the development of a vascular tissue supply adequate for the metabolic needs of the neoplastic tissue. Once a growing tumour reaches a critical mass, equivalent to 1 cubic millimeter (or approx. one million cells) diffusion of metabolites becomes insufficient and new blood vessel growth must occur for continued development. This observation has led to the development of new theraputic agents designed to inhibit angiogenesis, with the intention of restricting tumour growth and dissemination. The introduction of this new class of theraputic agents requires the development of measurement techniques to demonstrate the presence of angiogenic activity.

Until recently accurate measurements of blood flow within the capillary beds of the brain could be produced only by use of ^{15}O labeled water molecules and positron emission tomography. This technique is accurate but unsatisfactory for clinical examinations since it is extremely expensive, invasive and requires prior scheduling of the examinations which can be completely impossible in clinical emergencies. In order to overcome these problems two alternative clinical methodologies were developed. The first of these is the use of 99mTc HMPAO as a marker of perfusion in combination with single photon emission computed tomography (SPECT). This tracer is highly lipophilic and passes into the brain in quantities proportional to regional blood flow. Once in the brain the isotope is trapped and its distribution can be imaged for several hours after the injection. Unfortunately the method still requires exposure to radiation and produces low spatial resolution images which contain no other anatomical or structural data. As a result the SPECT examination must be routinely supplemented with other cross-sectional imaging such as CT or MRI. The introduction of Xe enhanced CT has provided a potential solution to these problems by providing high resolution anatomical images in combination with accurate high resolution measurements of cerebral blood flow. Despite this the Xe technique has not been widely accepted for clinical use due to the high radiation dose required and the potential clinical complications produced by the anaesthetic activity of the Xe.

In clinical practice MRI is now the investigation of first choice in the vast majority of cerebral disease. The ability to produce accurate maps of cerebral function on standard clinical MR scanners is therefore highly desirable. There are several different forms of MR functional imaging techniques under development in the research literature. The suitability of these techniques for particular tasks is generally limited by: equipment, patient tolerence and suitability. The main contenders are currently Contrast Susceptibility Perfusion, Permeability Measurement and Blood Oxygen Level Dependency (BOLD). Each of these techniques involve generating multiple brain volume images over a range of time intervals and useful measures have to be obtained by a complex analysis process.

Two generic methods have been described to produce MR based measurements of perfusion. The first, which is the subject of this material, is to derive measurements of perfusion from images which document the passage of a single bolus of contrast medium through the brain. The second is to magnetically label protons in blood which is passing through the brain and to use resulting, flow induced changes in signal intensity to calculate flow. These spin labeling techniques are attractive since they do not require contrast injection and can be repeated as often as is necessary without risk. Unfortunately, spin labeling techniques suffer from physical limitations imposed by the half life of the "spin tag". More importantly however, the methods have inherrently poor signal to noise making the technique a realistic proposition only for high field strngth systems. These problems have excluded the spin labeling methods from clinical practice at the present time.

Imaging of angiogenesis relies on the identification of surrogate markers of angiogenic activity such as Vascular Endothelial Growth Factor (VEGF). The relationship between tumour behaviour and microvascular

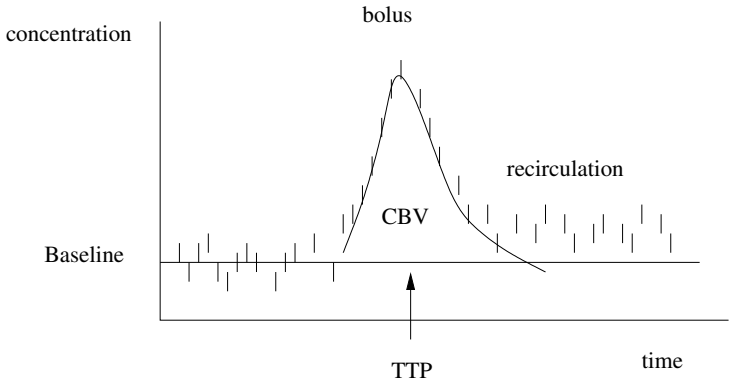

Figure 1: Concentration/ Time curves in Susceptibility Perfusion data.

density on histological studies has led several groups to investigate the measurement of cerebral blood volume using PET or MR based methods ([2, 7, 13, 14]). Since VEGF activity is associated with marked increase in endothelial permiability one alternative approach is to quantify the permiability of vascular endothelia [1, 11, 7, 17]. This can be be achieved by the application of established pharmacokinetic models of contrast distribution [20, 8, 26].

The BOLD technique is becoming increasingly popular as a clinical as well as a research tool to probe the workings of the brain. This technique does have some clinical uses, for example it has been used to map reqions of 'eloquent' cortex in order to avoid the more sensitive parts of the brain during surgery, but generally the technique is currently used mainly in research to map out functional relationships between brain regions, ie: an experimental replacement for more opportunistic lesion studies.

2 Contrast Susceptibility Perfusion

Contrast susceptibility perfusion has much in common with PET, the intention being to directly measure the flow characteristics of tissue via imaging the passage of an injection. However, MRI perfusion measurement has better spatial resolution and can mesure the relative time of arrival (Time To Peak) and also recirculation characteristics. MRI perfusion can also measure volume related quantities, particularly Relative Cerebral Blood Volume (RCBV). Whereas PET can generate absolute measures of Cerebral Blood Flow MRI CSP is again only relative (RCBF).

Contrast susceptibility perfusion has many potential clinical uses. The main physiological parameter which correlates most strongly with potential stroke is blood flow. The technique is potentially much more informative than PET particularly for observing tumour characteristics and ischaemia. However, the technique still has its problems and is still some way from being reliable enough for clinical use. These problems stem from both the difficulty of making accurate measurements and problems of physical modelling and stability of data processing.

The physical processes which give rise to a signal drop as a contrast agent (eg: Gadolinium DTPA) passes through the tissue is attributed to a magnetic spoiling effect on the local MR resonance process. The signal is monitored over time with typical temporal resolution of the order of seconds. (figure 1) The bolus itelf will pass entirely through the head in around ten seconds. The effect on signal is largest where a free water signal is close to a source of contrast molecules. In tissue this is likely to happen along the interface between capiliaries and body cells. If this barrier is impermiable to the contrast agent then this is the only source of signal loss and the effect is expected to be greatest for small capilliaries for a given fixed volume of contrast. Signal loss in arteries and veins is due to direct mixing of blood and contrast agent. As the size of the capiliaries in a given region of the tissue is unmeasureable all analysis methods have to assume a direct relationship between signal loss and total contrast volume within a voxel. The assumption of a linear relationship between relaxation rate and concentration of the contrast agent has been shown to be valid both by experiment and simulation for the blood volume fractions in the physiological and pathological range [9]. This is widely regarded to be an acceptable assumption though other assumptions need to be made which may be less justifiable. Though methods for reliably locating the bolus in a time course of data and extracting arrival times and RCBV are relatively easy to

devise, calculation of a genuine RCBF (which requires some way of assessing the velocity of blood though a voxel as an independent measure) has proved more difficult.

2.1 Analysis of Contrast Susceptibility Data

The use of first-pass bolus studies to measure cerebral perfusion is fundamentally attractive. The use of contrast injection produces controllable decreases in signal intensity, whilst basing the analysis purely on first pass data imposes a short image acquisition which can be easily incorporated into existing clinical imaging protocols. First-pass bolus kinetics are also well documented and highly generic, so that any successful technique can be used with a range of imaging technologies. In clinical practice, the need is for a technique that will work with both MRI and CT, which currently form the basis of all clinical scanning protocols. Equally important is the ability of first-pass first-pass analysis methods to produce maps of cerebral blood flow from MR data. These techniques use the area under the contrast concentration curve as an estimate of blood volume within the pixel (CBV) and the width of the contrast bolus as an estimate of the mean transit time (MTT).

The conventional approach to modelling the perfusion measurement process relies upon three key stages concerning;

- a relationship between contrast density and MR signal loss.
- a relationship between the integrated contrast density and flow variables.
- a relationship between the shape of the contrast density distribution and the transit time.

Given these relationships it is then possible to calculate tissue perfusion from the time varying MR signal following contrast administration.

The approach outlined above initially involves computation of relative cerebral blood volume [3, 22, 24] which is a well defined and easily measured parameter. The equations describing formation of T2* weighted image intensity values I_i for voxel i ignores flow based and partial volume measurement artifacts.

The MTT parameter can be estimated from the temporal width of the measured bolus. The standard approach is to assume that the width of the gamma variate time curve, generated by the passage of the bolus is representative of the time taken for the bolus to pass through a voxel. Clearly such an approach is highly dependent upon the shape of the active region and isotropic voxels would be preferred in order to eliminate net flow direction dependencies. Attempts to account for differences in cardiac output and administration of contrast are generally based on deconvolution. However, as the spatial resolution of the data improves the expected contribution of MTT to the width of the curve will decrease.

The importance of deconvolution with an input response function has recently been identified in order to obtain quantitative measurement of MTT [21] though for a fixed input function the area under the curve (and therefore CBV) should be unaffected.

Processing involves:

- Pre-processing, (Noise reduction).
- Calculation of Concentration time curve
- Fitting of this data to a gamma variate to locate the bolus and determine T0, TTP, MTT, RCBV. Only the early part of the bolus is fitted to avoid the contrast recirculation phase.
- Deconvolution to recover MTT.
- Recirculation can be measured as the excess signal drop following the fitted region.
- Error maps can also be used to identify regions of data which are not well modelled by a Gamma Variate function.

The time varying contrast concentration with in a voxel is assumed to be proportional to the relaxivity and is given by

$$C(t) \;=\; -K\ log(S(t)/S(0))$$

where K is tissue, pulse sequence and field strength dependent, $S(t)$ is the signal in the voxel and $S(0)$ is the baseline signal.
In the simplest form of analysis, this data is then modelled assuming the following Gamma Variate function by fitting to the early part of the signal attenuation to avoid recirculation effects.

$$C(t) \;=\; A(t-t_0)^{\alpha}\ exp(-(t-t_0)/\beta)$$

where α and β are shape parameters for the bolus. Notice that t_0 is extracted directly but other parameters must be extracted using the fitted function. For example $RCBV$ is obtained by integration.
The more sophisticated approaches involve modelling the data as a residue curve convolved with the arterial input function. The residue curve can therefore be obtained by deconvoluton.

Box 2: Perfusion Modelling.

This allows calculation of relative cerebral blood flow (CBF=CBV/MTT) and the production of parametric maps of each parameter. One major restriction of this technique is that the estimates of CBV and CBF are relative and not absolute which restricts clinical interpretation. Production of absolute measures of CBF requires absolute accurate measures of CBV and MTT. The production of accurate CBV measures is possible if inflow effects and other non-linear MR variables can be compensated for.

2.2 Interpretation of Parametric Images

The data generated by Perfusion measurement are often simply presented as images with the implication that raw parameters can be visually interpretted. The motivation for this follows directly from radiologists familiarity with medical image data. However, the values of parameters in regions of low RCBV will be very unstable for variables such as MTT and TTP. Such images have regional statistical characteristics due to varying accuracy of the data [16], (fitting failures or non-Gamma variate behaviour), which are easily mis-interpreted. In particular, if there is insufficent data to perform a good fit the values will often be left with default values set prior to the fitting. Ideally images should have the characteristic of uniform random noise with fit failures being excluded before being displayed for viewing, so that all visible features on the image have the same statistical significance. This often involves moving away from the raw physical parameters and displaying error scaled versions or scatter plots of variables. Even then, simply viewing ignores the potentially valuable quantitative nature of the data. Potentially, a well calibrated technique should be capable of measureing quantitative differences between succesive scan sessions.

The deconvolution approach to MTT (and hence velocity) estimation is based on several assumptions, one of which is that of zero dispersion of the contrast agent, either due to Brownian motion or inflow heterogeneity. If this were not true it would be wrong to deconvolve with the same arterial input function in all regions of the data. Unfortunately, the observed time curve may be affected not only by the input response at the base of the brain, but also by any intervening tissues en-route to a voxel.

We have found that images of T0 are very sensitive to various forms of brain dysfunction, but images of RCBV and RCBF (generally used for diagnosis from PET data) are very difficult to interpret as relative values of flow show little obvious correlation with functional deficiency. Use of these measures in clinical practice will require the development of a model of normal and abnormal flow patterns in brains on the basis of these parameters. One major complicating factor is simply the physiology itself. Understanding the function of the 'circle of Willis' plays a key role in this process.

3 Permeability Measurement

As with methods for constrast suceptibility perfusion, the measurement of permiability requires the administration of a contrast agent. However, the use of T1 weighted sequences means that the physical processes which generate signal change are modelled differently. Also, the leakage of contrast agents into the vascular endothelia results in different temporal behaviour of this signal change (Figure 2). In

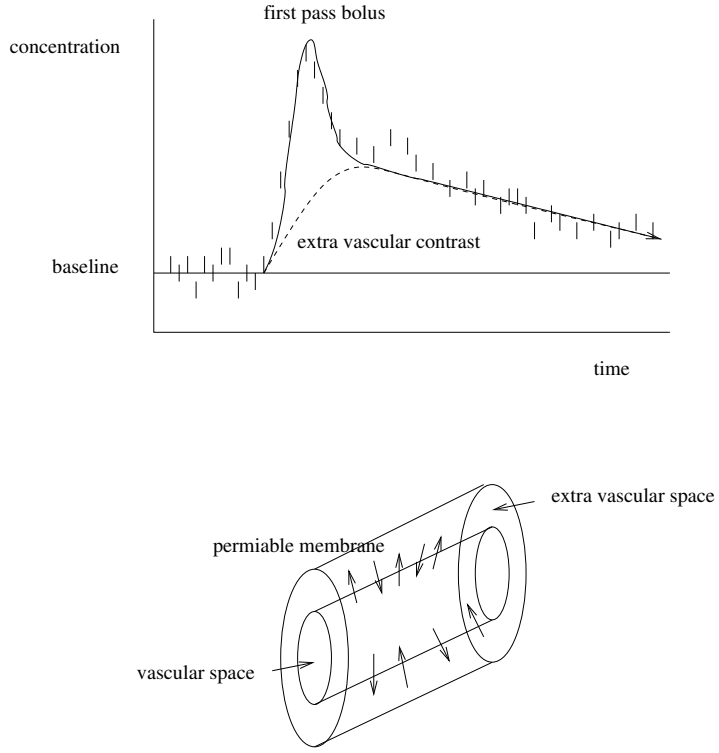

Figure 2: Concentration/ Time curves in Permiability data.

addition to a first pass bolus, contrast agent leaks into the vascular endothelia continuing to affect the signal change for a significant period after the exit of the first pass bolus. On time scales of minutes the leaked contrast is washed from the endothelia back into the blood supply and ultimately extracted by the kidneys. Quantitative analysis of the MR signal requires knowledge of the T1 of the region to be analysed. This can be done using several static scans at various flip angles. The pharmacokinetic models required to analyse the temporal development of contrast concentration at any point in the tissue must model all of theses processes and requires many parameters, of which the permiability itself is only one. Unfortunately, it is the complexity of this model and the near equivalent behaviour of the model parameters on the shape of the distribution which make reliable estimation of permiability difficult. Dealing with these problems requires careful control of the quality of the data and selection of modelling functions with a minimum number of relevant parameters.

3.1 Analysis of Data

Typical analysis of permiability data proceeds as follows.

- The T1 of the region to be analysed is calculated from co-registered data volumes.
- A supply artery is identified and used to estimate the time development of the input contrast concentration.
- The computed T1 maps are used to estimate the contrast time course at each point in the data.
- These curves are fitted to a phamacokinetic model which includes a first pass bolus contribution and terms for permiability leakage and subsequent wash out.

In the process this analysis detetermines both permiability and CBV.

The Ernst formula for the signal $S(\alpha)$ in a T1 weighted fast echo sequence, for a flip angle α (assuming $TE << T2^*$) is given by

$$S_\alpha \;=\; N_H sin(\alpha)(1 - exp(-TR/T_{10}))/(1 - cos(\alpha)exp(-TR/T_{10}))$$

where N_H is the spin density and TE is the echo time.
Putting

$$A \;=\; (S_\alpha(t) - S_\alpha(0))/(N_H sin(\alpha))$$

and

$$B \;=\; (1 - exp(-TR/T_{10}))/(1 - cos(\alpha)exp(-TR/T_{10}))$$

we can write the relaxivity as

$$R1(t) \;=\; -ln[(1 - (A + B))/(1 - cos(\alpha)(A + B))]/TR$$

quantitative concentration time curves are then given by the following linear relationship

$$C(t) \;=\; (R1(t) \;-\; 1/T_{10})/R1_{Gd}$$

This data is generally described by a function of the form

$$C(t) \;=\; v_p C_p(t) \;+\; K_{in} \int_0^t C_p(\tau) exp(-K_{out}(t - \tau)/v_e)\; d\tau$$

where v_p and v_e are the intra and extra-vascular blood volume within the voxel and K_{in} and K_{out} are the total permiability within the voxel. The first pass contribution from the inital bolus $C_p(t)$ is likely to have the same shape as those in the perfusion based methods. It is generally estimated from a nearby artery as the vascular input function, though this assumption takes no account of flow velocity dependencies as modelled in the perfusion techniques.

Box 2: Permiability Modelling.

3.2 Interpretation of Data.

The same comments for the interpretation of parametric images apply as for perfusion data. In addition however, it should be borne in mind that the estimate of permiability delivered by this technique is proportional to the quantity of contrast agent which crosses the permiable barrier. This is not simply the permiability, but the permiability surface area product. Therefore, the estimates of permiability are confounded by the local physiology and thus less directly interpretable than we might have hoped. Even so, repeated measurements on coregistered regions of the data should allow the observation of statistically significant changes.

4 BOLD

This technique relies on the variability of MRI signal due to the physical process of differeing proportions of de-oxyhaemaglobin in the blood. The process does not therefore require injection of any contrast agent. The level of this signal change in modern MR scanners is still quite small and of the same order as the noise in the data (a few percent). The most common way of extracting this signal has thus been based on a temporal integration of signal to boost statistical power. The most common technique requires a relatively restricted 'on' 'off' paradigm in order to generate data sets during known functional activity/inactivity. The idea is to saturate the oxygen concentration and then let it revert back to its normal state (Figure 3). The maximum rate that this can be achieved is determined by the so called "haemo-dynamic response function" which restricts saturated to non-saturated oxygen level change to an approximate six second separation. This mechanism fundamentally limits the temporal resolution of BOLD experiments independantly of the level of noise in the scanner.

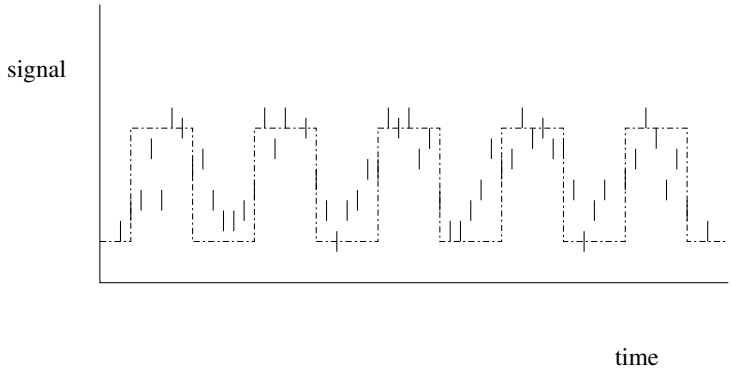

Figure 3: Signal/ Time curves in BOLD data.

4.1 Analysis of BOLD Data

Unfortunately, BOLD is not the only physical mechanism which can lead to a signal change. There are also Blood Flow Level Dependent (b-FOLD), CSF Oxygen Level Dependant (COLD), CSF Flow Level Dependant (c-FOLD) and also motion Level Dependent (MOLD) signal mechanisms [15]. Because of these multiple signal mechanisms much care has to be taken during data analysis to ensure that observed signal is genuinely due to BOLD. The b-FOLD signal can be considered as complementary to the BOLD signal as an alternative indicator of functional activation. The CSF related signal is not expected to correlate with the stimulus paradigm due to the much shorter time scales. Of the various other ways that signal can be generated, in a BOLD activation experiment, c-FOLD and COLD can be masked off. Therefore, the main problem with ensuring valid signal from a BOLD analysis is in controlling the effects of motion, which can be considerable during the course of an extended experiment and often correlate directly with the paradigm task.

The importance of motion correction in Functional Magnetic Resonance Imaging (fMRI) has been widely recognised in the literature [15]. Many of the stages of BOLD data analysis are geared towards minimising or eliminating this effect. The aim being to pre-process the data in order to obtain the data that would have be acquired had the subject remained perfectly motionless throughout the study. The solution to this problem involves the use of a co-registration proceeedure, the aligment in 3D of two volume datasets by automatic means.

Processing involves:

- Co-register volumes to the first time data set to determine the transformation between the volumes.
- Reslice the input data to obtain the data at time t aligned with time 0 interpolation (preferably SINC).
- Analyse for correlation with 'on' 'off' paradigm (some pre-processing may be needed to eliminate scanner artefacts such as field strength changes).
- Pool the high correlation results in a standardised co-ordinate system (eg; a Taliarach brain).

There seems to be a standard approach emerging to the problem in clinical environments making use of software available on the internet, such as the Automatic Image Registration package (AIR) [29, 30, 18] which assumes a rigid body motion. Depending upon the details of the data acquisition, a rigid body assumption may be considered a little naive depending on the sequence employed. In some cases slices of image data may undergo different amounts of motion and in other cases the data may suffer from motion blurring. These processes could leave residual motion artefacts in the data which bias subsequent interpretation. Many groups, now routinely make use of rigid body co-registration and it has been proven that the effects caused by motion are reduced to an acceptable level in the subsequent fMRI analysis (Thacker et al).

There have been many approaches to the analysis of functional NMR images proposed in the literature. Considered from a statistical point of view these techniques can be grouped as either non-parametric or parametric. It is generally accepted that whilst non-parametric techniques are initially more robust,

parametric techniques will ultimately have better discriminability once the analytical models have been refined. We therefore concentrate on these approaches here.

For parametric approaches, analysis can be basically decomposed into two stages, the application of a voxel by voxel time dependent analysis, followed by a regional analysis of clusters [12, 19]. The first of these is designed as a significance test, the hypothesis being that the data seen in the image can be accounted for entirely by random noise fluctuations. The voxel based null hypothesis test is generally implemented as a correlation measure. The details of this vary in the literature, but all successful measures have the same fundamental statistical origins, which is effectively that some measure of correlation C is normalised by it's expected variance $var(C)$ in order to produce a measure which can be treated like a 't test' or 'Z score' [19]. The subsequent thresholding of this measure, to detect significant signals, invariably assumes a Gaussian distribution [1] for this test statistic and must generally take into account temporal correlations in the image formation process [27]. The specific choice of correlation measure varies depending on the authors. Some have suggested using a set of sinusoidal correlation functions and computing the effective "power" of the data [10]. There seem to be two main justifications for this approach, the first is that although the stimulus in the experiment is invariably a simple "on" or "off" task (i.e. a box car function of known period), we do not know the true shape or phase of the signal. Such a Fourier approach to analysis thus gives a method of estimating signal content which is independent of phase or specific details of the shape of the response curve. The second justification is simply that such an approach delivers measures which are completely independent of phase.

A simpler analysis than a Fourier decomposition, involves correlation with a "box car" function [4] which can be shifted as necessary in order to locate the maximum phase response. Though this second technique does not take variability of shape into account there may be some merit in restricting the freedom of the response function to something resembling the initial stimulus. As we do not know the true shape of the signal we are looking for, it would be difficult to know which of these two approaches is superior. However, in general the "box car" approach will be more specific as it requires not only a signal, but a signal with a particular shape. One model, which has been justified empirically, is a convolution of the stimulus function with the Poisson distribution. This can be generalized to the Gamma variate which is also a popular choice for perfusion analysis [6]. Another simple variant is to construct pooled estimates of signal from "off" and "on" periods and then to apply a simple "t" test [25]. Simple algebra can show that this is statistically equivalent to correlation with a "box car" function. Clearly such an approach does not take correct account of either temporal correlations or the specific shape of the response curve.

Finally, some authors have suggested correlation measures which cannot be directly interpreted as a 't-test'. The measure used both in [5] and [23] in particular is a measure which occurs in the STIMULATE software which is commonly used in research laboratories. Though this has nice intuitive properties (it is normalised between -1 and 1) it cannot be reliably thresholded in order to identify true signal as the measure has different statistical scaling for each experimental design. In [28] the test statistic is defined as a power-quotient which is the power of the sought frequencies divided by a normalisation factor other than the expected variance. This particular form of measure is only monotonically related to the standard form described above. However, before this measure is used it is renormalised using a Monte-Carlo technique to re-impose the standard statistical interpretation. A similar step would also be necessary with the measure in [5] and [23] before it could be used in earnest. In doing so this would be reverting to the previous measures.

[1] This can ultimately be justified by the central limit theorem if the variance of the correlation measure is the combined affect of many small purtebations in the image data drawn from unknown but equal distributions.

The correlation methods used in block paradigm data analysis can be grouped into three alternative approaches.

- A simple correlation measure with no explicit (fixed) normalisation.

$$C_j^1 = \sum_{t=1}^{T} S_j(t).W(t)$$

where W is a normalised correlation waveform ($|W|^2 = 1$) and S_j is a mean subtracted temporal data set at voxel j . This correlation measure can be converted into a simple null hypothesis statistic by dividing by a pooled estimate of the standard deviation on the measure $\sqrt{var(C)}$ and will behave in the same way as any measure which makes the basic assumption of constant uniform image noise, including Fourier approaches. Such a simple measure is unlikely to be used unmodified in serious fmri analysis but it is included here for completeness.

- A correlation measure with individual voxel based normalisation.

$$C_j^2 = \frac{\sum_{t=1}^{T} S_j(t).W(t)}{1/(T-1)\sqrt{\sum_t^T (S_j(t) - W(t).C_j^1)^2}}$$

where the numerator is the estimate of variation about the assumed model. Once again S_j is a mean subtracted temporal data set at voxel j . This technique will behave in the same way as any measure which estimates variance from the data, such as 't-tests' and 'z-scores'.

- and finally a normalised correlation measure as used in STIMULATE

$$C_j^3 = \frac{\sum_{t=1}^{T} S_j(t).W_t}{\sqrt{\sum_t^T S_j(t)^2}}$$

with parameters as described above.

Box 2: Correlation of BOLD Data.

4.2 Interpretation of Activity Maps

An assumption (that oxygen level change is due to local brain activity) is required to attribute BOLD correlations solely to brain function. There are two aspects to this assumption, the first being that the signal change will be sited over the active region, in fact the maximum signal change is likely to be where there is a high blood volume and this may not be located directly over the site of source activation. The observed site of BOLD signal will be dependant upon the local physiology, perhaps limiting the spatial resolution of the approach to millimeters. Another complication arises from the way that the signal is extracted from the data using a correlation analysis. Such an analysis will measure local changes correctly, but if the brain is continually active the correlation with the paradigm will be small. Thus we have to be particularly careful when interpretting BOLD responses; absence of evidence is not evidence of absence. We cannot say that regions which do not correlate with the stimulus were not active and BOLD correlations should not be equated directly to brain activity.

5 Conclusions

Direct functional analysis of MRI data is possible but requires careful treatment of the data from the scanner and much further analysis in order to obtain quantitative measures.

The main problems with contrast enhanced perfusion are due to scanner artifacts and are almost certainly manufacturer dependant.

The main problems with BOLD analysis are due to subject motion.

Potentially both of these techniques could be of great value to clinicians for a new era of physilogical measurement. For example the action of VEGF based cancer treatements could be directly monitored via their affect on blood supply to the tumour.

Analysis of BOLD data, when coupled with more flexible approaches to paradigm construction and

analysis proceedures which model temporal dependancy of spatial activation, may give us more insights into brian function.

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