Methods for the detection of Drug Effects using EEG Data

Joint Supervisors

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Summary of project

Many potential drug targets are localised within the central nervous system (CNS) and it is therefore critical to understand if, and to what degree, the drug crosses the blood/brain barrier. However the key problem with central drug targets is that we cannot directly monitor drug levels in the brain, so indirect methods are required. One method is to measure the general activity of the brain via scalp electrodes (the so called electroencephalogram (EEG)). The EEG is normally used to study proconvulsant activity or to study sleep changes. "Snap shot" signatures in rats have been noted by Dimpfel (2003), but these are not time-varying, but other work has shown that the EEG signal contains a "signature" which can be used to directly measure the activity of drug in the brain over time.

Pfizer's current studies use a telemetrised Rat model, which yield a single-channel EEG signal, and data of this form will be available for the student to develop analysis and detection methods. They may also be able to access to EEG data from human subjects, which is more complex, with signal from multiple channels. If they have access to this data the student will be able to extend the methods used for the simpler rat EEG signals to the more complex human case. (See Saletu et al (2002) for previous work in this area).

The student will be working in a novel area needing primary statistical/data analysis skills, and will gain experience in the understanding of electrophysiological measurements, and analysing EEG data. The analysis skills developed and learned in the analysis of EEG data will be applicable to other high dimensional data problems. The analysis of high dimensional data is increasingly important, and poses a wide range of interesting questions.

Non-invasive biological markers of brain activity such as EEG data are important in the drug discovery process, and the student should be able to make a valuable contribution to improving these processes. The methods being developed are also translatable, as they can be used on both animal and man.

Introduction to EEG

EEG signals measure the activity of brain cells and in rats are typically measured as a differential recording from two electrodes attached to the skull and sampled at a rate of 250-500Hz. EEG signals in humans are recorded in a similar way, but have many more channels (currently up to 512) measuring brain activity at a range of positions on the skull. These are again base-lined by subtracting one of the probe signals from the signals from all other probes.

Having obtained the signal(s), a common way of analysing the EEG data is to subdivide it into time slices (epochs) which are small enough for the signal to be stationary, but large enough to give an adequate range of frequencies, and the signal in these time slices are then subject to a fast Fourier transform which gives the power of the signal at each frequency.

Typical experiments yielding EEG data

A typical experiment involves dosing an animal (or human subject) with a known dose of an active compound. The compound will enter the blood and will be circulated throughout the body, and, if capable of penetrating the blood/brain interface, will eventually enter the brain where if it is active it will cause an effect. Over time the concentration of compound in the

brain will rise to a maximum, then decay away as the body naturally disposes of it. We assume that the effect in the brain will be proportional to the concentration present. If the compound is active it should affect the EEG signal, so we would expect to see changes that will reflect this. A typical model to describe this behaviour over time for an injected compound is a two-compartment Pharmacokinetic/Pharmacodynamic (PK/PD) model, where the two compartments would be the blood system, and the brain, respectively. PK/PD models for this aspect of the work can be used, but for novel compounds we will not know the exact parameters of the models, as the effects in the brain depend on the compound leakage into the brain, which cannot be measured directly. PK/PD models are widely used in drug development, and are also used in EEG studies (see, for example, Lotsch (2005)).

Aim of the project

EEG signals will change depending on the status of the animal/human, as brain-wave patterns change markedly during deep sleep, sleep, active state, and resting. In rats, in particular, transition between the different states can occur many times during a typical 12 hour study. For a given drug type we are looking for a "signature" (a profile across frequencies) in the EEG signal which is independent of the sleep state. The amount of this profile present in a given spectrum at a given time will reflect the affect of the drug present in the brain. We expect these signals to follow a PK/PD model, but may not necessarily know the exact parameters, so these will need to be estimated as part of the signature detection.

Detecting this signature could provide an important biomarker for the drug discovery and development process. It will provide a non-invasive way of detecting drug effects that is translatable, so can be used in both animal and human studies.

Data

The rat data sets available for the study will be of the spectrum power tabulated by Time slice, electrode location and Frequency, for test subjects dosed with either vehicle/placebo, or different doses of a range of compounds. Pfizer are happy to provide this data.

Possible analysis methods

The data format takes the form of a matrix or a three dimensional array, so multivariate methods are expected to be useful (a relevant approach to the three dimensional case is Linder & Sundberg, 2002, and references therein). Pfizer's current approach uses a modified version of Canonical Correlation Analysis (MDCCA). A novel part of the study is that we have a functional form for the response we are trying to detect, so methods which are capable of detecting this underlying functional form and quantifying it (eg Ramsay & Silverman, 1997) will also be relevant. The MDCCA simply optimises the correlation across time between a linear combination of the power spectrum and the standard PK/PD curve parameterised according dose level. There are questions of robustness, alternatives to the simple two compartment PK/PD model, diagnostics for detecting inadequacies in the model and overall inferential properties both classical and Bayesian.

Pfizer Support

Pfizer in addition to providing data are happy for the student to spend some time at Pfizer to be involved more in the Biological context and current statistical techniques. They are also willing to significantly financially enhance the studentship. Drs Phil Brain (Statistical) and Magnus Ivarsson (Biological) would act as co-supervisors.

References

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