Institution: University of Aberdeen

Unit of Assessment: 10 (Mathematical Sciences)

Title of case study: A Mathematical Algorithm to Improve Diagnosis of Dementia

1. Summary of the impact

Alzheimer's disease is the most common form of dementia, with a cost to society estimated at €177 billion per annum across Europe, according to the European Collaboration on Dementia (EuroCoDe) project funded by Alzheimer Europe. Data-based modelling of network structures is a modern approach to study and understand many diseases including dementia. Research carried out at the Institute of Pure and Applied Mathematics (IPAM) at the University of Aberdeen has led to the development, implementation, and testing of novel mathematical algorithms to infer network structures by means of observations of their dynamics. The results of our research have been implemented as part of a software package now offered by the Netherlands-based company BrainMarker to researchers and practitioners across Europe in an online 'pay-per-click' platform (section 5.c1 and 5.c4). As such our research generated impact on clinical practitioners in addition to commercial impact.

2. Underpinning research

The concept of networks has become pivotal in many fields of research including the biological sciences. When analysing networks in neuroscience, a notoriously difficult task known as the "inverse problem" is faced. From measured time series of processes in the network, conclusions on the underlying system are sought. Of particular interest is the estimation of the interrelations between the processes and their directions.

The human brain is a prototypical example of a highly complex network. Of particular interest for the human brain is the study of neuronal oscillators reflecting brain activity. Measurement of electrical activities in the brain by means of electroencephalography (EEG) recordings is routinely used in the diagnosis, the prediction of progression and the effectiveness of potential therapeutic interventions for various diseases. As an illustration, relevant to this case study, diseases that affect the human brain and the central nervous system are typically related to pathological changes in the brain network structure. In dementia, brain regions such as the hippocampus and the prefrontal cortex and their interactions are believed to have an important role in our understanding of the underlying mechanisms. One of the goals in the analysis of the EEG signals is to obtain information on the direction and strength of the interactions between different parts of the brain and to obtain statistically significant results. Monitored over time, inference about these interactions may lead to novel biomarkers for an early detection of dementia.

In practice, the presence of noise in measurements is one obstacle to the achievement of this goal. Another is the presence of rapid changes in the system's parameters, which are extremely important in the analysis of the network but are computationally a major challenge as we explain below. As an example, consider human sleep with its different stages including Rapid Eye Movement (REM) sleep (the dreaming phase), which is important for dementia. The transition into REM sleep occurs in the order of seconds, and is marked by a significant change in the electric activity in the brain.

Several time series analysis techniques have been suggested to analyse interactions between processes. However none of which was able to provide a complete picture. For example, the directed transfer function (DTF) has been widely applied in neuroscience research since the early 90s; it provides the direction of information flow, but it cannot distinguish direct from indirect interactions. This inevitably leads to detection of spurious directed interactions in the network, which hampers the interpretability of the results. Other multivariate approaches such as “partial correlation” and “partial (cross-)spectral analysis” and “partial phase synchronisation analysis” promise to distinguish between direct and indirect interactions in networks but do not provide information about the direction of the interactions. The “renormalised partial direct coherence method” previously developed by **Schelter** (and collaborators) gives information on the strength of interactions, their direction, and can distinguish direct from indirect interactions, however is inherently incapable of coping with observational noise. Basically applied, it cannot detect rapid changes in the interaction parameters, which is a serious deficiency, especially in light of the importance of the transition between sleeping stages described above to the study of dementia. None of these techniques, or others that were available prior to the research described below carried out in IPAM, could provide the complete picture about the frequency, strength, and the direction of the direct interactions in a network of potentially non-stationary, noisy, non-linear systems.

Between 2010 and 2012 **Thiel**, **Schelter** and **Grebogi** developed a new mathematical and statistical theory to infer the connection topology of coupled complex systems from observations of their node dynamics alone [1]. No prior information or assumptions on the interactions is needed in contrast to many other approaches. The mathematical framework that has been developed by IPAM provides the complete picture in connection to the parameters mentioned above and was demonstrated to be superior to previously existing methods [2, 3]. The mathematical theory is based on nonlinear state space models. The estimation of the parameters that characterise the network’s structure is based on the expectation-maximisation algorithm, which maximises the incomplete data likelihood in an iterative procedure, and requires application of an improved version of the dual Kalman filter that we developed [2, 3]. The new technique called the “time-resolved renormalised partial directed coherence”, gives a time-resolved estimation of the direct, directed interaction structure for stochastic linear as well as non-linear systems in the presence of observational noise. Thus, our novel approach enables the inference of the ‘true’ network structure underlying noisy data, making little assumption about the type of signals or signal quality. Its ability to infer the network structure with temporal resolution only limited by the sampling rate promises to gain new insights into potentially rapidly changing signals or interaction structures.

3. References to the research

Researchers from IPAM in bold, lead author named last.

[1] Ramb, R., Eichler, M., Ing, A., **Thiel**, M., **Grebogi**, C., Schwarzbauer, Ch., Timmer, J., **Schelter,** B. *The impact of latent confounders in directed network analysis in neuroscience.* Phil. Trans. A 371, 2013, 20110612 (submitted 2012).
In this publication, we investigated the role of latent confounders and developed an algorithm to identify these. This is vital for investigating the “true” underlying network structure to avoid false positive conclusions.

[2] **Sommerlade**. L., **Thiel,** M., **Grebogi,** C., Platt, B., Plano, A., Riedel, G., Timmer, J., **Schelter**, B. *Time-Variant Estimation of Connectivity and Kalman Filter*, Taylor and Francis, 2013, eds. L.A. Baccala and K. Sameshima (submitted in 2011).
Here, we particularly investigated the superiority of the presented approach to more conventional approaches. We clearly show that the developed novel technique outperforms conventional approaches.

[3] **Sommerlade**, L., **Thiel**, M., Platt, B., Plano, A., Riedel, G., **Grebogi**, C., Timmer, J., **Schelter**, B. *Inference of Granger causal time-dependent influences in noisy multivariate time series.* J.

Neuroscience Methods **203**, 2012, 173-185
This is the key publication for the Impact Case Study. It presents for the first time the novel mathematical algorithm and its implementation that is key for investigating the complete 3 dimensional picture of time, frequency and strength of an interaction.

[4] Lenz, M., Musso, M., Linke, Y., Tüscher, O., Timmer, J., Weiller, C., **Schelter**, B. *Joint EEG/fMRI state space model for the detection of* directed *interactions in human brains.* Physiological Measurements **32**, 2011, 1725-1736
This publication investigates the role of the state space model. The superior information of EEG data over other common approaches to observe brain dynamics was investigated and shown.

4. Details of the impact

By 2012, the algorithms developed in IPAM based on the fundamental research described above, provided a time-resolved estimation of the directed interactions between brain structures [2, 3]. In a preclinical application, analysing data that had been obtained by Professor Bettina Platt at the Institute for Medical Sciences (IMS) in Aberdeen, we could clearly demonstrate in [2, 3 and further unpublished results] the implications of our novel approach to dementia research and, potentially to early diagnosis. Transitions between sleep stages (see above), which are critical in dementia, could be defined with a much higher temporal precision than before. Standard approaches had been allowing a resolution of around 4 seconds, whereas our new data-based modelling approach yields a resolution of typically 5ms. Additionally, we demonstrated through a pilot study that our theory and the corresponding algorithms outperform standard EEG based spectral analyses (unpublished results, [1]).

Between 2012 and early 2013, the promising findings of our pilot study led IPAM, under the lead of **Thiel** and **Schelter**, to build the mathematical algorithm into a software package which was integrated as part of in an online platform marketed commercially by BrainMarker BV in May 2013.

BrainMarker is a Dutch company whose vision is to "*provide the gold standard in mental healthcare by implementing an easy to use decision support and quality management system in clinical practice*" [c1]. They aim to bridge the gap between scientific knowledge and clinical practice "*for all lines of mental healthcare by implementing quantitative EEG (qEEG) measurements in a very user-friendly way into practices. This allows a swift knowledge transfer from the scientific community into the clinical practice*" [c1].

The software package developed by IPAM fits well into the vision and mission of BrainMarker. Via our joint collaboration partner Professor Platt, we began to discuss the potential exploitation of our algorithm through the BrainMarker Platform in 2012. This resulted in a sustained and fruitful collaboration between researchers of the IPAM and IMS on the one side, and the management and computer engineers of the company BrainMarker on the other.

Parallel to the development of the software package, extensive beta-testing of the software was carried out in applications to clinical data obtained by groups at the IMS at Aberdeen [2, 3], the Xi'an Jiaotong University (China), and a Neurologist Practitioner in Freiburg, Germany. In the beta-testing, our algorithm was applied by the team of medical specialists at X'ian Jiaotong to study various cognitive deficits [c2]. The Director of the Institute of Biomedical Engineering, Xi'an Jiaotong University, states "*We can confirm that this novel technique presents a milestone in data-based modelling and model-based data analysis"* and *"The new insights we gained by this technique that would have been impossible before enabled us to prepare a manuscript to publish our results in a high ranked international journal*" [c2]. The Practitioner in Freiburgh has applied it to research in Parkinson's disease [c3], and has stated: "*Based on my experience as a neurologist, I* *can confirm that the results I have obtained using this unique technique and looked at so far are very promising; I truly believe that this technique has the potential to provide the means for an early diagnosis of diseases like dementia*" [c3].

Given these facts, BrainMarker decided in early 2013 to offer practitioners access to the algorithm developed by IPAM, via their subscription-based online platform programmed in LabVIEW (National Instruments, http://uk.ni.com). According to the Managing Director of BrainMarker, "*the system has already been used in over 35 practices in the Netherlands, Germany, and Belgium and continues to grow. Among their users are hospitals and research institutions that have enabled them to expand their database of human EEGs in various pathologies*" [c4]. The revenue created through the IPAM research is substantial. Access to the pay-per-click software platform of BrainMarker, of which **Thiel** and **Schelter's** algorithm is one part, "costs €250 per month (hardware, software, technical support) and €5 per measurement for a clinic" [c4].

The service provides different environments for researchers and for practitioners who upload their EEG files and receive an analysis report of the data. The advantage of this approach is that it delivers new and sophisticated health-care methods to practitioners without requiring them to buy expensive hardware. Also any updates to the software, including improvement of algorithms, are immediately available to customers. It is an ideal platform for an optimised knowledge transfer between academia and the health industry.

The Managing Director of BrainMarker BV considers Aberdeen's contribution to have been "*a very valuable component of [their] portfolio*" and that it adds "*considerably to its functionality*" [c4]. In summary, the software framework developed by IPAM became in 2013 one of the key components in BrainMarker's platform to tackle dementia in Europe. Its impact is both commercial, and will potentially change procedures carried out by clinical practitioners. There is also strong potential for growth globally as the relationship with Brainmarker continues. BrainMarker anticipates that "*[this] highly competitive online system provides a novel approach to health care not only in Europe*" [c4].

Other companies have also become aware of the software tool. Companies such as AbbVie expressed their interest in continuing "*the previously started common efforts on pharmaco-EEG analysis together with Aberdeen University*". This particularly includes our novel data-based modelling approaches [c5].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[c1] http://www.brainmarker.com/en/about-us/94-vision-and-mission

This source confirms the approach to cutting-edge health care followed by BrainMarker.

[c2] The Director of the Institute of Biomedical Engineering, Xi'an Jiaotong University, Xi'an, Shaanxi, P.R. China, can corroborate the successful beta-testing of the software tool.

[c3] A Neurologist (practitioner), Freiburg, Germany who can confirm the importance of the software tool for various diseases and its importance for dementia patients from a practitioner's (neurologist) perspective.

[c4] The Managing Director of BrainMarker BV, Netherlands can confirm the role of the software tool in BrainMarker's online platform; and corroborates the economic impact to the company.

[c5] The Associate Director of AbbVie Deutschland GmbH & Co. KG, Germany can demonstrate the interest of other global companies in IPAM's software tools.