Institution: University of Aberdeen

Unit of Assessment: 10 (Mathematical Sciences)

Title of case study: Brainatics: A Unique Approach to Seizure Prediction in Epilepsy

1. Summary of the impact

Epilepsy is one of the most common neurological diseases. It is characterised by apparently unpredictable seizures that severely affect the quality of patients' life. In this case study we demonstrate how our research has derived commercial impact within the medical technology industry, as well as impact on researchers and practitioners in neuroscience and medical science. Mathematical research carried out at the Institute of Pure and Applied Mathematics (IPAM) at the University of Aberdeen has led to a threefold impact. First, our research shaped the development, implementation and validation of a new software platform, called EPILAB, containing a vast number of sophisticated algorithms targeting seizure prediction together with novel statistical tools to evaluate prediction performance. Second, our research resulted in commercial impact through the development of a new automatic long term monitoring device, called LTM-EU, by one of our industrial collaborators, Micromed (Italy). Third, a direct consequence of our research is the compilation and commercial exploitation of the world's largest epilepsy database of its type, which enables novel studies into seizure prediction in epilepsy.

2. Underpinning research

Seizure prediction in epilepsy is presently at the forefront of research in neuroscience. In a series of biannual workshops on seizure prediction running since 2000, four open key problems have been identified: (i) improvement of advanced signal (pre-) processing of electroencephalography (EEG) signals, i.e. measurements of brain activity; (ii) as epilepsy is believed to be a network phenomenon, quantification of the interactions between brain regions by means of interdependence measures; (iii) rigorous evaluation of the performance of seizure prediction algorithms based on large comprehensive data sets, and (iv) the need for a comprehensive database as a requirement to address issue (iii), and with obvious benefits to other issues in research on epilepsy. Researchers (**Thiel** and co-workers) at IPAM have investigated issues (i)–(iii) since 2008. **Schelter** became a member of staff in 2010, taking over the lead in nonlinear data analysis.

Schelter being part of the consortium EPILEPSIAE consisting of academic and clinical partners from Paris (France), Coimbra (Portugal), and Freiburg (Germany), and the company Micromed (Italy) took over the lead of the IPAM research in epilepsy in 2009/10. The research in pure and applied mathematics of **Thiel** and **Schelter** has resulted in the development of a long-term patient monitoring device called LTM-EU in 2010, in addition to the creation of the world's largest epilepsy database, thereby addressing issue (iv).

Between 2008 and 2012, IPAM carried out research to address issue (i), namely the improvement of the EEG signal pre-processing. In epilepsy monitoring, continuous acquisition of data is necessary as seizures can occur at any time. A seizure predictor that is too sensitive to artefacts, or which is hampered by natural changes in brain activity (e.g. during sleep), would be of little value, practically. One of our crucial contributions was the development, between 2010 and 2012, of a time-resolved estimation of so-called autoregressive processes that are used as an effective model for a signal. Our contribution [1] serves three purposes. First, by using so-called state space models in the estimation process, we are able to separate the signals of interest from the observational noise. Second, related to the removal of observational noise in our estimation procedure, signal outliers and artefacts that occur in long-term EEG recordings are inherently removed to a large extent. Third, in the estimation process the parameters of the autoregressive models are allowed to change over time. This enabled us to track the changes in brain activity, e.g. sleep transitions, etc. It is currently under investigation by neuroscientists to assess to what extent our approach advances seizure prediction performance. It outperforms standard approaches based on, for example, ordinary filtering [1].

There is growing evidence that epilepsy is a network phenomenon. Issue (ii) addresses this through the quantification of interactions between components of dynamical systems, in this case different regions in the brain. This presents a challenge directly related to the research of several members of IPAM [1, 2]. Of particular interest for epilepsy research are measures for synchronisation and measures for the directed information flow between signals. During an epileptic seizure, various brain regions synchronise their activity, often elicited by a small brain region called the epileptic focus. The location of the focus changes from patient to patient. Research during 2009/2010 at IPAM has led to the development of a new measure for synchronisation. In contrast to previous measures, which assume a single dominant oscillation in the signal, our new multivariate approach allows us to cope with multiple such oscillations in the signal as typically expected in brain activity [2]. In particular during a seizure, but also during sleep and transitions between the states, multiple oscillations characterise the signal. Only IPAM's new technique enables a reliable estimation of the network synchronisation. The state space modelling that enables the pre-processing of the data, developed in the IPAM between 2010 and 2012, also enables to infer directed information flow between brain regions [1]. The synchronisation analysis and the state space modelling and a combination of these approaches provided by IPAM turned out to be very successful at predicting epileptic seizures from signal analysis when tested 2012. They show a statistical significant prediction performance, although not yet good enough to be clinically relevant [unpublished results, in preparation].

In the 1990s, several groups made overoptimistic claims about seizure prediction performance. This was due to the fact that the statistical evaluation of seizure prediction performance poses certain challenges, which renders standard statistical tools useless. For seizure prediction a statistical evaluation should:

a) evaluate not only the sensitivity but also the specificity of the prediction performance – seizures, and only seizures, should be predicted;
b) account for a time window between the prediction itself and the seizure onset to render an intervention possible – ultimately the goal of seizure prediction is to provide novel therapeutic interventions such as the application of brain stimulation or the application of highly effective drugs locally into the brain which need some time to become effective; and
c) include a second time window that constrains the time interval during which the seizure needs to start – interventions are only effective for limited time.

Points (a) – (c) actually depend on the type of intervention. A locally applied drug needs a different intervention time than a warning via a mobile phone for instance. Early approaches to seizure prediction did not take all this into account. Only in the 2000's, first approaches for the evaluation of seizure prediction performance were suggested accounting for some of the features (a) to (c); they were based on Monte-Carlo algorithms, a numerically rather demanding approach. Research at IPAM between 2008 and 2011 [3, 4] has investigated a newly developed analytical approach. This analytic approach is based on a so-called random predictor, a predictor that predicts seizures at random without using the actual EEG measurements by raising alarms at a fixed mean rate. A Poisson process results as each point in time has the same probability for an 'alarm'. Accounting for (a)-(c), it can be compared to any seizure prediction algorithm. The statistical characteristics of the random predictor are known analytically; thus it has become possible to evaluate the prediction performance in a numerically efficient way. In terms of size and coverage, our analytic algorithm outperforms the Monte-Carlo based ones [4] and is numerically much more efficient.

3. References to the research

1. **Schelter,** B., **Thiel**, M., Mader, W., and Mader, M. Signal Processing of the EEG: Approaches Tailored to Epilepsy. World Scientific, eds. Tetzlaff, R., Elger, C.E., Lehnertz, K., Oct. 2013, ISBN: 978-981-4525-34-3. *In this publication, we investigate and discuss the pre-processing of EEG signals, focussing on the time-resolved estimation autoregressive models, which provide a robust means to model the dynamics that underlies EEG signals.*

2. Nawrath, J., **Romano,** M.C., **Thiel,** M., Kiss, I.Z., Wickramasinghe, M., Timmer, J., **Kurths,** J., **Schelter,** B. *Distinguishing direct and indirect interactions in oscillatory networks with multiple time scales.* Phys. Rev. Lett. **104**, 2010, 038701. *In this publication, we developed a new technique to investigate interactions between signals exhibiting various time scales in a multivariate analysis.*

3. Teixeira, C.A., Direito, B., Feldwisch, H., Valderrama, M., Costa, R.P., Alvarado-Rojas, C., Nikolopoulos, S., Le Van Quyen, M., Timmer, J., **Schelter,** B., Dourado, A.. *EPILAB: A software package for studies on the prediction of epileptic seizures.* J. Neurosci. Meth. **200**, 2011, 257-271. *In this publication, we introduce EPILAB, describing its features and content. In a small study we show how EPILAB advances seizure prediction studies.*

4. Feldwisch, H., Schulze-Bonhage, A., Timmer, J., **Schelter,** B. *Statistical validation of event predictors: A comparative study based on the field of seizure prediction.* Phys. Rev. E **83**, 2011, 066704, *and introduces the statistics that played a key role for the database and evaluation of prediction performance. We demonstrate the superiority of the approach followed in Aberdeen.*
5. Klatt, J., Feldwisch, H., Ihle, M., Navarro, V., Neufang, M., Teixeira, C., Adam, C., Valderrama, M., Alvarado-Rojas, C., Witon, A., Le Van Quyen, M., Sales, F., Dourado, A., Timmer, J., Schulze-Bonhage, A., **Schelter**, B. *The EPILEPSIAE database: An extensive EEG database of epilepsy patients.* Epilepsia **9**, 2012, 1669-1676. *In this publication, we demonstrate the content of the database and show its uniqueness.*
6. Ihle, M., Feldwisch, H., Teixeira, C.A., Witon, A., **Schelter,** B., Timmer, J., Schulze-Bonhage, A.. *EPILEPSIAE - A* European *epilepsy database.* Comp. Meth. Prog. Biomed. **106**, 2012, 127-138. *In this publication, we introduce the database. This paper in particular focuses on the structure and design of the database.*

4. Details of the impact

The research undertaken resulted in a threefold impact: (i) a software platform EPILAB, which has mainly been developed for academic purposes, nevertheless has strong potential for non-academic impact, (ii) a commercial device called LTM-EU for epilepsy monitoring, and (iii) the world's largest epilepsy database of its type with commercial and scientific impact.

EPILAB: Implementation of the methods we developed described in issues (i) and (iii) in the underpinning research, together with other multivariate algorithms and various pre-processing steps, led to the compilation of the open source software package EPILAB [3] between 2008 and 2012 under the co-supervision of **Schelter** (IPAM, Aberdeen) and collaborator Dr Teixeira (Coimbra, Portugal). It is available from http://www.epilepsiae.eu/project_outputs/epilab_software. The main contribution and impact of EPILAB is that researchers can run their own seizure prediction studies interactively without spending time working on data and programming data analysis algorithms. EPILAB's potential to non-academic impact is evident since it can be used as a toolkit to implement seizure prediction protocols. As of July 2013, at least 262 groups worldwide [c1] use this software platform. As we can only track the number of downloads and not its field of usage (academic or non-academic), we cannot investigate if EPILAB has a particular impact beyond academia already, although its' progression beyond mathematics is clear. The software was designed to facilitate research in seizure prediction but it has also been designed to be ready for use in a commercial device.

LTM-EU (also called **Brainatics**): The research in IPAM has provided major scientific contributions that have made it possible to define and significantly improve the requirements and specifications of a long-term monitoring device (LTM), which monitors a patient with epilepsy continuously over a long period of time. The device is a low energy hardware acquisition system for measuring brain activity in epilepsy patients using bluetooth roaming capabilities. It monitors the brain activity via electroencephalography; the device is wearable and therefore suitable for use in hospitals as well as ambulatory monitoring. It enables long-term monitoring over a period of days without requiring the patients to remain in their beds.

Knowledge gained through the analytical statistics and the seizure prediction algorithms implemented in EPILAB, has been key to defining the device specifications. Together with the company *Micromed* (Italy) a partner in the EPILEPSIAE consortium since 2008, the minimal requirements for such a device were identified [c2, c3]. Micromed phrases this as follows [c3]: "*These research results demonstrated that in particular in the field of EEG and seizure prediction (1) higher sampling rates of up to 2048 Hz, (2) wireless low-energy bluetooth coverage with roaming capabilities, and (3) high number of channels for an extensive spatial coverage were needed*." Micromed developed the LTM-EU, also marketed since 2010 under the name "Brainatics", based on their previous commercial product LTM-Express. Micromed also states [c3]: "*We discussed these requirements within the EPILEPSIAE consortium; we were able to meet all requirements and successfully developed the LTM-EU prototype device.*" The device and its software benefited several updates since then.

The LTM-EU is a medically certified device (CE 0051) [c3, c4]. Since its development, these devices have successfully been tested in 2011 on patients in hospital and ambulatory environments: "*After thorough in house testing and testing by the partners in the consortium in a* *clinical environment, we could prove the effectiveness of this acquisition prototype*" [c3]. Micromed refers to the device as follows [c5]: "*Though the EPILEPSIAE project was quite challenging, we believe that this gave us also the opportunity to improve a lot the hardware and software performances and allowed us to give our contribution for a better 'European Health.*" Micromed claims that: "*we would predict the benefits will develop with time, ultimately leading to improvements to early diagnosis and long term monitoring for patients suffering from various brain related diseases such as epilepsy. We anticipate that a fully automatic wearable seizure prediction and alarming device might then change the life for epilepsy patients*" [c3].

The EPILEPISAE Database: The EPILEPSIAE project defined the need for a comprehensive epilepsy database that contains well-annotated long-term continuous EEG recordings and the corresponding meta-data including information about medication, duration of the disease, and information about the seizures. The EPILAB software was pivotal to this, especially related to the statistical evaluation framework for seizure prediction developed in IPAM, which provided information about the minimum number of seizures, the minimum time between seizures, etc. that the database must contain. As part of his role in the EPILEPSIAE project, **Schelter** supervised the design and implementation of what has become the world's largest relational database for seizure prediction in epilepsy [5, 6, c6]. With considerable influence of **Schelter**, a working party was established to determine what information should be included in the database, in particular with respect to meta information and the minimum requirements of sampling rates, number of channels and other data types. Consequently, the necessary structure and tables in the database were created [5, 6] under guidance and supervision of **Schelter** and clinical partners in the EPILEPSIAE consortium then populated this database with datasets from 275 patients including highly annotated brain signals and meta data [c2]. The team led by **Schelter** (IPAM, Aberdeen) supervised the population of the database in Freiburg; including all necessary quality checks.

The database is marketed by and directly available through the University of Freiburg, Germany [see c7]. Although commercial exploitation of the database has only recently begun (September 2012), it has already generated revenue of approximately €24,000. The European Union projects the sales figures of the database to be in the order of €1 Million [c2]. Susan Arthurs, chair of the patient organisation Alliance for Epilepsy Research, phrases the importance and impact of the database in a letter of support as follows [c6]: "*Dr Schelter used advancements in technology to study detecting and treating seizures in very different, non-pharmaceutical ways. The keystone of much of this research is the European Epilepsy Database. Without standardized data it would be impossible to compare let alone replicate the many studies being conducted worldwide. In addition, having this data already collected reduces the workload in individual research laboratories and allows for exceptionally large research studies. This enables many researchers from around the world and from seemingly disparate fields such as physics, computer science, mathematics and engineering, as well as medicine, to run and validate their seizure prediction algorithms*."

5. Sources to corroborate the impact

[c1]: A contact at the Centre for Informatics and Systems (CISUC), University of Coimbra, Portugal verifies the number of users of EPILAB.

[c2]: A source at the Dept. of Physics, University of Freiburg, Germany, confirms the importance of the database, and verifies the economic impact to the consortium as well as the importance of Brainatics.

[c3]: The Technical Director, Micromed S.p.a., Italy, confirms the involvement of Dr. Schelter and the EPIELSPIAE consortium in the development of the LTM-EU, its testing in clinical environments and its impact for the company including the CE certification.

[c4]: http://www.micromed.eu/pdf/11-1-BRAIN_QUICK_LTM_ENG_3.01_web.pdf. *This source documents the specifications of the LTM devices.*

[c5]: http://www.epilepsiae.eu/project_outputs/brainatics. *This source describes the Brainatics device from the EPILEPSIAE consortium's perspective.*

[c6] A source at the Alliance for Epilepsy Research, USA, documents the importance of the database from a patient organisation's perspective.

[c7]: http://epilepsy-database.eu *This source corroborates the commercial availability of the database.*