Report on:

Embassy of France in the UK-Sponsored Scientific Workshop

"Multi-scale Approaches in Epilepsy Research"

20-21 September 2017
UCL Institute of Neurology, Queen Square, London, UK

Organisers: Richard Rosch[1], Louis Lemieux[1] and Viktor Jirsa[2]

Participants: Prof Karl J Friston[1], Prof Maxime Guye[2], Dr Yujiang Wang[3], Prof Catherine Schevon[4], Dr Marco Leite[1], Dr Viktor Sip[2], Dr Richard Rosch[1], Prof Louis Lemieux[1] and Prof Viktor Jirsa[2]
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Objective: bring together physicists, engineers, neuroscientists, and clinicians from France and the UK to facilitate the development of a collaborative research project proposal that uses the different approaches synergistically for epilepsy research.

Summary of the proceedings:
The event took place over one and half days, with Day 1 consisting of 6 presentations covering some of the very latest developments in epilepsy research focused on understanding epileptic seizures in the human brain: observations and experimental evidence on their origin and propagation, and computational modelling; but also including some work in animal models of the disease. Almost 40% of the time was allocated to Q&A and discussions following each presentation. Day 2 was a 4-hour round-table, brain-storming discussion by all participants, starting with the thoughts of KJF and VJ on the discussions of Day 1. LL chaired the proceedings on both days.

Day 1: **State of the art**

Rosch: *Tracking slow synaptic modulations using Parametric Empirical Bayes*. Dr Rosch presented an approach to estimating epileptic generator dynamics in terms of changes in neural mass model biophysical parameters in a Bayesian moving window framework. The approach is demonstrated using EEG data recorded in humans. The Q&A and discussion addressed issues linked to time vs frequency domain analyses, neural mass vs mean field modelling and EM vs other parameter estimation schemes, such as Chong et al (ICTALS 2017).

Leite: *Dynamical Mean Field Modelling and Estimation of Neuronal Oscillation*. Dr Leite presented his recently completed PhD work in which he demonstrated how commonly observed seizure onset fast activity can be effectively modelled computationally based on a population model of integrate and fire neurons. He then demonstrated how this kind of model can be estimated by fitting to empirical in vitro data characterised by gamma oscillations, and make empirically verifiable predictions. This approach is scalable to human data. he discussion focused on how this approach could be generalised to other brain systems, such as the human neocortex and the reliability of the inversion scheme.

Wang: *Modelling Human Epileptic Seizures*. Dr Wang's presentation covered mainly two issues: firstly, how a simple connected neural columns-based neocortical patch model is able to reproduce onset patterns observed in patients, and can be used to identify a small set of classes of model conditions under which such patterns arise. Furthermore, the scope for successful interventions to stop seizures can be assessed in terms of spatial patterns of excitability using patient-specific structural connectivity. The discussion focused on the use of interictal data to predict seizure-related effects and the characterisation of the system in terms of bifurcation analysis.

Guye: *Epileptogenic Networks*. Professor Guye's presentation focused on the findings of contrasting functional and structural connectivity patterns in human brain regions involved in the generation and propagation, respectively, of epileptic activity. This multimodal analytical approach, based on detailed anatomical, functional, and electrophysiological characterisation of zones, also highlights the importance of structural connectivity as the substrate for functional networks and offers a large body of complex observations for computational modelling. The discussion addressed the issue of the intrinsic difficulty of validating imaging and electrophysiological findings in epilepsy: the quality of the gold standard (icEEG), and value of predictions of surgical outcome in individual patients.

Sip: *The Virtual Brain Applied to Epilepsy*. Dr Sip described how The Virtual Brain (TVB) computational platform can be used to model human epileptic activity as recorded using stereo-EEG based on each

patient's structural and connectome imaging data, combined with a mathematical model of epileptic EEG patterns and model of connectivity. The presentation concluded with the challenges posed by the desire to go from the current forward modelling philosophy to model inversion; this was the subject of a substantial discussion offering a number of possible solutions, some already implemented in the DCM framework for example.

Schevon: *Seizure focus or epileptic network? Role of inhibitory control in seizure spread*. Dr Schevon presented her work (in collaboration with UK investigators) on the study of seizure onset based on micro-array electrophysiological measurements in humans, showing a travelling wave process, modulated by an inhibitory surround mechanism; this understanding has been further explored in a rodent model of seizures. She then showed a new computational model that predicts yet unobserved phenomenology up for validation. The Q&A and discussion touched on the new model and the interest in validating its predictions.

Day 2: **Way forward; Research proposal outline**

Several important gaps in our current knowledge have been identified that need urgent addressing for seizure modelling to become clinically useful at the level of individual patients. Three themes emerged in the discussion, which the participants agreed to address in a collaborative project going forward from the meeting.

Some recent insights into the microscale dynamics of epileptic seizures at the level of individual neurons that were presented during the meeting impressively indicated that a thorough understanding of this *micro*scale activity is essential for understanding the different ways seizures start and evolve. Yet the most commonly used computational models of seizure activity in the brain treat each brain area as essentially homogeneous, ignoring the ways in which a different coupling within a brain area can provoke, facilitate, or even impede epileptic seizures. One way forward is to adapt some existing models of physical phenomena - e.g. models of wave dynamics in excitable media – to applications in the neuroscience of epilepsy.

Such novel models are likely to add complexity to the modelling of epileptic seizures. However, we can harness dynamic systems theory to reduce this complexity. Building on an existing body of work, most of the changes that happen at seizure onset and offset can be captured in much simpler mathematical descriptions – or 'normal forms' – of dynamic systems near the transition between different states (e.g. non-seizure and seizure states). In future work, biophysical models of the intricate microscale dynamics as proposed above can be mapped onto the less complex normal forms to identify which aspects of the biophysical model are associated with which type of dynamic transition in the 'normal form'.

By establishing a mathematical mapping between simpler 'normal forms', and the detailed biophysical models, we will then be able to adapt the methods that fit models of epileptic activity to actual EEG data recorded from patients (e.g. dynamic causal modelling, DCM). Being able to use such a model inversion scheme would allow us to fit our models to individual patients' epileptic seizure recordings, and identify neurobiological mechanisms that lead to seizures and their propagation across the wider network for each individual patients.

The workshop participants collectively agreed that the following three-step approach would be transformational in the computational modelling of epileptic seizures: (1) identifying computational models that capture microscale seizure dynamics; (2) linking these models to our existing understanding of epileptic seizures within the context of dynamical systems theory, and (3) using this understanding to fit individual models to patient data. This would bring together the elegant microscale recording and modelling done by Schevon and Wang; the detailed understanding of seizure dynamics and their description in simplified mathematical 'normal forms' of Jirsa, Guye and Sip; and the experience with dynamic causal modelling of Friston, Rosch, Leite, Lemieux and collaborators.

The next step for this work is to implement the planned analysis pipeline using an illustrative example collaboratively with all participants of the workshop. We will aim to address the three themes outlined above using a single patient example to test the face validity of the proposed models in terms of how well the models reproduce known features of epileptic seizures. Such a case will be published as useful illustration and perspective for the future work required to implement our approach more broadly, and we will use this as the basis for a future application for additional funding to test how this could be used in clinical practice.