Modelling for understanding and prediction of epileptic seizures as a viable replacement for animal models

A.D.H. Peterson and M.J. Cook, Department of Medicine, University of Melbourne, St. Vincent's Hospital, 29 Regent Street, Fitzroy VIC 3065, Australia.

Epilepsy is a debilitating brain disease that affects around 2-4% of people worldwide. The disease is characterized by unprovoked and recurring seizures (abnormal electrical brain activity), which are patient specific and extremely difficult to predict. Although many patients can achieve some seizure control with current medications, about one third of patients with epilepsy do not respond adequately to medication and are far more challenging to treat.

Although it is widely acknowledged that epilepsy is a dysfunction of neuronal networks, the exact mechanisms by which seizures are generated (epileptogenesis), is poorly understood (Milton & Jung, 2013). This makes devising effective treatments, especially patient-specific ones, extremely difficult. The aim of this research is twofold: (i) to investigate epileptogenesis in terms of neuronal network dynamics that is performed by a combination of human data and a mathematical model; (ii) to provide a viable alternative methodology to replace animal models, which are the mainstay of most epilepsy and neuroscientific research.

The findings of a unique, unprecedented, long-term study that collected seizure data from 15 patients with an implantable recording device for 4 months (Cook *et al.*, 2013) demonstrate that seizure prediction is possible. This is the first data set that has been large enough to extract seizure statistics *e.g.* average seizure durations and inter-seizure intervals. An overview of a mathematical model of network dynamics is being currently developed that describes how specific network structures affect network dynamics *i.e.* patient-specific models. This model not only exploits anatomical structure and physiological function to constrain the model complexity, but also mathematical structure. The idea here is to relate neuronal network structure to the statistics of transitions to seizure from normal or resting state behaviour from the human data collected. It is then shown how these two approaches will be combined into a multi-disciplinary methodology that will serve as a viable replacement for current animal models and potential developments of future bionic devices and patient-specific therapies.

Cook MJ, O'Brien TJ, Berkovic SF, Murphy M, Morokoff A, Fabinyi G, D'Souza W, Yerra R, Archer J, Litewka L, Hosking S, Lightfoot P, Ruedebusch V, Sheffield WD, Snyder D, Leyde K, Himes D. (2013). Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. *Lancet Neurol* **12**, 563-571.

Milton J & Jung P. (Eds). (2013). *Epilepsy as a dynamic disease*. Springer Science & Business Media.