Recent Progress in Detection and Prediction of Epilepsy

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1 Overview of the Field

Human epilepsy is a common neurological disorder that is characterized by abnormal brain activity resulting in seizures. Approximately 0.6% of the Canadian population has epilepsy. The International League Against Epilepsy classified seizure types into 3 major groups, namely generalized onset seizures, focal onset seizures, and unknown onset seizures. Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy. About 6 out of 10 people with focal epilepsy have temporal lobe epilepsy. Seizures in TLE start or involve in one or both temporal lobes in the brain.

Different experimental methods such as electroencephalography (EEG), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), and proton emission tomography (PET) and in drug-resistant cases, intracranial EEG (iEEG) are utilized by teams of mathematicians, neurologists, epileptologists, neuroscientists and practicing doctors to diagnose epilepsy. The most commonly used EEG recordings measure electrical brain activity through a grid of electrodes or depth electrodes depending upon if the measurements were made on the scalp or intracranially.

The main purpose of this workshop was to bring together mathematicians, experts in neuroscience, psychology, and practicing medical doctors in order to exchange opinions and report on mathematical analyses of neurological data connected to seizures. The detection and prediction of different types of TLE using the data are two important topics of discussion in this workshop.

The neurological data are intracranial EEG data collected from drug-resistant TLE patients prior to resection surgery. The electric signals measured with iEEG are non-linear. For mathematical analysis of the data, we extensively use complex network theory, signal theory, non-linear time-series analysis, integral transforms, neuronal modelling, statistics and visualization techniques. For example, our recent results on bi-lateral tonic-clonic and impaired awareness seizures using transform methods such as phase coupling and variations of phase coupling methods suggest possible interpretations of the seizures during the pre-ictal, ictal, and post-ictal periods. Non-linear time-series analysis led to investigate the efficacy of estimating the largest Lyapunov exponents at all stages of the above-mentioned seizures. Detection and prediction components are inherent in these methods to seek diagnostics answers. Finally, focal onset seizures, impaired awareness seizure or bi-lateral tonic-clonic seizure, engage different regions of the brain. With this in mind, complex network analysis is performed to understand the community structure of the brain regions at different stages of the seizures.

2 Presentation Highlights and Scientific Progress

The lectures included a combination of talks focused on a rigorous dynamical systems approach to the brain functioning (Jörn Davidsen and Wilten Nicola) with extensive description of advanced experimental results and comparative analysis of brain functioning (Majid Mohajerani and Asad Beck), either human or implemented with laboratory mice, and machine learning and engineering approaches (Artur Luczak).

Application of Hilbert transform to the processed data for Foothills hospital patients suffering from epileptic seizures combined with the following windowed time-frequency analysis and tedious time frequency correlation analysis was illustrated in the talks of Daniel Girvitz and Yanina Bazhan.

The presentation of Jörn Davidsen focused on the connection of the chimera states with the critical brain hypothesis. One of the pillars of modern physics is the concept of symmetries. Spontaneously breaking such symmetries typically gives rise to non-trivial phenomena and can explain, e.g., why particles have mass. The occurrence of such symmetry-breaking phenomena is not limited to particle physics but occurs across a wide range of physical, chemical and biological systems. Recently discovered examples include chimera states. Chimera states are hybrid states characterized by the coexistence of localized synchronized and unsynchronized dynamics in a given system. Indeed, the name chimera is used here in analogy to the hybrid creature in Greek mythology. Such coexisting behavior can even occur in a homogeneous system, thus breaking the underlying symmetry - something that was long thought to be impossible. While over the last 20 years a significant mathematical understanding of this phenomenon has started to emerge, many challenges are left to be addressed. One particular challenge is the presence and role of chimeras in the context of epilepsy. Preliminary work by us and others has shown not only that chimera states might be play a role in brain dynamics but that they are in particular present at the onset of epileptic seizures. This opens the door for new mathematical approaches to understand and eventually control epileptic seizures and was discussed in detail at the workshop.

The lab of Artur Luczak is using electrophysiological and machine learning methods to study information processing in the brain. One of our main contributions is a development of 'neuronal packet' concept, which describes basic building blocks of neuronal code (Nature Rev Neurosci 2015, Neuron 2013, J Neurosci 2013, Neuron 2009, PNAS 2007). Moreover, they derived a predictive learning algorithm from basic cellular principles, i.e. from maximizing metabolic energy of a neuron, which may offer a step toward a general theory of neuronal learning (Nature Machine Intelligence; 2022). The lab is also studying changes in neuronal activity caused by neurological disorders, especially epilepsy (Brain 2017). To facilitate it, our lab developed Deep Neural Networks for detecting neurological deficits (PLOS Biology 2019).

The work presented by Scott Rich, Taufik Valiante, and Jeremie Lefebvre provided a detailed survey of the collaboration between the Valiante and Lefebvre labs (Dr. Rich is a postdoc co-supervised by Valiante and Lefebvre) applying tools from computational neuroscience and dynamical systems to the study of epilepsy. In mathematical models of epileptogenic neuronal circuits, a common analogue for seizure-onset is the sudden transition of circuit activity from asynchronous firing into hyper-synchronous and hyper-active neuronal oscillations. Mathematical analyses have historically shown that such dynamics are commonly associated with bifurcations, specifically those causing the fixed point of simplified neuronal circuits to shift from stable to an unstable oscillator. The group showcased multiple types of computational circuits in which these behaviors arise, as well as different mechanisms by which these transitions can be disrupted.

One such mechanism is the system's noise: increasing the intrinsic noise in an epileptogenic circuit or adding extrinsic noise (abstractly modeling potential new paradigms for neurostimulation via implantable neuromodulatory devices) stabilize network dynamics and mitigate the sudden transitions echoing seizure onset. Another mechanism is the intrinsic heterogeneity of the model neuron's intrinsic properties, a phenomenon which importantly has strong experimental support from the characterization of human neurons taken from non-epileptogenic and epileptogenic cortical tissue samples. In both cases, these mechanisms prevent sudden transitions into hyper-synchronous and hyper-active dynamics in spiking networks, and suppress multistability and bifurcations in associated stability analyses of systems simplified using mean-field analysis.

The group presented additional work on two fronts: how bistability can explain the tendency for increased interneuronal activity prior to seizure onset, and how neuronal heterogeneity might serve a physiological role in dynamical homeostasis in the brain. All the presented studies showcase the power of interdisciplinary research, particularly collaborations between experimental, computational, and mathematical neuroscientists, in the study of epilepsy. A myriad of pathological changes associated with epilepsy can be recast as decreases in cell and circuit heterogeneity. The group proposed recontextualizing epileptogenesis as a process where reduction in cellular heterogeneity, in part, renders neural circuits less resilient to seizure. By comparing patch clamp recordings from human layer 5 (L5) cortical pyramidal neurons from epileptogenic and non-epileptogenic tissue, we demonstrate significantly decreased biophysical heterogeneity in seizure-generating areas. Implemented computationally, this renders model neural circuits prone to sudden transitions into synchronous states with increased firing activity, paralleling ictogenesis. These findings are extended to the concept of resilience, where a system's dynamics persist despite changes in intrinsic and/or extrinsic control parameters, preserving associated function. To do this we computationally explore how excitability heterogeneity can influence system resilience to ”insults” like increases in network size, connection probability, strength and variability of synaptic weights, and modulatory fluctuations which promote stability transitions. The group found that excitability heterogeneity rendered the network more resilient to these insults. To then understand these computational findings, we used spectral theory for large random systems to reveal that excitability heterogeneity is a generic control mechanism promoting: 1) homeostasis, by tuning the distribution of eigenvalues complex plane in a context-dependent way; and 2) resilience, by anchoring this eigenvalue distribution and gradually making it less dependent on modulatory influences. Taken together, these results provide new vistas on the contribution of a fundamental organising principle of the brain - neural diversity - to brain resilience.

3 Some comments on the meeting

When planned in 2020, the meeting was expected to be co-organized with Kris Vasudevan who suddenly passed on August 22, 2022, so a part of the morning meeting was dedicated to his memory and featured a presentation of the department head (Tony Ware) where Kris worked, memories of his colleagues (E. Braverman, G.C. Tesky, J. Davidsen) and his son Alexander Vasudevan.

Due to the original COVID restrictions and other reasons, the workshop was not a large meeting but it included presenters at all the stages of their career: an undergraduate (Daniel Girvitz), a MSc (Yanina Bazhan), a PhD student (Asad Beck), a postdoctoral fellow (Scott Rich), all the others were faculty members from mathematics and statistics, biology departments, schools of medicine, two Brain institutes (Ottawa and Calgary).

4 Outcomes of the Meeting

The workshop brought in new results and critical comments from the participants, and fostered development of new methods and approaches. Also, it served as an ideal platform for associated postdoctoral fellows and graduate students to report their most recent results and exchange ideas with the experts. The results of the research groups are published in the front-line journals in neuroscience, biology and mathematical modeling, and there are more to come. We believe the useful exchange of opinions and new ideas will lead to new collaborations and stimulate progress in the area of describing, predicting and treatment of epilepsy, as well as our understanding how the brain works.