Computers, causality and cure in epilepsy

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Epilepsy continues to be a debilitating disease, not fully controlled through medication in many cases. Patients may then be referred for surgery to remove the piece of brain which appears to be the source of the problem – the epileptogenic zone (EZ). Unfortunately, surgical treatment is not always successful, partly because the methods for identifying the EZ and of identifying the influence of the EZ on the surrounding propagation zone (PZ) are still *ad hoc*. Formulation of more complex treatment plans is limited by our ignorance of the processes of brain function and dysfunction. Tools for brain imaging and manipulation – MRI, fMRI, dMRI, EEG, SEEG, MEG, brain stimulation and others – are improving rapidly. Further tools are expected in the near future due to major new brain measurement funding initiatives. The problem: "big data;" little theory. On page ???? of this issue, Drs. Proix, Bartolomei, Guye and Jirsa of Marseille take a bite out of our theoretical ignorance by providing *personalized* computer models of epileptic patients to begin to explain each patient's individual seizure genesis and spread [1].

William Lennox, epileptology pioneer, metaphorized epilepsy as a river – "the river of epilepsy" (Figure 1) [2]. This expressed the notion that epilepsy is a complex set of diseases – the epilepsies – with multiple possible causes that can combine in myriad ways to produce seizures. Experimentalists generally work at the lower scales, the contributory tributary level, assessing predisposing genetics, ion channel anomalies, responses to brain trauma, *etc.* Many computer modelers also work from this perspective, attempting to put together simulations that include the details of ion channels and synaptic connectivity [3]. The clinician, however, is faced with the river - the clinical syndromes that represent the many little pieces put together. Proix *et al.* have taken on the challenge of modeling this end-result, the river, by looking at final common pathways that govern the mathematical *dynamics* of seizure genesis and seizure spread. (An excellent brief description of dynamical systems theory in the context of neurobiological applications is found in Breakspear and Jirsa 2007 [4].)

Fifteen drug-resistant patients with EZs defined by SEEG were modeled. The personalized models were developed using the *Virtual Brain* (thevirtualbrain.org), a dynamical systems theory simulation tool developed by one of the authors [5]. Dynamical systems theory concerns itself with the understanding of coupled differential equations, describing how parts of a system interact over time through positive and negative feedback. For this study, each individual brain area was defined by an *Epileptor* [6]. Each epileptor has 5 state variables whose differential equations are given by

Equation 1 on page ????. These state variables provide fast seizure-like oscillations (x_1, y_1), slower spike-and-wave activity (x_2, y_2) and "permittivity" (z). $x_1 + x_2$, summed together, resemble a local field potential or SEEG. Epileptor nodes are localized based on MRI-aided individualized anatomical parcellation. Over 100 epileptor nodes (subscript i in Equation 1) are connected to form the complete *brain network model* (BMM) to simulate seizure activity in that patient's brain.

Each epileptor node has a baseline excitability parameter, $x_{0,i}$ (note that the $x_{1,i}$ is a state variable; $x_{0,i}$ is a parameter). A group of nodes with high excitability can become spontaneously active – these make up the EZ. Other nodes have lower excitability but can be driven into seizure – these are potentially part of the PZ (Figure 2). Full simulations of the BNM were complemented by analysis involving dimensional reduction and linearization. Individual epileptors are linked together by connectivity parameters K_{ij}, undirected weighted graph edges determined from that patient's white-matter tractography measured from dMRI. The K_{ij} connectivity parameters drives permittivity for a node using the sum of differences between that node's $x_{1,i}$ and those of each input area.

The patient's BNM will generate likely scenarios (hypotheses) about patterns of seizure spread. The pattern of activation of the PZs in sets of simulations are then compared to both the clinical estimation of the PZ and to the PZ pattern observed on SEEG during a seizure. Unfortunately, as is common in efforts to formalize clinical diagnosis and decision making, comparison is limited due to lack of a ground truth. The clinical assessment is hampered by precisely the missing theoretical understanding that this project attempts to alleviate. SEEG data is partial due to limited coverage and sampling. Note that there is no single model but rather a family of models that generate a set of hypotheses about origin and spread. For example, the location of the EZ is given, rather than being estimated from the data. The BNM can then be used to validate this hypothesis about the location of the EZ based on the accuracy of the predicted PZ.

This "Epileptor 0.1" software cannot yet be used directly in the clinic. Instead, we look to the future. Personalized data acquisition of cortical and subcortical parcellation, tractography, activity, and susceptibility will be more readily, rapidly, inexpensively, and noninvasively obtained. The Virtual Brain BNM will improve in precision and accuracy. These BNMs will then provide reasonably accurate, reasonably precise models of epilepsy spread (although never a single correct model – brain modeling is more akin to weather prediction than it is to the kinematics of satellites). Evidence from BNMs can be taken together with other models – genomic predictive models, detailed simulation models, statistical models – along with clinical judgment, to determine a treatment plan. The clinician will run BNMs with perturbations that correspond to possible surgical options, including removal of all or parts of the EZ, partial removal of parts of PZ, tractotomies dividing parts of EZ or dividing EZ from PZ, *etc.* This will provide plans for cure based on surgeries (or noninvasive ablations) that cannot currently be proposed.

How can the Virtual Brain help us understand the real one? Brain oscillations are thought to furnish the underpinnings of perception, motivation, thought and consciousness via mechanisms of firing synchronies creating representations. The VB recreates some of these dynamics and can potentially explain how these oscillations permit area-to-area synchronies, as well as how these dynamics are disturbed to create seizures and to produce various movement disorders. The 4 activity state variables x_1, y_1, x_2, y_2 can be grossly mapped onto the activity of underlying

excitatory-inhibitory population interactions that produce network effects [7]. The slow permittivity state variable z may be a reflection of changes in extracellular ionic concentrations, oxidative state, or metabolism. In a prior paper, the authors explicitly showed how these measures in whole *ex vivo* immature mouse hippocampus would map onto z [6]. Overall, however, the difficulty in mapping dynamic phenomenology remains a limitation of this type of phenomenological model which portrays the river (Figure 1) without reference to the tributaries. Meanwhile, multiscale mechanistic models, built from the bottom up, have the opposite failing – providing a view of the details but not providing any way to understand the overall functional mechanisms of the brain. Filling in "the missing middle" of mesoscopic modeling to connect top and bottom remains a major challenge for the future.

Finally, personalized modeling is an important step forward for *personalized medicine*. Personalized medicine and precision medicine emerged from the human genome project. It has now became apparent that big data does not equal big knowledge and big clinical plans. Theory now emerges at multiple scales to begin to fill these gaps.

Glossary of dynamical system terms

We use the examples of the Hodgkin-Huxley (HH) equations and of the solar system to illustrate some of the terminology.

- **ordinary differential equations (ODEs):** Equations that provide values for $\frac{dx_i}{dt}$, the change in state variable x_i with infinitesimal time dt. When the right-hand side of the equation depends on other state variables (coupled ODEs), these quantities interact with each other in complicated positive and negative feedback loops. ODEs can be distinguished from partial differential equations (PDEs) such as those describing reaction-diffusion. Note that $\dot{x_i}$ is an alternative notation for $\frac{dx_i}{dt}$.
- **state variable:** A representative of a quantity that is determined by a differential equation. State variables will thereby change in time. The state variables for HH are v, m, h, n: voltage, Na^+ channel activation, Na^+ channel inactivation, K^+ channel activation.
- **state space:** An abstract space whose dimensions correspond to the number of state variables. If there are 3 state variables x, y, z then the position of the entire system at a given time can be represented as a single point in 3-dimensional space.
- **trajectory:** The path of a state variable through state space. If the state space is only 2 or 3 dimensions this can be depicted graphically. Otherwise trajectories of each individual state variable can be depicted as line graphs of values on the y-axis with time on the x-axis. Note that the usual trajectory representations for orbits of planets in the solar system only show half of the state space since the state variables for the solar system include momentum as well as position for each planet.
- **initial conditions:** The starting values of the state variables. Along with the parameters and the ODEs, the initial conditions are part of the full description of a specific dynamical system.
- **parameters:** Fixed values in the system. For the solar system, a parameter would be the force of gravity. For the HH equations, parameters include C_m, g_l, I (capacitance, leak conductance, input current).
- **parameterization:** the setting-up and the organization of parameters. The functional forms that define the right hand side of the ODEs form part of the parameterization.
- **dimensionality:** The number of dimensions of the state space or of a subspace to which trajectories are restricted (called a manifold). The dimensionality of the HH equations is 4; for a pendulum 2: instantaneous position, instantaneous momentum. The dimensionality of the single epileptor is 5 while the group of n epileptors will have dimensionality $5n$.
- **dimensional reduction:** A high dimensional system such as HH or the epileptor cannot be directly visualized. Therefore, one attempts to simplify these systems by various methods – for example, noting where one state variable closely follows another; this will allow one to create a lower-dimensional system with similar dynamics.
- **equilibrium point:** A solution to a dynamical system that does not change with time. An equilibrium can be unstable as for example the proverbial pencil balanced on its point.
- **point attractor:** An equilibrium location in state space towards which all trajectories flow.
- **point repellor:** Opposite of an attractor – all trajectories move away from a this point in state space.
- **limit cycle attractor:** A stable recurring trajectory in state space, an orbit. A system perturbed slightly from a limit cycle attractor will return to it.
- **separatrix:** A boundary that separates two different regions of state space which feature different dynamical patterns. In the context of the epileptor there is a separatrix that keeps apart the region of epileptic dynamics from the region of physiological dynamics.
- **chaos:** Phenomenology seen in some dynamical systems which show high-dimension *strange attractors* and *sensitivity to initial conditions*. Chaotic systems are interesting since their trajectories appear to be random but are in fact deterministic.

- **bifurcation:** A dramatic change in dynamic pattern with change in one parameter. The classic case from neurobiology is the bifurcation with change in I (input current) in the HH equations. This bifurcation takes the stable resting membrane potential (a point attractor) and causes an oscillation (the spiking) along a limit cycle.
- **bistability:** The ability of a system to show two (or more for multistability) different dynamical patterns without any change in parameter. The ability of a system to show either seizure activity or normal physiological activity will in some cases be due to a situation of bistability across a separatrix.
- **analytic solution:** A solution to a set of differential equations that defines each state variable as a function in time. These solutions can generally not be found for linked ODE systems of 3 or more state variables.
- **numerical solution:** An approximate solution to a set of differential equations obtained through *simulation* on a computer. These simulations are done by approximating $\frac{dx}{dt}$ based on using a small but finite timestep Δt in place of the infinitesimal dt. This allows calculation of a Δx at each timestep which is used to update the current value of x.

Acronyms: **VB** – the Virtual Brain; **BNM** brain network model; **EZ** epileptogenic zone; **PZ** propagation zone; **MRI** magnetic resonance imaging – measures anatomy; **fMRI** functional MRI – measures activity via local oxygenation; **dMRI** diffusion MRI – traces white matter tracts; **MEG** magnetoencephalography; **EEG** electroencephalography; **SEEG** stereotactic EEG – local field potential from implanted electrodes; **ECoG** electrocorticography

References

[1] T Proix, F Bartolomei, M Guye, and VK Jirsa. Individual brain structure and modeling predict seizure propagation. *Brain*, 2017.

[2] WG Lennox and MA Lennox. *Epilepsy and related disorders*. Little Brown, NY, 1960.

[3] WW Lytton. Computer modelling of epilepsy. *Nat Rev Neurosci*, 9:626–637, 2008.

[4] M Breakspear and VK Jirsa. *Neuronal Dynamics and Brain Connectivity*, pages 3–64. Springer, New York, 2007.

[5] P Sanz-Leon, S Knock, M Woodman, L Domide, J Mersmann, A McIntosh, and VK Jirsa. The virtual brain: a simulator of primate brain network dynamics. *Frontiers in Neuroinformatics*, 7:10, 2013.

[6] VK Jirsa, WC Stacey, PP Quilichini, AI Ivanov, and C Bernard. On the nature of seizure dynamics. *Brain*, 137:2210–2230, 2014.

[7] HR Wilson and JD Cowan. Excitatory and Inhibitory Interactions in Localized Populations of Model Neurons. *Biophysical Journal*, 12:1–24, 1972.

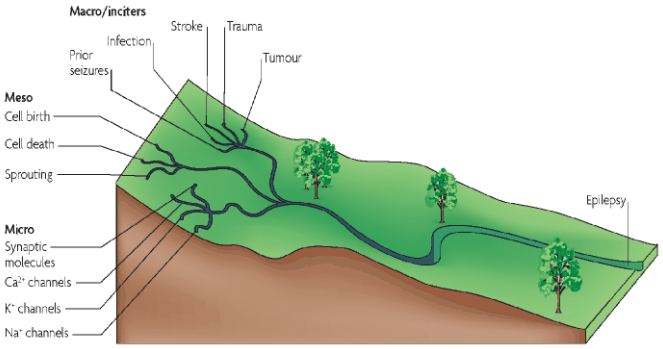

Figure 1: Multiple factors including genetic inheritance, life events such as head trauma, acute or chronic toxins or drugs contribute to the seizure. However, this complex, multifactorial causality all converges on some common dynamical patterns represented by final "river of epilepsy" and identified in Proix *et al.* [1] as involving a set of common state variables. (With permissions from Lytton 2008[3] Modified from Lennox and Lennox [2].)

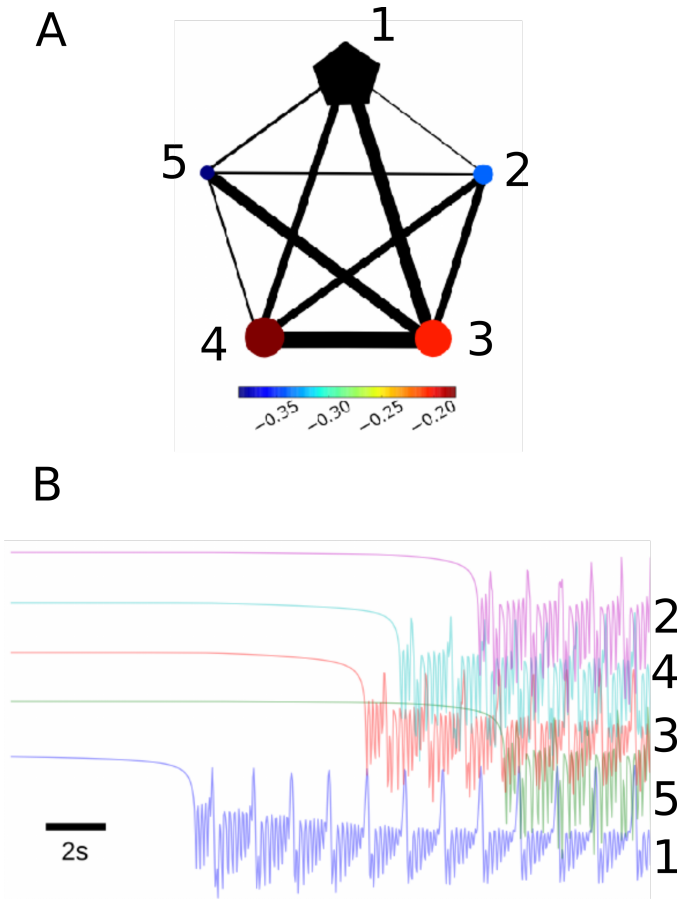

Figure 2: Schematic and simulation of a simple brain network model (BNM). (A) Five epileptor nodes connected into a BNM by undirected weighted edges (undirected because tractography cannot determine direction of a projection). Excitability $x_{0,i}$ for each node is represented by both color (referent spectrum at bottom) and size; only the node at the top is epileptogenic (high $x_{0,i}$) – a single node EZ. Other nodes would be the PZ. Connection strength is given by edge width. (B) Simulation of this network produces a sequence of activations. Note that the order of activation is not obvious since depends on strength of connections and on epileptogenicity of each area and can be multi-step across nodes. In this case the authors do not tell us the answer; my best guess is 1,3,4,2,5. (numbering clockwise from the top) (Modified from Proix *et al.* [1] supplementary material Fig. 1)