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Computational Models of Neurological Disorder

EDITORIAL

Multiscale modeling for drug discovery in brain disease

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Introduction

In this special issue on *Computational Models of Brain Disorders*, we introduce readers to a set of studies using *multiscale models* (MSMs) – computer simulations of brain areas used to understand diseases and disorders of the brain. Many of the MSMs in this issue are *mechanistic*. This means that they describe a high level in terms of what is going on at one or more lower levels. For example, the dynamics in a neuronal network can be explained in terms of cell or even of ion channel dynamics. Mechanistic MSM is directly explanatory. Mechanistic modeling can be contrasted with phenomenological modeling. Phenomenological models describe the external manifestations of observed data without reference to underlying mechanism. This approach follows the physics tradition of describing phenomena as sets of basic 'natural laws,' where either no underlying mechanism is known, or where one putatively describes an ur-reality so that no underlying mechanism exists.

MSM can play a number of roles in the clinical sphere, several related to drug development. 1. Models can be directly used to predict the effects of specific medications which can then be used in animal models to confirm efficacy before trying in a formal clinical trial. 2. Models can be used for *precision medicine*, that is, directed at identified subpopulations

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who have a particular subtype of disease, generally based on their genetic inheritance. 3. Models can be used for *personalized medicine*, where a simulation models an individual patient. This approach is already being used for epilepsy surgery, where every procedure is necessarily personalized due to the differences in each patients brain and seizure focus [1–4]. 4. Models can assist in our general understanding of pathophysiology. Understanding provides opportunities for judgement-based medicine, where drugs are proposed, and often used off-label, based on intuitive approaches without additional formal modeling. 5. Models can identify biomarkers. This is particularly important for diseases, such as Alzheimer, where the current lack of biomarkers makes it impossible to make a definitive diagnosis during life. Proper diagnosis is of course a prerequisite for proper treatment. 6. Models can be used to identify and treat disease subtypes – some brain diseases are not unitary but represent a final common pathway of expression for several different pathologies with different causes (Alzheimer here again an example). Different subtypes may benefit from different treatments. 7. Models can be used to identify the course of pathophysiology to permit *staging* of disease. In many cases, as with cancers, treatments will be different depending upon disease stage. 8. Models can assist in determining prognosis, an important clinical determination that assists in identifying the proper type of drug to be administered or discovered. Given the complexities of expression, a number of brain disease have *formes frustes* (forms of the disease with reduced or minimal symptomatology) which may or may not merit treatment.

The authors in this issue have used their models to investigate a variety of the brain diseases treated by neurology, neurosurgery, psychiatry, psychiatry, internal medicine and other specialties including Alzheimer, Parkinson, Huntington, ALS, epilepsy, depression, dystonia, and essential tremor. In many of these studies, an MSM is first used to replicate the dynamics of brain activity, and then modified to replicate the pathophysiological dynamics of the particular disorder. The pathophysiological simulations are explored to find pharmacologically related parameter changes that could suggest drug treatments to transform pathophysiological to physiological dynamics. In this way, the authors use the models to predict pharmacological or electrical-stimulation treatments which could be tested in animals for subsequent clinical use. In the following, we loosely group the contributions based on spatial scales used, on disorders discussed, or on proposed methodological advances.

Electrophysiology has been the focus of both traditional neurophysiology and computational neuroscience for decades. Only recently have these fields begun to appreciate the importance of extending their studies into the vast realms of chemophysiology associated with 'omics – particularly transcriptomics and proteomics. Incorporation of chemophysiology allows more detailed explorations of pharmacological treatments for brain disorders through specification of molecular signaling cascades that can be altered with pharmacological treatment. Several papers in this issue highlight recent developments in multiphysics simulation (multiphysics implies the combining of models representing different types of physical phenomenology) which allow this combining of chemophysiology and electrophysiology. In this issue, Anderson and Vadigepalli [5] use a multiphysics model to investigate inflammatory regulatory network dynamics in central nervous system disorders. Anwar [6] investigates the role of the ubiquitous second-messenger, calcium, and how its dysregulation can lead to neurodegenerative disorders. Extending this methodology from intracellular to extracellular diffusion, Newton and Lytton [7] investigate how spread of extracellular toxins produces a spreading depression that can contribute to pathological effects in epilepsy, migraine and stroke. Neymotin et al. [8] identify sources of hyperexcitability in a microcircuit model of motor cortex which includes detailed intracellular molecular dynamics, developing a methodology for classifying sets of parameters relating to disease which could be used to predict multitarget therapeutics.

Several models focus on the neuronal network level, including Cutsuridis and Moustafa [9] on Alzheimer disease, and Lytton [10] on epilepsy. Note that MSM techniques of neuronal network modeling are entirely different from *artificial neural networks*, a class of machine learning techniques that can also be used in drug discovery. Machine learning techniques are used in clinical analysis of *big data* including the big data associated with drug trials.

A pair of papers utilize computer models to determine how electrical treatments are used to treat movement disorders, with Holt and Netoff [11] looking at Parkinson, and Lee et al. [12] at essential tremor. Both of these diseases produce tremor, and both can be treated with electrical stimulation of telencephalic nuclei using deep brain stimulation (DBS). Modeling can help us better understand why DBS works for some patients and not for others, and how to best use DBS as a complement to traditional drug therapies.

At the highest spatial scale, a pair of reviews describe modeling of interactions across brain areas. Bernard and Jirsa [1] describe The Virtual Brain (TVB; thevirtualbrain.org), a simulation tool that can simulate the entire brain as a set of interconnected neural mass models. Arle and Carlson [13] demonstrate a multi-area circuit model in their Universal Neural Circuitry simulator (UNCuS) to look at depressive disorder.

In two papers, the authors describe phenomenological computational methods to evaluate pharmacological agents for neurological diseases without use of explicit simulation. Anastasio [14] introduces *process algebra*, a computer technique that is widely used to analyze complex computational systems, here used for computational neurology. Sirci et al.

[15] describe the use of network (graph) theory to identify similarities and differences between different pharmacological agents. In this type of study, each drug is a *node*, and *edges* between drugs represent chemical and transcriptional-based interactions that describe drug properties.

Overall, the series of papers in this issue represents an alternative to the classical medical approach which dates back to *Koch's postulates* of more than a century ago. Koch set forth rules for identifying an agent considered as sole cause for a given infectious disease. The early history of antimicrobial drug discovery involved the search for the 'magic bullet' drug to eradicate that agent. This thinking extended into the modern era, with many hoping and expecting that the human genome would reveal single gene causes of disease that could then eventually be fixed with genetic engineering. Instead, genetic analysis of human disease revealed polygenic risk factors (rather than causes) that combine with environmental risk factors, including infections, to produce disease. Multiscale modeling is now emerging to begin to master this complexity by disentangling how risks and causes combine in complex systems to produce disease, and how these diseases could be prevented or ameliorated, perhaps by multi-staged, multi-target, polypharmaceutical techniques.

Conflict of interest

The authors have no conflict of interest to declare.

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