<u>Commentary on a Unique and Exciting Interdisciplinary Focus Program at the Fields – "Towards Mathematical Modeling of Neurological Disease from Cellular Perspectives"</u>

In North America alone, tens of millions of people suffer from some form of neurological disease. While there has been tremendous progress in developing experimental techniques for identifying molecular, cellular and signaling processes involved in neurological diseases, the mechanisms underlying these pathologies remain poorly understood. Further, oscillations and other complex dynamic behaviors in the electrical activity of the brain networks have been implicated in several neurological diseases. Thus, it has become increasingly evident that mathematical models, together with both computational and mathematical analysis of them, can play an important role in making sense of the data, testing hypotheses and generating new ones.

There are many challenges to developing, analyzing and using mathematical models in the study of neurological disease. Interdisciplinary collaboration is always difficult; this is especially true among mathematicians and other theoreticians, experimental biologists and clinicians. The study of brain processes can be approached from multiple spatial and temporal scales, from sub cellular to single neurons, small and large neuronal networks, separate brain regions, brain imaging and behavior; and from milliseconds to seconds, minutes, hours and even years. Given the profuseness of data, it is often difficult to decide what details to include in a model; the model needs to be sufficiently complicated to account for relevant biological processes, but simple enough so that it can be studied using mathematical and computational methods. Finally, the study of biologically inspired models leads to very challenging mathematical problems. The models often take the form of large networks, whose individual elements exhibit complex dynamics that depend on their intrinsic properties, interactions with other elements and noise. It seems clear that substantial progress can only come about by the development of new mathematical tools and interactions among mathematicians from different disciplines. While there has been considerable progress in developing mathematical models of neuronal networks implicated in neurological diseases due to collaborations between experimentalists, mathematical modelers and theoreticians, such individuals often represent separate cultures and opportunities for meaningful dialogue between them can be difficult. Another challenge is that it is often not clear what the appropriate level of modeling is for a given neurological system, especially since relevant biological processes and corresponding experimental methods may range over multiple spatial and temporal scales.

For a month from mid-May to mid-June, a focused thematic program was held at the Fields Institute in Toronto http://www.fields.utoronto.ca/programs/scientific/11-12/neurodisease/ - *note that this link provides details of the program, talk abstracts and speaker slides where available*. The program was perhaps the first of its kind devoted exclusively to bringing mathematicians, experimentalists and clinicians together to address detailed issues related to the modeling of neurological disease. Such a Program is timely, not only because of the obvious importance of the issues to be addressed, but also because of the recent scientific advances made by each community represented at the meeting – that is, theoretical, experimental and clinical. The program consisted of a series of five workshops, each devoted to a separate neurological disease: Parkinson's disease, schizophrenia, epilepsy, Alzheimer's and anesthesiology/sleep disorders. The workshops were preceded by some tutorial sessions and were followed up with informal discussions and presentations. The program goals were to: (i) attract newcomers to the field; (ii) broaden and deepen perspectives of those in the field; and (iii) consider what mathematical tools, analyses and further developments are most needed to move forth in tackling neurological disease.

Although the workshops covered a variety of diseases for which the modeling is at very different stages of development, some consensus on important guidelines for modeling was observed (see below). It was noted that we need to understand the normal network to be able to understand the diseased network, and clearly, we can't go from theory to data – we need to pay attention to the data first. Importantly, as was brought up in discussions at all workshops, our ultimate goal is to help patients with neurological disease.

Below, we describe some challenges, observations and suggested ideas that collectively emerged from the program.

(Challenge/Observation) Although we have learned much about neurological disease in recent years, it is difficult to know what might be best to target in modeling 'disease behavior'. For example, in schizophrenia, there is a wide diversity of disease symptoms. Even more challenging is the fact that there are many different types of epilepsy (clinically, as well as experimental models). By contrast, in Parkinson's disease, due to a clear linkage of beta oscillations with movement, as well as the existence of cellular-based mathematical models of tremor and the effects of deep brain stimulation (DBS), the modeling has progressed to the stage of studying specific questions related to improved treatment (e.g., periodicity importance in DBS effectiveness).

(Suggested Idea) In discussions, there was consensus that focus on specific deficits (and their quantification) was much needed in the field. In this way, implications of different mathematical models of neurological disease could be used more effectively as we evolve toward a more integrated understanding of the disease. Also, several participants felt that more emphasis should be put on getting clarity about the (behavioral) disorder itself and what it means at the human level and in animal models. For example, working memory errors could be manifest in specific ways that could help constrain the modeling. Emphases in these directions could also help demystify whether model details such as attractor basins and oscillation properties are critical considerations in understanding disease.

(Challenge/Observation) An immediate issue that arises when constructing a mathematical model for a neurological disease is the appropriate level of abstraction. On the one hand, one needs a scaffolding or conceptual model to link with behavioral

(disease) aspects (it was noted that this is immensely helpful and needed at the patient population level, and that it is also quite hard to enter at a more detailed, cellular level). On the other hand, drug treatments and therapeutics target cellular/receptor levels, so mathematical models need to consider these aspects also. The workshops included several talks which attempted to link higher-level behavior to cellular-level models. One talk showed how attaching biological meanings to attractor network models could suggest mechanisms for the initiation and progression of Alzheimer's disease. Another showed modeling studies done for pharmaceutical companies which involve the incorporation of receptor kinetics into existing neuronal network models and tuned with behavioral level data. These models were used to examine drug concentration and combination effects. Finally, several talks showed that mean field theory can be used to link cellular-level and larger, abstract models.

(Challenge/Observation) A challenge that many researchers are already embracing is the requirement of a clear context for linking the mathematical models with experimental data. While each mathematical model may not encompass all cellular, network and behavioral aspects, we need to always be mindful of what is being represented, as well as having some way to measure or estimate parameters that are included in our models. Furthermore, it was noted that more effort should to be made to close the gap between clinical and experimental wet labs that in turn would inform the mathematical modeling.

(Observation) Mathematics and mathematical models are clear, unambiguous and logical, and as such, can be extremely powerful in bringing about a mechanistic understanding of neural systems and neurological disease. This power is greatest if there is a combination of good questions, good data and good clarity about what is being modeled. Such power was shown in several talks such as on seizure termination and absence seizure (Epilepsy workshop), and striatum beta oscillations (Parkinson's workshop). Much more will become possible as we strive for clarity.

(Observation/Challenge) As experimental techniques become even more sophisticated, so has our appreciation of the complexity of neurons and the neural circuits in which they are embedded. Not surprisingly given fast-paced technological developments in the field today (such as optogenetics), applications of optogenetics emerged in all of the workshops: as a consideration of a form of seizure control, an 'intelligent stimulator' targeting particular cell types, or as a way to help design better drugs and to understand how the drugs actually work by constraining particular cell types. Some speakers intentionally presented their talks from the perspective of "complexity", either in terms of the disease itself (e.g., Alzheimer's) or of the neural circuits - inhibitory/excitatory cells in hippocampus (Epilepsy workshop). This translates into more complexity in the corresponding mathematical models of neurons and networks to be developed. But we need to understand the model behavior to provide predictions and understanding about the disease.

(Observation) We can obtain understanding through mathematical analyses. While traditional approaches such as dynamical systems methods are still being used and developed to study models of neurological diseases, it was evident in many workshops

that tools from other areas of mathematical analysis are increasingly being applied. For example, dynamical causal modeling is being used to suggest appropriate network structure. Also, dominant scale analysis was seen to be an excellent methodological tool to apply to developed mathematical models to reduce them to their essential components. Several talks described the increasing accessibility of such tools as well as illustrating many ways in which unexpected output (e.g., spike adding) could emerge from the dynamics. With accessible tools, the possible contribution of such subtle aspects to neurological disease could be considered. Further, it was noted that when using 'simple' models, having the underlying mechanism from analyses is a way to differentiate between possible models when applying data constraints. Also, it was clearly stated that use of control theory and other methods in the investigation of neurological disease can have different goals. For example, the complexity of the model may be constrained by the ability to apply control theory, as opposed to determining whether there are enough and appropriate biological details in the model in the first place. Regardless of the analysis approach, it is apparent that much bridging work between the fundamental methodology and biology needs to be done to bring any methodology to bear on questions of importance to neurological disease.

At the end of the day, it was strongly acknowledged that it is really hard to develop the models *and* consider neuromodulation (as would be required in neurological disease consideration) *and* develop and use analyses. However, with more openness and sharing, mathematical models could be developed and constrained more efficiently and effectively with the biology and consideration of appropriate analyses. Given this, *it becomes even more urgent that much more model sharing and community attitudinal changes are needed to help us move forth in modeling neurological disease*.

Overall, the focus program was a resounding success with many participants expressing their profuse thanks and praise for the program which they not only found enjoyable, but from which much was learnt due to its unique nature. Of special note is the outstanding support provided by Fields in hosting this event. The local organizers would like to thank Fields for their generous support, as well as the National Science Foundation (NSF) and the Organization for Computational Neurosciences (OCNS) for funding. A big thanks also goes out to all speakers and participants who collectively made this a thought-provoking and exciting event.

Several people wanted to know whether it would happen again next year…! Not next year, but perhaps again in the not too distant future!

- Frances and Sue Ann, on behalf of the organizing committee, September 18, 2012.