

## *Does it Have to be This Complicated?* Focus on “Single-Column Thalamocortical Network Model Exhibiting Gamma Oscillations, Spindles, and Epileptogenic Bursts”

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In this issue, Traub et al. 2005 (p. 2194–2232) have given us a model of a single thalamocortical column. It has 3,560 cells of at least eight types, with up to dozens of compartments, each with many different intrinsic currents. Synapses include AMPA, *N*-methyl-D-aspartate (NMDA), and GABA receptor-mediated conductances as well as gap junctions. This is only a fraction of the cells actually found in a real cortical column, and many other kinds of cells and anatomical features, listed explicitly by the authors, have been left out. Thus the model is far less than a faithful description of an actual cortical column and far more than one can understand in detail. So what can we hope to learn from such a heroic effort, and what do Traub et al. actually learn?

This is the largest cortical model to be developed, one with many more anatomical and physiological features than previous models. The authors describe their effort with characteristic humility: after listing the many difficulties of learning from a model that size, they say “in our opinion, the only way to proceed is through a state of denial that any of the difficulties need be fatal.” In my opinion, the authors are far from a state of denial: as the preeminent group (especially the 1st author) working with large and unwieldy models, they have developed an uncanny intuition about what can be teased out of all that complexity, and what questions require that level of complexity to yield new hypotheses.

The central methodology of this paper is the “effort to be faithful to a range of interesting properties in different neuronal types and include a variety of between-cell interactions.” This does not mean including everything that is known or leaving out anything that is not known. The art of modeling is about shaping a model to the questions that motivate it and then making highly educated guesses. In the current case, the motivating questions concern the physiology of network oscillations and epileptogenesis, topics on which this group has previously made large contributions. Thus the elements included are those the authors believe they need to probe those topics further.

How does one draw a conclusion from such a model? It is almost universally believed that with enough parameters in a model, one can reproduce anything. But it is actually the inability to reproduce some details, while trying as hard as possible to be “faithful,” that produces the key clues. (The successful use of this methodology requires intense and ongoing self-criticism.) For example, in previous work on kainate-induced persistent gamma in the hippocampus and neocortex, the authors found that they could not reproduce in their

models the experimentally observed spikelets and high-frequency oscillations unless they included gap junctional coupling between axons of pyramidal cells. When the authors first put forward the hypothesis that axonal gap junctions were important for certain kinds of gamma oscillations and high-frequency oscillations (Draguhn et al. 1998; Traub et al. 1999, 2000), the hypothesis was very controversial. Since then, evidence has emerged to suggest that this is correct although still circumstantial; the current body of evidence, taken from many different lines of research, is described in the paper. To the best of my knowledge, no evidence has yet emerged to contradict this idea. It is hard to see how this important idea could have come out of simpler and smaller models with the same intellectual force. The current paper also makes strong predictions about electrical coupling, focusing here on the coupling between principal cortical neurons (pyramidal cells and spiny stellate cells) and contributions of the connectivity in the latter to epileptogenesis.

Traub et al. are well aware of what one cannot easily learn from a large model: what are the dynamical mechanisms underlying the simulations and (related) why do parameter changes have the effect they do? This can be done only by deconstructing the large model, which is a completely different task from reproducing experimental details. One example of that deconstruction (Kopell and Ermentrout 2004,) address the question of why small electrical conductances added to GABA<sub>A</sub>-mediated synapses can have a large effect on the ability of networks to synchronize in the gamma frequency range even when much larger additional chemical conductances do not (Traub et al. 2001). The deconstruction shows that this effect does not depend on the large numbers of neurons, multiple compartments, or spatial structure of the original model but on the difference in synchronizing mechanism of electrical and chemical synapses. Another, much used, example of deconstruction is the Pinsky-Rinzel (Pinsky and Rinzel 1994) model of Traub’s CA3 neuron; the work revealed how separation of voltages in different compartments can lead to behavior not robust in a single compartment. One of the great benefits of this and related papers by Traub is the large number of questions that it raises for those who read them carefully, both experimentalists and theorists who are more comfortable around smaller sets of differential equations.

There is one more opinion with which I disagree: the authors believe that it is not timely to “proceed from a network model to subtle aspects of brain function, such as learning or information processing.” The arguments given for that claim implicitly assume that the model is like the paper under discussion: detailed in its biophysics and anatomy. It is then first necessary to “calibrate” against simpler behaviors, as found in

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the in vitro and in vivo rhythms, and in pathologies such as epilepsy. I have no doubt that the insights acquired from this effort will indeed be useful for modeling issues of function. However, as the authors themselves point out, even a model of this magnitude is very preliminary and larger models can potentially capture still more details. At what point does it become timely to use the insights one already has? In my opinion, the answer is: early and often, using less-detailed models that incorporate some of the behavior and insight found through the larger models. Although also preliminary, such efforts can advance the ultimate modeling challenge, to create the bridges among all levels of investigation, from molecules to behavior.

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