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Complexity's finest

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Scientists buzz that beyond the genome and the proteome a higher level of informational organization is needed to understand the cell's inner workings. The new grail, a computational model of a living cell, surpasses in detail and difficulty the mere "parts lists" provided by genomic and proteomic sources. A group gathered at the New York Academy of Sciences on Friday to discuss their particularly intricate target - the neuron.

A marvel of complexity, the neuron has temporally and spatially restricted chemistries, and chemical reactions are converted to and from a wide array of electrical signals or mechanical forces. But, said Ravi Iyengar, who organized the event, there's a detailed and growing physiological and biochemical background from which to work. There's also an endpoint where you can connect single neurons to a multicell system - an increasingly attractive goal in systems biology.

Moving from the explicitly detailed parts list to a more abstracted diagram of the cell will require increased cooperation of fields ranging from biochemistry to math, physiology and mechanical engineering. These disciplines and more were represented at the conference titled, "Towards a Computational Model of a Mammalian Cell: The Neuron," on December 6.

Nobel Laureate Eric Kandel of Columbia University opened the conference with a startling picture of the elaborate system at hand. He presented data from a recent paper on epigenetic control of the conversion from short-term to long-term memory (Z. Guan *et al.*, *Cell* **111:**483-493). His work in the marine slug *Aplysia* represents the first instance where histone acetylation can be linked to memory formation. About preliminary work with mice, Kandel said, "We have indirect evidence that chromatin modifications are involved here." Though the work showed how chemical signals at the dendrite can stimulate downstream transcription, it didn't solve the spatial considerations of where to strengthen connections. This, he says, appears to be regulated at the local translational level.

Iyengar, a biochemist at Mount Sinai School of Medicine continued with the idea of localizing chemical reactions through the use of signaling gates. Iyengar's computational models show that gates anchored within the cell could effectively consolidate and prolong biochemical signals to particular areas perhaps coordinating such localized events as dendrite growth.

Charles S. Peskin, a mathematician from New York University reminded attendees that the neuron is essentially electrophysiologically neutral except at the very edges of the cell. He therefore proposed additions to the Hodgkin-Huxley model (Hodgkin, A.L. and Huxley, A.F., *J Physiol*, **117:**500-544) of neuronal conduction to place processes in a more relevant three-dimensional environment.

Shankar Subramaniam, a University of California, San Diego bioengineering and chemistry professor, asked that researchers look beyond component parts lists to the overview of a whole organism. With the Alliance for Cellular Signaling, Subramaniam is creating a database of component interactions from which he hopes a network of cellular signals will emerge. These networks he said could computationally produce testable hypotheses. But Eve Marder, a Brandeis Universitybiologist, asked if this shift from hypothesis-originated research represents an undesirable paradigm shift in biology. Subramaniam responded that once the model is created, questions can be asked in the context of the whole system. If a

model is explaining only what's been shown experimentally, he said, it's useless. "It has to be predictive."

Nam Suh, a mechanical engineer from Massachusetts Institute of Technology brought a wholly different view to the conference. Suh proposed looking at the functional requirements of a system and then breaking down those requirements into physical components. Axiomatic design theory, he said, can help break down a system into component molecular interaction. Complexity theory (a term which, he admits, means different things to different people), is "like looking at biology from 40,000 feet up." Via complexity theory, Suh argued, all components, modules, and living system must have periodicity - meaning alternating stages of activity and reset - just as an engine's piston must return to its starting position before firing again.

Though different approaches and different model organisms were proposed by the presenters, predictive computational models require a steady flow of experimental data. Marder blamed in part "the tyranny of the genome" for flooding the field with largely unquantifiable data. Marvin Cassman, director of the California Institute for Quantitative Biomedical Research, agreed, making a plea for more quantitation. "I blame molecular genetics, which has reduced quantitation to zero or one," he said, admittedly, to be controversial.

Though hope reigned, little was gained towards biology's new grail. As Iyengar had predicted at the start of the meeting, no one would come out of the conference with an answer, but perhaps with some new ideas and a closer familiarity with the varied scientists working in this field.

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