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True and effective – and beyond comprehension?

Computational Neurogenetic Modeling. (2007). By Lubica Benuskova and Nikola Kasabov. Springer. New York: 290 pp. Price \$89.95 ISBN-10: 0-387-48353-5

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The book of Benuskova and Kasabov is a substantial reinforcement of the view that “genes are not autonomous agents but function within networks”, as stated in the title of a recent editorial of Adam S. Wilkins in this journal⁽¹⁾. Canonical gene-centrism of molecular biology may await a similar fate as befell geocentrism four hundred years ago. Adding new and new epicycles did not save the Ptolemaic theory: it was becoming too complicated and the new paradigm, heliocentrism, has re-established simplicity. In this respect, however, the current replacement process will not repeat the previous one. The concept of genetic networks, which seems to be substituting “bean bag genetics”, “genes as beads on strings”, “gangs of selfish genes”, does not exhibit Copernican-Keplerian simplicity – relations between entities are nonlinear and simulation of them requires massive computation. As the human minds find it difficult to understand complex nonlinear interactions, Frank Gannon surmised that biological research, similar to research in quantum mechanics, may be approaching the state where the complexity will be beyond our comprehension.⁽²⁾

The science of brain and mind may be undergoing similar conceptual transition. While some researchers maintain that the brain is modular, something like a Swiss army knife, with a one-to-one mapping between a brain region and a mental state, others argue that the idea of “a module for...” is a similar simplification as is the idea of “a gene for...” In contrast to genetics, the notion of networks is not novel to neurobiology: artificial neural networks have long been used as models of brain functioning. The brain has been conceived as a computer executing formal operations on abstract symbols. Its hardware would be determined by genes and built up in ontogeny of the individual for keeps. However, as recently re-emphasized by the computer scientist David Gelernter, the brain is not a computer.⁽³⁾ In contrast to brains, computers do not know or care what instructions they are executing, just as the oven does not care what it is baking; they deal with outward forms, not meanings.

The brain is an intricately structured dynamical system, extensively dissipating energy to support continuously running biochemical processes. Transmitting signals between neurons, even though consuming the major portion of chemical energy, are not the only prominent brain processes, as customarily assumed. Neural transmission is underlain with intense incessant transcription of genes, protein synthesis, and rebuilding of cell structures. There are no crisp boundaries between inputs and outputs, processors and memories, structure and function. The notion of the brain as a fixed, ready-made hardware is utterly inadequate; a wetware is a more appropriate metaphor. The brain

consists of networks of neurons, and also of networks of extracellular chemicals. In turn, every single neuron consists of networks of proteins and networks of genes. Lately, a hidden layer of networks of non-coding RNAs and small RNAs has been uncovered, and RNA editing has been detected as a process which may have a pivotal role in neurons to integrate environmental signals with genetic and epigenetic ones. There are networks of networks of networks – at many hierarchical levels. To get an insight, how to approach them? For the time being, simulation by computation may be the only method of choice. But if we simulate processes by computation, it does not mean the processes themselves are computations. Protein folding is a case in point. To simulate folding of even a single protein, a process which in a cell or a test tube takes fractions of a second to pass, consortia of scientists are being organized worldwide to exploit untapped power and idle time of tens of thousands of personal computers for time- and energy-consuming computation. In nature, protein folding is not a computation, it is a dynamical process, fast and thermodynamically spontaneous. What holds for dynamics of a protein may well apply to dynamics of a neuron, or even of the brain as a whole. If it is so hard and exacting to simulate a single protein, what a tremendous task must it be to simulate the brain!

It is this state of conceptual turbulence that the pioneering monograph of Benuskova and Kasabov attempts to map and consolidate. The book starts with instructive, but rather traditional, overview of the structure and functions of the brain, followed by similar overviews of artificial neural networks and of genetic systems. Truly innovative is the second part of the book presenting the authors' computational neurogenetic modelling, which “integrates genetic, proteomic and brain activity data and performs data analysis, modelling, prognosis and knowledge extraction that reveals relationship between brain functions and genetic information”. The authors lay down an ambitious program of simulation of the activities of the brain as a network of networks and document it with results of incipient computer modelling, accomplished by themselves as well as by handful of other investigators. Computer simulations faithfully reproduced some experimental results, showing that gene expressions in the brain are affected by ongoing neural activities, and, the other way round, synaptic thresholds are modified by gene expressions and by a plethora of posttranslational protein modifications. The models indicate that the brain handles on a par signalling molecules coming from the exterior and the interior of the cells, and that relevant receptors of the brain are not only receptors in plasma membranes and in postsynaptic membranes, but transcription factors of neurons and glia as well. To make models computationally tractable, many variables had to be omitted. Interactions between nodes had been reduced to minimum, turnover rates of relevant RNAs and proteins, and affinities for receptors of signalling molecules had not been taken into consideration. The newly discovered universe of non-coding RNAs and small RNAs, and of RNA editing has not yet been mentioned in the book. In the future, computer simulations of the gene-brain-environment interactions might be able to reveal multidimensional patterns in the interplay of kilo- or megabytes of variables and parameters. The patterns that do exist in the real world – too complex to be visible and comprehensible to the human actors, yet, preconditions for any meaningful behaviour.

The neurobiologist Eric Kandel related in his autobiographical account how a single event in his youth determined the choice of his career.⁽⁴⁾ As a youngster in 1938 in

Vienna, he was a witness of orgies of people obsessed with mythophilic Nazi enthusiasm combined with racial contempt and hate. He asked a question that has remained his life companion ever since: “How are we to understand the sudden release of such great viciousness in so many people? How could a highly educated and cultured society that at one historical moment nourished the music of Haydn, Mozart and Beethoven, in the next historical moment sink into barbarism?” He attempted to find an answer by studying history; later by studying psychiatry; subsequently by studying biochemistry of the mammalian brain. This was a descent down the ladder of complexity. Eventually, he settled on a simple organism, the giant marine snail *Aplysia californica*. His research on single neurons and on single genes of *Aplysia* was so outstanding that he was awarded a Nobel Prize in 2000. In his time, the downward approach was necessary to allow such a success. Neurobiology may have since amassed knowledge and methods that now make possible explorations in the opposite direction: upwards. The neurogenetic modelling represents an ambitious start of an escalade from molecules to human affairs. Would it bring us closer to the answer of Kandel’s question? Would the answer be too complex for human comprehension, and yet comprehensive enough to equip (humans? robots?) for effective action? Does humanity have any other option?

References

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