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Complexity and Pharmacogenomics

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Articles in this issue of *The Pharmacogenomics Journal* address some of the most crucial topics in this field. Those include an overview of the role of genetic markers in prognosis and prediction (in colorectal cancer—see the article by Longley *et al*, pages 209–216), a review of the role of monoamine transporter genes in complex disorders (Hahn & Blakely, pages 217–235), strategies for discovery of coding single nucleotide polymorphisms (SNPs) (Hu *et al*, pages 236–242), and an assessment of the relation between gene expression data and molecular substructure (Blower *et al*, pages 259–271).

The perspective by McInerney (pages 207–208) is particularly noteworthy as it critically discusses the issue of reductionism and complexity in contemporary science. He wisely comments that it is not simply by understanding the fundamental properties of the elements that form a cell that we will understand how the organism functions in its complex interactions with the environment. Multiple and complex interactions among proteins, each of which having a small effect, determine phenotypic outcome. Modeling those interactions represents a challenge for bioinformatics. McInerney comments that the prediction of protein–protein interactions *in silico* requires 'a combination of bench experiments, computational analysis, and most importantly, integration'. In summary, the key issue here is how to use computer models to study complexity.

Complexity addresses issues that are disregarded by reductionist biology. It is a term that has been used in multiple contexts with different meanings. In the 11 July issue of *Nature*, Tamas Vicsek (page 131) summarizes this area, first stating that the science of complexity is about revealing the principles that govern the ways in which new properties appear as one moves from one scale to another. This way, describing a system solely by reducing it to its essential units and then bringing those together is essentially a flawed strategy because as we move scales from atomic to molecular, cellular, systemic, individual, and populational, different properties emerge that are not defined as the sum of reduced units. Vicsek summarized this particularly well, stating that 'the laws that describe the behavior of a complex system are qualitatively different from those that govern its units'. Contemporary science is undergoing a paradigm shift 'as we realize that the laws of the whole cannot be deduced by digging deeper into the details'.

What is the relevance of the science of complexity to pharmacogenomics? The phenotype of drug response is highly complex, representing a classical example of the outcome of gene-environment interactions. Many in the field proceed as if it could be broken down to a summation of its fundamental elements, in many instances thought to be at the genomic level. Will our understanding of gene variation fully explain the outcome of pharmacological treatment, particularly for common and complex disorders? The answer to this question is 'no'. A multitude of events and levels of interaction occur from the moment that a drug enters a person. Those include issues of absorption, distribution, interactions with multiple endogenous and exogenous factors, binding to target proteins, and interactions of those proteins with other proteins and DNA. As we move from the genomic level, where SNPs and haplotypes are of such importance, to the level of a complex phenotype, we go across many scales, and as we move from one scale to another new features emerge. It is probable that initial progress in pharmacogenomics will be made by ascertaining the relative contribution of genomic variation to the phenotype of drug response. However, such explanations will fail to completely dissect the phenotype. Subsequent work in this field will attempt to integrate knowledge from various scales and understand features that emerge as we move from genome to population.

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