Systems biology provides new tools for addressing Parkinson's disease

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Almost 200 years past after it was first described by the English doctor James Parkinson, Parkinson's disease (PD) still remains to be mysterious and incurable. Our lack of real success in controlling the disease is in large part due to its enormous complexity. PD involves uncounted internal and external factors, from genes, proteins, metabolites, and electrophysiological features to lifestyle choices and, presumably, exposures to pesticides and other environmental factors. But it is not sufficient by a long shot to list the many contributors to the disease. Instead, it is the system of functional interactions among these contributors that makes the disease so complicated. For instance, the factors listed above could affect the machinery of the antioxidant defense system and the ubiquitin-protease system, which are critically associated with PD, and there may be additional factors that are still unknown. These factors and processes span multiple organizational levels within the hierarchy of biology, as well as dramatically different timescales, with biochemical and electrical processes in the sub-second range and the cumulative effects of exposures and neuron loss approaching the human life span. To make the situation even more challenging, most of the interactions among the biological and exogenous contributors to the disease are not additive but nonlinear and synergistic. Thus, each risk factor by itself may often be harmless, but combinations of subtle alterations can ultimately lead to disease, possibly years after they occurred. This situation of many apparently minor changes, interacting in complex, nonlinear ways over a very long time horizon, greatly exceeds the unaided human brain and overwhelms any intuitive assessments.

Traditionally, biomedical phenomena have been addressed with are ductionistic research paradigm that utilizes a "divide-and-conquer" strategy and focuses on one aspect at a time. The efforts of uncounted biologists and clinicians have led to a huge amount of crucially important data and diverse information pertaining to the disease. However, considering the complexity of PD and the synergisms governing its systemic nature, one realizes that something is missing. Namely, even if we assemble a list of all contributors to the disease, it is necessary to integrate the huge amounts of data and the often heterogeneous information into a comprehensive, systemic representation of PD. Systems biology has the potential to facilitate this integration. Systems biology utilizes mathematical and computational methods that, in principle, can place thousands of pieces of information into functional structures that permit extremely efficient computational assessments of millions of health and disease scenarios. Thus, systems biology is a valuable and powerful approach, which complements there ductionistic research strategy. As an example, systems biology approach can exploit large scale sampling and exhaustive what-if simulations to screen out potential drug targets that might save huge money and time of a pharmaceutical company.

Notwithstanding its potential, systems biology is still at its beginning, and there are enormous challenges to be overcome. For example, we simply do not know yet how to infer the significance or specific effects of a particular genetic predisposition on metabolic pathways, cell function, physiology, or behavior. Only the merging of comprehensive molecular, cellular, physiological, animal, and epidemiological data with computational methods is likely to reveal such functional connections. These methods will include sophisticated statistics and bioinformatics, but must also effectively identify and characterize dynamic, highly regulated and adaptive mechanistic networks of causes and effects. Our current technologies are still too primitive to assess diseases like PD comprehensively and successfully, but we are already witnessing how systems biology is emerging as a potentially very efficacious, additional tool in the repertoire of biomedical methods that may eventually reveal what governs PD and how we might effectively intervene.