Mathematical models reveal how organisms transcend the sum of their genes

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(PhysOrg.com) -- Molecular and cellular biologists have made tremendous scientific advances by dissecting apart the functions of individual genes, proteins, and pathways. Researchers at the University of Wisconsin-Madison College of Engineering are looking to expand that understanding by putting the pieces back together, mathematically.

John Yin, a professor of chemical and biological engineering, developed computer models of a relatively simple virus to show that genes alone do not make an organism. With mathematical representations of the virus's known biology, he and former graduate student Kwang-il Lim demonstrate how genomic organization and regulation can have a large impact on biological outcomes. As shown in a new paper, simply shuffling the order of the five genes in the virus's genome has a huge impact on how well the virus grows and how it interacts with its simulated host cell.

Their new results are reported Friday, Feb. 6, in the journal *PLoS Computational Biology*.

The eventual goal is to understand the full picture of how an organism's genome guides its growth and development, Yin says. "How does the biology of individual genes come together in genetic interactions to ultimately give rise to behavior?"

He and Lim, now a postdoctoral fellow at the University of California-Berkeley, computationally modeled the lifecycle of the vesicular

stomatitis virus (VSV), a well-studied virus with only five genes and years of background research on its growth and function.

Virologists have previously created strains with 11 of the possible gene arrangements, but with their computational models, the Wisconsin researchers were able to simulate all 120 possible gene-order variants. Comparisons of the simulated strains revealed that the positions of the first and last genes are key to viral success.

The work has many potential applications. Understanding how to control the virus's growth and infectivity will help guide efforts to develop VSV as a cancer-targeting agent and create vaccines against more problematic viruses such as HIV-1 and influenza.

The models can also be used to investigate the genetic basis of other viral characteristics. For example, Yin is currently working to simulate drug effects on a virus to look for ways the virus can evolve drug resistance.

Ultimately he hopes his approach will scale up to more complex organisms with more complex genomes. For example, the completion of the Human Genome Project has inspired hopes of understanding how a person's genome determines their biology.

The era of such "predictive biology" is a long way off yet, Yin says, but the ability to identify key elements of genetic organization and regulation are a critical early step. "This establishes a foundation for linking a genome to developmental processes and ultimately to phenotypes or behavior of biological systems," he says.

More information: http://dx.doi.org/10.1371/journal.pcbi.1000283.

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