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Model Developed that Predicts Molecular Response of Living Cells to Genetic or Environmental Change

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Institute for Systems Biology and NYU Researchers Demonstrate that it is Possible to Discover how Complex Biological Systems Work

SEATTLE--(BUSINESS WIRE)--Scientists at the Institute for Systems Biology (ISB), in collaboration with researchers from New York University (NYU), have developed a model which rapidly characterizes and accurately predicts the molecular-level, mechanistic response of a free-living cell to genetic and environmental changes. The paper describing the EGRIN model was published today in the online edition of the journal *Cell*.

The knowledge gained through the Environmental and Gene Regulatory Influence (EGRIN) model demonstrates that it is possible to discover how complex biological systems work and opens the door to more complex genetic engineering that produces fewer unintended consequences.

Mechanics can fix cars because they know all the parts of a vehicle, what each part is supposed to do, how the parts are supposed to work together and what happens when parts wear out over time or stop functioning due to outside influences. Biologists, on the other hand, have trouble fixing and/or reengineering cells because they don’t have a comprehensive molecular parts list, let alone an understanding of how those parts work together to facilitate healthy functioning.

“Unraveling complex biological networks is why I came to ISB,” said Nitin Baliga, Ph.D., an associate professor at ISB. “The genomes of more than 500 organisms have been sequenced, yet we as a scientific community know very little about how their biological networks function.”

“The systems approach to biology, of which the founders of ISB were early champions, has proven to be a spectacular success in achieving a molecular level understanding of complex biology, which is necessary if we are to engineer cells back to health or reengineer organisms to improve bioenergy production or bioremediation, for example,” Baliga said.

The EGRIN model linked biological processes with previously unknown molecular relationships and accurately predicted both new regulation of know biological processes and the transcriptional responses of more than 1,900 genes to completely novel genetic and environmental experiments.

Baliga and colleagues used *Halobacterium salinarum NRC-1*, a member of the Archaea family of organisms, because it has been the subject of relatively little scientific study. Archael organisms are evolutionarily distinct from the two other forms of life, Eukaryotes and Prokaryotes. They have evolved to thrive in harsh environments that would be lethal to most other organisms. As a result, their unique biology could provide new solutions to challenges in environmental contamination, energy production and healthcare.

Working with an organism about which relatively little is known allowed the Baliga lab to demonstrate the value of taking a systems approach, which can lead to the rapid discovery of structure and function in unstudied biological networks.

“The ability to gather this level of information regarding a poorly characterized organism from a single study is significant and unprecedented,” Baliga said. “In addition, the nature of the EGRIN model is such that it’s applicable to many complex biological networks.”

The process of discovery involved perturbing cells (e.g. altering, individually and in combination, 10 environmental factors and 32 genes), characterizing growth and/or survival phenotype, quantitatively measuring steady state and dynamic changes in mRNA, assimilating the changes into a network model able to repeat the observations and experimentally validating hypotheses formulated through the model. More than 230 out of 413 microarray experiments used were collected and/or conducted specifically for this study. In addition, researchers used data from genome-wide binding location analysis for eight transcription factors, mass spectrometry-based proteomic analysis, protein structure predictions, computational analysis of genome structure and protein evolution as well as data from public sources.

The vast array of approaches to data gathering and validation required a systems biology approach, in which scientists of varied disciplines (e.g. biochemistry, physics, mathematics, computation, statistics, genetics and more) collaborate and contribute their skill sets to the achievement of a single scientific objective.

The researchers' next steps involve applying the EGRIN model to more complicated organisms and/or networks, and actually reengineering organisms based on knowledge obtained through the EGRIN model.

"It will take a lot more effort before the EGRIN model can be applied in a practical fashion," Baliga said. "At this point we've basically proven that we can develop a comprehensive understanding of how complex biological systems work, which has been an open question to this point."

About the Institute for Systems Biology

The Institute for Systems Biology (ISB) is an internationally renowned, non-profit research institute headquartered in Seattle and dedicated to the study and application of systems biology. Founded by Leroy Hood, Alan Aderem and Ruedi Aebersold, ISB seeks to unravel the mysteries of human biology and identify strategies for predicting and preventing diseases such as cancer, diabetes and AIDS. ISB´s systems approach integrates biology, computation and technological development, enabling scientists to analyze all elements in a biological system rather than one gene or protein at a time. Founded in 2000, the Institute has grown to 12 faculty and more than 200 staff members; an annual budget of more than $25 million; and an extensive network of academic and industrial partners. For more information about ISB, visit www.systemsbiology.org.

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