Project aims to fuse top-down, bottom-up approaches in systems biology

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The National Institutes of Health has awarded Virginia Tech researchers a $2.13 million grant to develop new systems biology approaches to study cells, one of the most basic units of life. Systems biology aims to study complex cellular systems by systematically stimulating them, monitoring cellular responses, formulating mathematical and computational models to understand the data, and proposing new experiments to refine these models.

T.M. Murali, associate professor of computer science at Virginia Tech, John Tyson, university distinguished professor of biology, and Jean Peccoud of the Virginia Bioinformatics Institute proposed to the National Institutes of Health a novel approach to link the two dominant paradigms in systems biology.

NIH is awarding the interdisciplinary team for their proposal titled "Integrating Top-Down and Bottom-Up Models in Systems Biology with Application to Cell Cycle Control in Budding Yeast."

Murali, principal investigator, described the project: "Two distinct approaches are being used to study complex cellular systems. The first, top-down approach automatically analyzes large-scale datasets for correlations between genes and proteins. However, it is often difficult to design experiments from these results.

"The second, bottom-up approach painstakingly crafts detailed models that can be simulated computationally. Although such simulations can

suggest wet lab experiments, developing the models is a manual process that can take many years. These approaches have largely been developed separately until now. Our project will meld the strengths of these two approaches into a single framework, thereby allowing efficient and automated data-driven analysis to augment models that can be simulated."

The advantage of the collaborative research is the merging of the expertise of the three researchers. Murali conducts research in network and combinatorial algorithms in the context of systems biology. Tyson's group has used differential equations to model regulatory networks for over 20 years. Peccoud is a molecular geneticist by training, and has proposed methods to map genotypes to phenotypes using differential equation models of molecular networks.

The three scientists will develop a framework for generating hypotheses from top-down models, test these hypotheses by integrating them into bottom-up models, and validating the hypotheses using experiments. They will use these developments to study cell division in budding yeast.

"With an improved understanding of cell cycle regulation in budding yeast, we should be able to suggest novel experiments that provide a better understanding of molecular control systems," Murali explained. Murali projected that the "methods developed in this project should be relevant to the study of any complex cellular system, including the development of cancer and the spread of infectious diseases. If we are successful, our project will result in significant advances in computationally driven experimental biology."

Provided by Virginia Tech

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