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Headline: Crunching Complex Data

Byline: n/a (Alex Philippidis)

A global research team led by scientists from Philip Morris International (PMI) and IBM Research are preparing to launch their second of four challenges over three to four years, part of a larger project designed to harness the wisdom of the broader science community and the power of high-performance computing to verify and analyze complex systems biology data.

During the second quarter, the project—Systems Biology Verification Industrial Methodology for Process Verification in Research or SBV IMPROVER—will launch its Species Translation Challenge. Scientists will work to tackle a longstanding challenge in preclinical science: Translating insights gleaned from rodent models into greater knowledge of how humans function.

"We're asking the question, 'Which bit of the rodent biology can actually be translated into the human biology?'" Manuel Peitsch, Ph.D., vp, biological systems research with PMI Research & Development, told GEN. "We are talking about rat bronchial epithelial cells versus human bronchial epithelial cells, rat aortic endothelium vs. human aortic endothelium, etc. By comparing the behavior of the biological networks in those systems, we expect to come back with a translatability factor between rodent and human."

Among key questions to be answered in the species challenge: Which gene expression regulatory processes, such as biological pathways and functions, are translatable and therefore predictable between species? Which are too divergent? How much translatability is there between species, and how can that be quantified? Also, how well can mathematical models using gene expression data predict protein phosphorylation and cytokine responses?

Researchers will pursue answers by looking across all available pathways, though it has yet to be decided whether the species challenge will narrow its focus to a few areas, J. Jeremy Rice, Ph.D., a research staff member who focuses on functional genomics and systems biology at IBM's T.J. Watson Research Center, told GEN.

"In this challenge, there will be gene expression data. There will be data on phosphoprotein levels. There will also be some data on cytokines. And we'll look at responses toward a panel of different stimuli," Dr. Rice said. "The real opportunity here is that the quality of the datasets will be great. Their uniformity and consistency is something that's not available anywhere else, and it's going to get a lot of people excited."

As in last year's challenge, SBV IMPROVER aims to analyze complex systems biology data quicker and more accurately than traditional peer review methods, thus enhancing the data's reliability while

lowering development costs. SBV IMPROVER consists of about 20 researchers combined from PMI and IBM, as well as biopharma giants Roche and Merck & Co.; smaller biopharmas like software developer and biodata curator Nebion, and biomarker-based diagnostics developer Selventa; and seven academic researchers.

PMI hopes data from the project can enhance efforts to produce safer cigarettes, which FDA labels "modified-risk tobacco products." "Part of the challenge of demonstrating risk reduction of a tobacco-based product is that conventional cigarettes take 30 to 40 years to wait for disease manifestation. We're trying to find an approach where with one year's clinical study, we can actually say something about that risk," Dr. Peitsch said, in part by pursuing potential biomarkers of disease onset.

SBV IMPROVER's third challenge will entail construction and verification of a biological network describing chronic obstructive pulmonary disease (COPD). The fourth will involve verifying the identification of biomarkers of disease onset in a translatable manner using animal and human data on early-onset COPD.

"We will have a biological network for the mouse as well as for the human COPD, with all the subnetworks reaching into the confines of inflammation and cell stress," Dr. Peitsch said, as well as the reversibility of changes caused by smoking: "We'll be uniquely posed to identify biomarkers than could be used later on in clinical trials for modified-risk tobacco products."

For IBM Research, best-known for its Jeopardy!-winning natural-language computer system Watson, SBV IMPROVER follows other IBM-led efforts to crunch systems biology data via crowdsourcing. These include the ongoing Dialogue on Reverse Engineering Assessment and Methods (DREAM), which explores how theory and experiment interact in the study of cellular network inference and quantitative model building.

In the first challenge, completed last year, 54 teams worldwide established predictive signatures on unlabeled gene expression data sets in four disease areas: COPD, lung cancer, multiple sclerosis, and psoriasis. Participants developed prediction models using public data in the four disease areas, then applied their models on blinded samples generated by the challenge organizers.

"People working in isolation tend to think their algorithms are better than the rest. When you put them up head-to-head, in a real double-blind comparison, you find out that not everybody can be better than the rest," Dr. Rice said. "These problems are very deep, they're complex, and it's really not feasible to do verification on very simple things. You really need the ability to reach out to the community and see how it can solve complex problems. Then you get a good grasp for what the state of the art is, and what can be done with today's technology."

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