In Silico: How IPA Helps Manchester Scientist Model Systems

At The University of Manchester, network modeling expert Adam Stevens uses Ingenuity Pathway Analysis to predict upstream regulators, molecular activity, and more for integrated 'omics data sets.

Long before he was integrating massive data sets to better appreciate the genetic complexity underpinning mechanisms such as growth rates in children, Adam Stevens started down the scientific path with a PhD in genetics. He was a bench scientist who spent his early years studying molecular endocrinology, for which he implemented yeast two-hybrid screens to look at protein-protein interactions.

That all changed when Stevens left academia for a pharmaceutical company and first encountered systems approaches to big data in biology. He was hooked. Thanks to his years in the pathway analysis group at the big pharma, Stevens says, "I went in as a wet-lab biologist and came out as an in silico biologist."

After several years in industry, Stevens headed back to academia, bringing with him an appreciation for complex analyses and crunching enormous data sets. Today, he is a senior research associate in endocrine sciences at The University of Manchester's Institute of Human Development. In this post, he uses his background in drug discovery on certain projects related to growth development.

Aside from the in silico skills, the other thing Stevens brought with him from pharma was a tool: Ingenuity Pathway Analysis (IPA) from QIAGEN. He used it initially for modeling protein interactions and now finds it essential for systems modeling, including predicting molecular activity and the function of upstream regulators. "My job is almost entirely in silico now," Stevens says, "and I'm loving every minute of it."

GROWTH RATES

The lab Stevens works in focuses on research into characterizing normal and abnormal growth from a genomic perspective. Conditions under study include short stature, responsiveness to growth hormone treatments, and influence of the development process on leukemia among others. Stevens and his colleagues rely on large data sets, both public and private, as well as internal data from metabolomics and gene expression studies.

A recent publication in *The Pharmacogenomics Journal* describes a large study in which Stevens and his team pulled together metabolomic and transcriptomic data to create a detailed view of how growth rates differ for children born smaller than normal. "Insights into the pathophysiology of catch-up compared with non-catch-up growth in children born small for gestational age: an integrated analysis of metabolic and transcriptomic data," a paper for which Stevens was lead author, reports biological differences between kids who later caught up to normal size and those who remained small for their age. In addition to being a useful source of information about differences in growth rates, the project was important because children who exhibit catch-up growth are more likely to develop cardiometabolic diseases later in life.

For this work, Stevens says, IPA played a key role in data analysis. "We used IPA because it has fantastic metabolomics features," he notes. "It helped me decode what was going on in these two data sets." The paper demonstrates Stevens' first use of the new Molecule Activity Predictor tool in IPA, which helped reveal the primary

functional relevance of the data. He also found the Upstream Regulator Analysis to be very powerful. "It's elegantly accessed in IPA and is tied in with Mechanistic Networks and the Molecule Activity Predictor," he says.

IN SILICO APPROACH

Stevens' appreciation for in silico science means that he reserves the relatively expensive bench work for procedures that can't be done any other way, such as validating computational observations. "Bench work is expensive and time-consuming," he says. "An Ingenuity Pathway Analysis license is a lot more affordable than somebody who's working with cell cultures and running all sorts of transfections."

That license gets Stevens and his collaborators access to the Ingenuity Knowledge Base, which powers the analysis performed within IPA. "The way in which the database is constructed results in a very impressive tool set," Stevens says. "Going into almost any sort of 'omics work, this is an essential starting point."

He particularly likes the upstream regulator tool, a function that "is not accessible anywhere else as extensively or easily as through IPA." He also finds it handy to walk through the summary analysis of diseases, functions, and canonical pathways that IPA generates from a data set. In his daily routine, he generally imports the findings from a primary analysis of interactome models to IPA, and then cross-references how they map onto upstream regulators. "Initial network analysis is prioritizing elements, but from those elements we really need to move toward a systems model," Stevens says. "That's what IPA is trying to do, and that makes it a fantastic piece of modeling software."

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