

# Integromics: the next step for systems biology

By Chris Tachibana

## **Transcriptome, metabolome, and proteome information are more powerful when combined**

In the beginning—long ago in the 1990s—we had genomics and transcriptomics: examining an entire genome and watching the expression of all its genes. We're beyond that now, with proteomics, metabolomics, lipidomics and more. The next step is integromics: combining data from different experimental approaches, says Professor Uwe Sauer, Institute of Molecular Systems Biology, ETH, Zurich, Switzerland, in an American Association for the Advancement of Science webinar sponsored by Agilent Technologies. This kind of analysis will let us see large-scale changes such as the downstream consequences for an entire network of transcription factors.

- For this we need integration. Without an integromics approach, we just have large piles of information that are not translatable into understanding, says Professor Uwe Sauer. But bringing together data from different 'omics disciplines requires strong data management with a clear indication of the

data source, context, and type, emphasises Professor Albert J. Fornace, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC. Realistic models and methods for data interpretation are needed, and researchers must understand the limits and capabilities of the approaches. They need to use solid models and apply explicit tests to validate predictions.

## **Integromics power**

Merging data from different systems-wide approaches can show the effects of network interactions, says Sauer. He described two examples, a steady-state analysis using yeast, and a dynamic analysis of responses to the environment using *Bacillus subtilis*. His group perturbed enzyme levels in yeast, measured metabolic flux using liquid chromatography/tandem mass spectrometry, and estimated in vivo enzyme activity by protein or transcript quantitation.

- In some cases, five-fold less enzyme gave only 40% less associated metabolite. This showed how metabolic networks are generally robust to mild fluctuations of constituent enzymes and

metabolites, says Professor Uwe Sauer. Dynamic shifts can also be measured, for example in an analysis of *B. subtilis* in a changing milieu of glucose and malate. Integromics allowed estimates of global metabolite flux under these changing conditions.

- We could not have measured this directly. Only a handful out of hundreds of transcript and metabolite changes are absolutely necessary for adaptation, and we would not know this without computational analysis, says Professor Uwe Sauer.

As an example of how integromics is used for discovery, Dr. Fornace described the NCI60 project, which is applying 100,000+ compounds to 60 human tumor cell lines and assessing parameters such as toxicity and drug response. Hundreds of molecular markers for these cell lines have been developed.

- The NCI60 panel can be used as a guide for systems medicine approaches in vivo, in patients. It has already led to animal studies, drug discovery, and clinical trials. We've examined several 'omics levels, and have, or are moving to include SNP [single nucleotide polymorphism] analysis, direct sequencing, deep sequencing efforts, proteomics, metabolomics, checkpoint activation, and multidrug resistance, says Professor Albert J. Fornace. Validation methods include real-time polymerase chain reaction, small interfering RNAs, and tissue array analysis, says Fornace. The data can be used to discover common responses and regulators to different types of pharmaco-

logical stress. It can also be used to identify gene clusters that respond to particular agents such as those that induce DNA damage. These approaches can be used to find biomarkers for particular stress pathways, and these can be used to characterize agents with unknown toxic mechanisms.

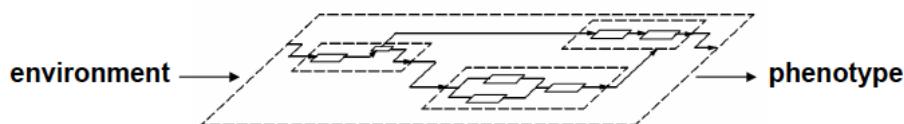
Sauer added that discovery can be a by-product of analysis on known pathways.

- When we work with *E. coli*, we conduct analysis with one eye open for when data are hard to fit to the model. When we go back and question the model, sometimes we discover new pathways.

Professor Richard W. Gross, Division of Bioorganic Chemistry and Molecular Pharmacology, Washington University in St. Louis agreed; - Starting with known pathways and comparing data to anticipated pathways can give insights into new metabolic pathways.

Integromics is also used in traditional hypothesis-driven research, says Gross, and offers a case study. His group developed shotgun lipidomics to identify and quantify different lipid from organic extracts of tissues. They used this technique to investigate diabetic cardiomyopathy, a heart disease associated with diabetes. Using mouse models of type I and type II diabetes.

- We used integrated 'omics to confirm a hypothesis, in this case that diabetic cardiomyopathy is a metabolic myopathy, with specific alterations in the lipidome, says Professor Richard W. Gross.



**Integrating 'omics webinar:**  
[www.tinyurl.com/integromicswebinar](http://www.tinyurl.com/integromicswebinar)

**NCI-60**  
[www.sanger.ac.uk/genetics/CGP/NCI60/](http://www.sanger.ac.uk/genetics/CGP/NCI60/)

### Integromics challenges

Sauer says that the systems biology community has several issues to address for integromics to proceed, including;

- The ways we communicate and share data, such as standardizing naming and formatting conventions. Metabolites have different names in different fields. Also, computational challenges are in combining overlapping dynamic data generated by different platforms, for example from two-dimensional and gel-free proteomics data.

Gross named biological complexities that must be considered in collecting and interpreting data.

- We cannot predict how SNPs alter transcript levels. Protein amounts do not necessarily correlate with enzyme activity or protein function because of protein modification and compartmentalization of reactions in cells. Examination of whole cells or tissue extracts

is not necessarily indicative of physical interactions within living cells.

We must also consider bidirectional signaling between compartments, for example between peroxisomes and mitochondria in regulating metabolic flux. In a broader context, says Gross, genomics and proteomics seldom ask the same basic questions. This complicates the mining and combining of data from separate disciplines.

### Integrating old school and new school biology

- We continue to need reductionist biology for learning molecular details. 'Omics and systems biology are not going to replace this, but there will be a fruitful interaction between the approaches, says Sauer.

Fortunately, integromics is an open and accessible field. Fornace pointed out that NCI60 has public datasets, and online tools for exploration that can be mastered with a little effort.

- Experiments with chips and metabolomics require specialized equipment, so for that we collaborate with colleagues. But integration of datasets is not costly. All it takes is a computer and a few good ideas, concludes Professor Uwe Sauer.