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Sauer, Uwe; Heinemann, Matthias; Zamboni, Nicola

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GENETICS

Getting Closer to the Whole Picture

A quantitative data set of RNA, proteins, and metabolites provides an unprecedented starting point to understand, at a systems level, the effects of perturbations on a cell.

Uwe Sauer, Matthias Heinemann, Nicola Zamboni

A major challenge of biology is to unravel the organization and interactions of cellular networks that enable complex processes such as the biochemistry of growth or cell division. The underlying complexity arises from intertwined nonlinear and dynamic interactions among large numbers of cellular constituents, such as genes, proteins, and metabolites. As well, interactions among these components vary in nature (regulatory, structural, and catalytic), effect, and strength. The reductionist approach has successfully identified most of the components and many interactions but, unfortunately, offers no convincing concepts and methods to comprehend how system properties emerge. To understand how and why cells function the way they do, comprehensive and quantitative data on component concentrations are required to quantify component interactions. On page 593 of this issue, Ishii *et al.* (*1*) provide unsurpassed complete and quantitative data of components at the various constituent levels in a bacterial cell.

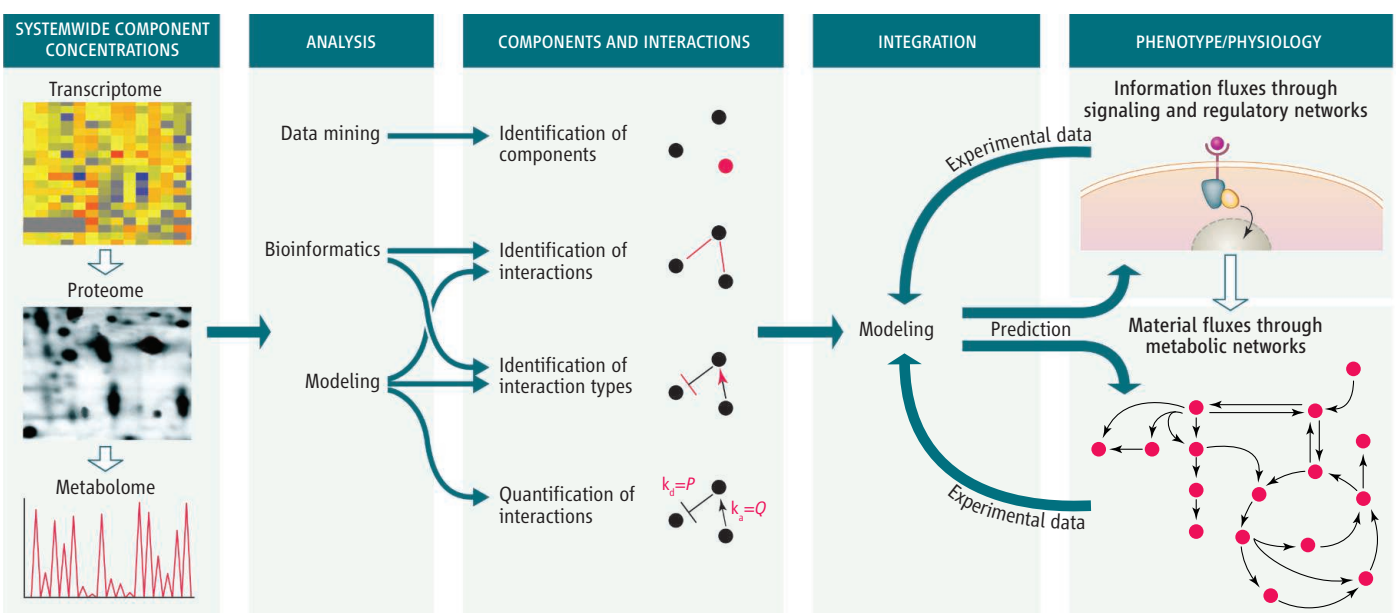
Rather than a reductionist viewpoint (that is, a deterministic genetic view), the pluralism of causes and effects in biological networks is better addressed by observing, through quantitative measures, multiple components simultaneously, and by rigorous data integration with mathematical models (*2*). Such a systemwide perspective (so-called systems biology) on component interactions is required so that network properties, such as a particular functional state or robustness (*3*), can be quantitatively understood and rationally manipulated.

The technical challenges of the systems biological approach (*4*) are mainly along four lines (see the figure): (i) systemwide component identification and quantification ("omics" data) at the level of mRNA, proteins, and small molecular weight metabolites; (ii) experimental identification of physical component interactions, primarily for information processing networks; (iii) computational inference of structure, type, and quantity of component interactions from data; and (iv) rigorous integration of heterogeneous data. The last step is required to achieve a holistic, quantitative, and predictive understanding through mathematical models that enable an iterative cycle between prediction and experiments, the hallmark of systems biology.

The development of experimental methods relating to the first challenge has made tremendous advances in the past decade, but the level of sophistication and the associated costs have led to a situation where primarily single-component data—that is, data solely on genes, proteins, or metabolites—are available. Until the study by Ishii *et al.*, at best two different types of component data were reported for a given experiment, which severely limited progression along the iterative cycle between experiments and theory.

By joining forces among specialized labs, Ishii *et al.* report systemwide data on three main component layers of cells—transcriptome (mRNA), proteome (protein), and metabolome (metabolites)—with a particular focus on central carbon metabolism of the model bacterium *Escherichia coli*. Beyond component concentrations, the functional endpoint of gene, protein, and metabolite interactions—the intracellular metabolic fluxes—were quantified from ^{13}C-labeling experiments (*5*). In a laborious procedure, data on steady-state growth were collected from 24 mutant strains of *E. coli* in which a different gene that functions in carbon metabolism was removed from each strain. All mutants were grown at the same specific rate (*6*), thus minimizing indirect effects of the

The authors are at the Institute of Molecular Systems Biology, ETH Zurich, Switzerland. E-mail: sauer@ethz.ch



A systems roadmap. The comprehensive component concentrations reported by Ishii *et al.* provide input data for inferring component interactions using computational methods. The challenge for computational modeling methods yet to be developed is to predict the functional network state from the concentrations and to infer the information processing network that controls the functional state.

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largely different mutant physiology that would otherwise hamper data interpretation from batch cultures.

The highly reproducible results from these genetic perturbation experiments were complemented with steady-state growth data from the wild-type bacterium grown at a range of growth rates in the same culture conditions, with the extreme cases of near starvation and almost unlimited supply of glucose (the limiting nutrient). An interesting observation is the active response of the bacterium's metabolic system to environmentally dictated changes in growth rate. There were global alterations in the expression level of many mRNAs and proteins. By contrast, upon genetic perturbation of the metabolic system, surprisingly few changes were observed at any component level (besides some obvious and inevitable local perturbations such as altered educt and product concentrations due to a deleted reaction). These results indicate that metabolic networks employ fundamentally different strategies to maintain active operation in the face of genetic or environmental perturbations. However, many important questions remain unanswered. Why does this particular distribution of flux in metabolism emerge from the determined component concentrations? What is actively regulated and by which mechanisms? Which mechanisms contribute to the observed robustness?

These questions remain open because the known component interactions have not yet been considered and because the regulatory network that controls metabolism is only partly known and qualitatively understood at best. But Ishii *et al*. provide, for the first time, a quantitative data set that includes both the constituting components and the functional state of a metabolic network. From these data, we can begin to unravel the conditional and quantitative relevance of regulatory interactions and discover new circuits, thereby addressing the question of how a functional state arises from the components. The call is thus open to integrate this heterogeneous data set into a coherent whole from which testable hypotheses on general principles and network regulation can be derived. Although this particular data set will not be sufficient—for example, it lacks time-resolved dynamic data, and the conditions studied are limited—its unprecedented completeness has the potential to become a cornerstone for computational systems biology.

A number of computational approaches are already available to integrate subsets of the Ishii *et al.* data. Statistical analyses of metabolic and transcriptional data, for example, can identify key features that are important for respiratory oscillations (*7*). Alternatively, computational mapping of transcriptome and metabolome data onto a graphic model of component interactions can provide guidance for dissecting control at the level of genetic regulation from regulation of protein activity (*8*). In contrast to statistical analyses, a method rooted in constraint-based modeling (*4*) allows combining metabolite concentrations with metabolite flux data using thermodynamic principles to derive hypotheses about active or new regulatory mechanisms (*9*).

The extensive data set reported by Ishii *et al*. now opens the way to use existing computational approaches and to develop new ones to extract new biological insights about a fundamental physiological process. From this starting point, model-based design of targeted experiments for further conditions will reduce the unrealistically tedious and expensive collection of large-scale data sets while working toward a truly holistic understanding of cellular behavior. We are one step closer.

References

1. N. Ishii *et al.*, *Science* **316**, 593 (2007).
2. H. Kitano, *Nature* **420**, 206 (2002).
3. J. Stelling, U. Sauer, Z. Szallasi, F. J. Doyle III, J. Doyle, *Cell* **118**, 675 (2004).
4. A. R. Joyce, B. O. Palsson, *Nat. Rev. Mol. Cell Biol.* **7**, 198 (2006).
5. U. Sauer, *Mol. Syst. Biol.* **2**, 62 (2006).
6. P. A. Hoskisson, G. Hobbs, *Microbiology* **151**, 3153 (2005).
7. D. B. Murray, M. Beckmann, H. Kitano, *Proc. Natl. Acad. Sci. U.S.A.* **104**, 2241 (2007).
8. T. Cakir *et al.*, *Mol. Syst. Biol.* **2**, 50 (2006).
9. A. Kümmel, S. Panke, M. Heinemann, *Mol. Syst. Biol.* **2**, 34 (2006).

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NEUROSCIENCE

How to Fill a Synapse

Phillip J. Robinson

Knockout of a member of a family of proteins that support neuronal signal transmission reveals a number of unexpected pathways at work at distinct times during neuron stimulation.

The basis of almost all communication between neurons relies on vesicles containing chemical neurotransmitters. At the junction, or synapse, between two neurons, synaptic vesicles laden with neurotransmitter release their contents (exocytosis) from terminals of one neuron. The chemicals act on the opposing neuron, propagating a specific signal. Replenishing the presynaptic neuron with synaptic vesicles is critical to the signaling that underlies processes such as learning, and failure to control this cycle of vesicle formation and deployment can lead to conditions such as epilepsy. On page 570 of this issue, Ferguson and colleagues (*1*) show that the mechanism producing new synaptic vesicles is not as simple as once envisioned, but involves a family of proteins that manages the supply of vesicles both during and after a neuron is stimulated. Their discoveries reveal how a synapse maintains its full complement of synaptic vesicles to support all functions of the nervous system.

A protein called dynamin 1 has generally been considered the great ensurer of neurotransmitter-filled synaptic vesicles in a presynaptic nerve terminal. These vesicles are poised to fuse with the plasma membrane when the neuron is stimulated. Dynamin 1 acts after fusion and neurotransmitter release in a process called endocytosis. After the plasma membrane invaginates, dynamin 1 forms a helix around the neck of the new budding vesicle, acting as a spring. As dynamin 1 expands and twists, it pinches the membrane into a synaptic vesicle that can subsequently be filled with newly synthesized neurotransmitter (see the figure). But Ferguson *et al.* show that, unexpectedly, synaptic vesicles can form in the absence of dynamin 1. By genetically engineering mice that lack dynamin 1 (knockout mice), they performed experiments that few thought would be fruitful. The mice appear normal at birth, with near-normal numbers of neurons and synaptic vesicles. However, the mice barely survive the first week after birth, and none survive two.

The data of Ferguson *et al*. are full of surprises. The first is that nerve terminals in the synapses of dynamin 1 knockout mice contain these vesicles at all. This reveals that another endocytosis mechanism can generate these vesicles. The next surprise is the heterogeneous size of the synaptic vesicles that are formed in the absence of dynamin 1. Synaptic vesicles are considered the smallest cellular

The author is in the Cell Signalling Unit, Children's Medical Research Institute, Sydney, Australia. E-mail: probinson@cmri.com.au

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