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Uwe Sauer and Bas Teusink

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**Sauer Uwe** – With a PhD in microbiology from the University of Göttingen, Uwe joined the chemical engineering lab of Jay Bailey at the ETH Zurich as a postdoc in 1993. Since 2006 he is professor for Systems Biology at the ETH Zurich. His lab pioneered development of quantitative mass spectrometry-based methods for flux analysis and metabolomics. His research combines quantitative experimentation with modeling to solve fundamental questions of how microbes coordinate their metabolism.

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**Bas Teusink** is part of the Systems Bioinformatics group and Scientific Director of the Amsterdam Institute of Molecules, Medicines and Systems (AIMMS), both at the Vrije Universiteit Amsterdam. He has a PhD in theoretical biochemistry (now called systems biology) from the University of Amsterdam. He combines experimental, theoretical and computational approaches to address fundamental questions about the design principles of biological networks, in particular metabolic networks and microbial ecosystems. He also applies the insights to more applied problems, often in collaboration with industrial partners.

Metabolic networks fuel every living cell with energy and building blocks, and the complicated flow through these networks is orchestrated by intertwined regulatory networks that enable adaptation to environmental changes and internal fluctuations. The complexity of these networks can be overwhelming such that computational approaches are often used, ideally to identify the most relevant individual mechanisms but also common and simplifying principles. Given that the field is too wide for a comprehensive coverage, this issue presents snapshot of topics that in our view are important and timely, and provide a representative picture of the current state of the art in the field.

Let us start at the beginning: the origin of life. Rather than the RNA or more recently also protein centric view, the metabolic perspective offered by Goldford and Segre focuses ancient metabolic networks. They discuss pre-enzyme chemistry, i.e. metabolism that (must have) preceded enzyme-based catalysis — a process that obviously needs a genetic code. They plead for more systems approaches in the field of origin of life research, to allow a more network-based and comprehensive perspective, which enable discovery, and perhaps more importantly, relevant constraints. These constraints are rather crucial not only for the origin of life, but also in further shaping evolved designs by natural selection. In a highly original contribution, the Ralser group discusses several constraints that can explain the secretion of often precious and seemingly costly metabolites. They argue that this apparently wasteful metabolic behavior — observed across all of cellular life - is the result of stoichiometric constraints that the chemistry of life demands, but also of other physicochemical constraints that deal with membrane permeability, diffusion, and area to volume ratios. Secreted metabolites create new metabolic niches, allowing other cells to specialize and improve their fitness by saving valuable resources.

Such secretion is the basis of metabolic interactions that underlie microbial communities and ecosystems. Largely driven by affordable sequencing technology, community research is presently booming, in particular on the gut microbiomes. To move beyond the current metagenomics approaches that mainly focus on finding out “who is there?”, systems biology approaches are bing developed to find out “what are they doing?”. The contribution by Wilmes describes resources and methods that allow to rapidly move from genome sequences to genome-scale metabolic reconstructions. While such networks still require manual curation, they allow to generate first hypotheses about metabolic

interactions in ecosystems. The authors discuss further methods and concepts to infer different types of interactions and metabolic niches, and how to integrate data, modeling and ecological theory. They hope to be able to move beyond classical descriptions of lifestyle strategies such as generalists and specialists, to adaptive strategies that incorporate trade-offs between strategies — trade-offs that again arise from constraints. An important challenge, they conclude, is to move beyond steady state, to dynamic and spatial descriptions, clearly essential aspects of real ecosystems. Stelling and colleagues address this challenge in their contribution by discussing recent genome-scale metabolic modeling approaches, highlighting the dynamic and spatial aspects, and the computational and technical challenges that come with it. They predict that dynamic flux balancing (FBA) approaches, in which extracellular metabolites are dynamically described, while intracellular metabolism is modeled at pseudo-steady state, will be an important step forwards. They discuss current examples, from microbial ecosystems to modeling exchanges between tissues in the human body. They note that with increasing complexity of the modeled systems, more kinetic parameters related to exchange fluxes are required, and resolving these issues will require novel concepts and methodologies.

Ultimately, one would like to arrive a predictive dynamic models and Tummler and Klipp discuss challenges towards developing kinetic metabolic models at genome scale. They discuss four challenges related to the availability of proper, quantitative data, standardized accessibility of such data, missing knowledge of the regulatory layer, and effective methods to deal with the large parameter spaces. One aspect that we as editors would like to add, is the challenge of the interpretation of the dynamic outcome of such complex models: often, for understanding dynamic metabolic behavior, we will need to simplify the models again, and model reduction techniques may need to be co-developed here. The problem of limited regulatory information pointed out by Tummler and Klipp is taken up by Yugi and Kuroda, who provide many recent examples that reinforce the view of mammalian metabolism not only being a workhorse process governed by signaling and gene expression, but actually an internal signal generator for these very regulation networks.

Two more specific examples of metabolism as regulatory signal provider are presented by Locasale and by Lundt and Fendt. Lundt and Fendt provide a global picture of key metabolic reprogramming events in tumorigenesis, underlining that metabolism is indeed a cornerstone of oncogenic transformation rather than the passive consequence of mutations. Not only does active proliferation require different metabolic fluxes that need to be regulated, the resultant changes in metabolic enzyme activities impact on epigenetic states and thus gene expression. Moreover, the products of metabolism are often secreted, as Ralser explained, and thus modify the extracellular milieu. Intriguingly, this milieu modification influences the immune system to alter cancer-immunity. Finally, they point out that microbial metabolism in the intestine affects drug action, and therefore indirectly affects cancer treatment. Locasale zooms in on glycolysis and describes classical and novel regulatory interactions, for example providing a new view on the high condition sensitivity of glyceraldehyde 3-phosphate dehydrogenase, a "housekeeping" protein normally used to normalize loadings on a gel.

These developments provide new and promising opportunities for interventions, but how to probe and find all the wiring, and how to start rewiring? Park and Wang discuss the latest molecular-biological technologies that enable us to do so. Focusing on microbes, they high-throughput screening methodologies that combine genetic and environmental perturbations to identify new regulatory components and interactions. The resultant gene regulatory networks provide the basis for understanding the design principles that govern the robustness and adaptive versatility of living cells. With modern DNA technologies that include synthesis and high precision editing tools, the possibilities to interfere with such networks are endless. Adler and Alon focus on the design principles of such networks and which topologies can perform which tasks. They explain the remarkable ability of some networks to detect fold changes, i.e. the output dynamics of the network is a function of a fold change of the input, not an absolute change. They provide many examples that cross several scales and organisms, and explain how fold change detection can be experimentally demonstrated. These detection systems appear particularly relevant for probing the environment, as they are implemented in processes such as chemotaxis, signaling, but also hearing and smelling. Finally, any cellular information processing system must deal with the unavoidable molecular noise that leads to uncertainty in inferring the environmental as well as internal states of cells. Bruggeman describes the origin of such molecular noise and how it propagates and impacts on processes at the cellular level, and ultimately on the fitness of a population. An important insight is that every cell is phenotypically different — even when the genotype is exactly the same — and this can lead to phenotypic diversifications and distinct subpopulations. It does not make the field easier, but all the more exciting in the years ahead.