Multiomics, AI and data-driven inverse modelling - from environmental sciences to molecular medicine

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Abstract

Genome sequencing and systems biology are revolutionizing life sciences. In the last decade transcriptomics and RNAseq techniques revealed that dynamics of mRNA represent only a small part of a complex regulatory biochemical network which is yet unpredictable from genome sequences [1](#_ENREF_1). Consequently, proteomics and metabolomics emerge as cornerstone technologies for gene function analysis and genome-scale reconstruction of dynamic metabolic networks[2](#_ENREF_2). Here, an integrated proteomics/phosphoproteomics/metabolomics platform suited for functional genomics and systems biology is presented. This platform serves also as the basis for a recently established Vienna Metabolomics Center (VIME) (<https://metabolomics.univie.ac.at/>). A convenient workflow for data processing, integration and mining will be presented. This strategy is based on the data mining toolbox **COVAIN** (***COVA***riance ***IN***verse) [3](#_ENREF_3) for data integration, multivariate statistical analysis, machine learning and genome-scale metabolic modelling [3](#_ENREF_3),[4](#_ENREF_4). A novel algorithm and applications from environmental sciences up to molecular medicine for data-driven inverse calculation of biochemical regulation from high throughput metabolomics data implemented in COVAIN will be presented [1](#_ENREF_1),[3](#_ENREF_3). The algorithm has been recently extended to a fully automated workflow integrating an automated genome-scale metabolic reconstruction (RECON) with a novel regression loss algorithm to determine strongest causal perturbations from metabolomics covariance networks (COV) in large metabolic networks. Based on the combination of covariance analysis (COV) and metabolic reconstruction (RECON) the algorithm is called COVRECON 5. We applied this algorithm to the analysis of mTOR-dependent immune system modulation [6](#_ENREF_5),7. Activation of immune cells is accompanied by a metabolic reconfiguration of their cellular energy metabolism including shifts in glycolysis and mitochondrial respiration that critically regulate functional effector responses. However, while current mass spectrometry strategies identify overall or flux-dependent metabolite profiles of cells or tissues, they fail to comprehensively identify the checkpoint nodes and enzymes that are responsible for different metabolic outputs. Here, we demonstrate that a data-driven inverse modelling approach from mass spectrometry metabolomics data can be used to identify causal biochemical nodes that influence overall metabolic profiles and reactions. Using multiomics metabolomics, proteomics, phosphoproteomics, transcriptomics analysis as well as enzymatic activity measurements we identified metabolic signatures of energy signaling and macrophage differentiation 6,7. The presented concept of data-driven inverse modelling and multiomics analysis allows for the systematic integration of genome-scale metabolic reconstruction, prediction and analysis of causal biochemical regulation in microbes, plants, animals and human.

References

1 Weckwerth, W. Unpredictability of metabolism—the key role of metabolomics science in combination with next-generation genome sequencing. *Analytical and bioanalytical chemistry* **400**, 1967 (2011).

2 Weckwerth, W. Metabolomics in systems biology. Annu Rev Plant Biol 54, 669-689, doi:10.1146/annurev.arplant.54.031902.135014 (2003)..

3 Sun, X. & Weckwerth, W. COVAIN: a toolbox for uni-and multivariate statistics, time-series and correlation network analysis and inverse estimation of the differential Jacobian from metabolomics covariance data. *Metabolomics* **8**, 81-93 (2012).

4 Leitner, M. *et al.* Combined Metabolomic Analysis of Plasma and Urine Reveals AHBA, Tryptophan and Serotonin Metabolism as Potential Risk Factors in Gestational Diabetes Mellitus (GDM). *Front Mol Biosci* **4**, 84, doi:10.3389/fmolb.2017.00084 (2017).

5 Li, J., Waldherr, S. & Weckwerth, W. COVRECON: automated integration of genome- and metabolome-scale network reconstruction and data-driven inverse modeling of metabolic interaction networks. Bioinformatics 39, doi:10.1093/bioinformatics/btad397 (2023).

6 Linke, M., Pham, H. T., Katholnig, K., Schnoller, T., Miller, A., Demel, F., Schutz, B., Rosner, M., Kovacic, B., Sukhbaatar, N., Niederreiter, B., Bluml, S., Kuess, P., Sexl, V., Muller, M., Mikula, M., Weckwerth, W., Haschemi, A., Susani, M., Hengstschlager, M., Gambello, M. J. & Weichhart, T. Chronic signaling via the metabolic checkpoint kinase mTORC1 induces macrophage granuloma formation and marks sarcoidosis progression. Nat Immunol 18, 293-302, doi:10.1038/ni.3655 (2017).

7 Wilson, J. L., Nagele, T., Linke, M., Demel, F., Fritsch, S. D., Mayr, H. K., Cai, Z., Katholnig, K., Sun, X., Fragner, L., Miller, A., Haschemi, A., Popa, A., Bergthaler, A., Hengstschlager, M., Weichhart, T. & Weckwerth, W. Inverse Data-Driven Modeling and Multiomics Analysis Reveals Phgdh as a Metabolic Checkpoint of Macrophage Polarization and Proliferation. Cell Rep 30, 1542-1552 e1547, doi:10.1016/j.celrep.2020.01.011 (2020).

**Brief Biography**

Wolfram Weckwerth is a German Biochemist and Professor of Systems Biology at the University of Vienna, Austria. He received his PhD in Biochemistry from Technical University of Berlin and his Habilitation in Molecular Plant Physiology and Systems biology from University of Potsdam. In 2008 he was appointed as full professor at the University of Vienna, Austria. Currently he is Head of Department for Functional and Evolutionary Ecology and Director of the Vienna Metabolomics Center (VIME). His research focuses on metabolomics in systems biology, the application of genomic, transcriptomic, proteomic, and metabolomic technologies to plants, microbes, animals, human and their interactions. Weckwerth has made significant contributions to the development of metabolomics and multiomics technologies and methods. In 2003 he developed a conceptual framework for metabolomics in systems biology. He later coined the term “Green Systems Biology”, an ecological concept which systematically integrates interdisciplinary fields of systems biology, evolution, natural genetic variation, stress physiology and adaptation, agroecology and sustainability up to biotechnology and public health. In 2015 Wolfram Weckwerth founded the Vienna Metabolomics Center (VIME). VIME integrates applied topics from environmental, biotechnological and biomedical research questions. In the framework of VIME a focus is on algorithms for data processing, biochemical interpretation, structural elucidation of unknown metabolites as well as metabolomics/life sciences databases. Following the concepts of metabolomics in systems biology from 2003, eventually, biochemical pathway dynamics were solved from metabolomics data using an inverse data-driven Lyapunov equation. This approach combined statistical features of metabolomics and other multiomics data with metabolic reconstruction and prediction from genome sequences and variable genotypes and therefore allowed the systematic analysis of the genotype-environment-phenotype-relationship in plants, microbes and animals and their interactions. Besides lectures in ecology and applied topics he also organizes an interdisciplinary seminar on Ethics in Science and Society presenting systems thinking in a broad context to students. He has published more than 300 papers with a H-index 77 (Google scholar) including Cell, Nature Biotechnology, Nature Immunology, PNAS, Cancer Cell, Plant Biotechnology and many others. He also serves in several advisory boards and is president of the Austrian Society of Plant Biology.