Systematic analysis of mechanistic metabolic disruptions in human inherited metabolic disorders

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Human metabolism can be represented as a dynamic, interconnected network of biochemical reactions, where perturbations at the level of a single reaction may propagate locally and systemically through complex network dependencies. Despite this dynamic nature, the disparity in timescales between fast metabolic reactions and slower enzyme expression dynamics justifies the application of a pseudo-steady-state assumption at the reaction level.

Metabolic reactions can be deconstructed into core biological elements, metabolite substrates and products, enzymatic catalysts, and their underlying genomic encoding. This gene–protein–reaction (GPR) structure underpins genome-scale metabolic models (GEMs), which integrate stoichiometric, thermodynamic, and mass balance constraints. Thermodynamic consistency is ensured through reaction directionality, while compartmentalized mass balance is achieved by assigning metabolites and reactions to defined cellular compartments, with transport and exchange reactions maintaining global mass conservation.

Advancements in omics technologies, such as RNA sequencing and mass spectrometry, enable high-throughput quantification of transcripts, proteins, and metabolites from clinical samples, biopsies, in vitro models, or cell lines. These data are typically obtained from biologically distinct cohorts (e.g., control, diseased, treated), and through statistical analysis, condition-specific metabolic alterations can be detected. However, due to the systemic connectivity of metabolic networks, full causality remains difficult to capture through correlation alone.

By integrating experimental omics data with consensus genome-scale metabolic models (e.g., Human1), condition-specific metabolic networks can be reconstructed to investigate physiological or pathological states. These personalized models are tailored to the molecular profile of each sample. In the absence of detailed kinetic parameters, flux distributions are estimated by solving a system of linear equations derived from the stoichiometric matrix, a matrix of stoichiometric coefficients of metabolites in reactions, under the assumption of pseudo-steady-state. Given that the system is underdetermined, it yields a solution space of feasible flux distributions. Sampling this space using Markov Chain Monte Carlo-based methods enables the generation of statistically representative flux profiles. Subsequent analysis reveals condition-specific perturbations in the metabolism, offering insight into reaction-level changes across physiological states.

This approach has been applied to study Methylmalonic aciduria , an inherited metabolic disorder caused by mutations in the Methylmalonyl-CoA mutase gene, using a reconstructed metabolic model of an in-vitro model from a human cell line. The results illustrate the power of genome-scale modeling in elucidating metabolic dysregulation and informing potential therapeutic strategies.

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