Personalized Whole-Cell Kinetic Models of Metabolism for Discovery in Genomics and Pharmacodynamics - DTU Orbit (08/11/2017)

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Understanding individual variation is fundamental to personalized medicine. Yet interpreting complex phenotype data, such as multi-compartment metabolomic profiles, in the context of genotype data for an individual is complicated by interactions within and between cells and remains an unresolved challenge. Here, we constructed multi-omic, data-driven, personalized whole-cell kinetic models of erythrocyte metabolism for 24 healthy individuals based on fasting-state plasma and erythrocyte metabolomics and whole-genome genotyping. We show that personalized kinetic rate constants, rather than metabolite levels, better represent the genotype. Additionally, changes in erythrocyte dynamics between individuals occur on timescales of circulation, suggesting detected differences play a role in physiology. Finally, we use the models to identify individuals at risk for a drug side effect (ribavirin-induced anemia) and how genetic variation (inosine triphosphatase deficiency) may protect against this side effect. This study demonstrates the feasibility of personalized kinetic models, and we anticipate their use will accelerate discoveries in characterizing individual metabolic variation.

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Authors: Bordbar, A. (Ekstern), McCloskey, D. (Ekstern), Zielinski, D. (Ekstern), Sonnenschein, N. (Intern), Jamshidi, N. (Ekstern), Palsson, B. (Intern)
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