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Interrogating the effect of enzyme kinetics on metabolism using differentiable constraint-based models

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Metabolic models are typically characterized by a large number of parameters. Traditionally, metabolic control analysis is applied to differential equation based models to investigate the sensitivity of predictions to parameters. A corresponding theory for constraint based models is lacking, due to their formulation as optimization problems. Optimal solutions of optimization problems can be efficiently differentiated using constrained optimization duality and implicit differentiation. We use this to calculate the sensitivities of predicted reaction fluxes and enzyme concentrations to enzyme turnover numbers in an enzyme-constrained metabolic model of Escherichia coli. The sensitivities quantitatively identify rate limiting enzymes. Further, efficient differentiation of constraint-based models unlocks the ability to use gradient information for parameter estimation. We demonstrate this by improving, genome-wide, the state-of-the-art turnover number estimates for E. coli.

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