First- and Second-Order Parameter Sensitivities of a Metabolically and Isotopically Non-Stationary Biochemical Network Model*

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The Jülich-Aachen Dynamic optimization Environment (JADE) is employed for computing first- and second-order parameter sensitivities of a metabolically and isotopically non-stationary biochemical network model. Based on a Modelica representation of the model, code generation, algorithmic differentiation and first- and second-order adjoint sensitivity analysis are employed for computing the gradient and the Hessian of a parameter estimation objective function. In particular, we use composite adjoints, an extension of the classical adjoint sensitivity analysis, and a numerical integrator based a modification of second-order discrete adjoints of the extrapolated linearly-implicit Euler method. Therewith, the 116×116-Hessian of the objective function with respect to 116 model parameters can be computed at the cost equivalent to only 18 objective function evaluations, while computing the same Hessian with the cheapest finite-difference formula would require 6845 evaluations of the objective function. These results make the JADE platform particularly attractive for large-scale applications with nonlinear numerical optimization solvers that require second-order derivatives.

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