Stan Functions for Bayesian Pharmacometric Modeling

Charles Margossian, William R. Gillespie
Metrum Research Group, Tariffville, CT

Objectives: Stan is a very flexible open source probabilistic programming language designed primarily to perform Bayesian data analysis (1). The Stan No U-Turn Sampler (NUTS), an adaptive Hamiltonian Monte Carlo simulation algorithm, is more efficient than more commonly used MCMC samplers for complex high dimensional problems. Stan also includes a penalized maximum likelihood method. The primary objective of the presented work is to develop new Stan functions to perform pharmacometric modeling tasks including implementation of compartmental PKPD models and schedules of discrete events, e.g., dosing.

Methods: New Stan functions for pharmacometric applications are programmed in C++. They are integrated with Stan software so that the new functions may be used in a manner identical to built-in Stan functions. Use of the new functions is illustrated by analysis of simulated data for plasma drug concentrations and 2 different PD responses: one from an effect compartment model, the other from an indirect action model.

Results: The current prototype Stan functions include one and two compartment models with first-order absorption, and general compartment models described by systems of first order ODEs. The latter uses the CVODES solver (2). The functions incorporate discrete event handling based on NONMEM conventions including recursive calculation of model predictions, bolus or constant rate inputs into any compartment, and dosing histories that include single, multiple and steady-state dosing. Implemented data items include TIME, EVID, CMT, AMT, RATE, ADDL, II, and SS.

Conclusions: The prototype Stan pharmacometric functions facilitate Bayesian pharmacometric modeling by simplifying user implementation of a wide range of pharmacometric models in Stan.

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