PMXstan: An R Library to Facilitate PKPD Modeling with Stan

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Objectives: Using Bayesian approach to make statistical inferences is gaining popularity in recent years. Stan, a probabilistic programming language that implements efficient Hamiltonian Monte Carlo method, attracts more and more users, pharmacometricians in particular. Our objective is to provide a tool (PMXstan, an R library) to facilitate practical Bayesian PKPD modeling and simulation using Stan.

Methods: PMXstan, consisting of a set of R and C++ functions, addresses two hurdles that have largely limited broad applications of Stan in pharmacometrics: 1) a steep learning curve for pharmacometricians to write PKPD model-specific C++-like Stan code; 2) no general and efficient ODE solver that works seamlessly with the No-U-Turn Sampler (NUTS) to handle generic PKPD models, often expressed as differential equations.

Results: PMXstan helps pharmacometricians to focus more on PKPD model building. It automatically handles irrelevant technical details using a set of wrapper functions. With a few model specification statements defined by a user, PMXstan generates model-specific ready-to-run Stan source code, followed by data-conversion functions transferring a conventional NONMEM dataset into a data list readable by Stan. The Stan code, fully accessible and modifiable by the user, is then compiled and an executable sampler generated. After reading the data list and running the sampler, another set of functions provide options for convergence checks and model diagnostics. Within PMXstan, closed-form solutions are provided for PK models when applicable. For a general PKPD model expressed as a set of ODEs, a NUTS compatible template LSODA solver will be called. This ODE-solver was tested to be stable and efficient for a broad range of PKPD models. Utility of PMXstan is illustrated by real project data and its performance is compared with other available tools.

Conclusions: PMXstan frees users from extensive Stan coding, challenging to master by most pharmacometricians. It thus allows them to focus more on model building based on pharmacological understandings. Minimizing the possibility of errors, it provides a fully extensible and customizable platform that facilitates a practical Bayesian PKPD modeling approach.