Supporting drug development as a Bayesian in due time!

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Background

Bayesian approaches can offer several interesting advantages for a pharmacist:
- Formal framework to add external information through the use of priors
- Additional control over model fit in terms of regularization by weakly-informative priors which aids in numerical stability
- Has advantages in terms of propagating uncertainty through the analysis (avoids the need for bootstraps)

Available open-source tools such as Stan [1] allow for a vast flexibility in terms of modeling choices which is relevant for specialty applications

... but there is no free lunch:
- Bayesian approaches oftentimes lead to excessive computation times which render the approach practically in-applicable for iterative modeling

Methods

Data
- Internal patient trial data included >1300 patients from 3 studies
- Monthly observation of pharmacodynamic effect
- External information in literature reported on 2400

Bayesian Aggregation of Average Data (BAAD) [2]
- Expands an existing model \( p(\theta | y) \) to include likelihood contribution of external summary data \( p(y | \delta) \)
- Approach is simulation based which increases numerical burden substantially (in addition to already 2.5 days runtime!)

Example simulation data set for BAAD

Basic Serial Stan Program

```
data {  
  int<lower=1> N;  
  real y[N,5];  
}  
parameters {  
  real mu;  
  real<lower=0> sigma;  
  real<lower=0> omega;  
  vector[N] theta;  
}  
model {  
  // data likelihood  
  for(i in 1:N)  
    y[i] ~ normal(theta[i], sigma);  
  // priors  
  mu ~ normal(0, 18);  
  omega ~ normal(0, 1);  
  theta ~ normal(mu, omega);  
  sigma ~ normal(0, 1);  
}  ```

Objective

At the example of combining aggregate and individual patient data in the context of a non-linear population model the goal is to illustrate different strategies which turn running times of days into less than one hour.

The example chosen was key for a Novartis development program and did require the extension of an existing non-linear population model for 1300 patients to also include aggregate data from the literature, see [2].

The key steps taken to expedite the computations are:
- Analytical shortcuts
- Approximation of the turn-over ordinary differential equation (ODE)
- Within-chain parallelization using the Message Passing Interface (MPI) in the upcoming Stan 2.18 version (machine local threads are an alternative)

Model

- Latent one-compartment model due to the unavailability of concentration measurements.
- Stimulation of kin turn-over model linking the latent pharmacokinetic model to the pharmacodynamic effect.
- Runtime of ODE model in Stan 2.5 days on full dataset

Parallelized Stan Program (using MPI or threading)

```
functions {  
  vector unit_logLik(vector shared, vector unit_specific, real[] y_data, int[] data_int) {  
    real mu = unit_specific[1];  
    real sigma = shared[1];  
    return [ normal_lpdf(y_data | mu, sigma) ];  
  }  
}  
data {  
  int<lower=1> N;  
  real y[N,5];  
}  
transformed data {  
  int x_i[N,5];  
}  
parameters {  
  real mu;  
  real<lower=0> sigma;  
  real<lower=0> omega;  
  vector[N] theta;  
}  
model {  
  vector[1] shared = [ sigma ];  
  vector[1] unit[N];  
  for(i in 1:N) unit[i] = theta[i];  
}  ```

Results

Reduction in runtime for ODE based model using MPI:

```
Results

- Major improvements in the execution times for ODE based pharmacometric models through the use of multiple CPUs on a MPI cluster or via threads on a local machine
- The performance gain for ODE based models does scale linearly over multiple orders of magnitude with high efficiency – 61x speedup using 80 cores on 8 machines.
- Analytical shortcuts, which avoid the need for an ODE integrator, can significantly reduce computation times already. However, these require a high level of technical skills and need a case-by-case implementation.

Outlook:
- MPI and threading based within-chain parallelization are becoming available in the upcoming 2.18 version of Stan
- User-friendly pharmacometric Stan libraries like Torsten will make these function readily accessible.

Analytic approximation of turn-over ODE

Due to a slow elimination half-life of 9 days it is possible to approximate the pharmacokinetic concentration with a step-wise constant function. A step-wise constant input to a turnover ODE can be solved (step-wise) using an analytic solution.

Conclusion

- User-friendly pharmacometric Stan libraries like Torsten will make these function readily accessible.

References: