Population and ODE-based models using Stan and Torsten

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Outline

Day 1

- Introduction and modeling framework
- Pharmacometrics models
- Ordinary differential equation based models

Day 2

- Population models
- Within chain parallelization

Logistics

We use the the cloud platform *Metworx* which has all the requisite files and softwares installed.

Logistics

The workshop package includes:

- R scripts and Stan files to do the exercises
- These slides
- Outline of the course
- Additional documentation

We will be using:

- Torsten v0.86
- RStan v2.19.1
- ggplot, plyr, tidyr, dplyr

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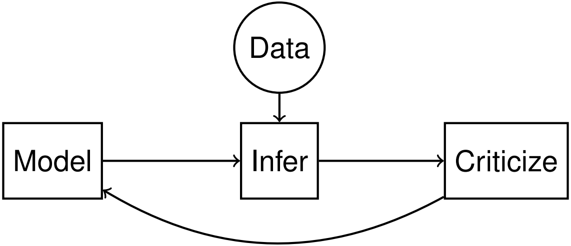
Introduction and modeling framework

Preliminary question

- Why Bayesian in a field such as pharmacometrics?
- Example - *Bayesian aggregation of average data: an application in drug development* [Weber et al., 2018].

Modeling framework

Box's loop:



Inference

- find the set of parameters consistent with our model and our data
- approximate this set with draws from the posterior distribution

Sampling algorithm

- Use the NUTS to sample $\pi(\theta|y)$
- Requires users the specify $\log \pi(\theta, y) = \log \pi(y|\theta) + \log \pi(\theta)$

The "criticism" step

This step can be broken up in two parts:

1. did we sample from the correct distribution?
2. does our model capture the characteristics of the data we care about?

Diagnosing the inference algorithm

- look at the trace and the density plots
- look at $\hat{R}$ and effective number of samples
- have any warning messages been issued, i.e. divergent transitions ?

Example: fitting a linear model

Likelihood:

$$Y \sim \mathrm{Normal}(x\beta, \sigma^2)$$

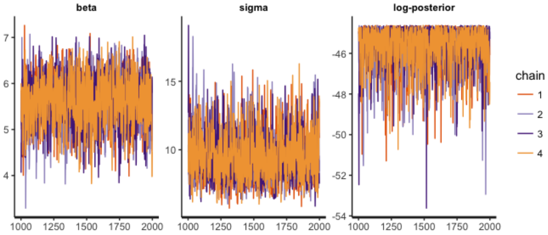
Prior:

$$\begin{aligned}\beta &\sim \mathrm{Normal}(2, 1)\\ \sigma^2 &\sim \mathrm{Normal}(1, 1)\end{aligned}$$

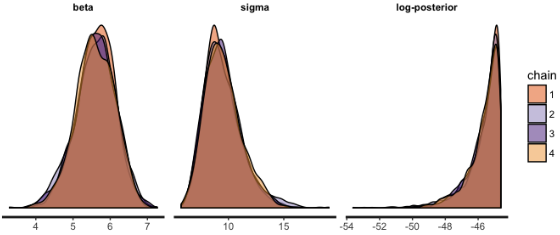
- No warning messages.

```
$summary
            mean     se_mean        sd       2.5%        25%        50%        75%
beta    5.601258 0.01359227 0.5305772   4.479154   5.264460   5.614632   5.966383
sigma   9.502691 0.04383169 1.6813433   6.859379   8.320122   9.282212  10.454978
lp__  -45.636140 0.02492619 1.0048605 -48.314041 -46.014181 -45.318003 -44.916883
           97.5%    n_eff      Rhat
beta    6.570396 1523.749 0.9998578
sigma  13.457200 1471.419 1.0013391
lp__  -44.651010 1625.173 1.0002468
```

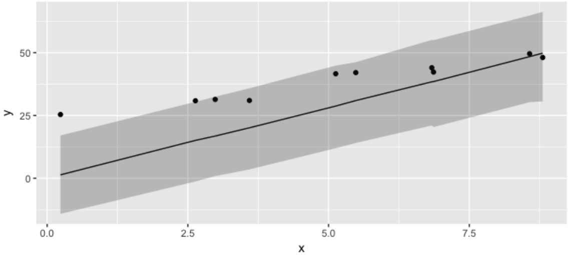
Trace plots


beta
sigma
log-posterior
7
6
5
4
15
10
-46
-48
-50
-52
-54
1000
1250
1500
1750
2000
chain
1
2
3
4

Density plots



Posterior predictive checks



So, how can we improve the model?

Likelihood:

$$Y \sim \mathrm{Normal}(x\beta, \sigma^2)$$

Prior:

$$\begin{aligned} \beta &\sim \mathrm{Normal}(2, 1) \\ \sigma^2 &\sim \mathrm{Normal}(1, 1) \end{aligned}$$

Further reading

- Philosophy and the practice of Bayesian statistics [Gelman and Shalizi, 2013]
- Build, Compute, Critique, Repeat: Data Analysis with Latent Variable Models [Blei, 2014]
- Visualization in Bayesian workflow [Gabry et al., 2018]
- Towards a principled Bayesian workflow [Betancourt, 2018]

References I

[Betancourt, 2018] Betancourt, M. (2018).
Towards a principled bayesian workflow.

[Blei, 2014] Blei, D. (2014).
Build, compute, critique, repeat: Data analysis with latent variable models.
Annual Review of Statistics and Its Application, 1.

[Gabry et al., 2018] Gabry, J., Simpson, D., Vehtari, A., Betancourt, M., and Gelman, A. (2018).
Visualization in bayesian workflow.
Royal Journal of Statistics, section A, 182:1 –14.

[Gelman and Shalizi, 2013] Gelman, A. and Shalizi, C. R. (2013).
Philosophy and the practice of bayesian analysis.
British Journal of Mathematical and Statistical Psychology, 66.

[Weber et al., 2018] Weber, S., Gelman, A., Lee, D., Betancourt, M., Vehtari, A., and Racine-Poon, A. (2018).
Bayesian aggregation of average data: an application in drug development.
The Annals of applied statistics, 12.