ODE parameter estimation in drug research: a deep dive into a Bayesian inference engine

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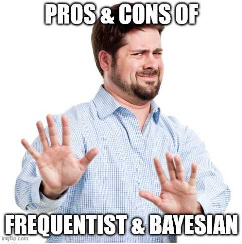
<2023-05-26 Fri>

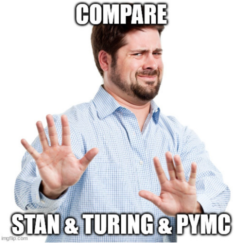
Outline

Thanks

- Stan development team (Bob Carpenter, Daniel Lee, Sebastian Weber, ...)
- Bill Gillespie (Metrum Research Group)

NOT to talk about





Inference engine/Probabilistic programing language(PPL)

- ~~Language design~~
- Inference algorithms
- ~~Model checking & diagnostics~~
- ~~Model assessment and comparison~~

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Pharmacokinetics (PK) data

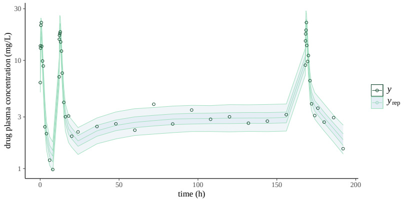
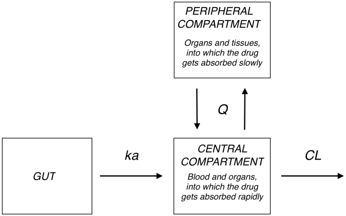


Figure: Subject plasma concentration history (q12hx14).



A Pharmacokinetics (PK) model

$$
\begin{aligned}
\frac{\mathrm{d}\hat{z}_{\mathrm{gut}}}{\mathrm{d}t} &= -k_a \hat{z}_{\mathrm{gut}} \\
\frac{\mathrm{d}\hat{z}_{\mathrm{cent}}}{\mathrm{d}t} &= k_a \hat{z}_{\mathrm{gut}} - \left(\frac{\mathsf{CL}}{V_{\mathsf{cent}}} + \frac{Q}{V_{\mathsf{cent}}} \right) \hat{z}_{\mathrm{cent}} + \frac{Q}{V_{\mathsf{peri}}} \hat{z}_{\mathrm{peri}} \\
\frac{\mathrm{d}\hat{z}_{\mathrm{peri}}}{\mathrm{d}t} &= \frac{Q}{V_{\mathsf{cent}}} \hat{z}_{\mathrm{cent}} - \frac{Q}{V_{\mathsf{peri}}} \hat{z}_{\mathrm{peri}},
\end{aligned}
$$

With $\hat{y} = \frac{\hat{z}}{V_{\mathsf{cent}}}$:

$$
\begin{aligned}
\theta &\equiv \{k_a, \mathsf{CL}, Q, V_{\mathsf{cent}}, V_{\mathsf{peri}}, \ldots\}, \\
\hat{y}(t) &= \hat{y}(t; \theta), \\
y(t) &\sim \mathsf{Normal}(\hat{y}(t; \theta), \sigma).
\end{aligned}
$$

A statistical model

- play mix & match with two models
- Likelihood $p(y|\theta)$

$$
\begin{aligned}
p(y|\theta) &= \frac{1}{\sqrt{2\pi\sigma^2}} \exp -\frac{(\hat{y}-y)^2}{2\sigma^2}, \\
\log p(y|\theta) &= -\frac{(\hat{y}-y)^2}{2\sigma^2} - \log 2\pi\sigma^2
\end{aligned}
$$

- Usually σ is also unknow so likelihood $p(y|\theta, \sigma)$

Estimate θ

- Maximum likelihood estimation $\theta_{\text{argmax}}(p(y|\theta))$

Estimate θ

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- Posterior distribution

$$p(\theta|y) = \frac{p(y|\theta)p(\theta)}{\bigcirc}$$
$$\log p(\theta|y) = C + \log p(y|\theta) + \log p(\theta)$$

Estimate θ

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\end{aligned}
$$

- Connection to regularization: $\log p(y|\theta) = -\frac{(\hat{y}-y)^2}{2\sigma^2}$

$$
\begin{aligned}
\min \|\hat{y}(\theta) - y\|^2 + \lambda\|\theta\|^2, \\
\log p(\theta|y) = -\frac{(\hat{y} - y)^2}{2\sigma^2} + \log p(\theta)
\end{aligned}
$$

"Tikhonov regularization", "ridge regression", "shrinkage"

Prior & likelihood

$$\log p(\theta|y) = C + \log p(y|\theta) + \log p(\theta)$$

Sample the posterior

target (distribution) $= \log p(\theta|y) = \log p(y|\theta) + \log p(\theta)$

- Posterior from an oracle: $\theta \to \log p(\theta|y)$

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Sample the posterior

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$$\lim_{n\to} \frac{1}{n} \sum f(\theta^{(i)}) = \mathbb{E}(f)$$

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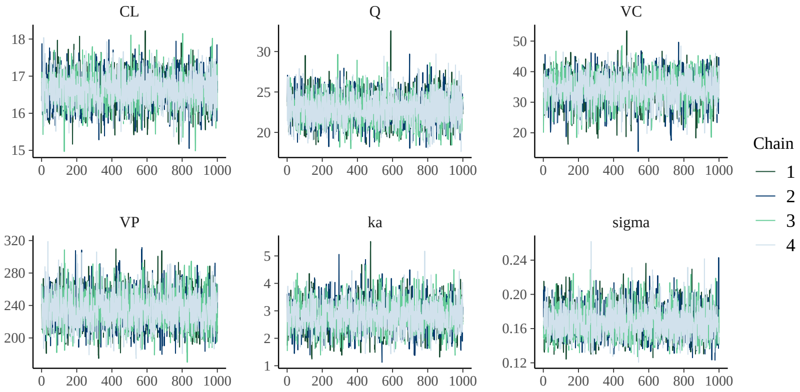
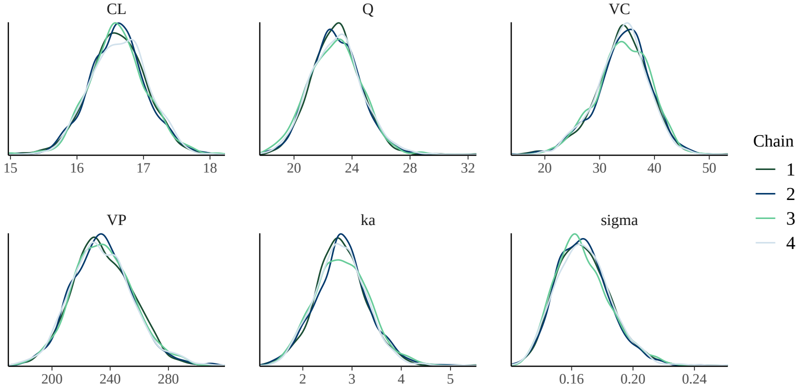
$$\lim_{n\to} \frac{1}{n} \sum f(\theta^{(i)}) = \mathbb{E}(f)$$

- MCMC: $p(\theta^{(i)}|y, \theta^{(i-1)}, \theta^{(i-2)}, \ldots, \theta^{(1)}) = p(\theta^{(i)}|y, \theta^{(i-1)})$

Posterior samples: trace



Posterior samples: density



The Metropolis-Hastings algorithm

Proposal-rejection from $\theta^{(i)}$ to $\theta^{(i+1)}$.

1. Propose $\theta^{(i+1)}$ according to transition density $q(\theta^{(i+1)}, \theta^{(i)})$.
2. Accept $\theta^{(i+1)}$ with probability

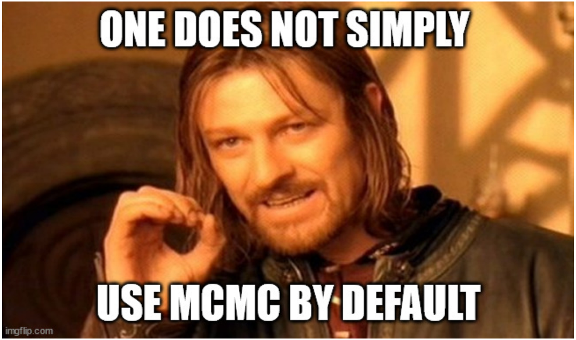
$$\alpha(\theta^{(i)}, \theta^{(i+1)}) = \min\left[1, \frac{p(\theta^{(i+1)}|y)q(\theta^{(i)}, \theta^{(i+1)})}{p(\theta^{(i)}|y)q(\theta^{(i+1)}, \theta^{(i)})}\right] \tag{1}$$

otherwise reject.

- Chain generated by M-H has detailed balance with $p(\theta|y)$ as its stationary distribution.
- Convergence in TVD with proper proposal that garantees irreducibility and aperiodicity.

Why MCMC?

Monte Carlo is an extremely bad method; it should be used only when all alternative methods are worse. – Sokal, A. D. (1989). "Monte carlo methods in statistical mechanics: foundations and new algorithms."



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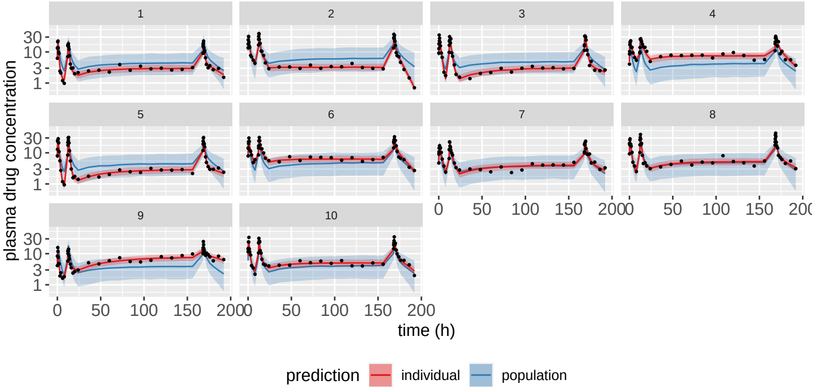
The problem



1
2
3
4
5
6
7
8
9
10
plasma drug concentration
30
10
3
1
0
50
100
150
200
time (h)
prediction
individual
population

Hierarchical model

- Posterior(likelihood) equation is an oracle

$$
\begin{aligned}
\theta_0 &\sim \mathrm{Prior}(\cdot), \\
\theta_i &\sim \mathrm{MultiNormal}(\theta_0, \Sigma), \\
y_i &\sim \mathrm{Normal}(\hat{y}_i(\theta_i), \sigma), \\
\theta &= \{\theta_0, \theta_1, \ldots, \theta_n, \Sigma\}
\end{aligned}
$$

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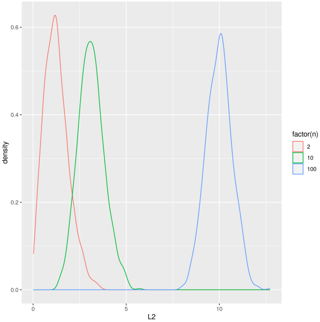
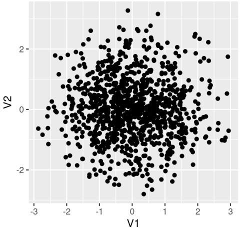
- Posterior(likelihood) equation is an oracle
- Curse of dimensionality
  - Computational tractability
  - Concentration of measure (e.g. high dimensional gaussian distribution is like uniform distribution)
- Geometry of posterior

Challenges: high dimensional gaussian distribution

$$p(|\|y_d\|_2 - \sqrt{d}| \geq t) \leq 2\exp\left(-ct^2\right), \forall t \geq 0.$$





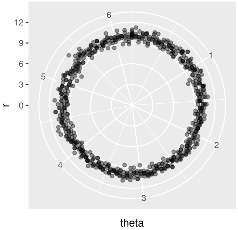


Figure: $\|y_d\|_2, y_d \sim \text{Normal}(0, \mathbb{I}_d)$

Average is not representative.
Random Walk sampler is not efficient.

Challenges: Geometry of posterior

$$
\begin{aligned}
\theta_0 &= 0, \\
\kappa &\sim \mathrm{Normal}(0, 3), \\
\theta_i(k) &\sim \mathrm{Normal}(0, \exp(\kappa/2)), \\
k &= 1, 2, \ldots
\end{aligned}
$$

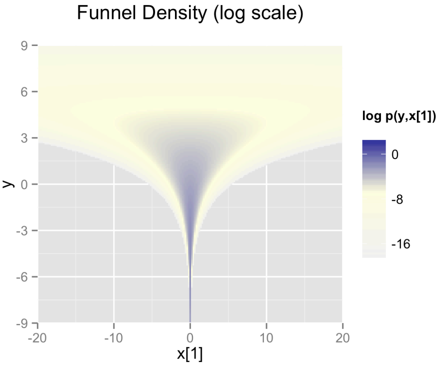


Figure: Neal's funnel

Mode is not representative.
Optimizer is not efficient.

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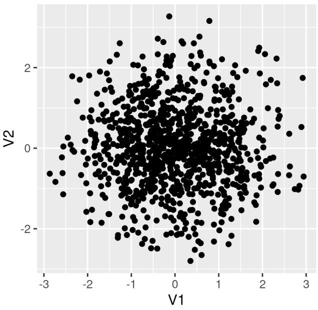
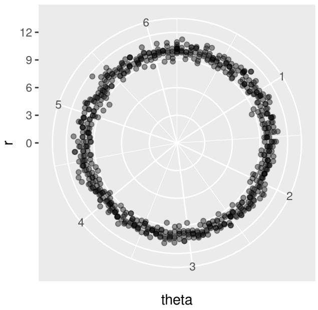
Hamiltonian Monte Carlo

$$H(\theta, r) = -\log p(r, \theta | y) = T(r) + V(\theta) = -\log r - \log p(\theta|y),$$

$$\frac{d\theta}{dt} = \frac{\partial H}{\partial r}, \qquad \frac{dr}{dt} = -\frac{\partial H}{\partial \theta},$$





Hamiltonian Monte Carlo

$$H(\theta, r) = T(r) + V(\theta) = \frac{1}{2} r^T M^{-1} r - \log p(\theta|y),$$
$$\frac{d\theta}{dt} = \frac{\partial H}{\partial r}, \qquad \frac{dr}{dt} = -\frac{\partial H}{\partial \theta},$$

Apply M-H to $p(r, \theta) \triangleq \frac{\exp\left[-H(\theta,r)\right]}{\bigcirc}$

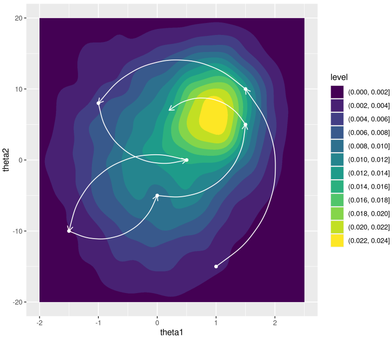
$$\alpha((r^{(i)}, \theta^{(i)}), (r^{(i+1)}, \theta^{(i+1)})) = \min\left[1, \frac{p(r^{(i+1)}, \theta^{(i+1)}|y)q()}{p(r^{(i)}, \theta^{(i)}|y)q()}\right]$$
$$= \min\left[1, \frac{p(r^{(i+1)}, \theta^{(i+1)}|y)}{p(r^{(i)}, \theta^{(i)}|y)}\right]$$

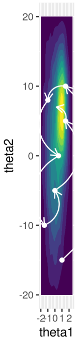
$$\alpha(\cdot, \cdot) = \min\left[1, \exp\left(H(\theta^{(i)}, r^{(i)}) - H(\theta^{(i+1)}, r^{(i+1)})\right)\right]$$

A principled sampler for $p(\theta|y)$

$$p(\theta^{(i)} \to \theta^{(i+1)}) = \min\left[1, \exp\left(H(\theta^{(i)}, r^{(i)}) - H(\theta^{(i+1)}, r^{(i+1)})\right)\right]$$

$$r \sim \text{Normal}(0, M^{-1}) \Longrightarrow (r^{(i)}, \theta^{(i)}) \to (r^{(i+1)}, \theta^{(i+1)})$$





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A tale of two ODEs

$\theta^{(\mathrm{i})} = \{\theta^{(\mathrm{i})}{}_{\mathrm{j}}\}$, j=1,2,...,n: $(r,\theta)(\tau^{(i)}) \to (r,\theta)(\tau^{(i+1)})$

$$\begin{cases} \theta_j^{(i)} \to \hat{y}_j(t;\theta_j^{(i)}), \\ y_{jk} \sim \mathrm{Normal}(\hat{y}_{jk}(\theta_j),\sigma), \quad p(y_{jk}|\theta_j) = \frac{1}{\sigma\sqrt{2\pi}}\exp\left[-\frac{(\hat{y}_{jk}(\theta_j)-y_{jk})^2}{2\sigma^2}\right] \end{cases}$$

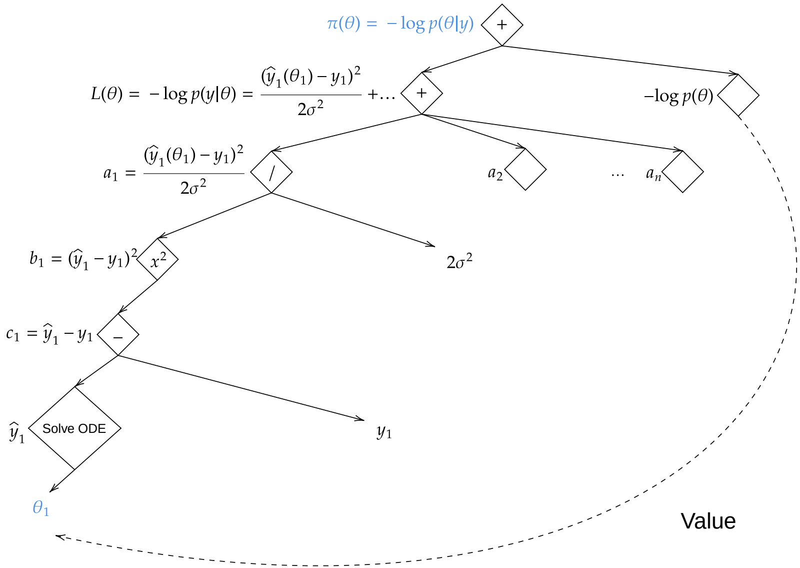
Nested ODE solvers:

$$r^{(i+1/2)} = r^{(i)} - \frac{h}{2}\nabla_\theta \log p(\theta^{(i)}|y), \text{ a step in leapfrog}$$

$$\nabla_\theta \log p(\theta^{(i)}|y) = \nabla_\theta \log p(\theta^{(i)}) + \nabla_\theta \log p(y|\theta^{(i)}),$$

$$\nabla_\theta \log p(y|\theta^{(i)}) = -(\cdots)\sum_{j,k}\nabla_\theta \frac{\hat{y}_{jk}(\theta_j^{(i)}) - y_{jk}}{\sigma^{(i)}} + \ldots$$

Automatic differentiation (1 obsv/subject: k=1)



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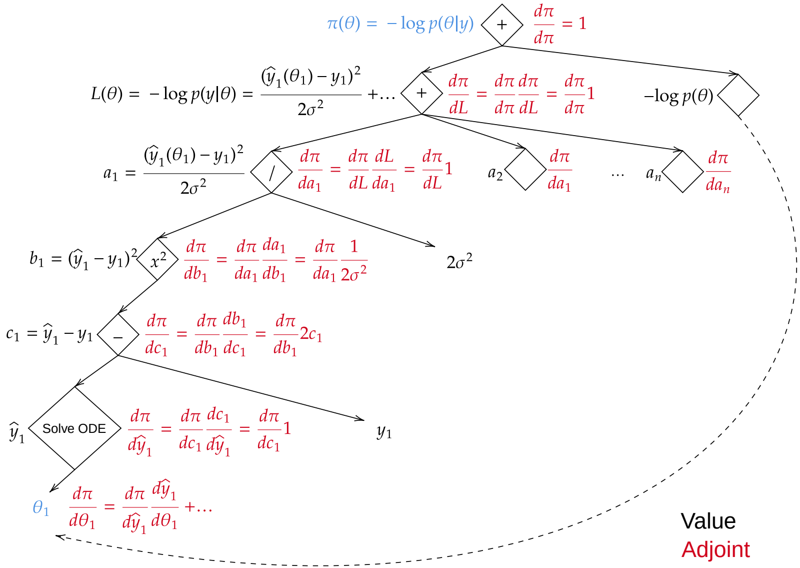

Automatic differentiation

function	*arguments*	*return*
abs	(real x)	real
acos	(real x)	real
acosh	(real x)	real
asin	(real x)	real
asinh	(real x)	real
atan2	(real x, real y)	real
atan	(real x)	real
atanh	(real x)	real
cos	(real x)	real
cosh	(real x)	real
cbrt	(real x)	real
ceil	(real x)	real
erf	(real x)	real
erfc	(real x)	real
exp2	(real x)	real
exp	(real x)	real
fdim	(real x, real y)	real
floor	(real x)	real
fma	(real x, real y, real z)	real
fmax	(real x, real y)	real
fmin	(real x, real y)	real
fmod	(real x, real y)	real
hypot	(real x, real y)	real
log	(real x)	real
log10	(real x)	real
log1p	(real x)	real
log2	(real x)	real
pow	(real x, real y)	real
round	(real x)	real
sin	(real x)	real
sinh	(real x)	real
sqrt	(real x)	real
tan	(real x)	real
tanh	(real x)	real
trunc	(real x)	real

Sensitivity solution

$$\frac{d\hat{y}}{dt} = f(t, \hat{y}; \theta) \rightarrow \nabla_\theta \frac{d\hat{y}}{dt} = \nabla_\theta f(t, \hat{y}; \theta)$$
$$\frac{d\nabla_\theta \hat{y}}{dt} = f_\theta + f_{\hat{y}} \nabla_\theta \hat{y}$$

Use the autodiff calculate f_θ and $f_{\hat{y}}$.

Thank you