

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

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Outline

The problem

You're Gonna Need a Bigger Boat

Up In the Air

Small moves, Ellie. Small moves

NOT to talk about

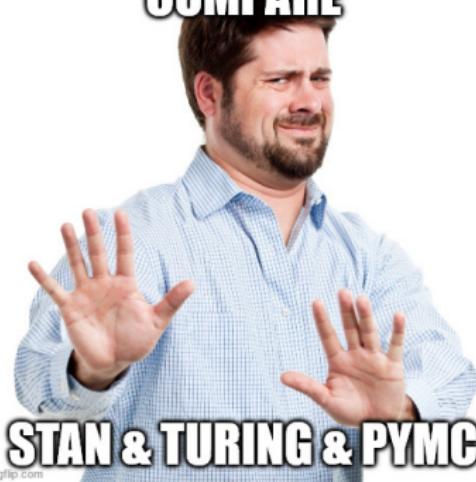
PROS & CONS OF



FREQUENTIST & BAYESIAN

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STAN & TURING & PYMC

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Pharmacokinetics (PK) data

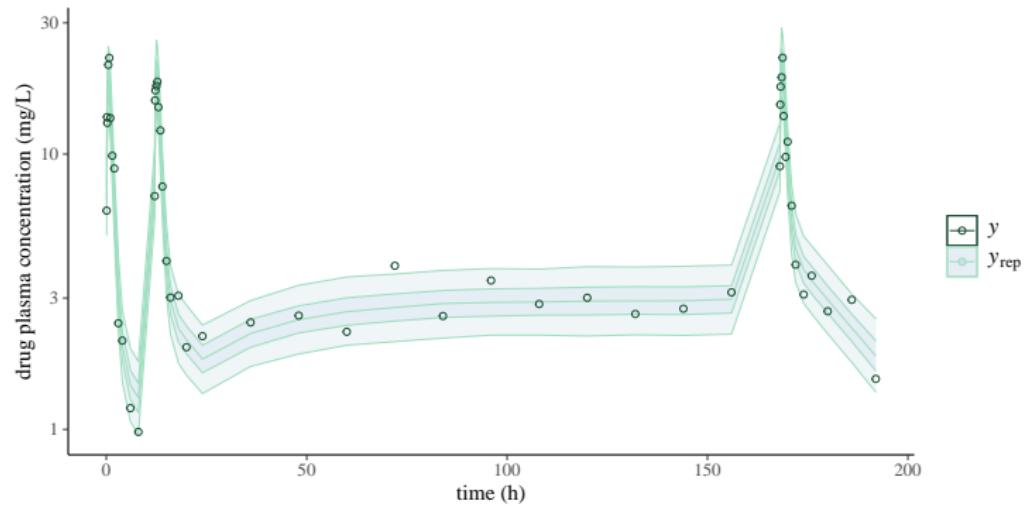


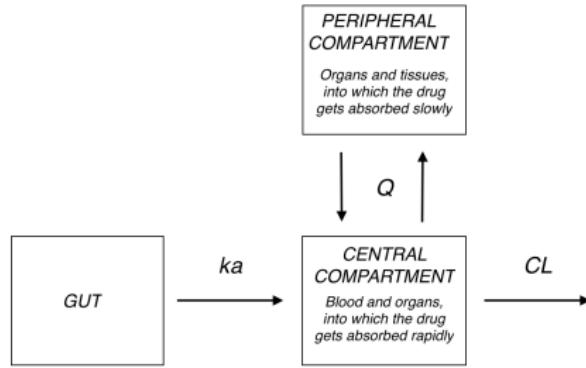
Figure: Subject plasma concentration history (q12hx14).

A Pharmacokinetics (PK) model

$$\frac{d\hat{y}_{\text{gut}}}{dt} = -k_a \hat{y}_{\text{gut}}$$

$$\frac{d\hat{y}_{\text{cent}}}{dt} = k_a \hat{y}_{\text{gut}} - (k_{\text{CL}} + k_{Q,\text{cent}}) \hat{y}_{\text{cent}} + k_{Q,\text{peri}} \hat{y}_{\text{peri}}$$

$$\frac{d\hat{y}_{\text{peri}}}{dt} = k_{Q,\text{cent}} \hat{y}_{\text{cent}} - k_{Q,\text{peri}} \hat{y}_{\text{peri}}$$



A statistical model

$$\begin{aligned}\theta &\equiv \{k_a, k_{\text{CL}}, k_{Q,\cdot}\}, \\ \hat{y}(t) &= \hat{y}(t; \theta), \\ y(t) &\sim \text{Normal}(\hat{y}(t; \theta), \sigma).\end{aligned}$$

- ▶ play mix & match with two models
- ▶ Likelihood $p(y|\theta)$.
- ▶ Usually σ is also unknown so likelihood $p(y|\theta, \sigma)$

Estimate θ

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

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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

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

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

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

$$\min \|\hat{y}(\theta) - y\| + \lambda \|\theta\|,$$

$$\log p(\theta|y) = -\frac{(\hat{y} - y)^2}{2\sigma^2} + \log p(\theta)$$

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

Prior & likelihood

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



Sample the posterior

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

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- ▶ Sampling procedure for a distribution: $\theta^{(1)}, \theta^{(2)}, \dots$

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

Sample the posterior

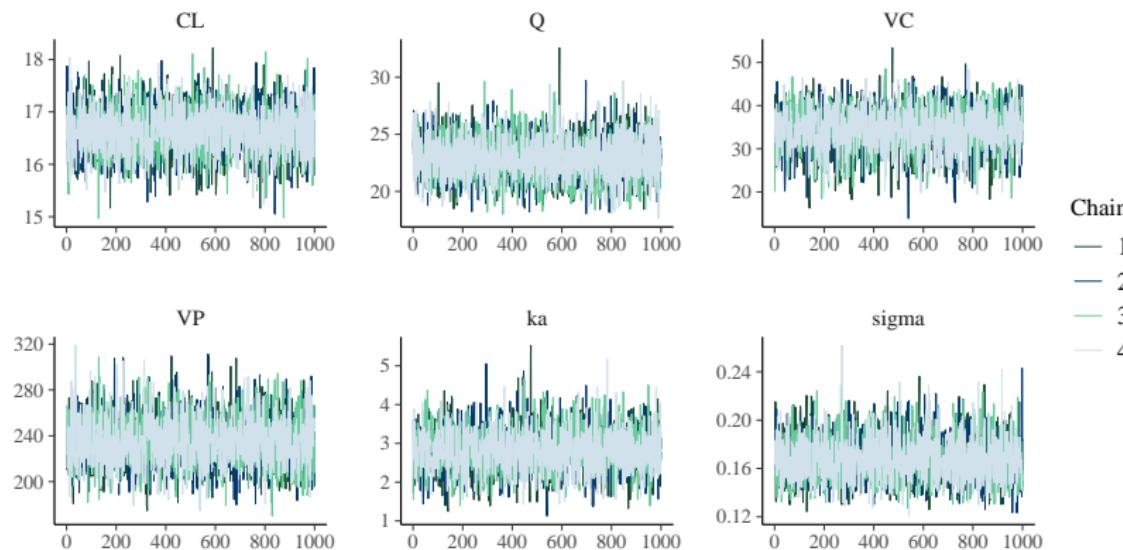
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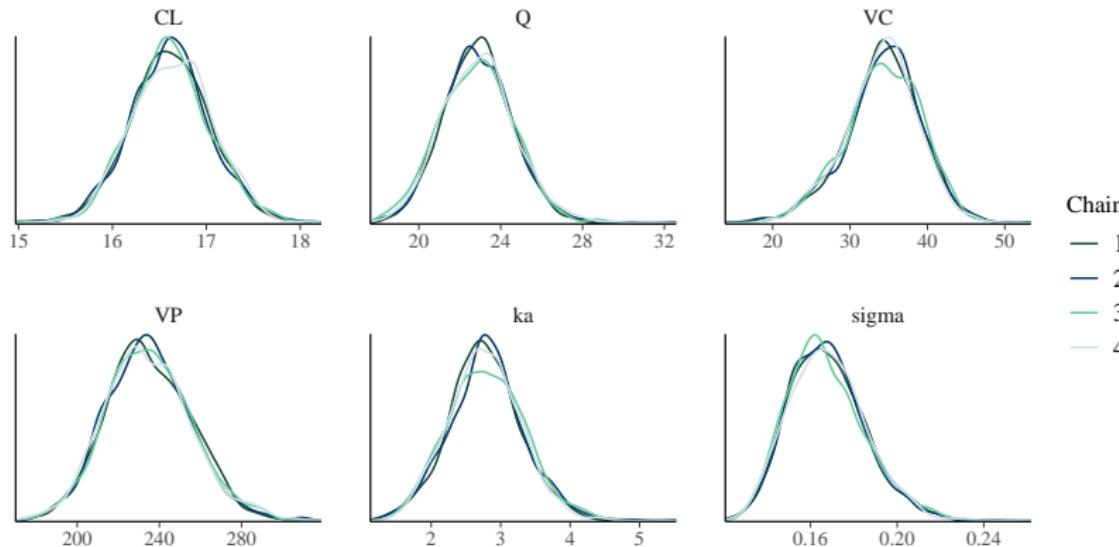
$$\lim_{n \rightarrow \infty} \frac{1}{n} \sum f(\theta^{(i)}) = \mathbb{E}(f)$$

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

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

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

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 guarantees 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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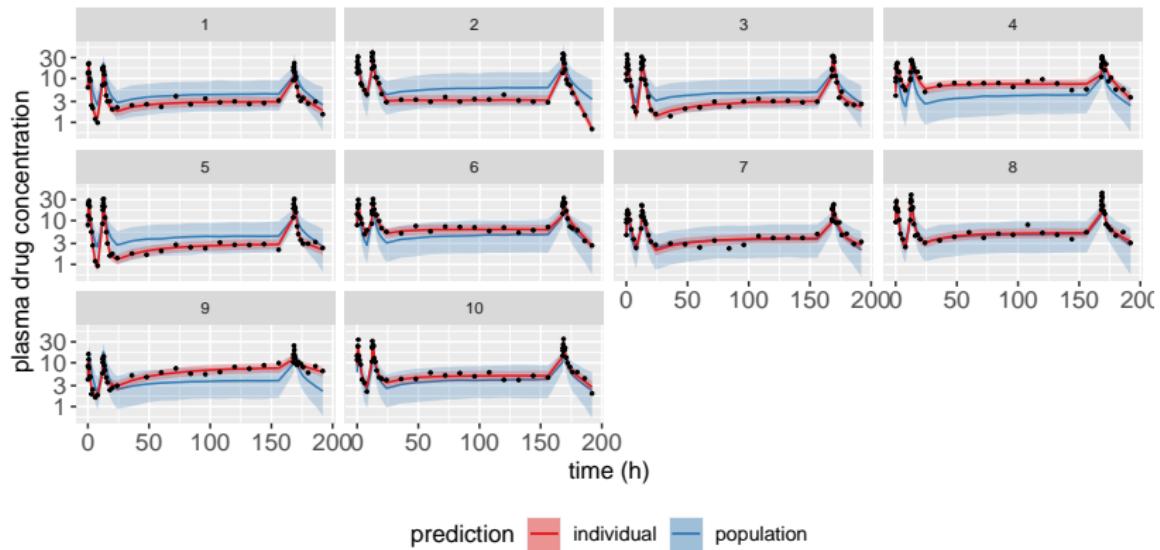
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The problem



Hierarchical model

- ▶ Posterior(likelihood) equation is an oracle

$$\theta_0 \sim \text{Prior}(\cdot),$$

$$\theta_i \sim \text{MultiNormal}(\theta_0, \Sigma),$$

$$y_i \sim \text{Normal}(\hat{y}_i(\theta_i), \sigma),$$

$$\theta = \{\theta_0, \theta_1, \dots, \theta_n, \Sigma\}$$

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 - ▶ Computational tractability

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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

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

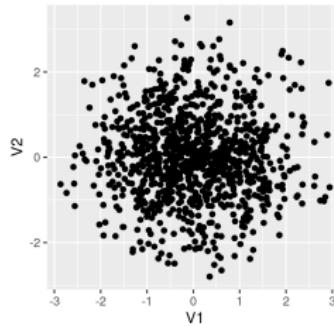
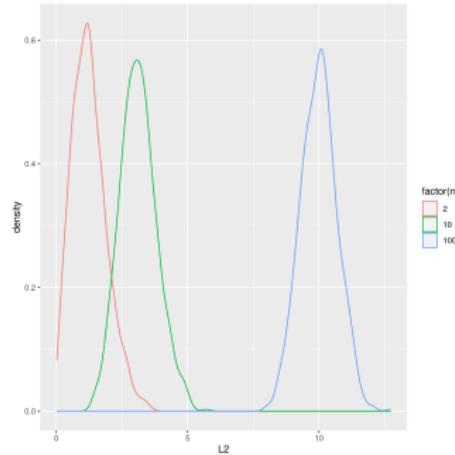
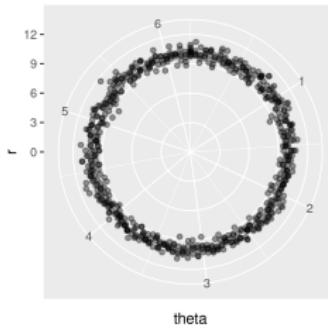


Figure: $\|y_d\|_2, y_d \sim \text{Normal}(0, \mathbb{I}_d)$

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



Challenges: Geometry of posterior

$\theta_0 = 0,$
 $\kappa \sim \text{Normal}(0, 3),$
 $\theta_i(k) \sim \text{Normal}(0, \exp(\kappa/2)),$
 $k = 1, 2, \dots$

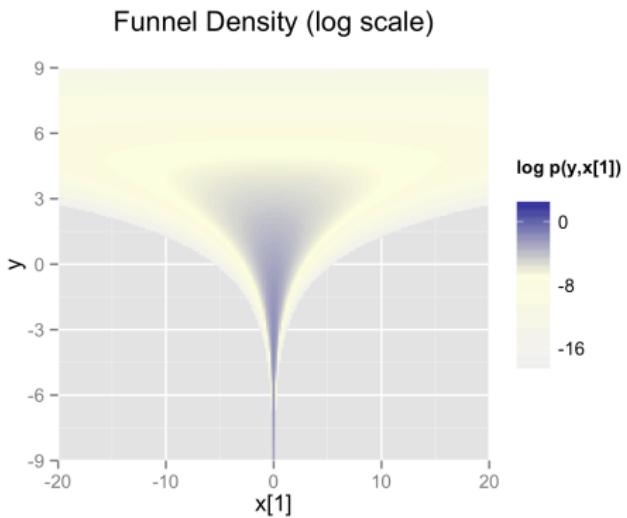


Figure: Neal's funnel

Mode is not representative.
Optimizer is not efficient.

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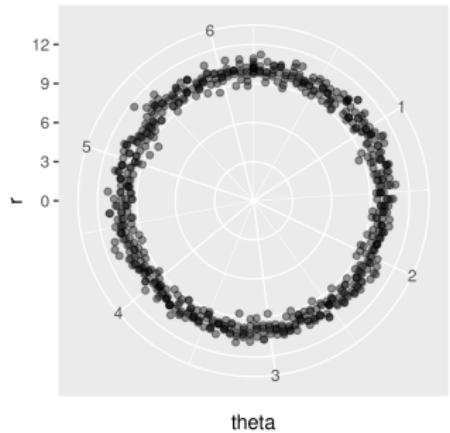
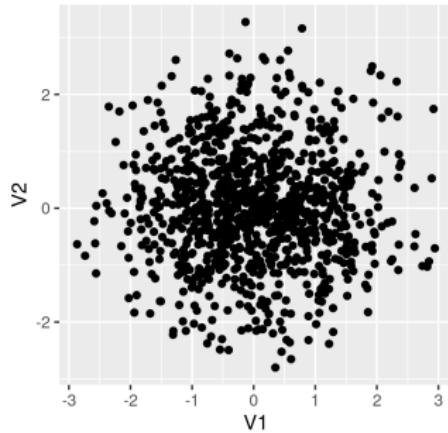
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Hamiltonian Monte Carlo

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

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



Hamiltonian Monte Carlo

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

Apply M-H to $p(r, \theta)$

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

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

Hamiltonian Monte Carlo

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

Proposal $(r^{(i+1)}, \theta^{(i+1)})$:

$$\begin{aligned} r &\sim \text{Normal}(0, M), \\ (r^{(i)}, \theta^{(i)}) &\rightarrow (r^{(i+1)}, \theta^{(i+1)}) \end{aligned}$$

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

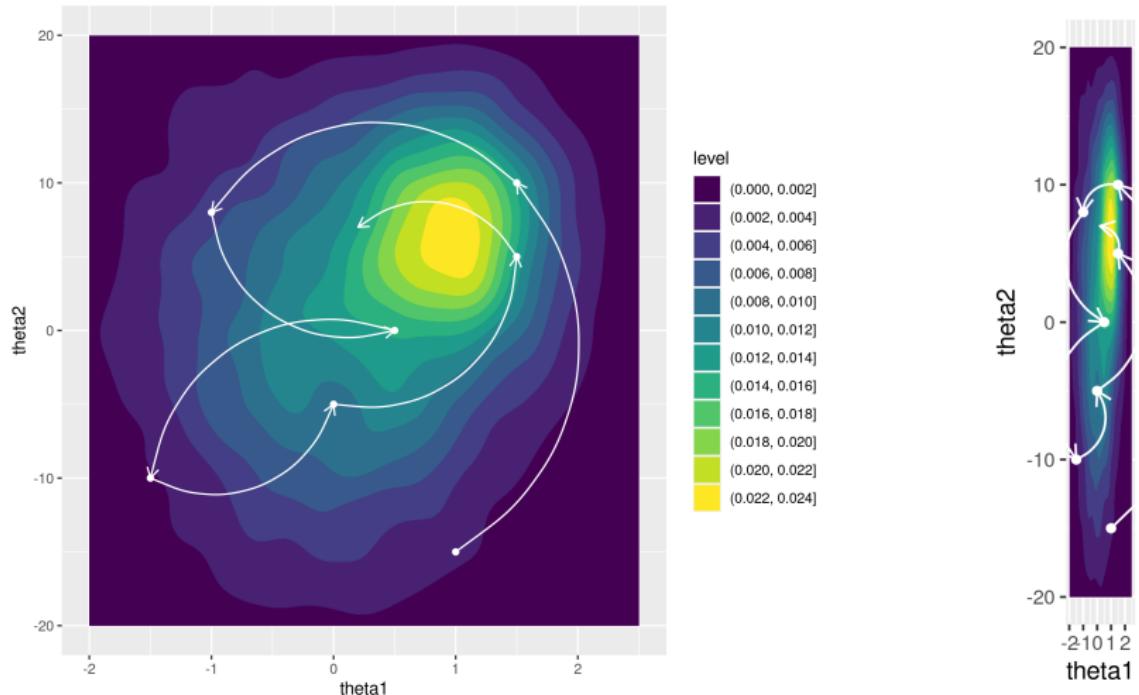


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A tale of two ODEs

$$\theta^{(i)} = \{\theta^{(i)}_j\}, j=1,2,\dots,n: (r, \theta)(\tau^{(i)}) \rightarrow (r, \theta)(\tau^{(i+1)})$$

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

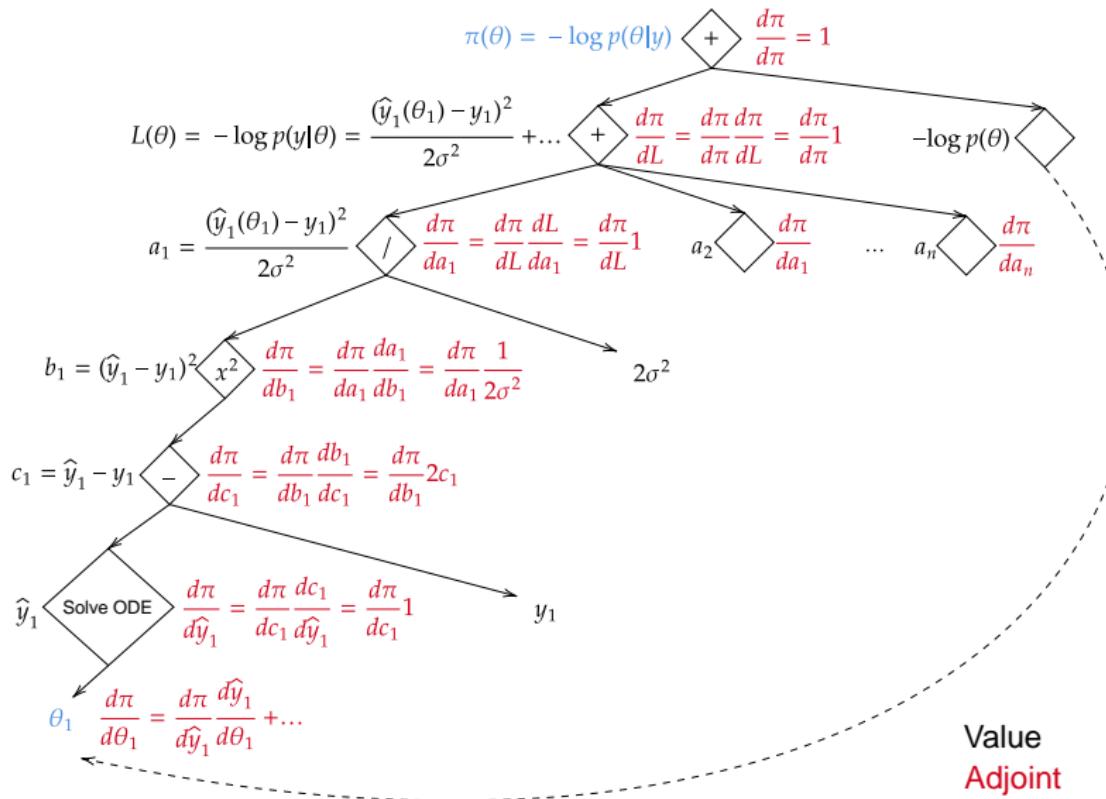
Nested ODE solvers:

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

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

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

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



Automatic differentiation

<i>function</i>	<i>arguments</i>	<i>return</i>
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



EKP GETS ADJOINT



ERF GETS ADJOINT



SINH GETS ADJOINT



EVERYONE GETS AN ADJOINT

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 $f_{\hat{y}}$.

Thanks



Statistics & Pharmacometrics



SPECIAL INTEREST GROUP



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