Bayesian Workflow for Hierarchical and ODE-based Models using Stan

September 2023

Summer School on Advanced Bayesian Methods

mc-stan.org

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Flatiron Institute

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KU Leuven

Outline:

- Review of Bayesian analysis
- Markov chain Monte Carlo
- Basics of Stan
- ODE-based models
- Leave-one-out cross validation

- Hamiltonian Monte Carlo
- Tuning ODEs in a Bayesian context
- Hierarchical models

- Torsten: an extension of Stan for pharmacometrics
- Population models

An `R` notebook to do the exercises can be found at:

https://github.com/charlesm93/stanTutorial

You can run the `R` code on your local machine or on the `Colab` cloud server.

I

Review of Bayesian Analysis

What is a Bayesian model?

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For a fixed θ, defines a data generating process.

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$p(\theta)$ is the *prior*:

quantitative assumptions and understanding about θ
information from previous analysis
regularization tool

RESEARCH ARTICLE

Estimation of SARS-CoV-2 mortality during the early stages of an epidemic: A modeling study in Hubei, China, and six regions in Europe

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Epidemiological model of the disease dynamic

Measurement model: test results, hospital deaths.

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Epidemiological model of the disease dynamic
Measurement model: test results, hospital deaths.

Prior:

Constraints on interpretable parameters
Meta-analysis for asymptomatic rate

Bayesian inference

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The variance in $p(f(\theta) \mid y)$ accounts for both the modeled noise and the uncertainty in our estimation of θ.

Example: normal-normal model

$$\begin{aligned} p(\theta) &= \text{normal}(\mu, \tau) \\ p(y_n \mid \theta) &= \text{normal}(\theta, \sigma) \end{aligned}$$

Suppose we have N i.i.d observations $y_1, y_2, \cdots, y_N$.

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In practice, the posterior is <u>not</u> tractable.

Need to estimate summary quantities: expectation values, variance, quantiles, $\cdots$

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- Start with a prior $p(\theta)$.
- Compute the posterior $p(\theta \mid \mathbf{y}_1, \mathbf{y}_2)$.

or

(2)

- Start with a prior $p(\theta)$.
- Compute the posterior $p(\theta \mid \mathbf{y}_1)$
- Use $p(\theta \mid \mathbf{y}_1)$ as a new prior.
- Compute the posterior $\tilde{p}(\theta \mid \mathbf{y}_2) \propto p(\mathbf{y}_2 \mid \theta) p(\theta \mid \mathbf{y}_1)$.

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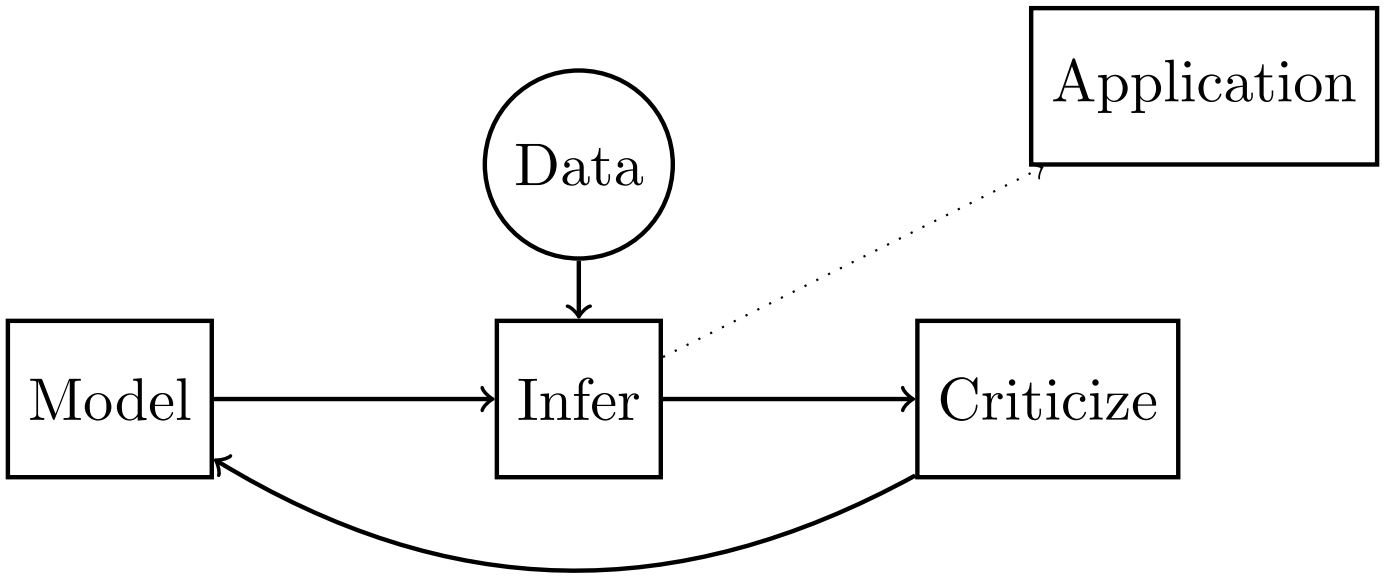
Bayesian workflow



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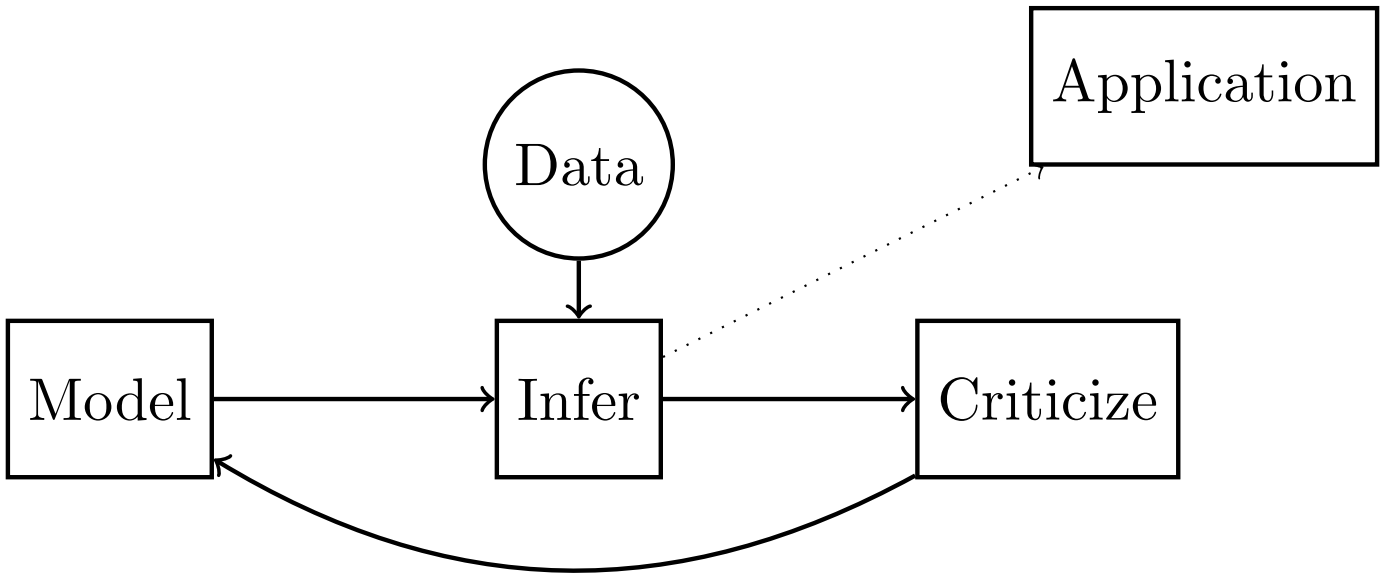

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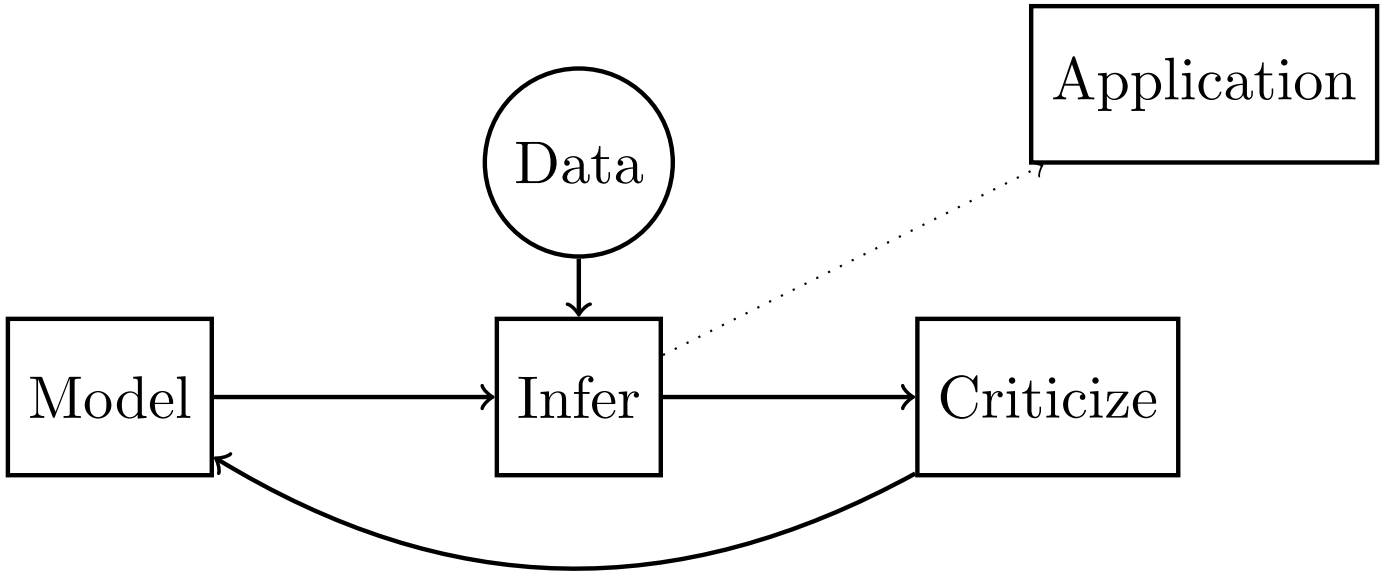
Bayesian workflow



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$p(f(\theta) \mid y)$

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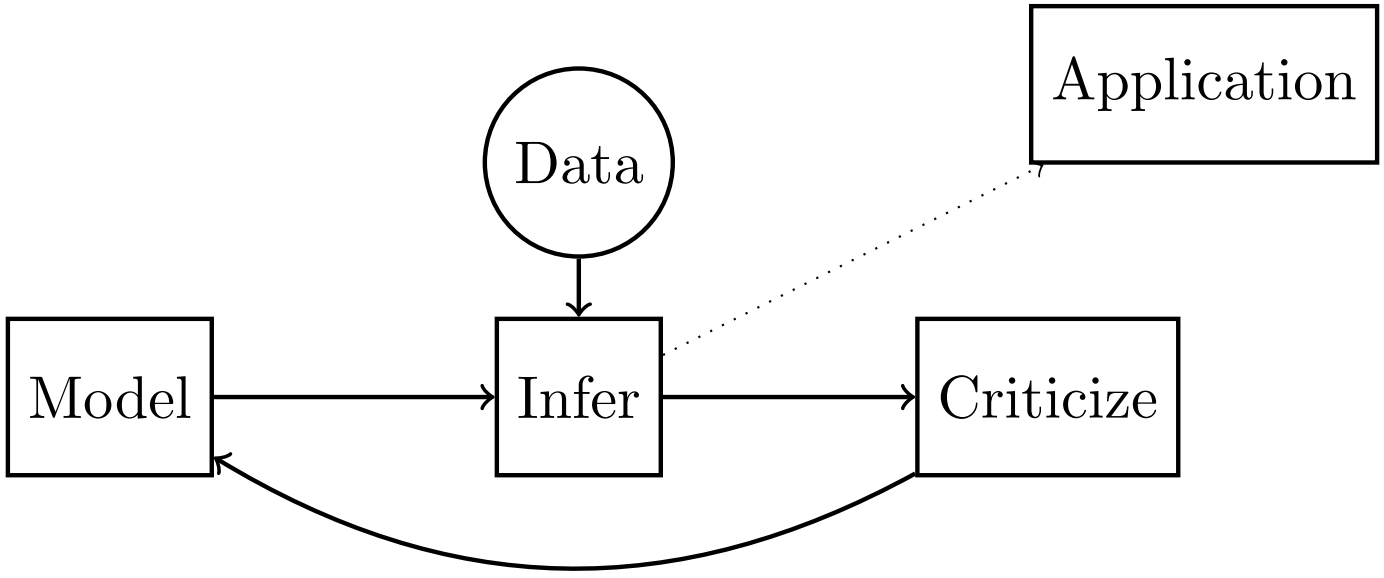

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$p(y, \theta)$

Infer

$p(f(\theta) \mid y)$

Criticize

Simulation,
prediction,
cross-validation,
etc.

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Grinsztajn et al. Bayesian workflow for disease transmission model in Stan, *Statistics in Medicine* (2021)

Gelman et al. Bayesian workflow, *arXiv:2011.01808* (2020)

II

Markov chain Monte Carlo

Characterizing the posterior distribution

Quantities of interest can often be expressed as integrals with respect to a probability measure

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Can get a sample estimator for mean, variance and quantiles.

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If $\theta^{(1)}, \theta^{(2)}, \cdots, \theta^{(N)}$ are i.i.d,

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We also have a Central Limit Theorem, i.e. for large N

$$\widehat{\mathbb{E}}[f(\theta)] \overset{\text{approx}}{\sim} \text{normal}\left(\mathbb{E}f(\theta), \sqrt{\frac{\text{Var}[f(\theta)]}{N}}\right).$$

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- Start with an initial draw $\theta^{(0)} \sim p_0(\theta)$.
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- The first samples suffer from a large bias.
- Discard these samples during a burn-in or *warmup* phase.

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3. Return the chain $(\theta^{(1)}, \theta^{(2)}, ..., \theta^{(N)})$.

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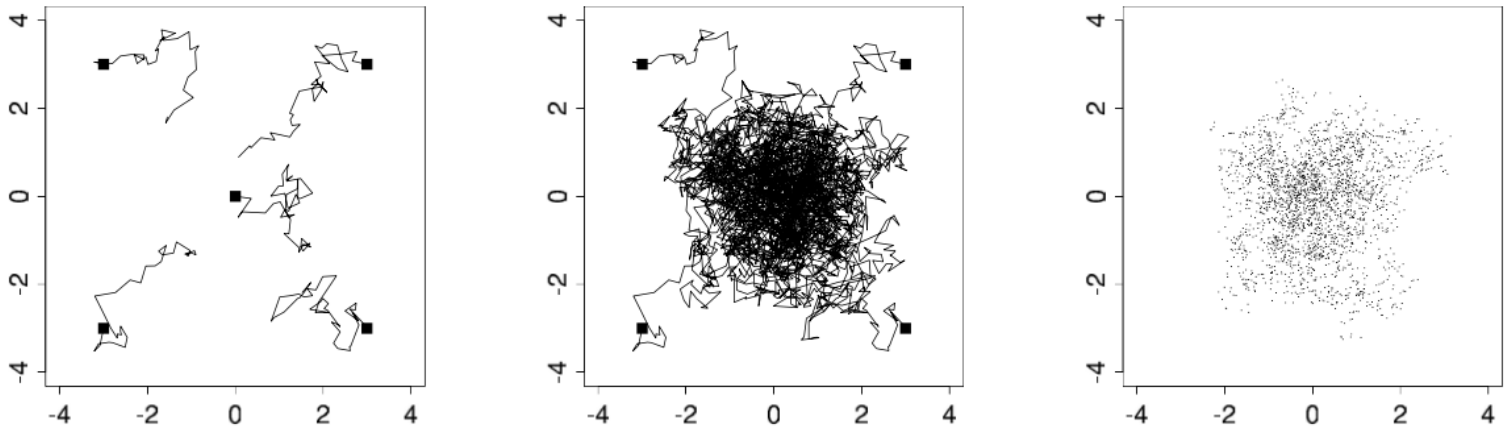

Figure from [Gelman et al., 2013].

Example: Metropolis algorithm

Benefits:

- Only requires evaluating $p(\theta, y) = p(\theta)p(y \mid \theta)$.
- Asymptotically, the algorithm samples from $p(\theta \mid y)$.

Drawbacks:

- In the finite regime, the samples are **biased**.
- The samples are not independent; there are correlated, which **increases the variance** of our Monte Carlo estimators.

Example: Continuous diffusion process

In the limit where we take infinitesimally small steps, many MCMC algorithms can be approximated by a random diffusion process [Gelman et al., 1997, Roberts and Rosenthal, 1998].

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Then after time T,

$$\theta^{(T)} \sim \text{normal}\left[(\mu_0 - \mu)e^{-T} + \mu, \quad \left(\sigma_0^2 - \sigma^2\right) e^{-2T} + \sigma^2\right].$$

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For T large enough, the bias becomes negligible.

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- Under certain conditions, Monte Carlo estimators observe a Central Limit Theorem, meaning that for large n,

$$\frac{1}{N}\sum_i f(\theta^{(n)}) \overset{\text{approx}}{\sim} \text{Normal}\left(\mathbb{E}[f(\theta)], \frac{\text{Var}\, f(\theta)}{N_{\text{eff}}}\right)$$

  where N_{eff} is the **effective sample size (ESS)**.

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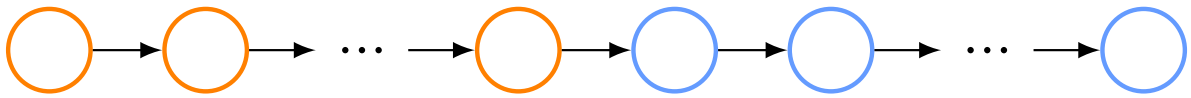
- The ESS by a process with autocorrelation ρ_t is

$$N_{\text{eff}} = \frac{N}{1 + 2\sum_{t=1}^{\infty} \rho_t}.$$

  Here ρ_t is the chain's autocorrelation for two variables separated by t iterations.

Handling the error of MCMC



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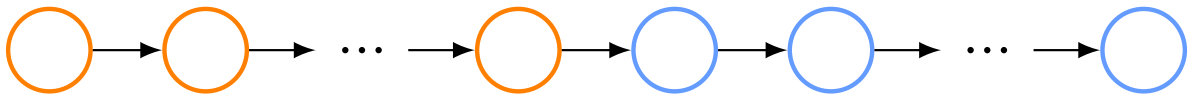

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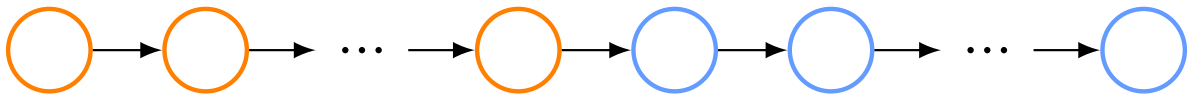

In practice, MCMC proceeds in two phases:

Warmup phase: We run the process for several steps for the bias to become negligible but don't use any of those samples in our Monte Carlo estimator.

Sampling phase: Collect enough samples to have a large ESS and reduce the variance of the Monte Carlo estimator.

Question: Which transition kernel, Γ, should we choose?
Many choices!

Metropolis, Metropolis-Hastings, Gibbs, **Hamiltonian Monte Carlo**, Metropolis-adjusted Langevin, ...

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- Difficult to tune!

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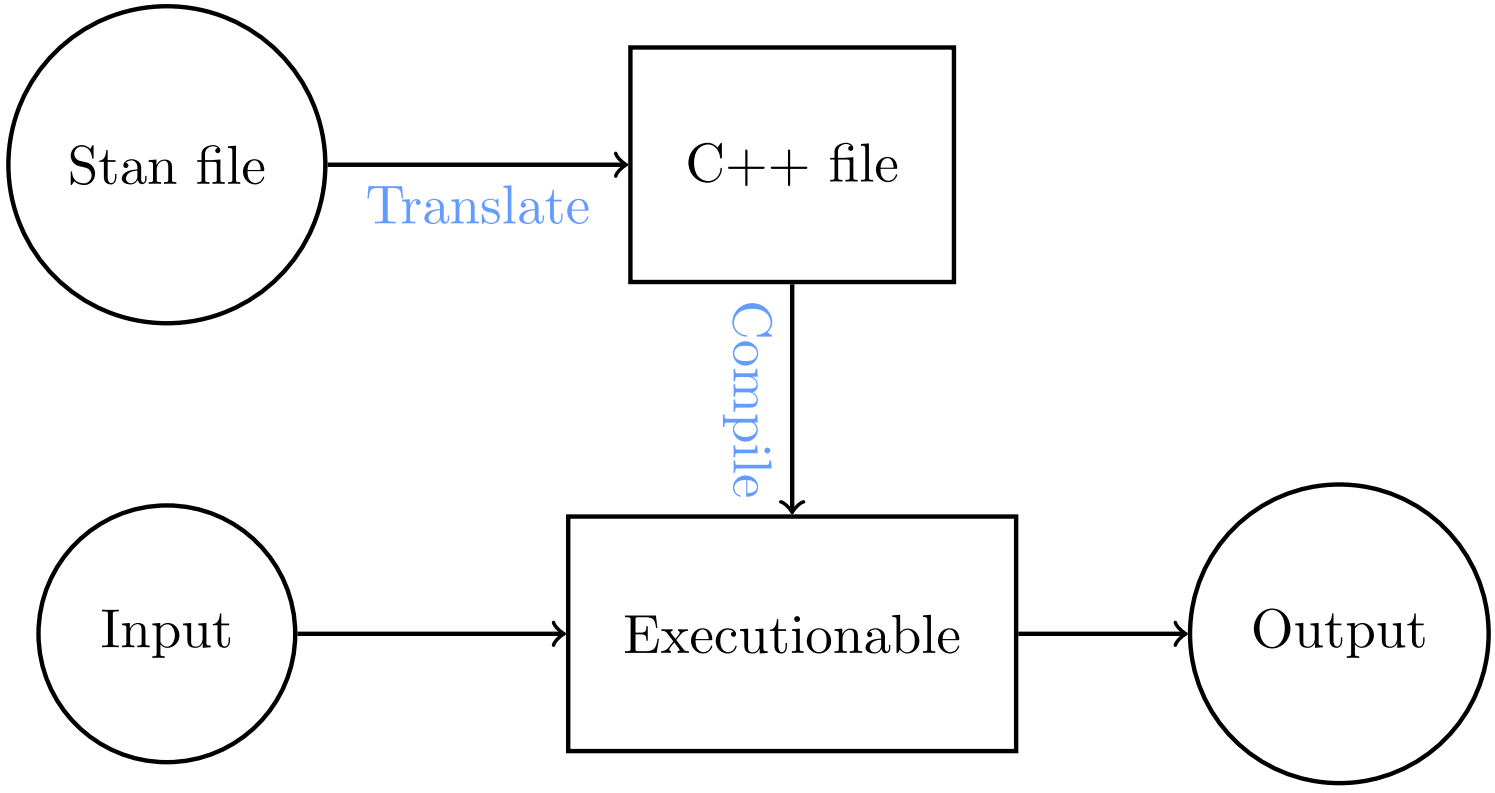
- Difficult to tune!
- `Stan` provides automated calculations of gradients and a self-tuning HMC algorithm.

III
Basics of Stan

- `Stan` is an expressive language for joint distributions.
- It "automatically" computes derivatives.
- It "automatically" performs inference algorithms.

How Stan works



How Stan works

- The Stan file specifies the joint distribution

$$p(\theta, y) = p(y|\theta)p(\theta) \propto p(\theta \mid y)$$

- The input includes:
  - the data, y
  - tuning parameters for the algorithm

- The output can include:
  - an approximate sample from the posterior distribution
  - summaries of the run which can help us diagnose problems.

Inference algorithms in `Stan`

- Hamiltonian Monte Carlo (HMC)
- No-U Turn Sampler (NUTS)
- Automatic differentiation variational inference (ADVI)
- Pathfinder Variational Inference
- ...

We can manage the `Stan` file, the input, and the output using a scripting language, such as:

- R
- Python
- Julia
- The command line
- . . .

Example: Bayesian linear regression

The data generating process is:

$$p(y \mid \theta) = \text{Normal}\,(\beta x, \sigma)$$

Our goal is to estimate $\theta = (\beta, \sigma)$, based on the observation $z = (x, y)$ and prior knowledge we have of β and σ.

Example: Bayesian linear regression

As a prior, we use:

- $\beta \sim \text{Normal}(2.0, 1.0)$
- $\sigma \sim \text{Gamma}(1.0, 1.0)$

which encode information from previously observed data.

Writing the `Stan` file

We need a statement that specifies the log joint distribution. Recall:

$$p(\theta, y) = p(y \mid \theta)p(\theta)$$

Then:

$$\log p(\theta, y) = \log p(y \mid \theta) + \log p(\theta)$$

Writing the Stan file

Stan retains certain C++ features:

- Variables need to be declared.
- Each statement must end with a semi-colon.

For example:

```
real x;
```

Writing the `Stan` file

A `Stan` program is divided into coding blocks:

- data
- parameter
- model

Writing the Stan file

```
data {
 Declare the data that will be given as an input.
}

parameters {
 Declare the parameters we want to sample.
}

model {
 Compute the log joint distribution.
}
```

Writing the Stan file

```
model {
 target += normal_lpdf(y | beta * x, sigma);

 // or equivalently

 y ~ normal(beta * x, sigma);
}
```

Writing the `Stan` file

Live demo.

Convergence diagnostic

Are the chains still biased by their initializations?

Proposition: Start each chain at a different location and check that they all converge to the same distribution. Look at:

- the trace plots and the density plots to compare estimates from each chain.
- the $\widehat{R}$ statistic.

The $\widehat{R}$ statistic,

$$\widehat{R} = \frac{\text{Standard deviation across all chains}}{\text{Standard deviation within chain}}$$

The $\widehat{R}$ statistic,

$$\widehat{R} = \frac{\text{Standard deviation across all chains}}{\text{Standard deviation within chain}}$$

- If the chains sample from the same target, expect $\widehat{R} \approx 1$.
- If the chains are disagreement, $\widehat{R} \gg 1$.

A more in-depth look at $\widehat{R}$

Let $\theta^{(nm)}$ be the n^{th} sample from the m^{th} chain.

A more in-depth look at $\widehat{R}$

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Can write $\widehat{R}$ as

$$\widehat{R} = \sqrt{\frac{N-1}{N} + \frac{\widehat{B}}{\widehat{W}}},$$

where

- $\widehat{B}$ is the sample variance of $\bar{\theta}^{(\cdot m)}$.
- $\widehat{W}$ is the (average) within-chain variance.

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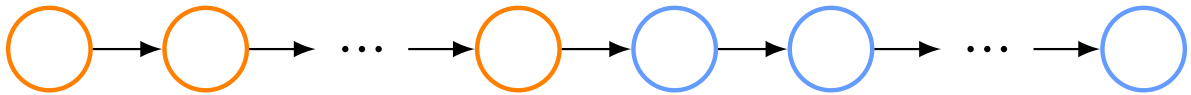
- $\widehat{W}$ is the (average) within-chain variance.

$\widehat{R} \leq 1 + \epsilon \iff \widehat{B} \leq 2\epsilon\widehat{W} + \mathcal{O}(\epsilon^2)$.

Want to make sure Var $\left(\bar{\theta}^{(\cdot m)}\right)$ is small.

A more in-depth look at $\widehat{R}$



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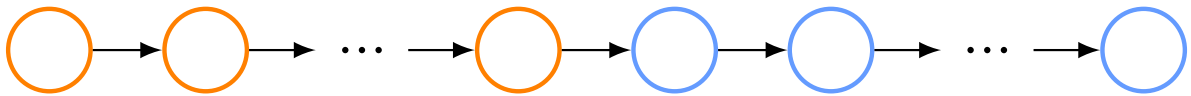

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$$\mathrm{Var}\left(\bar{\theta}^{(\cdot m)}\right) = \mathrm{Var}\left(\mathbb{E}\left(\bar{\theta}^{(\cdot m)} \mid \theta^{(0)}\right)\right) + \mathbb{E}\left(\mathrm{Var}\left(\bar{\theta}^{(\cdot m)} \mid \theta^{(0)}\right)\right).$$

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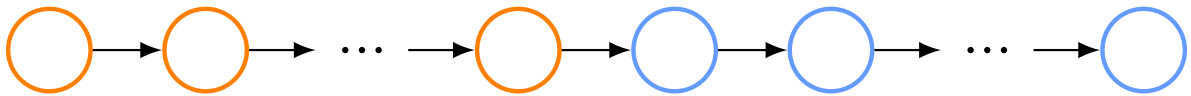

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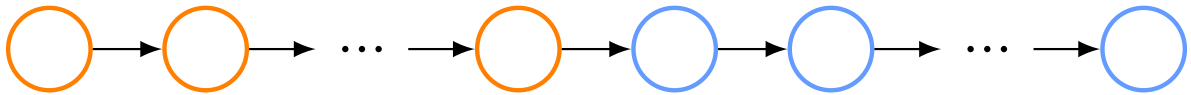
The nonstationary variance measures how well the chains forget their starting points.

A more in-depth look at $\widehat{R}$



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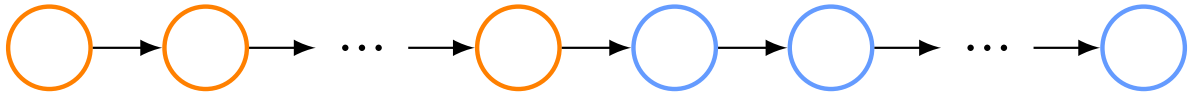
The nonstationary variance measures how well the chains forget their starting points.

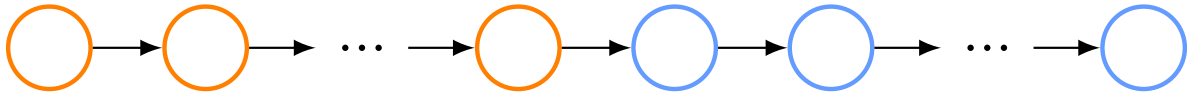
As we warmup the chains, both the nonstationary variance and squared bias decay to 0, and so $\widehat{R}$ acts as a "proxy clock" for bias.

A more in-depth look at $\widehat{R}$

- What quantity does $\widehat{R}$ measure and how close to 1 should it be?
  - [Vehtari et al., 2021] propose checking that $\widehat{R} \leq 1.01$.
  - [Moins et al., 2022] examine the property of $\widehat{R}$ for stationary chains.
  - [Margossian et al., 2023] examine $\widehat{R}$ for nonstationary chains and propose a more direct measure of the nonstationary variance.



- $\widehat{R}$ (ideally) tells us if the warmup phase is long enough.



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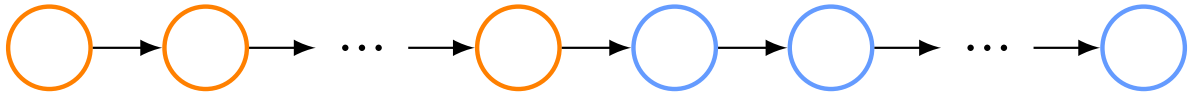

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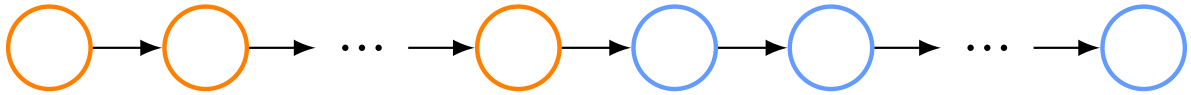

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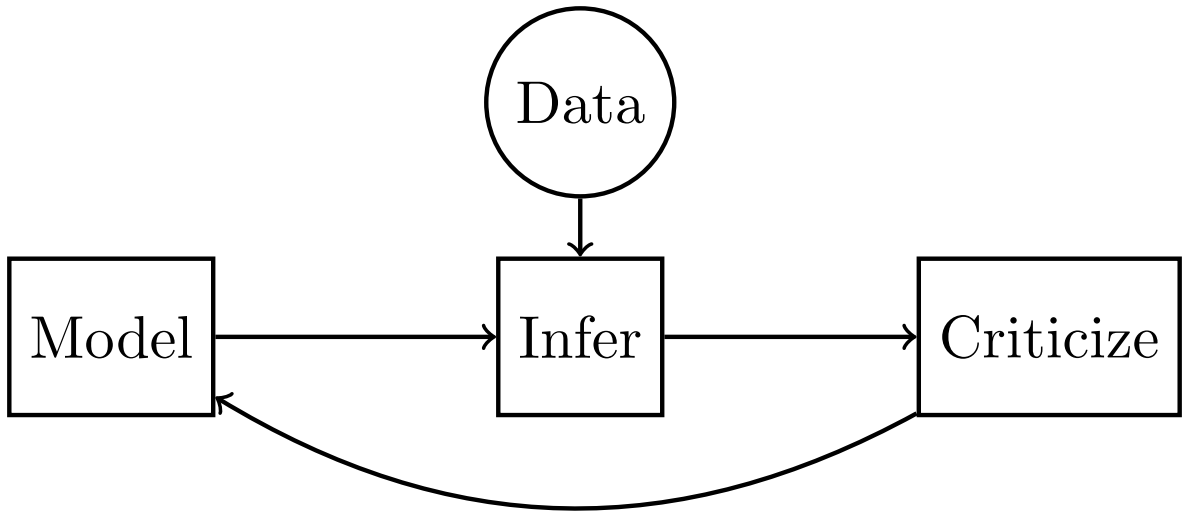
- ESS and Monte Carlo standard error (MCSE) tell us if the sampling phase is long enough.
- ESS_{tail} quantifies information for tail estimates [Vehtari et al., 2021].
- Median, $M(\theta)$ and Median Absolute Deviation (MAD),

$$M(|\theta^{(i)} - M(\theta)|)$$

can be helpful when the first moments are not finite.

Posterior predictive checks

- Recall Box's loop.
- Does our model accurately describe the data?



Posterior predictive checks

Proposition:
Each time we draw a sample, $\theta^{(i)} = (\beta^{(i)}, \sigma^{(i)})$*, we will also simulate data, according to*:

$$y_{\text{pred}}^{(i)} \sim \text{Normal}\left(x\beta^{(i)}, \sigma^{(i)}\right)$$

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Want to study the posterior predictive distribution,

$$p(y_{\text{pred}} \mid y) = \int_{\Theta} p(y_{\text{pred}} \mid \theta) p(\theta \mid y) \mathrm{d}\theta.$$

Posterior predictive checks

To do this, we will use the `generated quantities` block.

Live demo.

Improving the model

- The ppc suggest our model can improve with an intercept parameter.
- *Exercise: repeat the above procedure, but this time add an intercept parameter* β_0.

General resources to use Stan

- Stan User's Guide (https://mc-stan.org/docs/stan-users-guide/index.html)
- Stan Language Reference Manual (https://mc-stan.org/docs/reference-manual/index.html)
- Stan Language Functions Reference (https://mc-stan.org/docs/functions-reference/index.html)

- Stan Forum (http://discourse.mc-Stan.org/)

Parallel chains

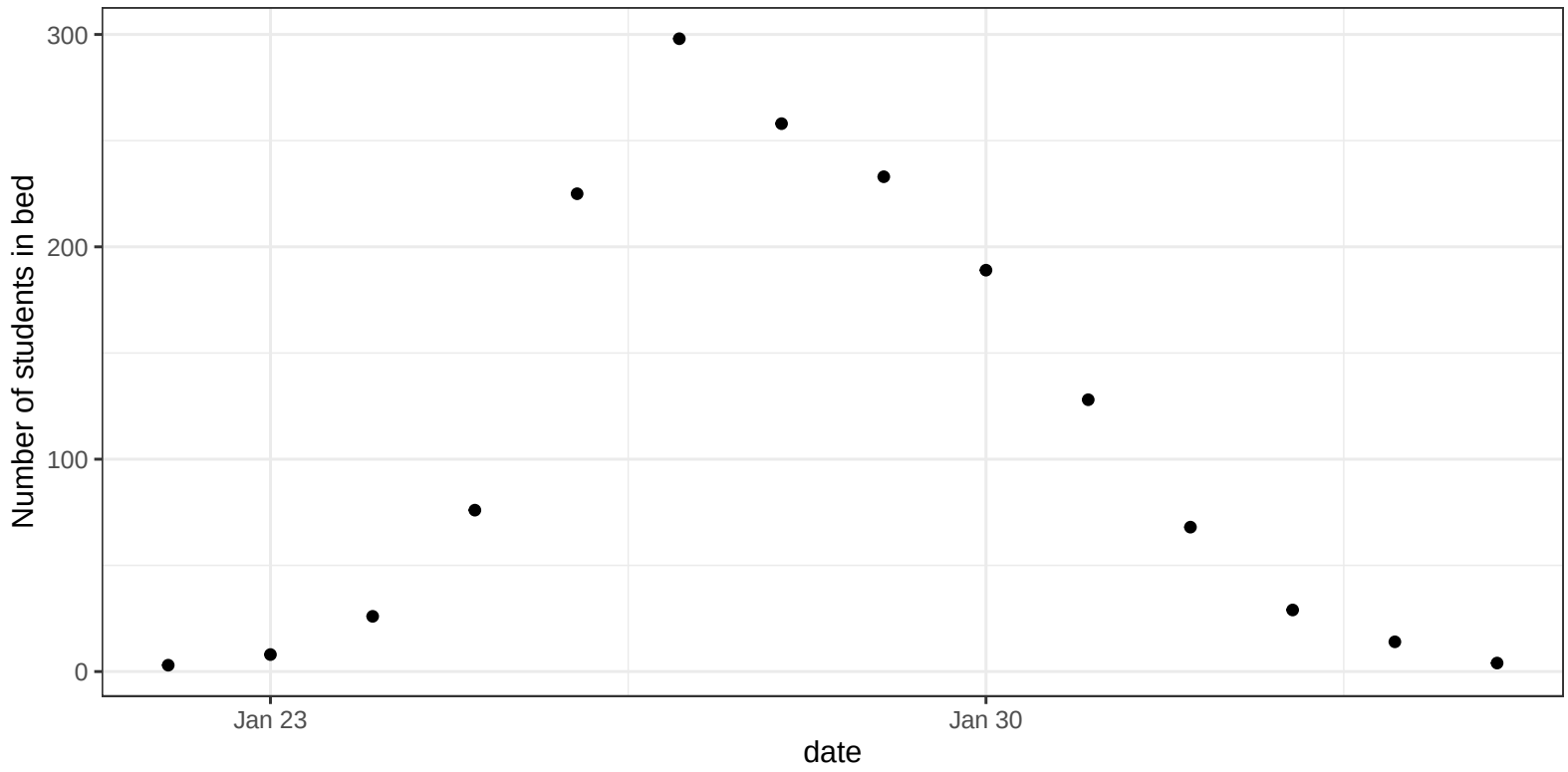
- Each chain is completely independent and can be run on a different core.

```
fit <- mod$sample(file = "model/linear.stan",
                  data = data, chains = 4,
                  init = init,
                  parallel_chains = 4)
```

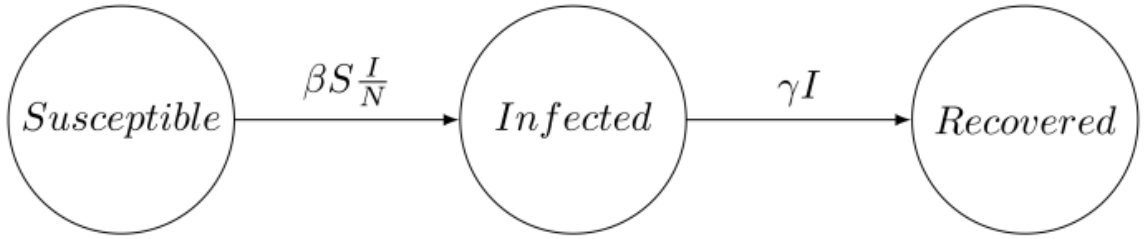
IV
ODE-based models

1978 influenza outbreak in a British boarding school.

Data: daily number of students in bed.



Susceptible-Infected-Recovered (SIR) model



$$
\begin{aligned}
\dot{S} &= -\beta SI/N \\
\dot{I} &= \beta SI/N - \gamma I \\
\dot{R} &= \gamma I
\end{aligned}
$$

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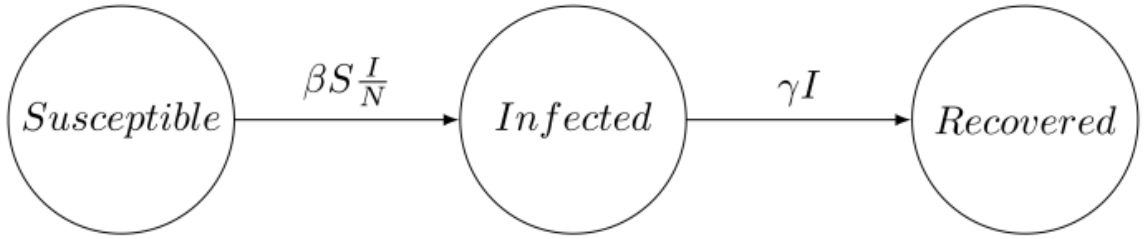

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β: transmission rate.

γ: rate of recovery of infected individuals.

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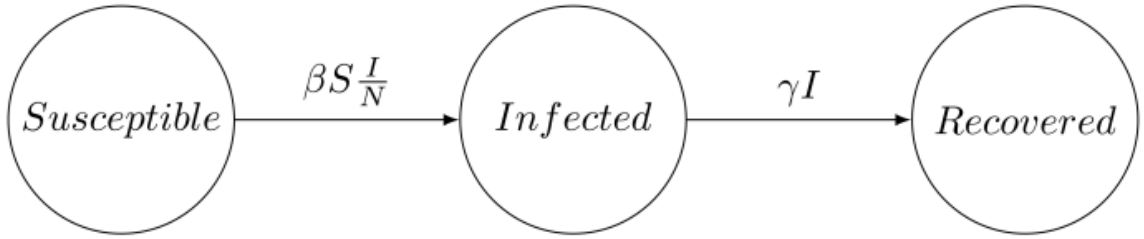

$$\begin{aligned}\dot{S} &= -\beta SI/N \\ \dot{I} &= \beta SI/N - \gamma I \\ \dot{R} &= \gamma I\end{aligned}$$

β: transmission rate.

γ: rate of recovery of infected individuals.

Interpretation:

- I/N is the proportion of infectious individuals.
- $\beta(I/N)$ is then the probability that a single susceptible individual becomes infected in one day.

Which measurement model should we use?

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1. *Poisson* likelihood parameterized by $\lambda(t) = I(t)$.
   - Then $\mathbb{E}(y(t)) = I(t)$ and $\text{Var}\,(y(t)) = I(t)$.

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   - In Stan use `neg_binomial_2`.
   - Define in `parameters` block ϕ^{-1}.

Which prior should we use?

- $p(\beta) = \text{normal}^+(2, 1)$: restricts β to be positive and $p(\beta < 4) = 0.975$.
- $p(\gamma) = \text{normal}^+(0.4, 0.5)$: restricts γ to be positive and $p(\gamma < 1) = 0.9$, i.e. 90% of the time, we expect the average time spent in bed to be less than 1 day).
- $p(\phi^{-1}) = \text{exponential}(5)$, see [Grinsztajn et al., 2021].

Need additional blocks to fit this model:

functions: Here we'll construct a function that returns $\{\dot{S}, \dot{I}, \dot{R}\}$, which we can then pass to an ODE solver.

- `vector sir (real t, vector y, real beta, real gamma, int N) { ··· return dy_dt };`
- `t`: time
- `y`: the solution to the ODE, $y(t) = [S(t), I(t), R(t)]$

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transformed parameters: Allows us to do manipulations on the parameters

- compute $I(t)$ by solving the ODE:
  ```
  array[n_days] vector[3] y
    = ode_rk45(sir, y0, t0, ts, beta, gamma, N);
  ```
- `y0`: initial condition for $t = t_0$.
- `ts`: times at which we require a solution.

Exercise: *Write and fit an SIR model for the 1978 influenza outbreak.*

- *Check the standard diagnostics ($\widehat{R}$ and ESS) and examine the density and trace plots. Is the inference reliable?*
- *Do the posterior predictive checks: does the model accurately describe the data?*
- *Report β, γ and*
$$R_0 = \beta/\gamma.$$
- *Compare the two proposed measurement models: Poisson and negative binomial.*

For more discussion about this model (e.g. choice of priors, sensitivity tests), see [Grinsztajn et al., 2021].

V
Model Comparison

Question: For the SIR model, do we get better predictions with the Poisson or the negative binomial likelihood?

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$$p(\theta \mid y_{\text{train}}).$$

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  - **Training set:** The data y_{train} used to learn the parameters, and on which we condition the posterior,

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  - **Validation set:** The data y_{val} we use to "test" the model's predictions.

    Example: At $t = 12$, the model predicts $\tilde{y}(t = 12)$.
    Compute the *prediction error*,

$$\text{Err} = \left(\tilde{y}(t = 12) - y_{\text{val}}(t = 12)\right)^2 .$$

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Suppose we have a normal likelihood, with point estimates for the learned parameters,

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and $\hat{\sigma}$ is unaccounted for!

Instead, let's evaluate the *point-estimate log predictive density*,

$$\begin{aligned} \text{p-lpd} &= \log p(y_{\text{val}}(t) \mid \hat{\mu}, \hat{\sigma}) \\ &= \text{const.} - \log \hat{\sigma} - \frac{1}{2\hat{\sigma}^2}\left(y_{\text{val}}(t) - \hat{\mu}(t)\right)^2. \end{aligned}$$

Testing *uncertainty calibration* in (point) predictions

Suppose we have a Bernoulli likelihood, with point estimates for the learned parameters,

$$\text{Bernoulli}(\hat{\pi}(t)).$$

Our "best" prediction is $\tilde{y}(t) = \mathbb{I}(\hat{\pi}(t) > 0.5)$.

Then the prediction error is

$$\text{Err} = \mathbb{I}(\tilde{y}(t) = y_{\text{val}}(t)).$$

Instead, let's evaluate the *point-estimate log predictive density*,

$$\begin{aligned} \text{p-lpd} &= \log p(y_{\text{val}}(t) \mid \hat{\pi}(t)) \\ &= y_{\text{val}}(t) \log \hat{\pi}(t) + (1 - y_{\text{val}}(t)) \log(1 - \hat{\pi}(t)). \end{aligned}$$

Testing *uncertainty calibration* in Bayesian predictions

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To be Bayesian, we integrate with respect to the posterior and obtain the *expected log predictive density*,

$$\begin{aligned} \text{elpd} &= \log p(y_{\text{val}}(t) \mid y_{\text{train}}) \\ &= \log \int_{\Theta} p(y_{\text{val}}(t) \mid \theta) p(\theta \mid y_{\text{train}}) \mathrm{d}\theta. \end{aligned}$$

How do we split the data (t, y) into a training and a test set?

Proposition: Do *leave-one-out cross validation* and compute

$$\text{elpd}_{\text{loo}} = \sum_{i=1}^{N} \log p(y_i \mid y_{-i}),$$

where

$$p(y_i \mid y_{-i}) = \int_{\Theta} p(y_i \mid \theta) p(\theta \mid y_{-i}) \mathrm{d}\theta.$$

Recap.

Prediction error based on "best" prediction, $(y_{\text{val}} - \tilde{y})^2$

$\rightarrow$ point-wise log predictive score, p-lpd $= \log p(y_{\text{val}} \mid \hat{\theta})$

$\rightarrow$ expected log predictive score, elpd $= \log p(y_{\text{val}} \mid y_{\text{train}})$

$\rightarrow$ loo CV, $\text{elpd}_{\text{loo}} = \sum_{i=1}^{N} \log p(y_i \mid y_{-i})$

How do we estimate elpd_{loo} efficiently?

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Proposition

When the y_j's are independent conditioned on θ, the importance sampling Monte Carlo estimator is

$$\widehat{p}(y_i \mid y_{-i}) = \frac{1}{\sum_{s=1}^{S} \frac{1}{p(y_i|\theta^{(s)})}},$$

where $\theta^{(s)} \sim p(\theta \mid y)$.

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- The R package `loo` computes PSIS.
- In Stan 's `generated quantities`, need to compute `log_lik`, where

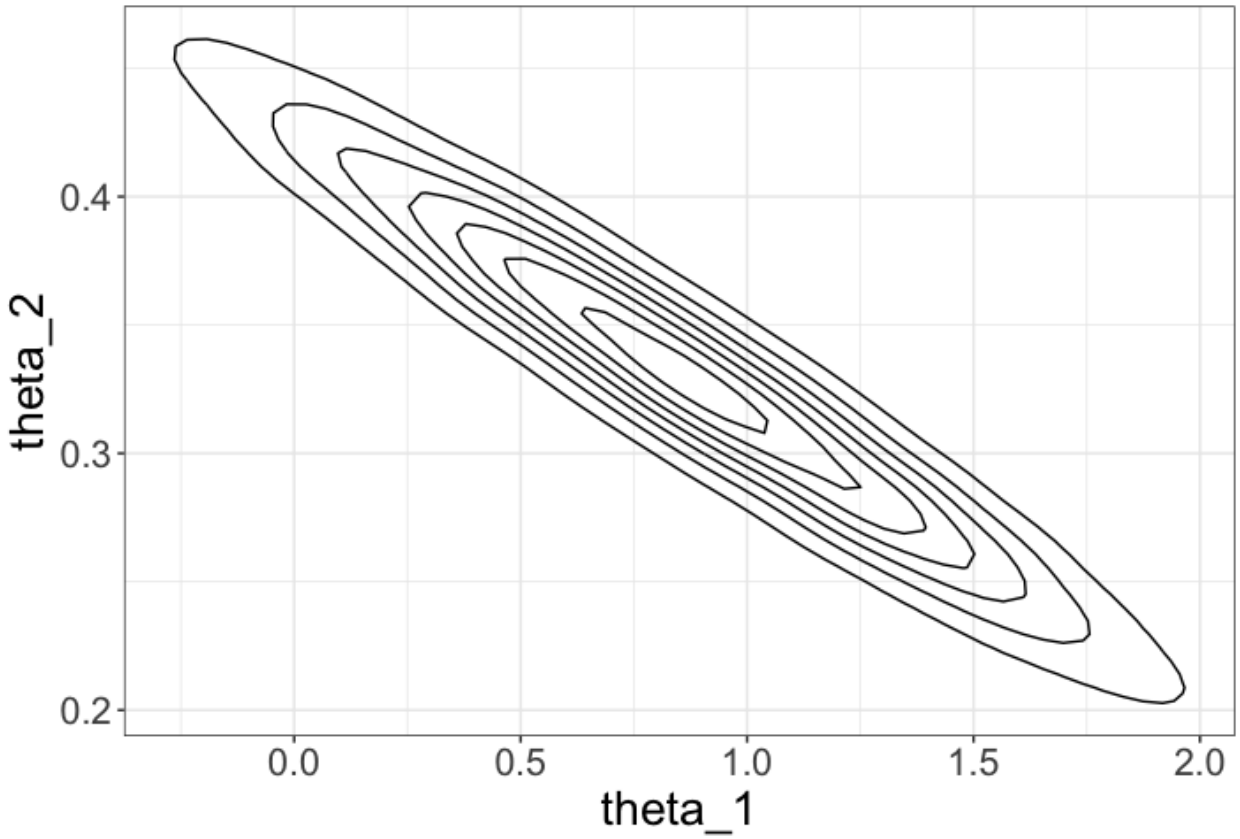
```
log_lik[i] = log p(cases[i] | theta);
```

Exercise: *Compare the predictive scores of the SIR models.*

- *Evaluate in* `generated quantities` *the log probability mass functions using* `poisson_lpmf` *and* `neg_binomial_2_lpmf`*.*
- *In R, use the* `loo` *package to compute the PSIS estimates of the* $elpd_{loo}$*.*
- *Check* $\hat{k}$ *to see if the IS estimators are reliable.*
- *Which likelihood achieves the best predictive score?*

VI
Hamiltonian Monte Carlo

Geometric structure in the distribution



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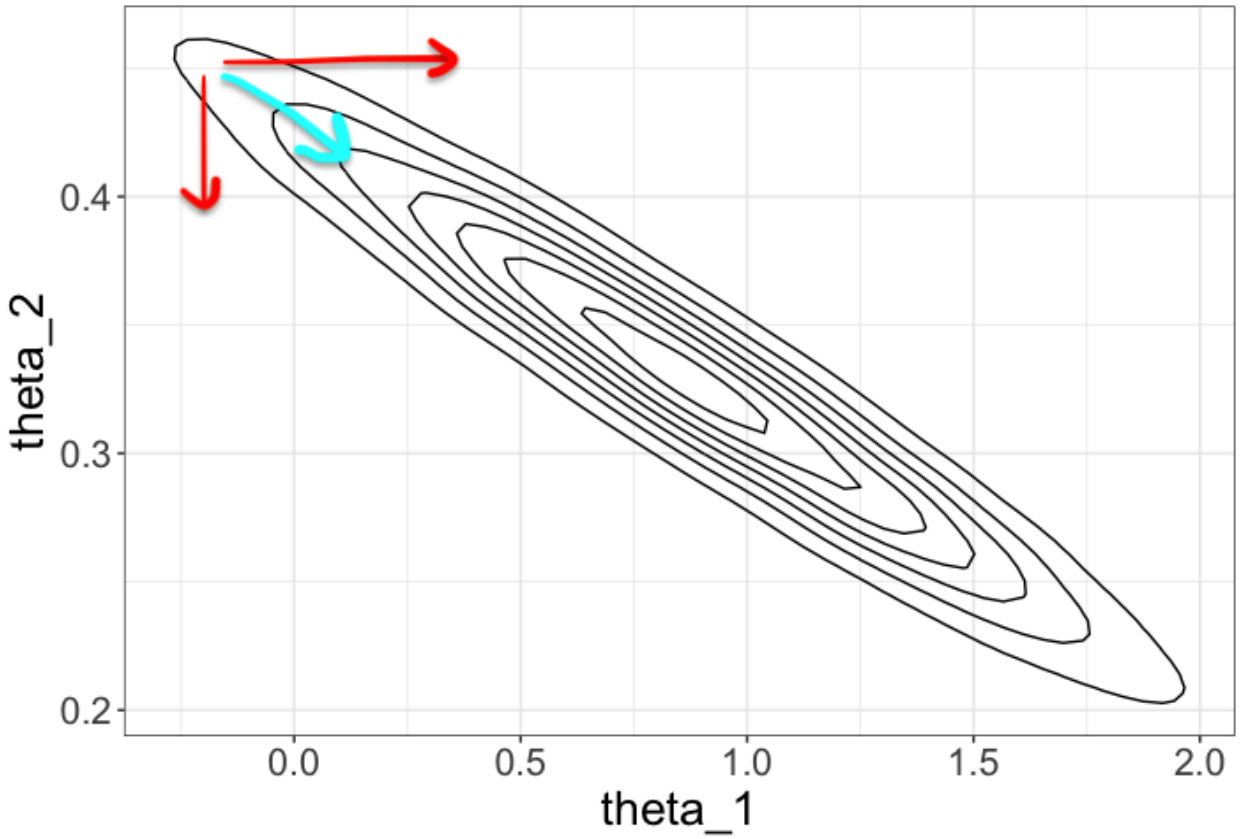

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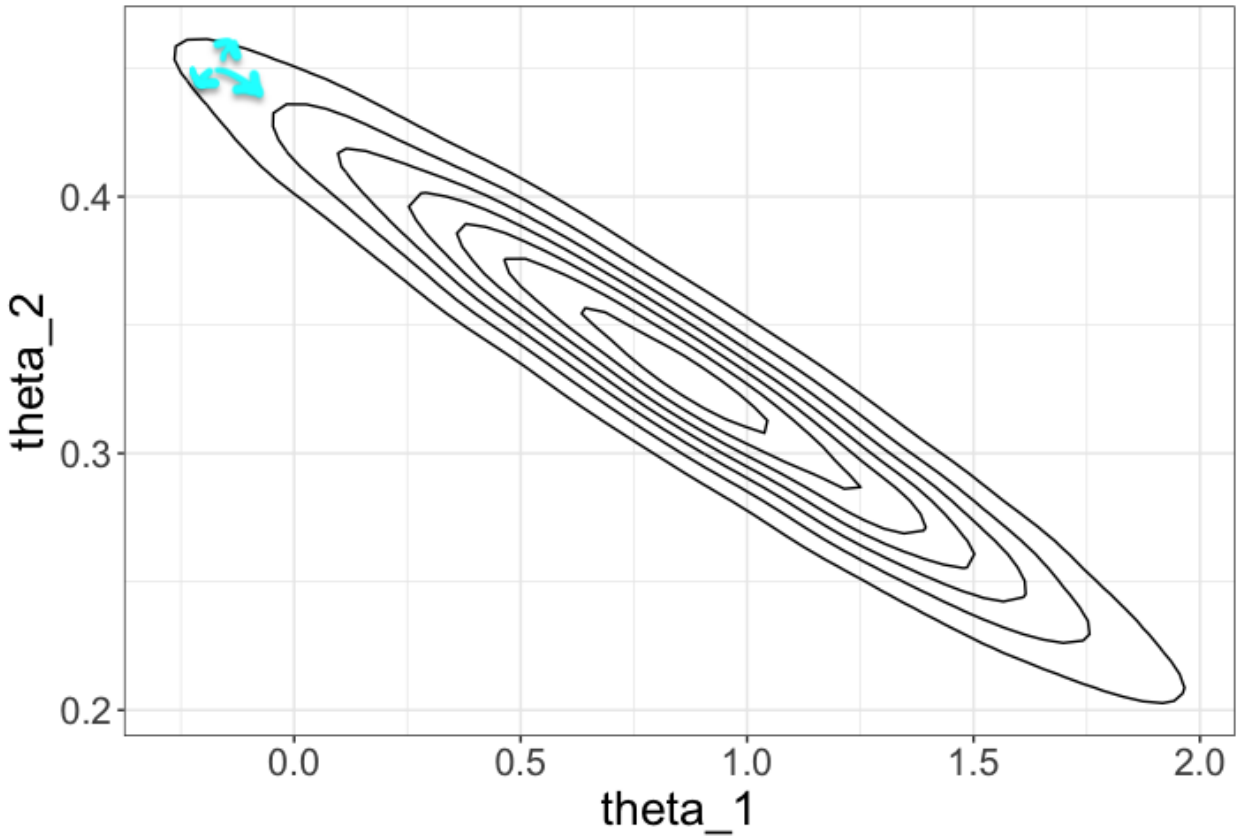

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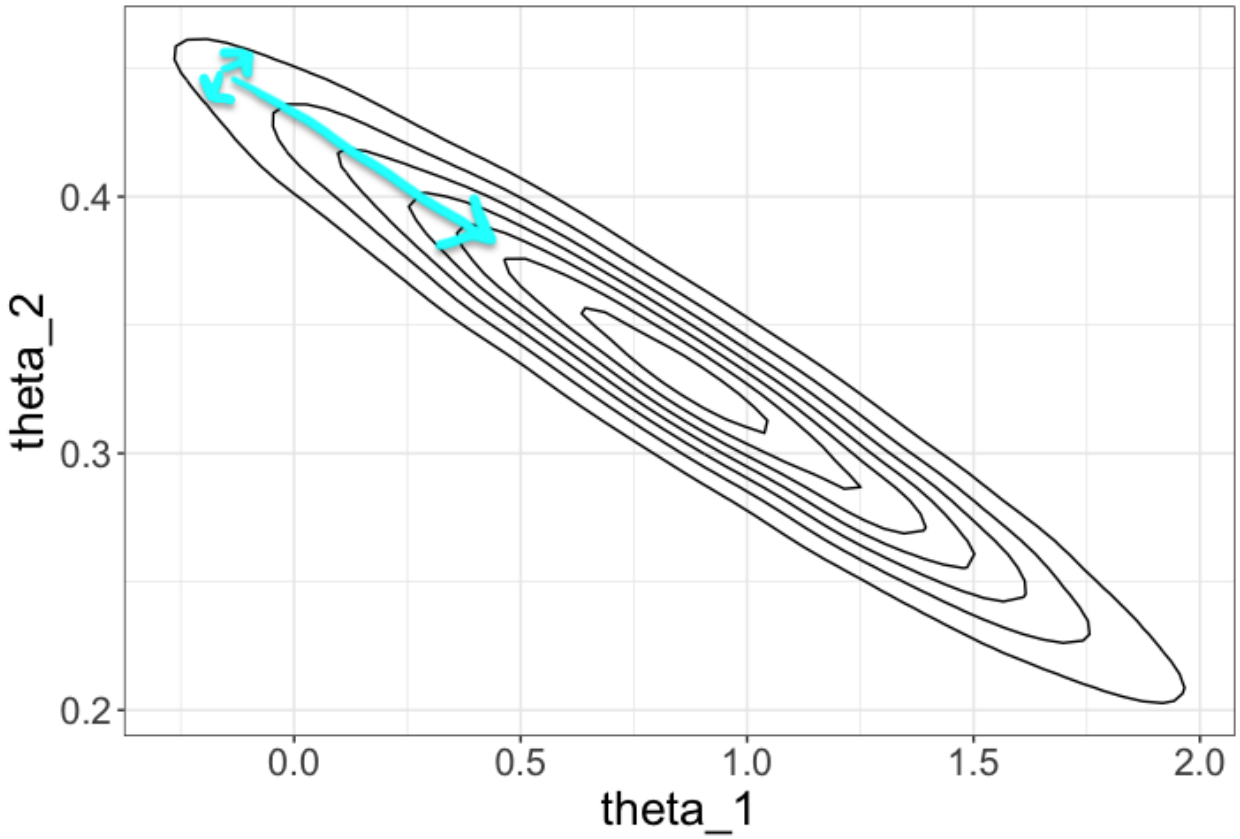

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$$\xi_0 \sim \text{normal}(0, M)$$

- Treat the negative log density as a physical *potential*,

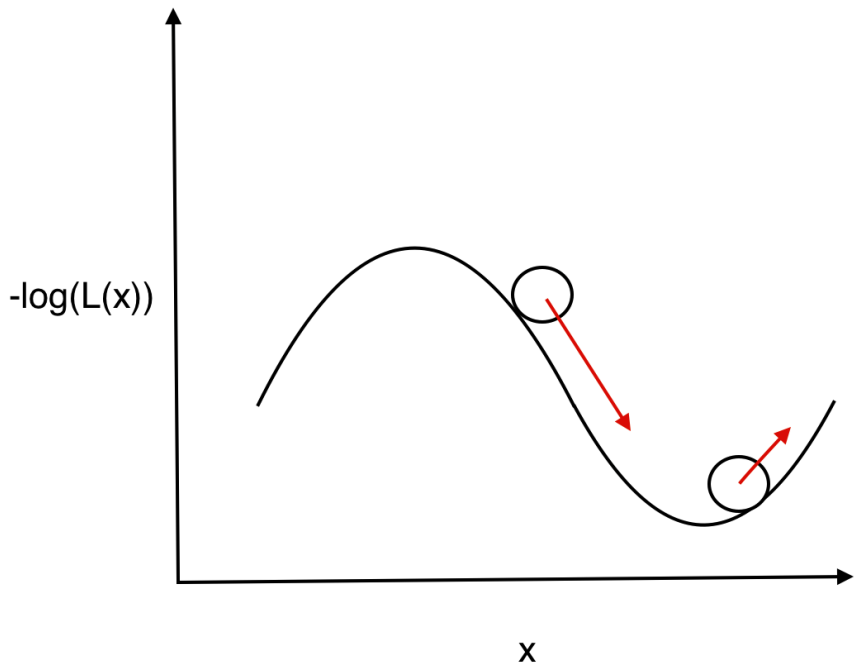
$$U(\theta) = -\log p(\theta \mid y).$$

- Simulate a the laws of classical mechanics for a time T,

$$(\theta_0, \xi_0) \to (\theta_T, \xi_T).$$

Hamiltonian Dynamics

$$\frac{\mathrm{d}\theta}{\mathrm{d}t} = M^{-1}\xi; \quad \frac{\mathrm{d}\xi}{\mathrm{d}t} = \nabla_\theta \log p(\theta \mid y).$$



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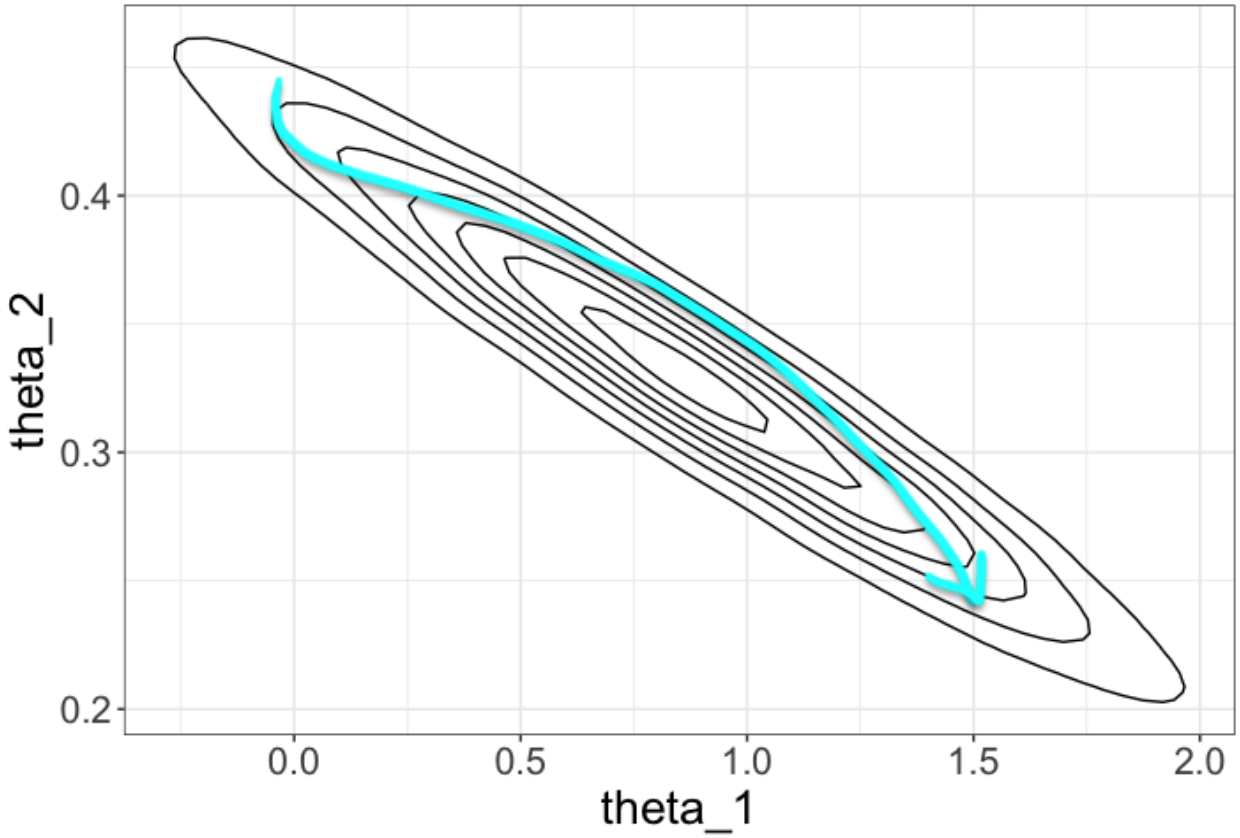

Canonical distribution (for stationary Markov chains),

$$
\begin{aligned}
p(\xi, \theta) &= p(\xi) p(\theta \mid y) \\
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During a Hamiltonian trajectory, $H(\theta, \xi)$ stays constant.

HMC can be seen as a Gibbs sampler, alternating between a *random* step $p(H \mid \theta)$ and a *deterministic* step $\delta(\theta \mid H)$.

Algorithm 1: Leapfrog integrator for simulating Hamiltonian trajectory.

input: trajectory length L, step size ϵ, mass matrix M, $\theta(0)$

$\xi(0) \sim \text{normal}(0, M)$

$t \leftarrow 0$

for $i \in \{0, 1, \cdots, L-1\}$ **do**

$\xi(t + \epsilon/2) \leftarrow \xi(t) + \frac{\epsilon}{2} \nabla_\theta \log p(\theta(t) \mid y)$

$\theta(t + \epsilon) \leftarrow \theta(t) + \epsilon M^{-1} \xi(t + \epsilon/2)$

$\xi(t + \epsilon) \leftarrow \xi(t + \epsilon/2) - \frac{\epsilon}{2} \nabla_\theta p(\theta(t + \epsilon) \mid y)$

$t \leftarrow t + \epsilon$

end

return: $\theta(T = L\epsilon)$

Algorithm 2: Leapfrog integrator for simulating Hamiltonian trajectory.

input: trajectory length L, step size ϵ, mass matrix M, $\theta(0)$

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*`Stan` uses something a bit more sophisticated than a Metropolis step, see [Betancourt, 2017].

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$$\Pr(\text{accept}) = \min\left(1, \exp\left(H(\theta(0), \xi(0)) - H(\theta(T), \xi(T))\right)\right).$$

- `Stan` uses a stochastic optimization strategy to adjust ϵ and hit a target acceptance rate, `adapt_delta`,

$$\delta_{\text{adapt}} = 0.8.$$

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Tuning Hamiltonian Monte Carlo [Hoffman and Gelman, 2014]

Trajectory length L:

- If L is too short, the Markov chain has a large autocorrelation.
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- *No U-Turn* criterion,

$$\frac{\mathrm{d}}{\mathrm{d}t} \frac{(\theta(T) - \theta(0))^T (\theta(T) - \theta(0))}{2} = (\theta(T) - \theta(0))^T \xi(T).$$

- Run simulation until $(\theta(T) - \theta(0))^T \xi(T) = 0$.

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Mass matrix M:

- The mass matrix determines the *resistance to acceleration*.

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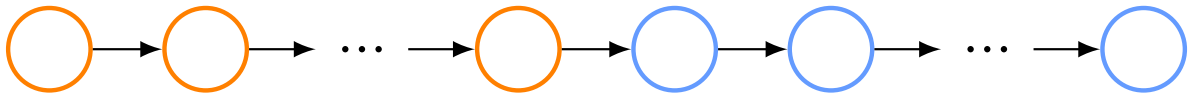
Tuning Hamiltonian Monte Carlo [Hoffman and Gelman, 2014]

Mass matrix M:

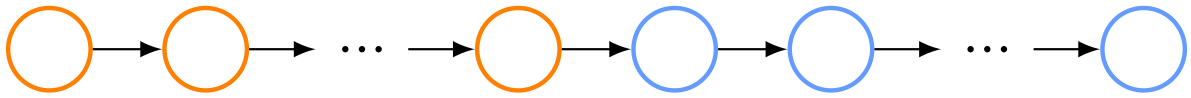
- The mass matrix determines the *resistance to acceleration*.
- **Idea:** set

$$M = \widehat{\Sigma}^{-1}(\theta),$$

  where $\widehat{\Sigma}(\theta)$ is the sample covariance of the posterior.
- To make the leapfrog cheaper, `Stan` uses a diagonal M.



Stan 's HMC learns ϵ and M during the warmup phase and then "freezes" these tuning parameters.



`Stan` 's HMC learns ϵ and M during the warmup phase and then "freezes" these tuning parameters.

The resulting algorithm is called the No U Turn Sampler (NUTS) or *dynamic Hamiltonian Monte Carlo*.

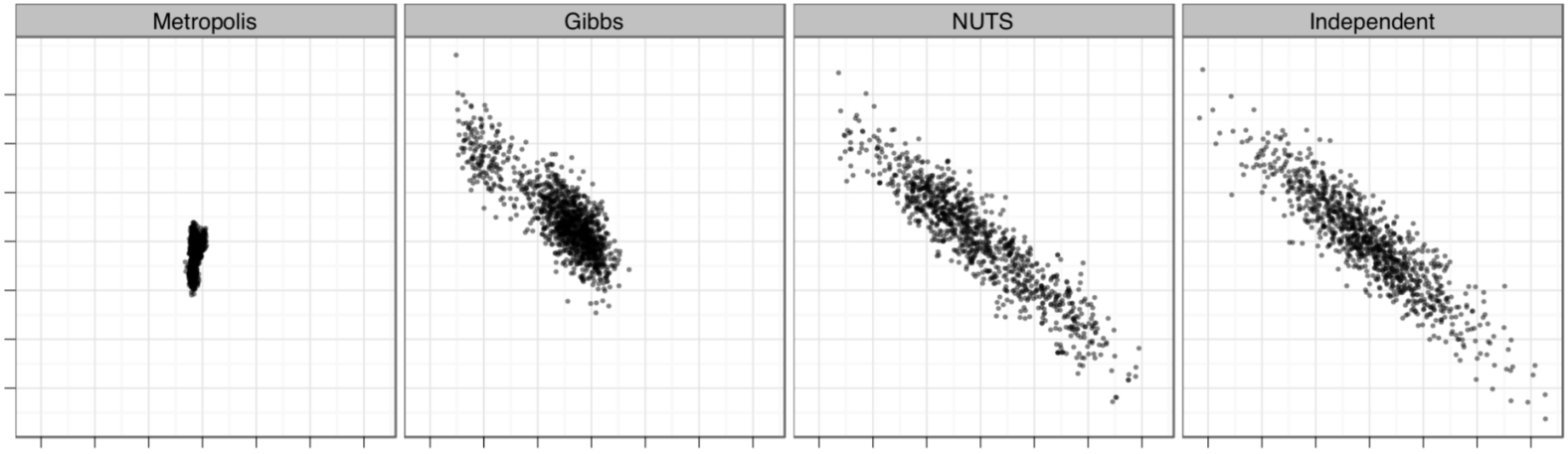


Figure from [Hoffman and Gelman, 2014].

To implement HMC, need

$$\begin{aligned}
\nabla_\theta \log p(\theta \mid y) &= \nabla_\theta \left(\log p(\theta) + \log p(y \mid \theta) - \log p(y) \right) \\
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`Stan` implements *automatic differentiation*.

Autodiff uses the chain rule to propagate derivatives through compositions of "analytical" functions; for some introductions, see [Baydin et al., 2018, Margossian, 2019].

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Suppose our likelihood depends on an implicit function g,

$$\log p(y \mid \theta) = f \circ g(\theta).$$

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Then

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Stan also supports an *adjoint method*, which is an augmented ODE with $2N + K$ states solved by $\mathrm{d}f/\mathrm{d}g \cdot \mathrm{d}g/\mathrm{d}\theta$ (but harder to use!).

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For a discussion on autodiff for implicit functions, see [Margossian and Betancourt, 2022].

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VII
Tuning ODEs in a Bayesian Context

It is possible in Stan to specify the tuning parameters of the ODE integrator.

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array[n_days] vector[3] y
 = ode_rk45_tol(sir, y0, t0, ts,
                rel_tol, abs_tol, max_num_steps, ···)
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array[n_days] vector[3] y
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                rel_tol, abs_tol, max_num_steps, ···)
```

- `rel_tol` or δ_{rel}: the relative tolerance to error.
- `abs_tol` or δ_{abs}: the absolute tolerance to error.
- `max_num_steps` : the maximum number of steps before the integrator "gives" up.

$\hat{u}$: numerical solution

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Solve adaptively reduces the step size until

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When $N = 1$, this is equivalent to

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When $N = 1$, this is equivalent to

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Remark: In Stan we're also setting a tolerance for the augmented ODE system which propagates derivatives.

Exercise: *Fit an SIR model and specify tuning parameters for the ODE solvers.*

- *The default we used was* $\delta_{tol} = \delta_{rel} = 10^{-6}$. *You may experiment with either stricter or more lenient tolerances.*
- *Compare the runtime between the default tuning parameter and your choice using* `fit$time()`.
- *Compare the returned posterior for* β, γ *and* R_0.

Can we check if the tolerance is strict enough?

An importance sampling approach for reliable and efficient inference in Bayesian ordinary differential equation models

Juho Timonen[1], Nikolas Siccha[1], Ben Bales[2], Harri Lähdesmäki[1], and Aki Vehtari[1]

[1]Department of Computer Science, Aalto University, Finland
[2]Earth Institute, University of Columbia, New York, USA

In practice, MCMC does not target $p(\theta \mid y)$ but a numerical approximation

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To correct for the error, can use IS estimator

$$\widehat{\mathbb{E}}_{\mathrm{IS}} f(\theta) = \frac{\sum_{s=1}^{S} f(\theta^{(s)}) r(\theta^{(s)})}{\sum_{s=1}^{S} r(\theta^{(s)})},$$

where

$$r(\theta^{(s)}) = \frac{p(y \mid \theta^{(s)})}{p_\delta(y \mid \theta^{(s)})}.$$

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Only feasible if

$$p_\delta(y \mid \theta^{(s)}) \approx p(y \mid \theta^{(s)}),$$

which we can check with PSIS and $\widehat{k}$.

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Instead we'll use a golden benchmark with $\delta^* \ll \delta$ and

$$r_{\delta,\delta^*}(\theta^{(s)}) = \frac{p_{\delta^*}(y \mid \theta^{(s)})}{p_\delta(y \mid \theta^{(s)})}.$$

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[Timonen et al., 2023] propose a strategy to find a suitable δ^*. We'll just stick to $\delta^* = 10^{-10}$.

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Exercise: *Check the tolerance of the ODE integrator in the SIR model.*

- *In* `generated quantities` *compute* `log_ratios` $= \sum_{i=1}^{N} \log p_{\delta^*}(y_i \mid \theta) - \log p_{\delta}(y_i \mid \theta)$.
- *Do a PSIS fit and check whether* $\widehat{k}$ *has an acceptable value. If applicable compute the IS estimator and compare to MCMC estimator.*
- *What are the least strict tolerances with which we still get accurate posterior estimates?*

Choices of ODE integrators in `Stan`

- `rk45`: Runge-Kutta $4^{\text{th}}/5^{\text{th}}$ order. Good place to start.
- `bdf`: Backward differentiation. Recommended for stiff systems.
- `adams`: Adams-Moulton solver – higher-order than rk45 and useful when a high precision is required for a very smooth solution.
- `ckrk`: a variant on rk45 for non-stiff and semi-stiff systems. Designed for problems where the solution evolves rapidly, where the derivatives becomes large.

For more, see `https://mc-stan.org/docs/stan-users-guide/ode-solver.html`.

Case study: Michaelis-Menten pharmacokinetic model [Margossian et al., 2021]

- Which numerical integrator should we use in `Stan` ?
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  - BDF (stiff solver)

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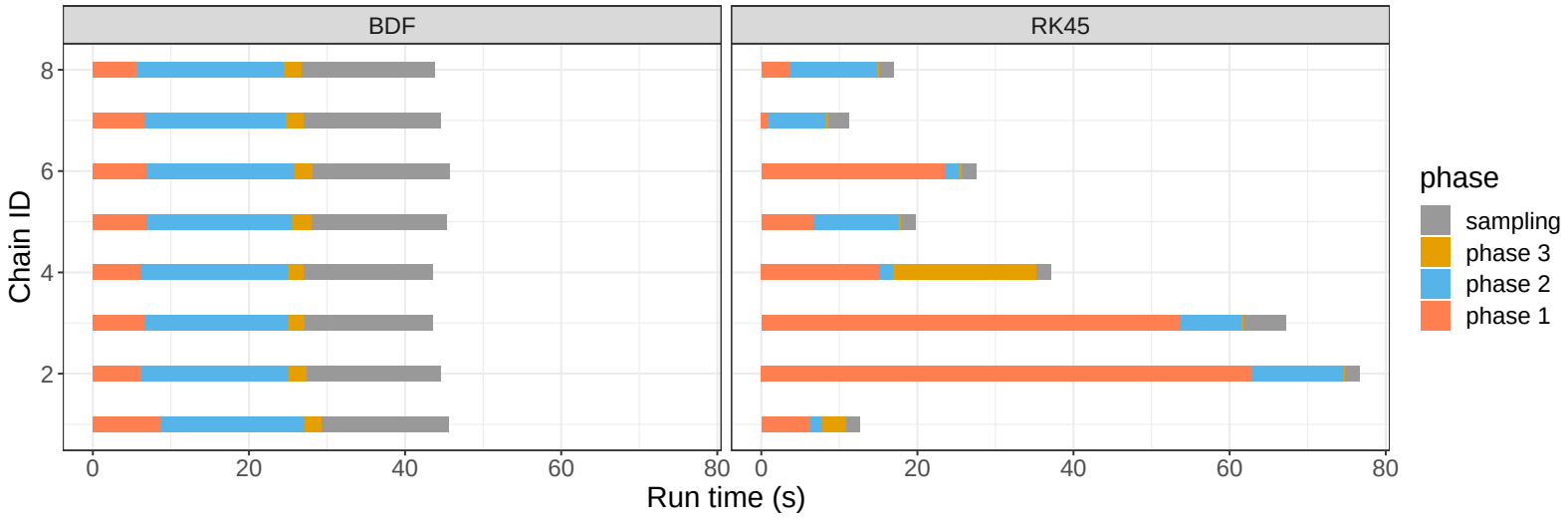

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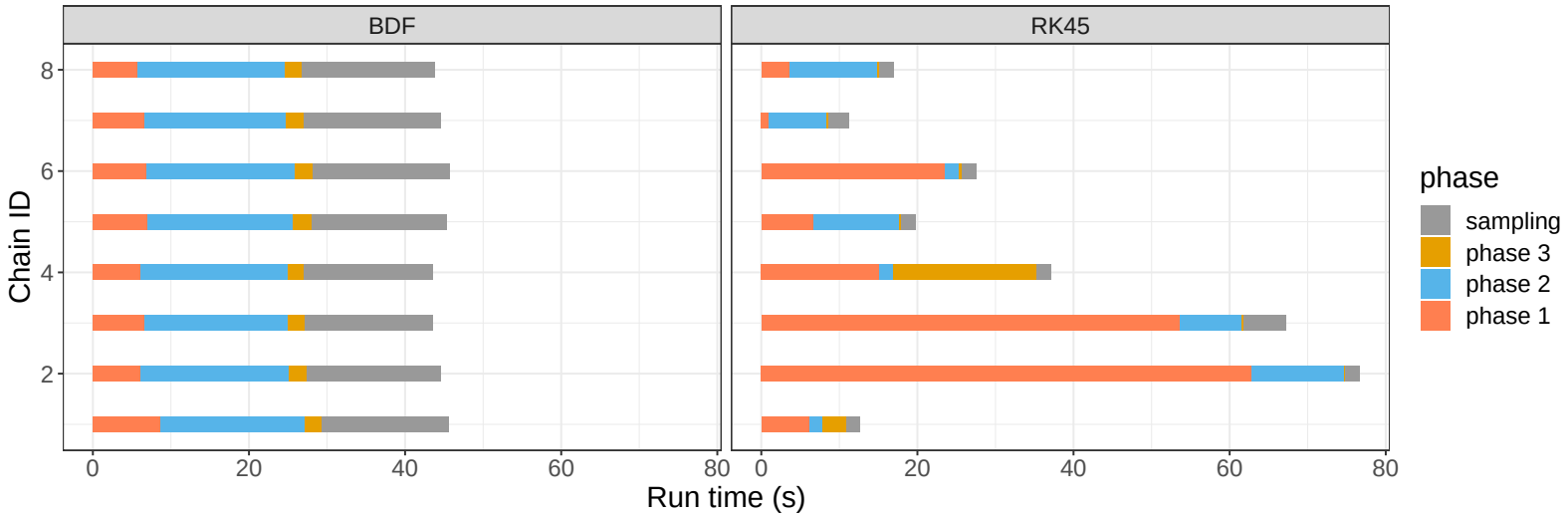

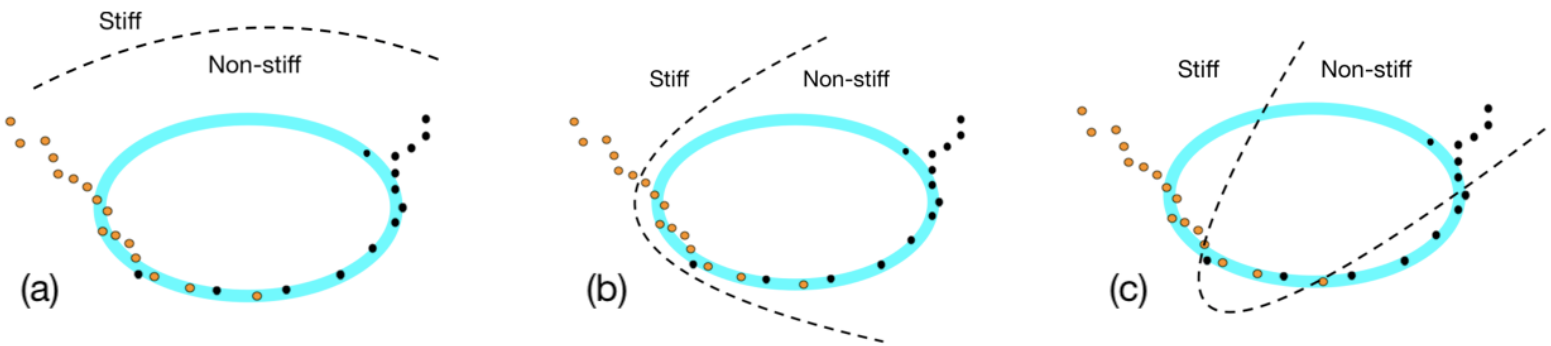

Some ideas:

- Switch ODE during MCMC phases.

	Phase I	Phase II	Phase III	Sampling
RK45	RK45	RK45	RK45	RK45
BDF	BDF	BDF	BDF	BDF
Early switch	BDF	RK45	RK45	RK45
Late switch	BDF	BDF	RK45	RK45

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Late switch	BDF	BDF	RK45	RK45

- Use careful initializations, e.g. with fast approximation of $p(\theta \mid y)$ to bypass difficult regions.

VIII
Hierarchical Modeling

Suppose our data can be split into groups.

- medical measurements are grouped by patients
- sport measurements are grouped by players
- people's voting intention can be grouped by states, age group, etc.

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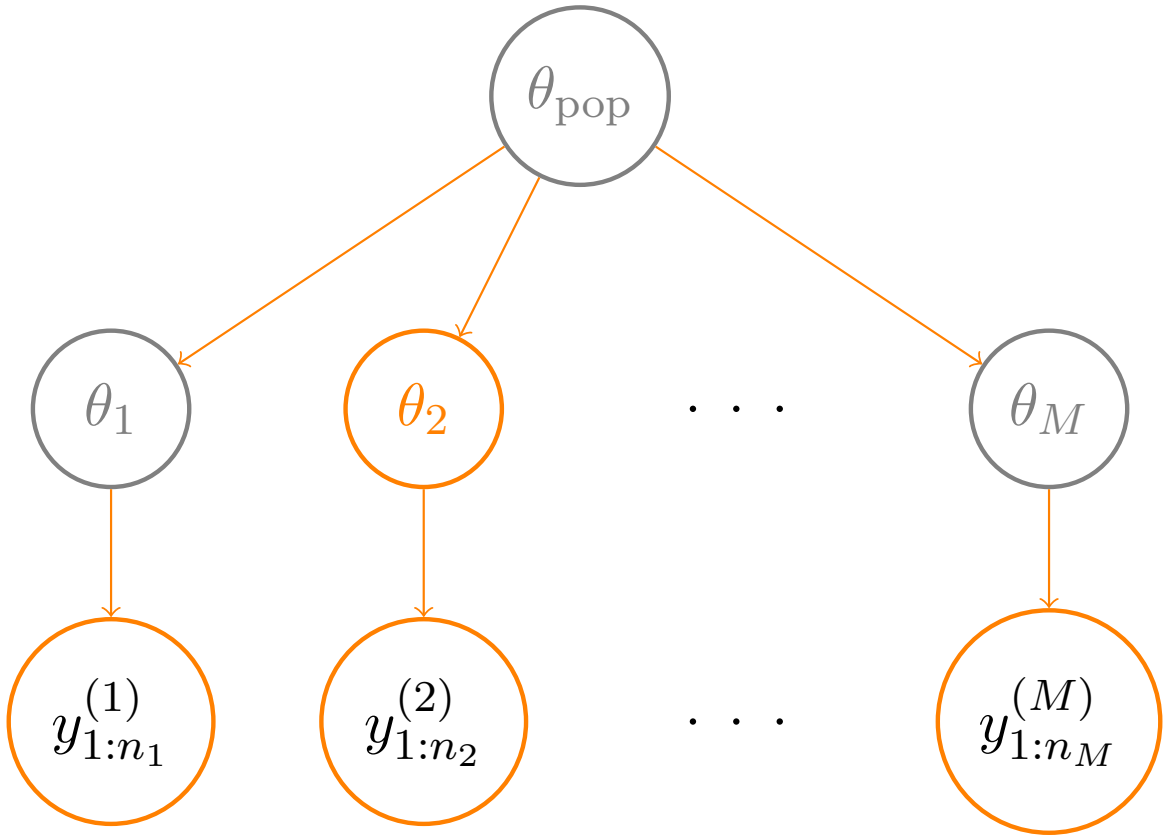
- sport measurements are grouped by players
- people's voting intention can be grouped by states, age group, etc.

With a hierarchical model, we can:

- model heterogeneity between groups
- estimate how similar groups are to one another.
- estimate "local" parameters using information from the entire population.

Hierarchical model

$$\begin{aligned} \theta_i &\sim p(\theta_i \mid \theta_{\text{pop}}) \\ y^{(i)}_{1:n_i} &\sim p(y^{(i)}_{1:n_i} \mid \theta_i) \end{aligned}$$



Example: 8 schools experiment [Gelman et al., 2013, Chapter 5]

How effective are prep programs for a standardized exam?

- y_i: estimated coaching effect for school i, based on student scores and covariate adjustments.
- σ_i: sampling standard deviation.
- θ_i: latent coaching effect for school i.
- μ: population level coaching effect
- τ: population standard deviation.

Example: 8 schools experiment [Gelman et al., 2013, Chapter 5]

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- μ: population level coaching effect
- τ: population standard deviation.

Generative model:

$$\begin{aligned} \mu &\sim \text{normal}(5, 3) \\ \tau &\sim \text{normal}^{+}(0, 10) \\ \theta_i &\sim \text{normal}(\mu, \tau) \\ y_i &\sim \text{normal}(\theta_i, \sigma_i) \end{aligned}$$

Exercise: *Write and fit the 8 schools model.*

- *Check the inference, i.e.* $\widehat{R}$ *and ESS.*
- *Report any warning messages.*
- *Record the estimated posterior and .9 coverage for* μ, τ *and* θ_1.

Divergent transitions

"There were 29 divergent transitions after warmup."

A divergent transition occurs when we fail to accurately compute a Hamiltonian trajectory, i.e. energy conservation is brutally violated.

Demo: Plot divergent transitions amongst MCMC draws.

In a hierarchical model, the joint prior $p(\tau, \theta)$ induces a funnel [Neal, 2003, Betancourt and Girolmi, 2015], which induces a high (sometimes non-finite) curvature.

Potential fixes

1. Increase the target acceptance rate of dynamic HMC.

   Forces the leapfrog integrator to use a smaller step size.
   `Stan` 's default is `adapt_delta` $= 0.8$.

   Exercise: Increase ***`adapt_delta`*** *and report results.*

Potential fixes

2. Use a non-centered parameterization.

   Consider the alternative data generative process,

$$
\begin{aligned}
\mu &\sim \text{normal}(5, 3) \\
\tau &\sim \text{normal}^{+}(0, 10) \\
\eta_i &\sim \text{normal}(0, 1) \\
\theta_i &= \mu + \tau \eta_i \\
y_i &\sim \text{normal}(\theta_i, \sigma_i)
\end{aligned}
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   What structure do we expect from the joint prior $p(\tau, z)$?

   Exercise: Implement a non-centered parameterization of the 8 schools model and report results.

Potential fixes

3. Marginalize out the local variable θ.
   - Use MCMC to sample from the marginal posterior,

$$p(\mu, \tau \mid y) \propto p(\mu)p(\tau)p(y \mid \mu, \tau).$$

   - Then recover θ by sampling from the conditional

$$\theta \sim p(\theta \mid \mu, \tau, y).$$

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$$\theta \sim p(\theta \mid \mu, \tau, y).$$

   - This strategy works here because the marginal likelihood and the conditional admit analytical expressions.

$$\begin{aligned} p(y_i \mid \mu, \tau) &= \text{normal}\left(\mu, \sqrt{\tau^2 + \sigma_i^2}\right) \\ p(\theta_i \mid \mu, \tau, y) &= \text{normal}\left(\frac{y_i/\sigma_i^2 + \mu/\tau^2}{1/\sigma_i^2 + 1/\tau^2}, \sqrt{\frac{1}{1/\sigma_i^2 + 1/\tau^2}}\right) \end{aligned}$$

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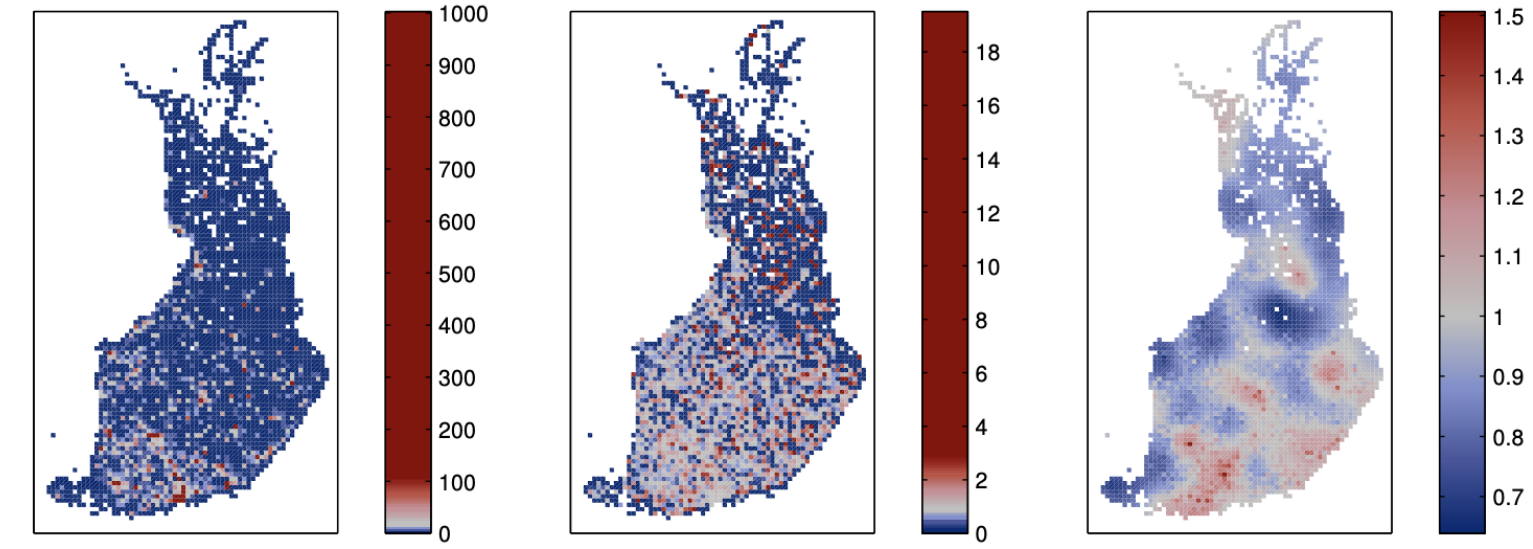
Exercise: *Write and fit a* `Stan` *model that samples from the marginal posterior and use* `generated quantities` *to recover draws for* θ*. Compare your results to previous strategies.*

Disease map of Finland [Vanhatalo et al., 2010]



(g) Number of deaths (h) Raw relative risk (i) Smoothed risk

Mortality count due to alcoholism across the country

- The country is split into 911 cells and all cells have the same area.
- In most cells, the population is sparse.

Disease map of Finland [Vanhatalo et al., 2010]

- The death count in cell i is

$$y_i \sim \text{Poisson}\left(y_e^i \exp(\theta_i)\right),$$

  where y_e^i is the standardized expected number of deaths, based on covariates, and $\exp(\theta_i)$ is the (relative) risk.
- Moreover $y_e^i \exp(\theta_i)$ is the expected number of deaths.

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  where y_e^i is the standardized expected number of deaths, based on covariates, and $\exp(\theta_i)$ is the (relative) risk.
- Moreover $y_e^i \exp(\theta_i)$ is the expected number of deaths.
- Expect similar risks in neighboring counties,

$$\boldsymbol{\theta} \sim \text{Normal}\left(0, K(\alpha, \rho)\right).$$

- The covariance between θ_i and θ_j is

$$K_{ij} = \alpha^2 \exp\left(-\frac{||x_i - x_j||^2}{2\rho^2}\right),$$

  where x_i is the 2D location of cell i.

Disease map of Finland [Vanhatalo et al., 2010]
Full model:

$$
\begin{aligned}
\alpha &\sim \text{invGamma}(10, 10) \\
\rho &\sim \text{invGamma}(2.42, 14.8) \\
\boldsymbol{\theta} &\sim \text{Normal}(0, K(\alpha, \rho)) \\
y_i &\sim \text{Poisson}\left(y_e^i \exp(\theta_i)\right)
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\end{aligned}
$$

Tipp:

- This model admits a non-centered parameterization, with

$$\boldsymbol{\eta} \sim \text{normal}(0, I) \; ; \; \boldsymbol{\theta} = L\eta,$$

  where L is the *Cholesky decomposition* of K, that is $K = LL^T$ and L is lower-triangular.
- For numerical stability, can add a "jitter" $\epsilon = 10^{-8}$ along the diagonal of K, to make sure eigenvalues are positive.

Exercise: *Fit the disease map model.*

- *For convenience, we only examine 100 cells.*
- *Make sure there are no divergent transitions.*
- *Examine* $\widehat{R}$*, ESS, and the trace plots for* α*,* ρ *and* θ_1*.*

Tips:

- *The type for* `x` *is* `array[n_obs] vector[n_coordinates]`*.*
- *The following* `Stan` *functions may come in handy:*
  - `gp_exp_quad_cov(x, alpha, rho)`
  - `cholesky_decompose(Sigma)`
  - `inv_gamma()`
  - `poisson_log()` *(but ok to use* `poisson()`*)*

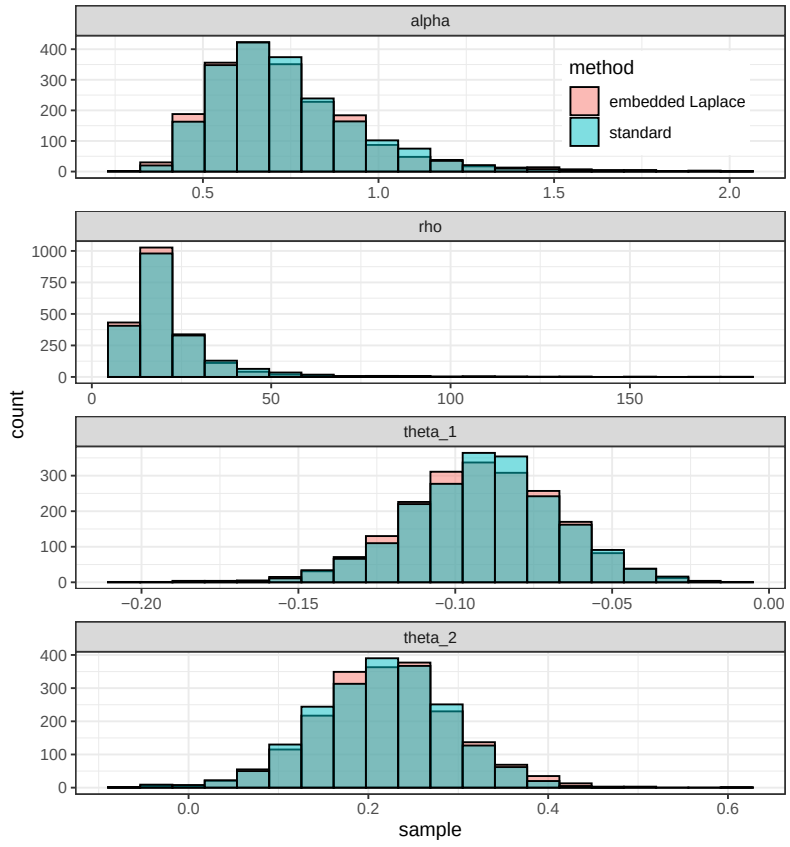
Can we marginalize out θ when $p(\boldsymbol{y} \mid \boldsymbol{\theta})$ is non-Gaussian?

- Can do a *Laplace approximation*,

$$\text{normal}(\mu^*, \Sigma^*) \approx p(\boldsymbol{\theta} \mid \boldsymbol{y}, \phi),$$

  where μ^* matches the mode of $p(\boldsymbol{\theta} \mid \boldsymbol{y}, \phi)$ and Σ^* its curvature.
- This also gives us an approximation for $p(\mathbf{y} \mid \phi)$.
- This is the driving idea behind the *integrated Laplace approximation* [Rue et al., 2009].

Stan supports a prototype integrated Laplace approximation [Margossian et al., 2020, Margossian et al., 2023].



For this application, integrated Laplace approximation is ∼10 times faster and does not require adjusting `adapt_delta`.

- `Stan` 's integrated Laplace approximation is a prototype.
- Works well for standard likelihoods and general linear models.

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- Works well for standard likelihoods and general linear models.

- The *adjoint differentiated Laplace approximation* [Margossian et al., 2020, Margossian, 2023] allows users to specify their own covariance function K and likelihood, rather than picking from a menu of options.
- The underlying autodiff method to compute $\nabla_\phi \log p_{\mathcal{G}}(\mathbf{y} \mid \phi)$ scales when ϕ is high-dimensional.
- **Ongoing work:** diagnostics to check if approximation is reliable.

- For more, see https://htmlpreview.github.io/?https://github.com/charlesm93/StanCon2020/blob/master/notebook-2022/lgm_stan.html

Strategies to deal with the geometry of hierarchical models:

- Increase the target acceptance probability, i.e. reduce the step size of the leap frog integrator.
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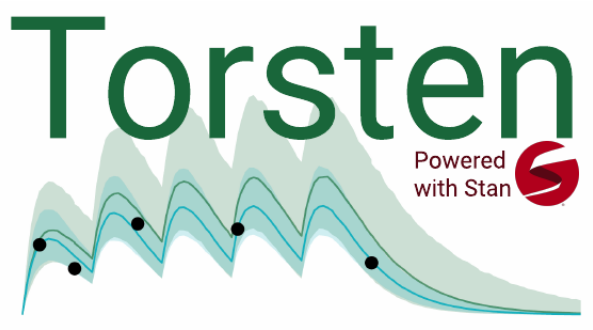
- Riemannian HMC: evaluate a dynamic mass matrix based on the local curvature [Girolami et al., 2011].
- Delayed rejection HMC: reduce step size after rejection [Modi et al., 2023].

IX
Torsten

`Torsten` offers additional built-in functions to write pharmacokinetics/pharmacodynamics (PK/PD) models

Each Torsten function requires users to specify:

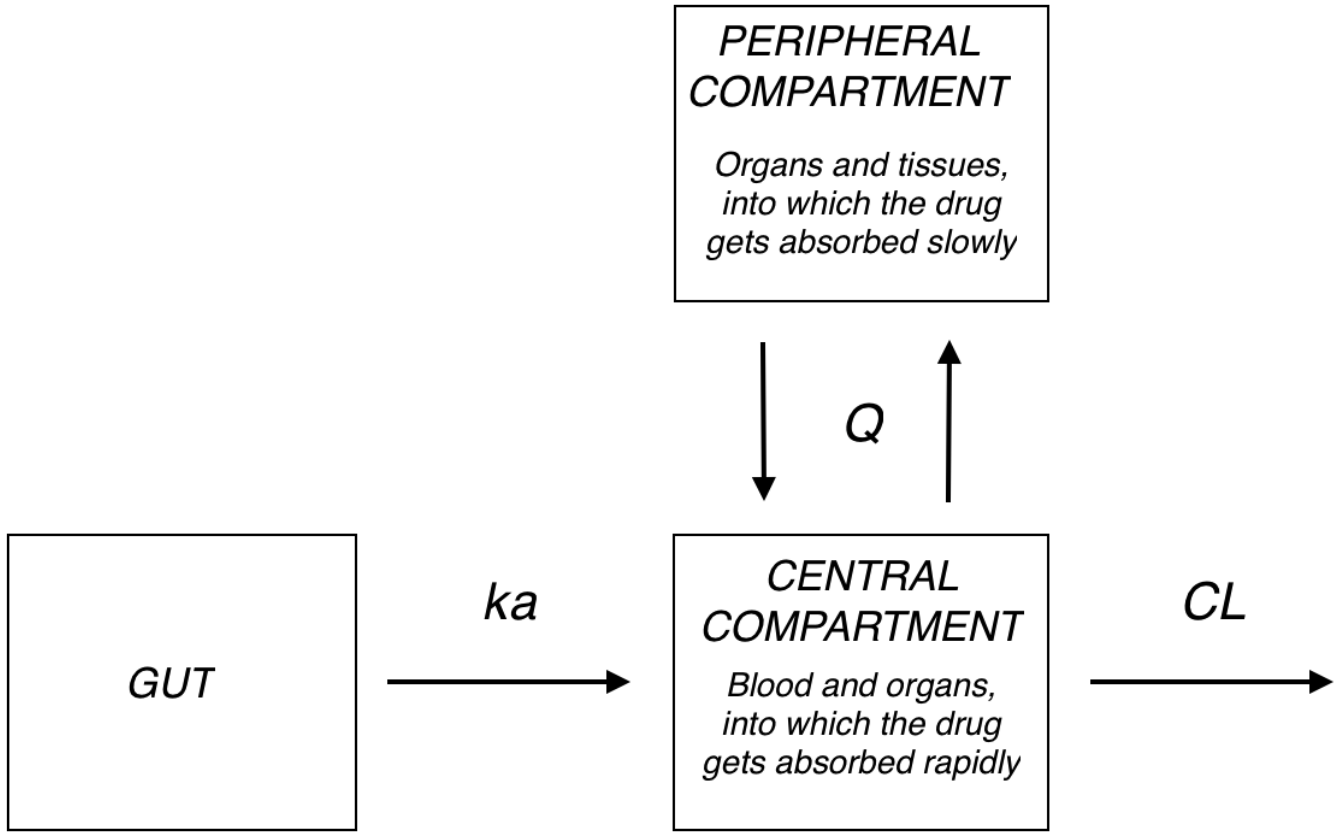
- A system of ODEs and a method to solve it.
- An event schedule, following the `PREDPP` convention from `NONMEM`



Helpful references:

- User manual:
  `https://metrumresearchgroup.github.io/Torsten/`
- Tutorial in *CPT: P&SP* [Margossian et al., 2022]

Two compartment model with absorption from the gut



Two compartment model with absorption from the gut

$$
\begin{aligned}
y'_{\text{gut}} &= -k_a y_{\text{gut}} \\
y'_{\text{cent}} &= k_a y_{\text{gut}} - \left(\frac{CL}{V_{\text{cent}}} + \frac{Q}{V_{\text{cent}}} \right) y_{\text{cent}} + \frac{Q}{V_{\text{peri}}} y_{\text{peri}} \\
y'_{\text{peri}} &= \frac{Q}{V_{\text{cent}}} y_{\text{cent}} - \frac{Q}{V_{\text{peri}}} y_{\text{peri}}
\end{aligned}
$$

Two compartment model with a absorption from the gut

Denote $\theta = \{CL, Q, VC, VP, k_a\}$, the ODE parameters. Then

$$y' = f(y, t, \theta)$$

Given an initial condition $y_0 = y(t_0)$, solving the above ODE gives us the *natural evolution* of the system at any given time point.

The event schedule

An event can be a(n):

- Sate changer: an (exterior) intervention that alters the state of the system; for example a bolus dosing or the beginning of an infusion.
- Observation: measurement of a quantity of interest at a certain time.

Example: single patient model

Event schedule:

- Bolus doses with 1200 mg, administered every 12 hours, for a total of 15 doses.
- Many observations for the first, second, and last doses
- Additional observation every 12 hours

The observation are plasma drug concentration measurement.

See `data/twoCpt.data.json`.

Torsten function

```
matrix pmx_solve_rk45(function system, int nCmt,
                      real[] time, real[] amt,
                      real[] rate, real[] ii,
                      real[] evid, int[] cmt,
                      int[] addl, int[] ss,
                      real[] theta,
                      real rel_tol, real abs_tol,
                      int max_num_steps)
```

- Returns a `matrix[nCmt, nEvent]` with the drug mass in each compartment at each event
- Takes in:
  - an ODE to solve, which takes in `theta`.
  - an event schedule
  - parameters for the ODEs
  - (optional) tuning parameters for ODEs

System function

Declare system in the `functions` block.

```
 vector system(real time,
               vector y,
               real[] theta,
               real[] x_r,
               int[] x_i) {
  array[3] real dydt;
  real CL = theta[1];
  real Q = theta[2];
  ⋮
  return dydt;
}
```

Remark: Torsten uses an older API for the ODE integrator, meaning f must follow a stricter signature (although not a less flexible one).

Prior:

$$\begin{aligned} CL &\sim \text{logNormal}(\log 10, 0.25) \\ Q &\sim \text{logNormal}(\log 15, 0.5) \\ VC &\sim \text{logNormal}(\log 35, 0.25) \\ VP &\sim \text{logNormal}(\log 105, 0.5) \\ ka &\sim \text{logNormal}(\log 2.5, 1) \\ \sigma &\sim \text{Normal}^{+}(0, 1) \end{aligned}$$

Likelihood:

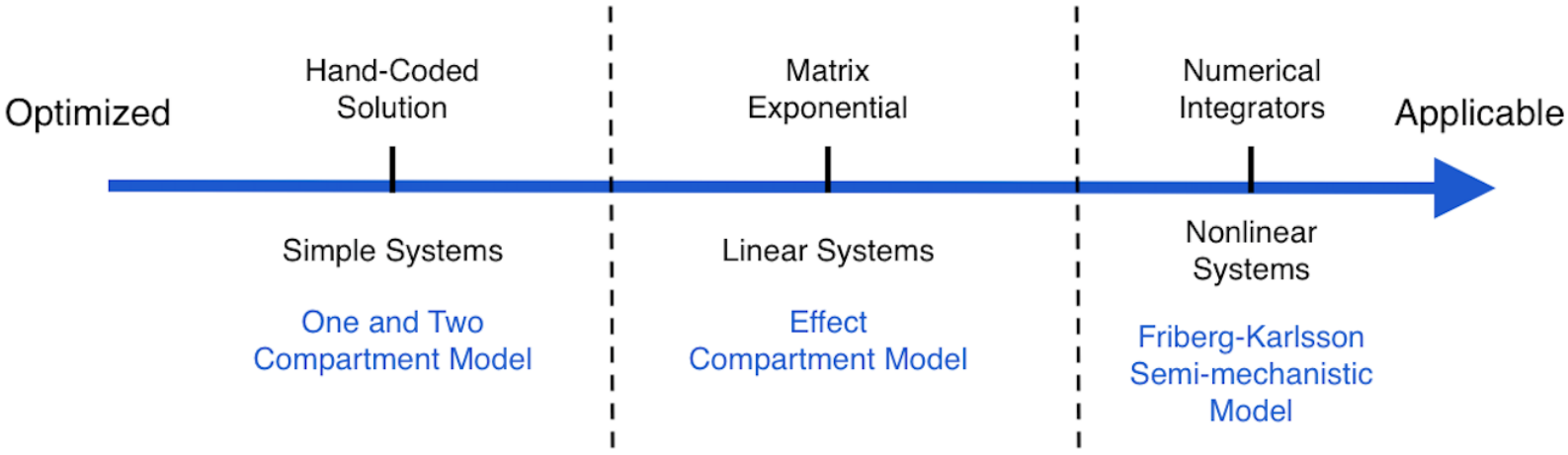
$$cObs \sim \text{logNormal}\left(\log\left(\frac{y_2}{VC}\right), \sigma\right)$$

Exercice: write, fit, and criticize the two compartment model for a single patient.

- *There's a bit of bookkeeping involved, so we'll write the* `data` *block together.*
- *As always, check the inference:* $\widehat{R}$*, ESS, and plots.*
- *Perform posterior predictive checks: do the simulations capture the characteristics in the data that we care about?*

- *Specify the control parameters of the ODE integrator and implement a PSIS diagnostic to check that the solver is sufficiently precise.*

Torsten supports alternatives to numerical integrators.



- It possible to combine multiple methods, e.g. solve the PK analytically and the PD numerically [Margossian and Gillespie, 2017].

Torsten function

```
matrix pmx_solve_twocpt(real[] time, real[] amt,
                        real[] rate, real[] ii,
                        real[] evid, int[] cmt,
                        int[] addl, int[] ss,
                        real[] theta)
```

- Returns a `matrix[nCmt, nEvent]` with the drug mass in each compartment at each event
- Takes in:
  - an event schedule
  - parameters for the ODEs

Analytical solutions are also available for the one compartment model.

```
matrix pmx_solve_onecpt(real[] time, real[] amt,
                        real[] rate, real[] ii,
                        real[] evid, int[] cmt,
                        int[] addl, int[] ss,
                        real[] theta)
```

- This time $\theta = (k_a, CL, V_{\text{cent}})$.

Exercise: Fit the one and two compartment models using analytical solutions.

- *Compare the posterior predictive checks obtain with each model.*
- *Estimate the loo-CV predictive score of both models.*

X
Population models

Usuaully we have multiple patients in our clinical trial.

With a hierarchical model, we can:

- estimate parameters for each patient,
- estimate population parameters and simulate new patients.

Population two compartment model

For the i^{th} patient, estimate

$$\theta_i = (\text{CL}_i, \text{Q}_i, \text{VC}_i, \text{VP}_i, k_{a_i})$$

Hierarchical prior:

$$\log \theta_i \sim \text{Normal}(\log \theta_{\text{pop}}, \Omega)$$

$$\Omega = \begin{pmatrix} \omega_1 & 0 & 0 & 0 & 0 \\ 0 & \omega_2 & 0 & 0 & 0 \\ 0 & 0 & \omega_3 & 0 & 0 \\ 0 & 0 & 0 & \omega_4 & 0 \\ 0 & 0 & 0 & 0 & \omega_5 \end{pmatrix}$$

Population two compartment model

Priors:

$$
\begin{aligned}
CL_{\text{pop}} &\sim \text{logNormal}(\log(10), 0.25) \\
Q_{\text{pop}} &\sim \text{logNormal}(\log(15), 0.5) \\
VC_{\text{pop}} &\sim \text{logNormal}(\log(35), 0.25) \\
VP_{\text{pop}} &\sim \text{logNormal}(\log(105), 0.5) \\
ka_{\text{pop}} &\sim \text{logNormal}(\log(2.5), 0.25) \\
\sigma &\sim \text{normal}^{+}(0, 1) \\
\omega_j &\sim \text{normal}^{+}(0, 0.2)
\end{aligned}
$$

Likelihood:

$$
\text{cObs} \sim \text{normal}\left(\log\left(\frac{y_2}{VC}\right), \sigma\right)
$$

Helpful bookkeeping

We now need to define parameters for each patient:

- `real theta[nSubjects, nTheta];`

We sequentially compute the concentration for each patient:

- `for (j in 1:nSubjects) {...}`

The `start` and `end` variables tell us which events belong to each patient. For the j^{th} patient, we need:

- `time[start[j]:end[j]], amt[start[j]:end[j]], ...`
- `theta[j, ]`

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- `time[start[j]:end[j]], amt[start[j]:end[j]], ...`
- `theta[j, ]`
- Such a `for` loop can be parallelized.

Exercise: *Build, fit, and criticize a hierarchical two compartment model.*

- *Make sure the inference is reliable. There should be no divergent transitions, $\widehat{R}$ should be close to 1 for all variables of interest, and the ESS sufficiently large.*
- *Perform posterior predictive checks:*
  - *Simulate data for existing patients.*
  - *Simulate data for new patients, drawn from the population distribution.*

Within-chain parallelization

Not every operation in Stan needs to be computed sequentially.

When there is conditional independence,

$$
\begin{aligned}
& \log p(\mathbf{y} \mid \theta) \\
= & \sum_{n=1}^{N} \log p(y_n \mid \theta) \\
= & \left(\sum_{n=1}^{I} \log p(y_n \mid \theta) \right) + \left(\sum_{n=I+1}^{J} \log p(y_n \mid \theta) \right) + \cdots
\end{aligned}
$$

and each sub-sum can be computed in parallel.

Within-chain parallelization

Can use the function

```
reduce_sum(F f, array[] T x, int grain_size, ···)
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- `f` computes a partial sum, given a subset of `x`.

  Each thread may compute more than one term in the sum.

- `grain_size` is the recommended number of terms in the sum computed on each thread.
- $\cdots$ additional arguments passed to all subsums.

- The partial sum has the following signature

```
f (array[] int x,
   int start_subject, int end_subject, ···)
```

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```
f (array[] int x,
   int start_subject, int end_subject, ···)
```

- We may pick `x` to be the index of the subject,

```
x = (1, 2, 3, 4, ···, n_subject)
```

- Then `start_subject` indexes the first subject and `end_subject` the last subject in the partial sum.

- The partial sum has the following signature

```
f (array[] int x,
   int start_subject, int end_subject, ···)
```

- We may pick `x` to be the index of the subject,

```
x = (1, 2, 3, 4, ···, n_subject)
```

- Then `start_subject` indexes the first subject and `end_subject` the last subject in the partial sum.
- For more guidance, see https://mc-stan.org/docs/stan-users-guide/reduce-sum.html.

Need to change our R script to enable multi-threading per chain:

```
mod <- cmdstan_model("model/twoCptPop_rs.stan"),
          cpp_options = list(stan_threads = TRUE))
```

```
n_chains <- 1
fit_rs <- mod$sample(data = data, chains = n_chains,
             init = init,
             parallel_chains = n_chains,
             threads_per_chain = 3,
             iter_warmup = 500, iter_sampling = 500,
             seed = 123, adapt_delta = 0.8)
```

Exercise: *Write the two compartment model using* `reduce_sum` *to parallelize the solving of the ODE and the evaluation of the log likelihood across patients.*

- *Make sure your posterior estimate is consistent with the previous model.*
- *Try running 1, 2, 3, 4+ threads per chain and examine the run time for a single chain.*

Torsten supports functions to do solve ODEs across patients using multiple threads,

`pmx_solve_ode_group_*`

- See https://metrumresearchgroup.github.io/Torsten/function/ode-group-integ/

XI
Concluding Remarks

Where does Stan fit in the Bayesian modeler's toolkit?

Historical contribution:

- Stan was born around 2012.
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Several algorithms were developed as part of Stan 's development:

- Adaptive Hamiltonian Monte Carlo [Hoffman and Gelman, 2014, Betancourt, 2017]
- ADVI: a black box variational inference [Kucukelbir et al., 2017]
- PathFinder: an improved variational inference [Zhang et al., 2022].

- Delayed rejection HMC [Modi et al., 2023]
- Adjoint-differentiated Laplace approximation [Margossian et al., 2020]

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- Many automatically deployed diagnostic tools.

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- A flexible and expressive language, with (in my view) the best user interface amongst probabilistic programming languages for specifying a model.
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- Reasonable support for parallelization across cores and GPUs (other languages are better in some settings).

What do `Stan` and `Torsten` bring to the table?

- A flexible and expressive language, with (in my view) the best user interface amongst probabilistic programming languages for specifying a model.
- Algorithms that are efficient for full Bayesian inference, and that warn you when they fail.
- Many automatically deployed diagnostic tools.
- Reasonable support for parallelization across cores and GPUs (other languages are better in some settings).
- It's free and open-source.

Our goals:

- More expressive features.
- Improved computation for large systems of ODEs.
- Algorithms for fast approximate Bayesian inference
- BridgeStan: a package that makes it easy for users to specify their own inference algorithm and run them on Stan models (`https://github.com/roualdes/bridgestan`).

Stan by the people, for the people

- Stan is open source: https://github.com/stan-dev
- So is Torsten : https://github.com/metrumresearchgroup/Torsten
- Contributing new functions to Stan : https://github.com/stan-dev/stan/wiki/Contributing-New-Functions-to-Stan

Other probabilistic programming languages out there!

- `PyMC`:
  - Written in `Python`
- `Turing`
  - Written in `Julia`
  - Very clean autodiff and good support for ODE solvers.
- `TensorFlow Probability`
  - Interfaces with `JAX` and designed to work on GPUs.
  - Hackable inference algorithms.
  - Supports GPU-friendly samplers.
- `PyTorch`
  - Designed to work on GPUs.
  - Support for neural networks and optimization algorithms.

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