Stan with R for analysis

R in Pharma

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The Abstract that Never Made It

This will be a quick, informal session about:

- what is Stan?
- what can it be used for? (what shouldn't it be used for?)
- why is there a lot of buzz around Stan now?
- how to use Stan from R
- examples in pharma
- time for questions

Before we start

- Questions
  - Who's heard of Stan?
  - Who's used Stan?
  - When did you start?
- Please ask questions at any time
  - Might get an immediate response
  - A delayed answer
  - Postponed for scope
    (and we'll take it offline)

What is Stan?

What is Stan?

1. Language

2. Inference algorithms

3. Interfaces

Stan is a language

- **Purpose:** specify statistical models

$$p(\theta, x)$$

  - Influenced by BUGS and JAGS
  - Imperative
  - Statically-typed

  - Ordinary differential equations!

Language

- Statistical model specification language
  - specify: data, parameters, joint probability distribution

- Domain specific language
  not C++, R, Python, BUGS, JAGS...
- Imperative language
  c.f. declarative (BUGS, JAGS), object oriented (Figaro)
- Language is built to formulate complicated statistical models, include ODEs.

What does Stan look like?

```
data {
  int<lower=0> N;
  int<lower=0,upper=1> y[N];
}
parameters {
  real<lower=0,upper=1> theta;
}
model {
  y ~ bernoulli(theta);
}
```

Technical aside

- Gradients available for everything in the Stan language!
  - Reverse mode automatic differentiation
  - O(1) with respect to function evaluation,
    irrespective of the number of parameters!!

- The Stan compiler accepts a Stan program (.stan)
  and generates a C++ header file (.hpp)
  - The backend is all C++

Inference Algorithms

- Bayesian inference; Markov Chain Monte Carlo (MCMC)
- Approximate Bayesian inference
- Optimization

Inference Algorithms

- Bayesian inference; Markov Chain Monte Carlo (MCMC)
  - $p(\theta \mid x)$ approximated with $\{\theta^{(1)}, \theta^{(2)}, \ldots, \theta^{(N)}\}$

- Approximate Bayesian inference
  - ex: $\hat{p}(\theta \mid x) \approx q(\hat{\phi})$ where $\hat{\phi} = \underset{\phi}{\operatorname{argmin}} \; D_{\mathrm{KL}}\left(q(\theta \mid \phi) \,||\, p(\theta \mid x)\right)$
- Optimization
  - $\hat{\theta} = \underset{\theta}{\operatorname{argmax}} \; p(\theta, x)$ (only holds when there's a single optima)

Inference Algorithms

- Bayesian inference; Markov Chain Monte Carlo (MCMC)
  - **No-U-Turn Sampler (NUTS)**
  - Hamiltonian Monte Carlo (HMC)
- Approximate Bayesian inference
  - Automatic Differentiation Variational Inference (ADVI)
- Optimization
  - Limited memory Brayden-Fletcher-Goldfarb-Shanno (L-BFGS)

Platforms and Interfaces

- Runs in **Windows**, **Mac OS X**, and **Linux**
- C++ API: portable, standards compliant (C++11)
- Interfaces
  - **RStan**: R interface (Rcpp in memory)
  - CmdStan: command-line or shell access (direct executable)
  - PyStan: Python interface (Cython in memory)
  - MatlabStan: Matlab interface (external process)
  - Stan.jl: Julia interface (external process)
  - StataStan: Stata interface (external process)

Open source

- Stan is freedom-respecting, open-source software
  - Math library, Stan library, **CmdStan**: **new BSD license**
  - **RStan**, PyStan: **GPL**
- Hosted on GitHub
  http://github.com/stan-dev/
- Over 65 contributors since 2011
- Active development

What can it be used for?

(what shouldn't it be used for?)

What shouldn't it be used for?

- Stan is not an R replacement.
  - Doesn't to general-purpose computing well.
  - No graphing built into the language.

- If there's already an R package for exactly what you want, you should probably use it.
- If you need it fast.

When should I use Stan?

- Limitations in your favorite package
  - You have a little more structure than the package allows for
  - It only does some custom inference algorithm
- Bayesian inference is needed: hierarchical models
  - Optimization / MLE isn't sensible for hierarchical models with less data
  - Conditions for approximate algorithms aren't met
- Have time to get it correct
  - Most uses are custom, requiring careful coding in Stan
  - Takes time to write models correctly

What's with the buzz?

Big advances in Bayesian computing

No-U-Turn Sampler is a game changer

MCMC algorithms

Goal: estimate $p(\theta \mid x)$

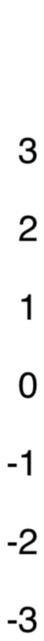
- Estimate distribution with draws $\theta^{(1)}, \theta^{(2)}, \ldots, \theta^{(N)}$
- $$\mathbb{E}[f(\theta)] = \int f(\theta) \times p(\theta \mid x)\, d\theta$$
$$\approx \frac{1}{N} \sum_{n=1}^{N} f\left(\theta^{(n)}\right)$$

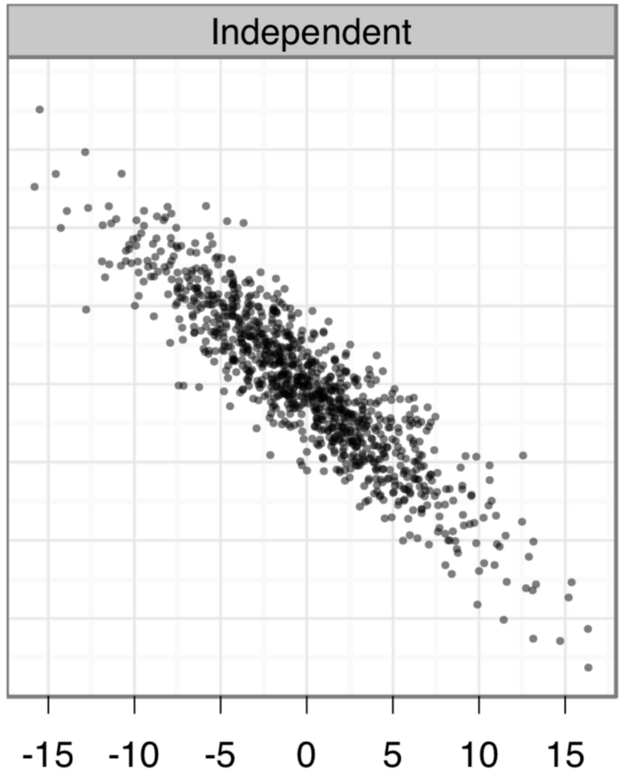
Efficiency of different MCMC algorithms

- Random-walk Metropolis Hastings
- Gibbs sampling
- Hamiltonian Monte Carlo with **No-U-Turn Sampler (NUTS)**

250 dimensional Normal distribution

2d projection



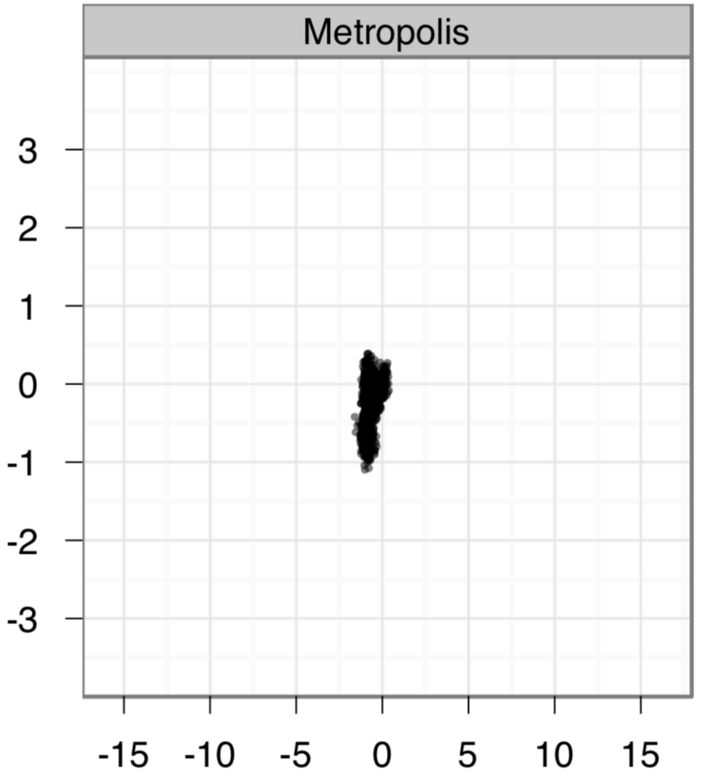


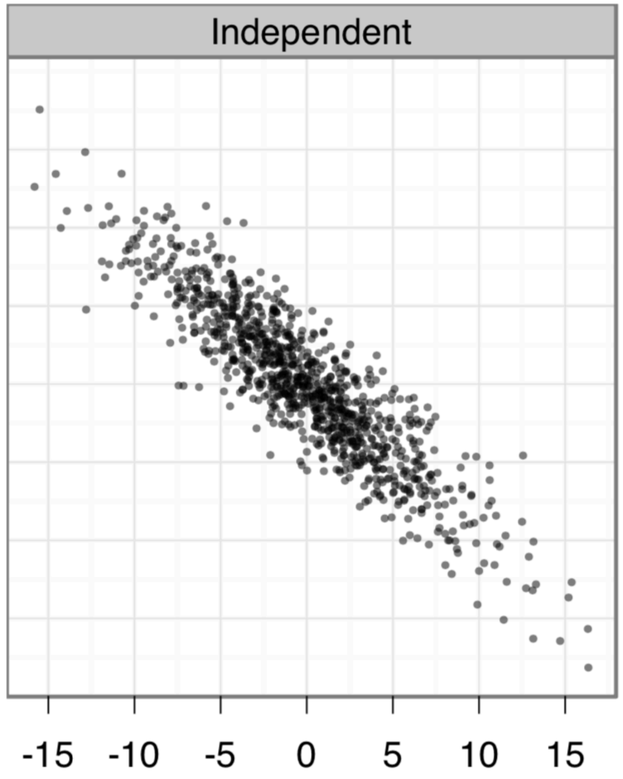
1000 independent draws

Hoffman and Gelman. "The No-U-Turn Sampler." JLMR. 2014.

250 dimensional Normal distribution

2d projection



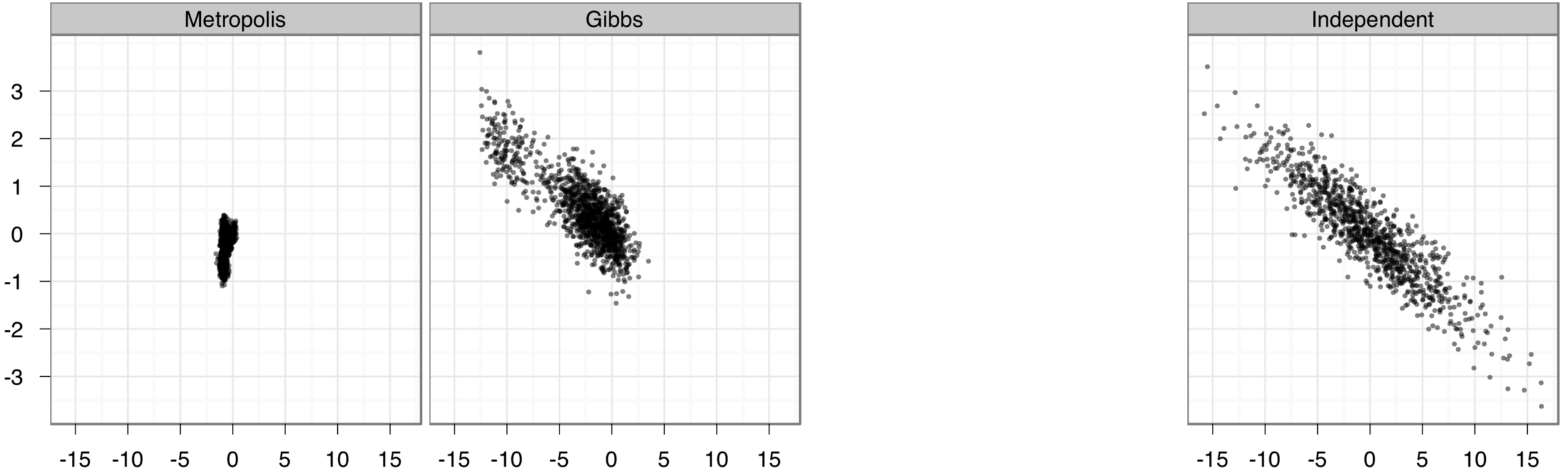


1M draws (thinned)

Hoffman and Gelman. "The No-U-Turn Sampler." JLMR. 2014.

250 dimensional Normal distribution

2d projection



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250 dimensional Normal distribution

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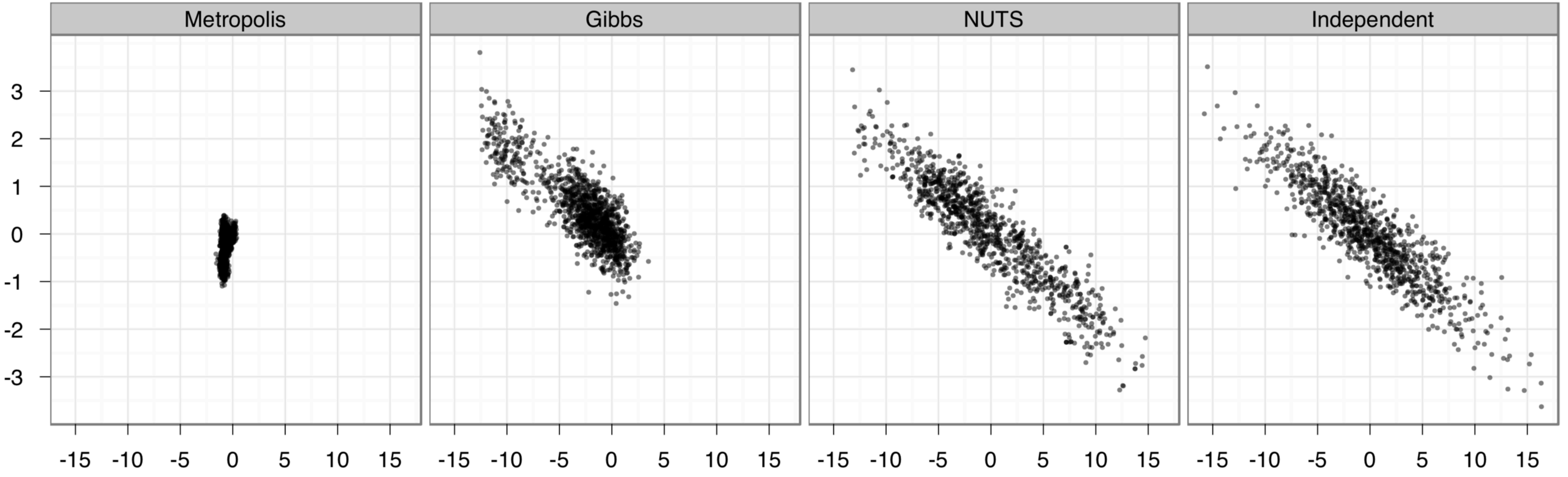
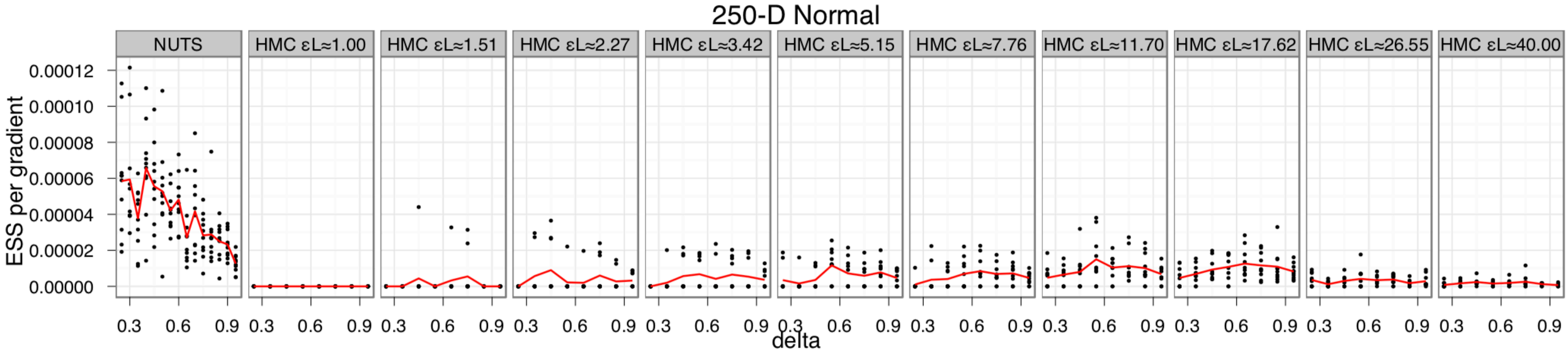


1000 draws

Hoffman and Gelman. "The No-U-Turn Sampler." JLMR. 2014.

Quick aside: HMC is not enough



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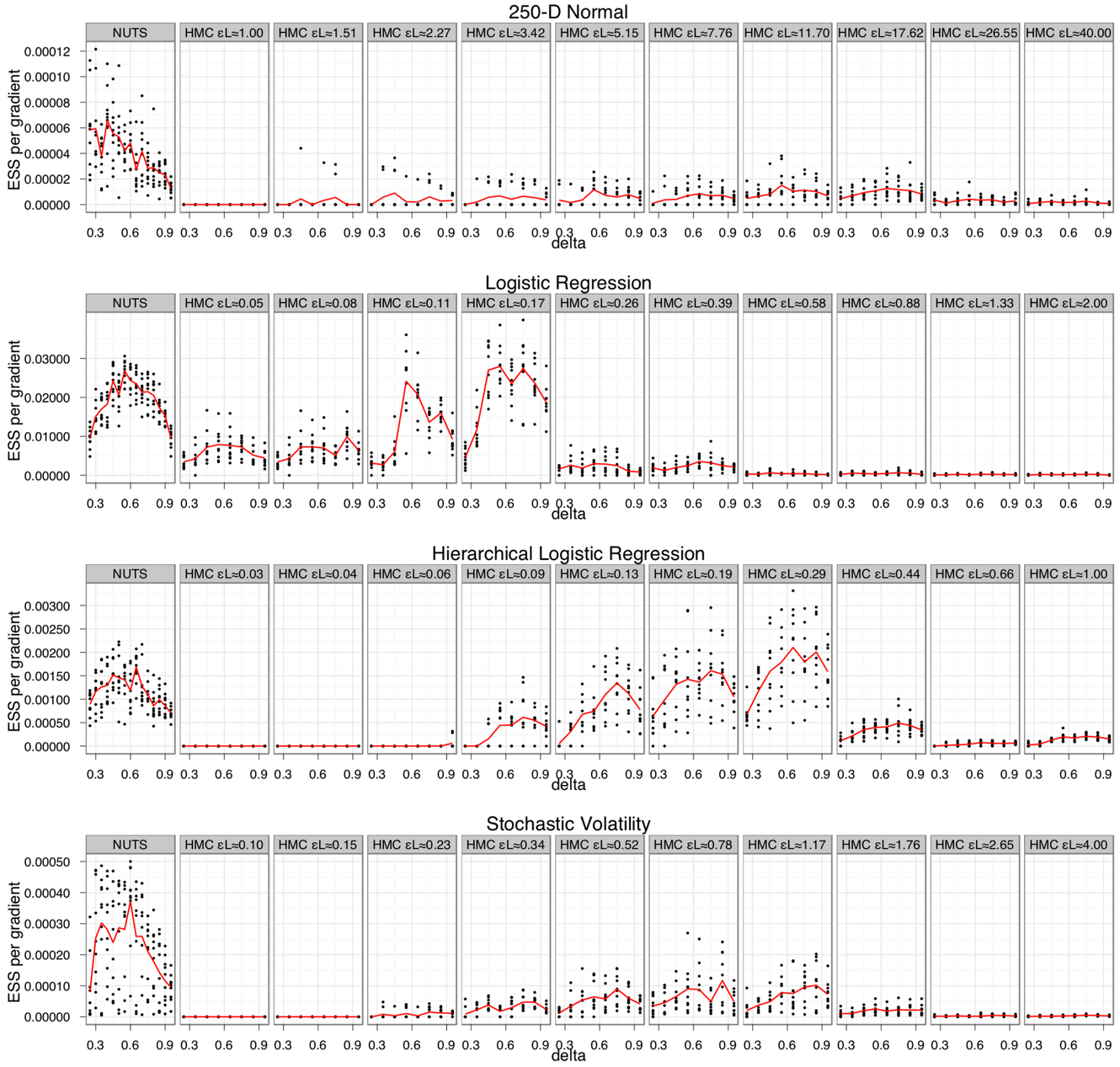


Statistical inference has changed since 2011!

What's with the buzz?

- New algorithms (NUTS) requires gradients
  - Every Stan's model has gradients! No need to hand-write gradients.
- Ordinary Differential Equations are in the language!
  - ODEs are part of the Stan language.
  - Specify ODE and a statistical model
  - Can fit PK/PD models with full Bayesian inference!
- Stan's a newcomer
  - But... it's been around since 2011.

How to use Stan from R?

RStan installation

- It's on CRAN.

```
install.packages("rstan")
```

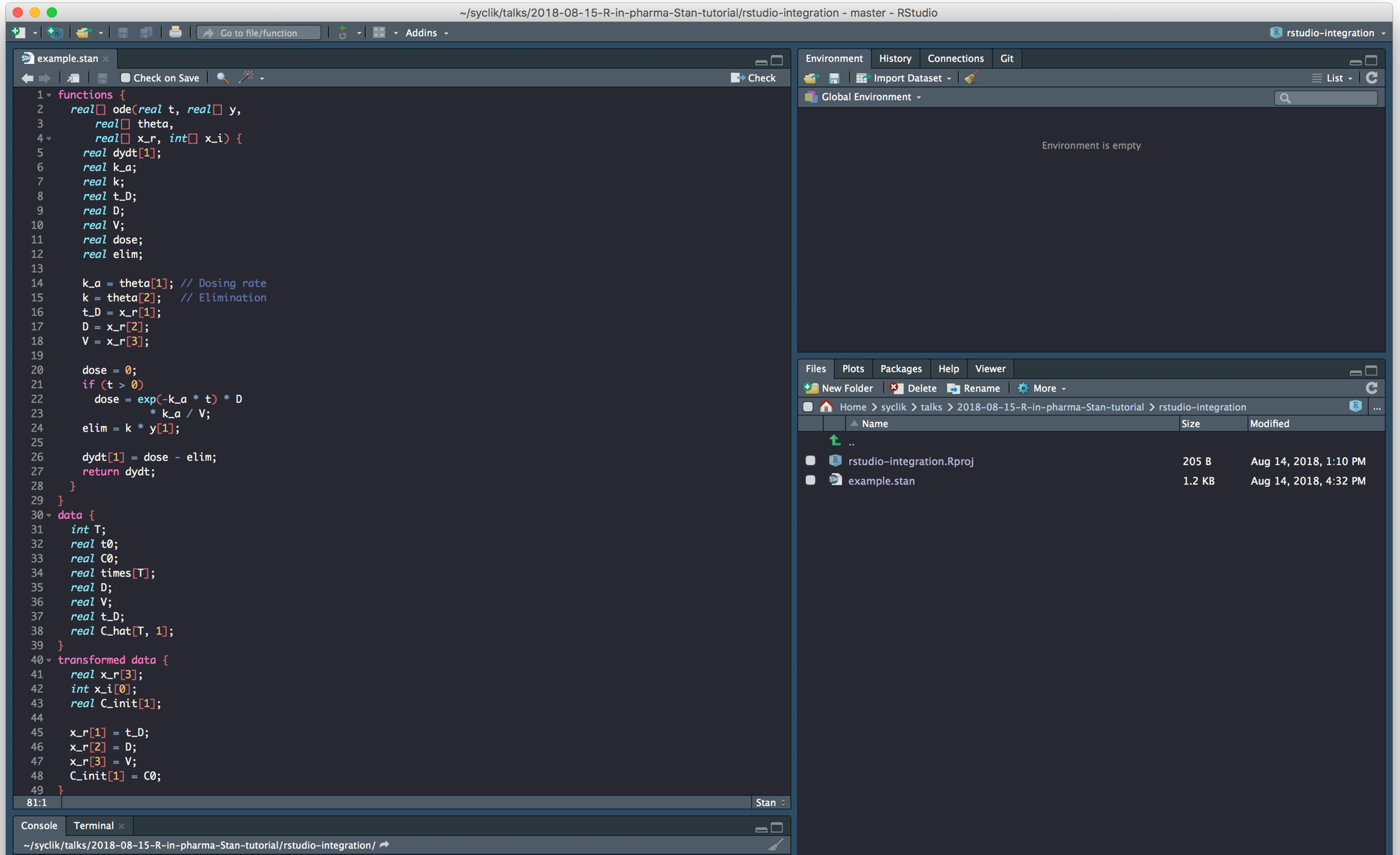
- Requires a C++ toolchain
  - Installing RStan on Mac or Linux
  - Installing RStan on Windows

RStudio Integration

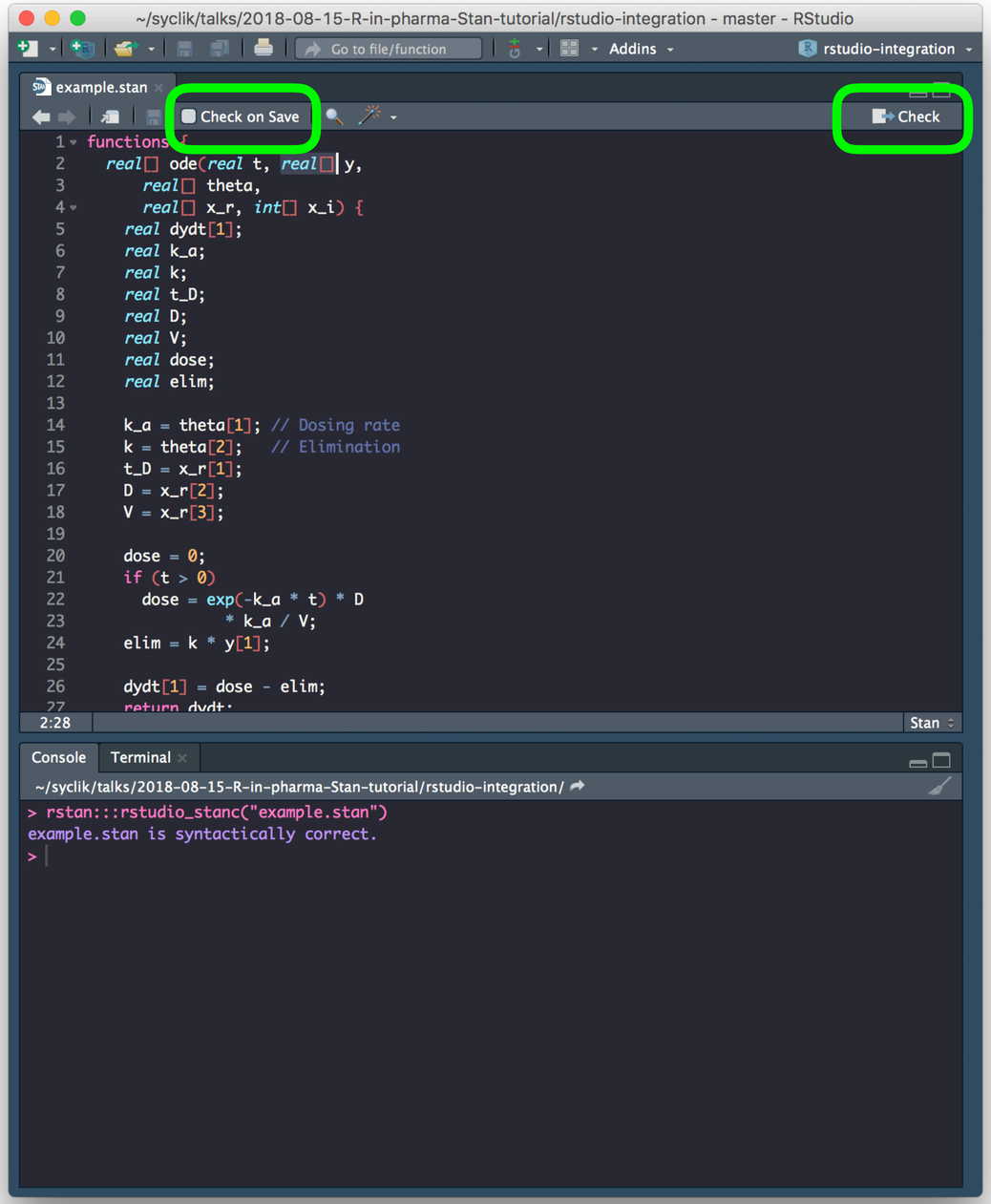
- Stan syntax highlighting

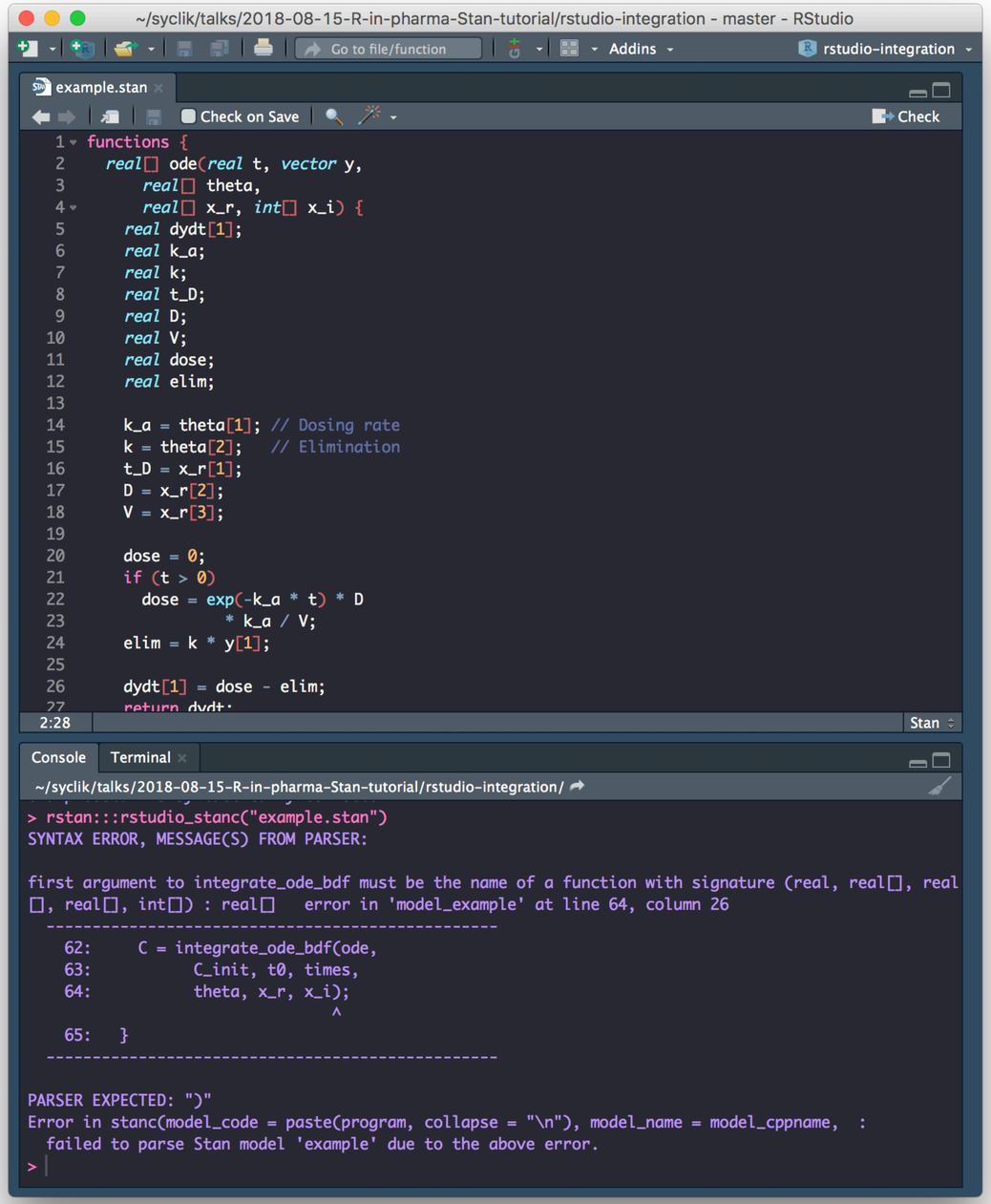
- Stan syntax checking

RStudio: syntax highlighting



RStudio: syntax validation





Running RStan: basics

1. Load library
   library(rstan)

2. Write program to file: example.stan

3. Create data (in R): dat

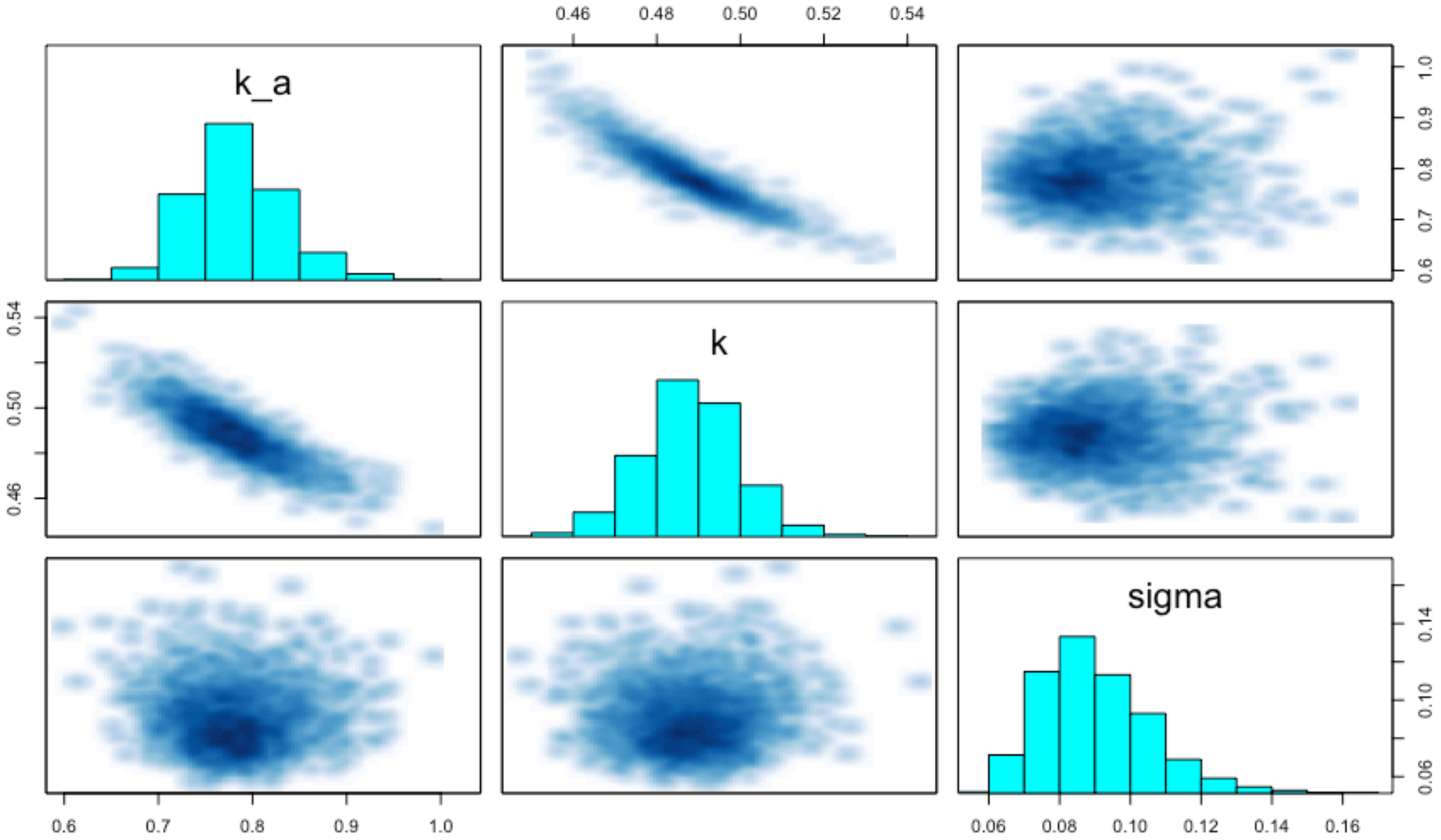
4. Run
   fit <- stan("example.stan", data = dat)

5. Posterior analysis
   print(fit)

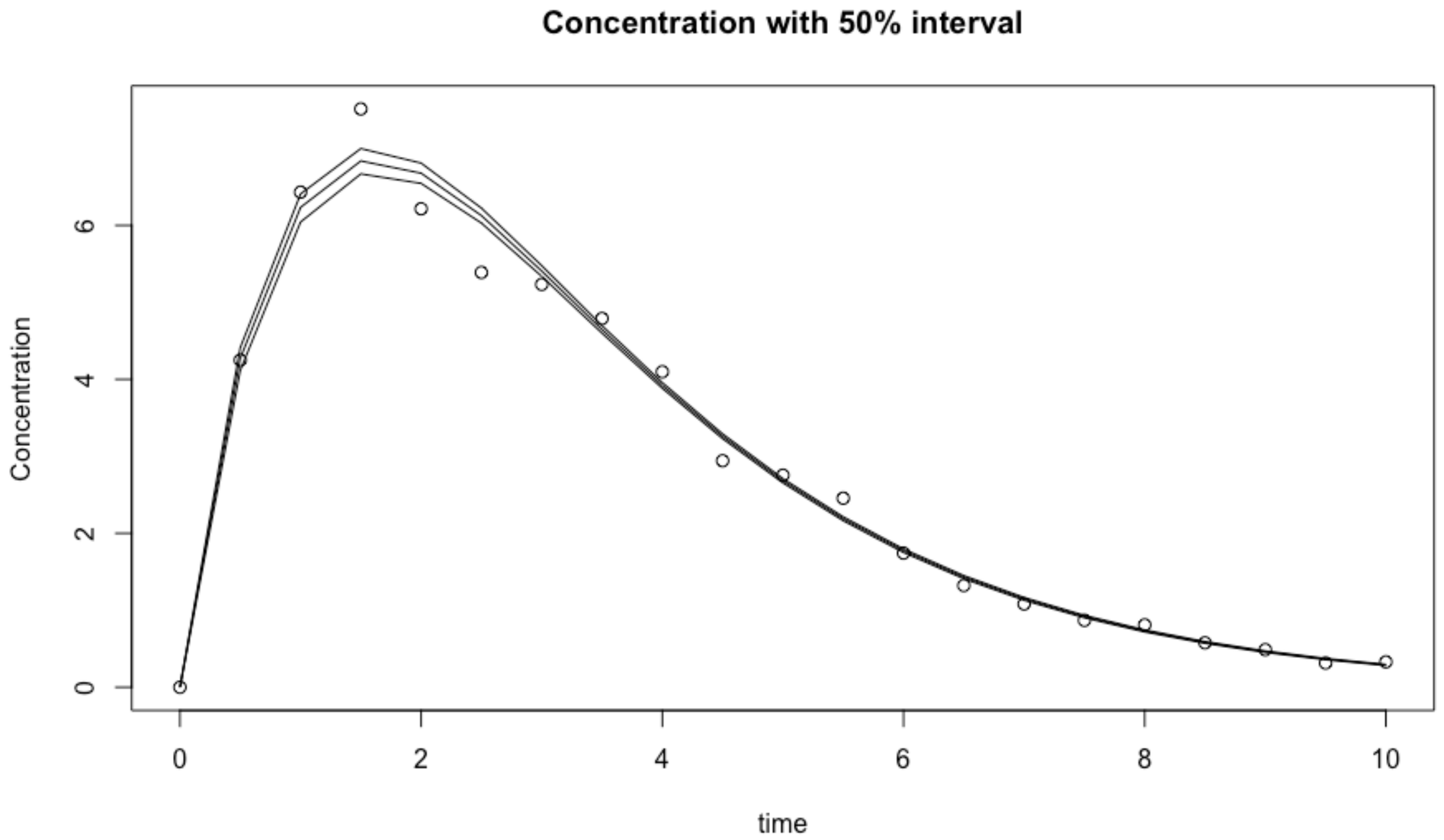
Posterior summary

```
> print(fit, c("k_a", "k", "sigma"))
Inference for Stan model: example.
4 chains, each with iter=2000; warmup=1000; thin=1;
post-warmup draws per chain=1000, total post-warmup draws=4000.

      mean se_mean   sd 2.5%  25%  50%  75% 97.5% n_eff Rhat
k_a   0.78       0 0.05 0.69 0.75 0.78 0.81  0.89  1785    1
k     0.49       0 0.01 0.47 0.48 0.49 0.50  0.51  1742    1
sigma 0.09       0 0.02 0.07 0.08 0.09 0.10  0.13  1788    1

Samples were drawn using NUTS(diag_e) at Tue Aug 14 16:42:20 2018.
For each parameter, n_eff is a crude measure of effective sample size,
and Rhat is the potential scale reduction factor on split chains (at
convergence, Rhat=1).
```

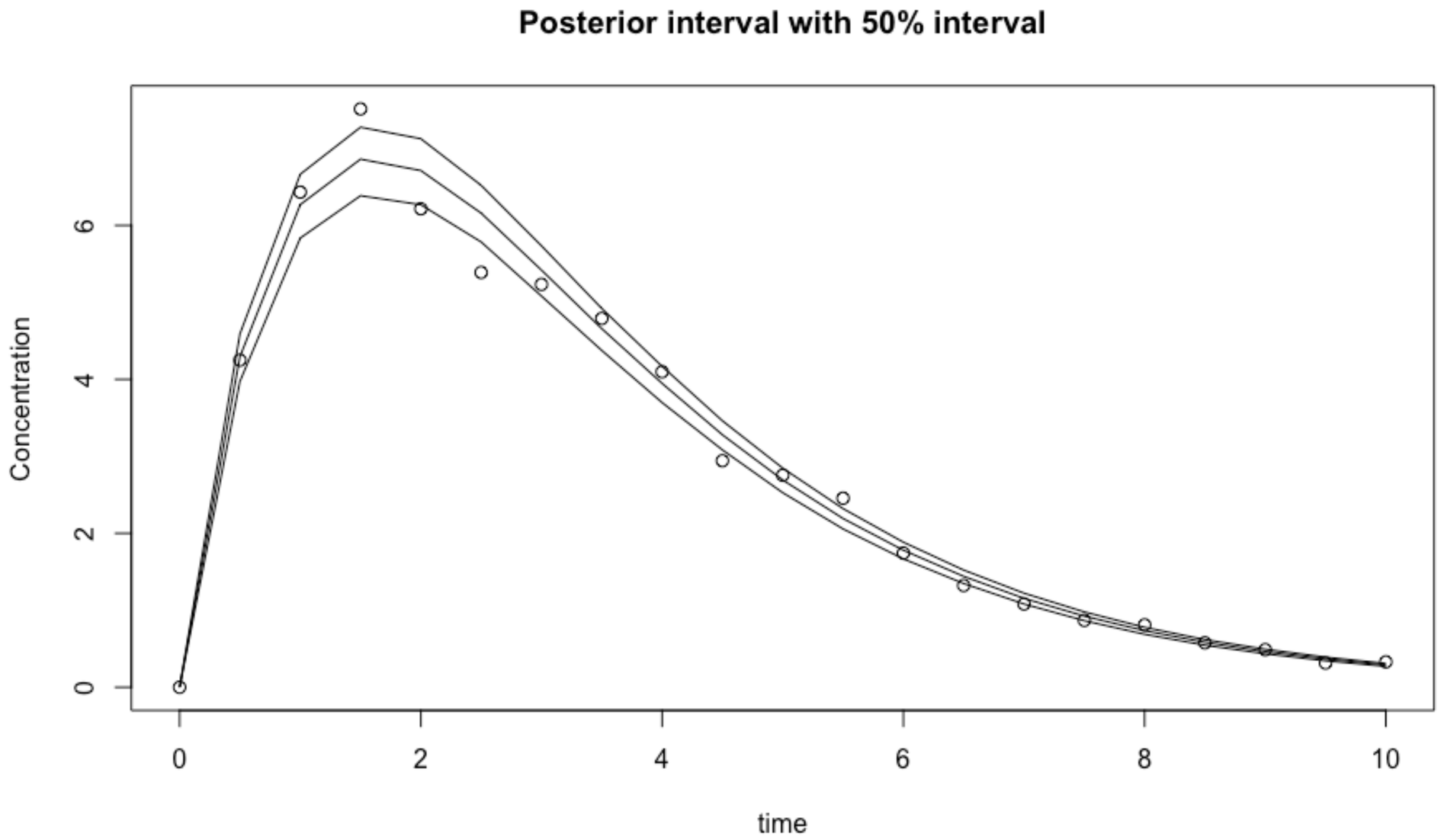
Access joint posterior distribution



Posterior distribution of concentration



Posterior predictive distribution



examples

Decompose PK example

- Switch to RStudio to take a look.
- Look at types in Stan.
  - Statically typed.
  - Different from R.
- Blocks.
- Model.
- Compiling.

questions?

Where to get help?

- Stan Forums
  http://discourse.mc-stan.org

- Stan Home Page
  http://mc-stan.org

- Stan Documentation
  http://mc-stan.org/documentation/

Contact

- Daniel Lee

- daniel@generable.com
- @djsyclik
- https://www.linkedin.com/in/syclik/
- www.generable.com
- www.syclik.com

Bayesian inference

The Goal of Bayesian Inference

$$p(\theta \mid x)$$

posterior distribution of parameters
conditioned on data

The Goal of Bayesian Inference

$$p(\theta \mid x)$$

θ parameters

x data, outcomes

$p(.)$ probability distribution

The Goal of Bayesian Inference

$$p(\theta \mid x)$$

θ parameters

x data, outcomes

$p(.)$ probability distribution

implicit: conditioned on a model

Computing $p(\theta \mid x)$ is tough

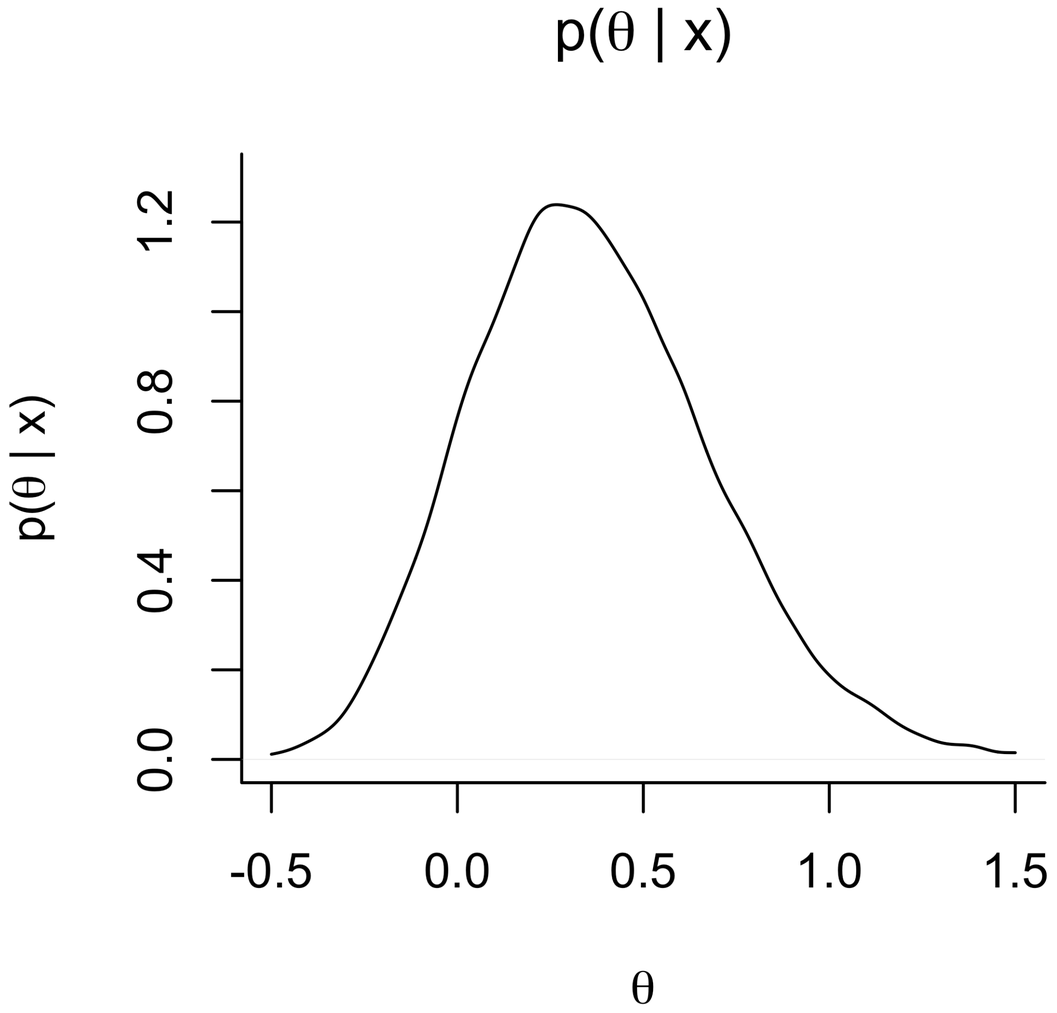
$$p(\theta \mid x) = \frac{p(\theta, x)}{\int p(\theta, x) d\theta}$$

Computing $p(\theta \mid x)$ is tough

$$p(\theta \mid x) = \frac{p(\theta, x)}{\int p(\theta, x) d\theta}$$

Why Bayesian inference?

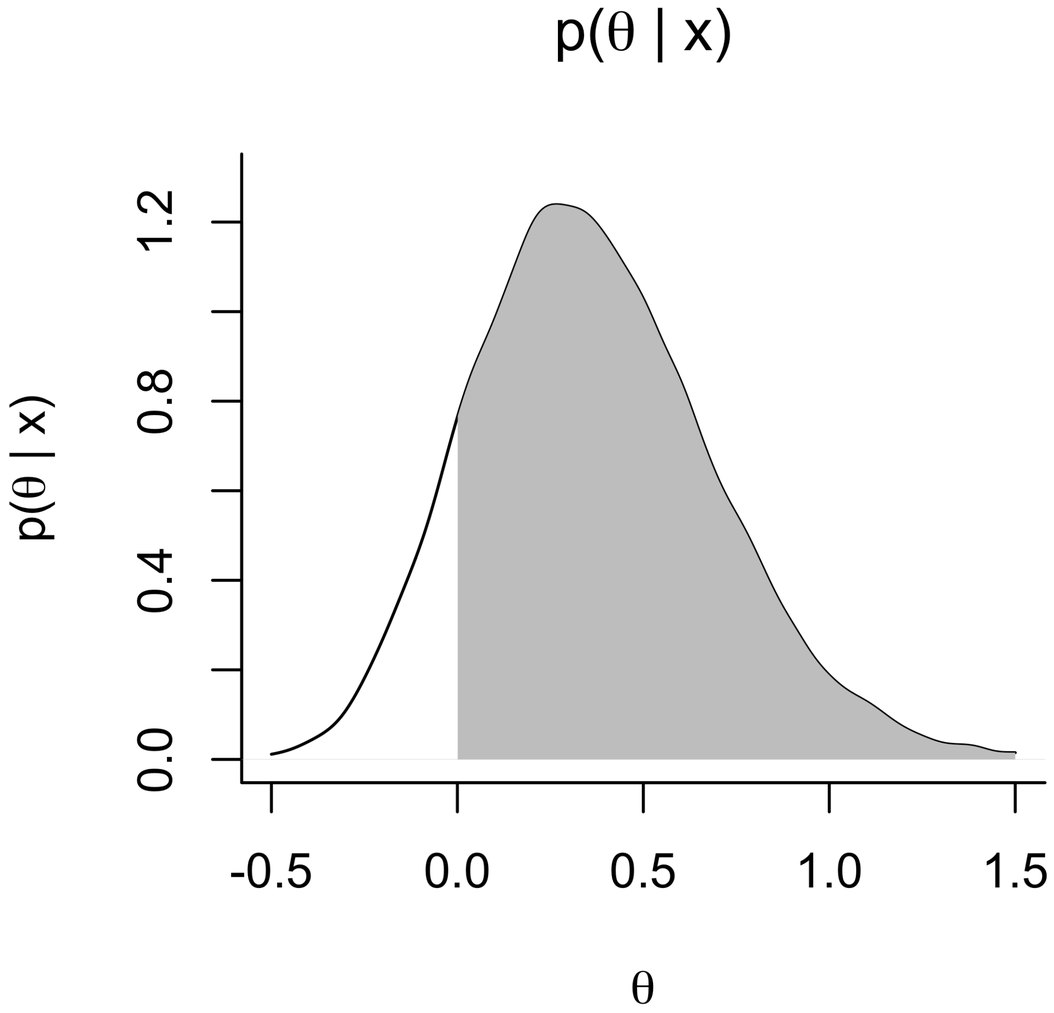
- Direct interpretation of probabilities
- Correct measure of uncertainty
- mode ≠ mean



Why Bayesian inference?

Direct interpretations of probabilities

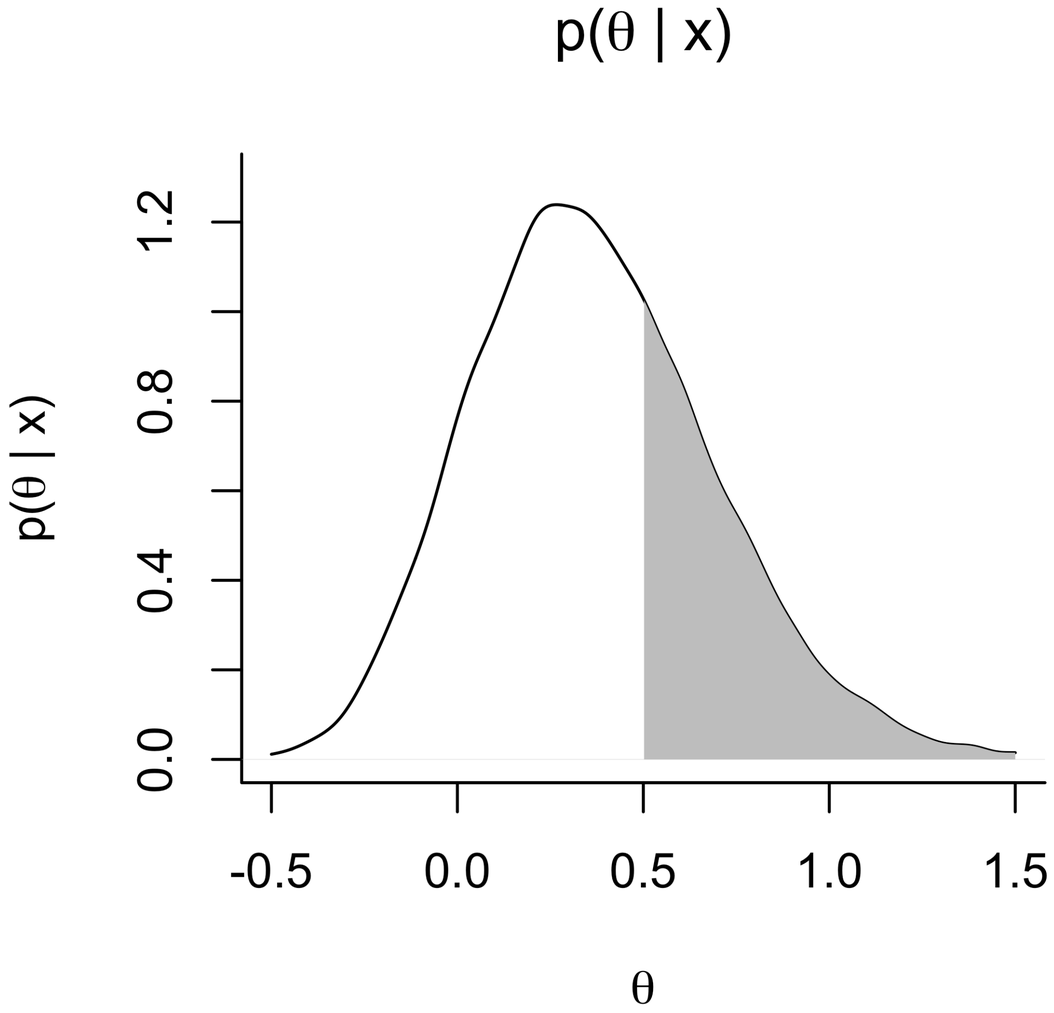
$$p(\theta > 0 \,|\, x) = 0.8748$$



Why Bayesian inference?

Direct interpretations of probabilities

$$p(\theta > 0.5 \,|\, x) = 0.3210$$

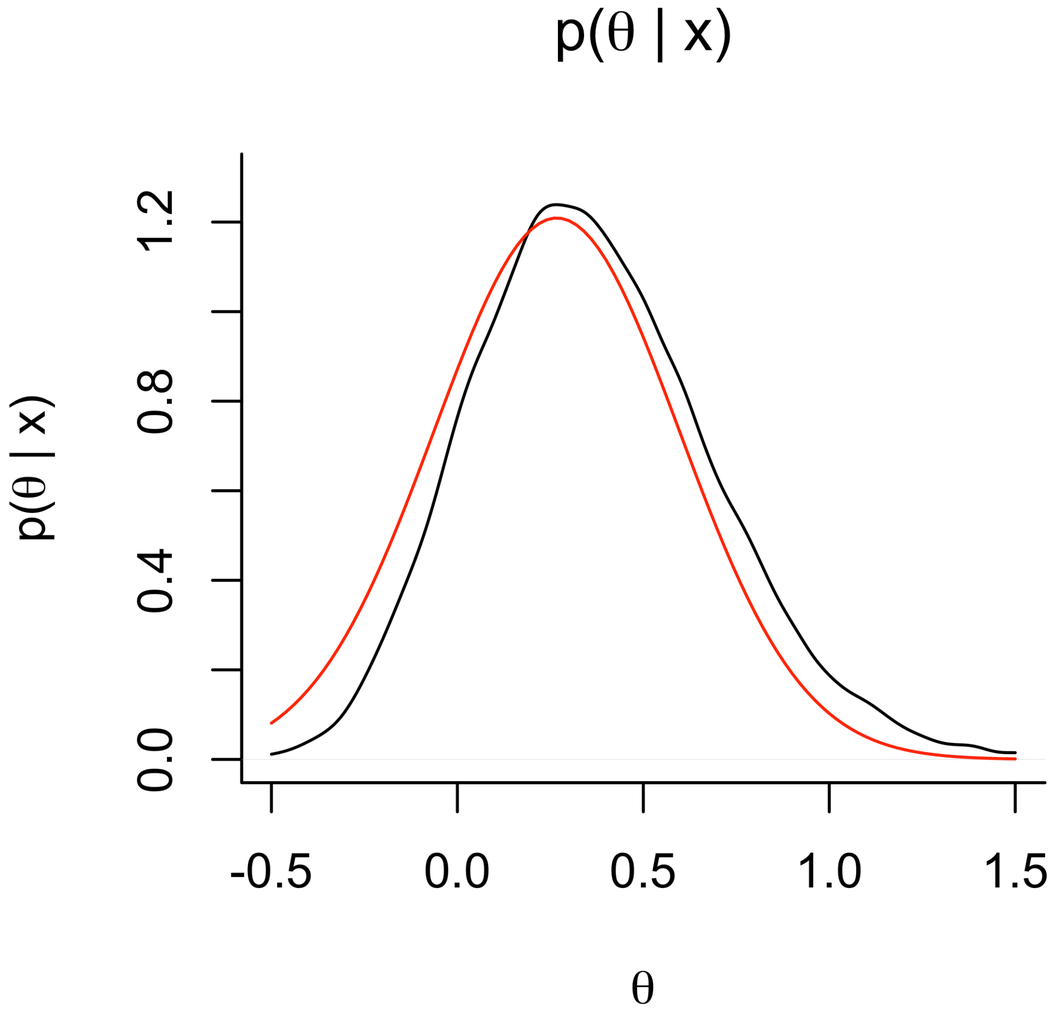


Why Bayesian inference?

Correct measure of uncertainty

- Red
  - approximating posterior with normal (mode, standard deviation)
  - needs conditions for this to work
- Estimates accounting for uncertainty:

$$\mathbb{E}[f(\theta)] = \int f(\theta) \times p(\theta \mid x)\, d\theta$$



Why Bayesian inference?

mode ≠ mean; affects decisions

- blue: $\mathbb{E}[\theta] = 0.367$
- red: $\hat{\theta} = 0.267$

- More importantly:
  can take any expectation