Bayesian Pharmacokinetics/Pharmacodynamics for Personalized Medicine

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Thesis

- Personalized Medicine
- Dr. Kim's clinic has concentration/dose/covariate data.
- Wants predictions for new patients + understanding of which covariates are most important for prediction
- Tried ML models previously
- Did not account for repeated observation
- Lots of unexplained variance

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Proposed Direction

- Use PK/PD models and estimate parameters using HMC/hierarchical models

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Why Bayesian

As argued in (Wakefield 1996),

a. PK/PD models are non-linear in parameters. Classical models rely on asymptotic arguments. Tough to validate for this data.
b. We eventually want to *predict* concentrations for new patients. Bayesian methods are good for this,
c. We have prior information since hundreds of patients have come through the clinic. This ~~can~~ should be leveraged.
d. Hierarchical models allow for easy analysis of assumptions to modelling process.
e. The between subject variability is very high. Variance propagation is crucial.
f. Want to estimate individual patient's parameters as well as population parameters (this is natural in Bayesian context)

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Why Differential Equations

- Natural, almost canonical, application to PK/PD
- Depending on the ODE, closed form solutions can be obtained, making inference all the easier
- Depending on the ODE, numerical integration may be required. Well developed tools to do this effectively and accurately
- Applied mathematicians don't usually care about inference for parameters
  - New venues for publication, conference presentations, collaboration

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A Thank You

The following examples are based of lectures from Michael Betancourt, a `Stan` developer and prominent Bayesian.

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An Example

- `Stan` is an open source project for MCMC.
- Well developed, widely used, fast.
- Accessible through numerous languages.

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Simulation of a PK Profile

Start with a PK model. Let D be the size of the dose, let V be the volume of the compartment, and let k the elimination rate, and k_a be the dosing rate.

$$\frac{d\mu}{dt} = k_a \frac{D}{V} \mathrm{e}^{-k_a t} - k\mu$$

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Simulation of a PK Profile

Subject to $\mu(0) = 0$, solution is

$$\mu(t) = \frac{Dk_a}{(k - k_a)V}\left(\mathrm{e}^{-k_a t} - \mathrm{e}^{kt}\right)$$

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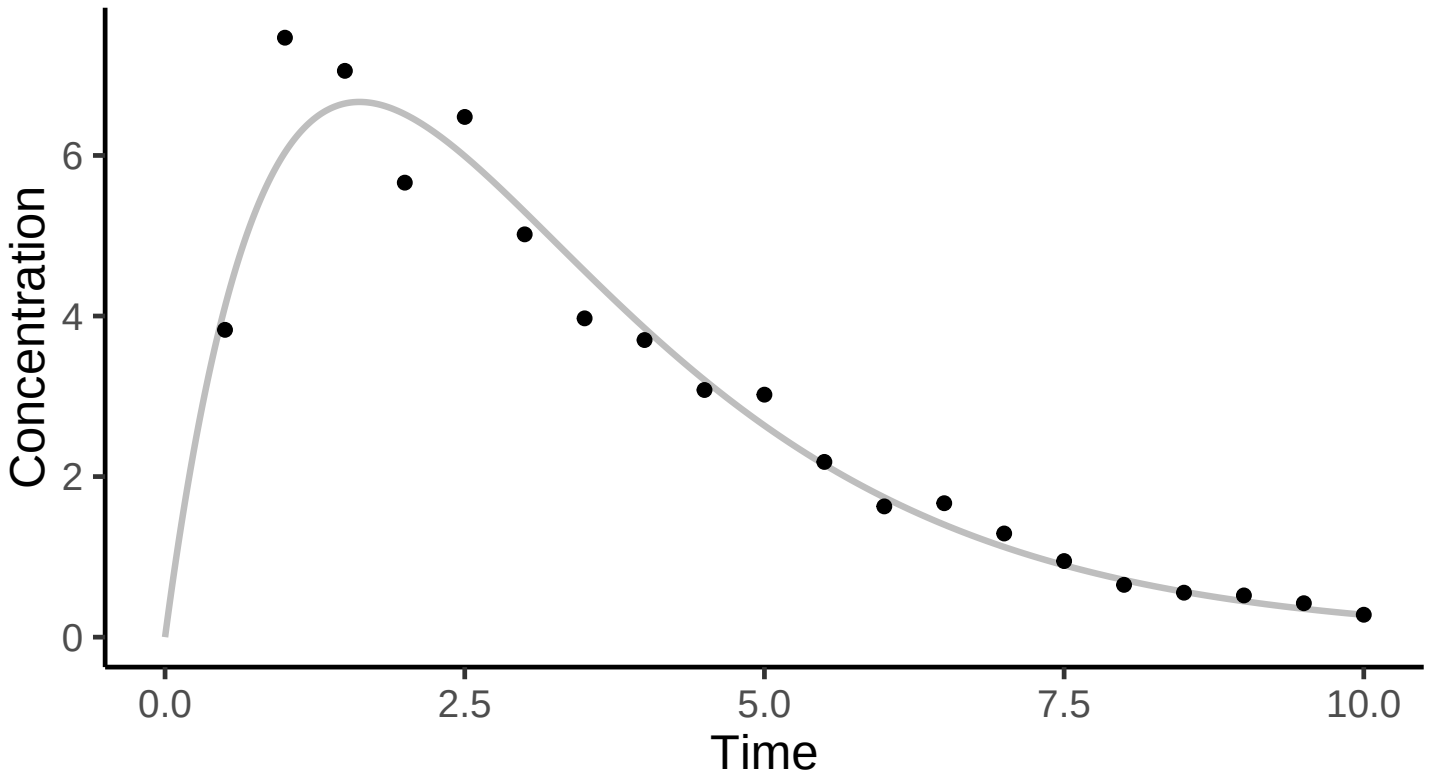
Simulation of a PK Profile

Assume that concentration at time t is

$$\log(Y) \sim \mathcal{N}(\mu(t), \sigma)$$

Simulation of a PK Profile



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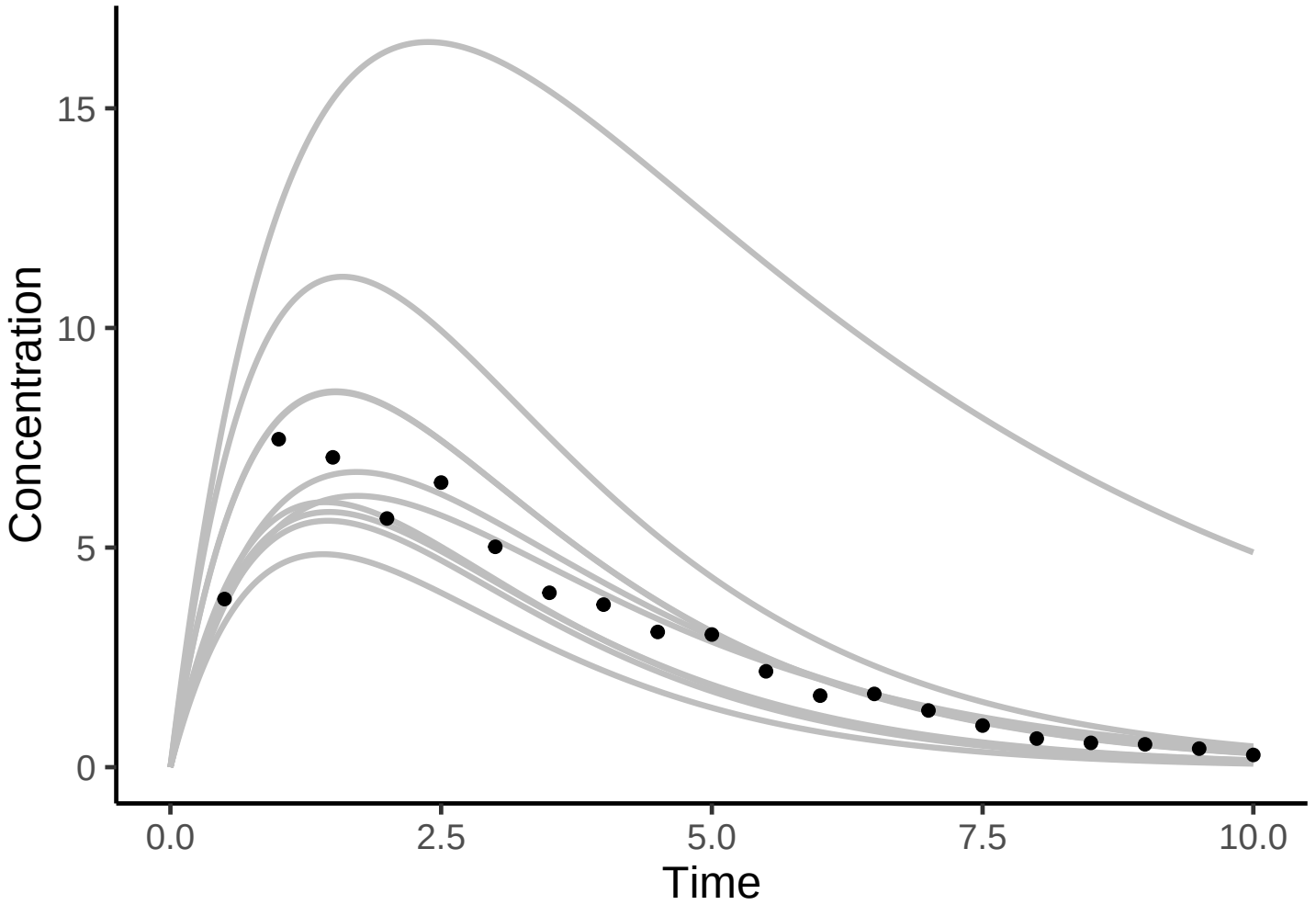
Our Problem is Really...



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Doing Bayesian Inference

One possible model is

$$
\begin{aligned}
k_a &\sim \text{Cauchy}(0, 1) \\
k &\sim \text{Cauchy}(0, 1) \\
\sigma &\sim \text{Cauchy}(0, 1) \\
\mu | t, k, k_a, D, V &= \left(\frac{D k_a \mathrm{e}^{t(k-k_a)}}{(k - k_a)\, V} - \frac{D k_a}{(k - k_a) V} \right) \mathrm{e}^{-kt} \\
\log(Y) | \mu &\sim \mathcal{N}(\mu, \sigma)
\end{aligned}
$$

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Stan Does the Rest

Code the model in Stan (not shown here) and sample from the posterior.

```
input_data <- read_rdump("one_comp_lin_elim_abs.data.R")

fit <- stan(file='one_comp_lin_elim_abs_ode.stan', data=input_data,
            iter=2000, chains=2, seed=4938483)
```

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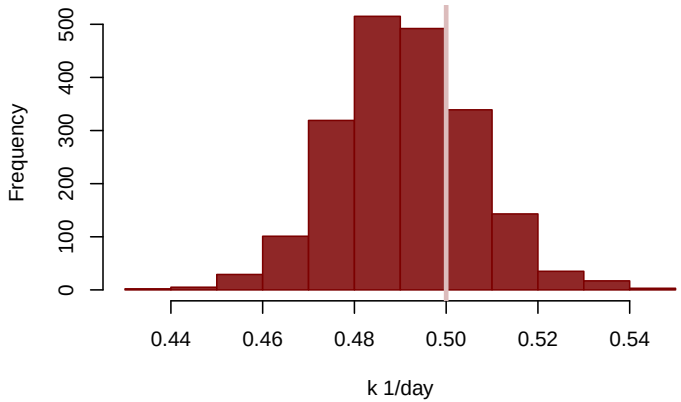
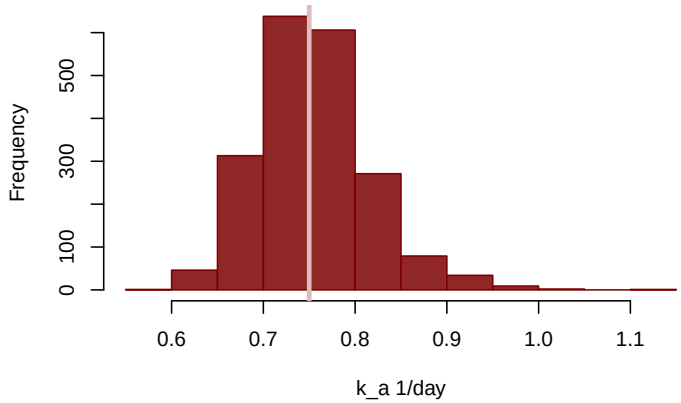
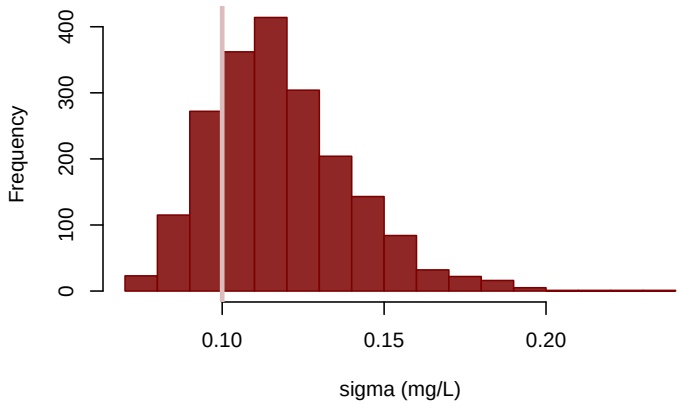
Marginal Posterior Distributions







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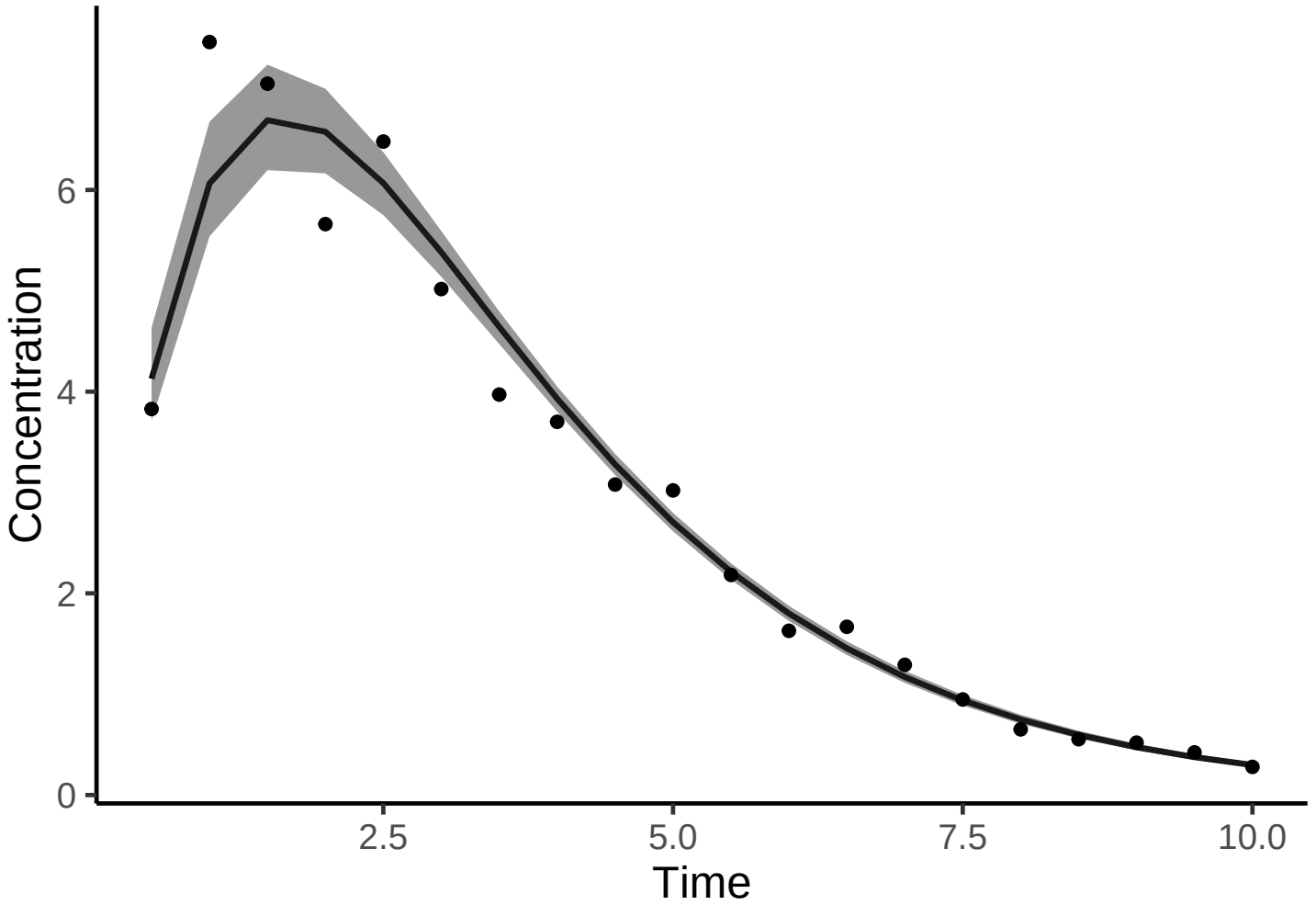
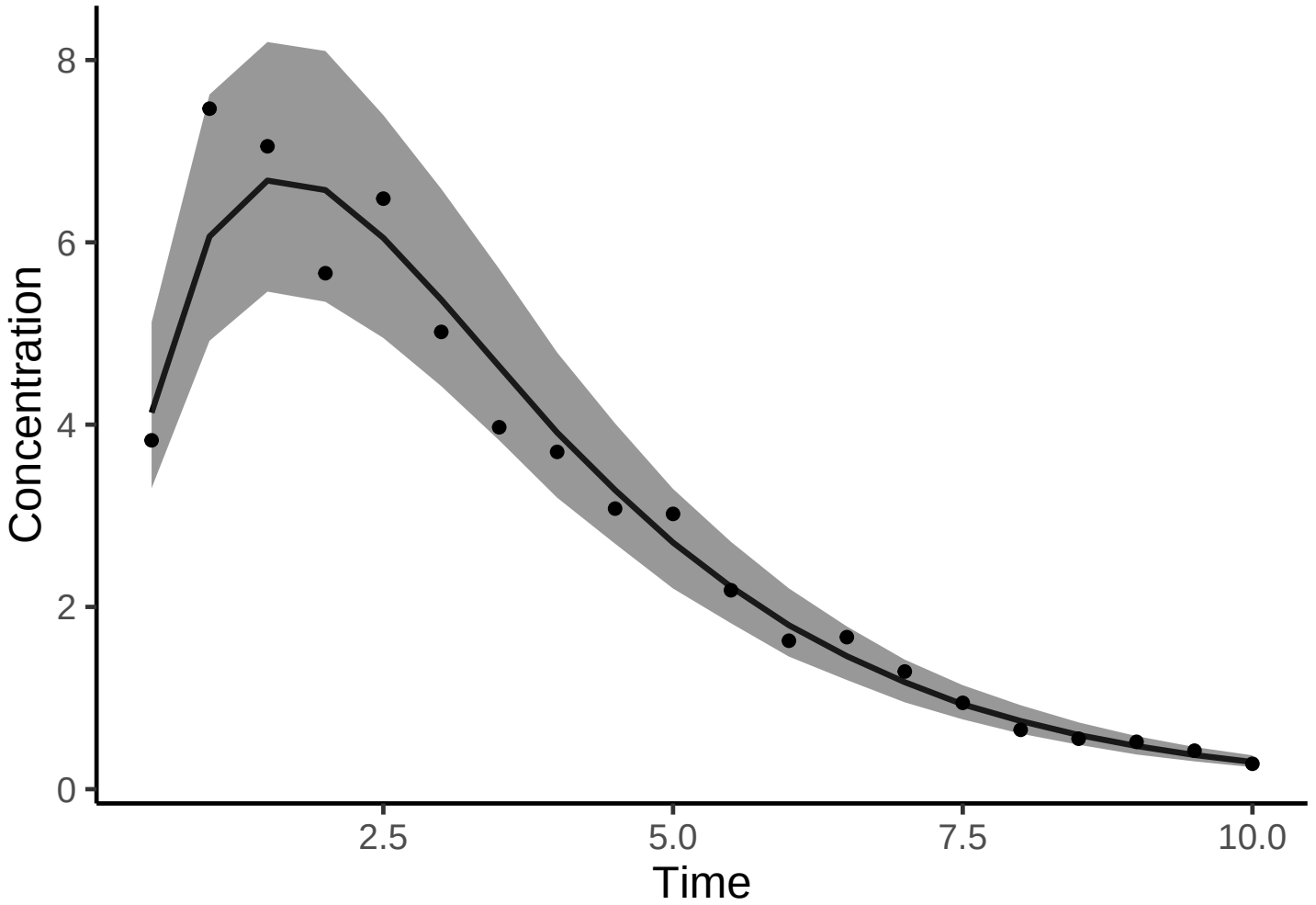
Credible Interval for $\mu(t)$



Posterior Predictive Check



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Extensions

Extend by:

- Include more compartments
- More complicated dynamics
- Non-uniformly sampled times
- Heirarchy

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What I Would Like To Do

- Determine exactly the population we are studying
- Determine the model for the dynamics
- Heirarchical generalized linear model for effect of clinical variables on PK/PD variables
- Determine how dosing influences concentration levels (therapy vs. poison)
- Cross validate predictive performance
- Hopefully show that Bayesian appraoch is better than any current practice
- Write an OSS library for Bayesian PK/PD (maybe)

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Questions

Ask me how I made this presentation in R

References

Wakefield, Jon. 1996. "The Bayesian analysis of population pharmacokinetic models." *J. Am. Stat. Assoc.* 91 (433): 62–75.

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