

Milestones, Deliverables, Plans for Year 3

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Milestones and Deliverables

- ▶ Rhiannon Rose successfully defended her PhD Aug 2018
 - ▶ Contribution to our knowledge of how to model plasma concentration in frequentist framework with nonlinear models, concomitant medications, potential new genetic factors (statins)
 - ▶ Manuscripts in prep
- ▶ Demetri completes courses, forms committee
 - ▶ Paper with Markus in prep on FXals
- ▶ Demetri identified Bayesian framework and software for PK/PD modelling.
 - ▶ Will allow “smooth” improvement of predictions as we acquire more data.

Plans for Year 3

- ▶ Demetri and Markus submit paper on FXals
- ▶ Development and explication of modelling framework and software
- ▶ Data acquisition and planning
 1. What data can we use that we already have? (E.g. Cerner)
 2. What additional data should we collect? (E.g. levels from existing patients)
- ▶ Conference presentation

Hey Kids, Wanna Model Some Drugs?

Bayesian Pharmacokinetic Models

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Work Done To Date

- ▶ Some modelling has been done for Apixiban in conjunction with Markus.
- ▶ Inputs Variables: Clinical, Demographic, Genetic, Temporal, etc.
- ▶ Outputs: Plasma concentration.
- ▶ Black box machine learning does not improve much over linear regression.
- ▶ Unexplained variance not so bad if it is from between subject variability.

Proposed Direction

- ▶ Use Bayesian statistics
- ▶ Incorporate prior information
- ▶ Estimate between subject variability using Heirarchical model

The “B”-Word

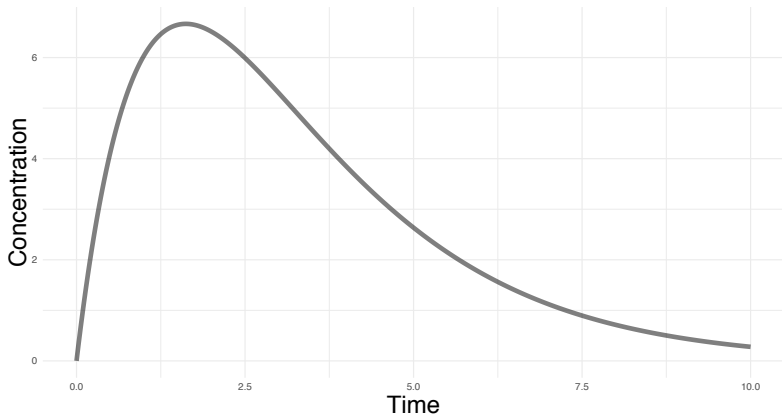
- a. Bayesian methods are good for prediction.
- b. Tons of prior information. This *should be incorporated*.
- c. Small sample sizes are not a problem.
- d. Can account for between subject variability.

The “B”-Word

- ▶ Start with *prior information* about the parameters of the model $p(\theta)$.
 - ▶ This could be a population distribution of some PK parameter.
- ▶ Determine how we think the data are generated $p(y|\theta)$.
- ▶ New observations give a posterior $p(\theta|y) \propto p(\theta) \cdot p(y|\theta)$
- ▶ In a Bayesian framework, probability is best interpreted as the strength of our belief.

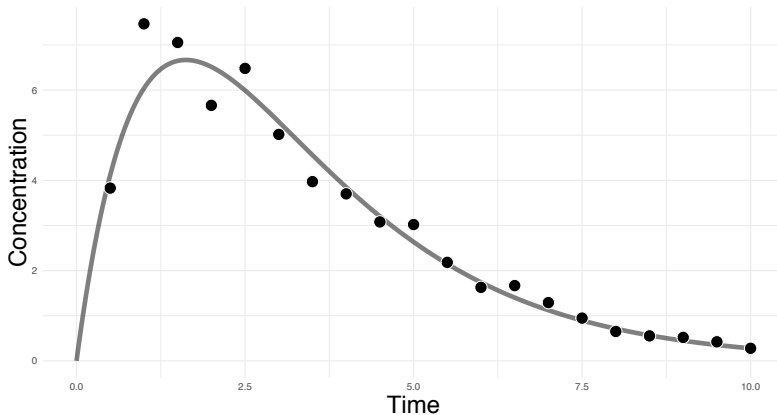
A Small Example

We think that each person has their own curve. The curve is determined by the absorption/elimination rates.



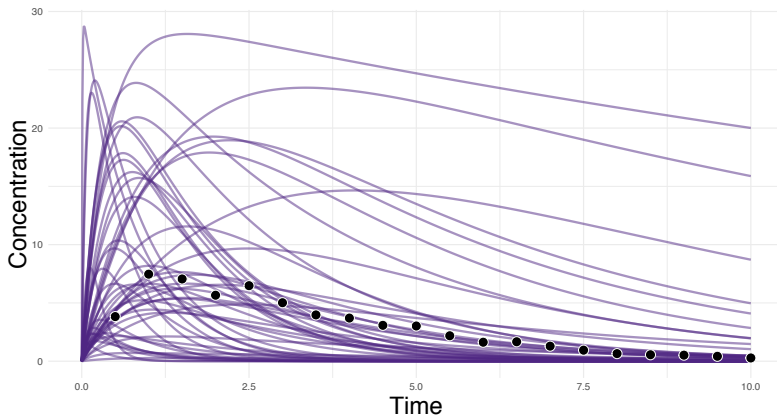
A Small Example

...and that when we measure concentration in plasma there is some noise.



Sample From The Prior

We have some prior information. Each curve corresponds to a unique pair of absorption and elimination rates.

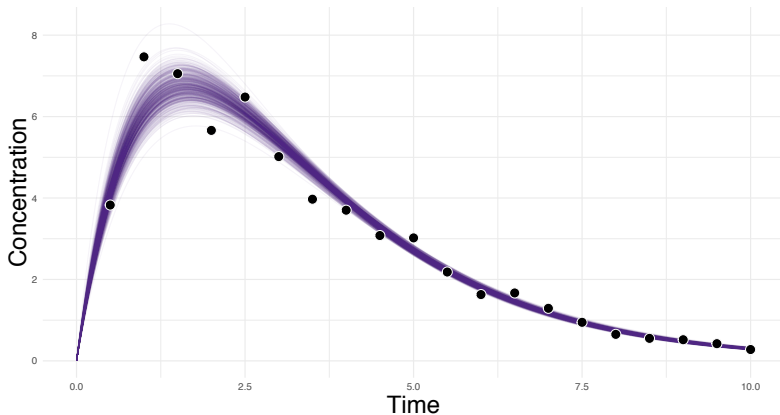


A Small Example

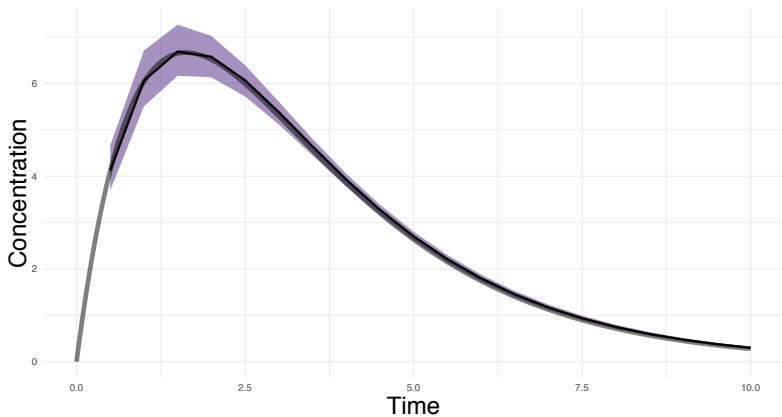
Once we observe data, we can then determine which curves have most probably generated the data

Sample From Posterior

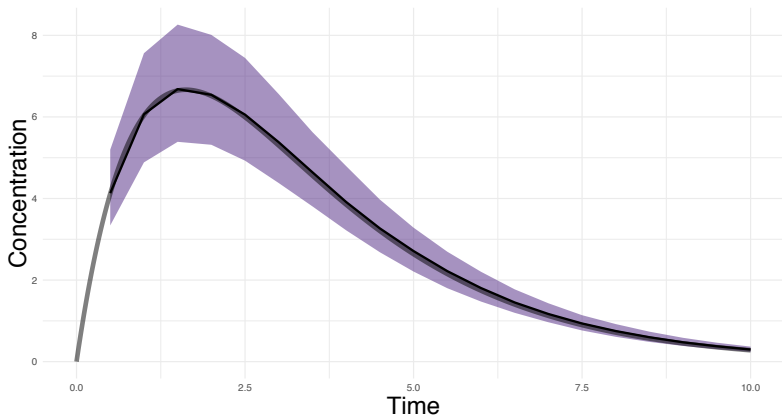
500 curves drawn from the posterior



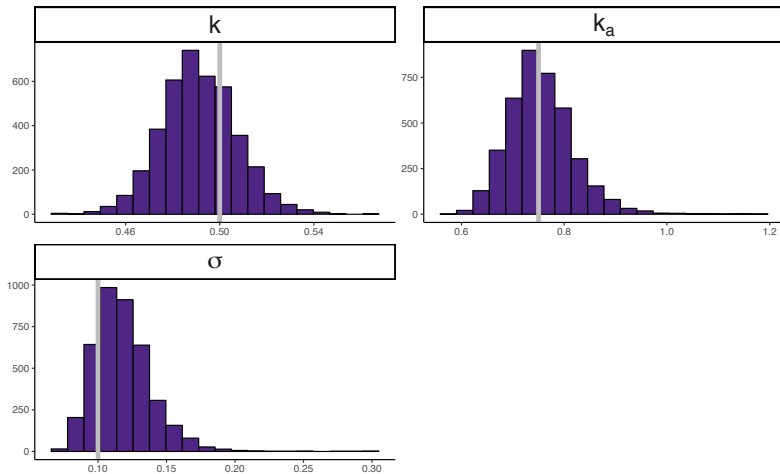
“Confidence Interval”



“Prediction Interval”



Distributions



This Was A Toy Example

Proposed next steps:

- ▶ Identify exactly what it is we want to study or estimate.
- ▶ Construct quality priors from our data using Empirical Bayesian techniques.
- ▶ Construct hierarchical models so that for example, weight has an effect on drug clearance.