Milestones, Deliverables, Plans for Year 3

Dan Lizotte

Western

Department of Computer Science
Faculty of Science
Department of Epidemiology & Biostatistics
Schulich School of Medicine & Dentistry
Western University

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Milestones and Deliverables

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

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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

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Hey Kids, Wanna Model Some Drugs?

Bayesian Pharmacokinetic Models

Dan Lizotte & Demetri Pananos

Western

Department of Epidemiology & Biostatistics
Schulich School of Medicine & Dentistry
Western University

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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.

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Proposed Direction

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

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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.

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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.

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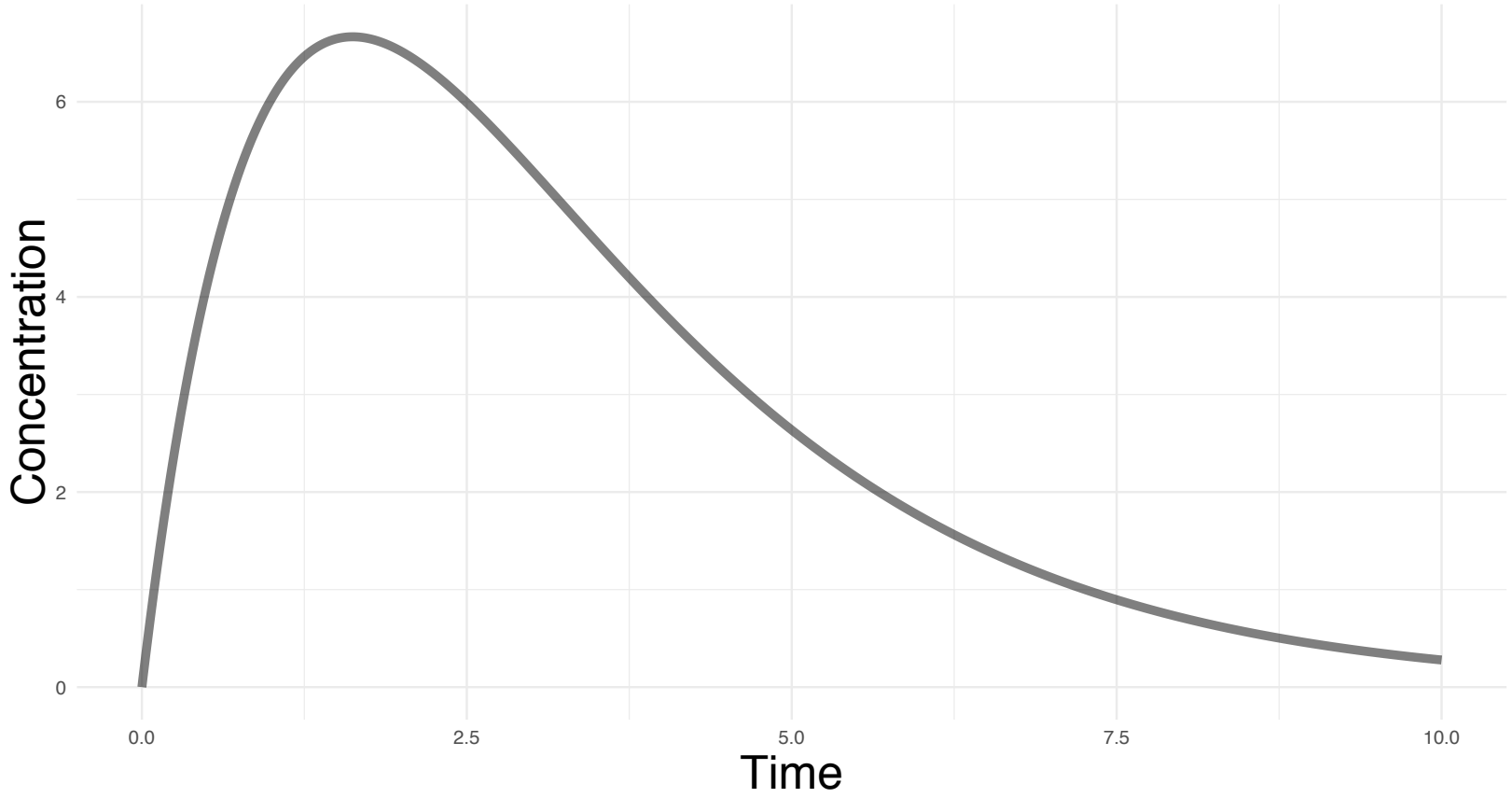
A Small Example

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



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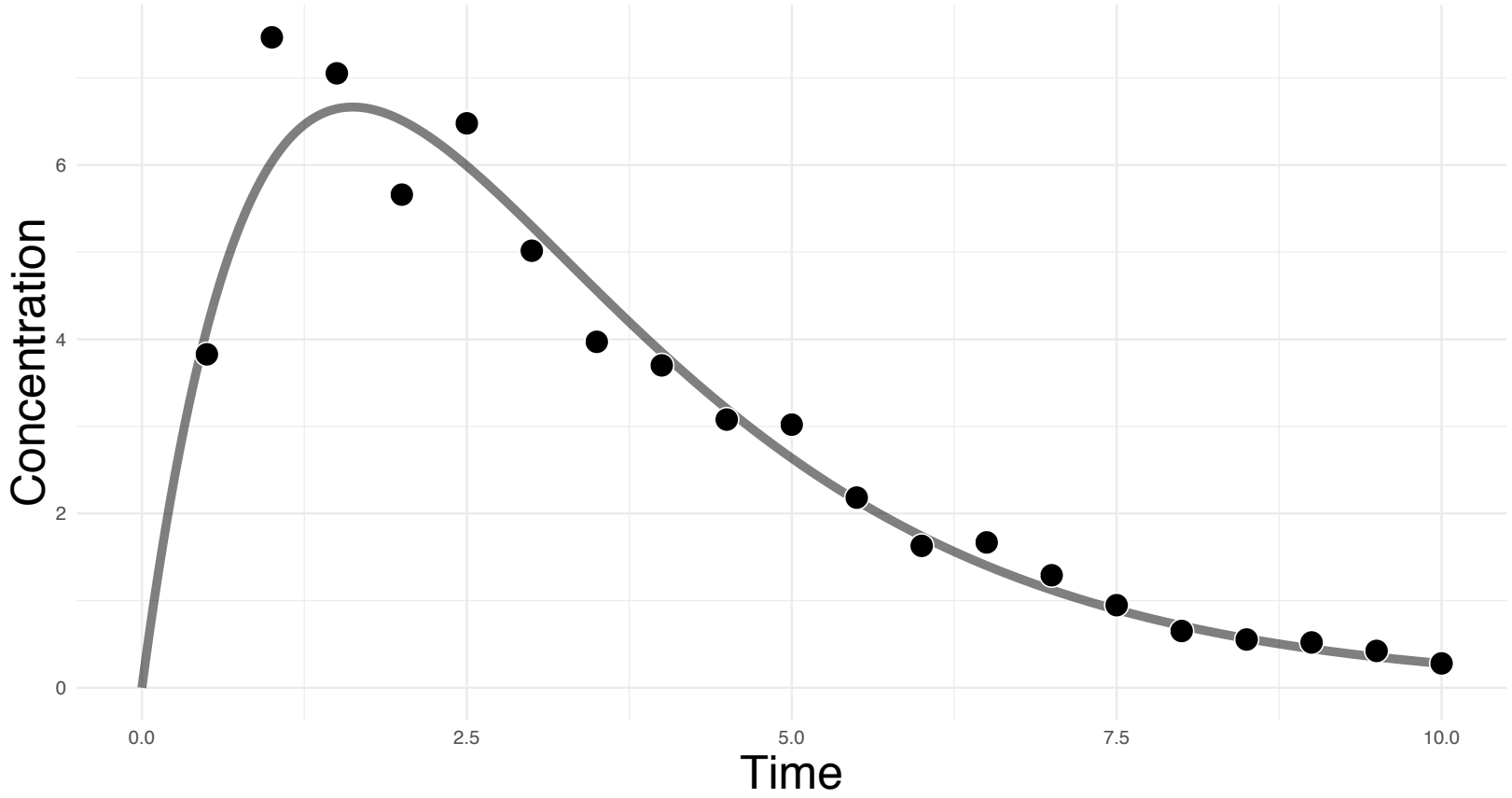
A Small Example

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



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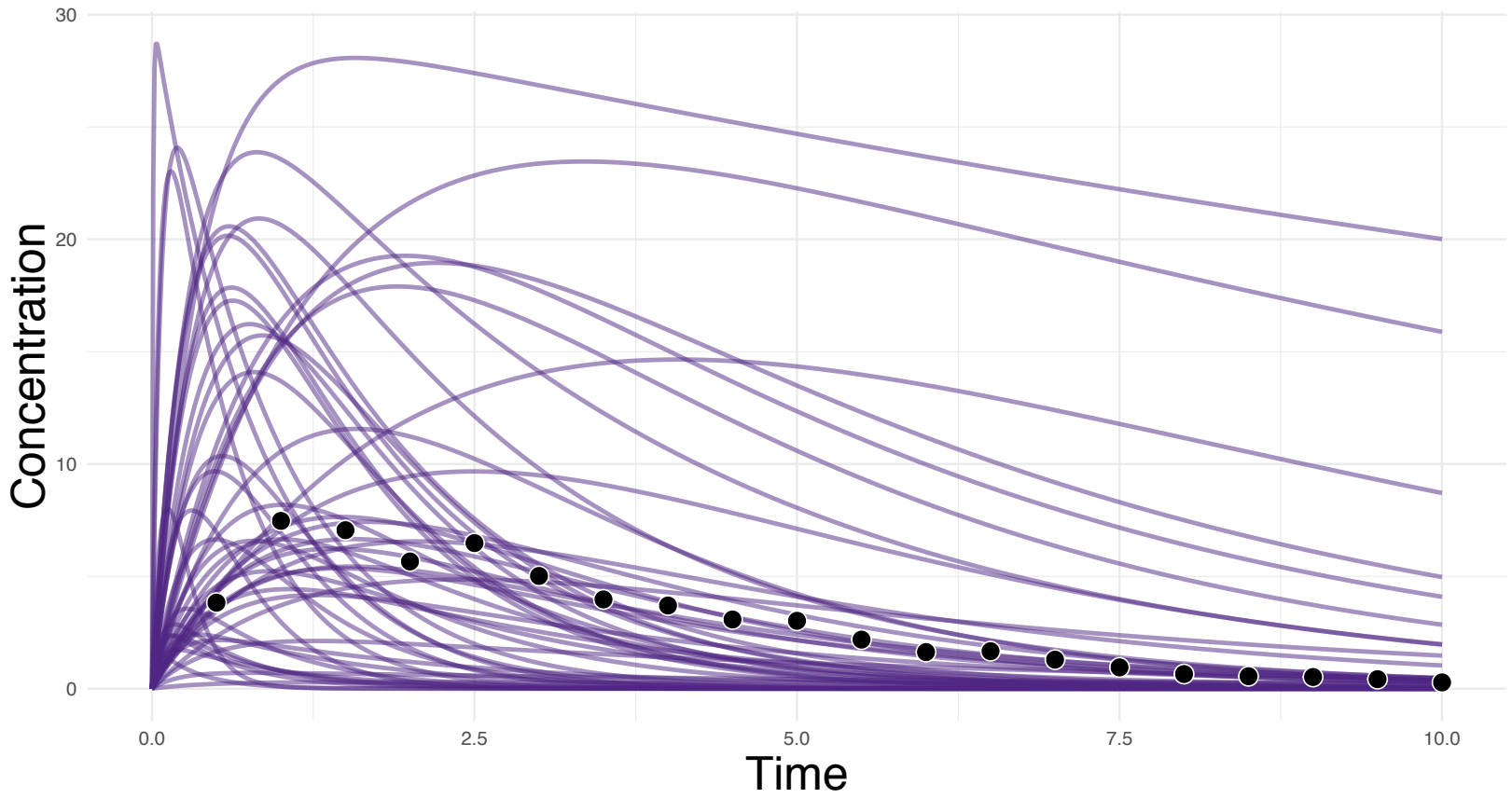
Sample From The Prior

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



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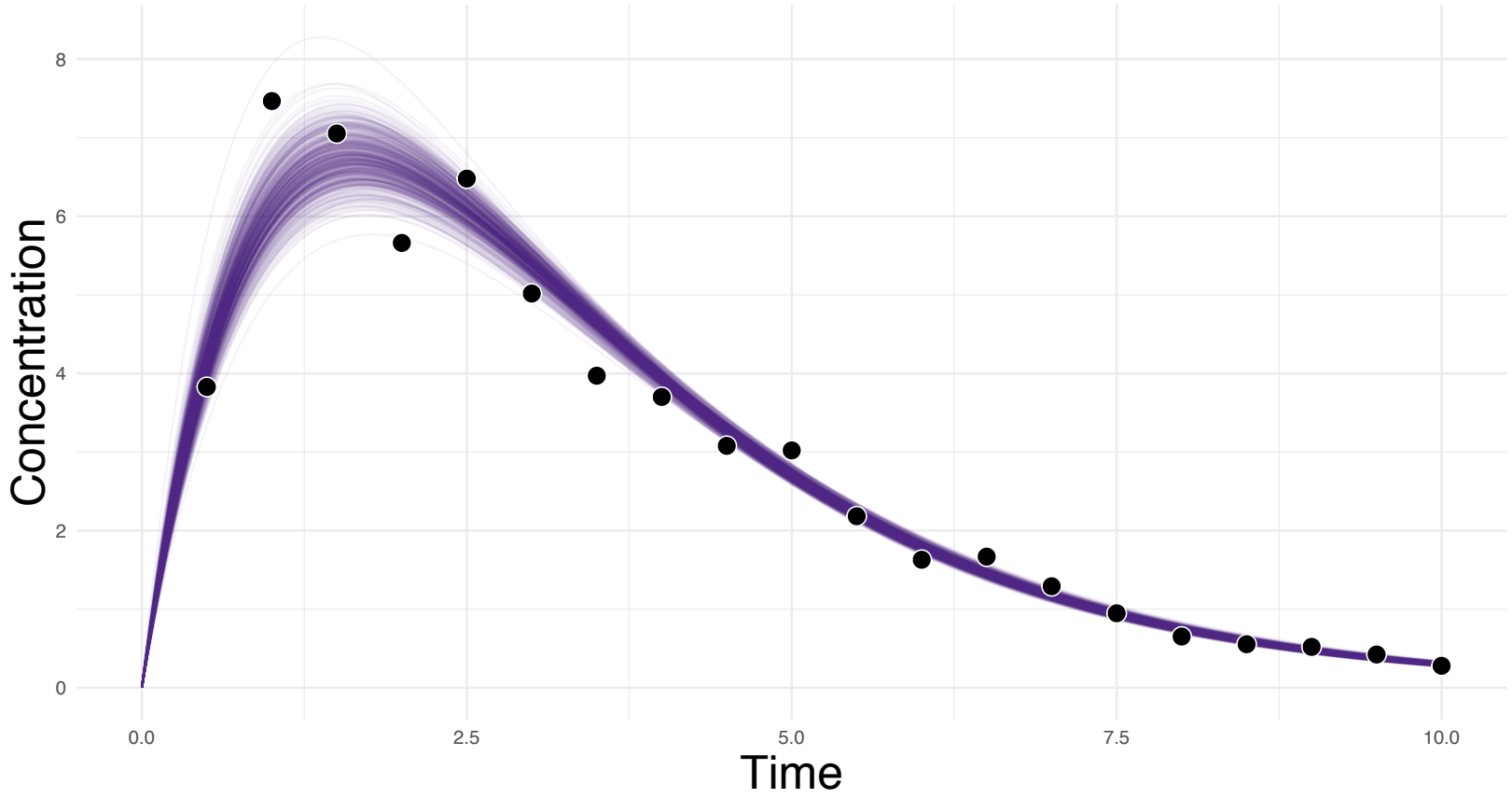
A Small Example

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



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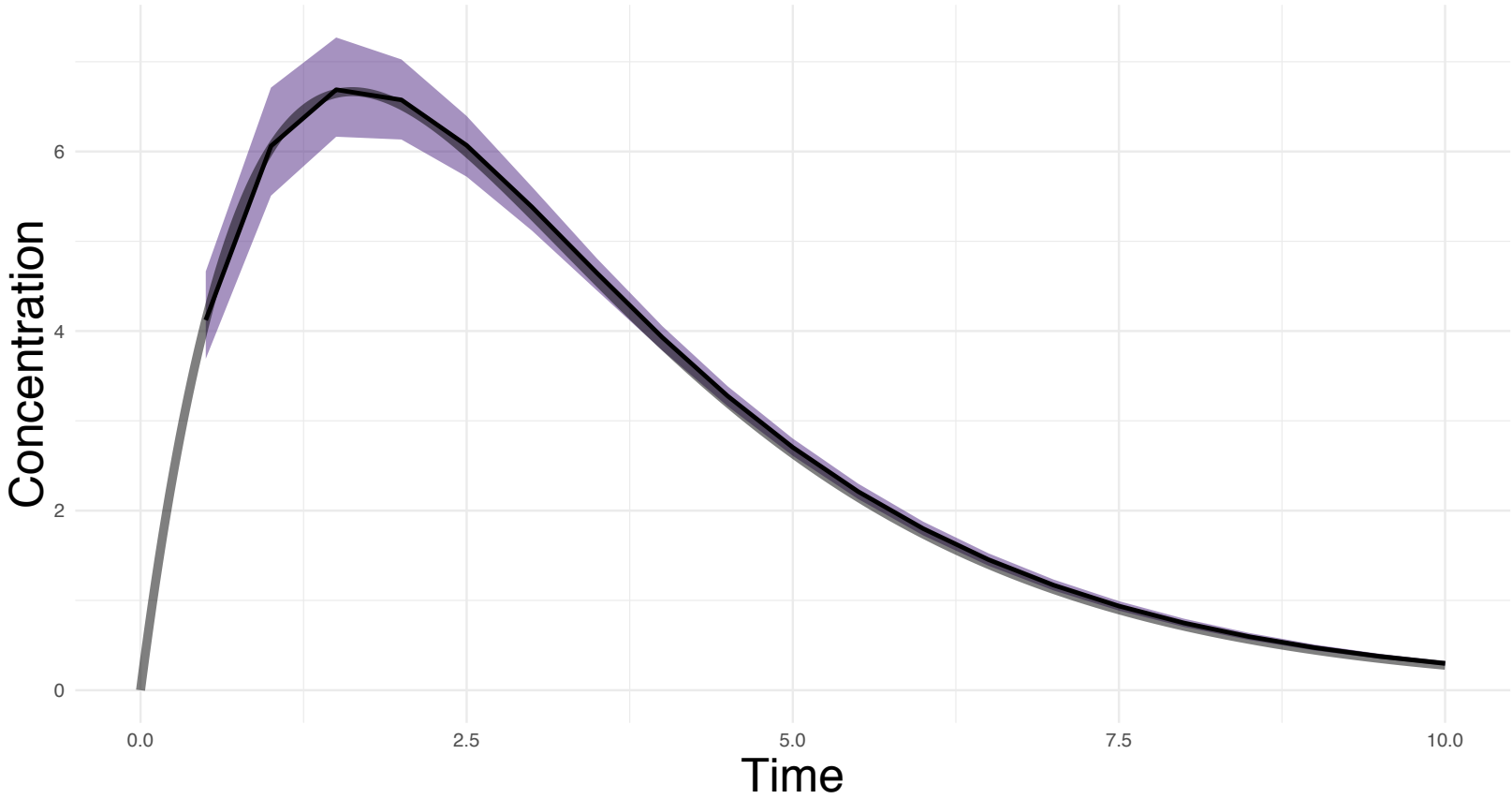
“Confidence Interval”



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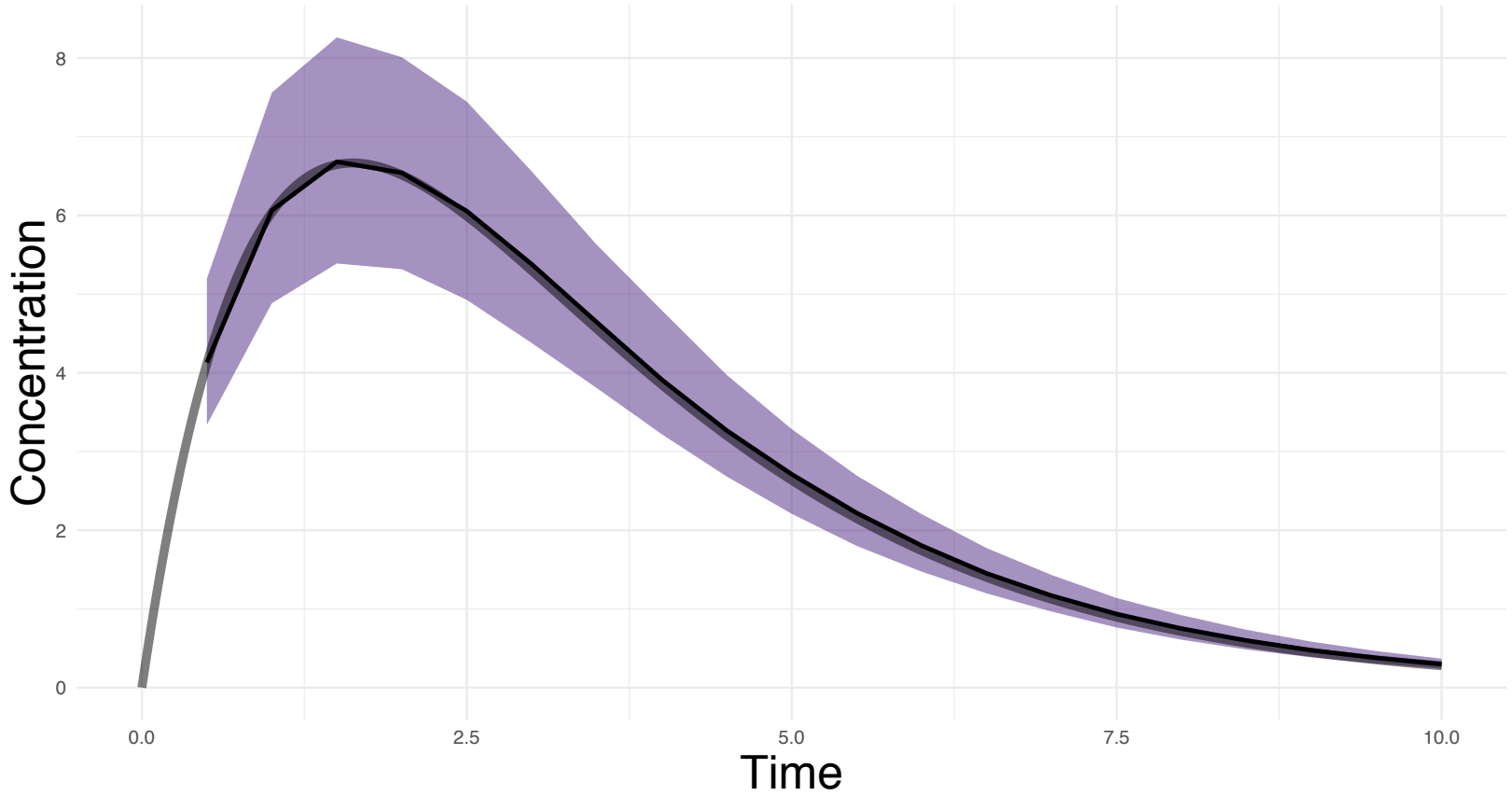
“Prediction Interval”



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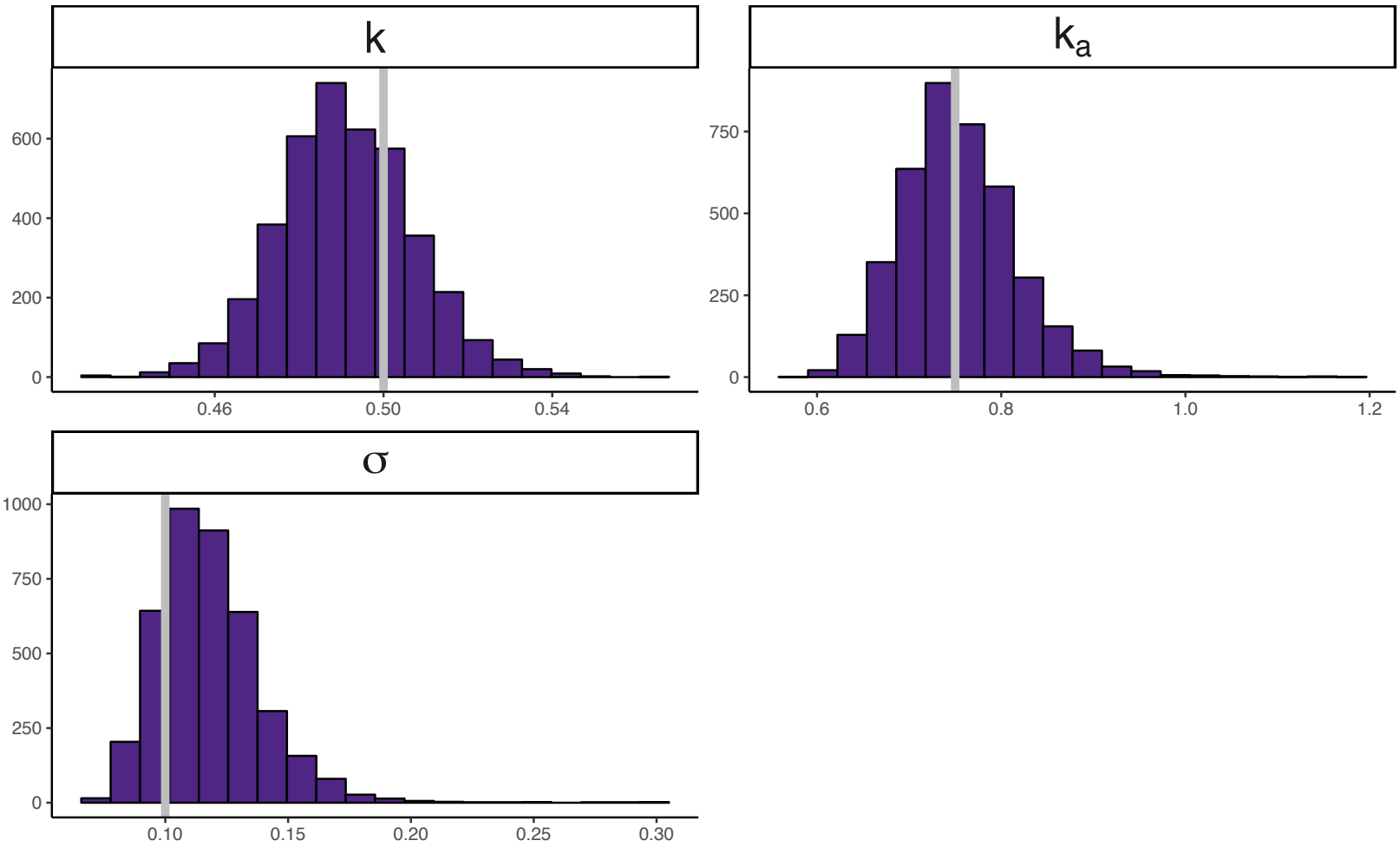
Distributions



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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 Emperical Bayesian techniques.
- Construct heirarchical models so that for example, weight has an effect on drug clearance.

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