Parameterizing a Type 1 Diabetes ODE Model[1]

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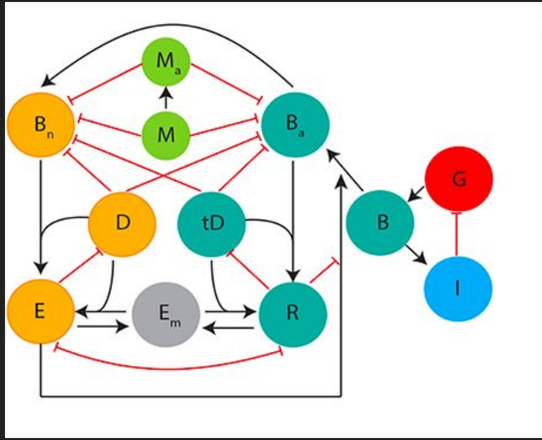
Recap of T1D Model

- 12 state, 53 parameter ODE model of pancreas
- Mouse glucose data available
- <u>Goal:</u> Estimate T1D model parameters using real data



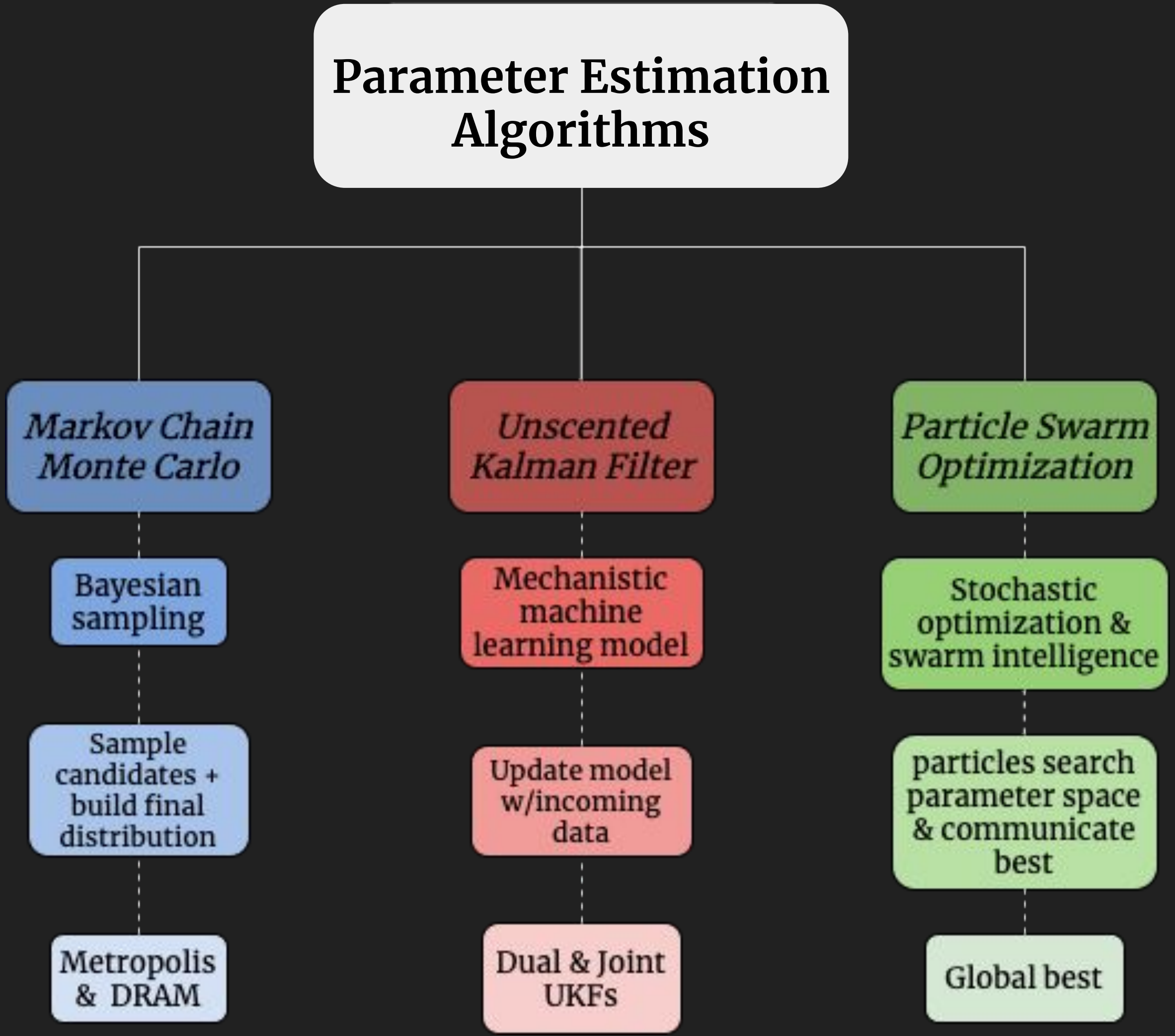
Variable	Description
B	Healthy β-cell population
Ba	Apoptotic β-cell population
Bn	Necrotic β-cell population
D	Immunogenic DC population
tD	Tolerogenic DC population
E	Effector T cell population
Em	Memory T cell population
R	Regulatory T cell population
Ma	Active macrophage population
M	Macrophage populations
G	Glucose levels
I	Insulin levels

Shtylla et al. 2019. A Mathematical Model for DC Vaccine Treatment of Type 1 Diabetes

Glucose ODE

$$\frac{d}{dt} G = R_o - (G_o + S_I I) G$$

Maya


Parameter Estimation Algorithms
Markov Chain Monte Carlo
Bayesian sampling
Sample candidates + build final distribution
Metropolis & DRAM
Unscented Kalman Filter
Mechanistic machine learning model
Update model w/incoming data
Dual & Joint UKFs
Particle Swarm Optimization
Stochastic optimization & swarm intelligence
particles search parameter space & communicate best
Global best

Maya

Parameter Estimation Algorithms

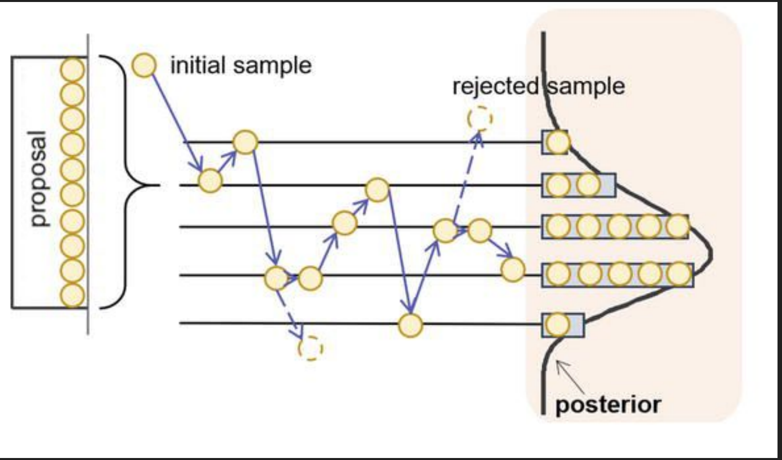
Markov Chain Monte Carlo

likelihood

prior

$$P(\theta \mid D, M) = \frac{P(D \mid \theta, M)\, P(\theta \mid M)}{P(D \mid M)}$$

evidence



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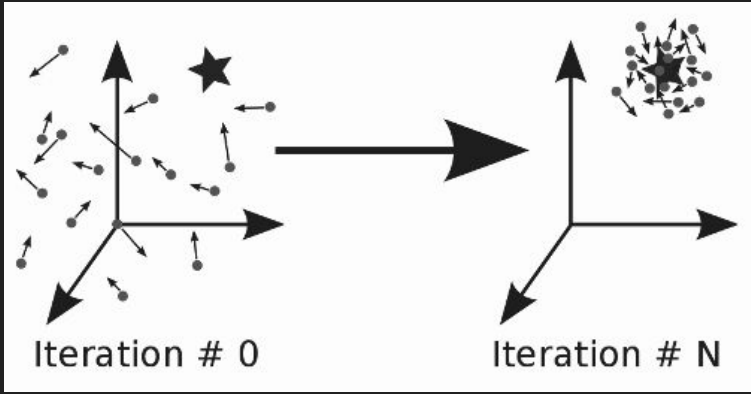
Parameter Estimation Algorithms

Particle Swarm Optimization



$$\vec{v}_i^{\,t+1} = w\vec{v}_i^{\,t} + \varphi_1 \vec{U}_1^{\,t}(\vec{b}_i^{\,t} - \vec{x}_i^{\,t}) + \varphi_2 \vec{U}_2^{\,t}(\vec{l}_i^{\,t} - \vec{x}_i^{\,t})$$

$$\vec{x}_i^{\,t+1} = \vec{x}_i^{\,t} + \vec{v}_i^{\,t+1}$$

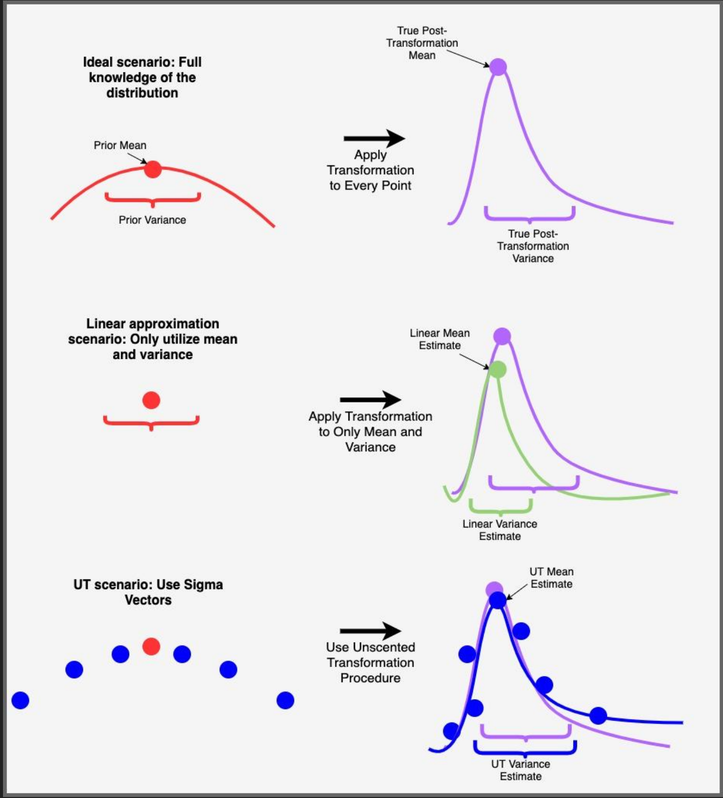
Rachel

Parameter Estimation Algorithms

Unscented Kalman Filter

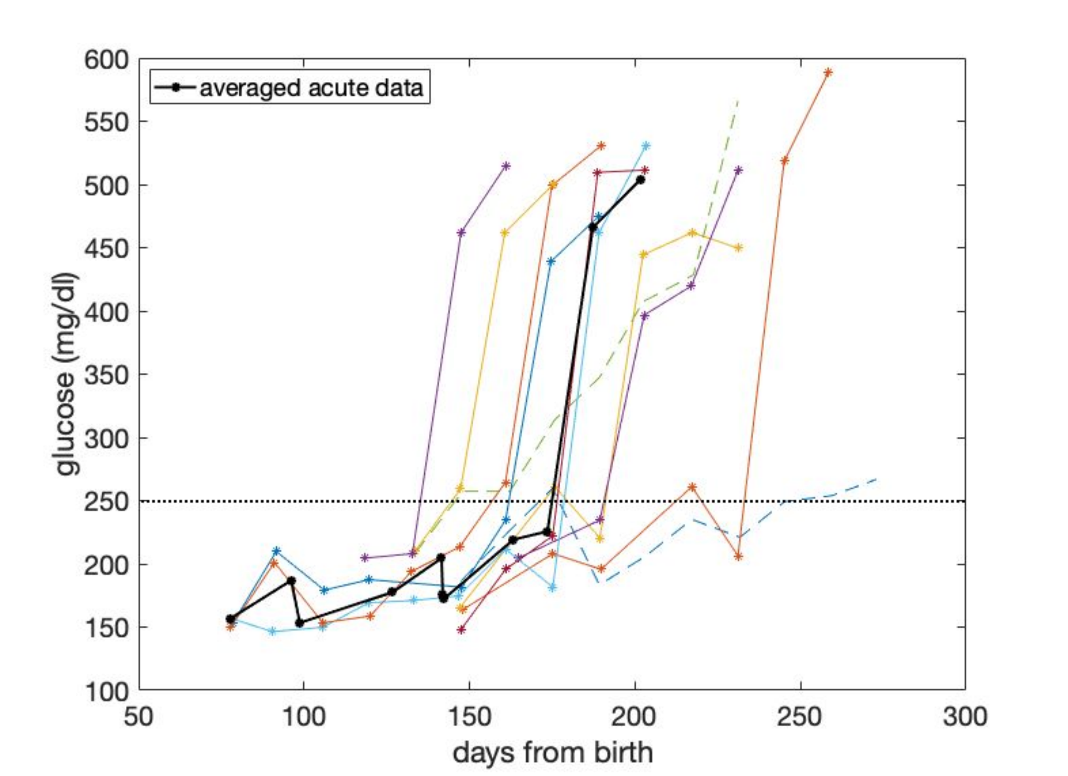
$$x_{k+1} = F_{k,k+1}(x_k) + r_k$$

$$y_k = H_k(x_k) + q_k$$



Methodology

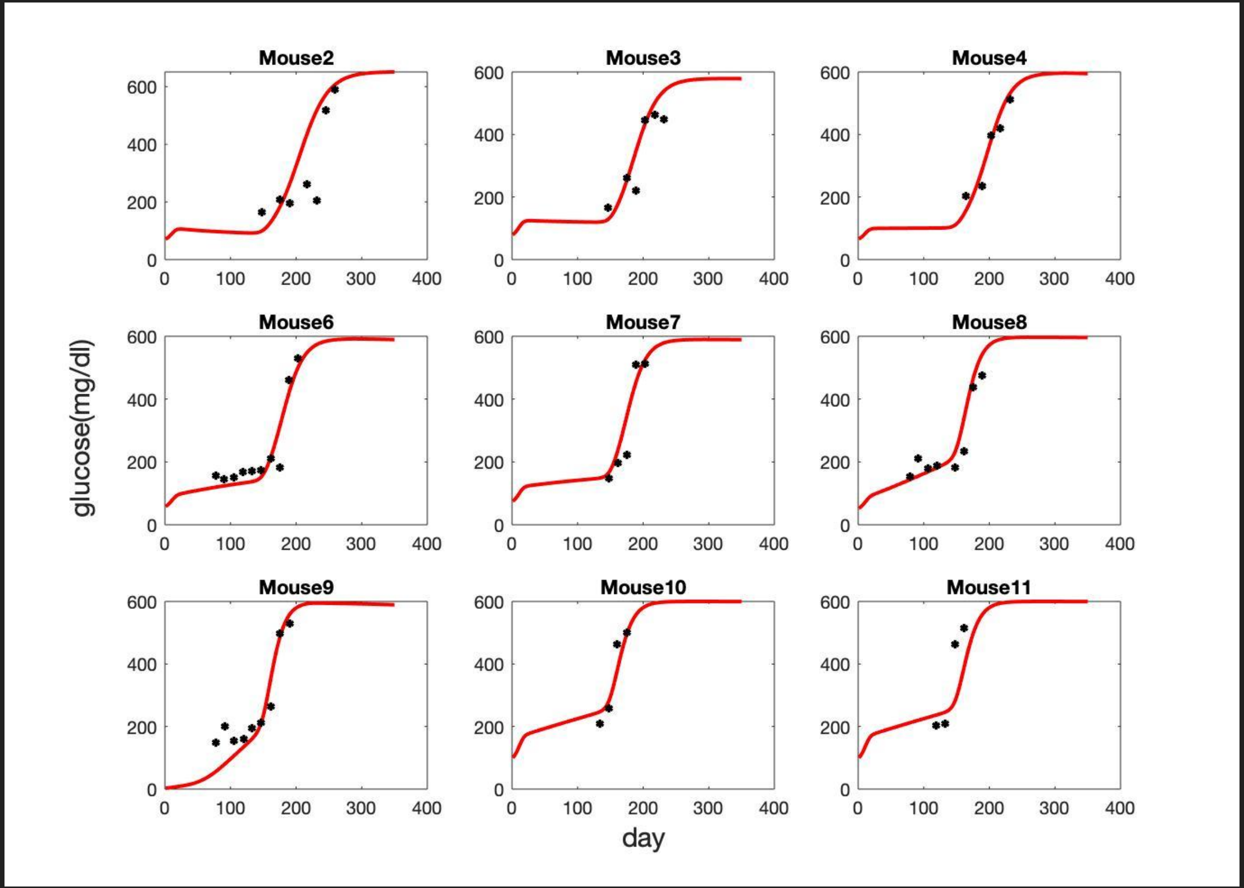
- Multiple goals
  - Individual mouse
  - Population-level
- Difficulty in constructing population-level parameters
  - ‘Fit then average’ vs. ‘Average then fit’ approach



Individual

Results: Dual UKF

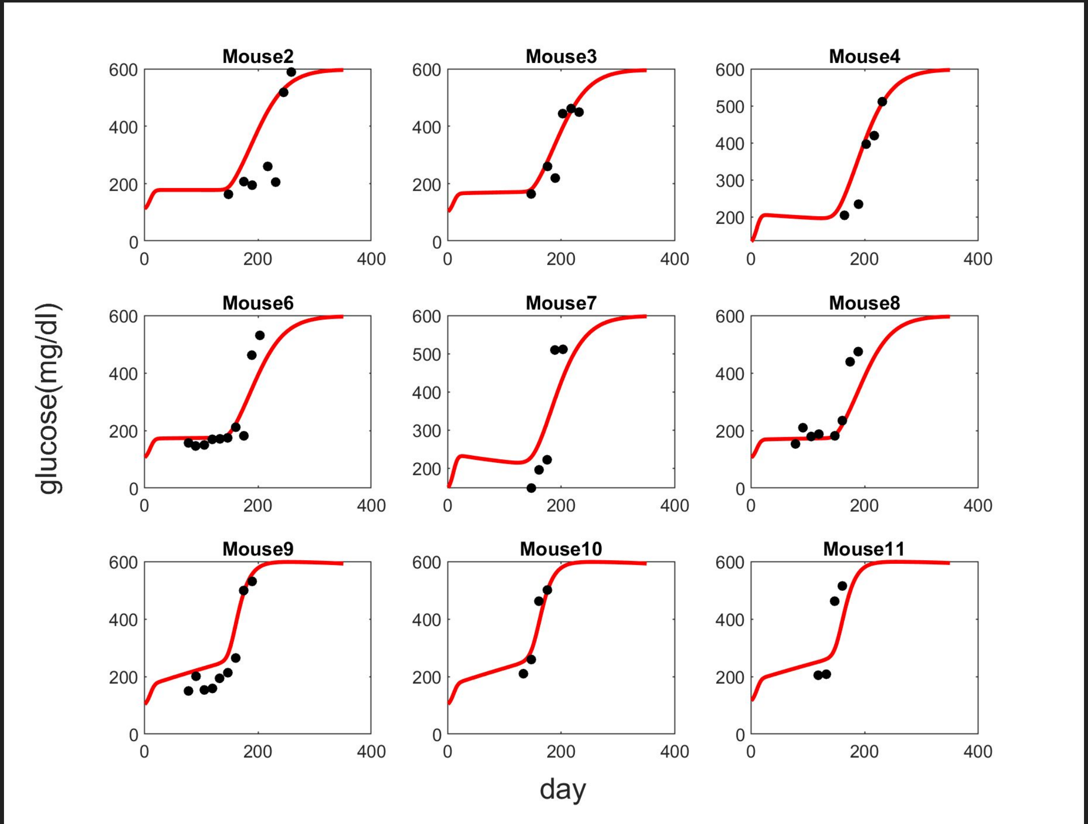
Daniel



Mouse Number	RMSE
2	141.074
3	67.4255
4	40.8032
6	50.1488
7	60.4445
8	50.6606
9	62.4348
10	45.3828
11	114.4727

Rachel

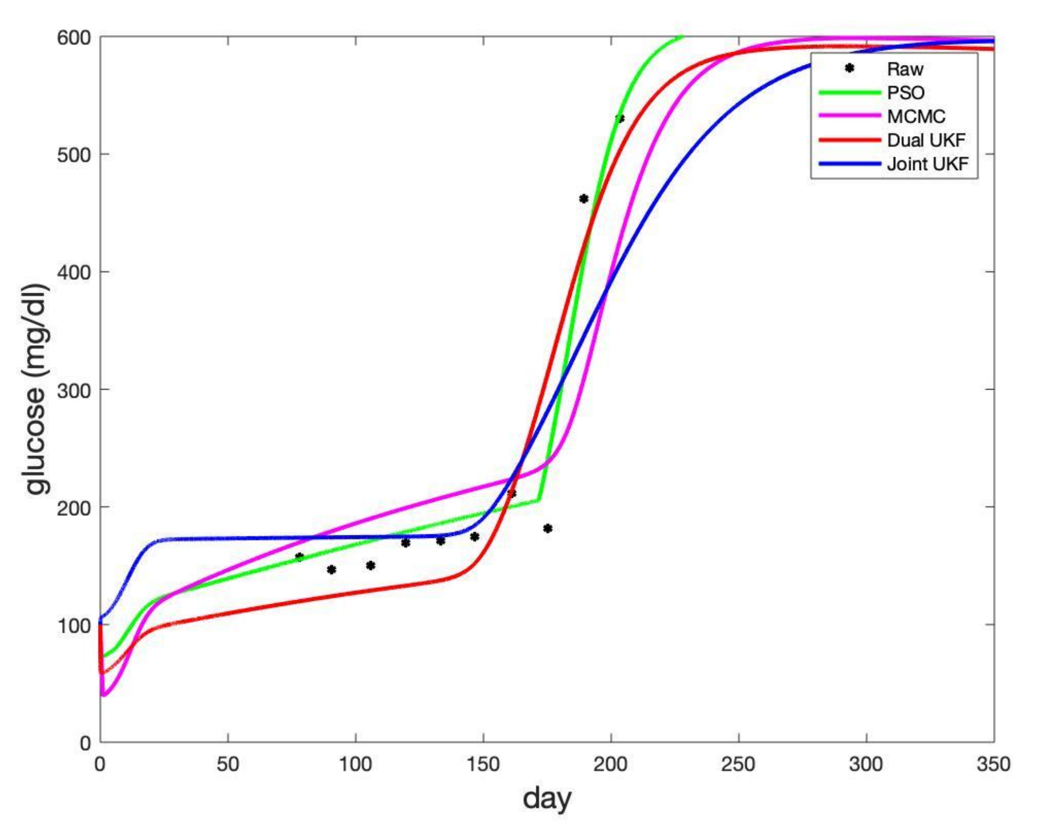
Results: Joint UKF



Mouse Number	RMSE
2	162.2097
3	182.9535
4	51.1009
6	67.1223
7	94.7998
8	64.5717
9	65.7906
10	46.5500
11	109.9000

Mouse 6: Comparison

Daniel



Algorithm	RMSE
PSO	28.2
MCMC	66.8
Dual UKF	50.2
Joint UKF	67.1

Population-level

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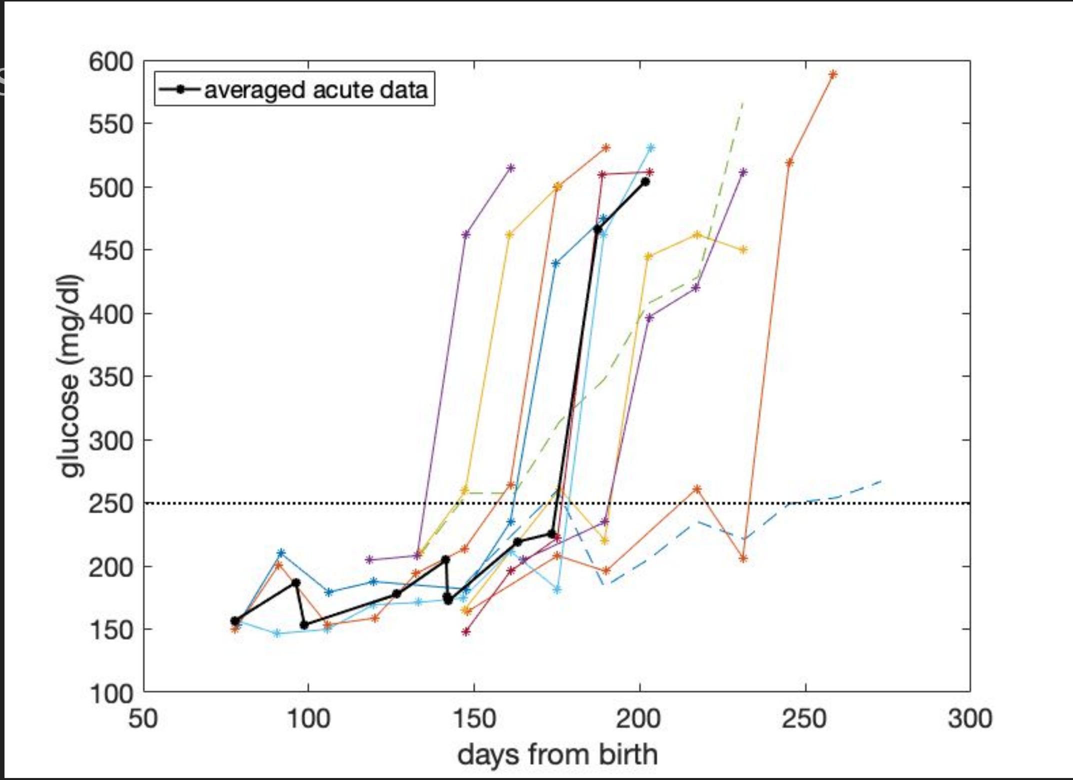
Construction of fits

- Techniques play to strengths of algorithms
  - UKF works best for individual data, while MCMC prefers averaged



<u>'Fit then Average':</u> fit all mice, find average parameter set

<u>'Average then Fit':</u> fit to averaged data

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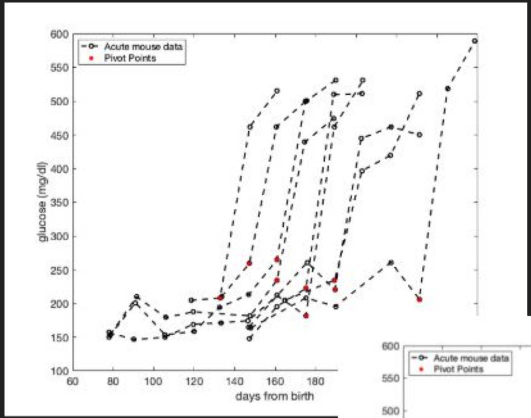
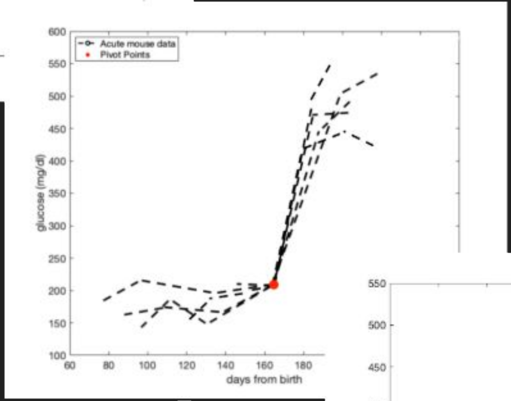
Average then Fit

1. Determine diabetes onset

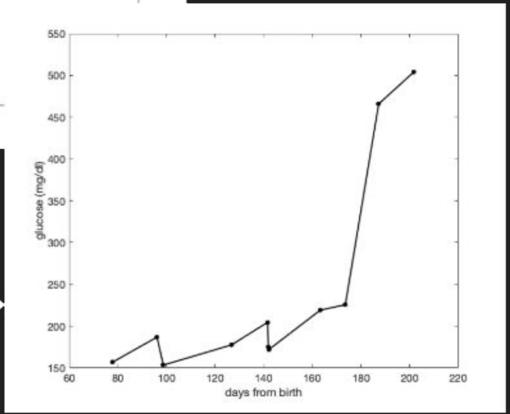


__Problem:__ Simple average loses shape

2. Align mouse data



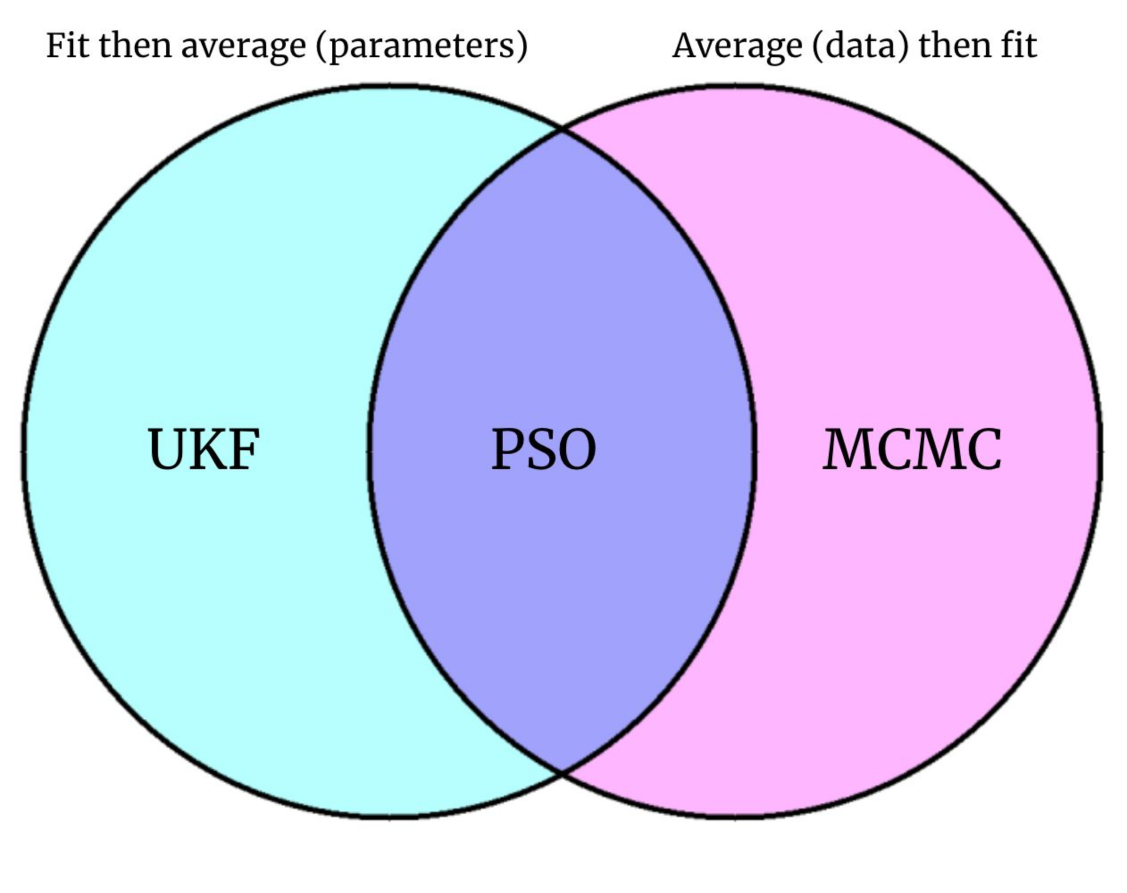
3. Average time and glucose



4. Position at average onset time

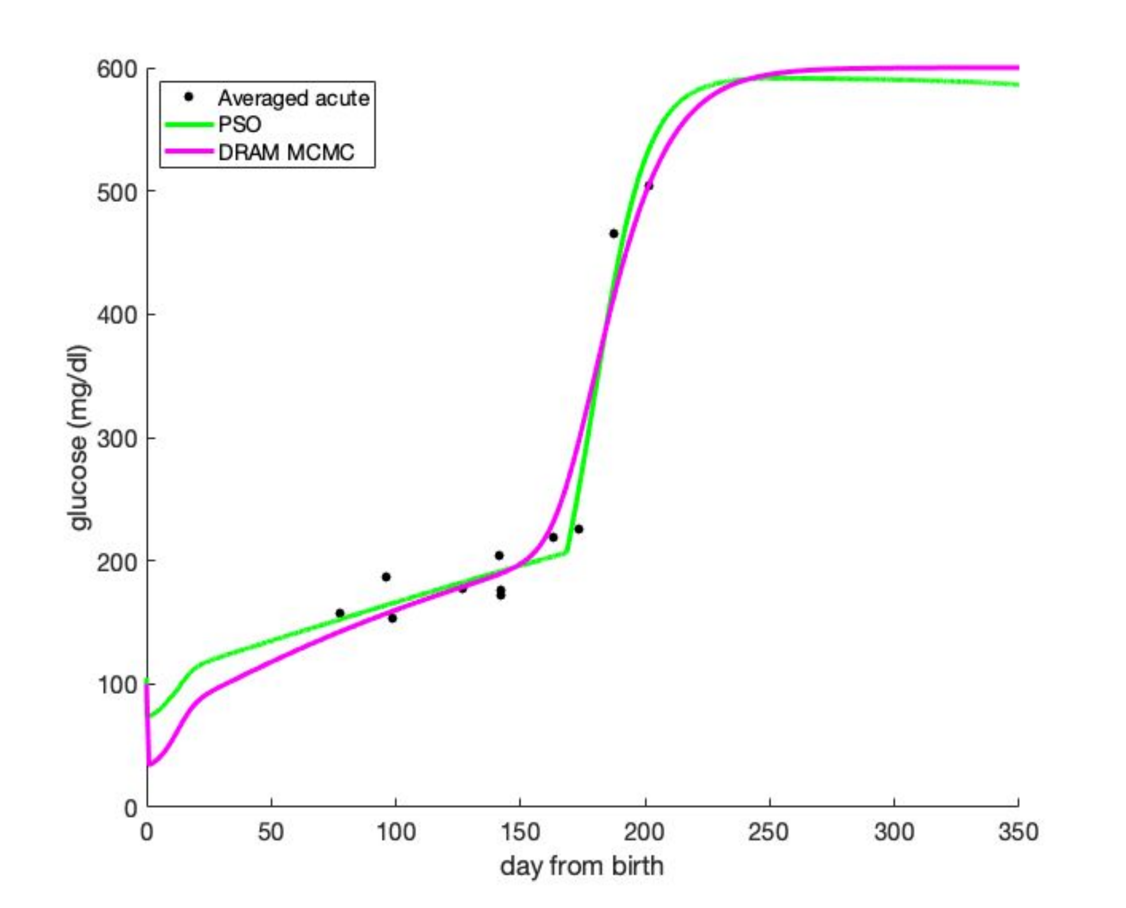
Construction of fits

Christina



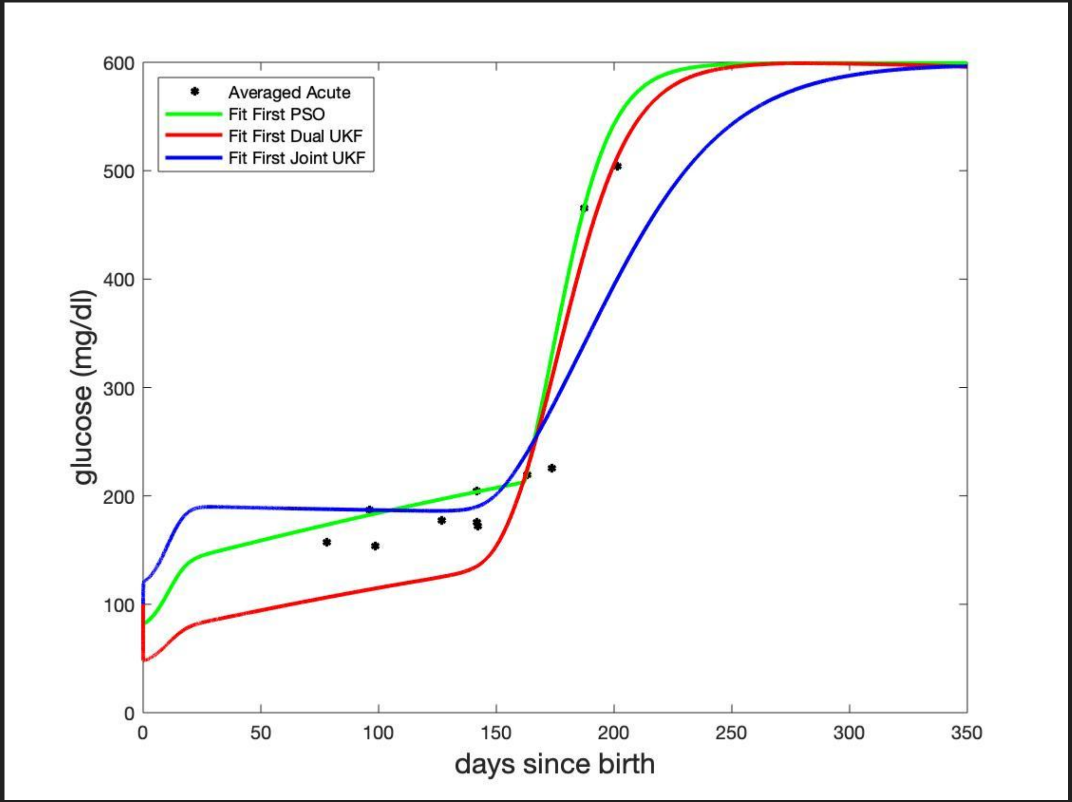
Results: *Average then Fit*

Algorithm	RMSE
PSO	22.75
DRAM MCMC	30.71



Results: *Fit then Average*

Algorithm	RMSE
PSO	35.46
Dual UKF	51.06
Joint UKF	52.07



Limitations

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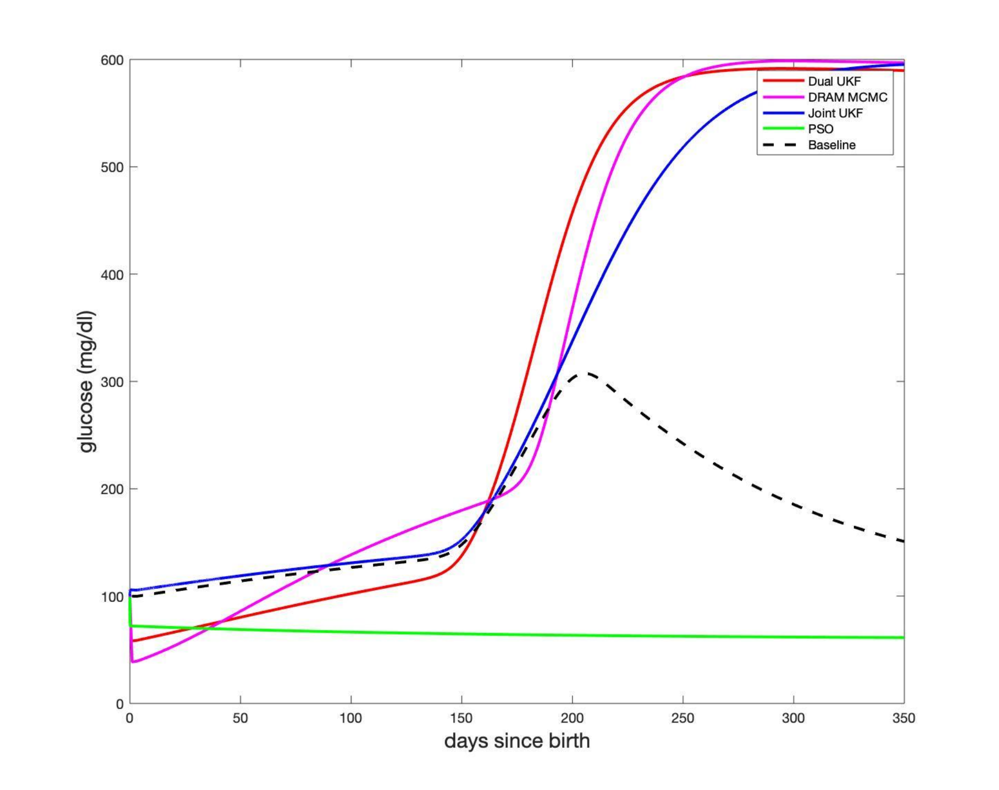
Limitations: Biological Checks

- Second situation of interest
  - Without catalyst 'wave' mouse should not become diabetic
- Simulation does not produce expected results
- Change objective/likelihood function to account for this



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Limitations: Parameter Set

- Need to formally identify which parameters to estimate
    - Currently lack consistency across algorithms
    - Informed by sensitivity analysis

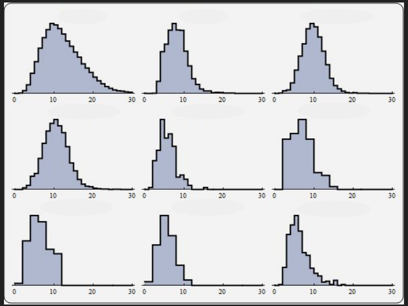
Multi-Method Expansions

Maya

Combination of UKF and MCMC

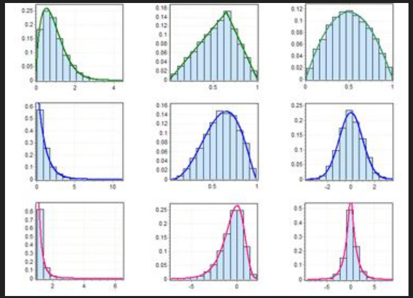
- Idea: MCMC is currently operating with uninformative (uniform) prior
- Providing informative prior thought to improve results
- Fit to individual mice using UKF to get prior distributions of parameters

Kalman Filters



initial parameter distributions

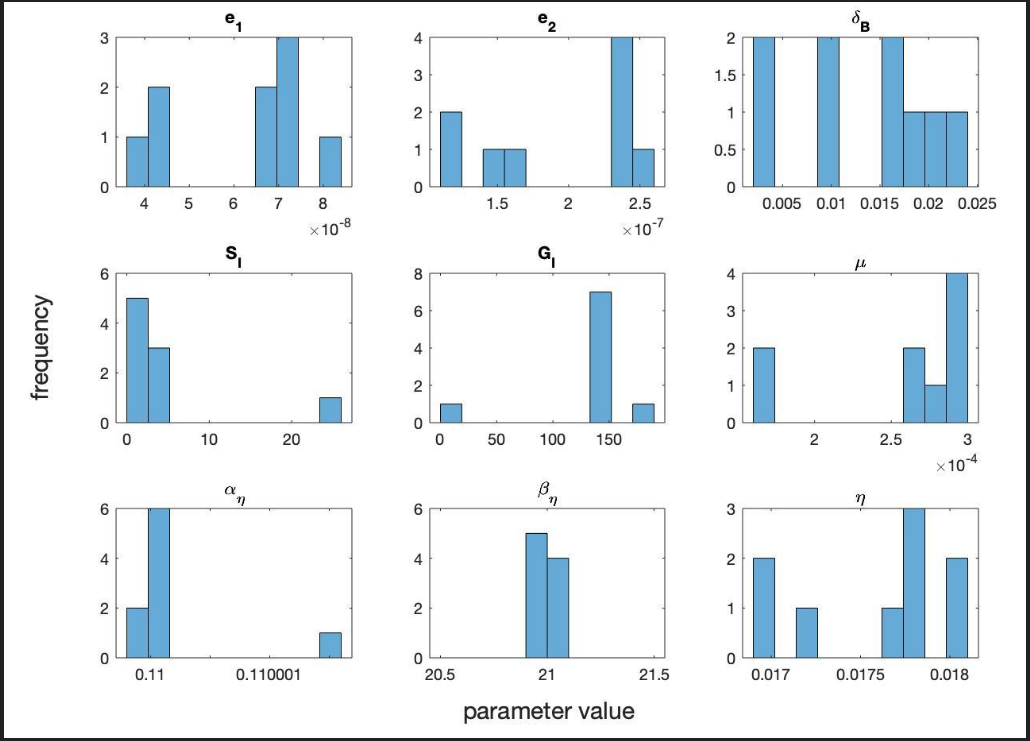
DRAM MCMC



final parameter distributions

UKF Parameter Distributions

- Fit normal distributions to key parameters
  - Large assumption
- Use as priors for MCMC



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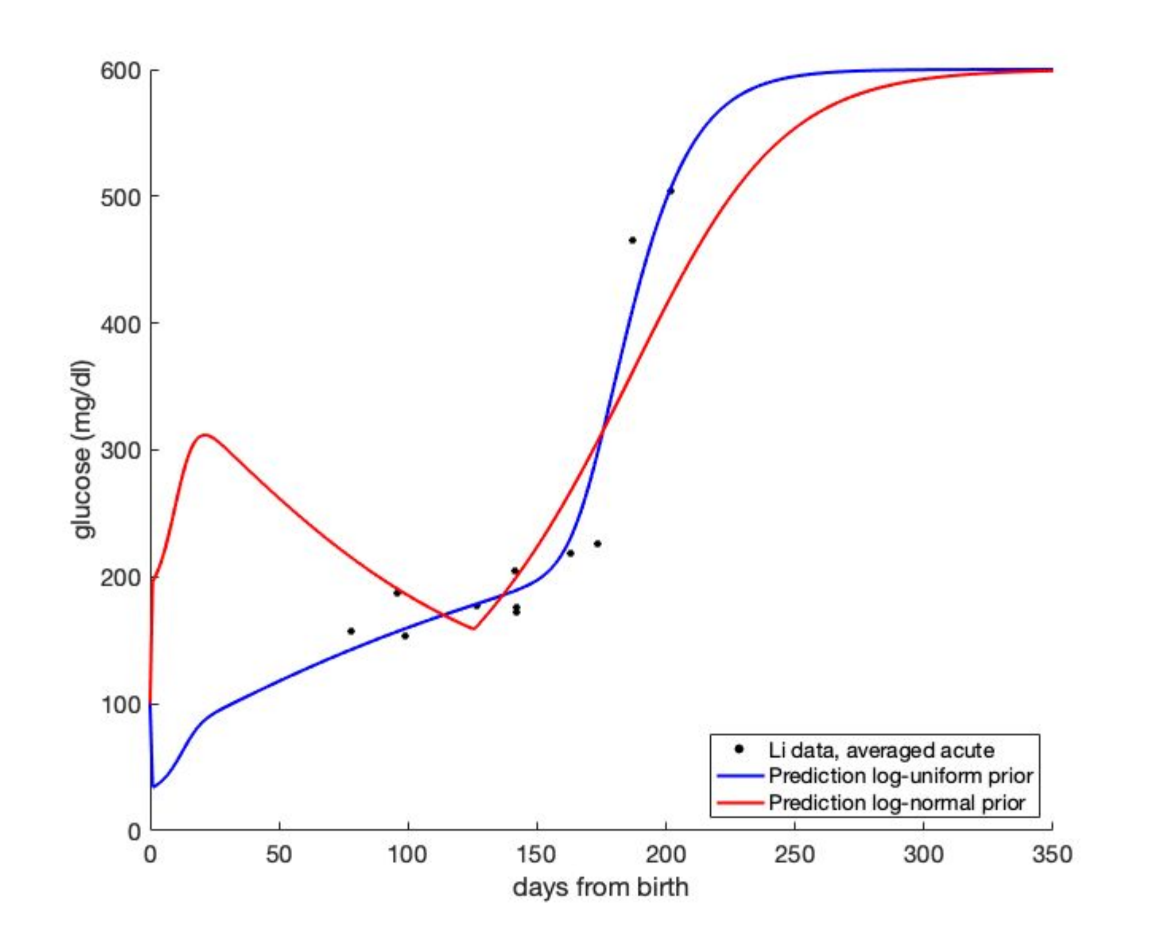
MCMC with an Informative Prior

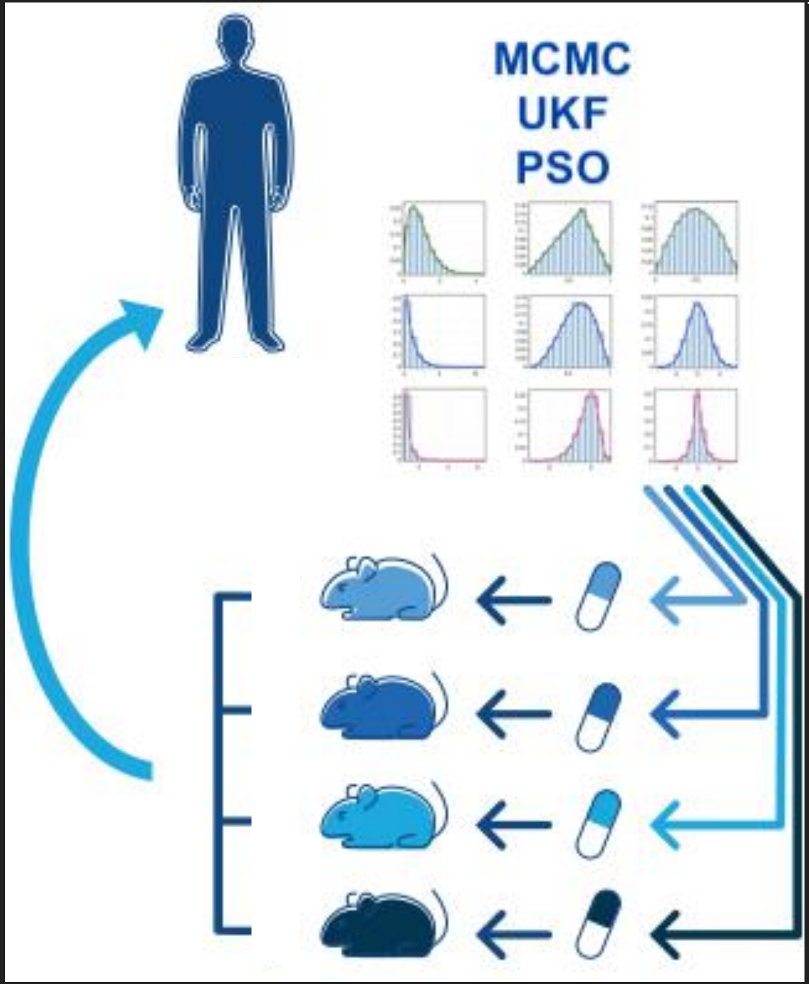
Prior Function	RMSE
Log-uniform	30.7
Log-normal	58.1



Daniel

Future Work

- Refining algorithms
- Incorporating new data
- Application to human models, support development and administration of treatments



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