Drug Kinetics in Genetically Modified Mice

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Outline

Why study drug kinetics in genetically modified mice?

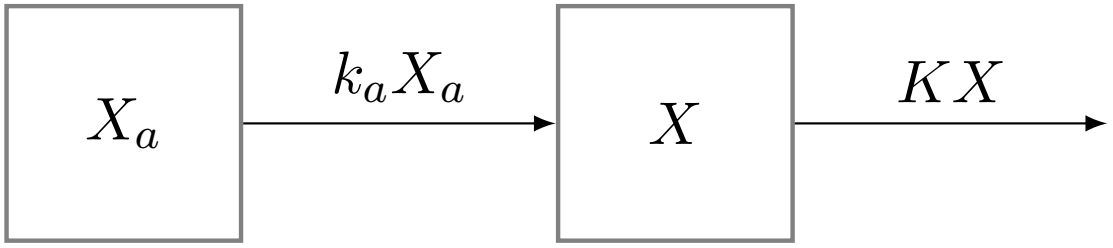
- Kinetics in humans differ on body weight, gender, and race
- Important to make sure drug doses work properly no matter such variables
- Unethical to do clinical trials in humans before know risks
- Can manipulate mice genes to mimic physiological behaviors in humans

The study

- 10 genetically modified mice and 10 normal mice
- Receive intramuscular injections of drug
- Initial drug doses held constant by the same μgram/kg of body weight
- Drugs administered and concentration checked t $t = 1, 2, 4, 8$ hr
- We look at two compartments: intramuscular and cell plasma/blood
- In particular we study drug absorption and drug elimination

The model

A cascading system:



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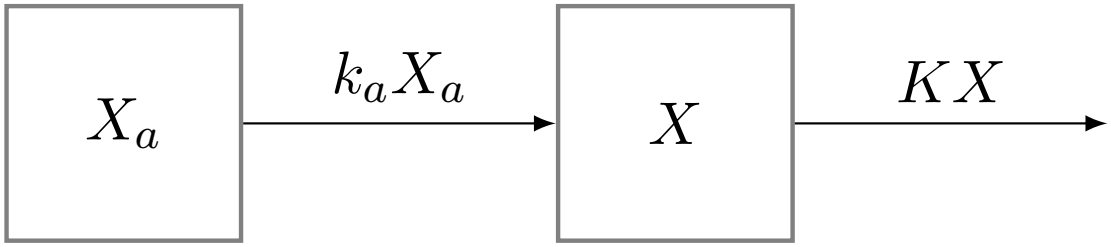

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This is a linear model that can be solved analytically:

$$X_a(t) = FX_0\big(k_a e^{-k_a t}\big), \quad X(t) = \frac{k_a F X_0}{k_a - K}\big(e^{-Kt} - e^{-k_a t}\big).$$

Question of interest

Will the same drug administered to the normal and genetically modified mice behave kinetically the same?

- We answer this question by seeing if both mice populations can be described by the same equation.
- We need to identify the parameters: $K, K_a, \frac{F}{V}$
- $\frac{F}{V}$ should be the same for any two mice from the same population since they will have about equal weight and ideally equal kinetics.
- Goal is to derive system of equations to fit data and then analyze parameters using statistics.

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- Use MCMC to get parameter distributions of $K, k_a, \frac{F}{V}$ for each mice population
- Test the difference between drug absorption coefficient for each mice population based upon the parameter distributions we obtained

Data With Different Initial Conditions

MICE GROUP A

drug concentration in plasma: microgram/ml

	t=1h	t=2h	t=4h	t=8h	initial dose: micrograms
mouse1a	26.97792	19.75837	12.76016	4.434793	31.43448
mouse2a	24.24753	22.72409	13.30686	4.812059	33.26047
mouse3a	24.77666	20.56166	11.41168	4.557679	30.97779
mouse4a	22.64532	19.94236	11.72876	4.045205	32.06939
mouse5a	21.28494	17.78286	8.705149	4.453663	31.45377
mouse6a	25.03974	16.68711	11.45587	4.022986	29.39312
mouse7a	23.85169	20.79003	8.796537	4.48717	30.58774
mouse8a	22.04373	14.48006	8.041883	4.058295	28.42543
mouse9a	27.03642	19.25051	11.79822	4.692525	31.77679
mouse10a	22.88891	13.54645	9.237231	3.70474	27.705

MICE GROUP B

	t=1h	t=2h	t=4h	t=8h	initial dose: micrograms
mouse1b	18.22752	10.02384	4.593106	0.496992	29.49211
mouse2b	17.73821	8.203042	3.365571	0.493685	27.14271
mouse3b	17.71877	13.10216	4.383508	0.568575	29.95828
mouse4b	20.32763	10.00664	4.03902	0.482287	28.87867
mouse5b	19.88525	12.80134	4.552165	0.612637	34.35556
mouse6b	20.26879	12.57416	3.916291	0.6134	32.27693
mouse7b	16.21579	9.327095	3.296307	0.374859	25.00623
mouse8b	18.93819	10.35912	4.153664	0.625798	30.88265
mouse9b	17.99845	9.563525	3.148519	0.620605	27.20372
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Modifying Sum Squared Error

- When fitting the data in standard way one needs only calculate the SSE for one model fit.
- Here we must fit the model to our data 10 times for each initial condition.
- Then we pool the SSE from each model fit. We find parameters that minimize

$$SSE = \sum_{i=1}^{10} \sum_{j=1}^{4} \left(C(t_j, y_{0i} | \hat{k}_a, \hat{K}, \widehat{F/V},) - Cobs_{i,j} \right)^2$$

Fitting the Model

Recall the exact solution:

$$X_a(t) = FX_0\big(k_a e^{-k_a t}\big), \quad X(t) = \frac{k_a F X_0}{k_a - K}\big(e^{-Kt} - e^{-k_a t}\big),$$

$$C(t) = \frac{X(t)}{V} = \frac{F}{V} \cdot X_0 \cdot \frac{k_a}{k_a - K}\big(e^{-Kt} - e^{-k_a t}\big).$$

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- Instead we optimize the numerical solution to the differential equation. This also gets around having to solve explicitly for V, the average volume of blood of the mice and F, the total fraction of the drug absorbed.
- Note that this will take about 10 times as long as a standard differential equation fit since each calculation of the SSE involves 10 model fits.

Estimating Parameter Distributions With MCMC

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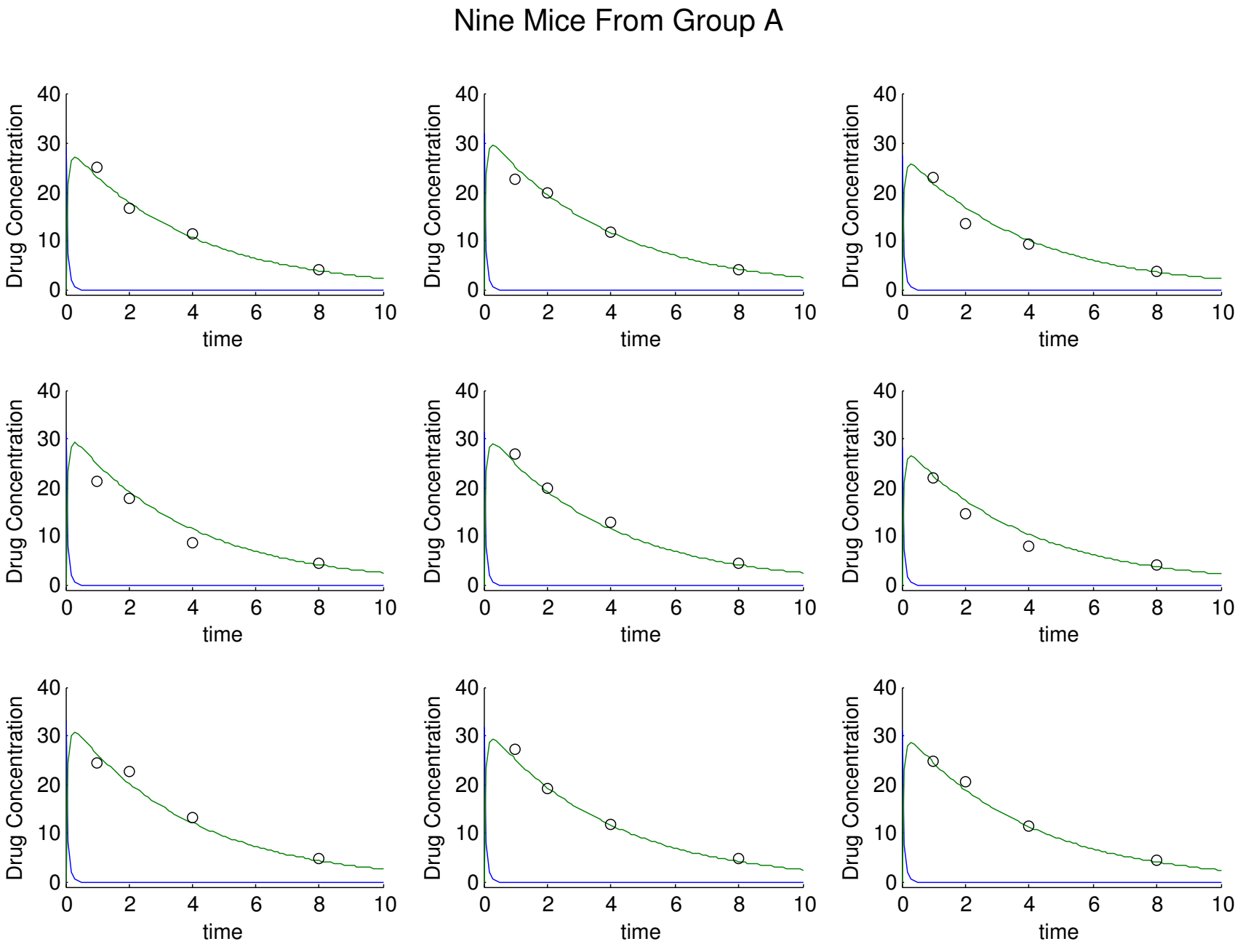
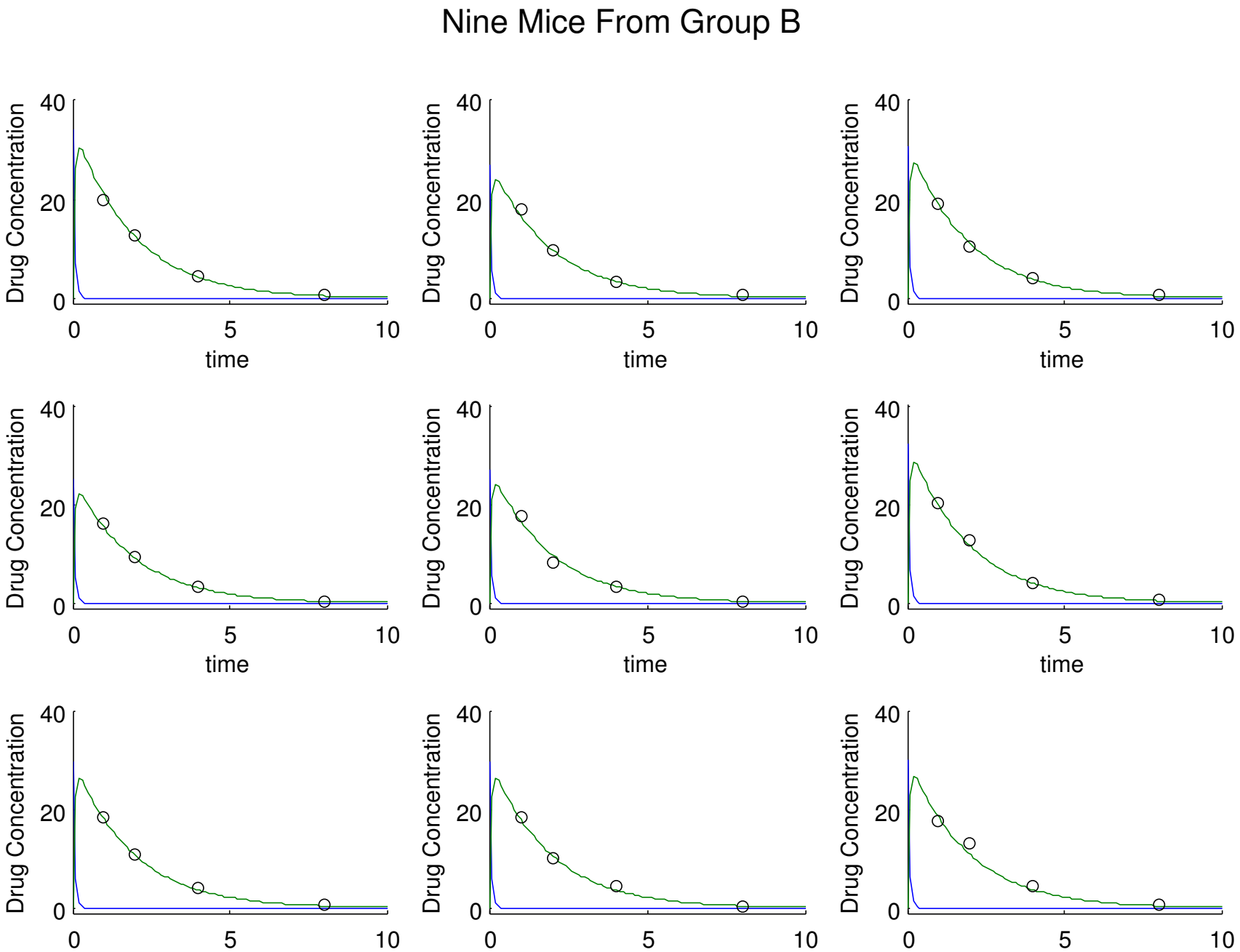
- The first runs were slow, but then we realized...
- We only used the ODE solver to avoid stability issues with *fitting*. Since we have an exact solution for concentration, we can use that to calculate MCMC. This significantly speeds up the MCMC calculations.
- From these, we obtain estimates for the parameter distributions, and since the mice populations are independent, we can obtain confidence intervals for the difference in each parameter by subtracting the distributions.

Outline

Model Fits


Nine Mice From Group A
Drug Concentration
time
0
10
20
30
40
0
2
4
6
8
10

Model Fits



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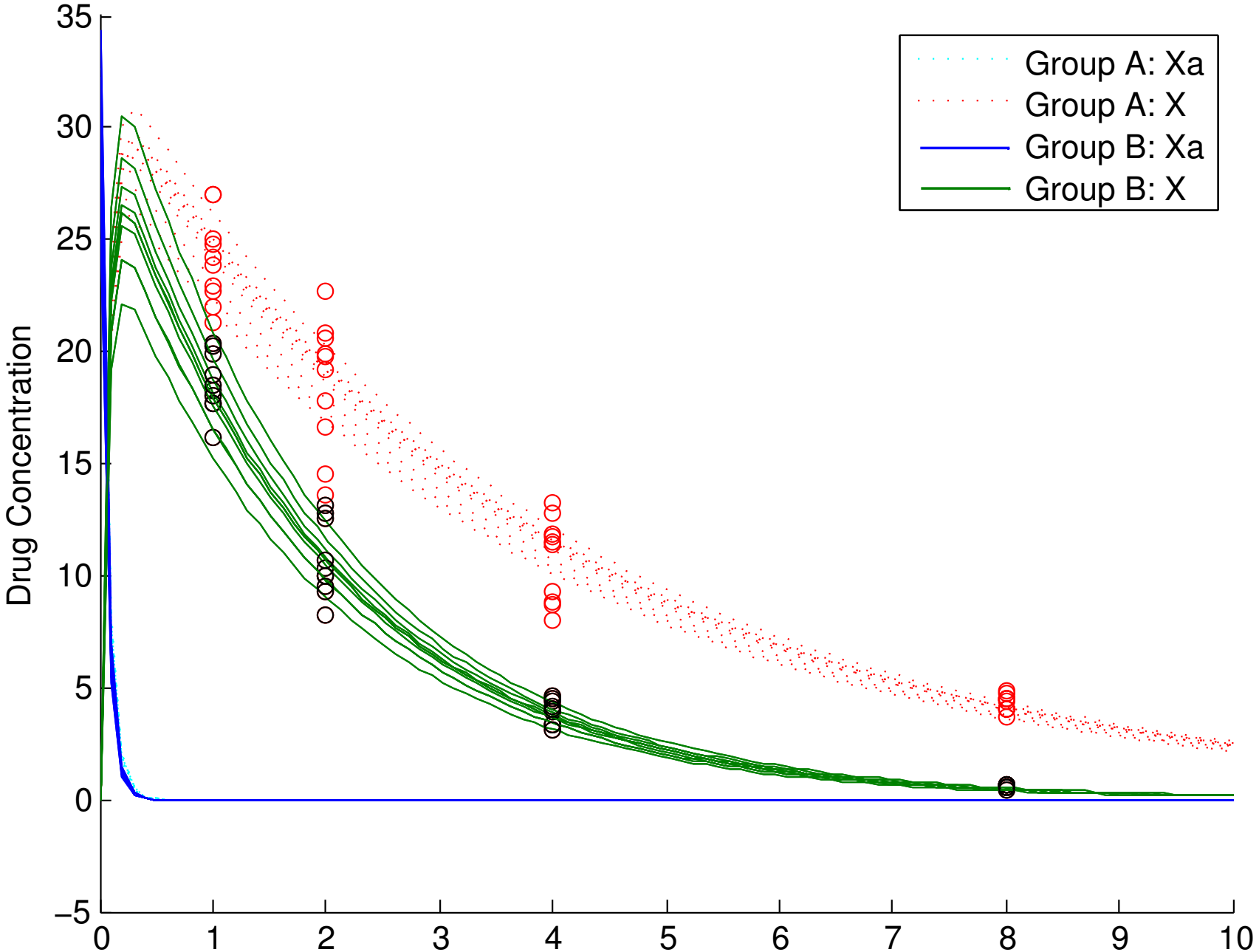
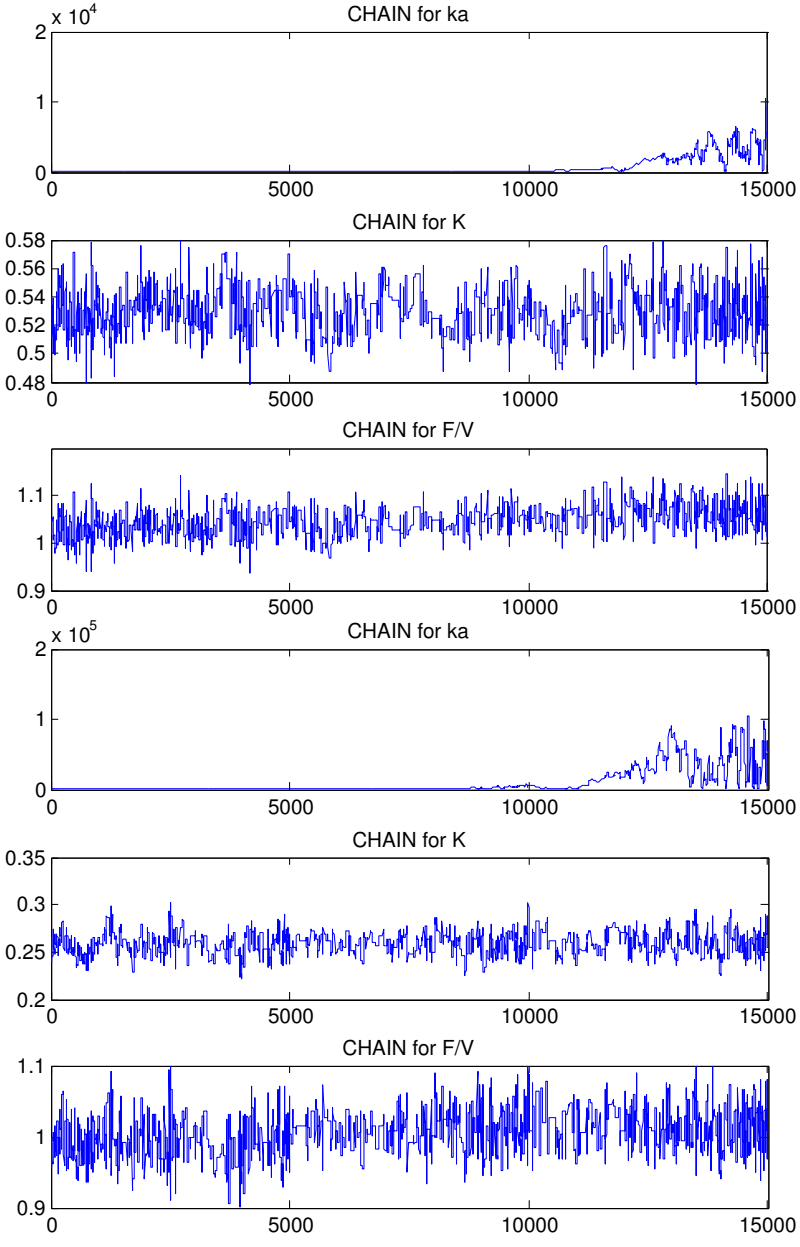
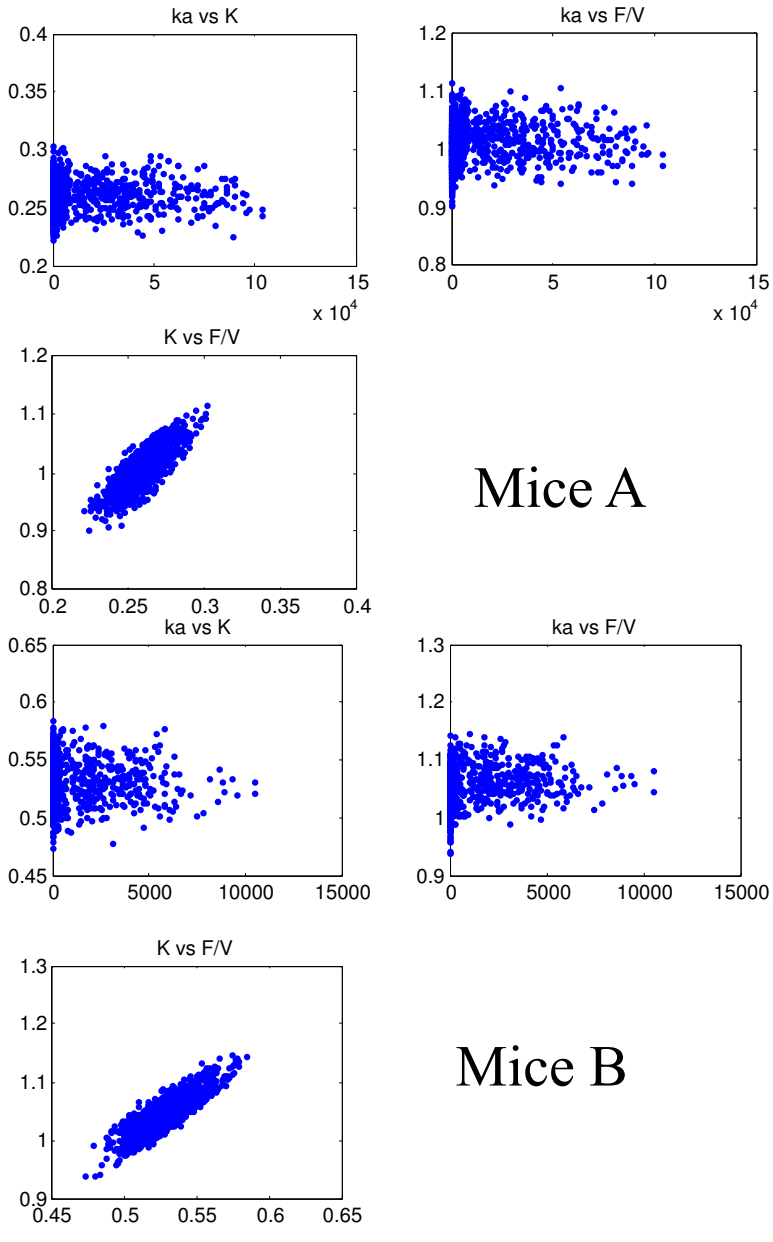

Group A: Xa
Group A: X
Group B: Xa
Group B: X
Drug Concentration
35
30
25
20
15
10
5
0
−5
0
1
2
3
4
5
6
7
8
9
10

MCMC Results





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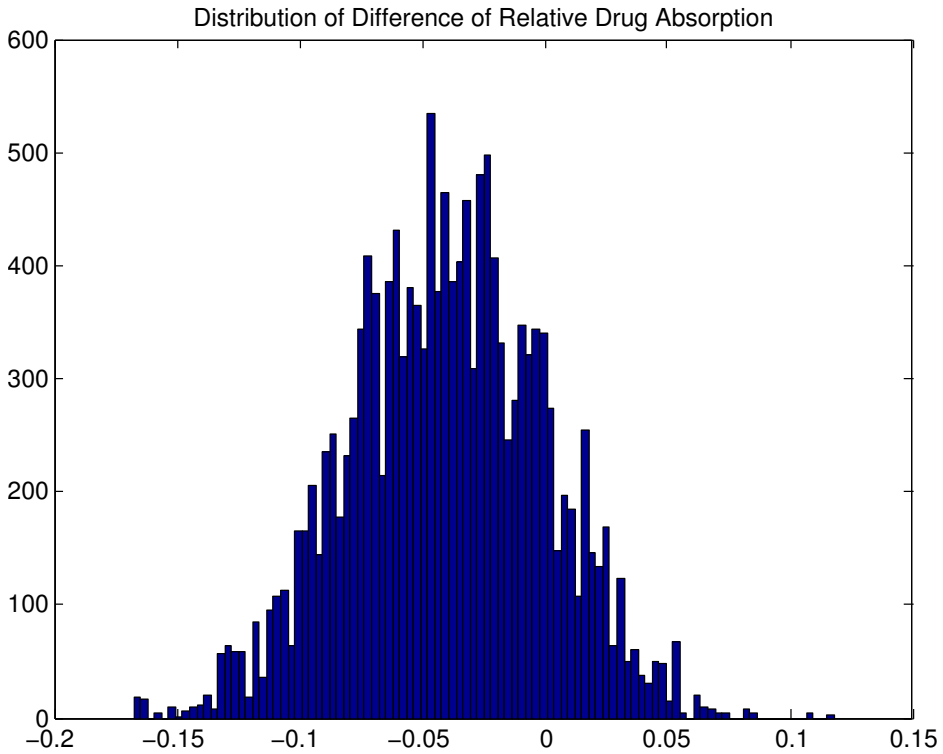
Parameter Differences



95 % Confidence Interval:$[-0.1187, \quad 0.0353]$.

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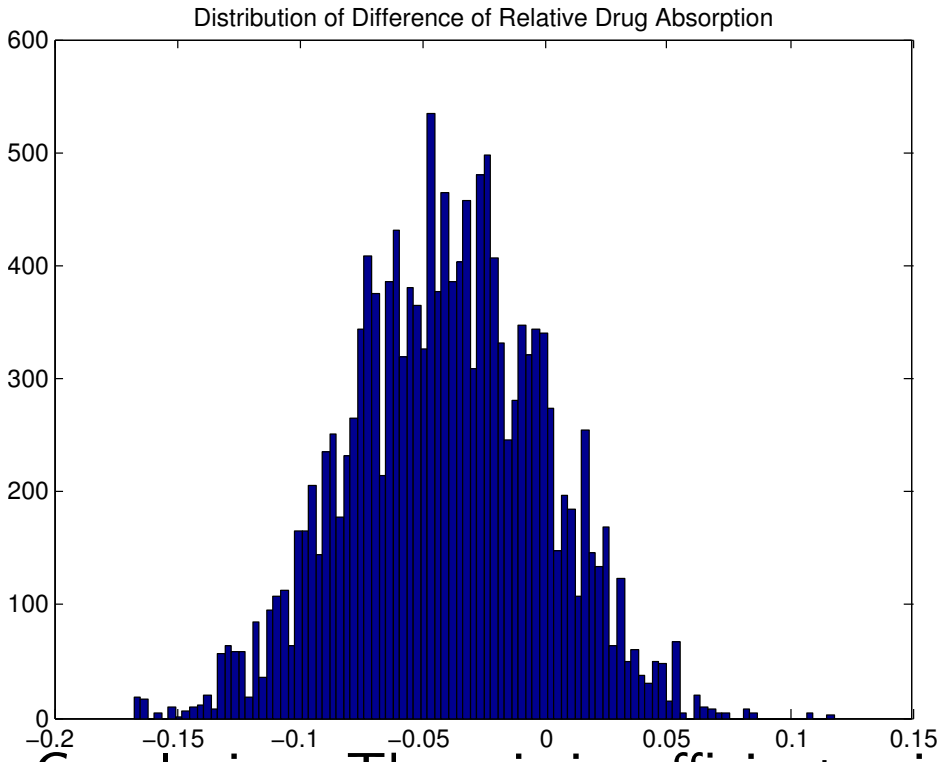

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Conclusion: There is insufficient evidence to suggest a difference in the drug absorption between the genetically modified and control mice.

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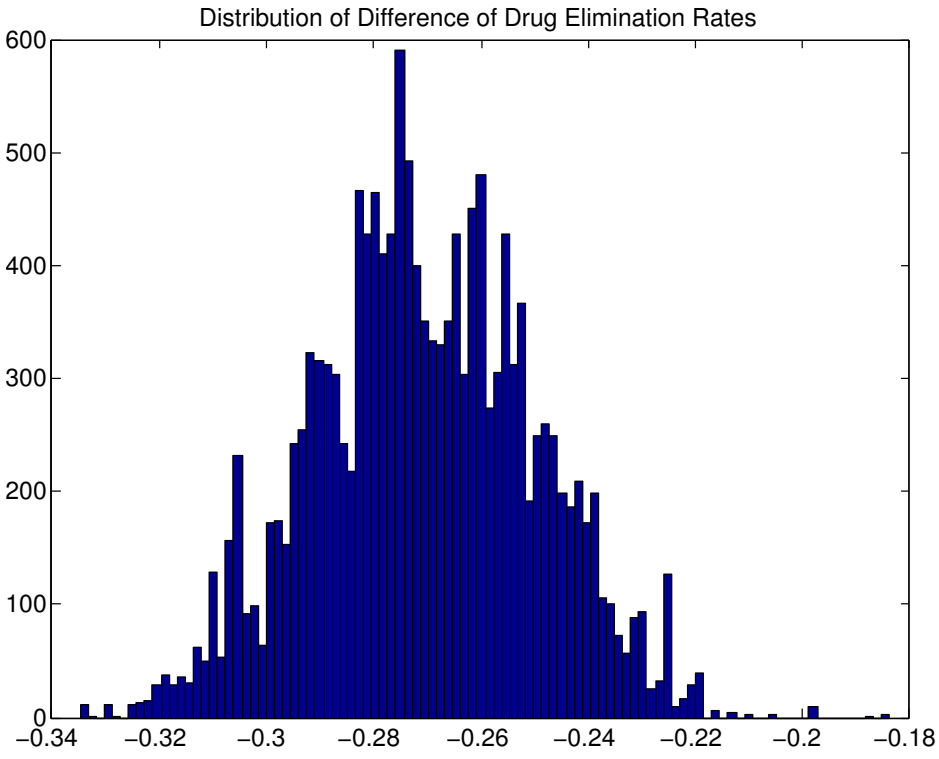

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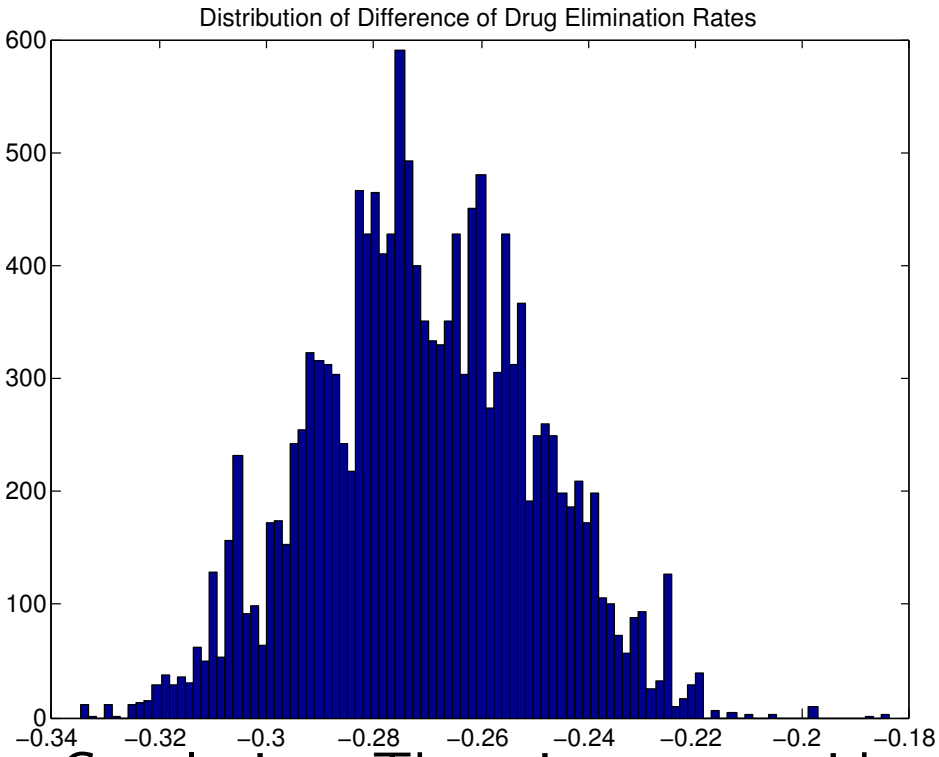

95 % Confidence Interval:
$[-0.3101, \quad -0.2296]$

Conclusion: There is strong evidence to suggest a difference in the drug elimination rate between the genetically modified and control mice.