Analyzing Rat Bioassays

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Introduction

In this report, we analyze data from an international validation study to measure the effectiveness of a rat uterotrophic bioassay. The bioassay we are studying measures the estrogenic effect of certain chemicals. The two chemicals used in this study (referred to using "Dose 1" and "Dose 2" in this paper) have well-known effects, so we will try to verify that the bioassay produces consistent results in rats that have been administered various amounts Dose 1. If the uterotrophic bioassay is an effective procedure for measuring the effects of these chemicals, then we expect to see consistent responses to various dosages across all labs.

The variables in this dataset are listed and described in the table below:

Name	Type	Description
lab	categorical (19 levels)	lab where bioassay was administered
proto	categorical (4 levels)	protocol of the bioassay
group	categorical (11 levels)	label for combination of dosage levels
dose1	continuous	amount of Dose 1 that the rat receives
dose2	continuous	amount of Dose 2 that the rat receives
body	continuous	body weight of the rat
wet	continuous	wet uterus weight
blot	continuous	blotted utuerus weight (response)

Table 1: Description of the Dataset

Methods

To measure the consistency of the responses, we fit a Bayesian hierarchichal model with a Gaussian mixture response. The model has random effects on Dose 1, Dose 2, and the intercept, which all vary by lab. Using one-fold cross validation, we compare this model's predictive error to that of previous models used in this analysis. Finally, we analyze between-lab variability using a visualization of the random effects. To create this visualization, we hold the other predictors constant (at the baseline protocol "A", a Dose 2 level of 0, and a body weight equal to the mean body weight of rats within the protocol). We then draw samples of the random intercept and Dose 1 effect from the model, and plot the results of blotted uterus weight by the amount of Dose 1.

Exploratory Data Analysis

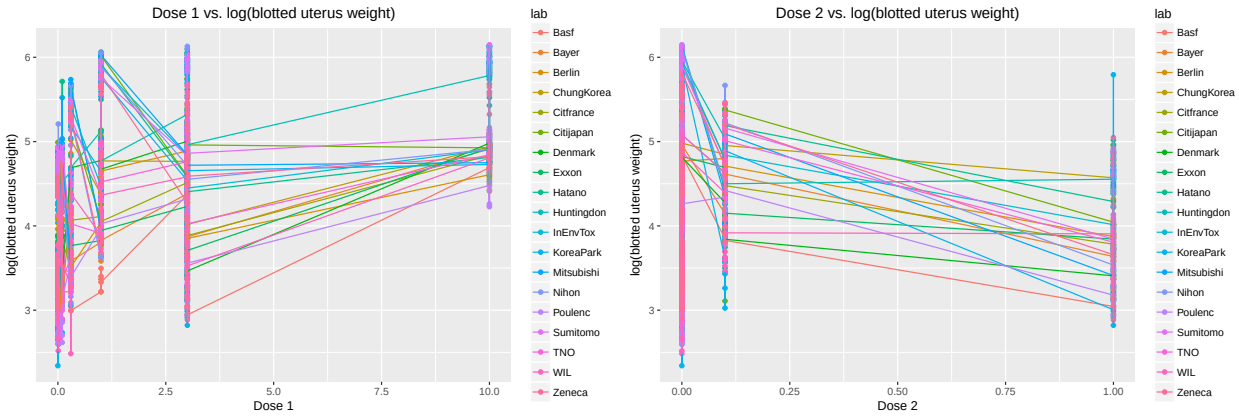


Fig. 1: Lab-to-Lab Variability in Intercepts and Slopes

This plot depicts why we added random effects on the intercept and the dosage variables. The slopes of the dosage effects and their starting points all vary by the lab in which the bioassay is administered.

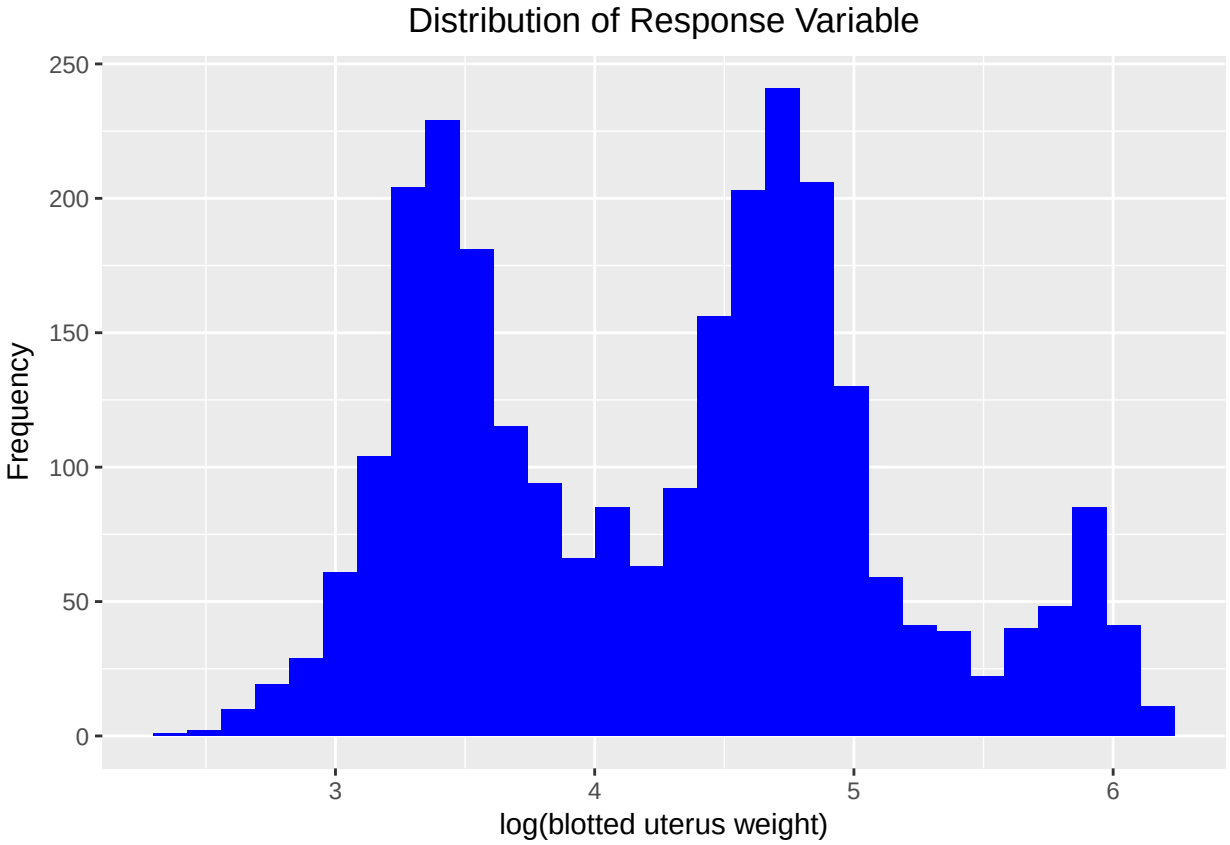


Fig. 2: Non-Gaussian Distribution of Response

This image shows that the response variable (log blotted uterus weight) is not normally distributed, which is what most of our previous approaches assumed. To fit this data, we use JAGS to build a Gaussian mixture

model with two clusters. The residual diagnostic plots for this model can be found in Appendix 2.

Previous Results

	MAE	RMSE
Mixed Effects	38.69420	63.71070
Mixed Effects, Transformed Dose 1	22.94010	38.73710
Mixed Effects, Kernels on Log Dose 1	21.71040	36.76390
Gaussian Mixture	23.32211	40.42922

Table 2: Predictive Errors of All Models

According to predictive accuracy on a single hold-out sample, our new Bayesian model is not our best-fitting model, but the performance is fairly close to our other ones. Therefore, we will continue with our analysis of between-lab variablility.

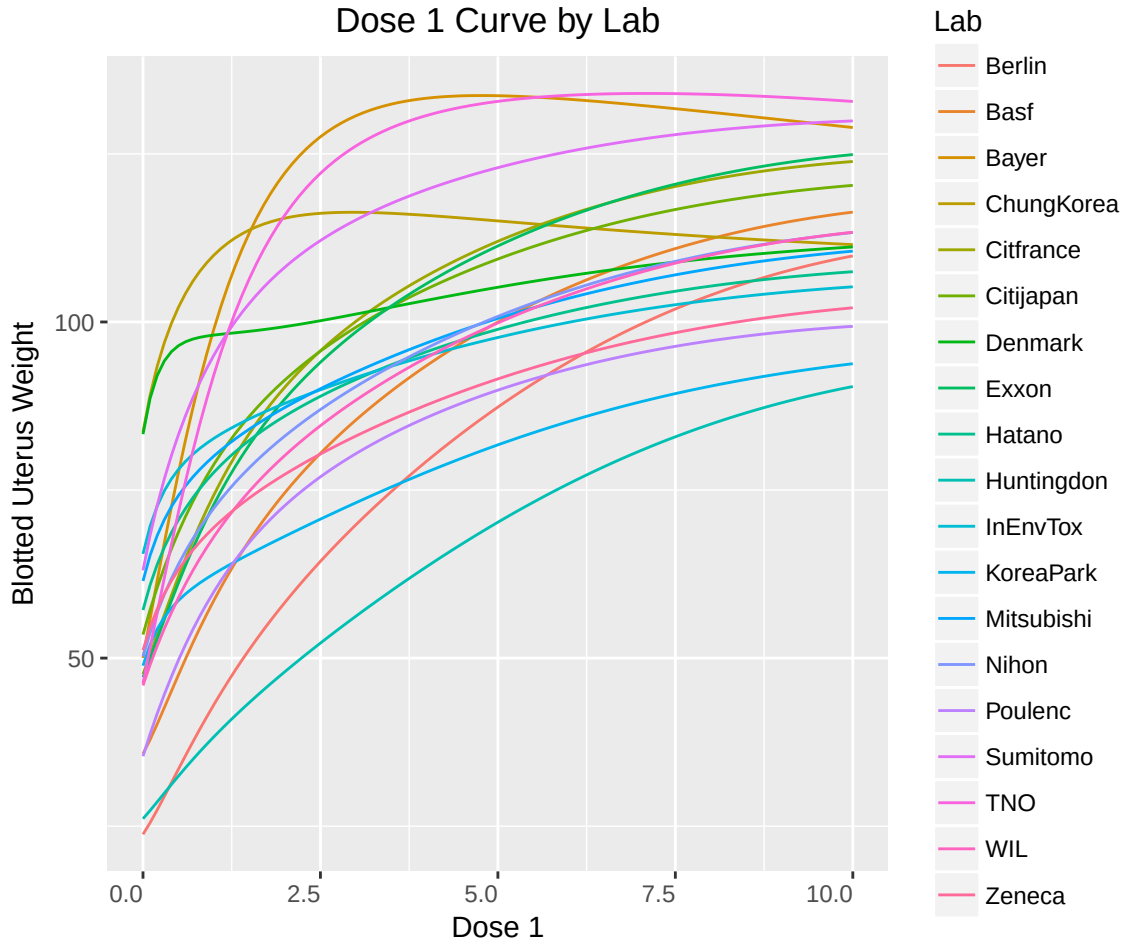


Fig. 3: Dose 1 Response Curves for Each Lab from Kernel Model

The figure above is the final result of our previous analysis of rat bioassays using the kernel model. To make it, we take samples of the random Dose 1 effects (slopes) and lab effects (intercepts) from our best-fitting

model, holding all other predictors constant, and plot the resulting dose response curve for each lab. From this plot, we drew the conclusion that the trends between labs were not homogenous enough, and we did not recommend this bioassay procedure as a method for consistently measuring the estrogenic effects of chemicals in rats. For our new clustered model, we recreate the same plot and interpret it in the next section.

Analysis of Between-Lab Variability

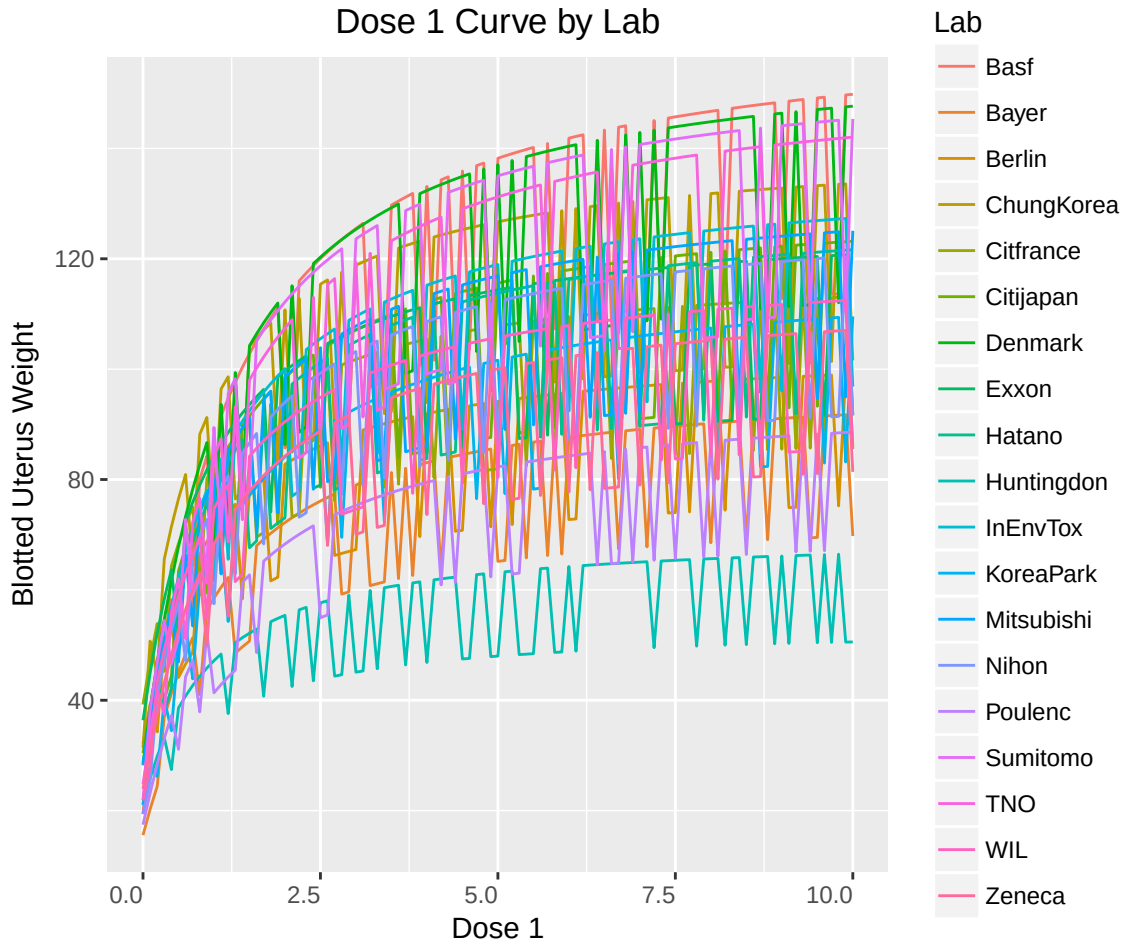


Fig. 4: Dose 1 Response Curves for Each Lab from Cluster Model

Both the cluster and the kernel models show similar shapes of the simulated Dose 1 response curves. However, two main differences between the output of the two models is that the cluster model has less variation between lab intercepts, and the simulated lines are not smooth. The oscillating behavior that we observe in the lines is a result of the clusters on the response variable.

Discussion

In our previous analysis, we concluded that there was too much variability between the curves, and therefore we could not claim that the Dose 1 effect is consistent between labs. The lines were too spread apart, and one lab even showed a decreasing effect of Dose 1 on blotted uterus weight. In our mixture model, however,

the trends are much more consistent. The intercepts are closer together, and all of the lines move in generally the same direction. Despite this, the spread between the uterus weights for high dosages is too high for us to conclude that the effecs of Dose 1 are homogenous between labs.

Appendix

1) Random Effects on Each Lab in Cluster Model:

lab	lower	estimate	upper
Basf	-3.380681	0.5195555	2.607738
Bayer	-3.317904	0.5586848	2.640111
Berlin	-2.844564	0.9998184	3.122657
ChungKorea	-3.020563	0.8515069	2.996333
Citfrance	-3.143160	0.7053441	2.833161
Citijapan	-3.084581	0.7903874	2.925118
Denmark	-2.920388	0.9941018	3.130232
Exxon	-3.153868	0.7658966	2.890442
Hatano	-3.071126	0.7911679	2.902831
Huntingdon	-3.719509	0.1710009	2.286871
InEnvTox	-3.033125	0.8432368	2.942381
KoreaPark	-3.192074	0.6868699	2.814083
Mitsubishi	-3.052819	0.8157964	2.906587
Nihon	-3.068833	0.7844948	2.935708
Poulenc	-3.402463	0.4913036	2.589554
Sumitomo	-2.882648	0.9584156	3.093376
TNO	-2.936380	0.9657392	3.070739
WIL	-3.154621	0.6948877	2.824978
Zeneca	-3.205643	0.6509009	2.772986

Table 3: Random Intercepts from Cluster Model

lab	lower	estimate	upper
Basf	-0.8876289	-0.7886078	-0.6892959
Bayer	-0.6865859	-0.5909539	-0.4955141
Berlin	-1.0301431	-0.9321536	-0.8213826
ChungKorea	-0.6897469	-0.6167851	-0.5382423
Citfrance	-0.6476647	-0.5566281	-0.4704728
Citijapan	-0.7880762	-0.7341953	-0.6806776
Denmark	-0.9639928	-0.8612836	-0.7616247
Exxon	-0.7178229	-0.6296314	-0.5340877
Hatano	-0.8224806	-0.7724315	-0.7224335
Huntingdon	-0.7062489	-0.6029612	-0.5028455
InEnvTox	-0.8437358	-0.7946182	-0.7360790
KoreaPark	-0.9434720	-0.8696064	-0.7841456
Mitsubishi	-0.8263992	-0.7793225	-0.7244427
Nihon	-0.8635951	-0.8163473	-0.7642029
Poulenc	-0.9361851	-0.8534099	-0.7741235
Sumitomo	-0.8986593	-0.8504026	-0.7982674
TNO	-0.9845442	-0.9176664	-0.8465417

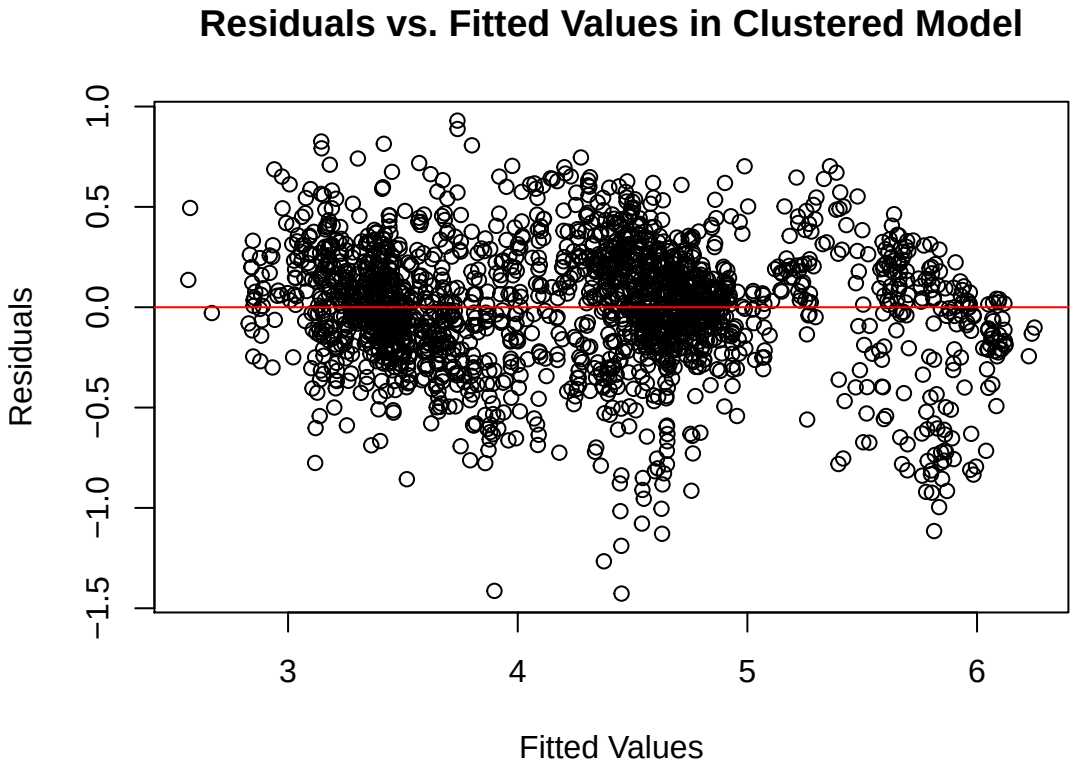
lab	lower	estimate	upper
WIL	-0.7805336	-0.7170327	-0.6489338
Zeneca	-0.8539290	-0.7876772	-0.7197038

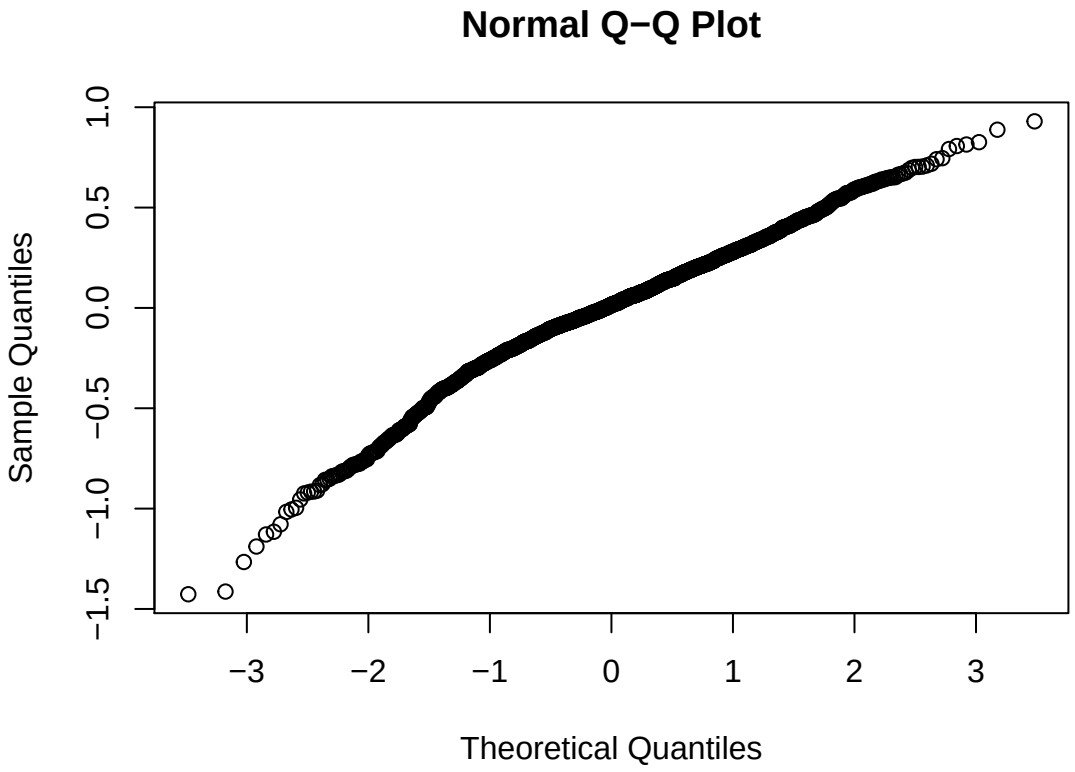
Table 4: Random Dose 1 Effects from Cluster Model

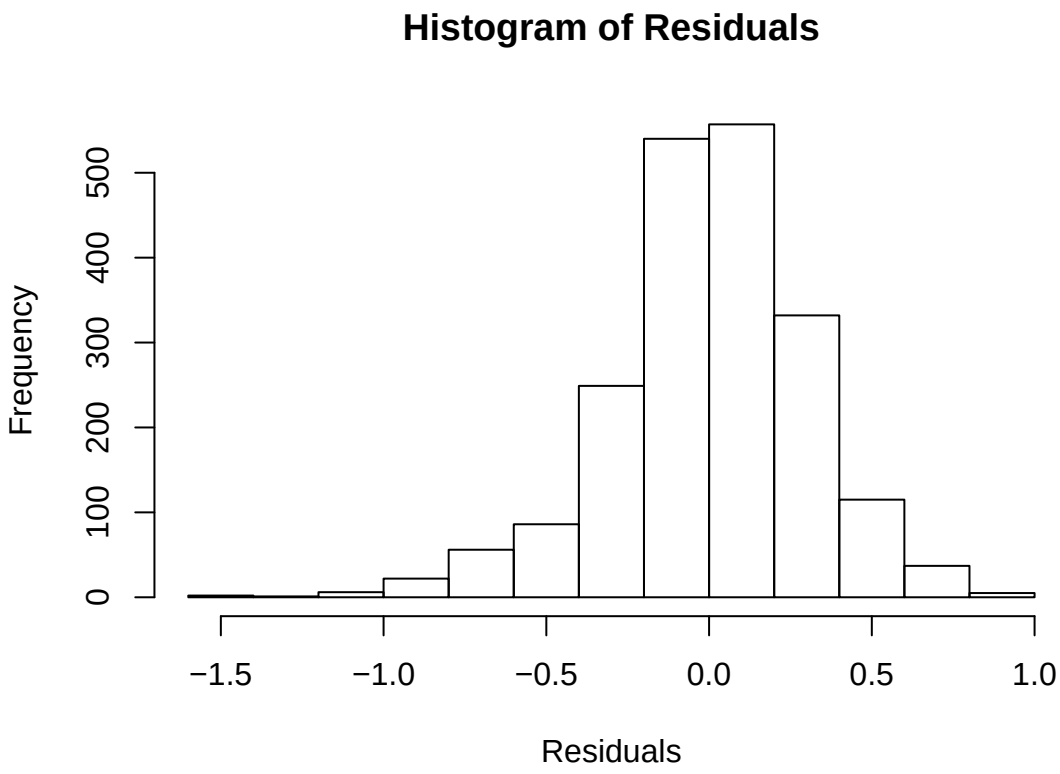
lab	lower	estimate	upper
Basf	-1.4449071	-1.2248805	-0.9737230
Bayer	-0.9832580	-0.7580706	-0.5239888
Berlin	-0.9345795	-0.7150665	-0.4537371
ChungKorea	-0.7522801	-0.5853259	-0.3728072
Citfrance	-1.0527975	-0.8120791	-0.5503159
Citijapan	-1.2711834	-1.1009891	-0.9216201
Denmark	-1.8096896	-1.5367644	-1.2425901
Exxon	-1.1854479	-0.9625848	-0.7169339
Hatano	-1.2327603	-1.0860911	-0.9158239
Huntingdon	-1.2158740	-0.9527325	-0.6576402
InEnvTox	-1.4116126	-1.2754156	-1.1212986
KoreaPark	-1.6163527	-1.4404259	-1.2563441
Mitsubishi	-1.4118389	-1.2752168	-1.1386856
Nihon	-1.4238512	-1.2715059	-1.1351120
Poulenc	-1.1385048	-0.8584730	-0.5093360
Sumitomo	-1.4547217	-1.2767677	-1.0714511
TNO	-1.0559653	-0.8581135	-0.6513877
WIL	-1.3478950	-1.1575193	-0.9648636
Zeneca	-1.3689625	-1.2066161	-1.0315372

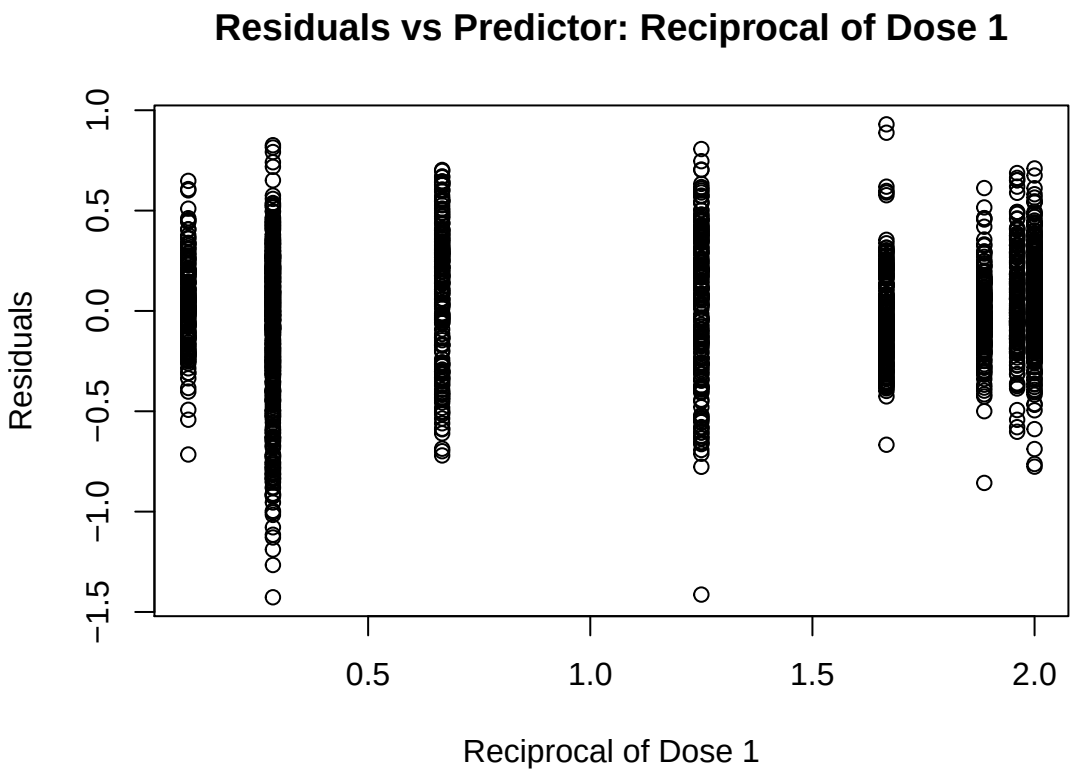
Table 5: Random Dose 2 Effects from Cluster Model

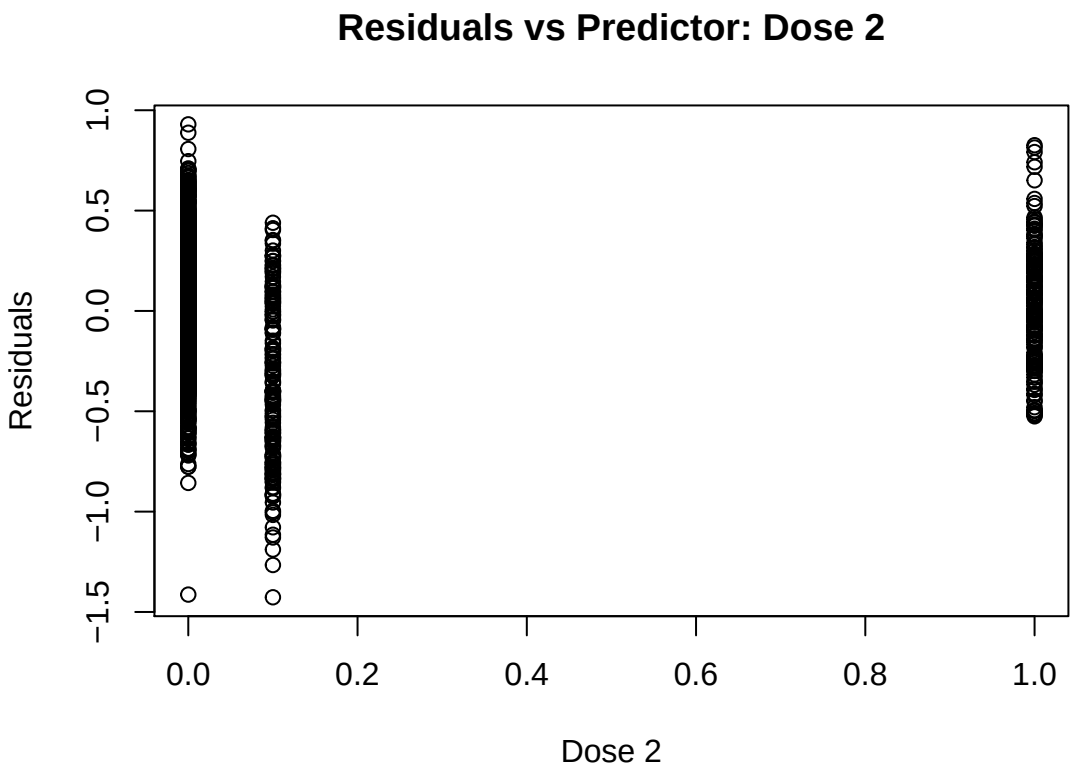
2) Diagnostic Plots of Cluster Model






Histogram of Residuals
Frequency
0
100
200
300
400
500
−1.5
−1.0
−0.5
0.0
0.5
1.0
Residuals


Residuals vs Predictor: Reciprocal of Dose 1
Residuals
1.0
0.5
0.0
−0.5
−1.0
−1.5
0.5
1.0
1.5
2.0
Reciprocal of Dose 1


Residuals vs Predictor: Dose 2
Residuals
1.0
0.5
0.0
−0.5
−1.0
−1.5
0.0
0.2
0.4
0.6
0.8
1.0
Dose 2

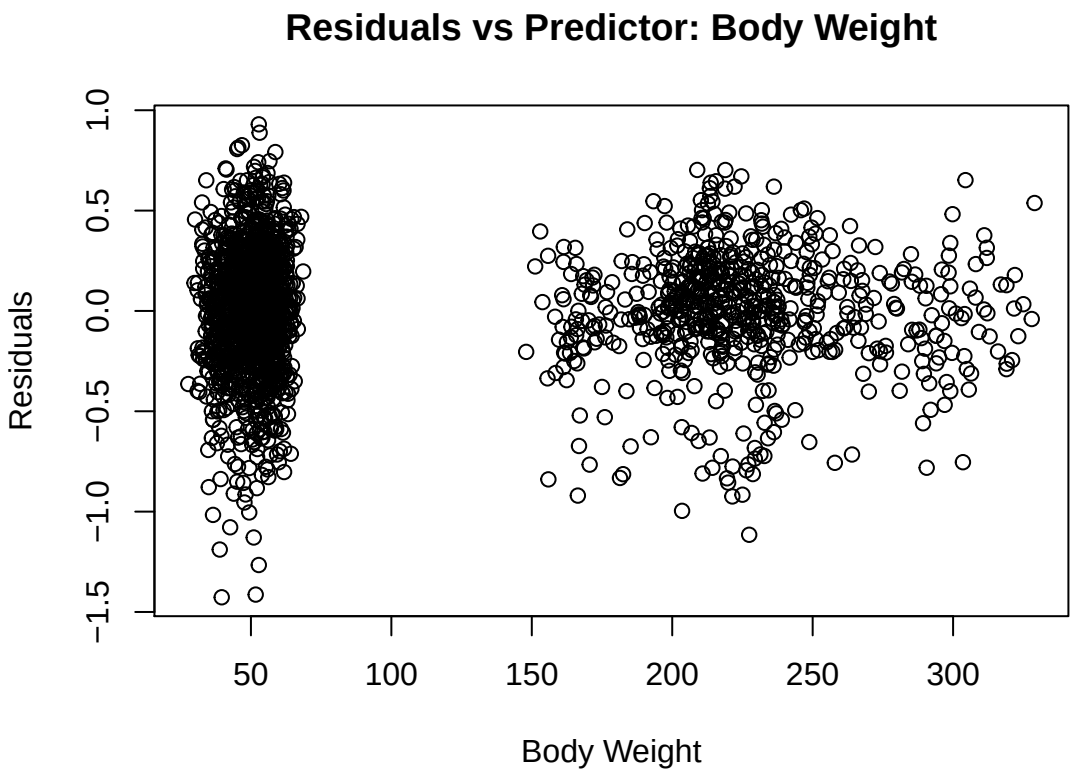


Fig. 5-10: Diagnostic Plots of Cluster Model