STA721 Final Project

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12/8/2018

1. Summary

International mutilaboratory studies shows that the weight of the uterus, with uterus weight expected to exhibit an increasing dose response trend for chemicals acting as estrogen agonists and with estrogen antagonists (ZM) acting to block such estrogen effects. After fitting a linear regression including the interaction term of `EE` and `ZM` with `lab` and `protocol`, we verify that as expected the effects are significant. But these results are are not consistent among labs, even some data from certain labs can be considered as outlier and fails to detect the effect. At dose level 3 of EE there is a change relative to the control. Protocols differs in sensitivity to detecting estrogenic and anti-estrogenic effects, and Protocol A, B are recommended.

2. Introductions

Using the rats to test the effect of estrogen agonists and antagonists on the weight of the uterus is one new approach for screening chemicals for endocrine disrupting effects. An international multilaboratory study was conducted to compare the results of the rat uterotrophic bioassay using a known estrogen agonist (EE) and a known estrogen antagonist (ZM), The overall effect is expected to be that the uterus gets heavier with the increase of estrogen agonist (EE) dose. The main goal of the study was to assess whether the results were consistent across the laboratories.

The dataset from different labs is in a dataframe format with a total of seven variables. The response variable is Uterus weight `uterus` in unit mg. The covariate variables are: `EE`(Dose of estrogen agonist,mg/kg/day), `ZM`(Dose of estrogen antagonist, mg/kg/day). Other variables such as `lab`, `protocol`, `group` explains which kind of rats are used in which location of lab in which group. These covariates are all in factor format and has different levels. Only body weight of rats `weight` is measured in gram.

3. EDA

After looking into the data, we find that all variables but `uterus` and `weight` should be encoded as a factor. And from table of `EE` and `ZM`, it shows that only for EE dose level 3, there is some data in change does of ZM. So it is wiser to exclude the interaction term `EE:ZM`.

The first plot listed int he third page is a side-by-side boxplot of uterus weight to ZM. It is obvious that different types of rats used will lie in different region of uterus weight. For example, for protocol A,B all the uterus weights are not larger than 200mg. And for protocol C,D the average uterus weights are larger than protocol A,B. This can be explained since protocol A,B uses immature rats and usually mature female shall have larger weight.

There is only two continuous variable, so in the next step of EDA we look at the relationship between uterus weight and body weight. The second plot listed in the third page is a side-by-side scatterplots of uterus weight to body weight in different labs. We find that in protocol D the slop is almost the same. Therefore, this effect is consistent across the labs. However in protocol A,B, there is no significant relationship between uterus weight and body weight.

4. Model and Result:

We build a linear regression model excluding the `group` variable, because the group index varies in labs and cannot be considered as a factor. We treat all variables but `uterus` and `weight` as a factor. In order to use one full model to address all question, we include the interaction term of EE:protocol, ZM:protocol, EE:lab, ZM:lab. From EDA part we can find that some experiments are not done in some EE:ZM combination. So we cannot include this interaction term. Then we use `boxcox` and find that the log transformation is preferred. Therefore, the final model will be:

$$
\begin{aligned}
\log(\text{uterus}) = \beta_0 + \beta_1 \log(\text{weight}) + \beta_2\text{EE} + \beta_3\text{ZM} + \beta_4\text{lab} + \beta_5\text{protocol} \\
+\beta_6\text{EE:lab} + \beta_7\text{ZM:lab} + \beta_8\text{EE:protocol} + \beta_9\text{ZM:protocol} + \epsilon \\
\epsilon \sim N(0, \sigma^2)
\end{aligned}
$$

For detecting effect of EE and ZM, we can do a F-test with the null hypothesis assuming all coefficients of EE an ZM are 0. The F-statistics is $F = \frac{\|(P_k - P_{k-1})Y\|^2/(r(P_k)-r(P_{k-1}))}{\hat{\sigma}^2}$. Instead of constructing a function, here we use anova function to do the test procedure.

From the result of the model, we can see that becasue there is only one combination of EE and ZM across all labs. That is when EE equals to 3. So the change does point for EE is 3. And we can see that the adjusted R^2 is really high about 0.9. So we think that we have verified the effect.

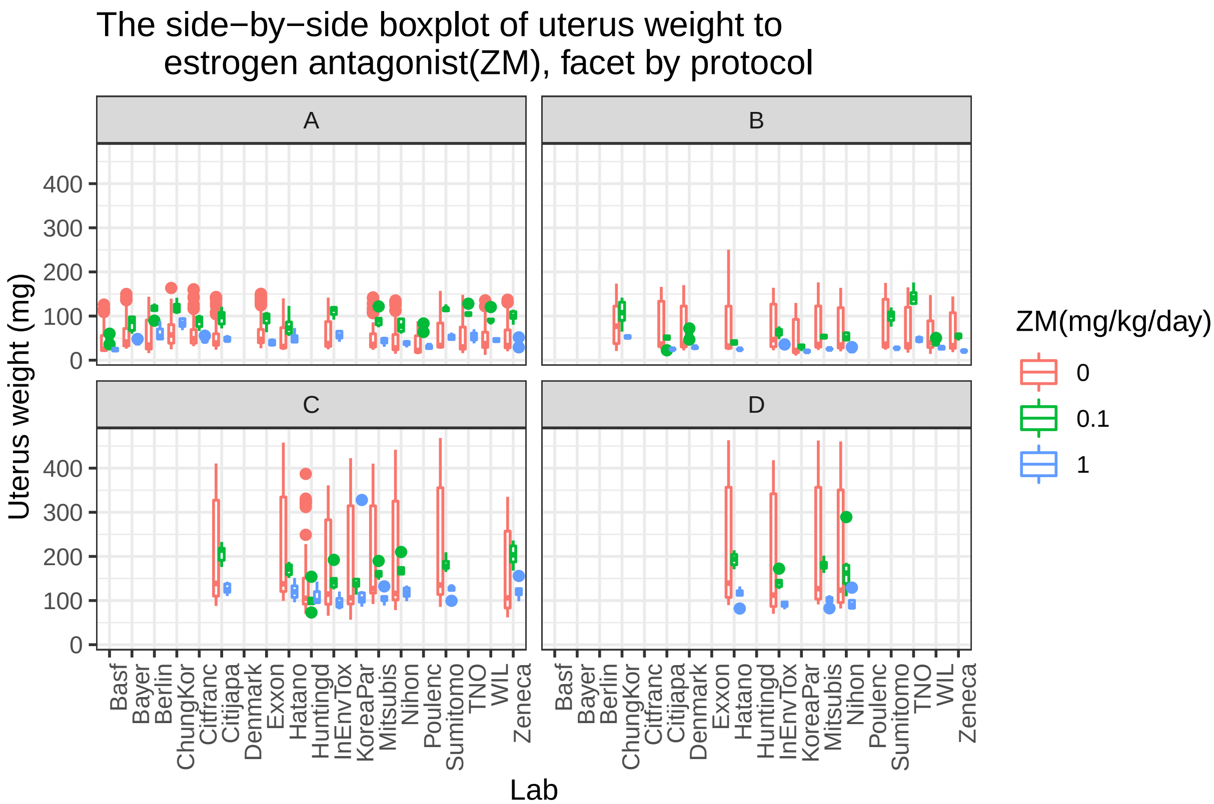
According the residuals and Cook's distance, there are three possible outliers(1426,926,1586). And they all shares the same feature from protocol C and D. And also small amount of experiments are done in protocol C and D. So protocol A and B are preferred.

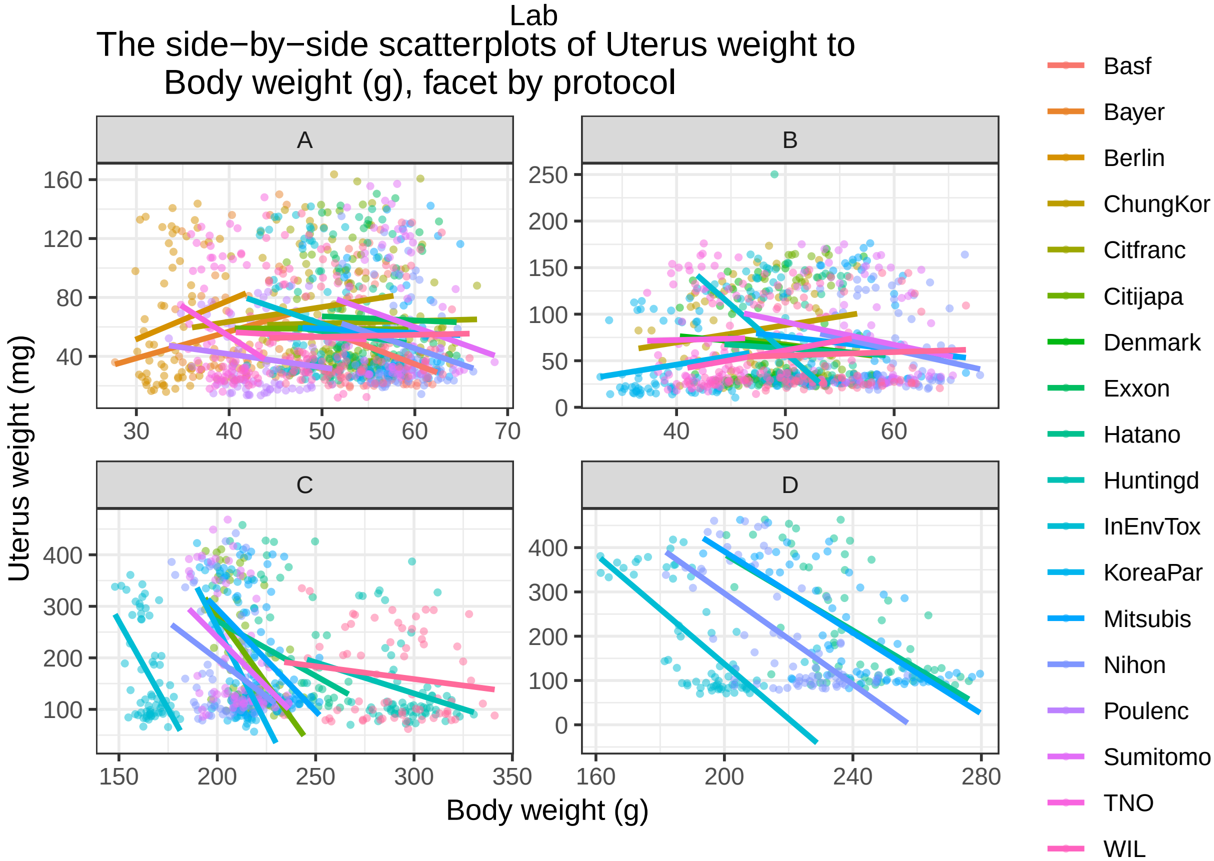
5. Conclusion

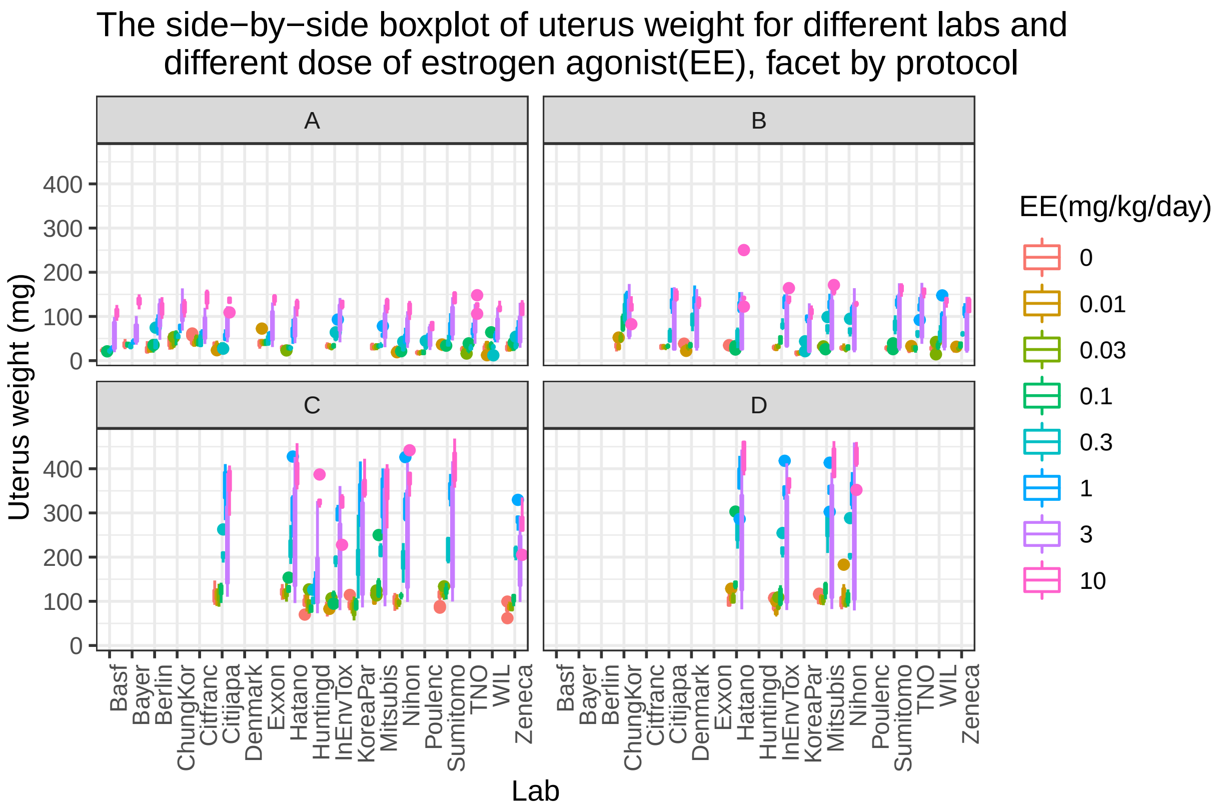
First of all, according to the results of our model, uterotrophic bioassay is significantly successful overall at identifying estrogenic effects of EE and anti-estrogenic effects of ZM. There are some labs which fail to detect such effects, i.e. Exxon. At the does 1 of EE, there is a significant change relative to the control ($\alpha = 0.05$). This level does vary across labs, for example, at Bayer lab, there is a significant change at the does 3 of EE.

The does response does vary across labs. At Bayer lab, there is a significant change at the does 3 of EE rather than does 1. At ChungKor, Citfranc and Huntingd, there are a significant changes at the does 0.1 of EE. At Denmark, InEnvTox, labPoulenc, labSumitomo, labTNO and labZeneca, there are a significant changes at the does 0.3 of EE.

Similarly, it is easy to see that the protocols do differ in their sensitivity to detect estrogenic and anti-estrogenic effects. Protocol A can be recommeded, because it is the most consistent one among labs. Moreover, compared with other protocols, the variance of protocol A is also much smaller than the rest protocols.


The side−by−side boxplot of uterus weight to
estrogen antagonist(ZM), facet by protocol
A
B
C
D
Uterus weight (mg)
Lab
Basf
Bayer
Berlin
ChungKor
Citfranc
Citijapa
Denmark
Exxon
Hatano
Huntingd
InEnvTox
KoreaPar
Mitsubis
Nihon
Poulenc
Sumitomo
TNO
WIL
Zeneca
ZM(mg/kg/day)
0
0.1
1


The side−by−side scatterplots of Uterus weight to
Body weight (g), facet by protocol
A
B
C
D
Uterus weight (mg)
Body weight (g)
Basf
Bayer
Berlin
ChungKor
Citfranc
Citijapa
Denmark
Exxon
Hatano
Huntingd
InEnvTox
KoreaPar
Mitsubis
Nihon
Poulenc
Sumitomo
TNO
WIL


The side−by−side boxplot of uterus weight for different labs and different dose of estrogen agonist(EE), facet by protocol
A
B
C
D
Uterus weight (mg)
0
100
200
300
400
Basf
Bayer
Berlin
ChungKor
Citfranc
Citijapa
Denmark
Exxon
Hatano
Huntingd
InEnvTox
KoreaPar
Mitsubis
Nihon
Poulenc
Sumitomo
TNO
WIL
Zeneca
Lab
EE(mg/kg/day)
0
0.01
0.03
0.1
0.3
1
3
10

Appendix

EDA

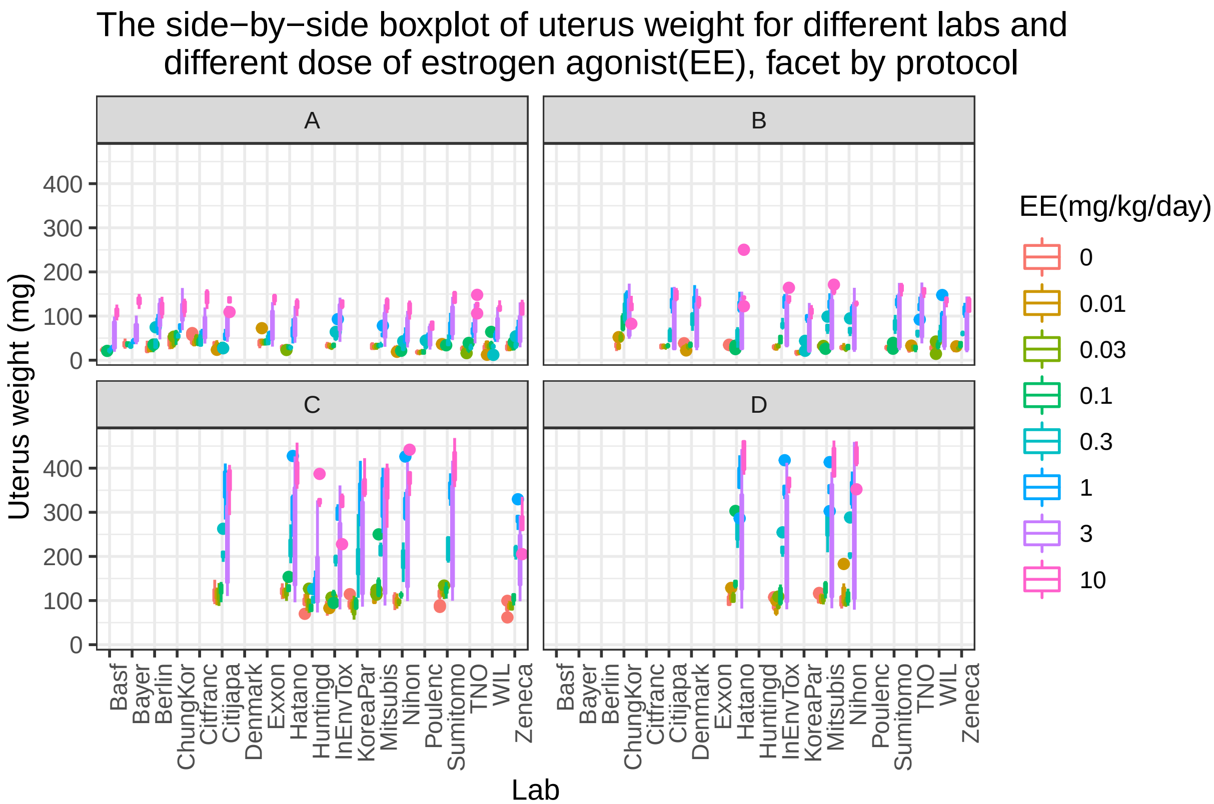
```
bioassay_lm = bioassay[,-7]
str(bioassay_lm)
```

```
## 'data.frame':    2677 obs. of  6 variables:
##  $ uterus  : num  21 22 21 26 24 25 22 26 24 22 ...
##  $ weight  : num  61.9 55.9 59.1 54.8 57.5 57.6 60.3 59 59.1 61.4 ...
##  $ protocol: Factor w/ 4 levels "A","B","C","D": 1 1 1 1 1 1 1 1 1 1 ...
##  $ EE      : Factor w/ 8 levels "0","0.01","0.03",..: 1 1 1 1 1 1 1 1 1 1 ...
##  $ ZM      : Factor w/ 3 levels "0","0.1","1": 1 1 1 1 1 1 1 1 1 1 ...
##  $ lab     : Factor w/ 19 levels "Basf","Bayer",..: 1 1 1 1 1 1 1 1 1 1 ...
```

```
table(bioassay_lm$EE, bioassay_lm$ZM)
```

```
##
##          0 0.1   1
##   0    484   0   0
##   0.01 234   0   0
##   0.03 239   0   0
##   0.1  246   0   0
##   0.3  246   0   0
##   1    246   0   0
##   3    246 245 246
##   10   245   0   0
```

```
ggplot(data=bioassay,mapping = aes(y = uterus,x = lab,color=EE))+
  geom_boxplot()+theme_bw()+facet_wrap(~ protocol) +
  theme(axis.text.x = element_text(angle = 90, hjust = 1)) +
  labs(x = "Lab", y="Uterus weight (mg)", title="The side-by-side boxplot of uterus weight for differen
       different dose of estrogen agonist(EE), facet by protocol", caption="", colour="EE(mg/kg/day)")
```



Model Part I

```
lm1 = lm(uterus~., data = bioassay_lm)
#summary(lm1)
step(lm1, k=log(2677))
```

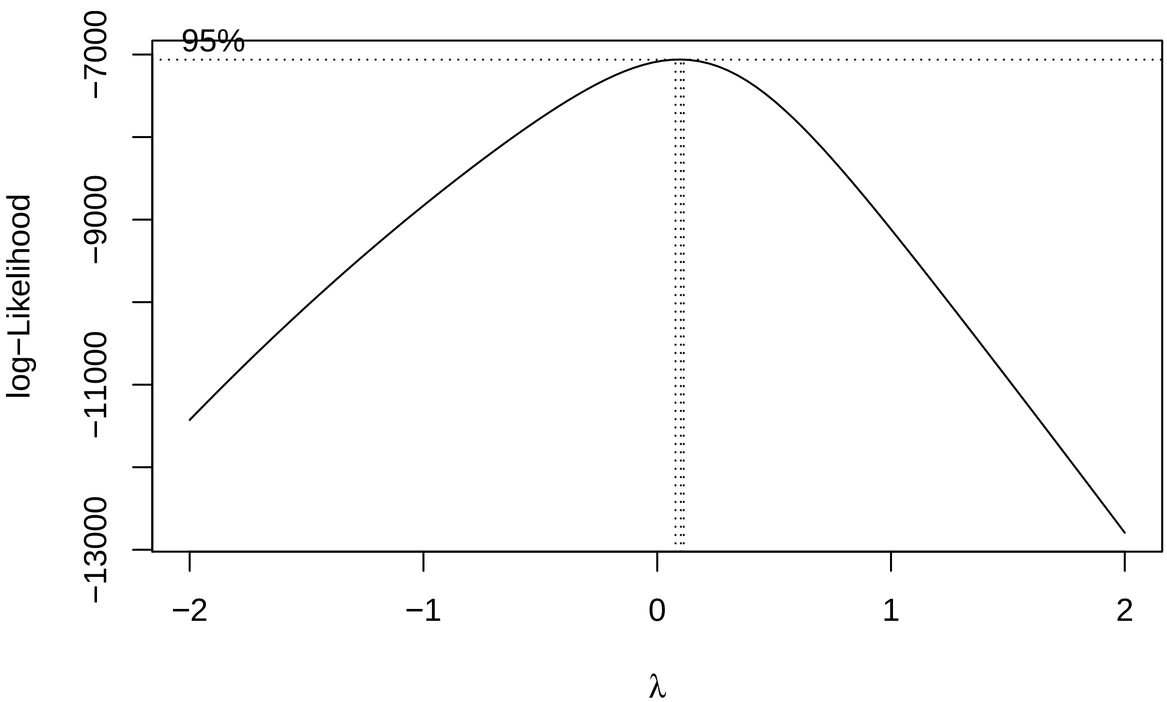
```
## Start:  AIC=20175.57
## uterus ~ weight + protocol + EE + ZM + lab
##
##            Df Sum of Sq      RSS   AIC
## <none>                   4568714 20176
## - lab      18    304839  4873553 20206
## - weight    1    117187  4685901 20236
## - protocol  3    855660  5424374 20612
## - ZM        2   2030817  6599531 21144
## - EE        7   7683826 12252540 22761

##
## Call:
## lm(formula = uterus ~ weight + protocol + EE + ZM + lab, data = bioassay_lm)
##
## Coefficients:
## (Intercept)       weight    protocolB    protocolC    protocolD
##    15.82251     -0.45365      7.84315    207.53588    221.22623
##      EE0.01       EE0.03        EE0.1        EE0.3          EE1
##    -0.60177      0.26008      8.01257     47.94479    106.35605
##         EE3         EE10        ZM0.1          ZM1     labBayer
```

```
##    136.45891    150.55730    -80.51563   -127.18576      2.60266
##    labBerlin  labChungKor  labCitfranc  labCitijapa   labDenmark
##     14.84134     32.46041     26.21060     21.52689     18.95727
##     labExxon    labHatano  labHuntingd  labInEnvTox  labKoreaPar
##     23.72114     26.83352      0.09856      0.58445     -2.51500
## labMitsubis     labNihon   labPoulenc  labSumitomo       labTNO
##     24.63683     13.18893     -4.14169     28.52520     16.56429
##       labWIL    labZeneca
##     10.05022     17.93047
```

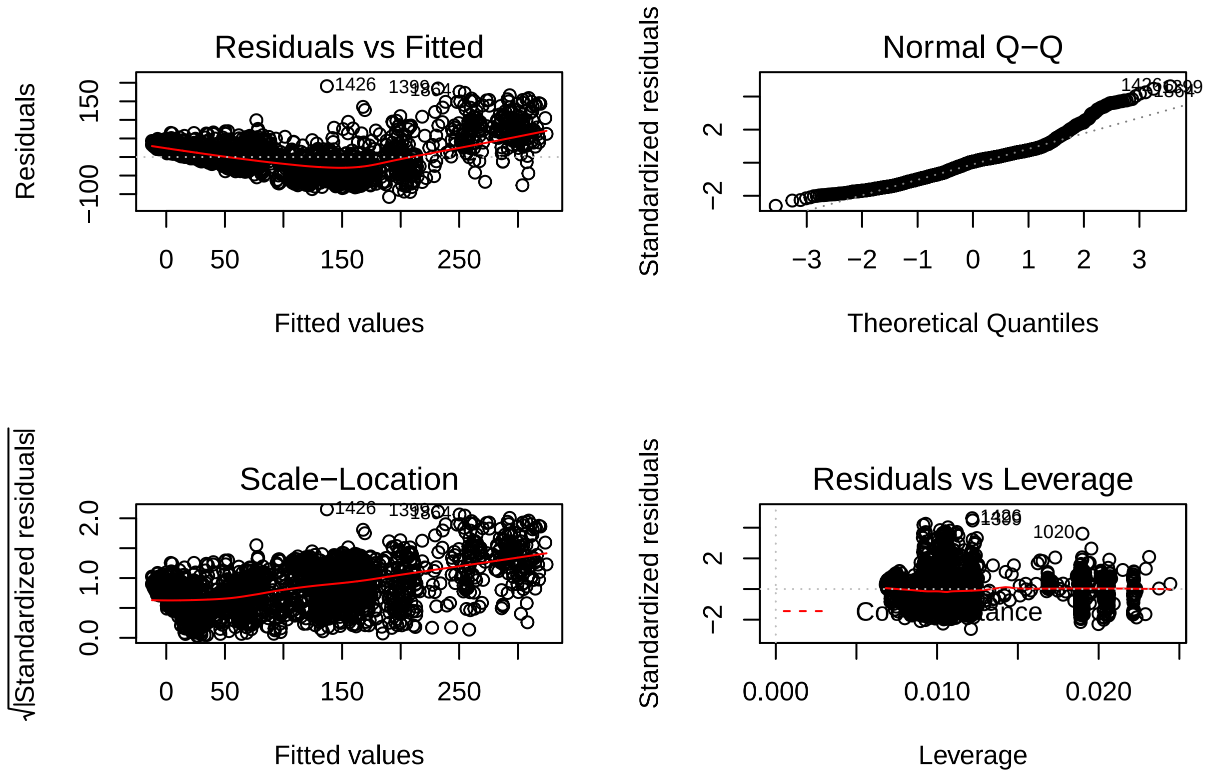
```r
library(MASS)
```

```
##
## Attaching package: 'MASS'

## The following object is masked from 'package:dplyr':
##
##     select
```

```r
box =boxcox(lm1)
```



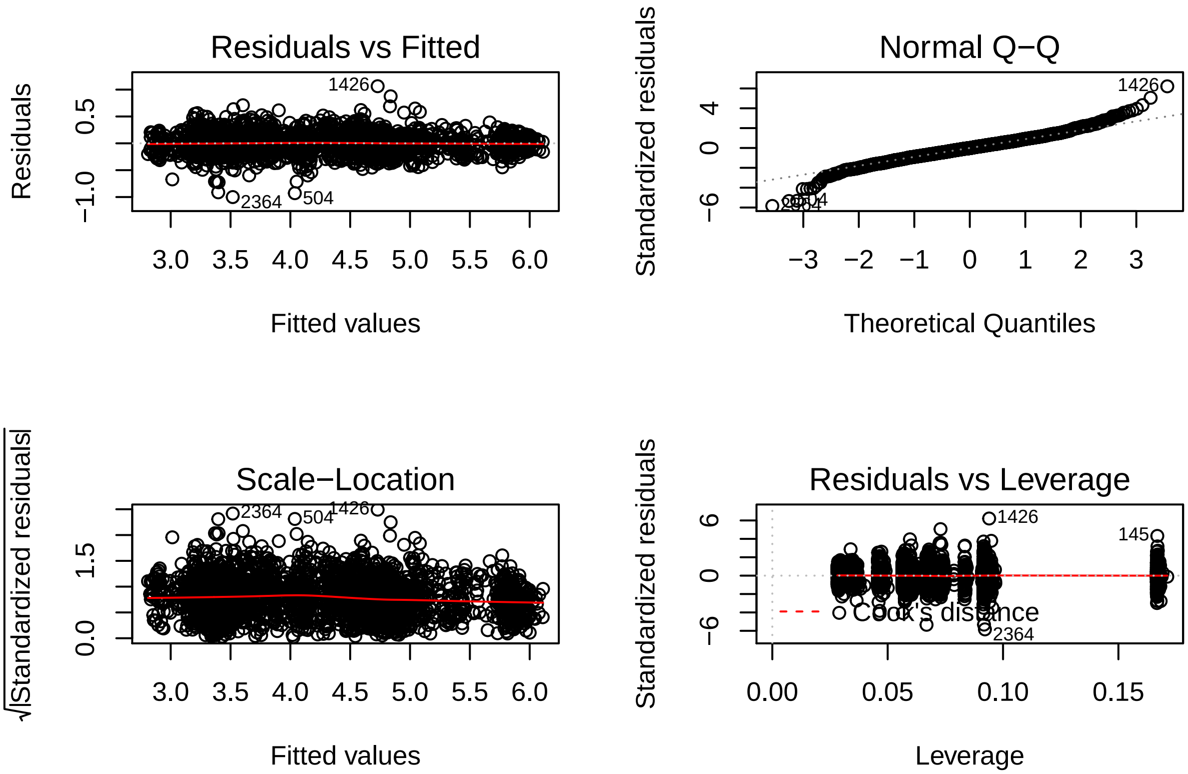

```r
lm2 = lm(formula = log(uterus) ~ log(weight) + protocol + EE + ZM + lab, data = bioassay_lm)
lm3 = lm(formula = log(uterus) ~ log(weight) + protocol + EE*lab +ZM*lab, data = bioassay_lm)
#summary(lm3)

par(mfrow=c(2,2))
plot(lm1)
```



Frequentist Random Effect Model:

```
library(lme4)
randomeffect = lmer(log(uterus) ~ log(weight) + protocol + EE + ZM + (1+EE+ZM|lab), data = bioassay_lm)
#summary(randomeffect)
```

```
par(mfrow=c(2,2))
lm.full = lm(log(uterus)~EE*lab+EE*protocol+ZM*lab+ZM*protocol+protocol+log(weight), data = bioassay)
plot(lm.full)
```



a.

Is the uterotrophic bioassay successful overall at identifying estrogenic effects of EE and anti- estrogenic effects of ZM? Do some labs fail to detect such effects? At what dose level of EE is there a change relative to the control and does this level vary across labs?

```
anova(lm.full)
```

```
## Analysis of Variance Table
##
## Response: log(uterus)
##                Df Sum Sq Mean Sq  F value    Pr(>F)
## EE              7 605.61  86.515 2675.644 < 2.2e-16 ***
## lab            18 232.09  12.894  398.765 < 2.2e-16 ***
## protocol        3 656.04 218.680 6763.098 < 2.2e-16 ***
## ZM              2 160.38  80.190 2480.037 < 2.2e-16 ***
## log(weight)     1   3.68   3.683  113.907 < 2.2e-16 ***
## EE:lab        123  48.92   0.398   12.302 < 2.2e-16 ***
## EE:protocol    21  39.97   1.903   58.860 < 2.2e-16 ***
## lab:ZM         36  14.57   0.405   12.515 < 2.2e-16 ***
## protocol:ZM     6  14.13   2.355   72.829 < 2.2e-16 ***
## Residuals    2459  79.51   0.032
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
coefs = summary(lm.full)$coefficients %>% data.frame()
colnames(coefs)=c("Estimate", "Std.Error", "t.value", "P.value")
kable(coefs)
```

	Estimate	Std.Error	t.value	P.value
(Intercept)	1.2900646	0.1698397	7.5957768	0.0000000
EE0.01	0.0118115	0.0573628	0.2059080	0.8368798
EE0.03	0.0260449	0.0912636	0.2853810	0.7753763
EE0.1	0.1192458	0.0912806	1.3063653	0.1915505
EE0.3	-0.0569755	0.0912611	-0.6243124	0.5324803
EE1	0.1858968	0.0912618	2.0369614	0.0417608
EE3	1.3895895	0.0912684	15.2253158	0.0000000
EE10	1.5605838	0.0912906	17.0946740	0.0000000
labBayer	0.5499291	0.0761935	7.2175331	0.0000000
labBerlin	0.3137917	0.0784417	4.0003193	0.0000651
labChungKor	0.5777287	0.0668202	8.6460189	0.0000000
labCitfranc	0.6112410	0.0750641	8.1429235	0.0000000
labCitijapa	0.4070388	0.0636274	6.3972254	0.0000000
labDenmark	0.3851293	0.0787104	4.8929935	0.0000011
labExxon	0.5102184	0.0912771	5.5897741	0.0000000
labHatano	0.3024433	0.0622042	4.8621052	0.0000012
labHuntingd	0.0515563	0.0799063	0.6452097	0.5188515
labInEnvTox	0.3183418	0.0628004	5.0691044	0.0000004
labKoreaPar	0.0447964	0.0695160	0.6444046	0.5193732
labMitsubis	0.3254197	0.0621959	5.2321731	0.0000002
labNihon	0.2113362	0.0622019	3.3975856	0.0006907
labPoulenc	-0.1334956	0.0758968	-1.7589100	0.0787172
labSumitomo	0.3003708	0.0635377	4.7274422	0.0000024
labTNO	0.2684862	0.0682720	3.9325971	0.0000864
labWIL	0.2958416	0.0670492	4.4123096	0.0000107
labZeneca	0.0938115	0.0635545	1.4760802	0.1400504
protocolB	-0.0708846	0.0230097	-3.0806339	0.0020885
protocolC	0.6093657	0.0621328	9.8074755	0.0000000
protocolD	0.4894383	0.0671910	7.2842788	0.0000000
ZM0.1	-0.6657915	0.1038200	-6.4129400	0.0000000
ZM1	-1.3554195	0.1038181	-13.0557139	0.0000000
log(weight)	0.4585177	0.0397149	11.5452241	0.0000000
EE0.1:labBayer	-0.0741826	0.1281114	-0.5790473	0.5626103
EE0.3:labBayer	0.0123780	0.1281290	0.0966055	0.9230476
EE1:labBayer	0.0534017	0.1281818	0.4166087	0.6770010
EE3:labBayer	-0.5736858	0.1281190	-4.4777565	0.0000079
EE10:labBayer	-0.2086836	0.1281277	-1.6287154	0.1035014
EE0.01:labBerlin	0.0311538	0.1066615	0.2920810	0.7702493
EE0.03:labBerlin	0.1299297	0.1281098	1.0142056	0.3105844
EE0.1:labBerlin	-0.0970658	0.1281966	-0.7571635	0.4490244
EE0.3:labBerlin	0.4574369	0.1281361	3.5699299	0.0003639
EE1:labBerlin	0.9734839	0.1281099	7.5988157	0.0000000
EE3:labBerlin	0.2808282	0.1281252	2.1918263	0.0284855
EE10:labBerlin	-0.0613067	0.1283429	-0.4776786	0.6329214
EE0.01:labChungKor	-0.0823106	0.0831540	-0.9898580	0.3223409
EE0.03:labChungKor	0.1016306	0.1129897	0.8994675	0.3684918
EE0.1:labChungKor	0.3890335	0.1130126	3.4423889	0.0005862
EE0.3:labChungKor	0.4770917	0.1130044	4.2218870	0.0000251
EE1:labChungKor	0.4631873	0.1129945	4.0992006	0.0000428
EE3:labChungKor	-0.3213246	0.1130028	-2.8435099	0.0044988
EE10:labChungKor	-0.4744599	0.1129999	-4.1987631	0.0000278
EE0.01:labCitfranc	-0.0895519	0.1066570	-0.8396245	0.4012006

	Estimate	Std.Error	t.value	P.value
EE0.03:labCitfranc	0.0348108	0.1281100	0.2717260	0.7858555
EE0.1:labCitfranc	-0.1681593	0.1281242	-1.3124717	0.1894835
EE0.3:labCitfranc	0.1043657	0.1281116	0.8146464	0.4153537
EE1:labCitfranc	0.2137180	0.1281116	1.6682178	0.0953998
EE3:labCitfranc	-0.5108090	0.1281121	-3.9872041	0.0000688
EE10:labCitfranc	-0.3608858	0.1281203	-2.8167725	0.0048896
EE0.01:labCitijapa	-0.0358182	0.0734214	-0.4878447	0.6257034
EE0.03:labCitijapa	-0.1230806	0.1077939	-1.1418141	0.2536425
EE0.1:labCitijapa	-0.1759647	0.1078048	-1.6322530	0.1027542
EE0.3:labCitijapa	0.0254003	0.1077903	0.2356451	0.8137277
EE1:labCitijapa	0.4528568	0.1077944	4.2011167	0.0000275
EE3:labCitijapa	-0.2187609	0.1077910	-2.0294915	0.0425157
EE10:labCitijapa	-0.1954409	0.1078036	-1.8129342	0.0699639
EE0.01:labDenmark	-0.0200793	0.1064116	-0.1886948	0.8503476
EE0.03:labDenmark	-0.0733957	0.1341644	-0.5470582	0.5843884
EE0.1:labDenmark	-0.1225528	0.1341477	-0.9135663	0.3610343
EE0.3:labDenmark	0.4697198	0.1341478	3.5015093	0.0004709
EE1:labDenmark	0.6141336	0.1341906	4.5765785	0.0000050
EE3:labDenmark	-0.1635394	0.1341512	-1.2190681	0.2229353
EE10:labDenmark	-0.2466313	0.1341790	-1.8380769	0.0661716
EE0.01:labExxon	0.1398713	0.1186097	1.1792564	0.2384102
EE0.03:labExxon	0.0188335	0.1382286	0.1362486	0.8916359
EE0.1:labExxon	-0.0577184	0.1382573	-0.4174705	0.6763707
EE0.3:labExxon	0.2344482	0.1382277	1.6961021	0.0899931
EE1:labExxon	0.1720545	0.1382283	1.2447125	0.2133561
EE3:labExxon	-0.3379718	0.1382615	-2.4444387	0.0145776
EE10:labExxon	-0.2660610	0.1382464	-1.9245410	0.0544021
EE0.01:labHatano	-0.0416340	0.0698889	-0.5957178	0.5514186
EE0.03:labHatano	-0.0874614	0.1054465	-0.8294388	0.4069367
EE0.1:labHatano	-0.1171050	0.1054296	-1.1107412	0.2667884
EE0.3:labHatano	0.0841336	0.1054212	0.7980709	0.4249064
EE1:labHatano	0.5221484	0.1054233	4.9528729	0.0000008
EE3:labHatano	-0.1375411	0.1054243	-1.3046435	0.1921363
EE10:labHatano	-0.1065560	0.1057089	-1.0080132	0.3135473
EE0.01:labHuntingd	0.0524325	0.1071221	0.4894649	0.6245563
EE0.03:labHuntingd	-0.1153035	0.1358421	-0.8488052	0.3960723
EE0.1:labHuntingd	-0.4098531	0.1358750	-3.0163982	0.0025842
EE0.3:labHuntingd	-0.4289792	0.1358447	-3.1578643	0.0016086
EE1:labHuntingd	-0.2344401	0.1358412	-1.7258397	0.0845019
EE3:labHuntingd	-0.4699551	0.1358843	-3.4584956	0.0005524
EE10:labHuntingd	-0.1012159	0.1358816	-0.7448826	0.4564139
EE0.01:labInEnvTox	-0.0689936	0.0698870	-0.9872172	0.3236333
EE0.03:labInEnvTox	-0.0738628	0.1054456	-0.7004821	0.4836925
EE0.1:labInEnvTox	-0.0297898	0.1054520	-0.2824965	0.7775866
EE0.3:labInEnvTox	0.3401291	0.1054213	3.2263792	0.0012701
EE1:labInEnvTox	0.6700054	0.1054213	6.3555046	0.0000000
EE3:labInEnvTox	-0.0666889	0.1054222	-0.6325892	0.5270608
EE10:labInEnvTox	-0.1317789	0.1054252	-1.2499758	0.2114273
EE0.01:labKoreaPar	-0.0549716	0.0829773	-0.6624901	0.5077193
EE0.03:labKoreaPar	-0.1631234	0.1170917	-1.3931255	0.1637078
EE0.1:labKoreaPar	-0.1705207	0.1171186	-1.4559652	0.1455299
EE0.3:labKoreaPar	0.1215352	0.1170970	1.0379015	0.2994180

	Estimate	Std.Error	t.value	P.value
EE1:labKoreaPar	0.7523217	0.1170950	6.4248851	0.0000000
EE3:labKoreaPar	0.0361179	0.1170989	0.3084395	0.7577740
EE10:labKoreaPar	0.0750326	0.1171491	0.6404878	0.5219152
EE0.01:labMitsubis	-0.1017214	0.0698890	-1.4554711	0.1456665
EE0.03:labMitsubis	-0.1094806	0.1055884	-1.0368616	0.2999023
EE0.1:labMitsubis	-0.1332176	0.1054311	-1.2635511	0.2065110
EE0.3:labMitsubis	0.1924748	0.1054258	1.8256894	0.0680183
EE1:labMitsubis	0.4828077	0.1054286	4.5794740	0.0000049
EE3:labMitsubis	-0.1436966	0.1054207	-1.3630783	0.1729826
EE10:labMitsubis	-0.1598549	0.1054237	-1.5163084	0.1295699
EE0.01:labNihon	0.0147811	0.0698897	0.2114922	0.8325208
EE0.03:labNihon	-0.1585644	0.1054447	-1.5037687	0.1327693
EE0.1:labNihon	-0.2024370	0.1054277	-1.9201510	0.0549544
EE0.3:labNihon	0.1672884	0.1054267	1.5867753	0.1126921
EE1:labNihon	0.5332423	0.1054265	5.0579533	0.0000005
EE3:labNihon	-0.0696955	0.1054218	-0.6611113	0.5086029
EE10:labNihon	-0.0752733	0.1054241	-0.7140044	0.4752922
EE0.01:labPoulenc	-0.0704827	0.1066508	-0.6608734	0.5087554
EE0.03:labPoulenc	-0.0350046	0.1281099	-0.2732388	0.7846926
EE0.1:labPoulenc	-0.0919665	0.1281176	-0.7178288	0.4729310
EE0.3:labPoulenc	0.6458780	0.1281192	5.0412275	0.0000005
EE1:labPoulenc	0.9186423	0.1281098	7.1707401	0.0000000
EE3:labPoulenc	-0.0110039	0.1281271	-0.0858825	0.9315668
EE10:labPoulenc	-0.0888265	0.1281233	-0.6932890	0.4881937
EE0.01:labSumitomo	-0.0368895	0.0734111	-0.5025058	0.6153568
EE0.03:labSumitomo	-0.0302378	0.1077982	-0.2805038	0.7791146
EE0.1:labSumitomo	-0.1673083	0.1077973	-1.5520649	0.1207754
EE0.3:labSumitomo	0.2895261	0.1077924	2.6859604	0.0072808
EE1:labSumitomo	0.6172446	0.1077915	5.7262822	0.0000000
EE3:labSumitomo	-0.0645720	0.1077938	-0.5990328	0.5492062
EE10:labSumitomo	-0.0112449	0.1077933	-0.1043196	0.9169243
EE0.01:labTNO	0.0736580	0.0834808	0.8823348	0.3776820
EE0.03:labTNO	-0.0023295	0.1132982	-0.0205611	0.9835975
EE0.1:labTNO	-0.1643272	0.1133066	-1.4502884	0.1471057
EE0.3:labTNO	0.2233222	0.1133063	1.9709600	0.0488404
EE1:labTNO	0.7097834	0.1133100	6.2640833	0.0000000
EE3:labTNO	0.0250281	0.1132986	0.2209036	0.8251858
EE10:labTNO	0.0533746	0.1133388	0.4709295	0.6377328
EE0.01:labWIL	0.0851243	0.0831444	1.0238128	0.3060244
EE0.03:labWIL	-0.0211363	0.1129880	-0.1870668	0.8516237
EE0.1:labWIL	0.0264442	0.1130392	0.2339385	0.8150522
EE0.3:labWIL	0.0592917	0.1129946	0.5247300	0.5998182
EE1:labWIL	0.3799368	0.1129960	3.3623921	0.0007845
EE3:labWIL	-0.2610851	0.1130191	-2.3100973	0.0209652
EE10:labWIL	-0.1329662	0.1130476	-1.1761965	0.2396302
EE0.03:labZeneca	0.0038508	0.1077955	0.0357229	0.9715062
EE0.1:labZeneca	-0.0306465	0.1078112	-0.2842609	0.7762344
EE0.3:labZeneca	0.3134968	0.1077900	2.9084022	0.0036654
EE1:labZeneca	0.5953355	0.1077901	5.5231021	0.0000000
EE3:labZeneca	-0.1834834	0.1078033	-1.7020203	0.0888780
EE10:labZeneca	-0.1463419	0.1078227	-1.3572455	0.1748278
EE0.01:protocolB	0.0373090	0.0397907	0.9376303	0.3485265

	Estimate	Std.Error	t.value	P.value
EE0.03:protocolB	0.0818212	0.0397907	2.0562900	0.0398599
EE0.1:protocolB	0.1680761	0.0397914	4.2239272	0.0000249
EE0.3:protocolB	0.6999117	0.0397903	17.5899993	0.0000000
EE1:protocolB	0.7243395	0.0397913	18.2034423	0.0000000
EE3:protocolB	0.3409295	0.0397909	8.5680242	0.0000000
EE10:protocolB	0.1899035	0.0398987	4.7596447	0.0000021
EE0.01:protocolC	0.0192851	0.0451741	0.4269055	0.6694855
EE0.03:protocolC	0.0643298	0.0451752	1.4240073	0.1545712
EE0.1:protocolC	0.1440592	0.0451774	3.1887428	0.0014469
EE0.3:protocolC	0.5626279	0.0451746	12.4545235	0.0000000
EE1:protocolC	0.3972777	0.0451952	8.7902559	0.0000000
EE3:protocolC	-0.0398253	0.0452275	-0.8805559	0.3786443
EE10:protocolC	-0.1932320	0.0452493	-4.2703877	0.0000203
EE0.01:protocolD	0.0664772	0.0573598	1.1589514	0.2465885
EE0.03:protocolD	0.1021418	0.0578853	1.7645531	0.0777630
EE0.1:protocolD	0.2623013	0.0573852	4.5708896	0.0000051
EE0.3:protocolD	0.7851387	0.0573882	13.6811827	0.0000000
EE1:protocolD	0.6157327	0.0575016	10.7081037	0.0000000
EE3:protocolD	0.1539306	0.0575760	2.6735174	0.0075557
EE10:protocolD	0.0672533	0.0576399	1.1667831	0.2434111
labBayer:ZM0.1	0.6901215	0.1468522	4.6994306	0.0000028
labBerlin:ZM0.1	0.5148808	0.1468206	3.5068700	0.0004615
labChungKor:ZM0.1	0.8936460	0.1292183	6.9157874	0.0000000
labCitfranc:ZM0.1	0.4904165	0.1468248	3.3401476	0.0008498
labCitijapa:ZM0.1	0.4724800	0.1231543	3.8364891	0.0001279
labDenmark:ZM0.1	0.5271593	0.1538367	3.4267450	0.0006209
labExxon:ZM0.1	0.4823221	0.1468398	3.2846837	0.0010353
labHatano:ZM0.1	0.3425681	0.1205854	2.8408753	0.0045360
labHuntingd:ZM0.1	0.3614376	0.1558719	2.3188115	0.0204869
labInEnvTox:ZM0.1	0.4352241	0.1203796	3.6154308	0.0003059
labKoreaPar:ZM0.1	0.1875622	0.1340032	1.3996845	0.1617339
labMitsubis:ZM0.1	0.4103542	0.1203814	3.4087839	0.0006630
labNihon:ZM0.1	0.4119930	0.1203860	3.4222656	0.0006312
labPoulenc:ZM0.1	0.7263401	0.1468218	4.9470874	0.0000008
labSumitomo:ZM0.1	0.6826167	0.1231616	5.5424455	0.0000000
labTNO:ZM0.1	1.0482355	0.1292116	8.1125480	0.0000000
labWIL:ZM0.1	0.4898728	0.1292083	3.7913407	0.0001534
labZeneca:ZM0.1	0.7557729	0.1231625	6.1363869	0.0000000
labBayer:ZM1	0.7190501	0.1468211	4.8974586	0.0000010
labBerlin:ZM1	0.5503108	0.1468225	3.7481369	0.0001823
labChungKor:ZM1	1.1172940	0.1292222	8.6463019	0.0000000
labCitfranc:ZM1	0.5447890	0.1468222	3.7105353	0.0002114
labCitijapa:ZM1	0.5027119	0.1231432	4.0823372	0.0000460
labDenmark:ZM1	0.5485091	0.1538336	3.5655993	0.0003699
labExxon:ZM1	0.3357462	0.1468279	2.2866657	0.0223000
labHatano:ZM1	0.5101471	0.1203768	4.2379195	0.0000234
labHuntingd:ZM1	0.8118432	0.1558086	5.2105158	0.0000002
labInEnvTox:ZM1	0.4842393	0.1203791	4.0226185	0.0000593
labKoreaPar:ZM1	0.5397564	0.1339872	4.0284174	0.0000579
labMitsubis:ZM1	0.3907909	0.1203767	3.2463997	0.0011844
labNihon:ZM1	0.3860625	0.1203767	3.2071197	0.0013579
labPoulenc:ZM1	0.5231226	0.1468244	3.5629137	0.0003737

	Estimate	Std.Error	t.value	P.value
labSumitomo:ZM1	0.4689472	0.1231428	3.8081576	0.0001434
labTNO:ZM1	0.8649874	0.1292071	6.6945798	0.0000000
labWIL:ZM1	0.7168653	0.1292068	5.5482018	0.0000000
labZeneca:ZM1	0.5601359	0.1231428	4.5486689	0.0000057
protocolB:ZM0.1	-0.7259455	0.0459176	-15.8097273	0.0000000
protocolC:ZM0.1	-0.5192508	0.0523531	-9.9182504	0.0000000
protocolD:ZM0.1	-0.5941240	0.0663671	-8.9520818	0.0000000
protocolB:ZM1	-0.8028005	0.0459141	-17.4848219	0.0000000
protocolC:ZM1	-0.2260328	0.0521771	-4.3320307	0.0000154
protocolD:ZM1	-0.4794924	0.0663336	-7.2284945	0.0000000

```
t.test(lm.obj = lm.full, str.ee = "EE", str.lab = "lab", str.ori = "lab") %>%
  kable(.,caption = "T-test of EE across labs")
t.test(lm.obj = lm.full, str.ee = "ZM", str.lab = "lab", str.ori = "lab") %>%
  kable(.,caption = "T-test of EE across labs")
```

b.

Does the dose response vary across labs? If so, are there certain labs that stand out as being different?

See tables in a.

c.

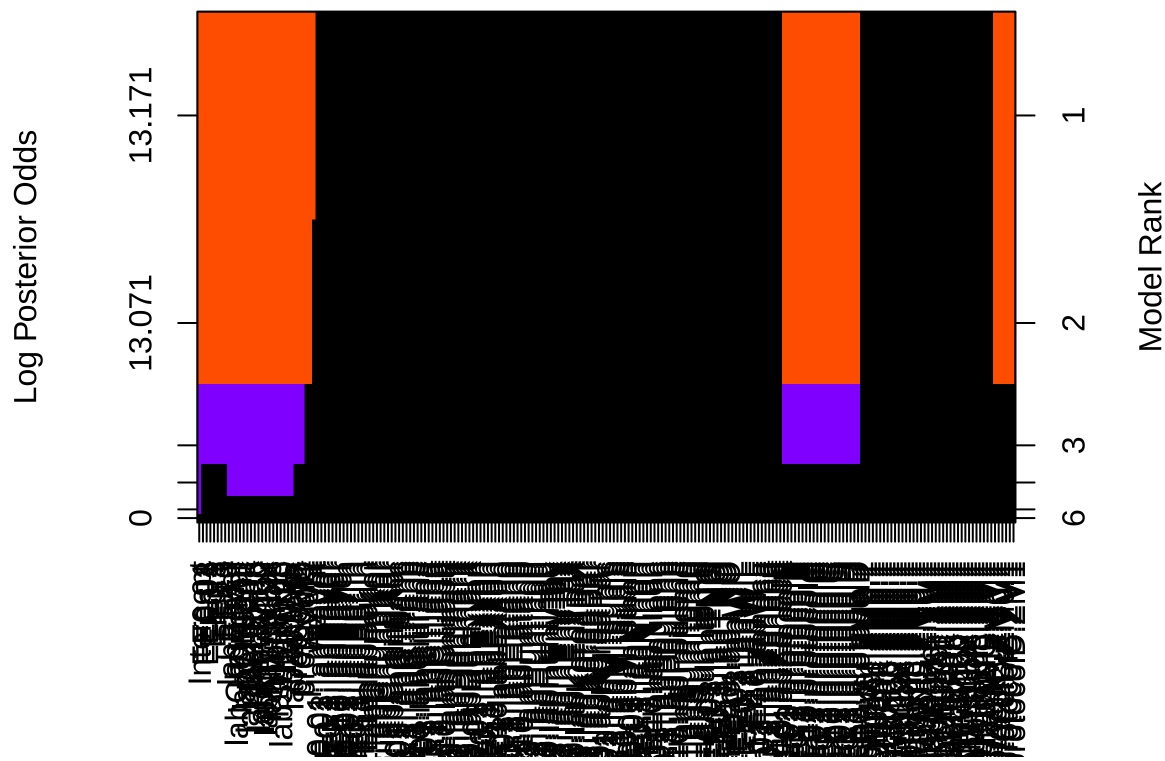
Do the protocols differ in their sensitivity to detecting estrogenic and anti-estrogenic effects? If so, is there one protocol that can be recommended?

See tables in a.

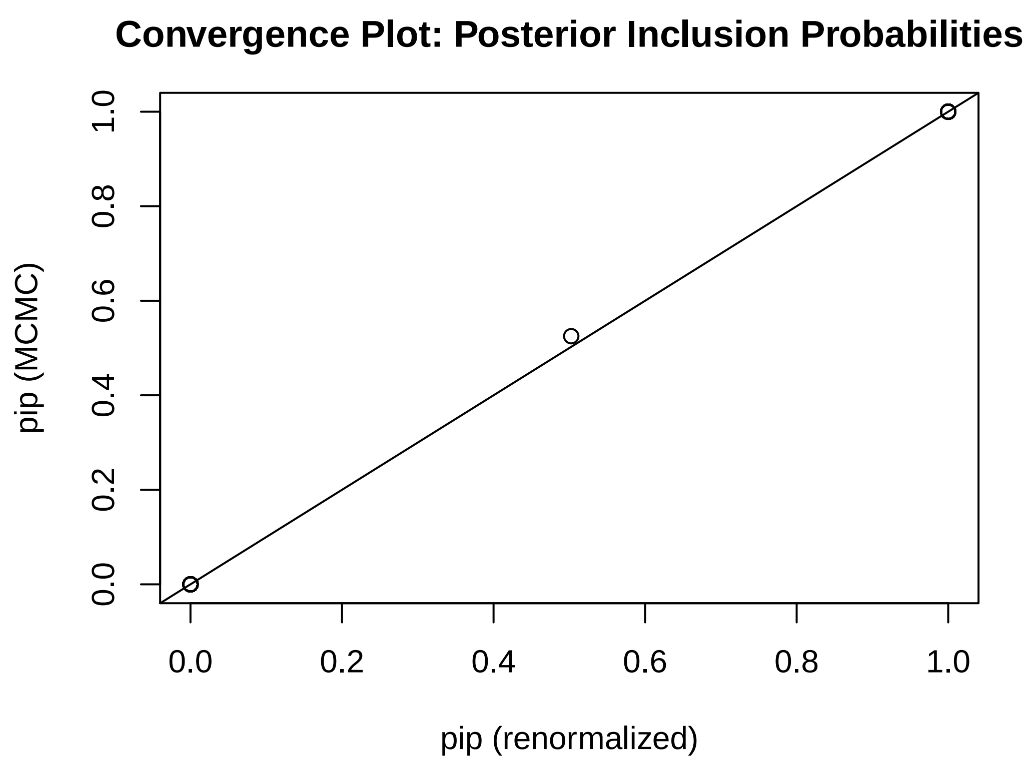
Model Part II

```
n = nrow(bioassay)
p = ncol(model.matrix(lm.full)) - 1

bas1 = bas.lm(log(uterus)~EE*lab+EE*protocol+ZM*lab+ZM*protocol+protocol+log(weight),
              data = bioassay,
              prior = "hyper-g-n",
              alpha = n,
              method = "MCMC",
              MCMC.iterations = 10^6)
```

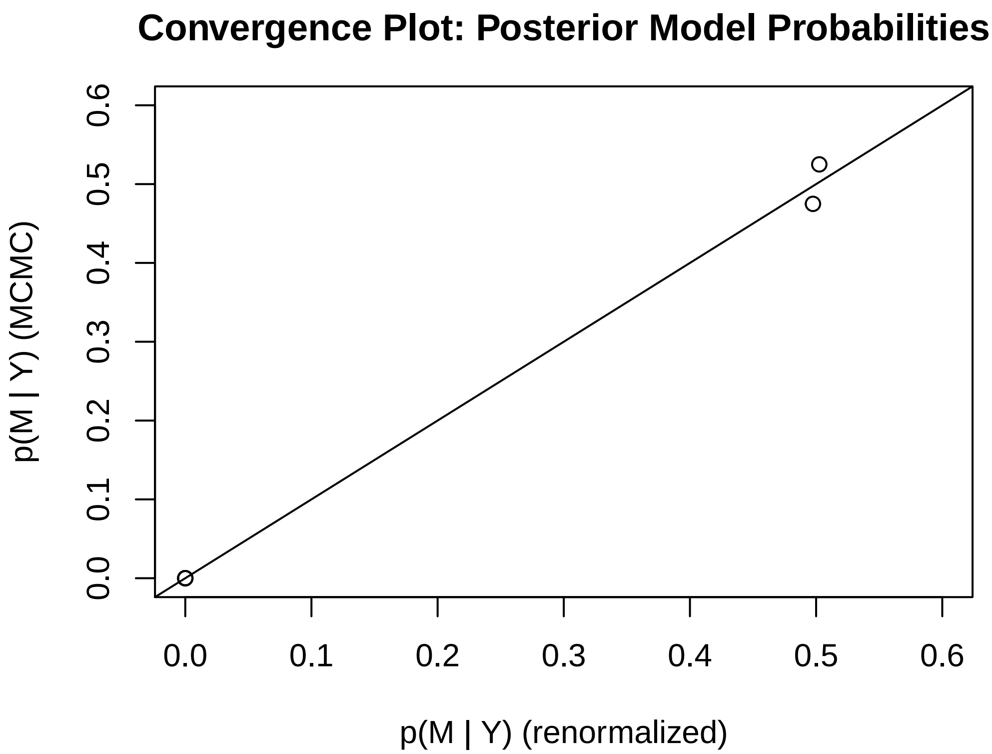
```
image(bas1)
```




```r
diagnostics(bas1, type = "pip")
```



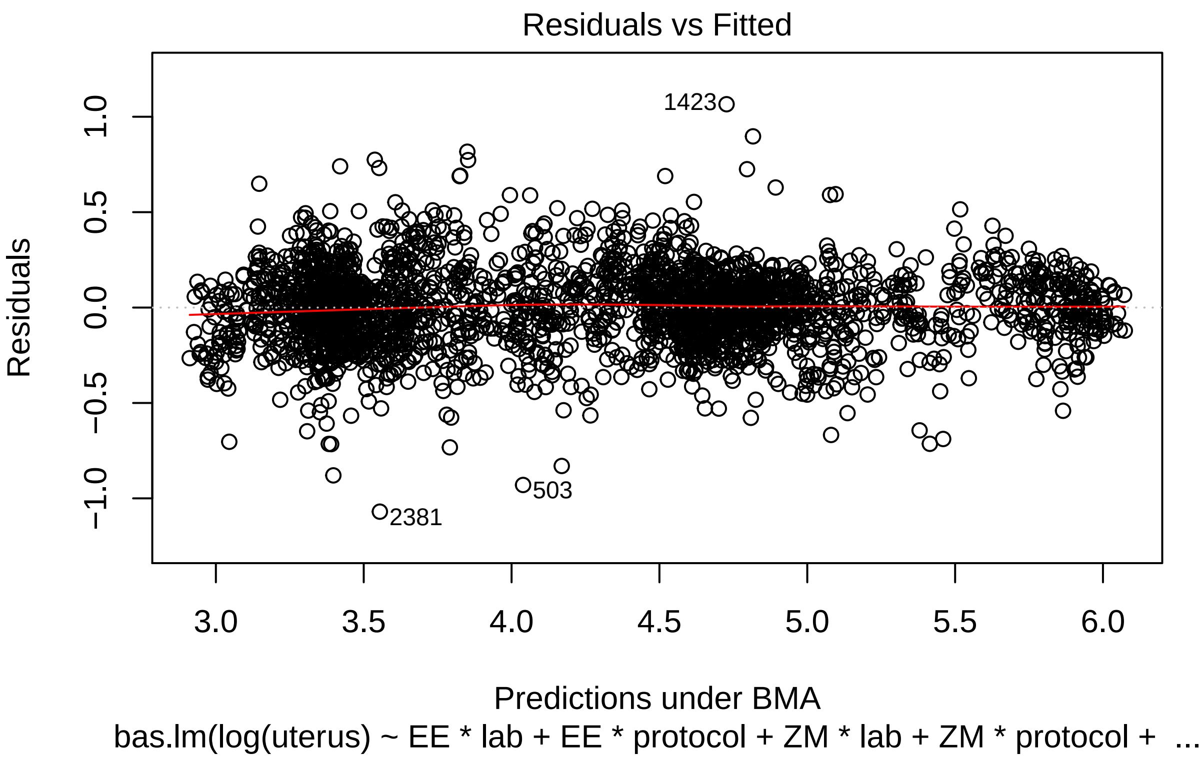

```r
diagnostics(bas1, type = "model")
```

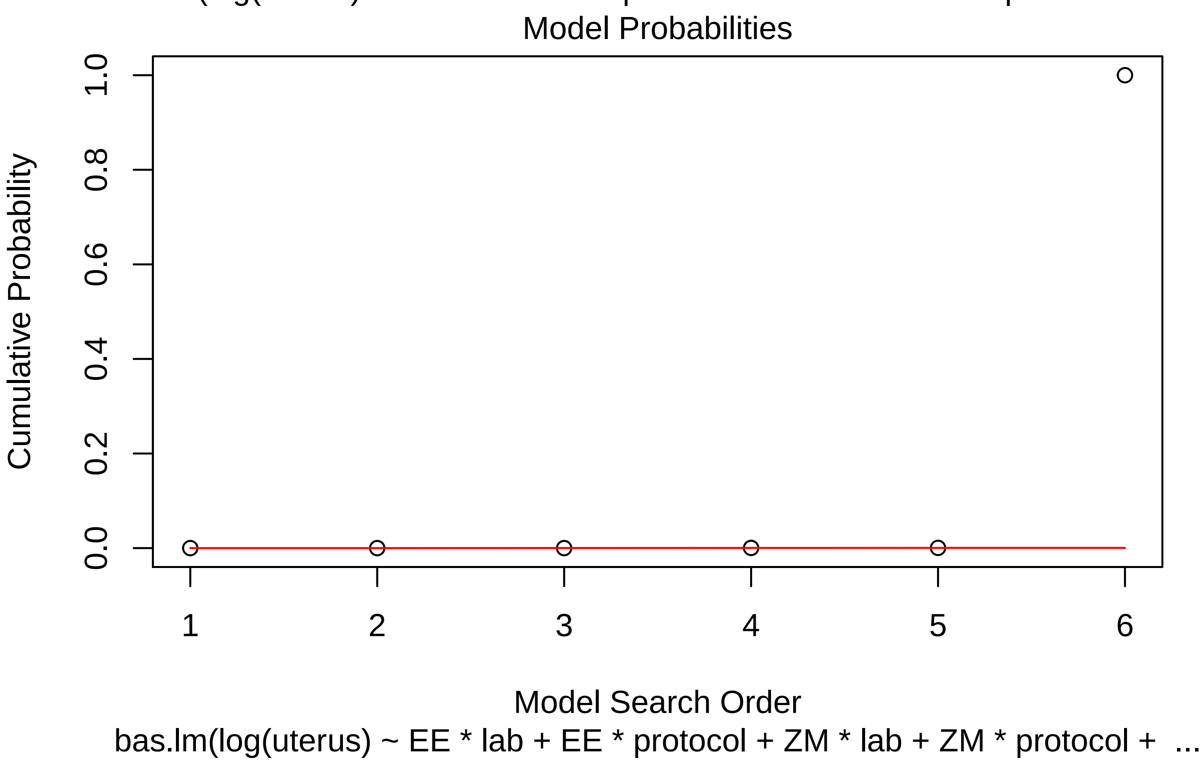


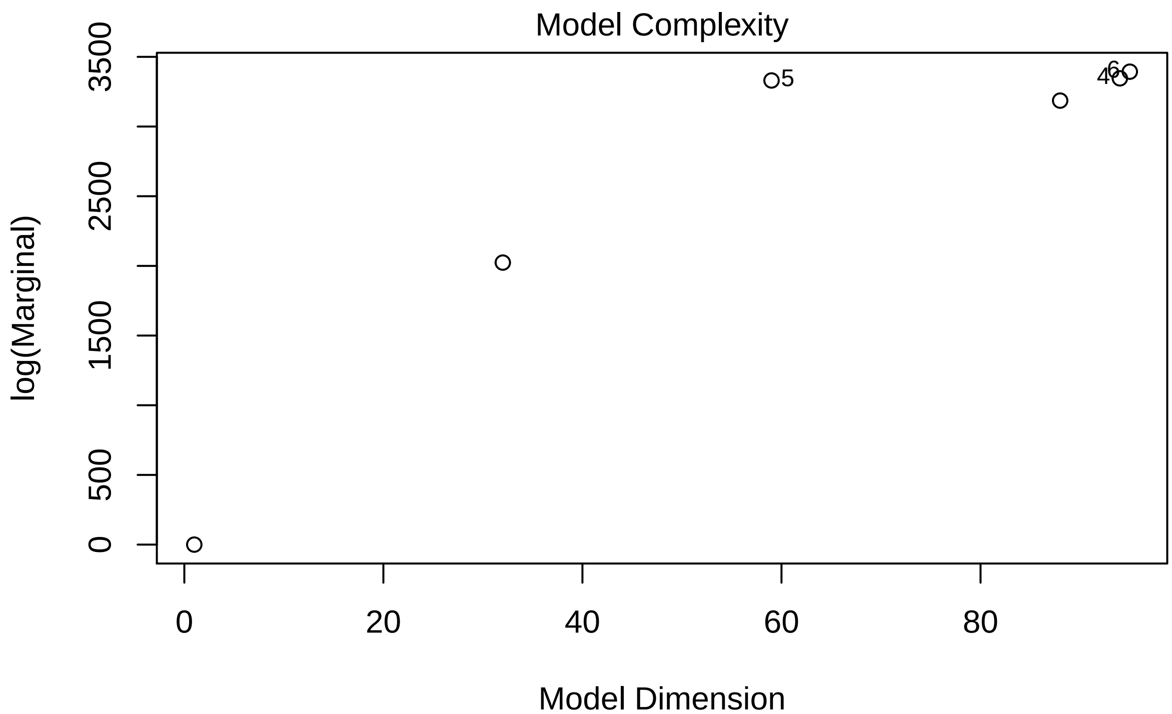
a.

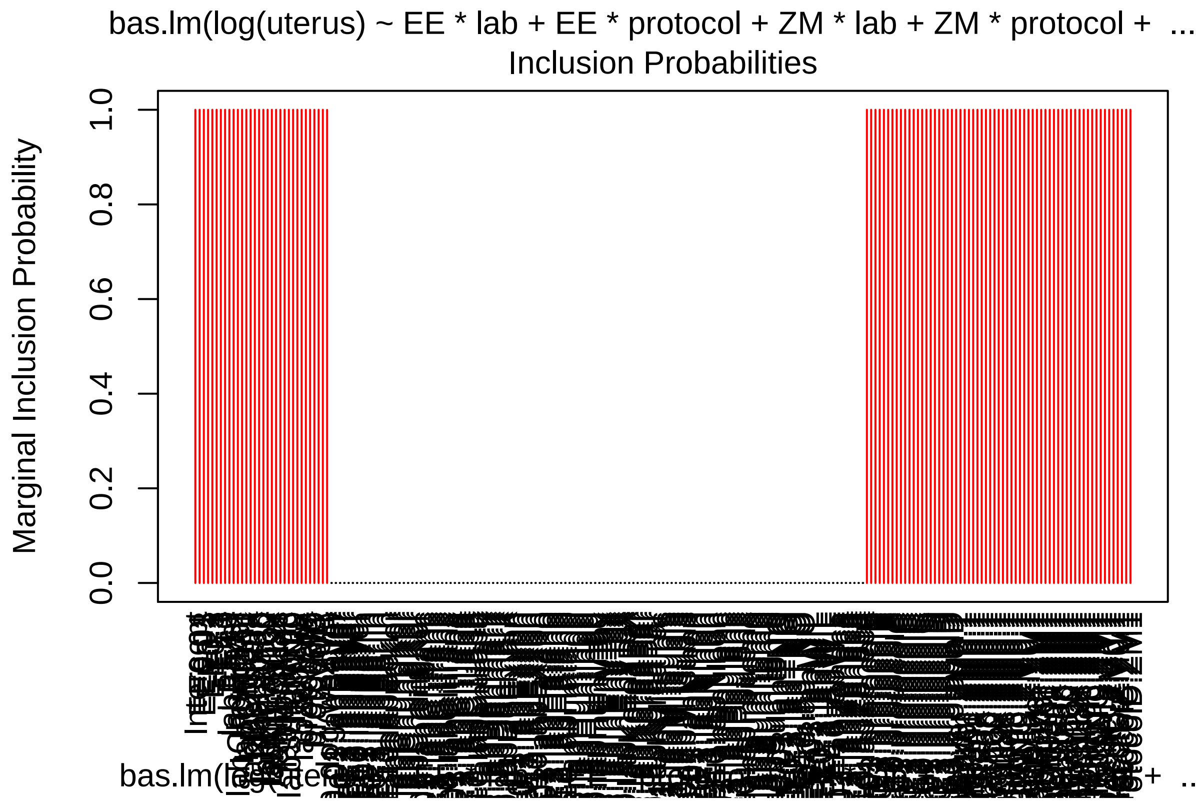
Is the uterotrophic bioassay successful overall at identifying estrogenic effects of EE and anti- estrogenic effects of ZM? Do some labs fail to detect such effects? At what dose level of EE is there a change relative to the control and does this level vary across labs?

```
plot(bas1)
```

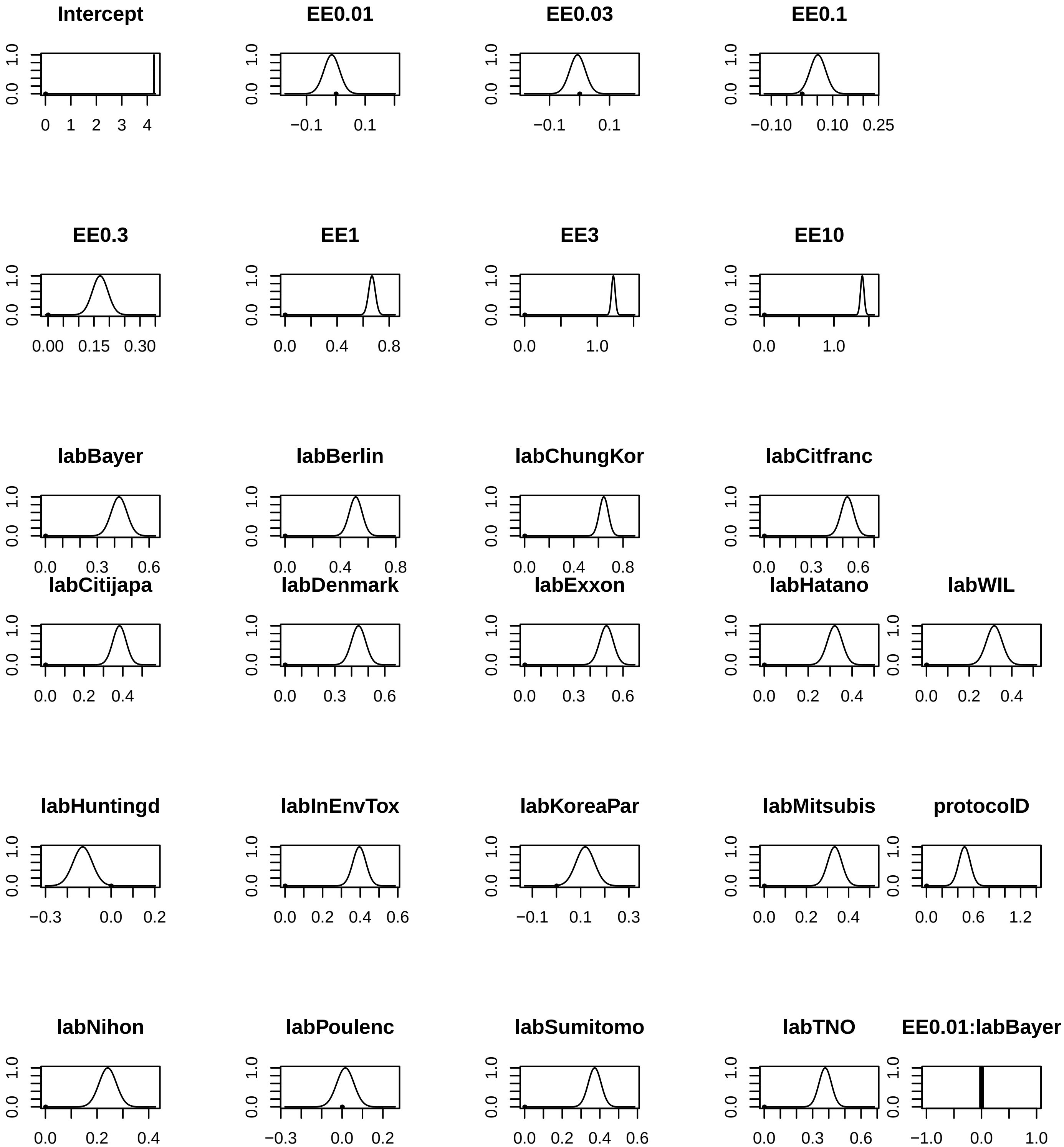

Residuals vs Fitted
Residuals
1.0
0.5
0.0
−0.5
−1.0
1423
503
2381
3.0
3.5
4.0
4.5
5.0
5.5
6.0
Predictions under BMA
bas.lm(log(uterus) ~ EE * lab + EE * protocol + ZM * lab + ZM * protocol + ...

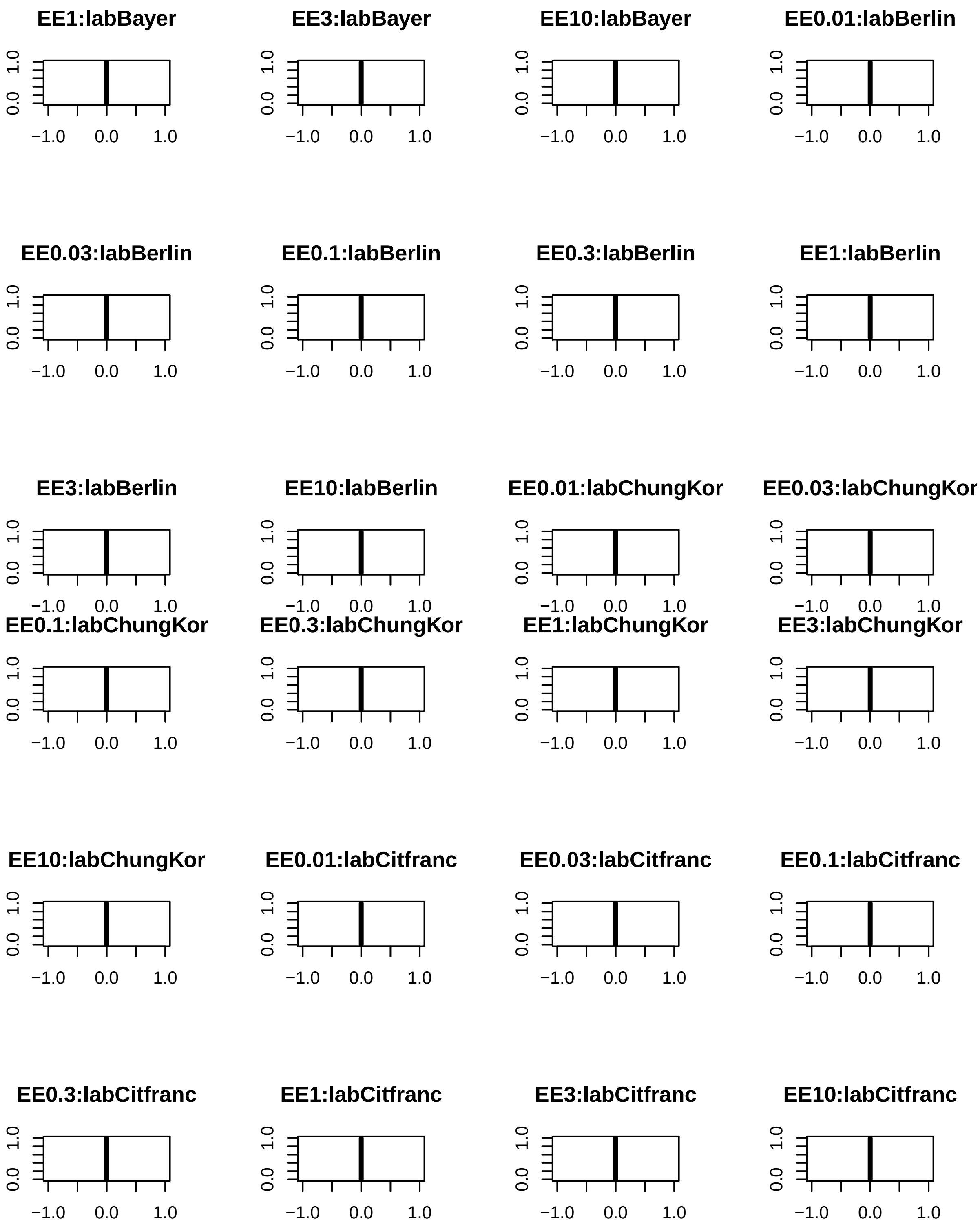

Model Probabilities
Cumulative Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
2
3
4
5
6
Model Search Order
bas.lm(log(uterus) ~ EE * lab + EE * protocol + ZM * lab + ZM * protocol + ...

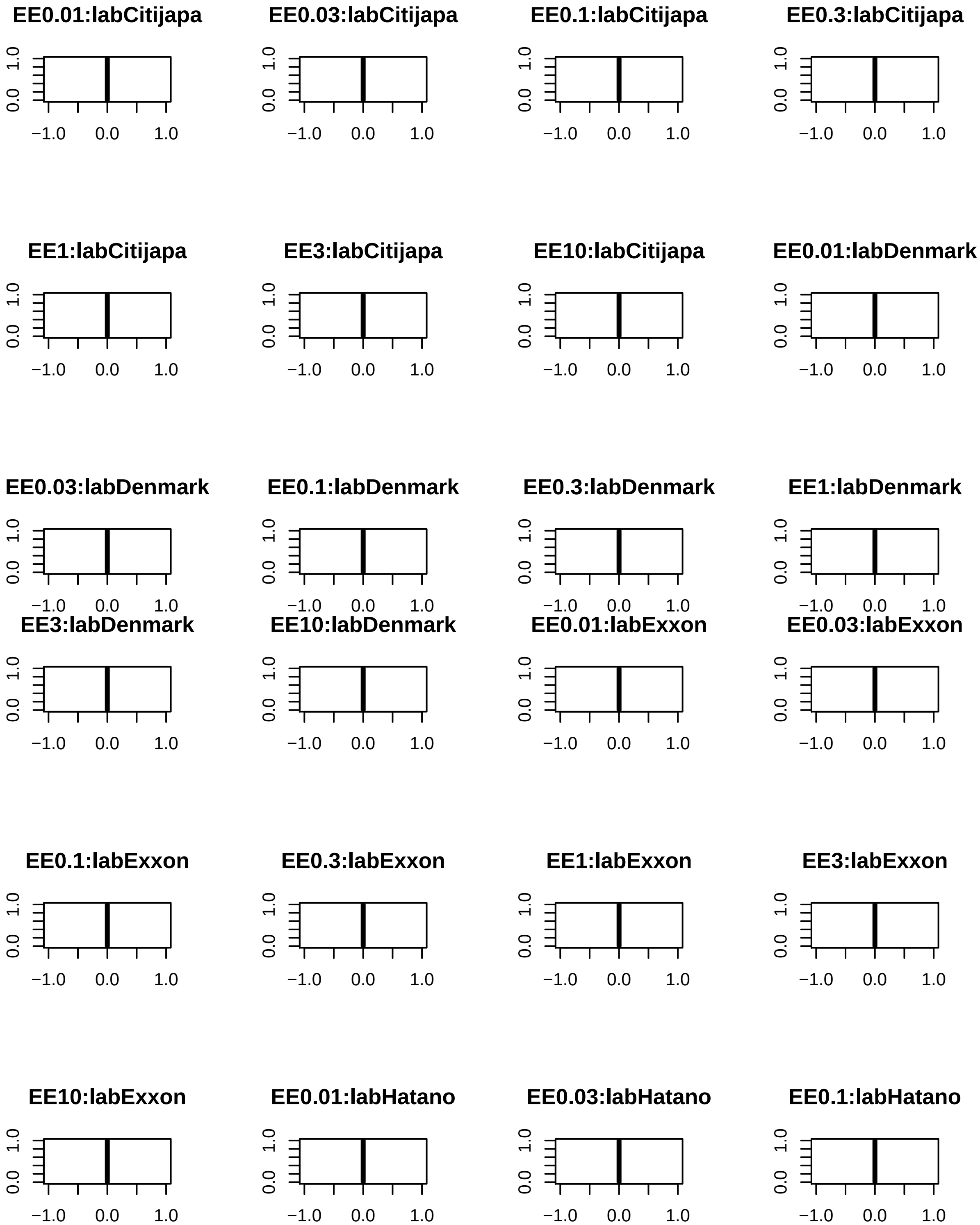


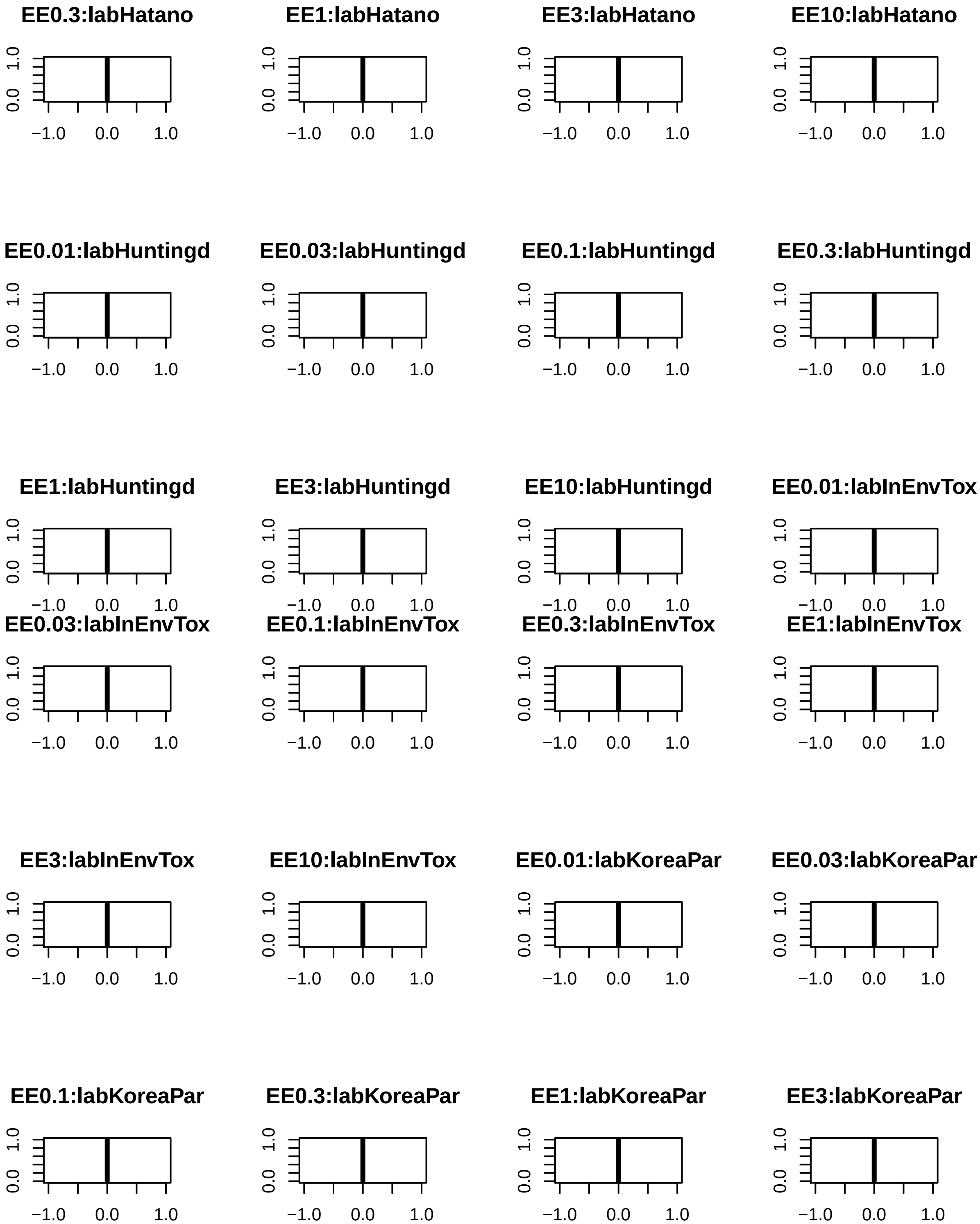


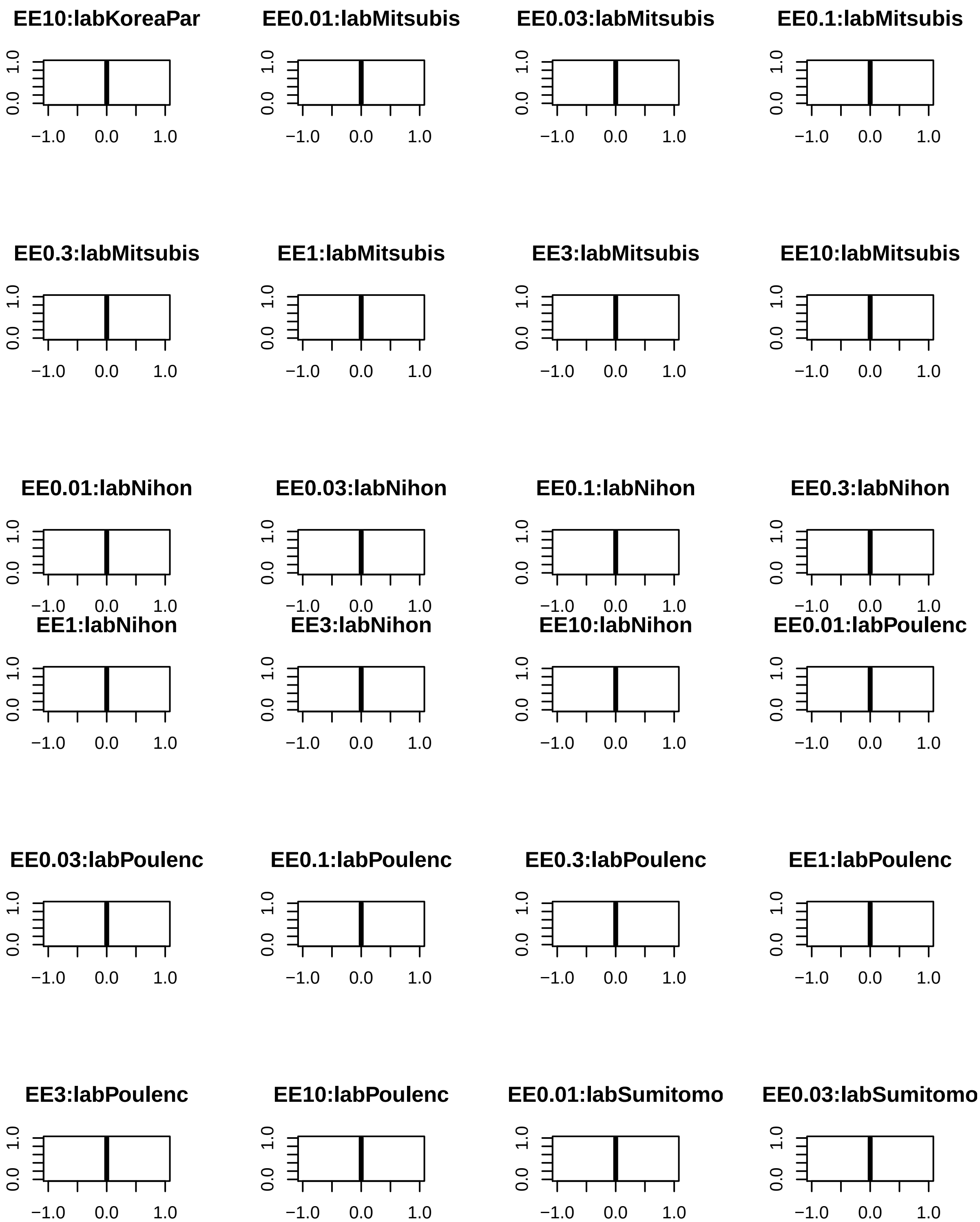

```r
par(mfrow=c(3,4))
plot(coef(bas1), ask=F)
```

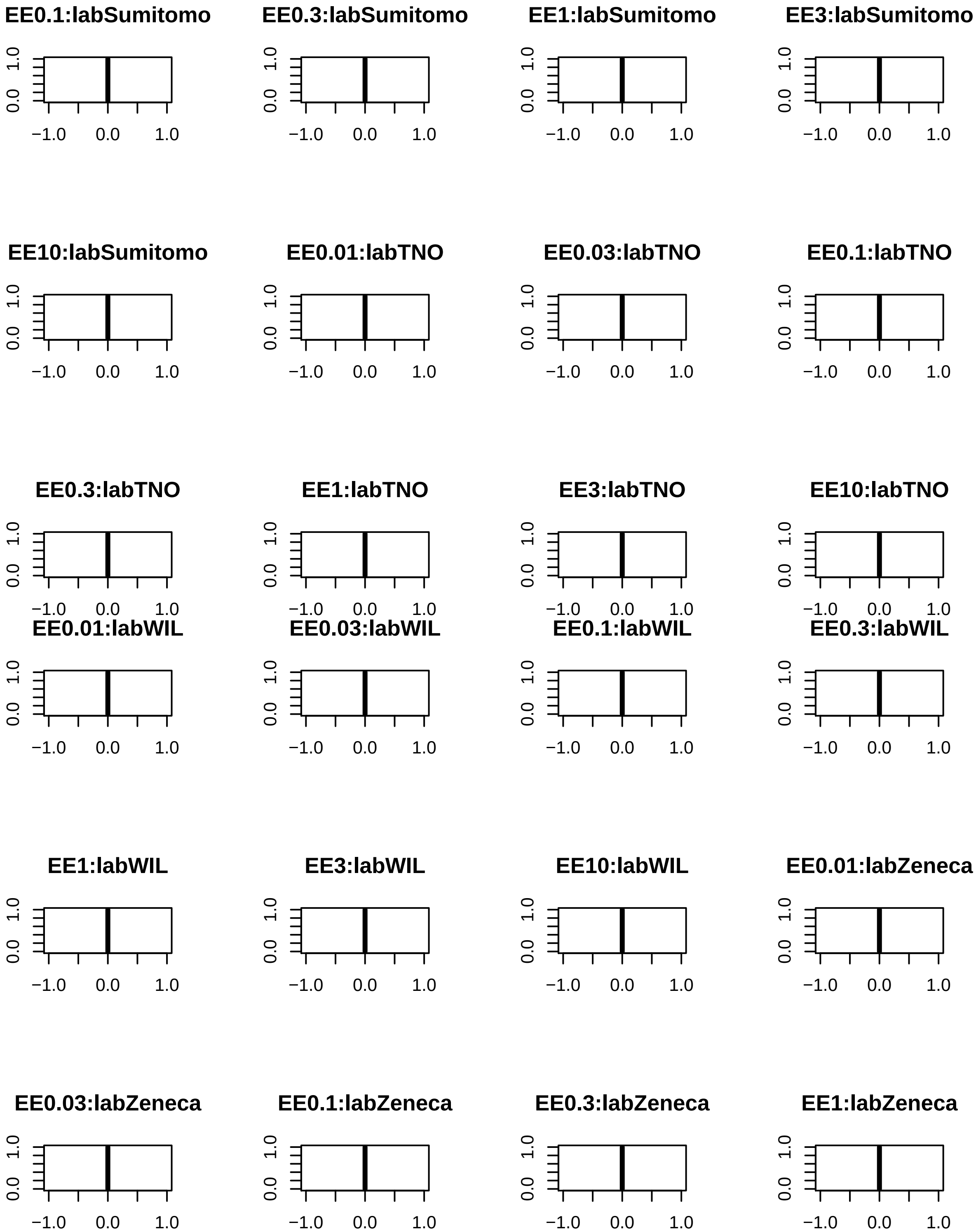

Intercept
EE0.01
EE0.03
EE0.1
EE0.3
EE1
EE3
EE10
labBayer
labBerlin
labChungKor
labCitfranc
labCitijapa
labDenmark
labExxon
labHatano
labWIL
labHuntingd
labInEnvTox
labKoreaPar
labMitsubis
protocolD
labNihon
labPoulenc
labSumitomo
labTNO
EE0.01:labBayer
0.0
1.0

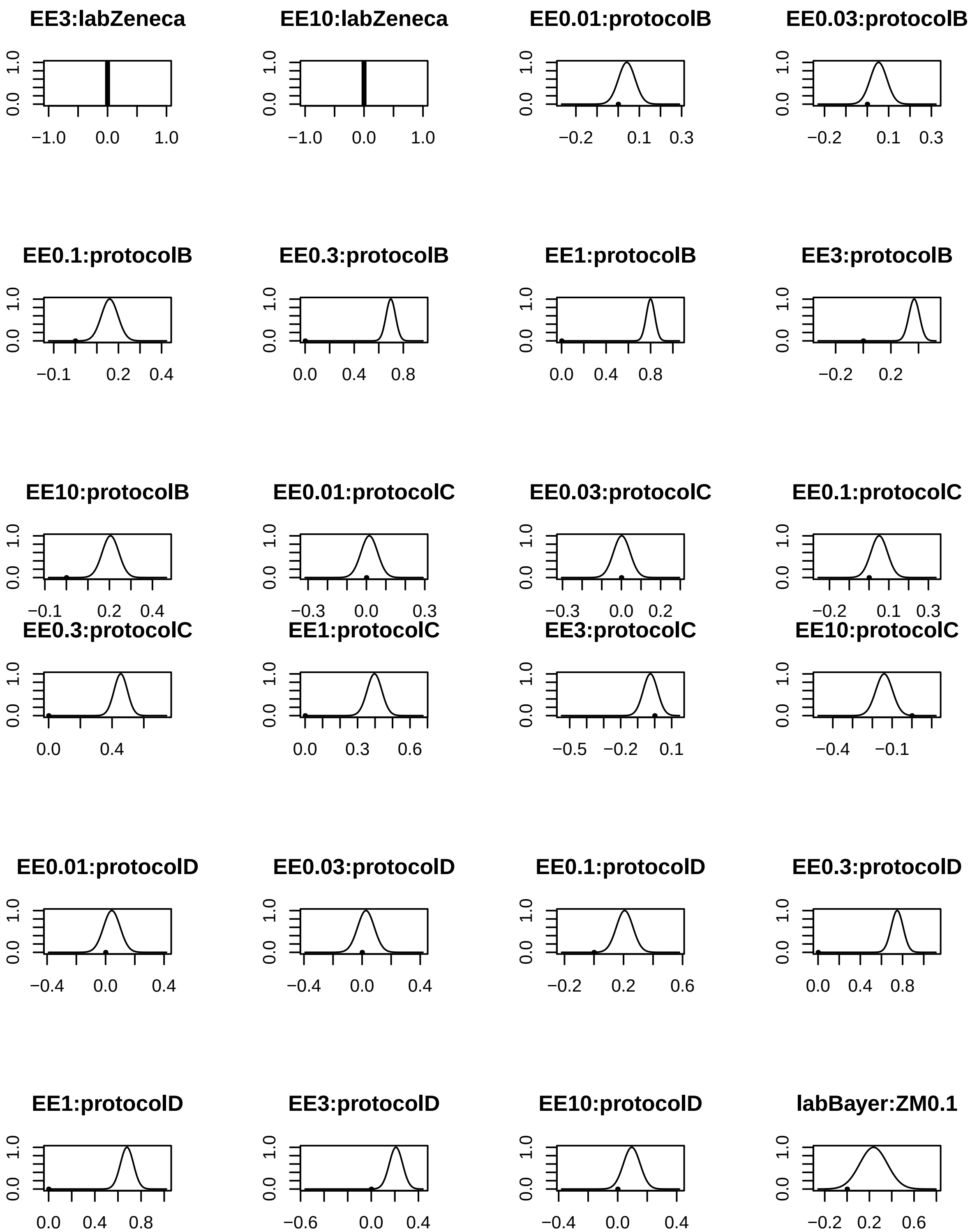

EE1:labBayer
EE3:labBayer
EE10:labBayer
EE0.01:labBerlin
EE0.03:labBerlin
EE0.1:labBerlin
EE0.3:labBerlin
EE1:labBerlin
EE3:labBerlin
EE10:labBerlin
EE0.01:labChungKor
EE0.03:labChungKor
EE0.1:labChungKor
EE0.3:labChungKor
EE1:labChungKor
EE3:labChungKor
EE10:labChungKor
EE0.01:labCitfranc
EE0.03:labCitfranc
EE0.1:labCitfranc
EE0.3:labCitfranc
EE1:labCitfranc
EE3:labCitfranc
EE10:labCitfranc
0.0
1.0
−1.0
0.0
1.0

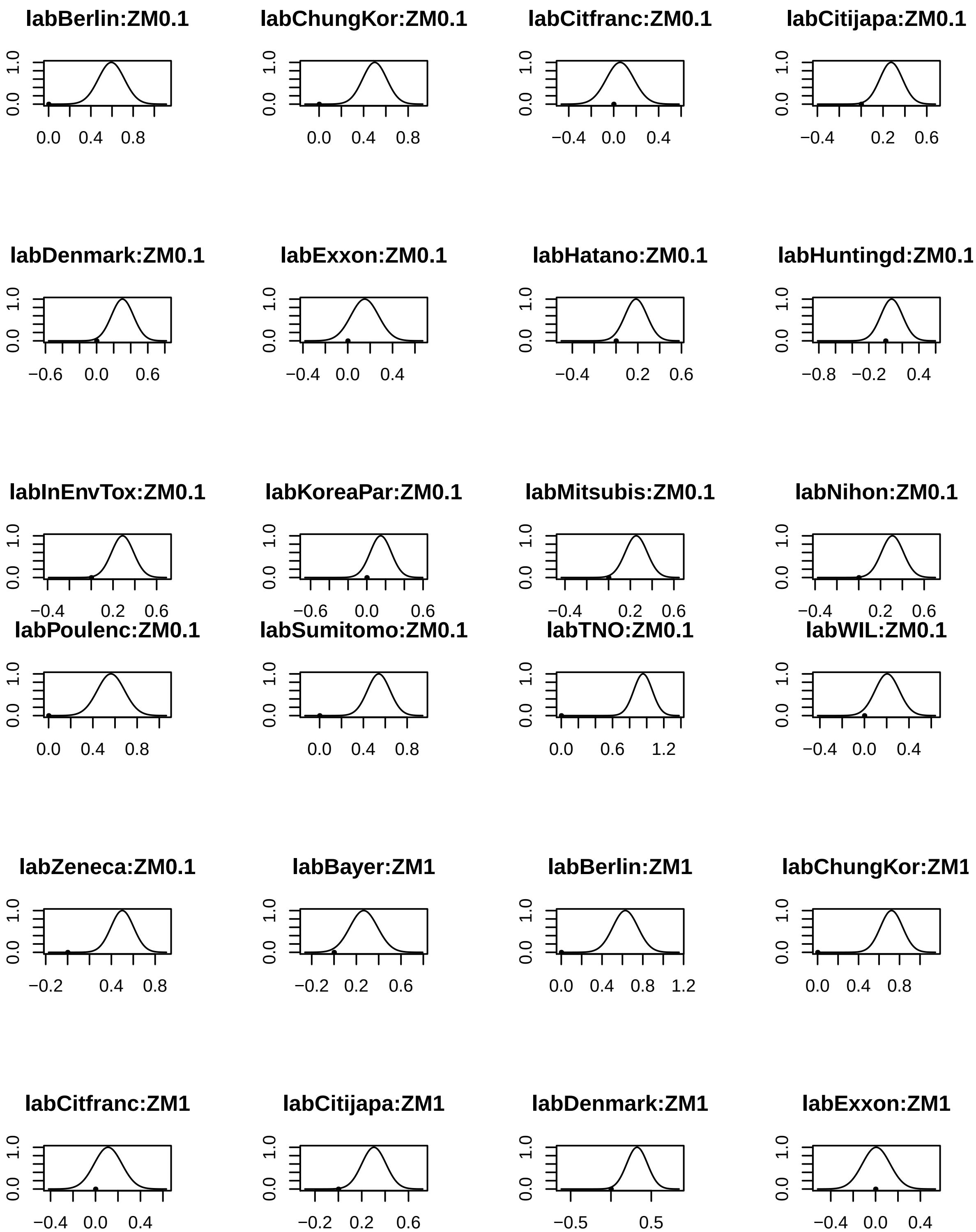

EE0.01:labCitijapa
EE0.03:labCitijapa
EE0.1:labCitijapa
EE0.3:labCitijapa
EE1:labCitijapa
EE3:labCitijapa
EE10:labCitijapa
EE0.01:labDenmark
EE0.03:labDenmark
EE0.1:labDenmark
EE0.3:labDenmark
EE1:labDenmark
EE3:labDenmark
EE10:labDenmark
EE0.01:labExxon
EE0.03:labExxon
EE0.1:labExxon
EE0.3:labExxon
EE1:labExxon
EE3:labExxon
EE10:labExxon
EE0.01:labHatano
EE0.03:labHatano
EE0.1:labHatano

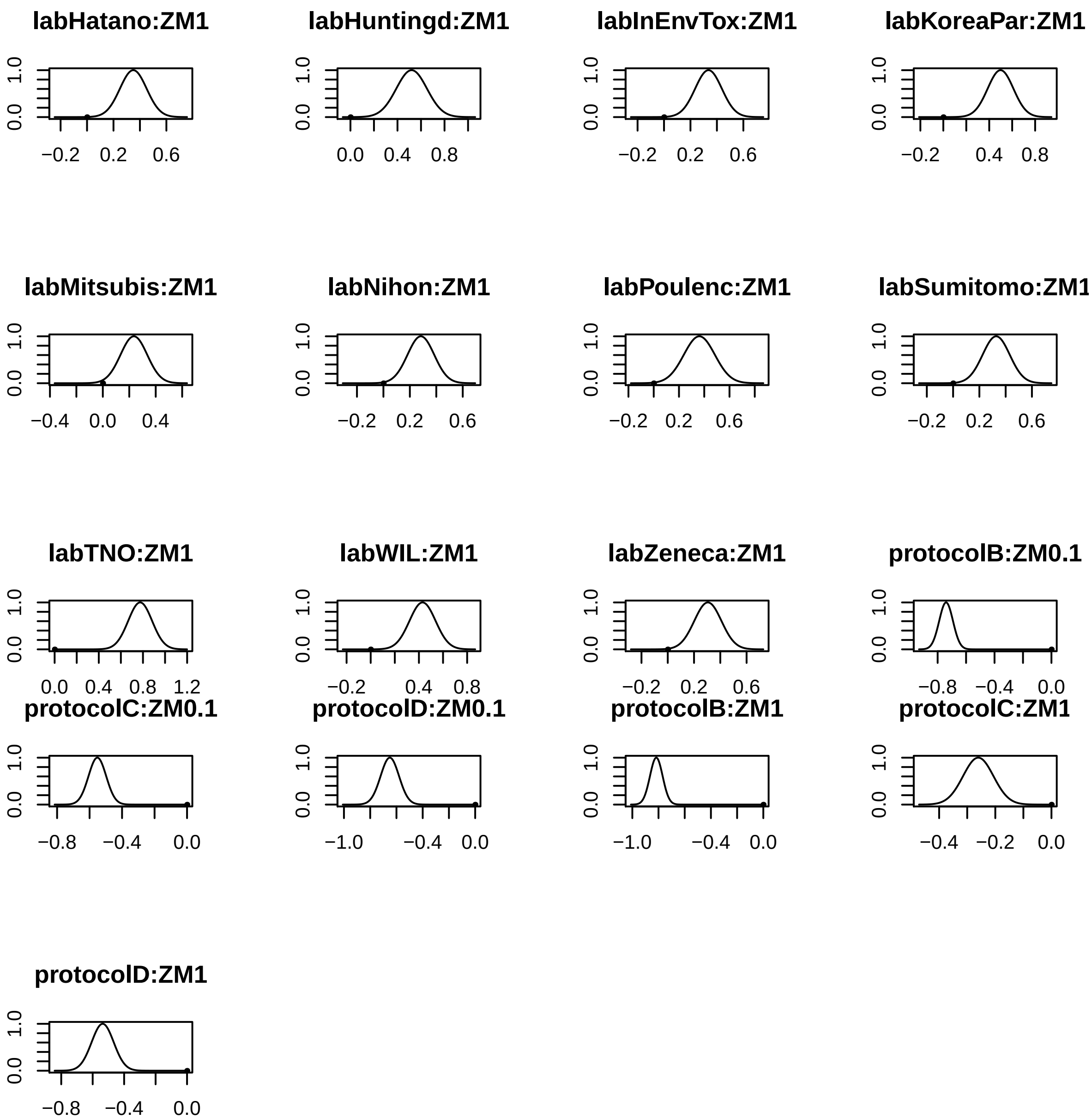

EE0.3:labHatano
EE1:labHatano
EE3:labHatano
EE10:labHatano
EE0.01:labHuntingd
EE0.03:labHuntingd
EE0.1:labHuntingd
EE0.3:labHuntingd
EE1:labHuntingd
EE3:labHuntingd
EE10:labHuntingd
EE0.01:labInEnvTox
EE0.03:labInEnvTox
EE0.1:labInEnvTox
EE0.3:labInEnvTox
EE1:labInEnvTox
EE3:labInEnvTox
EE10:labInEnvTox
EE0.01:labKoreaPar
EE0.03:labKoreaPar
EE0.1:labKoreaPar
EE0.3:labKoreaPar
EE1:labKoreaPar
EE3:labKoreaPar


EE10:labKoreaPar
EE0.01:labMitsubis
EE0.03:labMitsubis
EE0.1:labMitsubis
EE0.3:labMitsubis
EE1:labMitsubis
EE3:labMitsubis
EE10:labMitsubis
EE0.01:labNihon
EE0.03:labNihon
EE0.1:labNihon
EE0.3:labNihon
EE1:labNihon
EE3:labNihon
EE10:labNihon
EE0.01:labPoulenc
EE0.03:labPoulenc
EE0.1:labPoulenc
EE0.3:labPoulenc
EE1:labPoulenc
EE3:labPoulenc
EE10:labPoulenc
EE0.01:labSumitomo
EE0.03:labSumitomo


EE0.1:labSumitomo
EE0.3:labSumitomo
EE1:labSumitomo
EE3:labSumitomo
EE10:labSumitomo
EE0.01:labTNO
EE0.03:labTNO
EE0.1:labTNO
EE0.3:labTNO
EE1:labTNO
EE3:labTNO
EE10:labTNO
EE0.01:labWIL
EE0.03:labWIL
EE0.1:labWIL
EE0.3:labWIL
EE1:labWIL
EE3:labWIL
EE10:labWIL
EE0.01:labZeneca
EE0.03:labZeneca
EE0.1:labZeneca
EE0.3:labZeneca
EE1:labZeneca


EE3:labZeneca
1.0
0.0
−1.0 0.0 1.0
EE10:labZeneca
1.0
0.0
−1.0 0.0 1.0
EE0.01:protocolB
1.0
0.0
−0.2 0.1 0.3
EE0.03:protocolB
1.0
0.0
−0.2 0.1 0.3
EE0.1:protocolB
1.0
0.0
−0.1 0.2 0.4
EE0.3:protocolB
1.0
0.0
0.0 0.4 0.8
EE1:protocolB
1.0
0.0
0.0 0.4 0.8
EE3:protocolB
1.0
0.0
−0.2 0.2
EE10:protocolB
1.0
0.0
−0.1 0.2 0.4
EE0.01:protocolC
1.0
0.0
−0.3 0.0 0.3
EE0.03:protocolC
1.0
0.0
−0.3 0.0 0.2
EE0.1:protocolC
1.0
0.0
−0.2 0.1 0.3
EE0.3:protocolC
1.0
0.0
0.0 0.4
EE1:protocolC
1.0
0.0
0.0 0.3 0.6
EE3:protocolC
1.0
0.0
−0.5 −0.2 0.1
EE10:protocolC
1.0
0.0
−0.4 −0.1
EE0.01:protocolD
1.0
0.0
−0.4 0.0 0.4
EE0.03:protocolD
1.0
0.0
−0.4 0.0 0.4
EE0.1:protocolD
1.0
0.0
−0.2 0.2 0.6
EE0.3:protocolD
1.0
0.0
0.0 0.4 0.8
EE1:protocolD
1.0
0.0
0.0 0.4 0.8
EE3:protocolD
1.0
0.0
−0.6 0.0 0.4
EE10:protocolD
1.0
0.0
−0.4 0.0 0.4
labBayer:ZM0.1
1.0
0.0
−0.2 0.2 0.6


labBerlin:ZM0.1
labChungKor:ZM0.1
labCitfranc:ZM0.1
labCitijapa:ZM0.1
labDenmark:ZM0.1
labExxon:ZM0.1
labHatano:ZM0.1
labHuntingd:ZM0.1
labInEnvTox:ZM0.1
labKoreaPar:ZM0.1
labMitsubis:ZM0.1
labNihon:ZM0.1
labPoulenc:ZM0.1
labSumitomo:ZM0.1
labTNO:ZM0.1
labWIL:ZM0.1
labZeneca:ZM0.1
labBayer:ZM1
labBerlin:ZM1
labChungKor:ZM1
labCitfranc:ZM1
labCitijapa:ZM1
labDenmark:ZM1
labExxon:ZM1



b.

Does the dose response vary across labs? If so, are there certain labs that stand out as being different?

See figures in a.

c.

Do the protocols differ in their sensitivity to detecting estrogenic and anti-estrogenic effects? If so, is there one protocol that can be recommended?

```
confint(coef(bas1))
```

```
##                            2.5%      97.5%        beta
## Intercept           4.254297568 4.26990982 4.261851399
```

```
## EE0.01             -0.065649230  0.04107533 -0.014010798
## EE0.03             -0.057080852  0.04690983 -0.006765596
## EE0.1               0.002743891  0.10419880  0.051831727
## EE0.3               0.120878153  0.22233988  0.169967857
## EE1                 0.618885379  0.72034810  0.667974439
## EE3                 1.172162331  1.27364619  1.221258136
## EE10                1.356278597  1.45774813  1.405368935
## labBayer            0.337817133  0.52014562  0.425941455
## labBerlin           0.421099485  0.60614476  0.510507808
## labChungKor         0.572958518  0.71925589  0.643720620
## labCitfranc         0.451802484  0.61281711  0.529701003
## labCitijapa         0.316151816  0.45404809  0.382865585
## labDenmark          0.359457070  0.52979110  0.441855061
## labExxon            0.418959177  0.58472047  0.499155876
## labHatano           0.256181643  0.39061677  0.321220996
## labHuntingd        -0.214908891 -0.03953514 -0.129988276
## labInEnvTox         0.328090963  0.46762357  0.395540882
## labKoreaPar         0.044895077  0.19827356  0.119041546
## labMitsubis         0.269318156  0.40367858  0.334326171
## labNihon            0.176209830  0.31061749  0.241235757
## labPoulenc         -0.065472187  0.10291192  0.015923806
## labSumitomo         0.306108230  0.44323144  0.372449007
## labTNO              0.303205420  0.45760396  0.377826593
## labWIL              0.246602802  0.39318819  0.317504800
## labZeneca           0.095549628  0.23300134  0.162063976
## protocolB          -0.126142898 -0.03333795 -0.081241774
## protocolC           0.492830957  0.76233644  0.623445748
## protocolD           0.344240851  0.63690673  0.486069598
## ZM0.1              -0.635915977 -0.27845443 -0.462954575
## ZM1                -1.321255114 -0.96378827 -1.148290939
## log(weight)         0.373648648  0.54928125  0.458416796
## EE0.01:labBayer     0.000000000  0.00000000  0.000000000
## EE0.03:labBayer     0.000000000  0.00000000  0.000000000
## EE0.1:labBayer      0.000000000  0.00000000  0.000000000
## EE0.3:labBayer      0.000000000  0.00000000  0.000000000
## EE1:labBayer        0.000000000  0.00000000  0.000000000
## EE3:labBayer        0.000000000  0.00000000  0.000000000
## EE10:labBayer       0.000000000  0.00000000  0.000000000
## EE0.01:labBerlin    0.000000000  0.00000000  0.000000000
## EE0.03:labBerlin    0.000000000  0.00000000  0.000000000
## EE0.1:labBerlin     0.000000000  0.00000000  0.000000000
## EE0.3:labBerlin     0.000000000  0.00000000  0.000000000
## EE1:labBerlin       0.000000000  0.00000000  0.000000000
## EE3:labBerlin       0.000000000  0.00000000  0.000000000
## EE10:labBerlin      0.000000000  0.00000000  0.000000000
## EE0.01:labChungKor  0.000000000  0.00000000  0.000000000
## EE0.03:labChungKor  0.000000000  0.00000000  0.000000000
## EE0.1:labChungKor   0.000000000  0.00000000  0.000000000
## EE0.3:labChungKor   0.000000000  0.00000000  0.000000000
## EE1:labChungKor     0.000000000  0.00000000  0.000000000
## EE3:labChungKor     0.000000000  0.00000000  0.000000000
## EE10:labChungKor    0.000000000  0.00000000  0.000000000
## EE0.01:labCitfranc  0.000000000  0.00000000  0.000000000
## EE0.03:labCitfranc  0.000000000  0.00000000  0.000000000
```

```
## EE0.1:labCitfranc   0.000000000  0.00000000  0.000000000
## EE0.3:labCitfranc   0.000000000  0.00000000  0.000000000
## EE1:labCitfranc     0.000000000  0.00000000  0.000000000
## EE3:labCitfranc     0.000000000  0.00000000  0.000000000
## EE10:labCitfranc    0.000000000  0.00000000  0.000000000
## EE0.01:labCitijapa  0.000000000  0.00000000  0.000000000
## EE0.03:labCitijapa  0.000000000  0.00000000  0.000000000
## EE0.1:labCitijapa   0.000000000  0.00000000  0.000000000
## EE0.3:labCitijapa   0.000000000  0.00000000  0.000000000
## EE1:labCitijapa     0.000000000  0.00000000  0.000000000
## EE3:labCitijapa     0.000000000  0.00000000  0.000000000
## EE10:labCitijapa    0.000000000  0.00000000  0.000000000
## EE0.01:labDenmark   0.000000000  0.00000000  0.000000000
## EE0.03:labDenmark   0.000000000  0.00000000  0.000000000
## EE0.1:labDenmark    0.000000000  0.00000000  0.000000000
## EE0.3:labDenmark    0.000000000  0.00000000  0.000000000
## EE1:labDenmark      0.000000000  0.00000000  0.000000000
## EE3:labDenmark      0.000000000  0.00000000  0.000000000
## EE10:labDenmark     0.000000000  0.00000000  0.000000000
## EE0.01:labExxon     0.000000000  0.00000000  0.000000000
## EE0.03:labExxon     0.000000000  0.00000000  0.000000000
## EE0.1:labExxon      0.000000000  0.00000000  0.000000000
## EE0.3:labExxon      0.000000000  0.00000000  0.000000000
## EE1:labExxon        0.000000000  0.00000000  0.000000000
## EE3:labExxon        0.000000000  0.00000000  0.000000000
## EE10:labExxon       0.000000000  0.00000000  0.000000000
## EE0.01:labHatano    0.000000000  0.00000000  0.000000000
## EE0.03:labHatano    0.000000000  0.00000000  0.000000000
## EE0.1:labHatano     0.000000000  0.00000000  0.000000000
## EE0.3:labHatano     0.000000000  0.00000000  0.000000000
## EE1:labHatano       0.000000000  0.00000000  0.000000000
## EE3:labHatano       0.000000000  0.00000000  0.000000000
## EE10:labHatano      0.000000000  0.00000000  0.000000000
## EE0.01:labHuntingd  0.000000000  0.00000000  0.000000000
## EE0.03:labHuntingd  0.000000000  0.00000000  0.000000000
## EE0.1:labHuntingd   0.000000000  0.00000000  0.000000000
## EE0.3:labHuntingd   0.000000000  0.00000000  0.000000000
## EE1:labHuntingd     0.000000000  0.00000000  0.000000000
## EE3:labHuntingd     0.000000000  0.00000000  0.000000000
## EE10:labHuntingd    0.000000000  0.00000000  0.000000000
## EE0.01:labInEnvTox  0.000000000  0.00000000  0.000000000
## EE0.03:labInEnvTox  0.000000000  0.00000000  0.000000000
## EE0.1:labInEnvTox   0.000000000  0.00000000  0.000000000
## EE0.3:labInEnvTox   0.000000000  0.00000000  0.000000000
## EE1:labInEnvTox     0.000000000  0.00000000  0.000000000
## EE3:labInEnvTox     0.000000000  0.00000000  0.000000000
## EE10:labInEnvTox    0.000000000  0.00000000  0.000000000
## EE0.01:labKoreaPar  0.000000000  0.00000000  0.000000000
## EE0.03:labKoreaPar  0.000000000  0.00000000  0.000000000
## EE0.1:labKoreaPar   0.000000000  0.00000000  0.000000000
## EE0.3:labKoreaPar   0.000000000  0.00000000  0.000000000
## EE1:labKoreaPar     0.000000000  0.00000000  0.000000000
## EE3:labKoreaPar     0.000000000  0.00000000  0.000000000
## EE10:labKoreaPar    0.000000000  0.00000000  0.000000000
```

```
## EE0.01:labMitsubis  0.000000000  0.00000000  0.000000000
## EE0.03:labMitsubis  0.000000000  0.00000000  0.000000000
## EE0.1:labMitsubis   0.000000000  0.00000000  0.000000000
## EE0.3:labMitsubis   0.000000000  0.00000000  0.000000000
## EE1:labMitsubis     0.000000000  0.00000000  0.000000000
## EE3:labMitsubis     0.000000000  0.00000000  0.000000000
## EE10:labMitsubis    0.000000000  0.00000000  0.000000000
## EE0.01:labNihon     0.000000000  0.00000000  0.000000000
## EE0.03:labNihon     0.000000000  0.00000000  0.000000000
## EE0.1:labNihon      0.000000000  0.00000000  0.000000000
## EE0.3:labNihon      0.000000000  0.00000000  0.000000000
## EE1:labNihon        0.000000000  0.00000000  0.000000000
## EE3:labNihon        0.000000000  0.00000000  0.000000000
## EE10:labNihon       0.000000000  0.00000000  0.000000000
## EE0.01:labPoulenc   0.000000000  0.00000000  0.000000000
## EE0.03:labPoulenc   0.000000000  0.00000000  0.000000000
## EE0.1:labPoulenc    0.000000000  0.00000000  0.000000000
## EE0.3:labPoulenc    0.000000000  0.00000000  0.000000000
## EE1:labPoulenc      0.000000000  0.00000000  0.000000000
## EE3:labPoulenc      0.000000000  0.00000000  0.000000000
## EE10:labPoulenc     0.000000000  0.00000000  0.000000000
## EE0.01:labSumitomo  0.000000000  0.00000000  0.000000000
## EE0.03:labSumitomo  0.000000000  0.00000000  0.000000000
## EE0.1:labSumitomo   0.000000000  0.00000000  0.000000000
## EE0.3:labSumitomo   0.000000000  0.00000000  0.000000000
## EE1:labSumitomo     0.000000000  0.00000000  0.000000000
## EE3:labSumitomo     0.000000000  0.00000000  0.000000000
## EE10:labSumitomo    0.000000000  0.00000000  0.000000000
## EE0.01:labTNO       0.000000000  0.00000000  0.000000000
## EE0.03:labTNO       0.000000000  0.00000000  0.000000000
## EE0.1:labTNO        0.000000000  0.00000000  0.000000000
## EE0.3:labTNO        0.000000000  0.00000000  0.000000000
## EE1:labTNO          0.000000000  0.00000000  0.000000000
## EE3:labTNO          0.000000000  0.00000000  0.000000000
## EE10:labTNO         0.000000000  0.00000000  0.000000000
## EE0.01:labWIL       0.000000000  0.00000000  0.000000000
## EE0.03:labWIL       0.000000000  0.00000000  0.000000000
## EE0.1:labWIL        0.000000000  0.00000000  0.000000000
## EE0.3:labWIL        0.000000000  0.00000000  0.000000000
## EE1:labWIL          0.000000000  0.00000000  0.000000000
## EE3:labWIL          0.000000000  0.00000000  0.000000000
## EE10:labWIL         0.000000000  0.00000000  0.000000000
## EE0.01:labZeneca    0.000000000  0.00000000  0.000000000
## EE0.03:labZeneca    0.000000000  0.00000000  0.000000000
## EE0.1:labZeneca     0.000000000  0.00000000  0.000000000
## EE0.3:labZeneca     0.000000000  0.00000000  0.000000000
## EE1:labZeneca       0.000000000  0.00000000  0.000000000
## EE3:labZeneca       0.000000000  0.00000000  0.000000000
## EE10:labZeneca      0.000000000  0.00000000  0.000000000
## EE0.01:protocolB   -0.035780025  0.12202177  0.040569497
## EE0.03:protocolB   -0.022546654  0.13341678  0.052914245
## EE0.1:protocolB     0.084697839  0.23898999  0.159348571
## EE0.3:protocolB     0.623293929  0.77758117  0.697941791
## EE1:protocolB       0.724706402  0.87899936  0.799356107
```

```
## EE3:protocolB        0.294077028  0.44836304  0.368723375
## EE10:protocolB       0.130336422  0.28506001  0.205194411
## EE0.01:protocolC    -0.068184446  0.10329087  0.014781885
## EE0.03:protocolC    -0.080236749  0.08955142  0.001913519
## EE0.1:protocolC     -0.030185049  0.13807681  0.051224327
## EE0.3:protocolC      0.373244983  0.54149461  0.454648992
## EE1:protocolC        0.315254842  0.48358435  0.396693059
## EE3:protocolC       -0.106659487  0.06176546 -0.025178561
## EE10:protocolC      -0.221939086 -0.05324415 -0.140330250
## EE0.01:protocolD    -0.067514525  0.16034986  0.042734259
## EE0.03:protocolD    -0.084350998  0.14483946  0.026538462
## EE0.1:protocolD      0.098466210  0.32406878  0.207612477
## EE0.3:protocolD      0.639548415  0.86517906  0.748706391
## EE1:protocolD        0.568295973  0.79452034  0.677731381
## EE3:protocolD        0.099827620  0.32641924  0.209434884
## EE10:protocolD      -0.014564545  0.21254660  0.095311012
## labBayer:ZM0.1      -0.002686411  0.49295048  0.237130115
## labBerlin:ZM0.1      0.355541728  0.84756291  0.593593200
## labChungKor:ZM0.1    0.290007686  0.72349520  0.499739323
## labCitfranc:ZM0.1   -0.180504927  0.31151811  0.057556104
## labCitijapa:ZM0.1    0.074087879  0.48749965  0.274106299
## labDenmark:ZM0.1     0.053360702  0.56870575  0.302701849
## labExxon:ZM0.1      -0.087350466  0.40625839  0.151472365
## labHatano:ZM0.1     -0.012889640  0.39250970  0.183252195
## labHuntingd:ZM0.1   -0.179991476  0.34224782  0.072689227
## labInEnvTox:ZM0.1    0.092141302  0.49633193  0.287700510
## labKoreaPar:ZM0.1   -0.069075111  0.38039314  0.148393497
## labMitsubis:ZM0.1    0.058597420  0.46281387  0.254165631
## labNihon:ZM0.1       0.113559295  0.51776006  0.309119990
## labPoulenc:ZM0.1     0.325146022  0.81722017  0.563215839
## labSumitomo:ZM0.1    0.340415049  0.75383199  0.540431426
## labTNO:ZM0.1         0.746882812  1.18047824  0.956654677
## labWIL:ZM0.1        -0.005359057  0.42812948  0.204377874
## labZeneca:ZM0.1      0.299827388  0.71324152  0.499843382
## labBayer:ZM1         0.026308626  0.52183272  0.266058383
## labBerlin:ZM1        0.390714402  0.88274214  0.628770887
## labChungKor:ZM1      0.512306833  0.94579467  0.722034210
## labCitfranc:ZM1     -0.126434902  0.36558637  0.111622686
## labCitijapa:ZM1      0.104071118  0.51743665  0.304072258
## labDenmark:ZM1       0.074541372  0.58989579  0.323888722
## labExxon:ZM1        -0.233092664  0.26051064  0.005733627
## labHatano:ZM1        0.154155815  0.55835298  0.349719422
## labHuntingd:ZM1      0.267677166  0.78966018  0.520234753
## labInEnvTox:ZM1      0.140767573  0.54497496  0.336339422
## labKoreaPar:ZM1      0.281040456  0.73040661  0.498453302
## labMitsubis:ZM1      0.039102579  0.44328701  0.234659890
## labNihon:ZM1         0.087684573  0.49187630  0.283248107
## labPoulenc:ZM1       0.123151477  0.61520081  0.361214137
## labSumitomo:ZM1      0.127956859  0.54133112  0.327962972
## labTNO:ZM1           0.564719934  0.99829135  0.774485617
## labWIL:ZM1           0.220219575  0.65371334  0.429957200
## labZeneca:ZM1        0.105284801  0.51866467  0.305294507
## protocolB:ZM0.1     -0.834326010 -0.64060138 -0.740586682
## protocolC:ZM0.1     -0.657463668 -0.43974728 -0.552112087
```

```
## protocolD:ZM0.1    -0.786731858 -0.50518460 -0.650484522
## protocolB:ZM1      -0.910686984 -0.71696456 -0.816949127
## protocolC:ZM1      -0.365605145 -0.14871768 -0.260658808
## protocolD:ZM1      -0.672699050 -0.39130411 -0.536527855
## attr(,"Probability")
## [1] 0.95
## attr(,"class")
## [1] "confint.bas"
```

Model Part III

```
bioassay1 = bioassay
bioassay1$EE = bioassay1$EE %>% as.character() %>% as.numeric()
bioassay1$ZM = bioassay1$ZM %>% as.character() %>% as.numeric()
lm.jags = lm(log(uterus)~EE*lab+EE*protocol+ZM*lab+ZM*protocol+protocol+log(weight), data = bioassay1)

## X matrix and scale
X0 = model.matrix(lm.jags)[,-1]
X.scaled = scale(X0)/sqrt(n-1)

#c = data.frame(coef(lm(log(bioassay1$uterus)~X.scaled)))[,1]

n = nrow(X0)
p = ncol(X0)

## data for jags
data = list(Y = bioassay$uterus, X = X.scaled, p = p, n = n)
data$scales =  attr(X.scaled, "scaled:scale")*sqrt(n-1) #+ 0.00001
data$Xbar = attr(X.scaled, "scaled:center")

## JAGS
rr.model = function() {
  a <- 2
  shape<-a/2

  for (i in 1:n) {
    mu[i] <- alpha0 + inprod(X[i,], alpha)
    prec[i] <- phi
    Y[i] ~ dnorm(mu[i], prec[i])
  }
  phi ~ dgamma(1.0E-6, 1.0E-6)  ##jags do not allow improper prior
  alpha0 ~ dnorm(0, 1.0E-6)

  for (j in 1:p) {
    phi.l[j] <- pow(i.phi.l[j], -2)
    prec.beta[j] <- lambda.l[j]*phi*phi.l[j]
    alpha[j] ~ dnorm(0, prec.beta[j])
    # transform back to original coefficients
    beta[j] <- alpha[j]/scales[j]
    lambda.l[j] ~ dgamma(shape, shape)
    i.phi.l[j] ~ dt(0,1,1)%_%T(0,)
  }
```

```
  # transform intercept to usual parameterization
  beta0 <- alpha0 - inprod(beta[1:p], Xbar)

  sigma <- pow(phi, -.5)
}

## parameters to monitor
parameters = c("beta0", "beta", "sigma","lambda.l", "phi.l")

## run jags
jags.result = jags(data, inits=NULL, par=parameters,
                   model=rr.model, n.iter=30000)
```

```
## module glm loaded
```

```
## Compiling model graph
##    Resolving undeclared variables
##    Allocating nodes
## Graph information:
##    Observed stochastic nodes: 2677
##    Unobserved stochastic nodes: 200
##    Total graph size: 187836
##
## Initializing model
```

```
saveRDS(jags.result, "jags.result.rds")
jags.result=readRDS("jags.result.rds")
```

a.

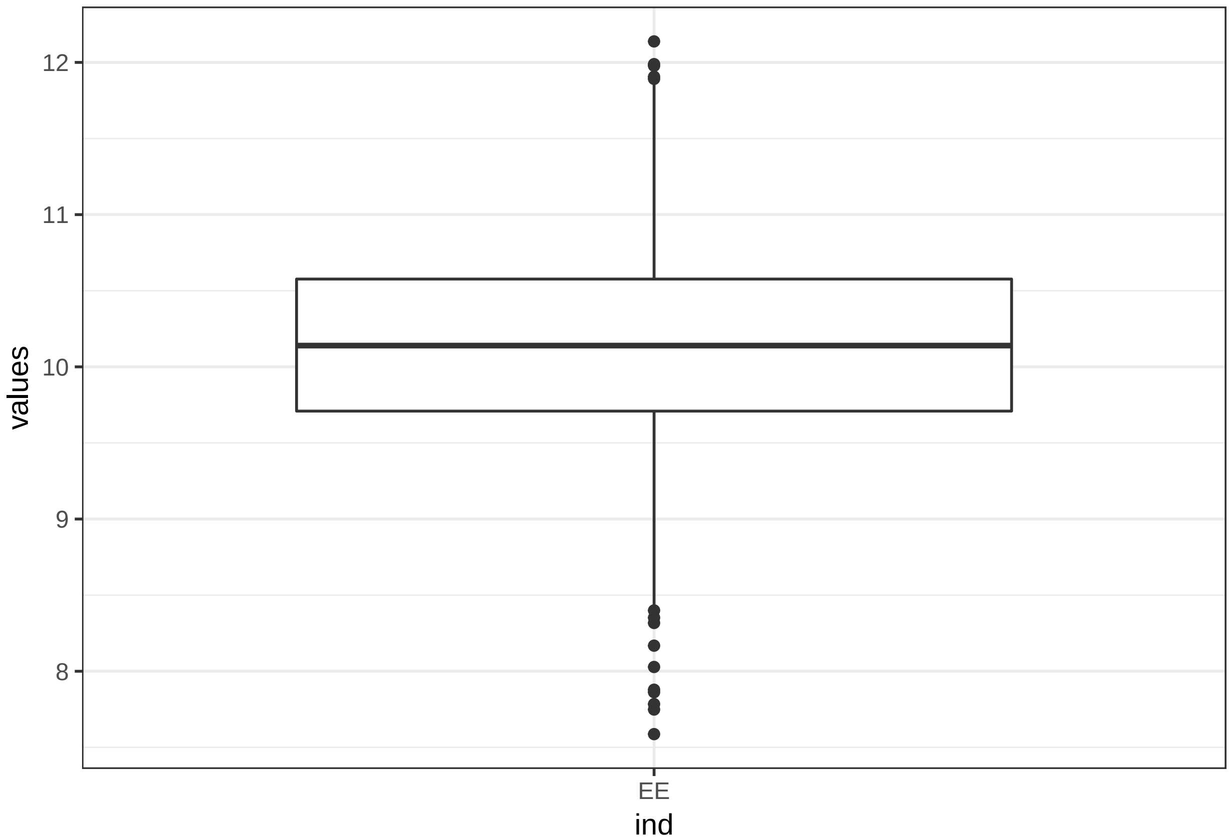
Is the uterotrophic bioassay successful overall at identifying estrogenic effects of EE and anti- estrogenic effects of ZM? Do some labs fail to detect such effects? At what dose level of EE is there a change relative to the control and does this level vary across labs?

```
jags.mcmc = as.mcmc(jags.result$BUGSoutput$sims.matrix)
jags.df = as.data.frame(jags.mcmc)
dim(jags.df)
```

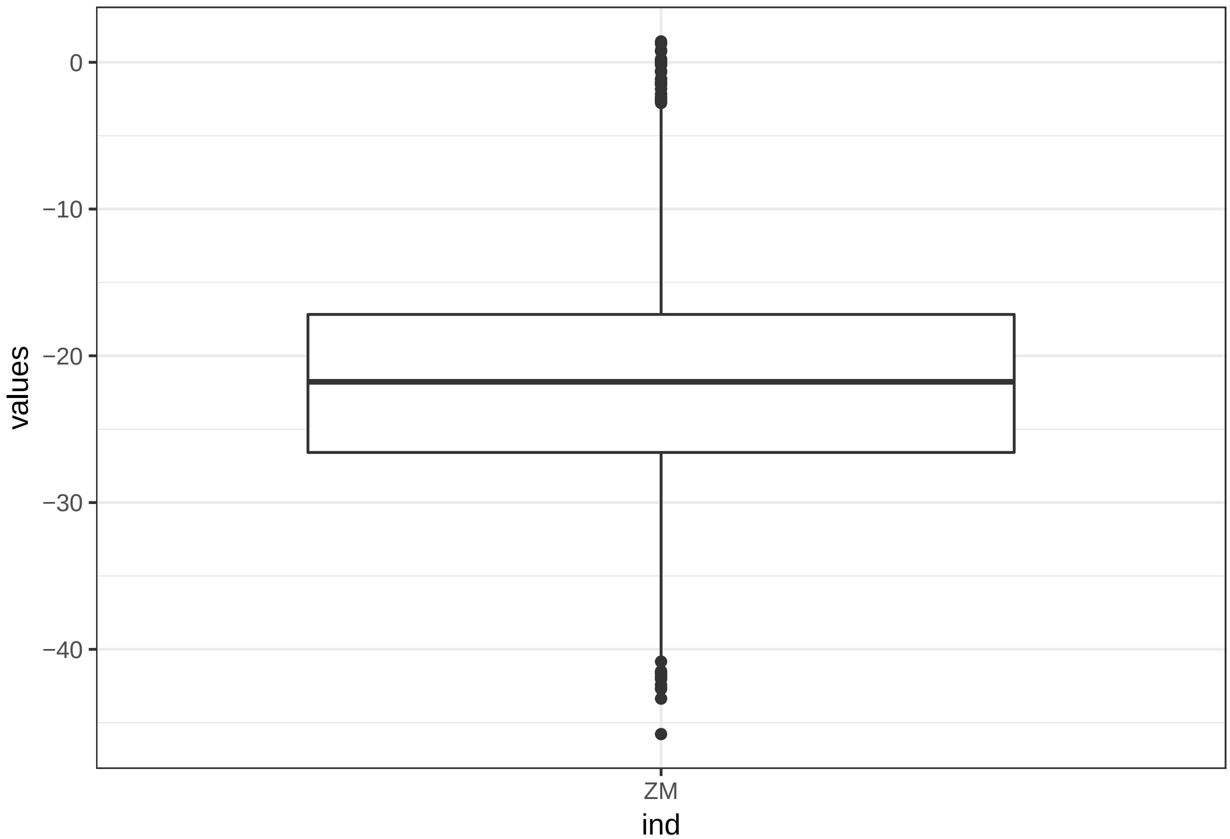
```
## [1] 3000  201
```

```
cnames = colnames(X0)
```

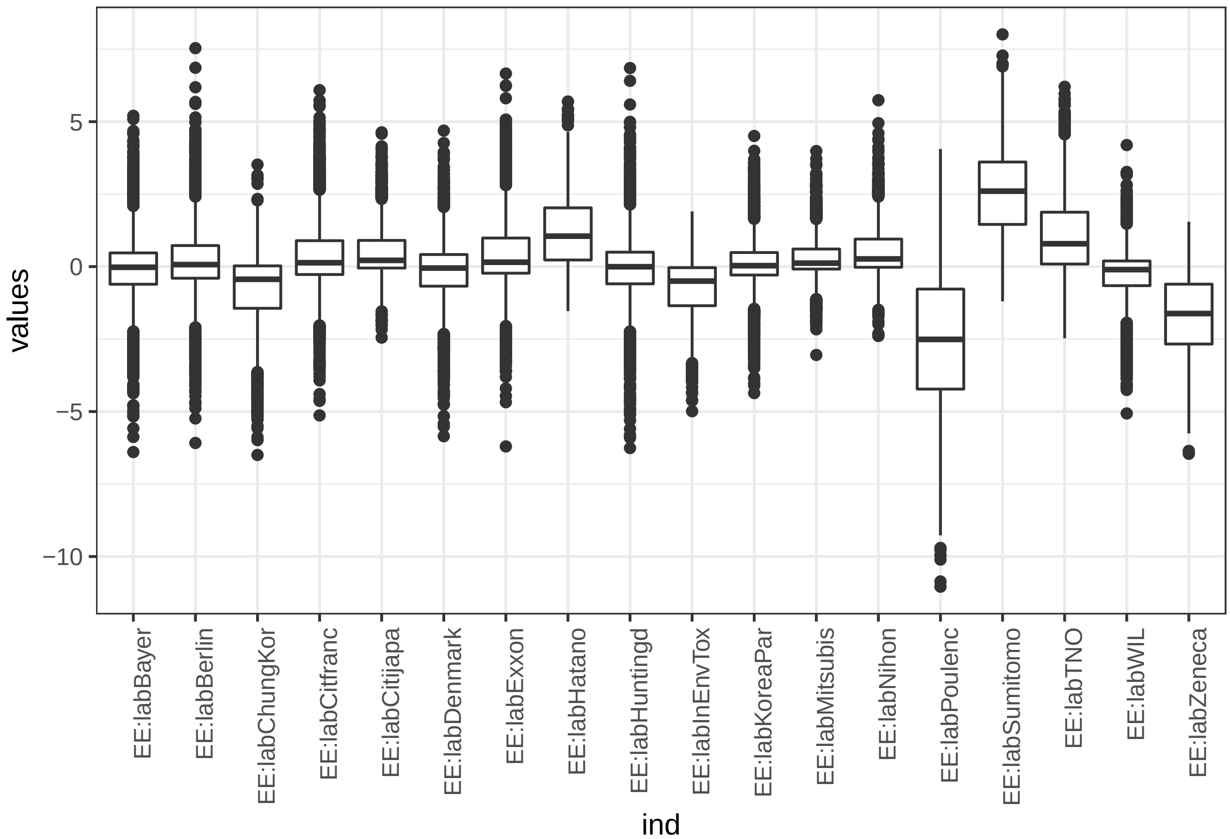
```
is.EElab = str_detect(cnames, "EE.*lab")
is.EEproto = str_detect(cnames, "EE.*protocol")
is.EE = str_detect(cnames, "EE.*")&(!is.EElab)&(!is.EEproto)

idx.EElab = which(is.EElab)
idx.EEproto = which(is.EEproto)
idx.EE = which(is.EE)

EE.df = jags.df[,idx.EE] %>% as.data.frame()
colnames(EE.df) = cnames[is.EE]
EE.df1 = stack(EE.df)

ggplot(data = EE.df1) + geom_boxplot(aes(x=ind, y=values))  + theme_bw()
```



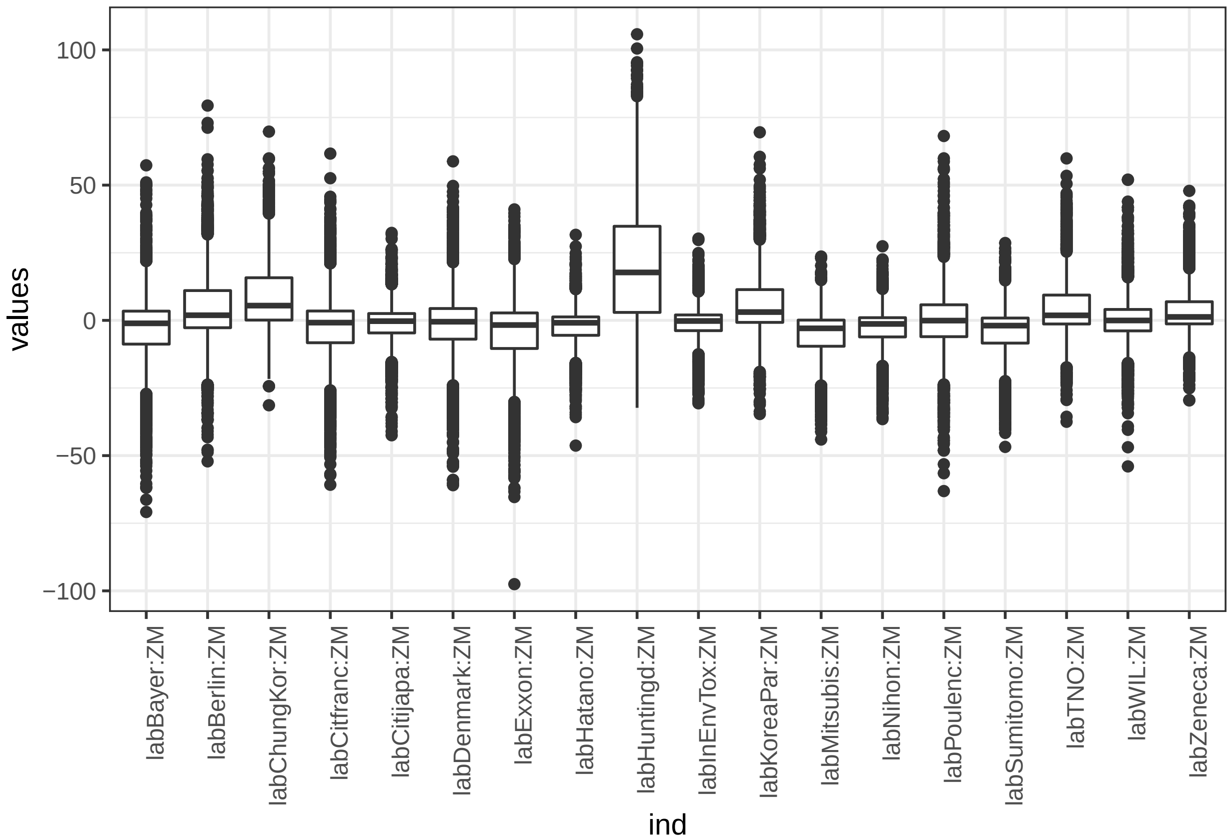

```
is.ZMlab = str_detect(cnames, "lab.*ZM")#str_detect(cnames, "ZM.*lab")
is.ZMproto = str_detect(cnames, "protocol.*ZM")#str_detect(cnames, "ZM.*protocol")
is.ZM = str_detect(cnames, "ZM.*")&(!is.ZMlab)&(!is.ZMproto)

idx.ZMlab = which(is.ZMlab)
idx.ZMproto = which(is.ZMproto)
idx.ZM = which(is.ZM)

ZM.df = jags.df[,idx.ZM] %>% as.data.frame()
colnames(ZM.df) = cnames[is.ZM]
ZM.df1 = stack(ZM.df)

ggplot(data = ZM.df1) + geom_boxplot(aes(x=ind, y=values)) + theme_bw()
```




```
EElab.df = jags.df[,idx.EElab]
colnames(EElab.df) = cnames[is.EElab]
EElab.df1 = stack(EElab.df)

ggplot(data = EElab.df1) + geom_boxplot(aes(x=ind, y=values)) +
  theme_bw() +
  theme(axis.text.x = element_text(angle = 90, hjust = 1))
```




```
ZMlab.df = jags.df[,idx.ZMlab]
colnames(ZMlab.df) = cnames[is.ZMlab]
ZMlab.df1 = stack(ZMlab.df)

ggplot(data = ZMlab.df1) + geom_boxplot(aes(x=ind, y=values)) +
  theme_bw() +
  theme(axis.text.x = element_text(angle = 90, hjust = 1))
```



b.

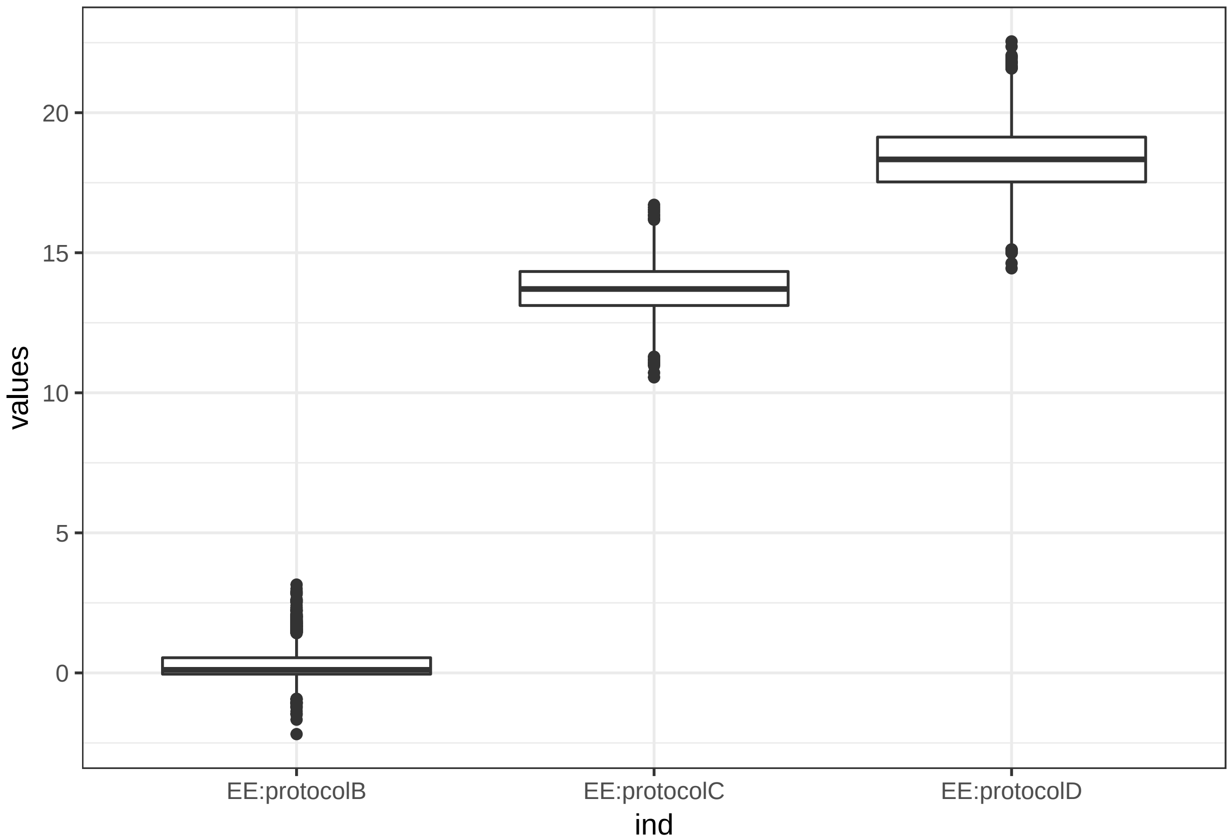
Does the dose response vary across labs? If so, are there certain labs that stand out as being different?

See figures in a.

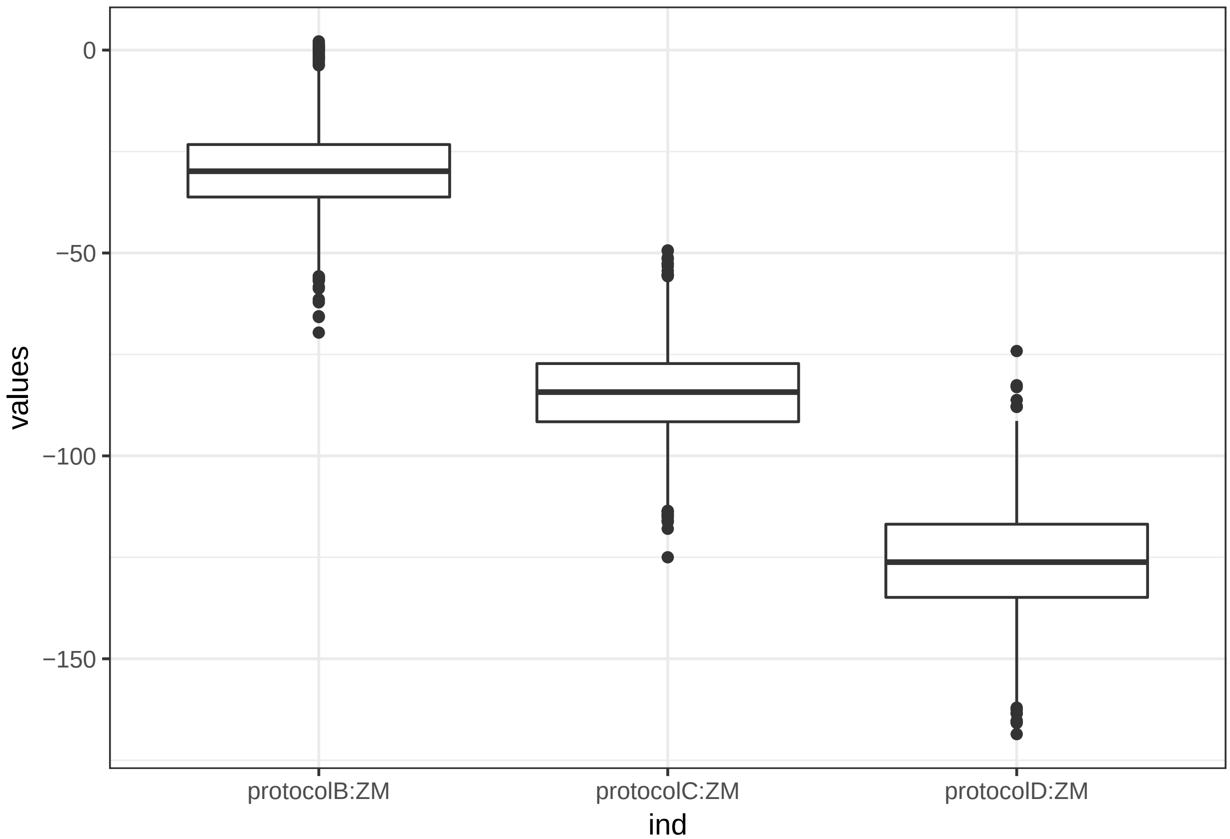
c.

Do the protocols differ in their sensitivity to detecting estrogenic and anti-estrogenic effects? If so, is there one protocol that can be recommended?

```
EEproto.df = jags.df[,idx.EEproto]
colnames(EEproto.df) = cnames[is.EEproto]
EEproto.df1 = stack(EEproto.df)

ggplot(data = EEproto.df1) + geom_boxplot(aes(x=ind, y=values)) + theme_bw()
```




```
ZMproto.df = jags.df[,idx.ZMproto]
colnames(ZMproto.df) = cnames[is.ZMproto]
ZMproto.df1 = stack(ZMproto.df)

ggplot(data = ZMproto.df1) + geom_boxplot(aes(x=ind, y=values)) + theme_bw()
```


0
−50
−100
−150
values
protocolB:ZM
protocolC:ZM
protocolD:ZM
ind