Initial Data:

```
     ID  Race     Age Menopause          Smoke Grade ER
1 x5055 White [46,55)      Post   Never Smoked     1  1
2 x5110 Black [46,55)       Pre   Never Smoked     3  0
3 x5539 White [46,55)       Pre   Never Smoked     3  0
4 x5550 Black [27,46)       Pre Current Smoker     1  1
5 x5561 White [46,55)      Post Current Smoker     2  0
6 x5737 White [27,46)      Post  Former Smoker     2  1

  ERorPR       HER2      IHC Regimen NumCycles ToxCall
1      Y Borderline     <NA>     2nd    [1, 5)       Y
2      N   Positive Her2/ER-     2nd    [1, 5)       N
3      N   Positive Her2/ER-     2nd    [1, 5)       Y
4      Y   Positive LuminalB     2nd    [5,18]       Y
5      N   Positive Her2/ER-     2nd    [5,18]       Y
6      Y   Positive LuminalB     2nd    [1, 5)       N

  Neutropenia Myalgia Neuropathy DoseInterval
1           N       N          Y        Q3wks
2           N       N          N        Q3wks
3           N       N          N        Q3wks
4           N       N          Y       Weekly
5           N       N          N       Weekly
6           N       N          N       Weekly

     TotalWeeks FollowupStatus StagePre StageFinal
1 [ 8.29,12.29)           LTFU     IIIA        IIB
2 [ 8.29,12.29)            NED     IIIB        IIA
3 [ 8.29,12.29)           Dead       IV         IV
4 [12.29,23.00]           Dead     IIIA          I
5 [12.29,23.00]           Dead     IIIB       IIIA
6 [ 1.00, 8.29)           Dead       IV         IV

  RespRegimens ResponseTaxane ResponseNonTaxane
1           PR             PR                PR
2           CR             CR                PR
3           PR             PR                PR
4           PR             SD                PR
5           CR             CR                SD
6           CR             UE                CR
```

Manova using all of the dose response variables:

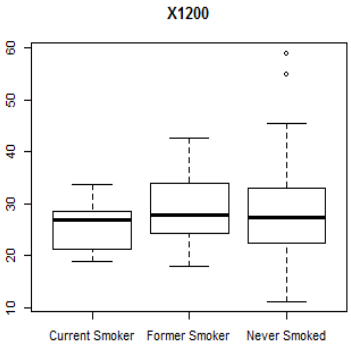
(see fig)

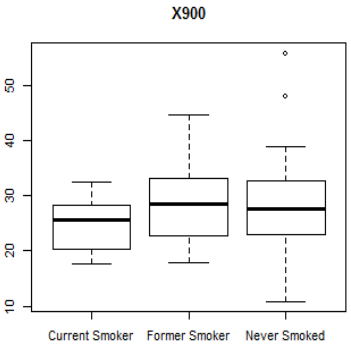
```
Multivariate Tests: Smoke
                 Df test stat approx F num Df den Df   Pr(>F)
Pillai            2 0.3472308 1.722741     20    164 0.034215 *
Wilks             2 0.6810383 1.715202     20    162 0.035507 *
Hotelling-Lawley  2 0.4268373 1.707349     20    160 0.036895 *
Roy               2 0.2769690 2.271146     10     82 0.021130 *
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```

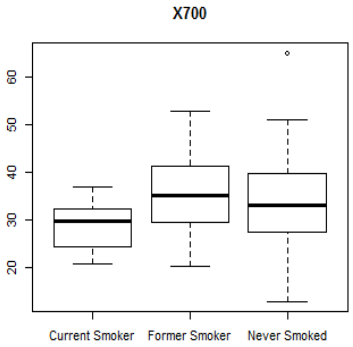
Pairwise contrasts:

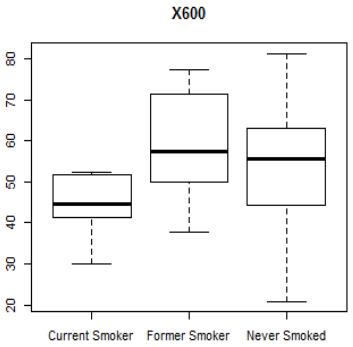
Used Bonferroni correction for multiple testing results in a significance level of .05/3 = .016

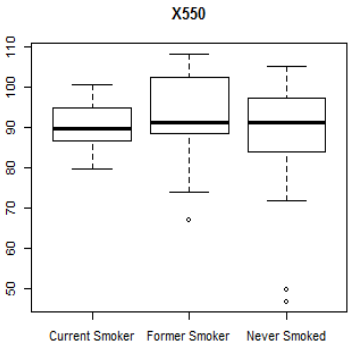
Contrast	X1200	X900	X700	X600	X550	X500	X450	X350	X250	X100	p-value
Former Smoker - Never Smoked	0.1695218	0.1530347	2.353009	4.151922	3.530092	3.52787	3.232719	3.239345	2.343049	1.898271	0.29
Former Smoker - Current Smoker	3.4979118	3.6110213	7.184981	13.77683	2.46673	0.230579	0.852648	-0.1651	-0.9725	0.413662	0.036
Never Smoked - Current Smoker	3.32839	3.457987	4.831971	9.62491	-1.06336	-3.29729	-2.38007	-3.40444	-3.31555	-1.48461	0.029

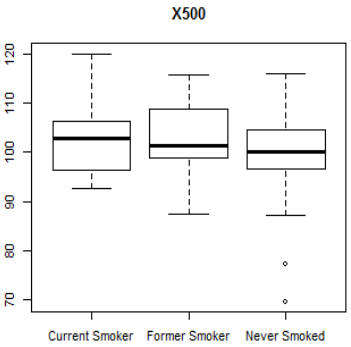


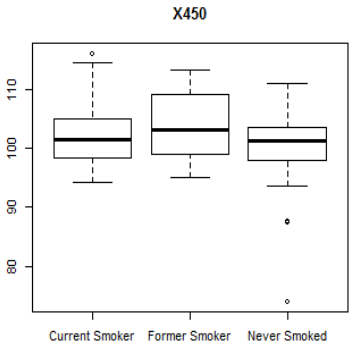


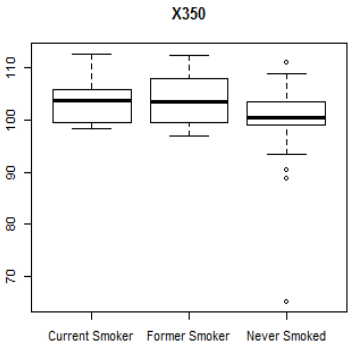


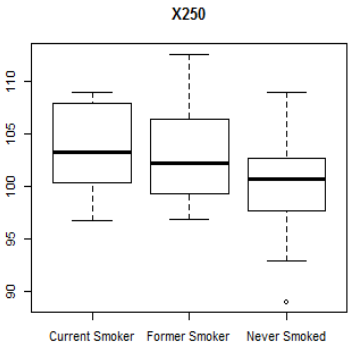


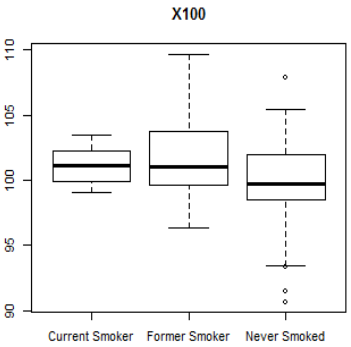


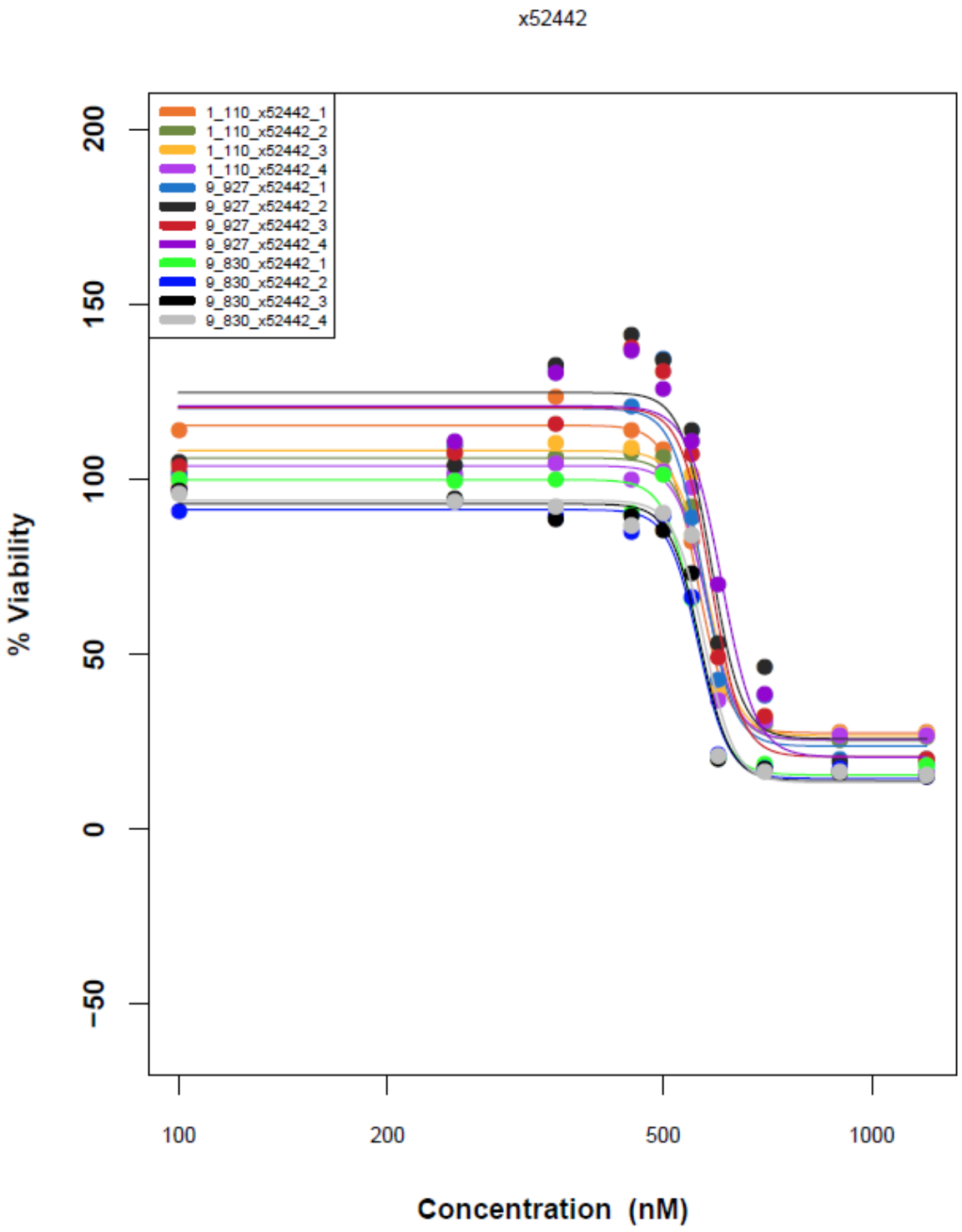




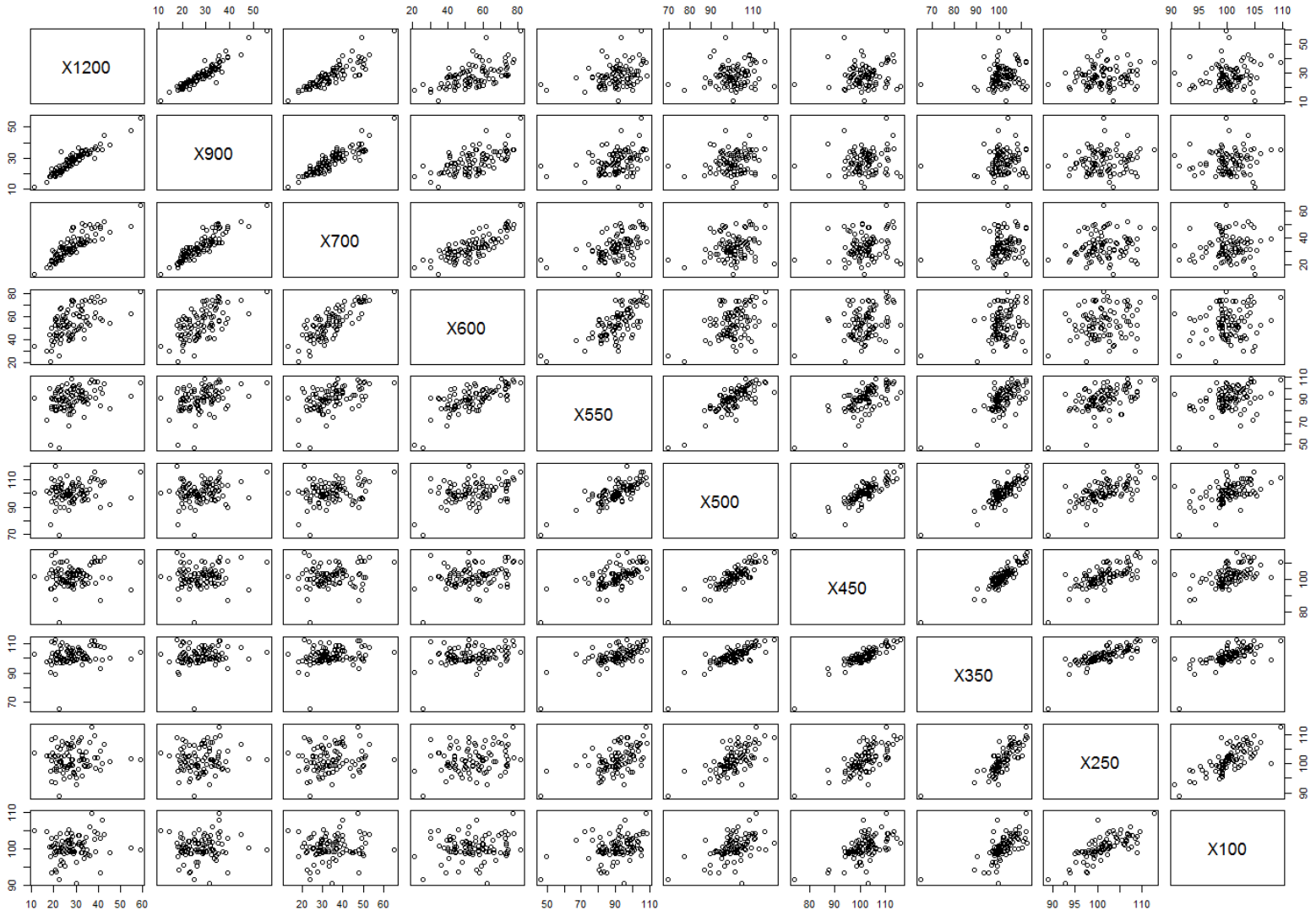




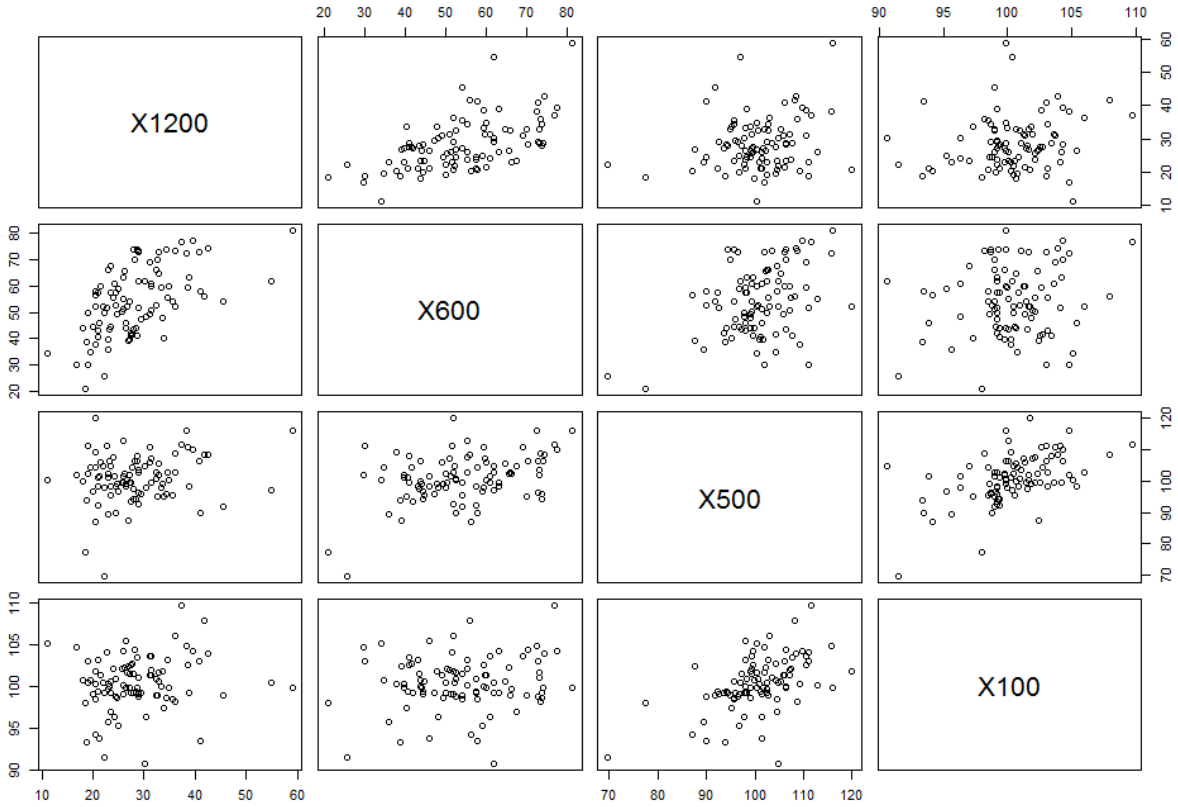



x52442
1_110_x52442_1
1_110_x52442_2
1_110_x52442_3
1_110_x52442_4
9_927_x52442_1
9_927_x52442_2
9_927_x52442_3
9_927_x52442_4
9_830_x52442_1
9_830_x52442_2
9_830_x52442_3
9_830_x52442_4
% Viability
200
150
100
50
0
−50
100
200
500
1000
Concentration (nM)

Manova using only the most uncorrelated dose response variables:



After distilled down to 4 of the least correlated variables:



New Correlation matrix:

```
          X1200      X600      X500      X100
X1200 1.0000000 0.5735777 0.2050327 0.1588358
X600  0.5735777 1.0000000 0.4065645 0.1411192
X500  0.2050327 0.4065645 1.0000000 0.5181742
X100  0.1588358 0.1411192 0.5181742 1.0000000
```

(See fig)

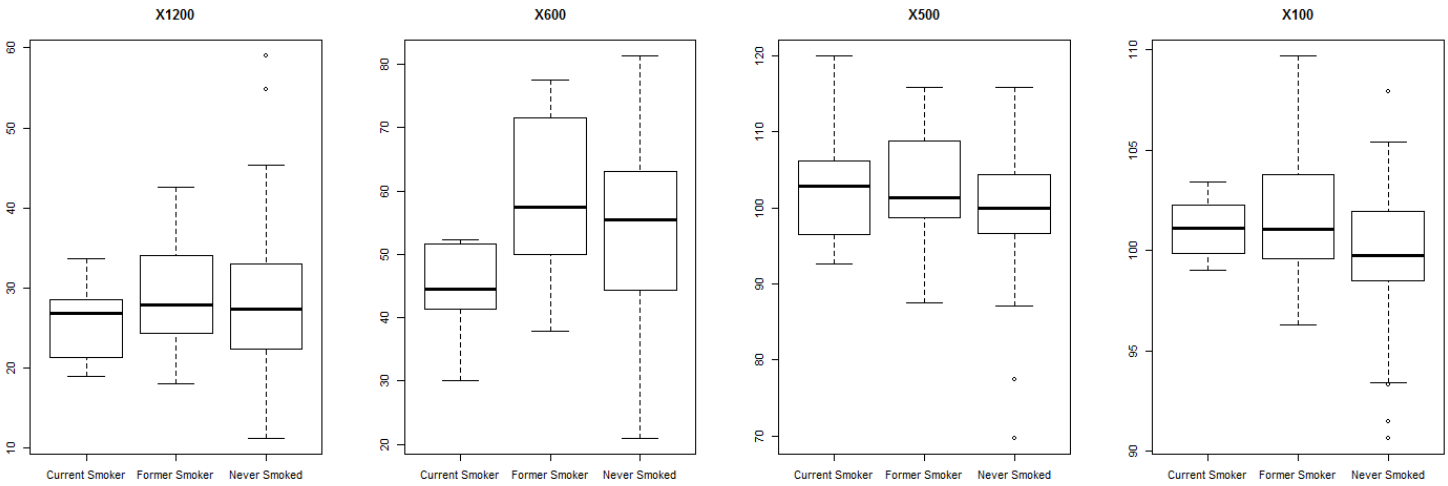
```
Multivariate Tests: Smoke
                 Df test stat approx F num Df den Df    Pr(>F)
Pillai            2 0.2308702 2.870984      8    176 0.0050083 **
Wilks             2 0.7819378 2.846490      8    174 0.0053729 **
Hotelling-Lawley  2 0.2624942 2.821812      8    172 0.0057659 **
Roy               2 0.1603322 3.527309      4     88 0.0101953 *
```

Bonferroni correction for multiple testing results in a significance level of .05/20 = .0025. This probably way too conservative though, because there are many variables that probably should not have been included in the test. And its Bonferroni.

Contrasts:

Used Bonferroni correction for multiple testing results in a significance level of .05/3 = .016

Contrast	X1200	X600	X500	X100	p-value
Former Smoker - Never Smoked	0.1695218	4.1519222	3.52787	1.898271	0.071
Former Smoker - Current Smoker	3.4979118	13.7768349	0.230579	0.413662	*0.014
Never Smoked - Current Smoker	3.32839	9.624913	-3.29729	-1.48461	*0.01

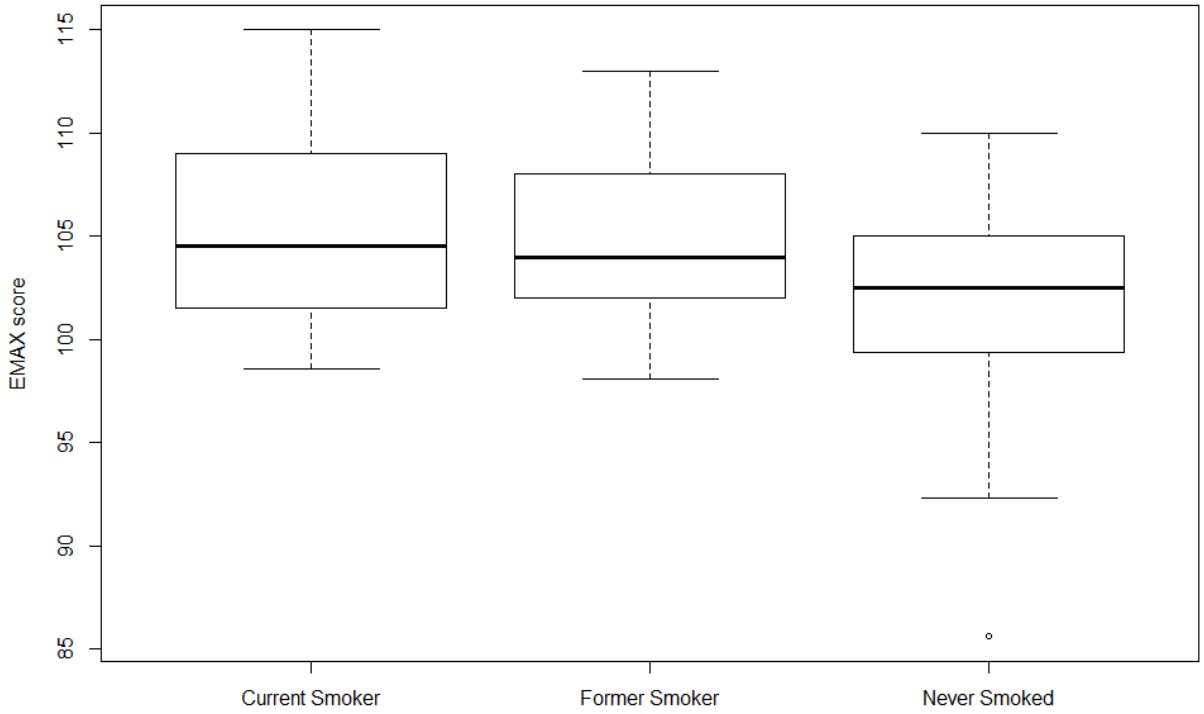


Focus on X600:

```
> summary(aov(resp2[,2]~Smoke))
            Df Sum Sq Mean Sq F value  Pr(>F)
Smoke        2   1577   788.5   5.186 0.00739 **
Residuals   90  13685   152.1
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
> TukeyHSD(aov(resp2[,2]~Smoke))
  Tukey multiple comparisons of means
    95% family-wise confidence level

Fit: aov(formula = resp2[, 2] ~ Smoke)

$Smoke
                                    diff         lwr       upr     p adj
Former Smoker-Current Smoker 13.776835   3.5816127 23.972057 0.0050232
Never Smoked-Current Smoker   9.624913   0.2466723 19.003153 0.0429193
Never Smoked-Former Smoker   -4.151922 -11.0782118  2.774367 0.3306578
```

Only significant result from John Jack's previous experiment:

```
  Tukey multiple comparisons of means
    95% family-wise confidence level

Fit: aov(formula = nocurves$EMAX_Score ~ nocurves$Smoke)

$`nocurves$Smoke`
                                   diff       lwr         upr     p adj
Former Smoker-Current Smoker -0.7222222 -4.458943  3.01449871 0.8897986
Never Smoked-Current Smoker  -3.5092593 -6.946543 -0.07197593 0.0442884
Never Smoked-Former Smoker   -2.7870370 -5.325639 -0.24843506 0.0278635
```



Conclusions:

1. The differences between the dose response profiles for people with different smoking status may not be significant if we correct for multiple testing. Pvalue: 0.034
2. When only one dose response variable is taken per group of highly correlated response variables, differences between dose response profiles will probably be significant after correction for multiple testing. Pvalue: 0.005.
3. For higher concentrations Non Smokers have higher viability than Current Smokers, while for lower concentrations, Non Smokers have lower viability. Former Smokers always have higher viability than Current Smokers, but may not have a significant difference from Non Smokers.
4. If we only look at the X600 response variable, Former Smokers and Non Smokers have higher viability than Current Smokers.

Future Directions

1. Accounting for repeated measurements in MANOVA
2. Include many grouping variables and do model selection (lasso for MANOVA)
3. Check joint normality of responses (small sample size so this is a concern)
4. Do other diagnostics on MANOVA
5. Perform Multidimensional Scaling on distance matrix that accounts for all variables used in Linear Regression to motivate machine learning approach
6. Machine learning (some tree base method that still accounts for variable importance)