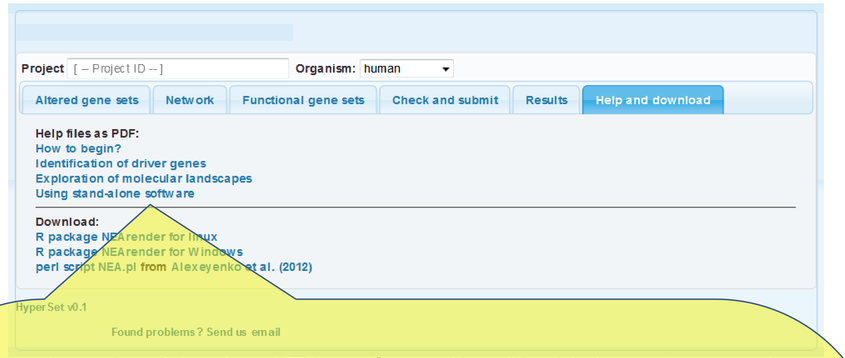
How to use stand-alone R software for NEA?

https://www.evinet.org

The same procedures that run at the web site can be more systematically implemented using the package NEArender. It contains basic functions for network and gene set enrichment analyses, creating, re-formatting, and saving gene set lists, as well as benchmarking the networks.



Download a version of R package **`NEArender`** and install it with the usual commands. The only recommendation is to install first the required package ROCR (it might be sensitive to some other dependencies):

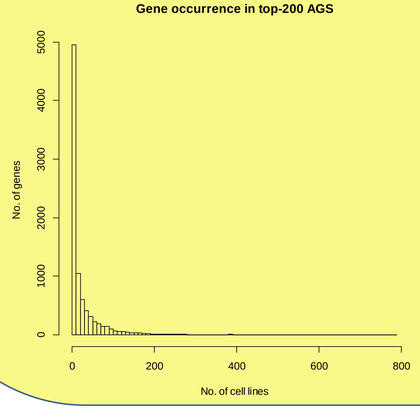
```
install.packages("ROCR");
install.packages("NEArender_1.1.zip");
library("ROCR");
library("NEArender");
```

We first could create a set of AGS that distinguish each cell line sample in the collection from the others.

```
m0 <- Data$CTD$GE$Affymetrix1
AGS<-samples2ags(m0, Ntop=200, method="top", Lowercase = 1)
save_gs_list(AGS, File="CTD.Affy1.top200.txt")
hist(table(unlist(AGS)), breaks=100, main="Gene occurrence in
top-200 AGS", xlab="No. of cell lines", ylab="No. of genes")
```

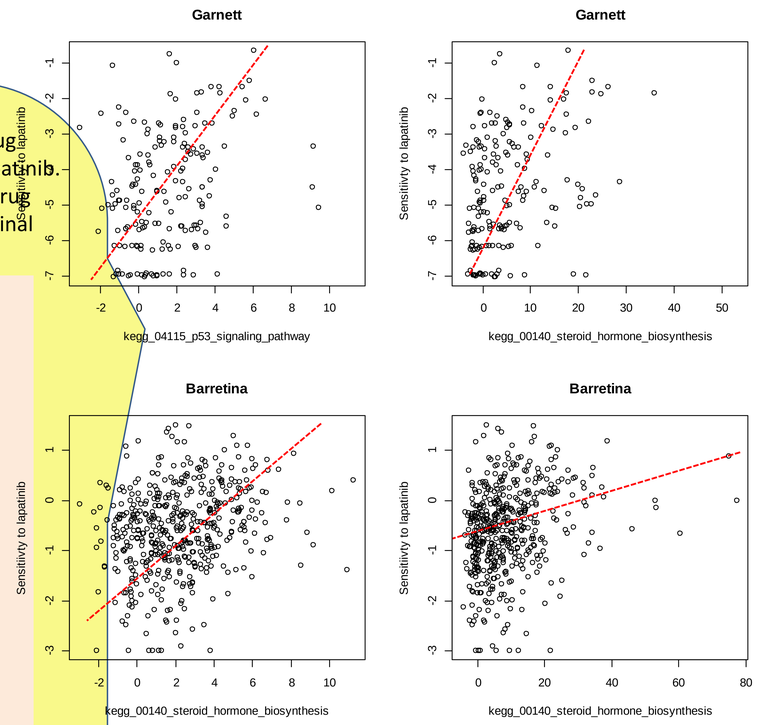
Plotting the gene frequency distribution demonstrates that the most of the genes are quite unique (below). Next, we run the network enrichment analysis, analyzing enrichment of each of these cell-line specific AGSs against each of the 330 pathways in the FGS collection:

```
FGS <- import.gs ("Related_and_CAN_MET_SIG_GO2", Lowercase=1,
col.gene = 2, col.set = 3, gs.type = 'f');
NET <- import.net("merged6_and_wir1_HC2");

Data$CTD$NEA$top.200.affymetrix1 <- nea.render(AGS = AGS, FGS =
FGS, NET = NET, echo=1, Parallelize=1);
```



We now are in the position to identify pathway-level correlates of drug sensitivity, such as these two pathways associated with resistance to lapatinib. Furthermore, this correlation can be traced between two independent drug screens (Barretina et al., 2012 and Garnett et al., 2012). While using original gene expression values, such correlation would be much weaker.

```
d1 <- "lapatinib"
sc1 <- "Garnett"; sc2 <- "Barretina";
drug1<- Data$CTD$CLIN$DRUGSCREEN[[sc1]];
drug2<- Data$CTD$CLIN$DRUGSCREEN[[sc2]];
expr <- Data$CTD$NEA$top.200.affymetrix1;
usedSamples1 <- commonIdx(drug1, expr, Dir="col")
usedSamples2 <- commonIdx(drug2, expr, Dir="col")
pw1 = "kegg_04115_p53_signaling_pathway";
pw2 = "kegg_00140_steroid_hormone_biosynthesis";

par(mfrow=c(2,2))
plot( expr[pw1,usedSamples1],
drug1[d1,usedSamples1], xlab=pw1,
ylab=paste("Sensitiivty to ", d1, sep=""),
main=sc1)
plot( expr[pw2,usedSamples1],
drug1[d1,usedSamples1], xlab=pw2,
ylab=paste("Sensitiivty to ", d1, sep=""),
main=sc1)
plot( expr[pw1,usedSamples2],
drug2[d1,usedSamples2], xlab=pw2,
ylab=paste("Sensitiivty to ", d1, sep=""),
main=sc2)
plot( expr[pw2,usedSamples2],
drug2[d1,usedSamples2], xlab=pw2,
ylab=paste("Sensitiivty to ", d1, sep=""),
main=sc2)
```



The two pathways seems to have discovered a global trend: correlation coefficients from the two drug screens correlate with each other, too.

```
plot(
cor(drug1[d1,usedSamples1],
t(expr[,usedSamples1]),
use="pairwise.complete.obs", method="spearman"),
cor(drug2[d1,usedSamples2],
t(expr[,usedSamples2]),
use="pairwise.complete.obs", method="spearman"),
main=NA, ylab="Pathway-drug correlation in
Barretina", xlab="Pathway-drug correlation in
Garnett", col=ifelse(rownames(expr) %in% c(pw1,
pw2), "red", "grey3"));
```