

Mrna, Mirna and Methylation data liver cancer, differentially expressed analysis

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R Markdown

Loading all the necessary libraries for the differentially expressed analysis of Mirna MRNA Methylation data

```
library(tidyverse)
```

```
## Warning: package 'tidyverse' was built under R version 4.3.1
```

```
## Warning: package 'forcats' was built under R version 4.3.1
```

```
## Warning: package 'lubridate' was built under R version 4.3.1
```

```
## -- Attaching core tidyverse packages ----- tidyverse 2.0.0 --
```

```
## v dplyr     1.1.2     v readr     2.1.4
```

```
## v forcats   1.0.0     v stringr   1.5.0
```

```
## v ggplot2   3.4.2     v tibble    3.2.1
```

```
## v lubridate 1.9.2     v tidyr    1.3.0
```

```
## v purrr    1.0.1
```

```
## -- Conflicts ----- tidyverse_conflicts() --
```

```
## x dplyr::filter() masks stats::filter()
```

```
## x dplyr::lag()   masks stats::lag()
```

```
## i Use the conflicted package (<http://conflicted.r-lib.org/>) to force all conflicts to become errors
```

```
library(RColorBrewer)
```

```
library(ggrepel)
```

```
## Warning: package 'ggrepel' was built under R version 4.3.1
```

```
library(DESeq2)
```

```
## Loading required package: S4Vectors
```

```
## Loading required package: stats4
```

```
## Loading required package: BiocGenerics
```

```
##
```

```
## Attaching package: 'BiocGenerics'
```

```
##
```

```
## The following objects are masked from 'package:lubridate':
```

```

##      intersect, setdiff, union
##
## The following objects are masked from 'package:dplyr':
##
##      combine, intersect, setdiff, union
##
## The following objects are masked from 'package:stats':
##
##      IQR, mad, sd, var, xtabs
##
## The following objects are masked from 'package:base':
##
##      anyDuplicated, aperm, append, as.data.frame, basename, cbind,
##      colnames, dirname, do.call, duplicated, eval, evalq, Filter, Find,
##      get, grep, grepl, intersect, is.unsorted, lapply, Map, mapply,
##      match, mget, order, paste, pmax, pmax.int, pmin, pmin.int,
##      Position, rank, rbind, Reduce, rownames, sapply, setdiff, sort,
##      table, tapply, union, unique, unsplit, which.max, which.min
##
##      second, second<-
##
## The following objects are masked from 'package:dplyr':
##
##      first, rename
##
## The following object is masked from 'package:tidyR':
##
##      expand
##
## The following object is masked from 'package:utils':
##
##      findMatches
##
## The following objects are masked from 'package:base':
##
##      expand.grid, I, unname
##
## Loading required package: IRanges
##
## Attaching package: 'IRanges'
##
## The following object is masked from 'package:lubridate':
##
##      %within%
##
## The following objects are masked from 'package:dplyr':
##
##      collapse, desc, slice

```

```

## 
## The following object is masked from 'package:purrr':
##   reduce
## 
## The following object is masked from 'package:grDevices':
##   windows
## 
## Loading required package: GenomicRanges
## Loading required package: GenomeInfoDb

## Warning: package 'GenomeInfoDb' was built under R version 4.3.1

## Loading required package: SummarizedExperiment
## Loading required package: MatrixGenerics
## Loading required package: matrixStats
## 
## Attaching package: 'matrixStats'
## 
## The following object is masked from 'package:dplyr':
## 
##   count
## 
## 
## Attaching package: 'MatrixGenerics'
## 
## The following objects are masked from 'package:matrixStats':
## 
##   colAlls, colAnyNAs, colAnys, colAvgsPerRowSet, colCollapse,
##   colCounts, colCummaxs, colCummins, colCumprods, colCumsums,
##   colDiffs, colIQRDiffs, colIQRs, colLogSumExps, colMadDiffs,
##   colMads, colMaxs, colMeans2, colMedians, colMins, colOrderStats,
##   colProds, colQuantiles, colRanges, colRanks, colSdDiffs, colSds,
##   colSums2, colTabulates, colVarDiffs, colVars, colWeightedMads,
##   colWeightedMeans, colWeightedMedians, colWeightedSds,
##   colWeightedVars, rowAlls, rowAnyNAs, rowAnys, rowAvgsPerColSet,
##   rowCollapse, rowCounts, rowCummaxs, rowCummins, rowCumprods,
##   rowCumsums, rowDiffs, rowIQRDiffs, rowIQRs, rowLogSumExps,
##   rowMadDiffs, rowMads, rowMaxs, rowMeans2, rowMedians, rowMins,
##   rowOrderStats, rowProds, rowQuantiles, rowRanges, rowRanks,
##   rowSdDiffs, rowSds, rowSums2, rowTabulates, rowVarDiffs, rowVars,
##   rowWeightedMads, rowWeightedMeans, rowWeightedMedians,
##   rowWeightedSds, rowWeightedVars
## 
## Loading required package: Biobase
## Welcome to Bioconductor
## 
##   Vignettes contain introductory material; view with
##   'browseVignettes()'. To cite Bioconductor, see
##   'citation("Biobase")', and for packages 'citation("pkgname")'.
## 
## 
## Attaching package: 'Biobase'

```

```
##  
## The following object is masked from 'package:MatrixGenerics':  
##  
##      rowMedians  
##  
## The following objects are masked from 'package:matrixStats':  
##  
##      anyMissing, rowMedians
```

```
library(data.table)
```

```
##  
## Attaching package: 'data.table'  
##  
## The following object is masked from 'package:SummarizedExperiment':  
##  
##      shift  
##  
## The following object is masked from 'package:GenomicRanges':  
##  
##      shift  
##  
## The following object is masked from 'package:IRanges':  
##  
##      shift  
##  
## The following objects are masked from 'package:S4Vectors':  
##  
##      first, second  
##  
## The following objects are masked from 'package:lubridate':  
##  
##      hour, isoweek, mday, minute, month, quarter, second, wday, week,  
##      yday, year  
##  
## The following objects are masked from 'package:dplyr':  
##  
##      between, first, last  
##  
## The following object is masked from 'package:purrr':  
##  
##      transpose
```

```
library(RTCGAToolbox)  
library(dplyr)  
library(tibble)  
'if (!require("BiocManager", quietly = TRUE))  
  install.packages("BiocManager")'
```

```
BiocManager::install("limma")'
```

```
## [1] "if (!require(\"BiocManager\"), quietly = TRUE))\n  install.packages(\"BiocManager\")\n\nBiocMan
```

```

library(limma)

## 
## Attaching package: 'limma'
## 
## The following object is masked from 'package:DESeq2':
## 
##     plotMA
## 
## The following object is masked from 'package:BiocGenerics':
## 
##     plotMA

'if (!require("BiocManager", quietly = TRUE))
  install.packages("BiocManager")

BiocManager::install("MethylMix')

## [1] "if (!require(\"BiocManager\", quietly = TRUE))\n      install.packages(\"BiocManager\")\n\nBiocMan
library(ggrepel)
library(MethylMix)
#library(DESeq2)
```

Reading the mirna and mrna files, and making the syntax of the sample names in both mirna and mrna files same as that in the survival file.

```

mirna_data<-fread("C:/Users/bless/OneDrive/MS_Studies/DS/Project pitch/liver/mirna")

## Warning in fread("C:/Users/bless/OneDrive/MS_Studies/DS/Project
## pitch/liver/mirna"): Detected 424 column names but the data has 425 columns
## (i.e. invalid file). Added 1 extra default column name for the first column
## which is guessed to be row names or an index. Use setnames() afterwards if this
## guess is not correct, or fix the file write command that created the file to
## create a valid file.

mrna_data<-fread("C:/Users/bless/OneDrive/MS_Studies/DS/Project pitch/liver/exp")

## Warning in fread("C:/Users/bless/OneDrive/MS_Studies/DS/Project
## pitch/liver/exp"): Detected 423 column names but the data has 424 columns (i.e.
## invalid file). Added 1 extra default column name for the first column which is
## guessed to be row names or an index. Use setnames() afterwards if this guess is
## not correct, or fix the file write command that created the file to create a
## valid file.

survival_data<-fread("C:/Users/bless/OneDrive/MS_Studies/DS/Project pitch/liver/survival")
#fixing sample names for mirna and mrna data
for(i in 2: length(colnames(mirna_data)))
{
  colnames(mirna_data)[i]<-gsub("\\.", "-", colnames(mirna_data)[i])
```

```

#group$sample[i]<-gsub("\\.", "-", group$sample[i])
#print(colnames(mirna)[i])
}

for(i in 2: length(colnames(mrna_data)))
{
  colnames(mrna_data)[i]<-gsub("\\.", "-", colnames(mrna_data)[i])
  #group$sample[i]<-gsub("\\.", "-", group$sample[i])
  #print(colnames(mirna)[i])
}

```

storing the common samples in the mirna and survival data in mirna_data1
 $\text{mirna_data1} \leftarrow \text{select}(\text{mirna_data}, \text{all_of}(\text{intersect}(\text{colnames}(\text{mirna_data}), \text{survival_data}[\text{PatientID}])))$
 $\text{storing the common samples in the mrna and survival data in}$
 $\text{mirna_data1} \leftarrow \text{select}(\text{mrna_data}, \text{all_of}(\text{intersect}(\text{colnames}(\text{mrna_data}), \text{survival_data}[\text{PatientID}])))$ storing the common samples in the survival data and mirna in survival_mirna

selecting the samples which are common in mirna and survival file

```

survival_mirna<-data.frame(PatientID=intersect(survival_data$PatientID,colnames(mirna_data)))
survival_mirna$Death=NA
survival_mirna$Survival=NA
survival_mirna$co=NA
for(i in survival_mirna$PatientID)
{
  for(j in survival_data$PatientID)
  {
    if(i==j)
    {
      survival_mirna$Death[survival_mirna$PatientID==i]=survival_data$Death[survival_data$PatientID==j]
      survival_mirna$Survival[survival_mirna$PatientID==i]=survival_data$Survival[survival_data$PatientID==j]
      survival_mirna$co[survival_mirna$PatientID==i]=1
    }
  }
}
#The row having no death/survival data is removed
survival_mirna$co[is.na(survival_mirna$Death) | is.na(survival_mirna$Survival) | is.na(survival_mirna$PatientID)] = 0
#Removing rows from sur data set where co == 0, i.e. those samples are not present in our methylation data
survival_mirna<-survival_mirna[survival_mirna$co!=0,]
#storing the common samples in the mirna and survival data in mirna_data1
mirna_data1<-select(mirna_data, all_of(intersect(colnames(mirna_data),survival_mirna$PatientID)))

```

selecting the samples which are common in mrna and survival file

```

survival_mrna<-data.frame(PatientID=intersect(survival_data$PatientID,colnames(mrna_data)))
survival_mrna$Death=NA
survival_mrna$Survival=NA
survival_mrna$co=NA
for(i in survival_mrna$PatientID)
{
  for(j in survival_data$PatientID)
  {
    if(i==j)
    {

```

```

survival_mrna$Death[survival_mrna$PatientID==i]=survival_data$Death[survival_data$PatientID==j]
survival_mrna$Survival[survival_mrna$PatientID==i]=survival_data$Survival[survival_data$PatientID==j]
survival_mrna$co[survival_mrna$PatientID==i]=1
}
}
}

#The row having no death/survival data is removed
survival_mrna$co[is.na(survival_mrna$Death) | is.na(survival_mrna$Survival) | is.na(survival_mrna$PatientID)] = 0
#Removing rows from sur data set where co == 0, i.e. those samples are not present in our methylation data
survival_mrna<-survival_mrna[survival_mrna$co!=0,]
#storing the common samples in the mrna and survival data in mrna_data1
mrna_data1<-select(mrna_data, all_of(intersect(colnames(mrna_data),survival_mrna$PatientID)))

```

Conducting DEseq based differentially expressed analysis on mirna data

```

#mirna_data2<-as.matrix(mirna_data1)
mirna_data2<-round(mirna_data1)
mirna_data2<-as.matrix(mirna_data2)
sur_mir<-data.frame(PatientID=survival_mirna$PatientID,Death=survival_mirna$Death)
#row.names(sur_mir)<-survival_mirna$PatientID
mirna_deseq<-DESeqDataSetFromMatrix(countData = mirna_data2[],colData = sur_mir,design = ~ Death)

## converting counts to integer mode

## the design formula contains one or more numeric variables with integer values,
## specifying a model with increasing fold change for higher values.
## did you mean for this to be a factor? if so, first convert
## this variable to a factor using the factor() function

mirna_estimate<-estimateSizeFactors(mirna_deseq)
mirna_des<-DESeq(mirna_estimate)

## using pre-existing size factors

## estimating dispersions

## gene-wise dispersion estimates

## mean-dispersion relationship

## final dispersion estimates

## fitting model and testing

## -- replacing outliers and refitting for 156 genes
## -- DESeq argument 'minReplicatesForReplace' = 7
## -- original counts are preserved in counts(dds)

## estimating dispersions

## fitting model and testing

```

```

mirna_result<-results(mirna_des)
mirna_result

## log2 fold change (MLE): Death
## Wald test p-value: Death
## DataFrame with 1046 rows and 6 columns
##   baseMean log2FoldChange      lfcSE      stat     pvalue     padj
##   <numeric>      <numeric> <numeric> <numeric> <numeric>
## 1    7968.04     -0.00671509  0.0640728 -0.1048042  0.91653117  0.9569664
## 2   15903.42     -0.00492610  0.0642372 -0.0766861  0.93887327  0.9581520
## 3    7987.47     -0.00575931  0.0640767 -0.0898815  0.92838140  0.9572729
## 4   8144.18      0.27625984  0.0888647  3.1087692  0.00187868  0.0160984
## 5   2715.71      0.04559520  0.1117975  0.4078374  0.68339303  0.8340153
## ...
## 1042   7.47337    0.0315411  0.1290511   0.244408  0.80691473  0.9002650
## 1043   12.96381   -0.0862599  0.2056755  -0.419398  0.67492533  0.8340153
## 1044   59.79467    0.1301957  0.0793693   1.640378  0.10092657  0.2833927
## 1045   959.33757   -0.1717443  0.1197870  -1.433748  0.15164426  0.3521832
## 1046  12363.42934   0.2722771  0.1030972   2.640975  0.00826679  0.0507234

mirna_result_filter <- mirna_result[which(mirna_result$padj < 0.1 & abs(mirna_result$log2FoldChange) > 1), ]
mirna_result_filter

## log2 fold change (MLE): Death
## Wald test p-value: Death
## DataFrame with 4 rows and 6 columns
##   baseMean log2FoldChange      lfcSE      stat     pvalue     padj
##   <numeric>      <numeric> <numeric> <numeric> <numeric>
## 1    2.67301     1.01941  0.287290   3.54837 3.87622e-04  0.00458687
## 2  2798.40483    -1.00064  0.264436  -3.78404 1.54306e-04  0.00213028
## 3    3.88611     -1.99312  0.504239  -3.95272 7.72674e-05  0.00132420
## 4    5.21128     -2.33709  0.669387  -3.49139 4.80512e-04  0.00555382

mirna_data3<-data.frame(V1=mirna_data$V1,mirna_data1,mirna_result)
mirna_data4<-mirna_data3[which(mirna_data3$padj < 0.1& abs(mirna_data3$log2FoldChange) > 1), ]
write.csv(mirna_data4,file = "Differ_mirna_padj0.08_log2fold0.05.csv")

```

Building volcano plot for the differentially express data, with the labeling of the up and down regulated mirna

```

mirna_data3 <- mirna_data3[!is.na(mirna_data3$padj), ]

mirna_data3$diffexp<-NaN
res_gen<-mirna_data3$V1
#res_gen
mirna_data3$names<-NaN
for(i in 1:nrow(mirna_data3))
{
  if(mirna_data3$padj[i]<0.1 & mirna_data3$log2FoldChange[i] > 1)
  {

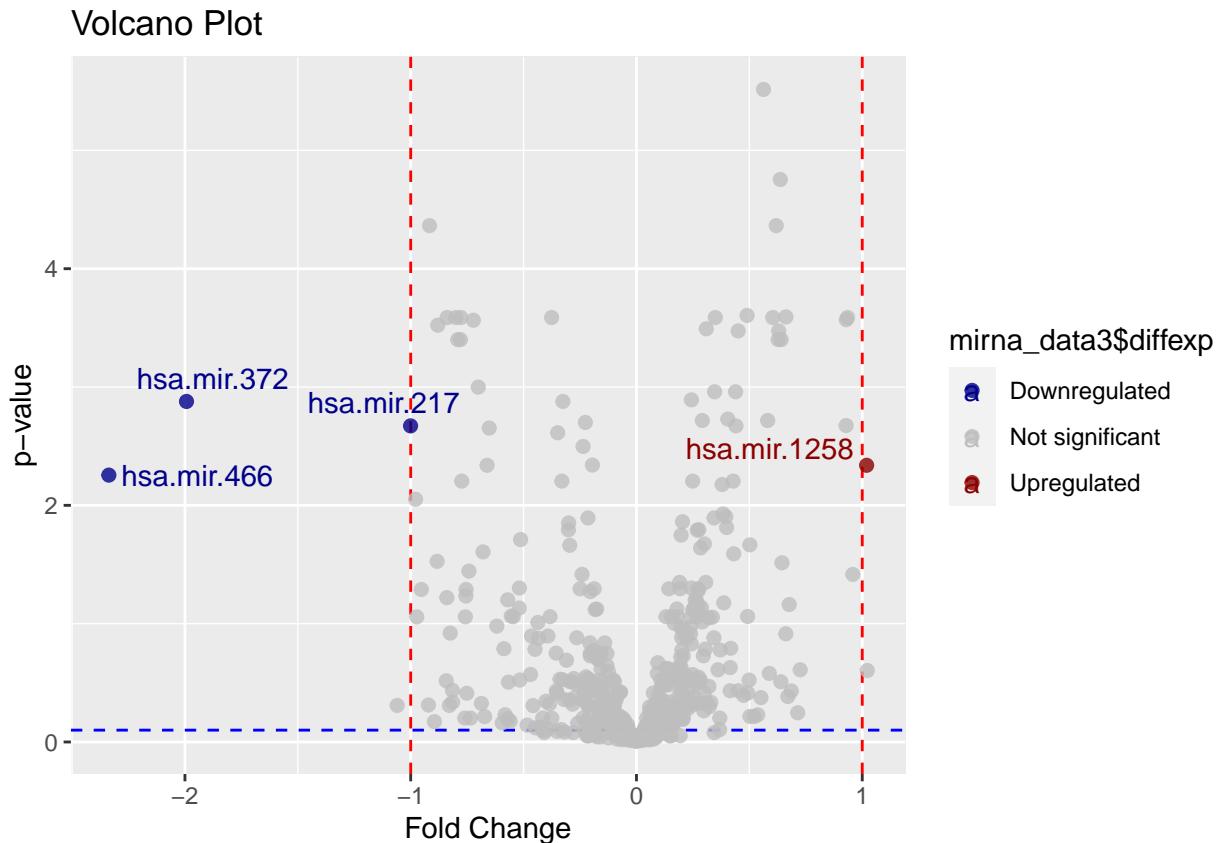
```

```

    mirna_data3$diffexp[i] <- "UP"
    mirna_data3$names[i] <- res_gen[i]
}
else if(mirna_data3$padj[i] < 0.1 & mirna_data3$log2FoldChange[i] < -1)
{
    mirna_data3$diffexp[i] <- "DOWN"
    mirna_data3$names[i] <- res_gen[i]
}
}

ggplot(data.frame(mirna_data3$log2FoldChange,mirna_data3$padj),aes(x = mirna_data3$log2FoldChange,y = -log10(mirna_data3$padj))) +
  geom_vline(xintercept = c(-1,1),col = "red", linetype ='dashed')+
  geom_hline(yintercept = 0.1,col='blue',linetype='dashed')+
  geom_point(alpha = 0.8, size = 2)+ 
  scale_color_manual(values = c("darkblue", "grey", "darkred"),
                      labels = c("Downregulated", "Not significant", "Upregulated"))+
  labs(x = "Fold Change", y = "p-value", title = "Volcano Plot")+
  geom_text_repel(aes(label = ifelse(mirna_data3$diffexp != "UP" & mirna_data3$diffexp != "DOWN", "",mirna_data3$names)))
## Warning in geom_text_repel(aes(label = ifelse(mirna_data3$diffexp != "UP" & :
## Ignoring unknown aesthetics: max.overlaps

```



Conducting Limma based differentially expressed analysis on mirna data

```

mirna_limma<-as.matrix(mirna_data1)

design_matrix<-model.matrix(~ Death, data = survival_mirna)
normalized_data <- normalizeBetweenArrays(mirna_limma, method = "quantile")
fit <- lmFit(normalized_data, design_matrix)
eb_fit <- eBayes(fit)

## Warning: Zero sample variances detected, have been offset away from zero

result_table <- topTable(eb_fit, number = 5000)

## Removing intercept from test coefficients

result_table$adj.P.Val <- p.adjust(result_table$P.Value, method = "BH")
mirna_limma1<-data.frame(V1=mirna_data$V1,mirna_data1,result_table)
result_table[which(result_table$adj.P.Val<0.05)]

```

	logFC	AveExpr	t	P.Value	adj.P.Val	B
## 626	7.697190e+01	1.742779e+02	4.108469958	4.797620e-05	0.03320276	-0.2119914
## 4	1.955712e+03	8.137665e+03	3.998189040	7.551390e-05	0.03320276	-0.6428711
## 305	-1.465534e+00	2.390099e+00	-3.933952604	9.788711e-05	0.03320276	-0.8888461
## 310	4.300961e+02	2.458275e+03	3.868673254	1.269704e-04	0.03320276	-1.1350235
## 971	-2.290481e+01	9.401237e+01	-3.748402517	2.031162e-04	0.04249190	-1.5785284
## 85	2.152300e+00	3.115652e+00	3.668362858	2.757871e-04	0.04807889	-1.8664219
## 464	2.056888e+00	5.815252e+00	3.564054476	4.074906e-04	0.06089074	-2.2328565
## 942	1.096269e-01	2.502531e-01	3.330190973	9.452307e-04	0.11756966	-3.0181692
## 734	1.191603e+00	1.769229e+00	3.299100493	1.053372e-03	0.11756966	-3.1187722
## 475	4.402405e+00	1.132682e+01	3.244961740	1.269515e-03	0.11756966	-3.2918165
## 286	9.714359e+01	2.031679e+02	3.241456493	1.284838e-03	0.11756966	-3.3029266
## 195	4.846963e+00	1.210984e+01	3.204323356	1.458012e-03	0.11756966	-3.4199207
## 478	4.695870e+00	2.257977e+01	3.192940082	1.515275e-03	0.11756966	-3.4555287
## 168	9.983701e-02	1.213909e-01	3.180798447	1.578639e-03	0.11756966	-3.4933759
## 976	-1.640568e+01	6.564743e+01	-3.161220362	1.685989e-03	0.11756966	-3.5541143
## 110	1.530194e+00	3.932414e+00	3.098506046	2.076883e-03	0.12857140	-3.7462688
## 292	-1.974594e+00	7.415521e+00	-3.096655569	2.089593e-03	0.12857140	-3.7518828
## 810	-3.475528e+02	1.621863e+03	-3.067022715	2.303121e-03	0.13383692	-3.8413465
## 311	1.957224e+02	1.294002e+03	2.962403295	3.227482e-03	0.17768138	-4.1506162
## 587	-4.683933e-01	2.647464e+00	-2.878963793	4.195621e-03	0.21533035	-4.3898964
## 243	-1.653493e+03	1.059336e+04	-2.869322143	4.323076e-03	0.21533035	-4.4171226
## 891	-3.889235e-01	1.437869e+00	-2.851413862	4.569196e-03	0.21724452	-4.4674593
## 1022	1.224574e-02	7.364554e-03	2.768148143	5.889309e-03	0.24963882	-4.6975186
## 242	-1.271660e+03	8.757397e+03	-2.757017590	6.089773e-03	0.24963882	-4.7277741
## 759	1.817487e+00	8.357789e+00	2.748427970	6.248669e-03	0.24963882	-4.7510424
## 1006	3.569627e-02	2.682091e-02	2.734115779	6.521762e-03	0.24963882	-4.7896569
## 248	5.562407e+01	3.732956e+02	2.729538124	6.611356e-03	0.24963882	-4.8019664
## 521	-3.113951e-02	2.715218e-02	-2.715703339	6.888922e-03	0.24963882	-4.8390479
## 893	9.262641e+01	2.668546e+02	2.708336655	7.040966e-03	0.24963882	-4.8587186
## 747	-2.679678e+00	1.670909e+01	-2.699744604	7.222118e-03	0.24963882	-4.8815962
## 30	7.893837e+00	2.767824e+01	2.691564526	7.398474e-03	0.24963882	-4.9033117
## 582	-2.363236e-01	1.006897e+00	-2.674583415	7.777003e-03	0.25014706	-4.9481878
## 227	2.840506e-01	6.493648e-01	2.669579157	7.891829e-03	0.25014706	-4.9613602

```

## 842 -4.791754e-01 1.921266e+00 -2.602971792 9.572064e-03 0.29448174 -5.1344150
## 474 9.605933e+00 4.799363e+01 2.586754269 1.002683e-02 0.29965890 -5.1759098
## 11 2.829618e+01 2.719453e+02 2.568025126 1.057597e-02 0.30729080 -5.2235183
## 903 4.202625e+00 7.015639e+00 2.519534385 1.212446e-02 0.34276165 -5.3452215
## 182 1.072643e+04 5.357221e+04 2.483846009 1.338976e-02 0.36857066 -5.4333553
## 284 7.706780e-01 4.421092e+00 2.463549545 1.416044e-02 0.37296878 -5.4829337
## 411 5.354399e-01 2.297687e+00 2.460361703 1.428499e-02 0.37296878 -5.4906847
## 546 -1.051773e-02 9.211281e-03 -2.451927013 1.461924e-02 0.37296878 -5.5111462
## 863 2.520646e-01 2.362327e-01 2.427658880 1.561981e-02 0.38900773 -5.5696369
## 400 -2.027898e-02 1.845998e-02 -2.393352914 1.713729e-02 0.41315687 -5.6513554
## 206 -3.024599e+01 2.429990e+02 -2.380096514 1.775757e-02 0.41315687 -5.6826298
## 439 1.109206e-01 3.371172e-01 2.377284794 1.789164e-02 0.41315687 -5.6892414
## 613 2.711487e-01 1.023283e+00 2.371517739 1.816942e-02 0.41315687 -5.7027787
## 939 1.594895e+01 8.585628e+01 2.342868587 1.960627e-02 0.43048432 -5.7695533
## 289 -1.461618e+03 2.775492e+03 -2.335129559 2.001111e-02 0.43048432 -5.7874557
## 469 3.939474e+00 3.252322e+01 2.324166312 2.059714e-02 0.43048432 -5.8127176
## 169 3.566722e-01 5.200168e-01 2.312650730 2.122881e-02 0.43048432 -5.8391276
## 288 -3.512720e+01 6.171727e+01 -2.312471796 2.123876e-02 0.43048432 -5.8395369
## 970 -4.472198e-01 2.409611e+00 -2.306562233 2.156958e-02 0.43048432 -5.8530393
## 23 5.067558e+00 1.305858e+01 2.299847397 2.195094e-02 0.43048432 -5.8683408
## 104 3.721860e-01 2.134696e+00 2.295104230 2.222386e-02 0.43048432 -5.8791231
## 155 -4.975775e-02 9.789043e-02 -2.269795206 2.373073e-02 0.44694392 -5.9362892
## 758 1.565809e+00 8.616033e+00 2.266583670 2.392816e-02 0.44694392 -5.9434990
## 236 -1.174234e-02 1.309804e-02 -2.253206605 2.476599e-02 0.44715937 -5.9734228
## 287 -3.084933e+01 5.893337e+01 -2.252755453 2.479469e-02 0.44715937 -5.9744290
## 586 -2.548031e-01 1.365317e+00 -2.237897990 2.575598e-02 0.45220644 -6.0074553
## 25 -2.019382e+01 1.618444e+02 -2.230258705 2.626273e-02 0.45220644 -6.0243534
## 293 -4.316925e-01 7.214774e-01 -2.228635553 2.637150e-02 0.45220644 -6.0279365
## 978 -1.411223e-01 2.049737e-01 -2.194301438 2.876571e-02 0.48397264 -6.1031330
## 179 -1.627868e+02 1.754853e+03 -2.189030781 2.914940e-02 0.48397264 -6.1145755
## 604 4.071894e-03 1.578102e-03 2.171998854 3.041966e-02 0.48587808 -6.1513676
## 343 2.327595e-02 3.037688e-02 2.171932417 3.042470e-02 0.48587808 -6.1515106
## 16 -1.848422e+01 1.200860e+02 -2.167374586 3.077267e-02 0.48587808 -6.1613084
## 748 -1.992824e+00 1.272339e+01 -2.162840621 3.112221e-02 0.48587808 -6.1710349
## 280 -2.639446e+00 4.297361e+00 -2.133773803 3.344532e-02 0.51034123 -6.2329176
## 309 2.849621e-01 1.883863e+00 2.131116283 3.366496e-02 0.51034123 -6.2385345
## 425 -2.512028e-02 2.837306e-02 -2.115098481 3.501520e-02 0.52322711 -6.2722448
## 480 -6.427087e+01 3.989000e+02 -2.064337021 3.960482e-02 0.58347388 -6.3774296
## 445 -1.218785e-01 5.976740e-01 -2.041568962 4.182434e-02 0.59806869 -6.4237950
## 538 1.152097e+00 5.603228e+00 2.037825082 4.219924e-02 0.59806869 -6.4313708
## 479 2.416222e-01 4.230576e-01 2.036716551 4.231079e-02 0.59806869 -6.4336114
## 314 3.964700e+02 4.711250e+03 2.026039879 4.339805e-02 0.60525813 -6.4551296
## 451 -2.378279e-02 4.764346e-02 -2.001308125 4.600791e-02 0.63321410 -6.5045491
## 728 -7.464148e+00 1.123863e+01 -1.978895263 4.848647e-02 0.64526279 -6.5488206
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## 1012 9.331286e-03 3.616431e-03 1.963079497 5.030243e-02 0.64526279 -6.5797666
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## 892 -1.480561e-01 8.207389e-01 -1.960664792 5.058465e-02 0.64526279 -6.5844699
## 745 -1.262880e+00 8.917682e+00 -1.948800311 5.199077e-02 0.64988303 -6.6074966
## 1046 2.808489e+03 1.320606e+04 1.947145611 5.218946e-02 0.64988303 -6.6106972
## 8 -3.257824e+00 2.871184e+01 -1.931512158 5.409830e-02 0.66572736 -6.6408040
## 421 1.493892e-02 2.046167e-02 1.909427735 5.689417e-02 0.67136891 -6.6829277
## 303 2.027918e+02 1.640028e+03 1.907771403 5.710864e-02 0.67136891 -6.6860678

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## 826 -6.973495e-02 1.866696e-01 -1.907312102 5.716823e-02 0.67136891 -6.6869381
## 256 2.166385e+02 1.208200e+03 1.903930246 5.760861e-02 0.67136891 -6.6933397
## 37 -1.947987e-01 4.759393e-01 -1.895964744 5.865704e-02 0.67136891 -6.7083735
## 90 5.343425e-03 3.702382e-03 1.891193028 5.929269e-02 0.67136891 -6.7173498
## 174 -3.359884e+01 6.272427e+01 -1.887619475 5.977247e-02 0.67136891 -6.7240576
## 233 2.687183e-02 4.133261e-02 1.882358194 6.048473e-02 0.67136891 -6.7339107
## 211 -1.541834e+02 1.198959e+03 -1.872405525 6.185141e-02 0.67136891 -6.7524757
## 962 -7.418561e-01 5.141784e+00 -1.870012221 6.218385e-02 0.67136891 -6.7569256
## 910 -4.868679e-02 1.440136e-01 -1.869190973 6.229826e-02 0.67136891 -6.7584512
## 847 -1.223626e-01 8.086470e-01 -1.867550318 6.252736e-02 0.67136891 -6.7614972
## 489 3.491649e-02 9.509301e-02 1.852319002 6.468781e-02 0.67136891 -6.7896489
## 240 -6.115133e+01 6.449103e+02 -1.848237127 6.527719e-02 0.67136891 -6.7971548
## 338 -5.086305e-01 3.638796e+00 -1.844010916 6.589208e-02 0.67136891 -6.8049090
## 323 -4.329594e+01 3.863816e+02 -1.843698762 6.593769e-02 0.67136891 -6.8054811
## 98 -5.073791e-03 3.683532e-03 -1.833737610 6.740679e-02 0.67136891 -6.8236855
## 181 3.653627e+02 1.836914e+03 1.828805158 6.814419e-02 0.67136891 -6.8326638
## 265 -2.849545e+01 6.357296e+01 -1.826008631 6.856522e-02 0.67136891 -6.8377436
## 696 4.461830e-03 2.619073e-03 1.822250020 6.913447e-02 0.67136891 -6.8445590
## 501 -4.427915e-02 9.997148e-02 -1.819920959 6.948916e-02 0.67136891 -6.8487753
## 322 -4.039481e+01 3.574353e+02 -1.817980241 6.978586e-02 0.67136891 -6.8522845
## 913 -8.850564e-03 8.510884e-03 -1.816955533 6.994294e-02 0.67136891 -6.8541359
## 725 -4.913852e+00 7.155138e+00 -1.816837800 6.996100e-02 0.67136891 -6.8543485
## 62 -1.398711e-02 1.678206e-02 -1.811305703 7.081424e-02 0.67337907 -6.8643253
## 160 7.942974e+00 6.904622e+01 1.777965266 7.613953e-02 0.69479886 -6.9238181
## 6 4.843691e+01 5.022204e+02 1.773402396 7.689321e-02 0.69479886 -6.9318755
## 916 9.8111181e-03 1.120419e-02 1.767905306 7.780928e-02 0.69479886 -6.9415554
## 467 -2.768900e-01 6.749313e-01 -1.767702639 7.784323e-02 0.69479886 -6.9419117
## 898 5.151566e-03 1.996540e-03 1.767143352 7.793696e-02 0.69479886 -6.9428948
## 423 2.057272e-03 7.973159e-04 1.761983313 7.880613e-02 0.69479886 -6.9519504
## 739 -3.743226e+00 1.134971e+01 -1.761384786 7.890746e-02 0.69479886 -6.9529991
## 825 -5.890599e-02 1.868852e-01 -1.756823957 7.968308e-02 0.69479886 -6.9609788
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## 721 3.488483e+02 9.811517e+02 1.741971525 8.225211e-02 0.69479886 -6.9868234
## 508 -8.775190e+00 8.614453e+01 -1.738944985 8.278379e-02 0.69479886 -6.9920633
## 599 1.964860e+01 1.523871e+01 1.738889942 8.279349e-02 0.69479886 -6.9921585
## 486 4.384584e-02 1.336776e-01 1.738129492 8.292753e-02 0.69479886 -6.9934737
## 963 2.825527e+00 2.305486e+01 1.735667703 8.336267e-02 0.69479886 -6.9977272
## 219 -6.489750e-03 3.974584e-03 -1.730712343 8.424420e-02 0.69479886 -7.0062713
## 932 -9.916288e-03 1.276822e-02 -1.729893113 8.439067e-02 0.69479886 -7.0076815
## 509 -8.533613e+00 8.416165e+01 -1.729448108 8.447031e-02 0.69479886 -7.0084472
## 619 -1.957162e+01 4.739665e+01 -1.726368359 8.502319e-02 0.69479886 -7.0137414
## 185 -4.288918e+00 2.190984e+01 -1.717163621 8.669315e-02 0.70295373 -7.0295091
## 853 4.797838e-01 1.988627e+00 1.700694160 8.974736e-02 0.71357009 -7.0575139
## 197 3.237718e+02 3.023678e+03 1.692915798 9.121976e-02 0.71357009 -7.0706477
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## 276 1.672607e+02 5.873654e+02 1.676003224 9.448849e-02 0.71357009 -7.0989998
## 488 1.201361e-01 5.910788e-01 1.675484270 9.459026e-02 0.71357009 -7.0998653
## 278 -2.274505e-01 2.003133e+00 -1.673395448 9.500078e-02 0.71357009 -7.1033464
## 418 -2.218889e-02 4.980529e-02 -1.670832157 9.550651e-02 0.71357009 -7.1076125
## 969 4.017033e-02 1.651922e-01 1.666549924 9.635621e-02 0.71481272 -7.1147248

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## 622 -1.144151e+01 1.445419e+01 -1.661186469 9.742899e-02 0.71768117 -7.1236076
## 466 -2.334988e-01 6.292115e-01 -1.639962042 1.017685e-01 0.73821752 -7.1584817
## 548 2.756364e-01 1.082532e+00 1.636268378 1.025393e-01 0.73821752 -7.1645056
## 365 1.010357e+00 5.633838e+00 1.632374366 1.033569e-01 0.73821752 -7.1708417
## 577 -1.321020e+01 3.133277e+01 -1.630910687 1.036656e-01 0.73821752 -7.1732195
## 362 4.760112e-01 3.615843e+00 1.628522091 1.041708e-01 0.73821752 -7.1770952
## 572 -4.597621e-02 1.490219e-01 -1.621409583 1.056871e-01 0.73821752 -7.1886029
## 457 8.838405e-02 3.869575e-01 1.620686489 1.058422e-01 0.73821752 -7.1897700
## 306 4.297931e+00 4.406577e+01 1.620589823 1.058629e-01 0.73821752 -7.1899260
## 463 -1.024767e-02 6.276085e-03 -1.614050475 1.072743e-01 0.74182906 -7.2004571
## 606 -6.042515e-03 5.228564e-03 -1.611635536 1.077993e-01 0.74182906 -7.2043356
## 485 1.959362e+01 9.327074e+01 1.605522844 1.091372e-01 0.74311665 -7.2141271
## 307 1.070114e+02 1.462986e+03 1.604296244 1.094072e-01 0.74311665 -7.2160874
## 258 -2.047732e+00 1.457096e+01 -1.594197663 1.116508e-01 0.74391414 -7.2321709
## 271 1.185259e-02 5.521390e-03 1.593316137 1.118484e-01 0.74391414 -7.2335702
## 1013 2.603602e+01 1.631239e+01 1.590417071 1.125000e-01 0.74391414 -7.2381663
## 422 1.566159e-03 6.069801e-04 1.588974455 1.128254e-01 0.74391414 -7.2404503
## 1003 5.942866e-02 8.586788e-02 1.587845284 1.130806e-01 0.74391414 -7.2422367
## 204 -4.980538e+00 1.016961e+01 -1.578766405 1.151493e-01 0.74767500 -7.2565537
## 372 8.456830e-02 4.418705e-01 1.577693821 1.153956e-01 0.74767500 -7.2582398
## 368 1.286377e-02 1.968561e-02 1.575350070 1.159354e-01 0.74767500 -7.2619202
## 458 6.208357e-02 2.644071e-01 1.569884094 1.172019e-01 0.74767500 -7.2704823
## 543 2.631123e-01 1.792429e+00 1.569779419 1.172263e-01 0.74767500 -7.2706460
## 1011 -2.605332e+01 5.733806e+01 -1.565528214 1.182190e-01 0.74943699 -7.2772845
## 578 3.239044e+00 5.598432e+00 1.561715890 1.191149e-01 0.75056736 -7.2832226
## 737 -1.353565e+01 3.042687e+01 -1.554945118 1.207191e-01 0.75612105 -7.2937334
## 341 1.110985e+03 1.826545e+04 1.540885624 1.241045e-01 0.76676725 -7.3154149
## 361 -1.427858e-02 2.612142e-02 -1.537448249 1.249434e-01 0.76676725 -7.3206862
## 1004 4.970938e+00 3.128774e+01 1.535714429 1.253682e-01 0.76676725 -7.3233406
## 701 -1.381530e+01 2.287014e+01 -1.532237584 1.262235e-01 0.76676725 -7.3286546
## 724 1.008551e+02 9.268931e+02 1.531600891 1.263806e-01 0.76676725 -7.3296264
## 482 5.282769e+00 4.878298e+00 1.526507531 1.276430e-01 0.76676725 -7.3373864
## 454 -7.576770e-01 4.382551e+00 -1.524105943 1.282417e-01 0.76676725 -7.3410364
## 849 -7.541383e-02 4.352029e-01 -1.523939431 1.282832e-01 0.76676725 -7.3412893
## 814 -6.235785e-01 2.124944e+00 -1.511015456 1.315433e-01 0.77210801 -7.3608321
## 685 -1.822503e-02 4.396723e-02 -1.509219676 1.320013e-01 0.77210801 -7.3635346
## 568 -7.934683e-01 2.895538e+00 -1.509132557 1.320236e-01 0.77210801 -7.3636656
## 193 -1.026571e+04 1.144144e+05 -1.508718559 1.321294e-01 0.77210801 -7.3642881
## 340 -2.091988e+03 1.549516e+04 -1.501673318 1.339397e-01 0.77833859 -7.3748562
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## 876 1.553442e-02 2.662211e-02 1.492941776 1.362100e-01 0.78283340 -7.3878859
## 382 1.696002e-02 3.623262e-02 1.486506254 1.379023e-01 0.78822859 -7.3974413
## 986 -3.770151e+00 1.172820e+01 -1.479646840 1.397240e-01 0.79136862 -7.4075810
## 366 -1.444556e-02 2.854454e-02 -1.476618396 1.405341e-01 0.79136862 -7.4120430
## 902 2.514665e-03 1.585211e-03 1.474867094 1.410043e-01 0.79136862 -7.4146191
## 865 -4.121012e+01 6.626691e+01 -1.473107133 1.414779e-01 0.79136862 -7.4172049
## 912 -6.210876e-03 3.803790e-03 -1.469725556 1.423915e-01 0.79224228 -7.4221648
## 1010 1.981213e-01 1.153574e-01 1.462465826 1.443682e-01 0.79640417 -7.4327747
## 564 2.669892e-02 6.936211e-02 1.461392264 1.446623e-01 0.79640417 -7.4343393
## 610 1.436377e-01 9.127191e-02 1.455674502 1.462364e-01 0.79643216 -7.4426529
## 506 8.240943e-01 4.460906e+00 1.452192797 1.472014e-01 0.79643216 -7.4476996
## 302 4.931811e+00 4.008783e+01 1.451929663 1.472745e-01 0.79643216 -7.4480805
## 1015 5.574964e-01 3.032901e-01 1.450353692 1.477130e-01 0.79643216 -7.4503605
## 544 2.345441e-03 1.210597e-03 1.443476059 1.496386e-01 0.80106924 -7.4602818

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## 1014  1.475631e-01 7.636367e-02  1.441102491 1.503076e-01 0.80106924 -7.4636949
## 321   7.462862e+02 8.437822e+03  1.436812077 1.515226e-01 0.80106924 -7.4698504
## 253   6.101509e-03 4.778426e-03  1.434811499 1.520917e-01 0.80106924 -7.4727144
## 516   7.351940e-03 1.010535e-02  1.433722350 1.524023e-01 0.80106924 -7.4742719
## 135   -7.290921e-02 5.251683e-01 -1.429193268 1.536988e-01 0.80317676 -7.4807362
## 731   -3.197318e+00 9.569910e+00 -1.426245002 1.545472e-01 0.80317676 -7.4849333
## 620   -1.720901e+01 3.583802e+01 -1.424307352 1.551068e-01 0.80317676 -7.4876871
## 312   7.871401e+01 7.160822e+02  1.419854381 1.563986e-01 0.80561130 -7.4940015
## 848   -3.951153e-03 2.822571e-03 -1.417389081 1.571173e-01 0.80561130 -7.4974890
## 689   -1.771462e+01 2.925691e+01 -1.409155951 1.595357e-01 0.80884635 -7.5090922
## 14    -7.902542e+02 7.097855e+03 -1.408302951 1.597879e-01 0.80884635 -7.5102905
## 811   -6.029599e+00 1.375368e+01 -1.399496915 1.624088e-01 0.80884635 -7.5226196
## 967   -3.013370e-01 9.137991e-01 -1.397209808 1.630949e-01 0.80884635 -7.5258092
## 28    3.267726e-03 2.383839e-03  1.395549362 1.635943e-01 0.80884635 -7.5281216
## 409   6.769406e-03 8.971642e-03  1.393107724 1.643308e-01 0.80884635 -7.5315169
## 1016  8.688284e-02 4.706275e-02  1.387246911 1.661088e-01 0.80884635 -7.5396430
## 1044  5.674778e+00 6.681927e+01  1.384146378 1.670553e-01 0.80884635 -7.5439282
## 31    4.512377e-02 1.691528e-01  1.382859265 1.674494e-01 0.80884635 -7.5457043
## 91    -1.339237e-02 2.926151e-02 -1.379934136 1.683477e-01 0.80884635 -7.5497347
## 380   -2.333143e-01 7.917431e-01 -1.374999124 1.698714e-01 0.80884635 -7.5565152
## 740   -1.982883e+00 4.501038e+00 -1.373891256 1.702149e-01 0.80884635 -7.5580340
## 542   -4.155982e-01 6.274089e-01 -1.370978922 1.711203e-01 0.80884635 -7.5620209
## 718   5.376594e-01 5.486185e+00  1.370232830 1.713528e-01 0.80884635 -7.5630410
## 481   1.217086e+00 1.006686e+00  1.369181957 1.716807e-01 0.80884635 -7.5644768
## 938   1.101996e+00 1.404006e+01  1.368630226 1.718531e-01 0.80884635 -7.5652301
## 344   8.282735e-03 1.339700e-02  1.360523563 1.744006e-01 0.80884635 -7.5762650
## 605   2.520614e-01 1.886943e+00  1.360364217 1.744509e-01 0.80884635 -7.5764813
## 854   4.731352e-03 4.995724e-03  1.355025680 1.761443e-01 0.80884635 -7.5837118
## 161   -7.482712e+00 5.607264e+01 -1.353190775 1.767292e-01 0.80884635 -7.5861905
## 393   -1.247990e-03 7.643190e-04 -1.351984936 1.771143e-01 0.80884635 -7.5878176
## 712   -8.241857e-01 2.420600e+00 -1.351444234 1.772872e-01 0.80884635 -7.5885467
## 440   6.316823e-02 4.609256e-01  1.348964996 1.780816e-01 0.80884635 -7.5918863
## 914   1.095495e-03 4.245700e-04  1.347692185 1.784905e-01 0.80884635 -7.5935984
## 176   1.531826e-01 3.133891e-01  1.347459838 1.785652e-01 0.80884635 -7.5939108
## 763   4.313593e-02 4.820249e-02  1.346676731 1.788172e-01 0.80884635 -7.5949632
## 566   -7.924131e-01 2.617515e+00 -1.346079548 1.790095e-01 0.80884635 -7.5957653
## 290   -1.320651e-01 5.475903e-01 -1.343093545 1.799736e-01 0.80884635 -7.5997709
## 813   2.196123e+01 2.727224e+02  1.342476574 1.801732e-01 0.80884635 -7.6005974
## 443   -4.931264e-03 4.428595e-03 -1.328787376 1.846461e-01 0.81822478 -7.6188394
## 381   7.327924e-02 4.045587e-01  1.308316992 1.914878e-01 0.81822478 -7.6457721
## 294   -9.114151e+03 1.563736e+05 -1.306265916 1.921835e-01 0.81822478 -7.6484478
## 97    1.287070e+00 8.008944e+00  1.304005882 1.929523e-01 0.81822478 -7.6513913
## 453   -1.766312e-03 1.081760e-03 -1.303932734 1.929772e-01 0.81822478 -7.6514864
## 437   -7.356399e-02 4.802824e-01 -1.297302802 1.952456e-01 0.81822478 -7.6600917
## 556   -4.202322e+00 1.379691e+01 -1.296526494 1.955125e-01 0.81822478 -7.6610964
## 565   -2.825771e+03 8.179812e+03 -1.293708233 1.964837e-01 0.81822478 -7.6647390
## 988   2.811375e-03 2.635205e-03  1.287843242 1.985161e-01 0.81822478 -7.6722943
## 377   -4.042691e-03 2.475906e-03 -1.285592385 1.993001e-01 0.81822478 -7.6751848
## 113   -2.932228e-01 2.716896e+00 -1.284373340 1.997257e-01 0.81822478 -7.6767482
## 94    -4.498193e-03 3.726996e-03 -1.283199619 2.001361e-01 0.81822478 -7.6782520
## 575   -8.523001e-01 2.058053e+00 -1.282289898 2.004547e-01 0.81822478 -7.6794167
## 817   -9.595871e-02 7.944152e-01 -1.281058972 2.008862e-01 0.81822478 -7.6809913
## 173   -1.801548e+00 3.412528e+00 -1.279828094 2.013185e-01 0.81822478 -7.6825643
## 873   2.083926e-01 4.607449e-01  1.279206214 2.015371e-01 0.81822478 -7.6833584

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## 533 -4.750836e-03 4.181252e-03 -1.276748790 2.024028e-01 0.81822478 -7.6864929
## 730 -5.517151e-01 2.160244e+00 -1.276118431 2.026253e-01 0.81822478 -7.6872960
## 828 1.089154e+00 5.476790e-01 1.275443907 2.028635e-01 0.81822478 -7.6881549
## 823 -8.727303e-01 6.375009e+00 -1.272755240 2.038154e-01 0.81822478 -7.6915741
## 134 -8.797770e-02 6.016334e-01 -1.272132213 2.040364e-01 0.81822478 -7.6923653
## 927 -7.896445e-03 1.026003e-02 -1.264892084 2.066177e-01 0.81822478 -7.7015324
## 59 -2.117418e-02 6.789920e-02 -1.264703548 2.066853e-01 0.81822478 -7.7017704
## 172 -3.719836e-01 9.281120e-01 -1.264306213 2.068277e-01 0.81822478 -7.7022719
## 567 -4.302148e-01 1.359092e+00 -1.260708668 2.081201e-01 0.81822478 -7.7068056
## 353 2.660066e-03 1.030935e-03 1.257989516 2.091008e-01 0.81822478 -7.7102237
## 408 2.015480e-03 7.811190e-04 1.257755250 2.091855e-01 0.81822478 -7.7105179
## 957 1.406776e-03 5.452099e-04 1.257176852 2.093946e-01 0.81822478 -7.7112439
## 291 -9.445848e+00 3.239343e+01 -1.257069142 2.094335e-01 0.81822478 -7.7113790
## 526 1.211427e-03 4.695004e-04 1.256784222 2.095366e-01 0.81822478 -7.7117365
## 655 1.202233e-03 4.659371e-04 1.256760908 2.095450e-01 0.81822478 -7.7117658
## 490 9.860489e-04 3.821529e-04 1.256011447 2.098164e-01 0.81822478 -7.7127057
## 657 7.785737e-04 3.017439e-04 1.254631972 2.103164e-01 0.81822478 -7.7144343
## 530 6.251198e-04 2.422713e-04 1.252620774 2.110471e-01 0.81822478 -7.7169511
## 588 5.730605e-04 2.220952e-04 1.251549693 2.114369e-01 0.81822478 -7.7182898
## 105 1.461374e-03 9.211572e-04 1.244445199 2.140360e-01 0.81822478 -7.7271408
## 644 3.791112e-04 1.469283e-04 1.243026809 2.145577e-01 0.81822478 -7.7289019
## 679 3.791112e-04 1.469283e-04 1.243026809 2.145577e-01 0.81822478 -7.7289019
## 329 1.116462e-01 4.501136e-02 1.238861449 2.160950e-01 0.81822478 -7.7340621
## 878 3.175528e-04 1.230707e-04 1.236695599 2.168974e-01 0.81822478 -7.7367384
## 392 1.437663e-02 4.598919e-02 1.236281315 2.170512e-01 0.81822478 -7.7372498
## 217 2.077914e+03 9.726152e+03 1.234960431 2.175419e-01 0.81822478 -7.7388792
## 858 -6.084684e-02 2.398657e-01 -1.229539308 2.195642e-01 0.81822478 -7.7455484
## 881 1.650192e-01 1.403687e+00 1.228983117 2.197725e-01 0.81822478 -7.7462310
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## 435 1.307080e-01 3.913672e-01 1.224438800 2.214793e-01 0.81822478 -7.7517966
## 921 -8.067965e-03 1.525407e-02 -1.222126981 2.223512e-01 0.81822478 -7.7546201
## 328 1.291555e-01 5.457787e-02 1.220382430 2.230109e-01 0.81822478 -7.7567472
## 552 -6.156942e+00 2.108780e+01 -1.220320288 2.230344e-01 0.81822478 -7.7568229
## 430 3.478691e-03 2.267630e-03 1.215030766 2.250431e-01 0.81822478 -7.7632538
## 1009 4.460305e-01 4.414338e+00 1.213951767 2.254545e-01 0.81822478 -7.7645622
## 609 3.443067e-02 1.497911e-01 1.210692338 2.267003e-01 0.81822478 -7.7685077
## 494 1.601654e-02 3.580573e-02 1.207713760 2.278432e-01 0.81822478 -7.7721039
## 441 -9.932392e-03 1.419602e-02 -1.206909362 2.281525e-01 0.81822478 -7.7730736
## 223 2.012415e+01 3.339670e+02 1.206547695 2.282917e-01 0.81822478 -7.7735094
## 491 -1.964381e+00 2.271152e+01 -1.206085030 2.284698e-01 0.81822478 -7.7740667
## 295 -1.477860e+01 1.410272e+02 -1.203517625 2.294601e-01 0.81822478 -7.7771553
## 662 1.779367e-02 5.001252e-02 1.203468643 2.294790e-01 0.81822478 -7.7772142
## 716 -1.455547e-02 2.867486e-02 -1.203440540 2.294899e-01 0.81822478 -7.7772479
## 143 1.233966e+00 1.216740e+01 1.201565512 2.302151e-01 0.81822478 -7.7794993
## 111 7.396158e-02 3.757254e-01 1.200849550 2.304925e-01 0.81822478 -7.7803581
## 1045 -9.285812e+01 9.623568e+02 -1.200156260 2.307613e-01 0.81822478 -7.7811892
## 812 -1.369644e+00 1.782974e+00 -1.194841341 2.328294e-01 0.82118564 -7.7875446
## 122 -2.391653e-01 3.611510e-01 -1.193978275 2.331665e-01 0.82118564 -7.7885740
## 177 7.370557e-02 2.536360e-01 1.189301252 2.349991e-01 0.82323547 -7.7941394
## 26 1.644016e+03 1.639102e+04 1.188478568 2.353226e-01 0.82323547 -7.7951161
## 40 -1.486248e-01 2.537699e-01 -1.182967481 2.374973e-01 0.82614339 -7.8016418
## 777 -7.938258e+00 1.017020e+01 -1.182370770 2.377336e-01 0.82614339 -7.8023465
## 776 -8.349018e+00 1.063872e+01 -1.176234823 2.401733e-01 0.82614339 -7.8095730
## 330 5.631712e-03 2.550929e-03 1.175478323 2.404753e-01 0.82614339 -7.8104613

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## 367  1.913431e-01 4.672087e-01  1.173668768 2.411989e-01 0.82614339 -7.8125840
## 503  4.020780e+00 1.017095e+01  1.171151863 2.422077e-01 0.82614339 -7.8155310
## 345  -1.401469e-02 4.505946e-02 -1.169025419 2.430624e-01 0.82614339 -7.8180159
## 356   8.309360e-03 1.916285e-02  1.168051678 2.434545e-01 0.82614339 -7.8191523
## 561  -7.731456e+00 5.600094e+00 -1.164407849 2.449257e-01 0.82614339 -7.8233965
## 208   3.146374e+01 5.116444e+02  1.162217222 2.458132e-01 0.82614339 -7.8259416
## 557  -5.371460e+00 3.424476e+00 -1.162001895 2.459006e-01 0.82614339 -7.8261916
## 29    2.554639e-02 1.227463e-01  1.161387526 2.461499e-01 0.82614339 -7.8269044
## 38    -4.606269e-02 1.731399e-01 -1.160719275 2.464214e-01 0.82614339 -7.8276793
## 896  -4.907129e-02 2.167635e-01 -1.157151295 2.478742e-01 0.82690399 -7.8318093
## 984  4.186024e-02 2.551077e-01  1.154397536 2.489996e-01 0.82690399 -7.8349882
## 616  -1.369499e-02 2.857319e-02 -1.152787621 2.496592e-01 0.82690399 -7.8368431
## 201   3.753588e-02 2.708901e-01  1.140541589 2.547166e-01 0.82690399 -7.8508689
## 1033 -1.426780e-02 4.495486e-02 -1.137497583 2.559847e-01 0.82690399 -7.8543322
## 164   2.737657e-03 1.990089e-03  1.137324518 2.560569e-01 0.82690399 -7.8545289
## 756   4.551785e+00 2.914124e+00  1.137235471 2.560941e-01 0.82690399 -7.8546300
## 460  -2.697536e+00 7.377742e+00 -1.132369363 2.581311e-01 0.82690399 -7.8601461
## 935  -7.413596e+00 6.783255e+01 -1.131876737 2.583379e-01 0.82690399 -7.8607032
## 778  -1.543473e+00 2.186795e+00 -1.129535900 2.593224e-01 0.82690399 -7.8633471
## 484  -3.278521e-03 3.139699e-03 -1.128918011 2.595826e-01 0.82690399 -7.8640441
## 597   5.205250e-04 3.268423e-04  1.127040431 2.603747e-01 0.82690399 -7.8661597
## 68   -2.209949e-03 1.353462e-03 -1.126693537 2.605212e-01 0.82690399 -7.8665502
## 17   -2.337388e+03 3.019319e+04 -1.121606771 2.626763e-01 0.82690399 -7.8722626
## 950  -8.693874e-04 5.324478e-04 -1.121489819 2.627260e-01 0.82690399 -7.8723936
## 859   2.960281e-01 3.928919e+00  1.121294228 2.628091e-01 0.82690399 -7.8726127
## 953  -5.510371e-03 7.944268e-03 -1.120541191 2.631293e-01 0.82690399 -7.8734560
## 627   1.609330e+01 2.061631e+02  1.119218416 2.636924e-01 0.82690399 -7.8749358
## 1029 -1.535968e-01 2.177376e-01 -1.116990164 2.646429e-01 0.82690399 -7.8774247
## 283  -4.603085e-03 4.439289e-03 -1.112257528 2.666694e-01 0.82690399 -7.8826946
## 768   5.771211e+00 4.322291e+00  1.111742319 2.668907e-01 0.82690399 -7.8832670
## 456  -6.527271e-02 4.027178e-01 -1.111196636 2.671252e-01 0.82690399 -7.8838729
## 766   6.001436e+00 4.383533e+00  1.109931125 2.676695e-01 0.82690399 -7.8852770
## 247  -2.451643e+01 9.078704e+01 -1.108499245 2.682864e-01 0.82690399 -7.8868637
## 3    3.119966e+02 7.828338e+03  1.106074494 2.693331e-01 0.82690399 -7.8895461
## 754  2.910603e+00 2.113264e+00  1.103642641 2.703858e-01 0.82690399 -7.8922304
## 906  -1.893106e-03 1.159414e-03 -1.103028672 2.706520e-01 0.82690399 -7.8929072
## 844  -1.756499e-02 8.369098e-02 -1.102045281 2.710788e-01 0.82690399 -7.8939904
## 1000 -1.098199e+00 2.177800e+01 -1.101968689 2.711121e-01 0.82690399 -7.8940748
## 764  3.219182e-02 4.204642e-02  1.100121123 2.719152e-01 0.82690399 -7.8961072
## 9    9.155535e+02 1.355240e+04  1.099532190 2.721715e-01 0.82690399 -7.8967543
## 354  -6.689640e-04 4.097004e-04 -1.098740671 2.725163e-01 0.82690399 -7.8976235
## 767  6.192934e+00 4.508892e+00  1.096720197 2.733978e-01 0.82690399 -7.8998395
## 171  -1.938613e+00 6.722244e+00 -1.096346842 2.735609e-01 0.82690399 -7.9002485
## 222  -7.563737e+00 1.330462e+02 -1.094617872 2.743171e-01 0.82690399 -7.9021409
## 799  -1.290098e+00 2.166867e+00 -1.090315264 2.762051e-01 0.82778840 -7.9068372
## 755  2.772492e+00 2.078065e+00  1.088248567 2.771151e-01 0.82778840 -7.9090865
## 65   5.372119e-03 8.844936e-03  1.086534533 2.778714e-01 0.82778840 -7.9109488
## 1041 -9.178964e-01 2.817903e+00 -1.086450008 2.779087e-01 0.82778840 -7.9110405
## 27   2.895546e+03 1.987633e+04  1.084048318 2.789709e-01 0.82778840 -7.9136448
## 427  -5.669745e-03 9.065448e-03 -1.081831423 2.799538e-01 0.82778840 -7.9160436
## 723  -6.862392e-01 9.278907e+00 -1.081389122 2.801502e-01 0.82778840 -7.9165216
## 827  -7.397980e-02 7.768658e-01 -1.074836639 2.830705e-01 0.83096560 -7.9235803
## 86   3.151845e+01 3.681393e+02  1.073798834 2.835350e-01 0.83096560 -7.9246944
## 273  -7.613725e+01 7.622700e+02 -1.073634136 2.836087e-01 0.83096560 -7.9248711

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## 264 -1.594680e+02 1.195130e+03 -1.065495569 2.872694e-01 0.83561183 -7.9335693
## 452 -4.936672e+01 4.986206e+02 -1.063663547 2.880978e-01 0.83561183 -7.9355182
## 342 8.033935e-01 1.620187e+00 1.061843700 2.889224e-01 0.83561183 -7.9374509
## 112 -4.731070e-02 3.325316e-01 -1.057567672 2.908660e-01 0.83561183 -7.9419790
## 1001 -2.818946e-02 6.799443e-02 -1.055324463 2.918891e-01 0.83561183 -7.9443472
## 438 1.520350e-02 7.077364e-02 1.055200656 2.919457e-01 0.83561183 -7.9444778
## 591 -1.128276e-03 6.910014e-04 -1.055077946 2.920017e-01 0.83561183 -7.9446072
## 1040 -1.214994e-02 3.689965e-02 -1.050873576 2.939264e-01 0.83561183 -7.9490313
## 889 2.210165e-02 8.916863e-02 1.048763146 2.948957e-01 0.83561183 -7.9512455
## 765 9.747730e-02 1.688299e-01 1.048568756 2.949851e-01 0.83561183 -7.9514492
## 119 -8.052193e-04 4.931487e-04 -1.045025769 2.966176e-01 0.83561183 -7.9551556
## 1024 -1.759590e+02 1.589391e+03 -1.042801054 2.976457e-01 0.83561183 -7.9574766
## 541 7.404163e-02 3.855231e-01 1.038780709 2.995098e-01 0.83561183 -7.9616584
## 603 1.096502e-02 3.609978e-02 1.037712689 3.000063e-01 0.83561183 -7.9627666
## 167 9.796353e-01 5.517068e+00 1.036471468 3.005840e-01 0.83561183 -7.9640531
## 127 3.401238e+00 2.643635e+01 1.036268631 3.006785e-01 0.83561183 -7.9642632
## 507 -2.738374e-03 2.455664e-03 -1.029251397 3.039593e-01 0.83561183 -7.9715062
## 67 -9.955701e-04 6.097271e-04 -1.023349505 3.067370e-01 0.83561183 -7.9775601
## 75 4.202900e-02 1.612733e-01 1.021454124 3.076326e-01 0.83561183 -7.9794970
## 346 -1.258900e-01 5.078144e-01 -1.021026429 3.078350e-01 0.83561183 -7.9799335
## 216 -7.459842e-01 7.523428e+00 -1.018857260 3.088626e-01 0.83561183 -7.9821448
## 221 -1.066565e+01 2.003290e+01 -1.017834824 3.093477e-01 0.83561183 -7.9831855
## 231 -2.670583e-01 1.285503e+00 -1.016019995 3.102101e-01 0.83561183 -7.9850302
## 726 8.802344e+01 3.358959e+02 1.014731554 3.108233e-01 0.83561183 -7.9863378
## 515 2.563162e-02 1.437540e-01 1.013975376 3.111835e-01 0.83561183 -7.9871044
## 326 9.242154e-01 1.001819e+01 1.013067713 3.116163e-01 0.83561183 -7.9880240
## 331 7.196886e-03 4.237054e-03 1.012597096 3.118409e-01 0.83561183 -7.9885004
## 790 -1.651350e+00 2.788600e+00 -1.012166770 3.120463e-01 0.83561183 -7.9889358
## 416 2.330563e-02 1.193700e-01 1.012106369 3.120752e-01 0.83561183 -7.9889969
## 383 -2.668205e-03 1.932294e-03 -1.009401385 3.133686e-01 0.83561183 -7.9917298
## 327 -3.940789e-01 1.814387e+00 -1.006547289 3.147372e-01 0.83561183 -7.9946053
## 743 3.116747e+00 4.278537e+00 1.005348794 3.153130e-01 0.83561183 -7.9958104
## 241 -1.6119430e+01 2.370881e+02 -1.005310860 3.153313e-01 0.83561183 -7.9958486
## 203 7.875036e-03 2.120067e-02 1.005013536 3.154742e-01 0.83561183 -7.9961473
## 50 -4.217710e-01 7.329410e-01 -1.004391557 3.157735e-01 0.83561183 -7.9967719
## 668 -5.277704e+00 2.573038e+01 -1.003822649 3.160473e-01 0.83561183 -7.9973429
## 720 -1.082124e+00 1.629093e+01 -1.001818405 3.170134e-01 0.83561183 -7.9993520
## 402 9.715247e-02 3.523806e-01 1.001704077 3.170685e-01 0.83561183 -7.9994665
## 274 8.226278e+00 2.250293e+01 1.001028437 3.173946e-01 0.83561183 -8.0001428
## 753 2.593325e+01 2.324371e+01 1.000910518 3.174516e-01 0.83561183 -8.0002607
## 792 -2.950156e+01 4.139991e+01 -0.998638351 3.185501e-01 0.83561183 -8.0025315
## 39 -1.334524e-02 2.637341e-02 -0.998232135 3.187468e-01 0.83561183 -8.0029369
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## 695 3.696734e-03 5.046664e-03 0.983240415 3.260603e-01 0.84004699 -8.0177844
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## 933 3.742619e-03 4.725231e-03 0.954992515 3.401358e-01 0.85037005 -8.0451528
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## 593 1.233034e-01 9.882259e-01 0.945617856 3.448921e-01 0.85037005 -8.0540600
## 934 -3.101138e-01 4.533053e+00 -0.945067388 3.451727e-01 0.85037005 -8.0545803
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## 395 2.380386e-03 2.170244e-03 0.940153955 3.476839e-01 0.85037005 -8.0592111
## 407 3.996313e-03 6.018076e-03 0.939180048 3.481830e-01 0.85037005 -8.0601261
## 212 8.195047e+01 7.998082e+02 0.938145842 3.487135e-01 0.85037005 -8.0610968
## 299 4.491855e-02 3.186492e-01 0.936934285 3.493357e-01 0.85037005 -8.0622326
## 213 -1.577752e+01 2.239155e+02 -0.936766472 3.494219e-01 0.85037005 -8.0623897
## 388 1.200223e-02 3.363177e-02 0.936461753 3.495785e-01 0.85037005 -8.0626751
## 187 9.413822e+00 9.501475e+01 0.931400648 3.521863e-01 0.85281210 -8.0674014
## 975 -1.626347e-03 9.960401e-04 -0.930087784 3.528647e-01 0.85281210 -8.0686232
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## 786 -1.939954e+01 2.851915e+01 -0.927497267 3.542059e-01 0.85281210 -8.0710291
## 476 -2.714436e+00 5.704788e+01 -0.925935283 3.550162e-01 0.85281210 -8.0724765
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## 246 -4.055780e-01 1.129615e+00 -0.883680669 3.773787e-01 0.87100241 -8.1107099
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## 5 1.596487e+02 2.659481e+03 0.842659952 3.999026e-01 0.87893314 -8.1461250
## 194 -7.995556e+00 2.268812e+02 -0.841055225 4.007999e-01 0.87893314 -8.1474764
## 595 1.147489e-02 1.142719e-02 0.840222775 4.012659e-01 0.87893314 -8.1481764
## 138 -6.896351e-01 2.910346e+00 -0.840192668 4.012827e-01 0.87893314 -8.1482017
## 375 1.030725e-02 3.576121e-02 0.839529876 4.016540e-01 0.87893314 -8.1487585
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## 729 4.203351e+01 2.073036e+02 0.827267753 4.085593e-01 0.88802430 -8.1589811
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## 254 5.056447e+01 6.719398e+02 0.805654326 4.209022e-01 0.88802430 -8.1766345
## 846 -1.120814e-02 6.243094e-02 -0.804502829 4.215659e-01 0.88802430 -8.1775620
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## 116 -7.671274e+00 1.500010e+02 -0.774915560 4.388295e-01 0.89651505 -8.2009389
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## 982 2.115007e-01 1.949567e+00 0.764747944 4.448550e-01 0.89815620 -8.2087708
## 569 -1.013626e+00 8.349488e+00 -0.763135519 4.458149e-01 0.89815620 -8.2100033
## 339 -3.313743e+01 8.228877e+02 -0.759711144 4.478573e-01 0.89815620 -8.2126123
## 21 3.957168e+00 1.833718e+01 0.756688629 4.496645e-01 0.89815620 -8.2149053
## 2 4.689754e+02 1.629358e+04 0.756361805 4.498602e-01 0.89815620 -8.2151528

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## 313 9.300442e+01 2.540048e+03 0.754285325 4.511044e-01 0.89815620 -8.2167221
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## 717 6.033104e-03 1.552692e-02 0.745345521 4.564835e-01 0.89921240 -8.2234297
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## 887 -1.115767e+00 2.088015e+01 -0.726717596 4.678075e-01 0.91634196 -8.2371499
## 304 -5.877930e+01 1.665235e+03 -0.725215579 4.687273e-01 0.91642758 -8.2382411
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## 202 -2.258115e-02 1.792890e-01 -0.710499205 4.777925e-01 0.92107362 -8.2488134
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## 640 -3.217942e-03 2.349908e-03 -0.709925014 4.781482e-01 0.92107362 -8.2492215
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## 470 -4.242682e+01 1.216118e+02 -0.697930455 4.856104e-01 0.92691325 -8.2576716
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## 334 -8.571435e+00 6.865786e+01 -0.686800415 4.925910e-01 0.93681843 -8.2653842
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## 483 9.412259e-02 2.321516e+00 0.659629650 5.098563e-01 0.94853037 -8.2836925
## 95 -9.532507e-03 1.688920e-02 -0.658150357 5.108054e-01 0.94853037 -8.2846681
## 87 -2.850716e+01 6.648861e+02 -0.657212803 5.114073e-01 0.94853037 -8.2852853
## 386 1.754026e-02 1.486126e-01 0.656792441 5.116774e-01 0.94853037 -8.2855618
## 207 1.298942e+01 2.825740e+02 0.655009435 5.128235e-01 0.94853037 -8.2867324
## 499 1.930183e-02 1.625217e-01 0.654442631 5.131881e-01 0.94853037 -8.2871038
## 785 -4.426562e+00 8.381536e+00 -0.654333558 5.132583e-01 0.94853037 -8.2871753
## 209 5.184859e-01 1.181410e+01 0.644903886 5.193448e-01 0.95777632 -8.2933070
## 224 6.745099e-01 4.066781e+00 0.642183928 5.211073e-01 0.95777632 -8.2950592
## 625 -5.677935e+00 1.880191e+02 -0.640506869 5.221956e-01 0.95777632 -8.2961358
## 795 -6.398656e-01 1.666306e+00 -0.640019266 5.225122e-01 0.95777632 -8.2964483
## 15 9.905888e+02 2.361913e+04 0.639065865 5.231316e-01 0.95777632 -8.2970587
## 301 -7.678240e-03 4.622671e-02 -0.637799638 5.239548e-01 0.95777632 -8.2978679
## 259 -1.514925e+01 2.499988e+02 -0.636698926 5.246710e-01 0.95777632 -8.2985700

```

```

## 946  2.188512e-02 2.182052e-01  0.619824204 5.357127e-01 0.97401846 -8.3091829
## 1028 -4.039751e-03 1.316007e-02 -0.618865455 5.363435e-01 0.97401846 -8.3097773
## 909  -1.248878e-01 2.641771e-01 -0.618837434 5.363620e-01 0.97401846 -8.3097947
## 54   1.440013e-01 2.812006e+00  0.617059245 5.375330e-01 0.97445330 -8.3108947
## 364  -3.537793e-02 3.587132e-01 -0.614159564 5.394454e-01 0.97480621 -8.3126817
## 226   1.659067e+00 2.386213e+01  0.610277288 5.420112e-01 0.97480621 -8.3150611
## 417   1.174885e-02 9.694513e-02  0.609792250 5.423322e-01 0.97480621 -8.3153573
## 261  -1.537489e+01 1.412987e+02 -0.608768094 5.430103e-01 0.97480621 -8.3159820
## 979   1.318343e-02 2.184965e-02  0.608315922 5.433098e-01 0.97480621 -8.3162575
## 183   2.697118e+01 2.402281e+02  0.608301475 5.433193e-01 0.97480621 -8.3162663
## 1042 -6.013718e-01 8.641389e+00 -0.603197188 5.467061e-01 0.97920297 -8.3193616
## 584   3.982303e-03 1.699203e-02  0.594858948 5.522610e-01 0.98512309 -8.3243621
## 989  -6.955032e-03 4.066290e-02 -0.594249479 5.526681e-01 0.98512309 -8.3247249
## 1018  1.359323e+02 6.257192e+02  0.593997067 5.528368e-01 0.98512309 -8.3248751
## 210  -8.489347e+01 1.527419e+03 -0.591973817 5.541895e-01 0.98585415 -8.3260762
## 757   7.020462e-03 1.102738e-02  0.589100192 5.561136e-01 0.98668827 -8.3277751
## 923   1.096398e-03 1.533338e-03  0.587827697 5.569667e-01 0.98668827 -8.3285248
## 200  -2.686009e+00 1.091143e+01 -0.587050151 5.574883e-01 0.98668827 -8.3289821
## 998  -7.364660e-01 1.871207e+01 -0.584917152 5.589204e-01 0.98755185 -8.3302335
## 856  -1.162163e-01 6.151588e-01 -0.581656406 5.611130e-01 0.98923945 -8.3321377
## 899  -1.308872e-02 5.511976e-02 -0.578781230 5.630499e-01 0.98923945 -8.3338079
## 424   1.443227e-03 1.899736e-03  0.578016146 5.635658e-01 0.98923945 -8.3342509
## 141  -1.580694e-01 4.151373e-01 -0.577878818 5.636584e-01 0.98923945 -8.3343304
## 518  -4.461163e-03 1.602751e-02 -0.576321192 5.647096e-01 0.98942420 -8.3352304
## 103  -2.222045e-01 1.163216e+00 -0.572648730 5.671917e-01 0.98967300 -8.3373427
## 794  -8.492264e-01 2.513061e+00 -0.570248710 5.688167e-01 0.98967300 -8.3387159
## 868  -5.941127e-03 1.639098e-02 -0.569567632 5.692782e-01 0.98967300 -8.3391045
## 1036  1.918766e-03 4.926231e-03  0.569382881 5.694035e-01 0.98967300 -8.3392098
## 615  -7.449382e-02 9.098373e-01 -0.569118996 5.695824e-01 0.98967300 -8.3393602
## 10   2.264997e+01 8.801104e+02  0.567633208 5.705901e-01 0.98977983 -8.3402057
## 184   6.412173e+01 1.255269e+03  0.562975966 5.737544e-01 0.99240084 -8.3428417
## 100  -7.141076e+01 6.493578e+02 -0.562617044 5.739986e-01 0.99240084 -8.3430440
## 888  -1.915206e-01 1.121695e+00 -0.553472673 5.802370e-01 1.00000000 -8.3481533
## 907   8.039751e-03 6.599758e-02  0.548902684 5.833666e-01 1.00000000 -8.3506754
## 369  -3.408811e-03 1.230856e-02 -0.548790489 5.834435e-01 1.00000000 -8.3507371
## 513  -5.150347e-01 1.072267e+01 -0.547499380 5.843291e-01 1.00000000 -8.3514457
## 573  -1.536016e+00 2.569945e+01 -0.547240566 5.845068e-01 1.00000000 -8.3515875
## 781  -4.612784e+00 1.291984e+01 -0.546663382 5.849029e-01 1.00000000 -8.3519036
## 690   1.351176e-03 2.307068e-03  0.544331185 5.865051e-01 1.00000000 -8.3531775
## 133   2.155172e-03 3.906459e-03  0.542334779 5.878781e-01 1.00000000 -8.3542636
## 925   1.365158e-01 6.066721e-01  0.536165181 5.921308e-01 1.00000000 -8.3575949
## 32    3.081939e-03 7.725717e-03  0.534025699 5.936088e-01 1.00000000 -8.3587412
## 1025  1.004192e+03 2.112582e+04  0.528941884 5.971277e-01 1.00000000 -8.3614467
## 139   2.110336e-01 5.038982e+00  0.526695804 5.986854e-01 1.00000000 -8.3626338
## 549  -1.024303e-02 1.016893e-01 -0.525416274 5.995736e-01 1.00000000 -8.3633078
## 800   2.526447e-01 7.557593e-01  0.522558725 6.015594e-01 1.00000000 -8.3648071
## 722   1.682546e+01 2.889305e+02  0.519253015 6.038603e-01 1.00000000 -8.3665314
## 405   5.884000e-03 3.186637e-02  0.518374857 6.044722e-01 1.00000000 -8.3669876
## 495  -2.348436e-03 5.652296e-03 -0.518144258 6.046329e-01 1.00000000 -8.3671073
## 816   9.108544e-03 6.148322e-02  0.516569640 6.057310e-01 1.00000000 -8.3679230
## 806   1.518355e-02 5.203855e-02  0.512110021 6.088456e-01 1.00000000 -8.3702199
## 505   3.308432e-01 7.443275e+00  0.506962872 6.124493e-01 1.00000000 -8.3728462
## 798  -1.470236e+00 4.830834e+00 -0.505510229 6.134681e-01 1.00000000 -8.3735826
## 61    5.585652e-03 3.918757e-02  0.491762117 6.231468e-01 1.00000000 -8.3804475

```

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## 879  1.442024e-03 2.915388e-03  0.490423168 6.240929e-01 1.00000000 -8.3811059
## 809  4.629526e-01 1.698042e+00  0.490127877 6.243017e-01 1.00000000 -8.3812509
## 803  -3.267722e-01 1.266530e+00 -0.487779362 6.259630e-01 1.00000000 -8.3824009
## 741   7.094375e-01 2.252243e+01  0.485987197 6.272320e-01 1.00000000 -8.3832747
## 66   -7.181924e-03 4.246884e-02 -0.485385316 6.276584e-01 1.00000000 -8.3835674
## 387  -2.644253e-02 3.920840e-01 -0.484921637 6.279870e-01 1.00000000 -8.3837927
## 783  -2.109929e-02 8.324494e-02 -0.484154260 6.285310e-01 1.00000000 -8.3841651
## 88   1.365732e+00 3.495001e+01  0.481077775 6.307140e-01 1.00000000 -8.3856519
## 373   6.676742e-03 3.977583e-02  0.480446013 6.311627e-01 1.00000000 -8.3859561
## 517  -3.802109e-03 1.606730e-02 -0.479835157 6.315967e-01 1.00000000 -8.3862498
## 585   8.433638e-03 5.278418e-02  0.477795739 6.330464e-01 1.00000000 -8.3872277
## 504   1.866694e-03 6.255927e-03  0.477744582 6.330828e-01 1.00000000 -8.3872522
## 774  -1.384576e+00 4.015098e+00 -0.475436571 6.347252e-01 1.00000000 -8.3883538
## 1027  2.966467e+02 6.436938e+03  0.474215143 6.355952e-01 1.00000000 -8.3889346
## 884   2.025949e-02 1.301782e-01  0.470877561 6.379748e-01 1.00000000 -8.3905141
## 1017  1.214436e+02 6.601544e+02  0.470073891 6.385484e-01 1.00000000 -8.3908927
## 634   -3.310469e-04 4.146762e-04 -0.469743139 6.387845e-01 1.00000000 -8.3910484
## 974   -2.900341e-02 4.229440e-01 -0.466527515 6.410820e-01 1.00000000 -8.3925559
## 752   1.229670e-02 3.013978e-02  0.460138866 6.456568e-01 1.00000000 -8.3955204
## 107   -1.376792e-03 3.979419e-03 -0.459817629 6.458872e-01 1.00000000 -8.3956684
## 455   -3.611279e-02 6.936721e-01 -0.453008417 6.507787e-01 1.00000000 -8.3987808
## 883   3.022761e-03 1.321020e-02  0.451204468 6.520772e-01 1.00000000 -8.3995976
## 983   5.556929e-01 1.840911e+01  0.447802473 6.545287e-01 1.00000000 -8.4011292
## 237   -6.866846e-03 6.993846e-02 -0.444566110 6.568644e-01 1.00000000 -8.4025754
## 473   1.091265e+00 3.996703e+01  0.442902412 6.580664e-01 1.00000000 -8.4033147
## 574   -1.555129e+02 1.281023e+03 -0.442183834 6.585858e-01 1.00000000 -8.4036332
## 238   1.935615e-02 1.687434e-01  0.439243667 6.607129e-01 1.00000000 -8.4049310
## 406   1.974391e-03 6.294572e-03  0.432663043 6.654837e-01 1.00000000 -8.4078042
## 260   -1.279018e+01 1.564701e+02 -0.431907332 6.660324e-01 1.00000000 -8.4081314
## 124   -7.750785e-03 5.695300e-02 -0.431016112 6.666798e-01 1.00000000 -8.4085165
## 702   -7.113248e-04 9.997399e-04 -0.427938491 6.689172e-01 1.00000000 -8.4098404
## 77   -2.291215e-03 1.329744e-02 -0.425154334 6.709439e-01 1.00000000 -8.4110298
## 404   -7.824559e-03 7.488179e-02 -0.424643268 6.713162e-01 1.00000000 -8.4112473
## 384   7.352856e-04 1.496258e-03  0.424432872 6.714694e-01 1.00000000 -8.4113367
## 396   3.211668e-02 7.274434e-01  0.417129550 6.767987e-01 1.00000000 -8.4144147
## 1043  -9.852929e-01 1.422911e+01 -0.412142540 6.804471e-01 1.00000000 -8.4164857
## 337   -2.234273e+01 7.494676e+02 -0.409586410 6.823201e-01 1.00000000 -8.4175376
## 547   -6.838531e-04 1.404868e-03 -0.408385857 6.832004e-01 1.00000000 -8.4180294
## 869   8.154076e-02 2.254908e+00  0.404492633 6.860583e-01 1.00000000 -8.4196143
## 96   -6.259859e-04 1.712632e-03 -0.404204648 6.862698e-01 1.00000000 -8.4197309
## 520   5.206053e-02 1.550423e-01  0.401606413 6.881798e-01 1.00000000 -8.4207795
## 199  -1.403746e-01 7.792399e-01 -0.401278120 6.884213e-01 1.00000000 -8.4209115
## 545   -1.337468e-02 2.504389e-01 -0.401203420 6.884762e-01 1.00000000 -8.4209415
## 733   3.319953e-02 3.046241e-01  0.400294703 6.891448e-01 1.00000000 -8.4213062
## 436   -1.071269e-02 1.632223e-01 -0.398009465 6.908273e-01 1.00000000 -8.4222199
## 602   -1.580692e-02 1.782465e-01 -0.394851705 6.931546e-01 1.00000000 -8.4234737
## 228   -1.718669e-01 4.337473e+00 -0.389558873 6.970620e-01 1.00000000 -8.4255530
## 1008  -1.352900e+01 4.341473e+02 -0.388167840 6.980903e-01 1.00000000 -8.4260948
## 188   -9.296755e+01 1.865049e+03 -0.388082386 6.981535e-01 1.00000000 -8.4261280
## 157   1.562927e-02 4.478100e-02  0.387958412 6.982451e-01 1.00000000 -8.4261762
## 563   -2.752744e+00 1.049297e+02 -0.387487762 6.985932e-01 1.00000000 -8.4263590
## 76    3.047727e-01 2.227099e+00  0.386184734 6.995572e-01 1.00000000 -8.4268639
## 797  -1.427105e+00 6.356247e+00 -0.386045914 6.996599e-01 1.00000000 -8.4269176
## 180   1.082345e+01 5.141908e+01  0.383065726 7.018666e-01 1.00000000 -8.4280655

```

```

## 262 7.208778e+01 3.412232e+02 0.380927884 7.034511e-01 1.00000000 -8.4288835
## 621 -1.200645e+00 1.271988e+01 -0.380699056 7.036208e-01 1.00000000 -8.4289708
## 550 -5.215354e-03 1.769994e-02 -0.380162616 7.040186e-01 1.00000000 -8.4291752
## 234 2.898371e-01 1.612352e+00 0.380076996 7.040821e-01 1.00000000 -8.4292078
## 56 -1.699975e-03 5.972760e-03 -0.379887547 7.042227e-01 1.00000000 -8.4292799
## 459 6.609081e-03 7.485713e-02 0.378641413 7.051472e-01 1.00000000 -8.4297533
## 389 -8.943136e-03 1.194432e-01 -0.373321804 7.090990e-01 1.00000000 -8.4317567
## 394 -1.136700e-03 2.762751e-03 -0.371346796 7.105682e-01 1.00000000 -8.4324932
## 555 4.222232e-03 3.967738e-02 0.370544091 7.111656e-01 1.00000000 -8.4327915
## 159 5.570288e+01 2.310335e+03 0.368903268 7.123874e-01 1.00000000 -8.4333992
## 554 -1.661727e-02 4.202532e-01 -0.366766136 7.139798e-01 1.00000000 -8.4341866
## 789 -7.023507e-01 2.894884e+00 -0.366650870 7.140658e-01 1.00000000 -8.4342289
## 336 -7.398825e+02 2.485497e+04 -0.363147688 7.166789e-01 1.00000000 -8.4355094
## 376 1.134737e-02 2.095865e-01 0.359282573 7.195659e-01 1.00000000 -8.4369079
## 589 -1.408269e-03 4.293706e-03 -0.356548580 7.216104e-01 1.00000000 -8.4378881
## 63 4.096426e-03 2.314271e-02 0.355608648 7.223138e-01 1.00000000 -8.4382233
## 433 1.159296e-02 2.290266e-01 0.354101440 7.234422e-01 1.00000000 -8.4387591
## 715 -1.428137e-02 2.003764e-01 -0.348766350 7.274411e-01 1.00000000 -8.4406372
## 524 5.860952e-02 1.510690e+00 0.342706196 7.319925e-01 1.00000000 -8.4427360
## 412 8.793312e-03 7.456134e-02 0.342544546 7.321140e-01 1.00000000 -8.4427915
## 714 1.831380e-03 8.304860e-03 0.342095393 7.324518e-01 1.00000000 -8.4429455
## 838 1.680805e-05 6.514125e-06 0.341415659 7.329630e-01 1.00000000 -8.4431782
## 598 2.315912e-02 6.021298e-01 0.339918404 7.340894e-01 1.00000000 -8.4436891
## 1030 7.489296e-02 1.327545e+00 0.337465935 7.359358e-01 1.00000000 -8.4445212
## 71 2.148900e-03 1.055792e-02 0.337445315 7.359513e-01 1.00000000 -8.4445282
## 704 -6.810663e-04 1.258713e-03 -0.335756799 7.372234e-01 1.00000000 -8.4450975
## 937 5.048076e-02 2.043763e+00 0.335098388 7.377197e-01 1.00000000 -8.4453187
## 462 9.527633e-01 4.461573e+01 0.334773039 7.379649e-01 1.00000000 -8.4454279
## 922 -1.691707e-02 1.861561e-01 -0.330246159 7.413801e-01 1.00000000 -8.4469357
## 205 1.327810e+01 2.705391e+02 0.328460622 7.427286e-01 1.00000000 -8.4475248
## 787 -2.574730e+00 1.313348e+01 -0.328375862 7.427926e-01 1.00000000 -8.4475527
## 750 2.511235e+00 9.693000e+01 0.326735298 7.440323e-01 1.00000000 -8.4480910
## 117 2.331688e+00 9.536917e+01 0.326607130 7.441292e-01 1.00000000 -8.4481329
## 843 1.471438e-02 3.450903e-01 0.324518418 7.457086e-01 1.00000000 -8.4488141
## 947 -2.681580e-04 5.801439e-04 -0.321573641 7.479371e-01 1.00000000 -8.4497671
## 114 -6.188804e-03 8.791384e-02 -0.317641331 7.509163e-01 1.00000000 -8.4510261
## 374 -5.149032e-03 6.989417e-02 -0.315028479 7.528979e-01 1.00000000 -8.4518541
## 945 -1.216294e-03 3.664273e-03 -0.313614897 7.539706e-01 1.00000000 -8.4522992
## 732 1.643054e-02 2.280934e-01 0.305421901 7.601975e-01 1.00000000 -8.4548395
## 60 -2.384728e-03 1.913778e-02 -0.305054674 7.604770e-01 1.00000000 -8.4549518
## 539 3.996981e-02 1.047916e+00 0.303588281 7.615933e-01 1.00000000 -8.4553989
## 297 1.367580e+01 2.002586e+02 0.302444888 7.624640e-01 1.00000000 -8.4557460
## 511 3.864952e-02 9.390389e-01 0.299227881 7.649155e-01 1.00000000 -8.4567155
## 83 5.522242e-03 1.011816e-01 0.294616027 7.684341e-01 1.00000000 -8.4580873
## 796 -3.083377e-01 1.690505e+00 -0.290388964 7.716633e-01 1.00000000 -8.4593259
## 735 5.109971e-02 2.210948e+00 0.289227535 7.725513e-01 1.00000000 -8.4596631
## 822 7.225585e-04 2.472007e-03 0.285074157 7.757291e-01 1.00000000 -8.4608579
## 257 2.455018e+00 6.471457e+01 0.284168054 7.764229e-01 1.00000000 -8.4611163
## 399 3.228482e-03 3.998578e-02 0.283262018 7.771168e-01 1.00000000 -8.4613738
## 398 6.884317e-03 1.520575e-01 0.279939964 7.796626e-01 1.00000000 -8.4623110
## 239 6.793465e+02 4.682471e+04 0.270969689 7.865487e-01 1.00000000 -8.4647864
## 102 -9.782717e-02 1.139654e+00 -0.267810981 7.889775e-01 1.00000000 -8.4656388
## 390 1.109423e-03 4.294442e-03 0.267113797 7.895138e-01 1.00000000 -8.4658256
## 468 -4.071858e-01 1.932060e+01 -0.262545984 7.930304e-01 1.00000000 -8.4670376

```

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## 170 -3.235479e+01 4.125138e+02 -0.261319509 7.939754e-01 1.00000000 -8.4673594
## 277 -1.060355e-01 1.281158e+00 -0.258855751 7.958745e-01 1.00000000 -8.4680014
## 442 -1.968966e-03 1.683553e-02 -0.258606795 7.960665e-01 1.00000000 -8.4680659
## 379 2.774110e-03 3.769441e-02 0.257753556 7.967245e-01 1.00000000 -8.4682866
## 1026 7.596366e-01 2.024971e+01 0.256094535 7.980044e-01 1.00000000 -8.4687136
## 951 -1.064738e-02 2.769862e-01 -0.253310607 8.001533e-01 1.00000000 -8.4694240
## 780 1.932178e-01 1.431966e+00 0.252233670 8.009850e-01 1.00000000 -8.4696967
## 156 5.526188e-02 1.234023e+00 0.250378803 8.024180e-01 1.00000000 -8.4701637
## 414 7.850531e-03 1.880631e-01 0.249982695 8.027241e-01 1.00000000 -8.4702630
## 618 -2.364291e-03 2.668355e-02 -0.243586894 8.076708e-01 1.00000000 -8.4718443
## 808 -7.213738e+00 4.720216e+01 -0.241271840 8.094632e-01 1.00000000 -8.4724066
## 128 1.739246e-02 6.871202e-01 0.239813695 8.105927e-01 1.00000000 -8.4727580
## 772 1.274636e+00 7.455790e+00 0.233123949 8.157798e-01 1.00000000 -8.4743428
## 851 2.357346e-03 3.508957e-02 0.232726827 8.160879e-01 1.00000000 -8.4744355
## 131 -9.093375e-02 9.701515e-01 -0.228002206 8.197565e-01 1.00000000 -8.4755259
## 371 2.601967e-03 2.404751e-02 0.227935978 8.198079e-01 1.00000000 -8.4755411
## 861 -4.522531e-04 1.960141e-03 -0.221520810 8.247956e-01 1.00000000 -8.4769854
## 514 7.089234e-03 1.590755e-01 0.213870562 8.307527e-01 1.00000000 -8.4786540
## 744 -6.984289e+00 4.200826e+02 -0.207452728 8.357578e-01 1.00000000 -8.4800085
## 820 2.977338e-03 4.301432e-02 0.206084376 8.368258e-01 1.00000000 -8.4802920
## 901 2.247740e-01 2.549420e+01 0.204174745 8.383167e-01 1.00000000 -8.4806845
## 850 -1.850566e-02 7.285487e-01 -0.203145026 8.391210e-01 1.00000000 -8.4808946
## 779 2.593939e-01 2.254496e+00 0.196710238 8.441503e-01 1.00000000 -8.4821835
## 51 1.862831e-03 2.690600e-02 0.196410029 8.443851e-01 1.00000000 -8.4822426
## 958 5.440379e-04 2.016672e-03 0.193033923 8.470266e-01 1.00000000 -8.4829013
## 74 2.814166e-02 1.936042e+00 0.190845747 8.487395e-01 1.00000000 -8.4833221
## 80 -1.017846e-02 4.078718e-01 -0.190622956 8.489139e-01 1.00000000 -8.4833647
## 527 -4.389659e-03 1.035586e-01 -0.189683976 8.496492e-01 1.00000000 -8.4835436
## 391 -2.382301e-03 4.284665e-02 -0.189562961 8.497440e-01 1.00000000 -8.4835666
## 885 1.435906e+00 1.483972e+02 0.188465610 8.506035e-01 1.00000000 -8.4837744
## 279 3.689188e-03 1.933364e-02 0.188074818 8.509097e-01 1.00000000 -8.4838481
## 413 8.983389e-03 4.995536e-01 0.187544744 8.513249e-01 1.00000000 -8.4839478
## 214 1.211390e-01 5.266605e+00 0.185427716 8.529839e-01 1.00000000 -8.4843434
## 300 -1.754593e-02 1.059218e+00 -0.179569241 8.575781e-01 1.00000000 -8.4854146
## 215 -5.781977e-01 3.551337e+01 -0.178866472 8.581296e-01 1.00000000 -8.4855408
## 363 -3.231068e-03 8.020657e-02 -0.178692384 8.582662e-01 1.00000000 -8.4855720
## 1039 8.917653e-02 6.270639e+00 0.177604093 8.591203e-01 1.00000000 -8.4857662
## 594 -1.353092e-03 1.909596e-02 -0.175440884 8.608185e-01 1.00000000 -8.4861488
## 13 -3.075879e-01 1.097947e+01 -0.170922066 8.643681e-01 1.00000000 -8.4869329
## 727 6.815565e-01 8.162495e+01 0.170856585 8.644196e-01 1.00000000 -8.4869441
## 44 3.011687e-04 1.211364e-03 0.170315397 8.648449e-01 1.00000000 -8.4870366
## 397 -1.475383e-03 2.872705e-02 -0.163072435 8.705405e-01 1.00000000 -8.4882463
## 977 1.389036e-02 3.981722e-01 0.162298158 8.711498e-01 1.00000000 -8.4883725
## 93 2.053505e-02 7.888419e-01 0.161332753 8.719096e-01 1.00000000 -8.4885290
## 355 -7.333310e-04 6.755044e-03 -0.158151033 8.744145e-01 1.00000000 -8.4890382
## 997 -9.908921e-03 4.537897e-01 -0.157336472 8.750560e-01 1.00000000 -8.4891670
## 895 6.586538e-01 5.828827e+01 0.154077780 8.776231e-01 1.00000000 -8.4896754
## 360 2.015237e-03 3.395915e-02 0.152605406 8.787834e-01 1.00000000 -8.4899016
## 908 2.434988e-01 1.795538e+01 0.150958598 8.800815e-01 1.00000000 -8.4901520
## 136 -7.536359e-03 1.052390e-01 -0.150918531 8.801131e-01 1.00000000 -8.4901581
## 864 3.065506e-01 8.843355e+00 0.150812747 8.801965e-01 1.00000000 -8.4901741
## 831 4.716380e-04 3.257880e-03 0.146713820 8.834289e-01 1.00000000 -8.4907850
## 403 1.140841e-03 1.972692e-02 0.146137911 8.838833e-01 1.00000000 -8.4908695
## 492 -7.704308e-02 5.154280e+00 -0.144524121 8.851566e-01 1.00000000 -8.4911045

```

```

## 872   1.715244e-03 3.158967e-02  0.142558340 8.867080e-01 1.00000000 -8.4913872
## 614   8.124800e-03 5.938976e-01  0.140197212 8.885720e-01 1.00000000 -8.4917217
## 129  -7.575817e-04 1.106586e-02 -0.139611357 8.890346e-01 1.00000000 -8.4918038
## 123  -6.864338e-03 3.902716e-01 -0.138511492 8.899032e-01 1.00000000 -8.4919571
## 949  -8.848193e-03 4.863080e-01 -0.137581367 8.906378e-01 1.00000000 -8.4920857
## 770  -8.064850e-02 9.962698e-01 -0.134321034 8.932136e-01 1.00000000 -8.4925298
## 596   1.814914e-03 6.129277e-02  0.133571482 8.938060e-01 1.00000000 -8.4926304
## 434  -5.002060e-03 1.958392e-01 -0.132179800 8.949059e-01 1.00000000 -8.4928157
## 444  -2.073324e-03 6.731733e-02 -0.131691678 8.952918e-01 1.00000000 -8.4928802
## 49   -2.094711e+02 2.576537e+04 -0.130774747 8.960167e-01 1.00000000 -8.4930008
## 55  -1.576811e-02 7.988789e-01 -0.128308108 8.979671e-01 1.00000000 -8.4933210
## 890  -1.219722e-02 1.098263e+00 -0.127192384 8.988496e-01 1.00000000 -8.4934638
## 771  -7.854920e-02 9.725630e-01 -0.125936173 8.998433e-01 1.00000000 -8.4936231
## 385   1.448962e-03 4.438580e-02  0.125604091 9.001060e-01 1.00000000 -8.4936649
## 432  -8.616103e-04 1.300373e-02 -0.123175753 9.020274e-01 1.00000000 -8.4939676
## 931  -7.586669e-03 3.871498e-01 -0.120729967 9.039632e-01 1.00000000 -8.4942664
## 218   1.135651e-03 2.637144e-02  0.119476724 9.049553e-01 1.00000000 -8.4944172
## 802   3.246700e-01 4.329957e+00  0.116142872 9.075953e-01 1.00000000 -8.4948108
## 617  -9.761180e-03 9.588097e-01 -0.108911150 9.133254e-01 1.00000000 -8.4956261
## 522   1.743484e-02 9.557850e-01  0.108227489 9.138674e-01 1.00000000 -8.4957005
## 493  -6.970369e-02 9.767269e+00 -0.106799259 9.149997e-01 1.00000000 -8.4958544
## 70   -9.299385e-03 6.513180e-01 -0.105575373 9.159701e-01 1.00000000 -8.4959846
## 631   5.922273e-04 4.590426e-03  0.104908935 9.164986e-01 1.00000000 -8.4960549
## 571   9.528498e+00 1.204371e+03  0.096767439 9.229577e-01 1.00000000 -8.4968775
## 89   -2.902567e+01 5.905212e+03 -0.095688796 9.238138e-01 1.00000000 -8.4969815
## 472  -1.123947e+01 6.021514e+02 -0.094276359 9.249350e-01 1.00000000 -8.4971159
## 773  -3.261300e-01 5.175642e+00 -0.092238868 9.265526e-01 1.00000000 -8.4973063
## 296   2.494251e-01 3.641088e+01  0.089748335 9.285304e-01 1.00000000 -8.4975333
## 664   2.916641e-03 1.960282e-01  0.088614733 9.294307e-01 1.00000000 -8.4976346
## 964  -7.430410e-01 1.665892e+01 -0.088566749 9.294688e-01 1.00000000 -8.4976389
## 73   -5.278655e-02 1.976573e+00 -0.085682160 9.317603e-01 1.00000000 -8.4978907
## 263  -2.258917e-02 5.453411e-01 -0.085191138 9.321504e-01 1.00000000 -8.4979327
## 275   6.928822e+02 2.040365e+05  0.083029458 9.338680e-01 1.00000000 -8.4981149
## 477   6.408636e-01 1.117382e+02  0.079950220 9.363153e-01 1.00000000 -8.4983663
## 981   5.652280e+00 2.813173e+02  0.076795186 9.388234e-01 1.00000000 -8.4986141
## 528  -1.471009e-04 2.138302e-03 -0.075824889 9.395948e-01 1.00000000 -8.4986883
## 7    5.780937e+00 9.864281e+02  0.074420570 9.407115e-01 1.00000000 -8.4987940
## 915  -2.409388e-03 2.296257e-01 -0.071295097 9.431971e-01 1.00000000 -8.4990222
## 84   -7.707495e-04 2.734256e-02 -0.070375375 9.439287e-01 1.00000000 -8.4990874
## 860  -1.454079e-02 2.958461e+00 -0.068795489 9.451854e-01 1.00000000 -8.4991976
## 252   2.889978e-02 7.778904e+00  0.057098337 9.544943e-01 1.00000000 -8.4999354
## 900  -4.263755e-01 1.102001e+02 -0.055895938 9.554515e-01 1.00000000 -8.5000034
## 1007  1.064481e-02 2.146543e+00  0.055047699 9.561269e-01 1.00000000 -8.5000506
## 245   4.483205e-01 1.699605e+01  0.054708540 9.563969e-01 1.00000000 -8.5000692
## 461  -6.663545e-02 5.523689e+00 -0.051354878 9.590674e-01 1.00000000 -8.5002474
## 118  -1.189685e-04 2.205048e-03 -0.049391535 9.606310e-01 1.00000000 -8.5003465
## 871  -6.507999e-05 9.412368e-04 -0.046112022 9.632431e-01 1.00000000 -8.5005034
## 487  -1.089908e+00 5.8666959e+02 -0.046002964 9.633299e-01 1.00000000 -8.5005085
## 178   7.022983e-01 1.875875e+02  0.045915512 9.633996e-01 1.00000000 -8.5005125
## 536  -1.461270e-04 4.861972e-03 -0.040528416 9.676913e-01 1.00000000 -8.5007458
## 746   2.203896e-01 6.998469e+01  0.040275793 9.678926e-01 1.00000000 -8.5007560
## 897  -1.565365e-04 5.310750e-03 -0.036197372 9.711423e-01 1.00000000 -8.5009123
## 540  -7.850825e-04 1.228566e-01 -0.031308074 9.750389e-01 1.00000000 -8.5010776
## 807  -3.321719e-03 1.381916e-01 -0.028262319 9.774665e-01 1.00000000 -8.5011685

```

## 132	1.151206e-02	1.064919e+00	0.024599186	9.803865e-01	1.00000000	-8.5012656
## 52	5.634977e-03	1.502726e+00	0.024155978	9.807398e-01	1.00000000	-8.5012764
## 999	-1.586407e-01	2.563939e+01	-0.022619500	9.819646e-01	1.00000000	-8.5013124
## 298	5.716533e-01	1.870359e+02	0.021572330	9.827994e-01	1.00000000	-8.5013356
## 607	1.741695e-03	6.545235e-01	0.018168157	9.855134e-01	1.00000000	-8.5014033
## 784	5.065543e-02	4.731400e+00	0.017365988	9.861530e-01	1.00000000	-8.5014176
## 926	1.159450e-02	1.116348e+01	0.013040246	9.896019e-01	1.00000000	-8.5014835
## 553	1.108272e-03	6.896349e-01	0.011942610	9.904771e-01	1.00000000	-8.5014973
## 562	-7.082413e-01	1.488202e+03	-0.008051341	9.935799e-01	1.00000000	-8.5015362
## 601	-6.593267e-05	7.732352e-02	-0.002668902	9.978718e-01	1.00000000	-8.5015652
## 18	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 33	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 34	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 35	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 36	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 41	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 42	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 45	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 46	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 47	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 48	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 57	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 58	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 69	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 78	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 81	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 82	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 92	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 99	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 106	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 108	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 109	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 115	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 120	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 125	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 140	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 142	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 144	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 145	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 146	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 147	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 149	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 150	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 151	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 152	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 153	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 154	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 163	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 166	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 186	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 189	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 190	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 191	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687
## 249	0.000000e+00	0.000000e+00	0.000000000	1.000000e+00	1.00000000	-8.5015687


```

## 833 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 834 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 835 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 836 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 837 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 839 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 840 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
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## 845 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 857 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 866 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 867 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 870 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 874 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 875 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 877 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 880 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 886 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 894 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 905 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 911 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 918 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 924 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 929 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 930 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 936 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 943 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 944 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 956 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 959 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 960 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 961 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 973 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 987 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 992 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 996 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 1020 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 1023 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 1031 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 1037 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687
## 1038 0.000000e+00 0.000000e+00 0.000000000 1.000000e+00 1.000000000 -8.5015687

```

Building volcano plot for the visualization of the up and down regulated genes(DEseq worked better than Limma based on the distribution of data in volcano plot)

```

mirna_limma1 <- mirna_limma1[!is.na(mirna_limma1$adj.P.Val), ]

mirna_limma1$diffexp<-NaN
res_gen<-mirna_limma1$V1
#res_gen
mirna_limma1$names<-NaN
for(i in 1:nrow(mirna_limma1))
{

```

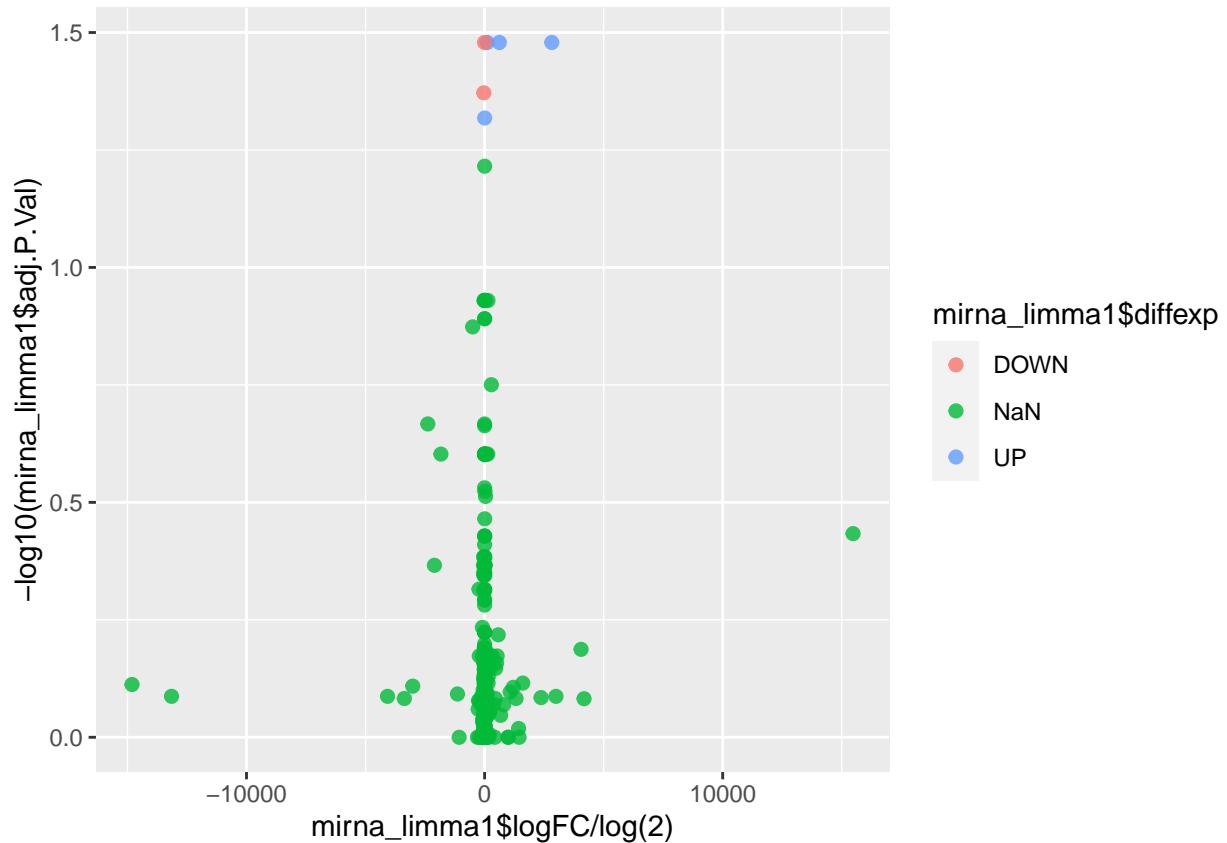
```

if(mirna_limma1$adj.P.Val[i]<0.05 & mirna_limma1$logFC[i]/log(2) > 1)
{
  mirna_limma1$diffexp[i] <- "UP"
  mirna_limma1$names[i] <- res_gen[i]
  print(mirna_limma1$names[i])
}
else if(mirna_limma1$adj.P.Val[i]<0.05 & mirna_limma1$logFC[i]/log(2) < -1)
{
  mirna_limma1$diffexp[i] <- "DOWN"
  mirna_limma1$names[i] <- res_gen[i]
  print(mirna_limma1$names[i])
}
}

## [1] "hsa.let.7a.1"
## [1] "hsa.let.7a.2"
## [1] "hsa.let.7a.3"
## [1] "hsa.let.7b"
## [1] "hsa.let.7c"
## [1] "hsa.let.7d"

ggplot(data.frame(mirna_limma1$logFC/log(2),mirna_limma1$adj.P.Val),aes(x = mirna_limma1$logFC/log(2),y
  geom_point(alpha = 0.8, size = 2)

```

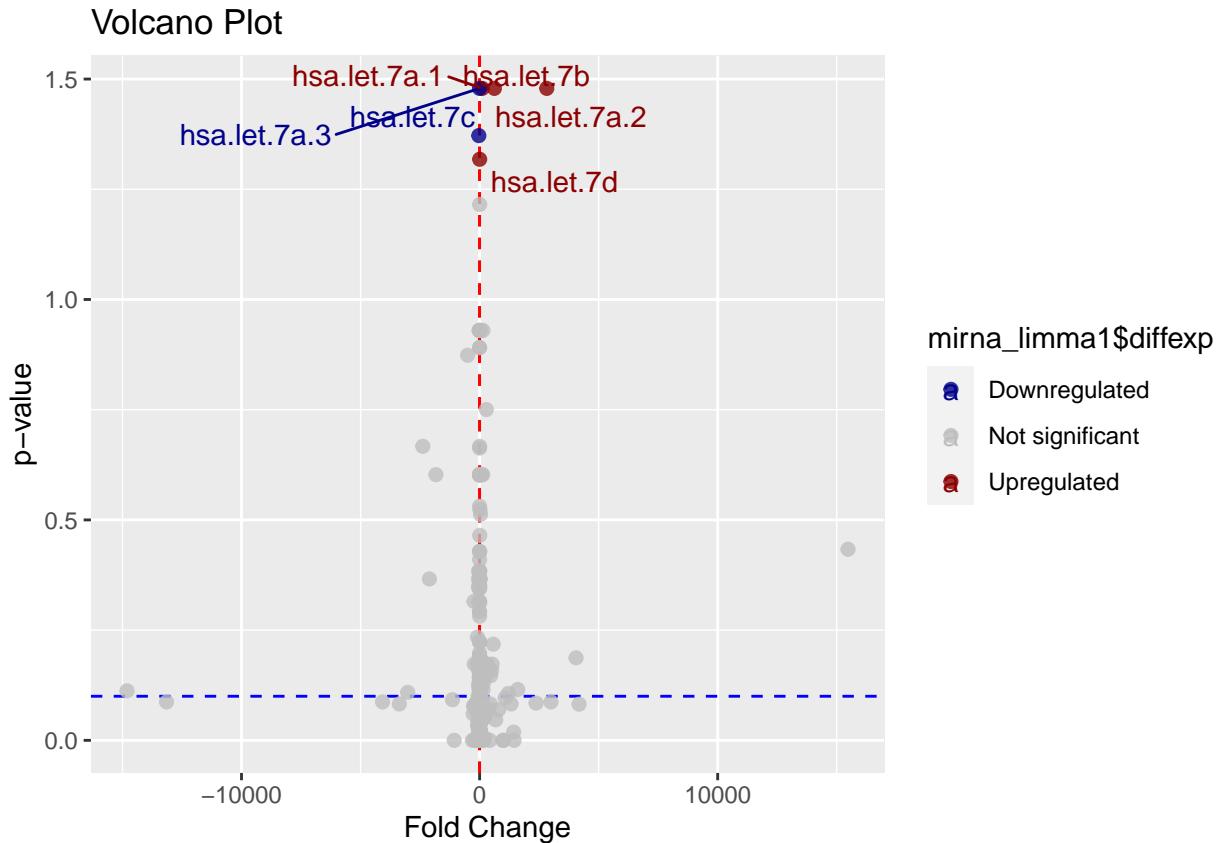


```

ggplot(data.frame(mirna_limma1$logFC/log(2),mirna_limma1$adj.P.Val),aes(x = mirna_limma1$logFC/log(2),y =
  geom_vline(xintercept = c(-1,1),col = "red", linetype ='dashed')+
  geom_hline(yintercept = 0.1,col='blue',linetype='dashed')+
  geom_point(alpha = 0.8, size = 2)+
  scale_color_manual(values = c("darkblue", "grey", "darkred"),
                     labels = c("Downregulated", "Not significant", "Upregulated"))+
  labs(x = "Fold Change", y = "p-value", title = "Volcano Plot")+
  geom_text_repel(aes(label = ifelse(mirna_limma1$diffexp != "UP" & mirna_limma1$diffexp != "DOWN", "",

## Warning in geom_text_repel(aes(label = ifelse(mirna_limma1$diffexp != "UP" & :
## Ignoring unknown aesthetics: max.overlaps

```



Conducting DESeq based differentially expressed analysis on the mRNA data

```

mrna_data2<-round(mrna_data1)
mrna_data2<-as.matrix(mrna_data2)
sur_mrn<-data.frame(PatientID=survival_mrna$PatientID,Death=survival_mrna$Death)
#row.names(sur_mir)<-survival_mirna$PatientID
mrna_deseq<-DESeqDataSetFromMatrix(countData = mrna_data2,colData = sur_mrn,design = ~ Death)

## converting counts to integer mode

## the design formula contains one or more numeric variables with integer values,
## specifying a model with increasing fold change for higher values.

```

```

## did you mean for this to be a factor? if so, first convert
## this variable to a factor using the factor() function

mrna_estimate<-estimateSizeFactors(mrna_deseq)
mrna_des<-DESeq(mrna_estimate)

## using pre-existing size factors

## estimating dispersions

## gene-wise dispersion estimates

## mean-dispersion relationship

## final dispersion estimates

## fitting model and testing

## -- replacing outliers and refitting for 3120 genes
## -- DESeq argument 'minReplicatesForReplace' = 7
## -- original counts are preserved in counts(dds)

## estimating dispersions

## fitting model and testing

mrna_result<-results(mrna_des)
mrna_result

## log2 fold change (MLE): Death
## Wald test p-value: Death
## DataFrame with 20531 rows and 6 columns
##   baseMean log2FoldChange      lfcSE       stat      pvalue      padj
##   <numeric>      <numeric> <numeric> <numeric> <numeric> <numeric>
## 1     0.059655      0.0363372  1.0062077  0.036113  0.97119226      NA
## 2     4.306723     -0.3354919  0.1574811 -2.130363  0.03314167  0.2334080
## 3     4.481233     -0.2605446  0.1304435 -1.997375  0.04578445  0.2731878
## 4    93.771058      0.1646386  0.0561130  2.934056  0.00334564  0.0649924
## 5   1163.673365      0.1154445  0.0479113  2.409544  0.01597246  0.1598258
## ...
## 20527  3742.98363      0.0630377  0.0774010  0.814431  0.41539814  0.7552017
## 20528   686.58844     -0.1404530  0.0601110 -2.336562  0.01946198  0.1786036
## 20529   562.86270      0.0709398  0.0509726  1.391723  0.16400618  0.5114769
## 20530    6.91842      0.4883490  0.1653800  2.952890  0.00314814  0.0626061
## 20531   95.91193     -0.1537932  0.1894066 -0.811973  0.41680688  0.7563504

mrna_result_filter <- mrna_result[which(mrna_result$padj < 0.05 & abs(mrna_result$log2FoldChange) > 1),
mrna_result_filter

```

```

## log2 fold change (MLE): Death
## Wald test p-value: Death
## DataFrame with 181 rows and 6 columns
##   baseMean log2FoldChange      lfcSE      stat     pvalue     padj
##   <numeric>      <numeric> <numeric> <numeric> <numeric> <numeric>
## 1    10.00285       1.24614  0.360186  3.45972 5.40730e-04 0.020619564
## 2   105.15280       1.07372  0.266186  4.03371 5.49039e-05 0.004524078
## 3   164.50590      -1.12469  0.269804 -4.16853 3.06573e-05 0.002919681
## 4    1.36286        1.22476  0.246296  4.97271 6.60221e-07 0.000174499
## 5    2.52251      -1.11108  0.299825 -3.70575 2.10764e-04 0.011347717
## ...
## 177   8.41103       1.00461  0.243251  4.12992 3.62892e-05 0.00330230
## 178   6.32900       1.01533  0.225748  4.49761 6.87217e-06 0.00105033
## 179   53.06356      1.06091  0.287457  3.69067 2.23665e-04 0.01177474
## 180   24.59882      -1.10756  0.290712 -3.80982 1.39070e-04 0.00861621
## 181   19.90095      1.37406  0.329100  4.17521 2.97706e-05 0.00287864

mrna_data3<-data.frame(V1=mrna_data$V1,mrna_data1,mrna_result)
mrna_data4<-mrna_data3[which(mrna_data3$padj < 0.05 & abs(mrna_data3$log2FoldChange) > 1), ]
write.csv(mrna_data4,file = "Differ_mrna_padj0.05_log2fold1.csv")

```

Building volcano plot for the visualization of the up and down regulated mrna

```

mrna_data3 <- mrna_data3[!is.na(mrna_data3$padj), ]

mrna_data3$diffexp<-NaN
res_gen<-mrna_data3$V1
#res_gen
mrna_data3$names<-NaN
for(i in 1:nrow(mrna_data3))
{
  if(mrna_data3$padj[i]<0.05 & mrna_data3$log2FoldChange[i] > 1)
  {
    mrna_data3$diffexp[i]<"UP"
    mrna_data3$names[i]<-res_gen[i]
    print(mrna_data3$names[i])
  }
  else if(mrna_data3$padj[i]<0.05 & mrna_data3$log2FoldChange[i] < -1)
  {
    mrna_data3$diffexp[i]<"DOWN"
    mrna_data3$names[i]<-res_gen[i]
    print(mrna_data3$names[i])
  }
}

## [1] "ABCB5.340273"
## [1] "ABP1.26"
## [1] "ACTN2.88"
## [1] "ACTN3.89"
## [1] "ADIG.149685"
## [1] "ALDH3B2.222"
## [1] "ALOX15B.247"

```

```
## [1] "AMHR2.269"
## [1] "ANO2.57101"
## [1] "APOL5.80831"
## [1] "AQP6.363"
## [1] "ARHGAP36.158763"
## [1] "ARHGDIG.398"
## [1] "ART3.419"
## [1] "ART5.116969"
## [1] "BMPER.168667"
## [1] "C12orf36.283422"
## [1] "C14orf180.400258"
## [1] "C1QTNF3.114899"
## [1] "C1orf111.284680"
## [1] "C20orf114.92747"
## [1] "C21orf62.56245"
## [1] "C4orf7.260436"
## [1] "CACNA1I.8911"
## [1] "CALB1.793"
## [1] "CALCA.796"
## [1] "CAPN6.827"
## [1] "CBLN4.140689"
## [1] "CCBE1.147372"
## [1] "CCL23.6368"
## [1] "CDC20B.166979"
## [1] "CDK5R2.8941"
## [1] "CEACAM5.1048"
## [1] "CHGB.1114"
## [1] "CHIA.27159"
## [1] "CHL1.10752"
## [1] "CHODL.140578"
## [1] "CLEC4GP1.440508"
## [1] "CLEC4G.339390"
## [1] "CLEC4M.10332"
## [1] "CLSTN2.64084"
## [1] "COL22A1.169044"
## [1] "CPA1.1357"
## [1] "CPNE6.9362"
## [1] "CRHBP.1393"
## [1] "CSDC2.27254"
## [1] "CSF3.1440"
## [1] "CXCL14.9547"
## [1] "CXCL5.6374"
## [1] "CYP19A1.1588"
## [1] "CYP1A1.1543"
## [1] "CYP26A1.1592"
## [1] "CYP26B1.56603"
## [1] "DAPL1.92196"
## [1] "DIO2.1734"
## [1] "DLK1.8788"
## [1] "DPF1.8193"
## [1] "DRD1.1812"
## [1] "DUSP13.51207"
## [1] "DYNC1I1.1780"
## [1] "EPHA8.2046"
```

```

## [1] "EPO.2056"
## [1] "ESRP1.54845"
## [1] "FCGR2B.2213"
## [1] "FCGR2C.9103"
## [1] "FCN2.2220"
## [1] "FCN3.8547"
## [1] "FIGF.2277"
## [1] "FREM1.158326"
## [1] "FRMD1.79981"
## [1] "GAGE4.2576"
## [1] "GDNF.2668"
## [1] "GLP2R.9340"
## [1] "GPR110.266977"
## [1] "GPR123.84435"
## [1] "GRIN3B.116444"
## [1] "GRM8.2918"
## [1] "GSC.145258"
## [1] "GUCA2A.2980"
## [1] "HAMP.57817"
## [1] "HAVCR1.26762"
## [1] "HOXA11.3207"
## [1] "HOXC6.3223"
## [1] "HOXC8.3224"
## [1] "HRASLS.57110"
## [1] "HSPB3.8988"
## [1] "IGFN1.91156"
## [1] "IL13RA2.3598"
## [1] "IL1RL1.9173"
## [1] "INSM1.3642"
## [1] "IRX2.153572"
## [1] "KBTBD12.166348"
## [1] "KCNJ16.3773"
## [1] "KCNJ9.3765"
## [1] "KLK3.354"
## [1] "KRT1.3848"
## [1] "KRT4.3851"
## [1] "KRT5.3852"
## [1] "KRT85.3891"
## [1] "KRTAP1.1.81851"
## [1] "LEP.3952"
## [1] "LHB.3972"
## [1] "LOC100131726.100131726"
## [1] "LOC389332.389332"
## [1] "LOC642597.642597"
## [1] "LRFN5.145581"
## [1] "LUZP2.338645"
## [1] "MACC1.346389"
## [1] "MAG.4099"
## [1] "MARCO.8685"
## [1] "MGAT4C.25834"
## [1] "MSC.9242"
## [1] "MT1B.4490"
## [1] "MYCN.4613"
## [1] "MYH1.4619"

```

```

## [1] "MYH3.4621"
## [1] "MYH4.4622"
## [1] "MYT1L.23040"
## [1] "NCRNA00162.378825"
## [1] "NEFM.4741"
## [1] "NKAIN1.79570"
## [1] "NKX2.5.1482"
## [1] "NROB1.190"
## [1] "OCA2.4948"
## [1] "ODAM.54959"
## [1] "OPN4.94233"
## [1] "P2RY4.5030"
## [1] "PAEP.5047"
## [1] "PAGE4.9506"
## [1] "PCDHGB2.56103"
## [1] "PCSK1.5122"
## [1] "PGC.5225"
## [1] "PLA2G4F.255189"
## [1] "PLD5.200150"
## [1] "POU2F3.25833"
## [1] "PRAMEF1.65121"
## [1] "PRAMEF9.343070"
## [1] "PROK1.84432"
## [1] "PRSS21.10942"
## [1] "PVALB.5816"
## [1] "PZP.5858"
## [1] "RAB25.57111"
## [1] "REG3A.5068"
## [1] "REG3G.130120"
## [1] "REN.5972"
## [1] "RET.5979"
## [1] "RGSL1.353299"
## [1] "RPS6KA6.27330"
## [1] "RSP02.340419"
## [1] "RYR2.6262"
## [1] "S100A8.6279"
## [1] "SAGE1.55511"
## [1] "SCN2B.6327"
## [1] "SGCZ.137868"
## [1] "SLC16A11.162515"
## [1] "SLC1A7.6512"
## [1] "SLC6A19.340024"
## [1] "SLC9A3.6550"
## [1] "SLITRK2.84631"
## [1] "SMYD1.150572"
## [1] "SNORD15B.114599"
## [1] "SOX21.11166"
## [1] "SPARCL1.8404"
## [1] "SPINK5.11005"
## [1] "STAB2.55576"
## [1] "STAC2.342667"
## [1] "STMN4.81551"
## [1] "TBX4.9496"
## [1] "TEDDM1.127670"

```

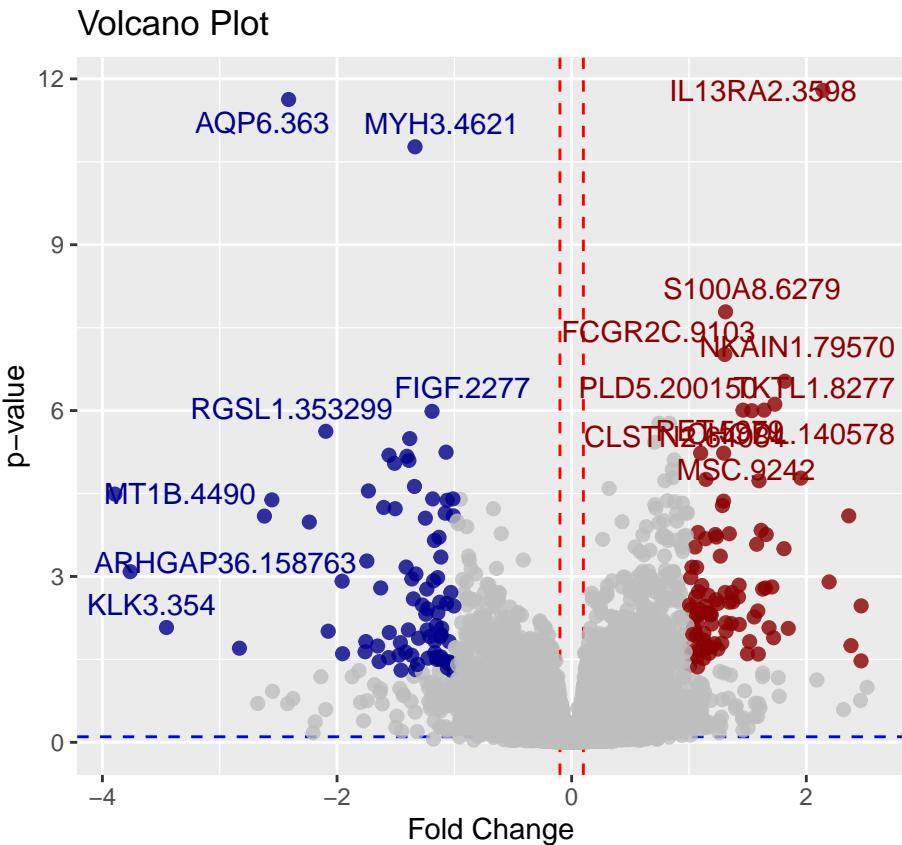
```

## [1] "TERT.7015"
## [1] "TG.7038"
## [1] "TKTL1.8277"
## [1] "TMC4.147798"
## [1] "TREM1.54210"
## [1] "TRIM50.135892"
## [1] "TRIM54.57159"
## [1] "UPK1A.11045"
## [1] "VIPR2.7434"
## [1] "VTCN1.79679"
## [1] "ZNF385D.79750"
## [1] "ZPLD1.131368"

ggplot(data.frame(mrna_data3$log2FoldChange,mrna_data3$padj),aes(x = mrna_data3$log2FoldChange,y = -log
  geom_vline(xintercept = c(-0.1,0.1),col = "red", linetype ='dashed')+ 
  geom_hline(yintercept = 0.1,col='blue',linetype='dashed')+ 
  geom_point(alpha = 0.8, size = 2)+ 
  scale_color_manual(values = c("darkblue", "grey", "darkred"),
                     labels = c("Downregulated", "Not significant", "Upregulated"))+ 
  labs(x = "Fold Change", y = "p-value", title = "Volcano Plot")+
  geom_text_repel(aes(label = ifelse(mrna_data3$diffexp != "UP" & mrna_data3$diffexp != "DOWN", "",mrna
  ## Warning in geom_text_repel(aes(label = ifelse(mrna_data3$diffexp != "UP" & :
  ## Ignoring unknown aesthetics: max.overlaps

## Warning: ggrepel: 164 unlabeled data points (too many overlaps). Consider
## increasing max.overlaps

```



Reading methylation data and based on partitioning, conducting the analysis below first on the subset of first 3000 methylation cg probes. And after obtaining the desired analysis, moving on to the analysis of second partition, i.e. for 1000 to 4000 cg probes and then 2000 to 5000 cg probes. the selection of the partition is conducted manually by mentioning the subsetting while fetching the data.

```
methyl<-data.frame(fread("C:/Users/bless/OneDrive/MS_Studies/DS/Project pitch/liver/methy"))

## Warning in fread("C:/Users/bless/OneDrive/MS_Studies/DS/Project
## pitch/liver/methy"): Detected 429 column names but the data has 430 columns
## (i.e. invalid file). Added 1 extra default column name for the first column
## which is guessed to be row names or an index. Use setnames() afterwards if this
## guess is not correct, or fix the file write command that created the file to
## create a valid file.

#the beta values are converted into m values as the analysis of methylation data require m values
mval<-log2(methyl[2:ncol(methyl)] / (1 - methyl[2:ncol(methyl)]))
methyl[2:ncol(methyl)]<-mval
#the subsetting of the data to conduct analysis subset wise
#after the analysis of first 3000, the analysis of 1000 to 4000 and 2000 to 5000 cg probes is conducted
methyl<-methyl[1:3000,]
sur<-data.frame(fread("C:/Users/bless/OneDrive/MS_Studies/DS/Project pitch/liver/survival"))

#In the survival data there are many NA present, removing the samples that have NA in Death column
sur$co<-1
sur$co[is.na(sur$Death) | is.na(sur$Survival) | is.na(sur$PatientID)]<-0
sur<-sur[sur$co!=0]
```

```

#the syntax of the names of the samples in the survival data and methylation data is made same

for(i in 2: length(colnames(methyl)))
{
  colnames(methyl)[i]<-gsub("\\.", "-", colnames(methyl)[i])
  #group$sample[i]<-gsub("\\.", "-", group$sample[i])
  #print(colnames(mirna)[i])
}
#The samples which are common in the datasets
all_common<-intersect(colnames(methyl),sur$PatientID)

#Dataframe made up of the common samples in all three datasets
methyl_com<-data.frame(methyl[,as.character(all_common)])
sur_com<-sur[sur$PatientID %in% all_common,]
sur_com<-sur_com[,1:3]
methyl_com=data.frame(CPGnames=methyl$V1,methyl_com)
row.names(methyl_com)=methyl_com$CPGnames
methyl_com=methyl_com[,-1]
for(i in 1:nrow(sur_com))
{
  if(sur_com$Death[i]==1)
  {
    sur_com$Group[i]='Dead'
  }
  else if(sur_com$Death[i]==0)
  {
    sur_com$Group[i]='Alive'
  }
}

```

Now we have common elements in all the three datasets

```

cpgnames<-methyl[,1]
#cpgnames
probe<-data.frame(fread("C:/Users/bless/OneDrive/MS_Studies/DS/Project pitch/liver/GPL8490-65.txt"))
#intersect(methyl$V1,probe$ID)

```

loading champ library for the methylation analysis using champ

```

'if (!requireNamespace("BiocManager", quietly = TRUE))
  install.packages("BiocManager")
BiocManager::install("ChAMP")'

## [1] "if (!requireNamespace(\"BiocManager\", quietly = TRUE))\n      install.packages(\"BiocManager\")\n\nlibrary(ChAMP)\n\n## Loading required package: minfi\n\n## Loading required package: Biostrings"

```

```

## Loading required package: XVector

##
## Attaching package: 'XVector'

## The following object is masked from 'package:purrr':
##      compact

##
## Attaching package: 'Biostrings'

## The following object is masked from 'package:base':
##      strsplit

## Loading required package: bumphunter

## Loading required package: foreach

## Warning: package 'foreach' was built under R version 4.3.1

##
## Attaching package: 'foreach'

## The following objects are masked from 'package:purrr':
##      accumulate, when

## Loading required package: iterators

## Warning: package 'iterators' was built under R version 4.3.1

## Loading required package: parallel

## Loading required package: locfit

## locfit 1.5-9.8    2023-06-11

##
## Attaching package: 'locfit'

## The following object is masked from 'package:purrr':
##      none

## Setting options('download.file.method.GEOquery'='auto')

## Setting options('GEOquery.inmemory.gpl'=FALSE)

```

```

## Loading required package: ChAMPdata

## Loading required package: DMRcate

## 

## Loading required package: Illumina450ProbeVariants.db

## Loading required package: IlluminaHumanMethylationEPICmanifest

## Loading required package: DT

## Warning: package 'DT' was built under R version 4.3.1

## Loading required package: RPMM

## Warning: package 'RPMM' was built under R version 4.3.1

## Loading required package: cluster

## No methods found in package 'RSQLite' for request: 'dbListFields' when loading 'lumi'

## Warning: replacing previous import 'plyr::mutate' by 'plotly::mutate' when
## loading 'ChAMP'

## Warning: replacing previous import 'plyr::rename' by 'plotly::rename' when
## loading 'ChAMP'

## Warning: replacing previous import 'plyr::arrange' by 'plotly::arrange' when
## loading 'ChAMP'

## Warning: replacing previous import 'plyr::summarise' by 'plotly::summarise'
## when loading 'ChAMP'

## 

## Warning: replacing previous import 'plotly::subplot' by 'Hmisc::subplot' when
## loading 'ChAMP'

## Warning: replacing previous import 'plyr::summarize' by 'Hmisc::summarize' when
## loading 'ChAMP'

## Warning: replacing previous import 'plyr::is.discrete' by 'Hmisc::is.discrete'
## when loading 'ChAMP'

## Warning: replacing previous import 'GenomicRanges::sort' by 'globaltest::sort'
## when loading 'ChAMP'

```

```

## Warning: replacing previous import 'plotly::last_plot' by 'ggplot2::last_plot'
## when loading 'ChAMP'

## Warning: replacing previous import 'globaltest::model.matrix' by
## 'stats::model.matrix' when loading 'ChAMP'

## Warning: replacing previous import 'globaltest::p.adjust' by 'stats::p.adjust'
## when loading 'ChAMP'

## >> Package version 2.21.1 loaded <<
##
##      / _\ | |_ / \ \ \ \ \ \ \
##      | ( _| ' \ / _ \ \ \ \ \ \ \ \ \
##      \_\_\_|_|/_/_/\_\_\_|_|_|_|_|_
##      -----
##      If you have any question or suggestion about ChAMP, please email to champ450k@gmail.com.
##      Thank you for citating ChAMP:
##
##      Yuan Tian, Tiffany J Morris, Amy P Webster, Zhen Yang, Stephan Beck, Andrew Feber, Andrew E Tesch
##      -----

```

conducting champ analysis using m values

```

champ_result<-data.frame(champ.DMP(beta = methyl_com, pheno = sur_com$Group,adjPVal = 1))

## [=====]

## [<<<< ChAMP.DMP START >>>>]

## -----
## !!! Important !!! New Modification has been made on champ.DMP():

##     (1): In this version champ.DMP() if your pheno parameter contains more than two groups of phenoty
##     (2): champ.DMP() now support numeric as pheno, and will do linear regression on them. So covaria
## -----
## 
## [ Section 1: Check Input Pheno Start ]

##     You pheno is character type.

##     Your pheno information contains following groups. >>
##     <Dead>:166 samples.
##     <Alive>:257 samples.

```

```

##      [The power of statistics analysis on groups contain very few samples may not strong.]

##      pheno contains only 2 phenotypes

##      compare.group parameter is NULL, two pheno types will be added into Compare List.

##      Dead_to_Alive compare group : Dead, Alive

##
## [ Section 1: Check Input Pheno Done ]

##
## [ Section 2: Find Differential Methylated CpGs Start ]

## -----
##      Start to Compare : Dead, Alive

##      Contrast Matrix

##      Contrasts
##      Levels   pDead-pAlive
##      pAlive      -1
##      pDead       1

##      You have found 3000 significant MVPs with a BH adjusted P-value below 1.

##      Calculate DMP for Dead and Alive done.

##
## [ Section 2: Find Numeric Vector Related CpGs Done ]

##
## [ Section 3: Match Annotation Start ]

##
## [ Section 3: Match Annotation Done ]

## [<<<<< ChAMP.DMP END >>>>]

## [=====]

## [You may want to process DMP.GUI() or champ.GSEA() next.]


#champ_dataout<-result_table[which(result_table$adj.P.Val<0.1 & abs(result_table$l2fc) > 1), ]
#write.csv(champ_result,file = "champgenes.csv")

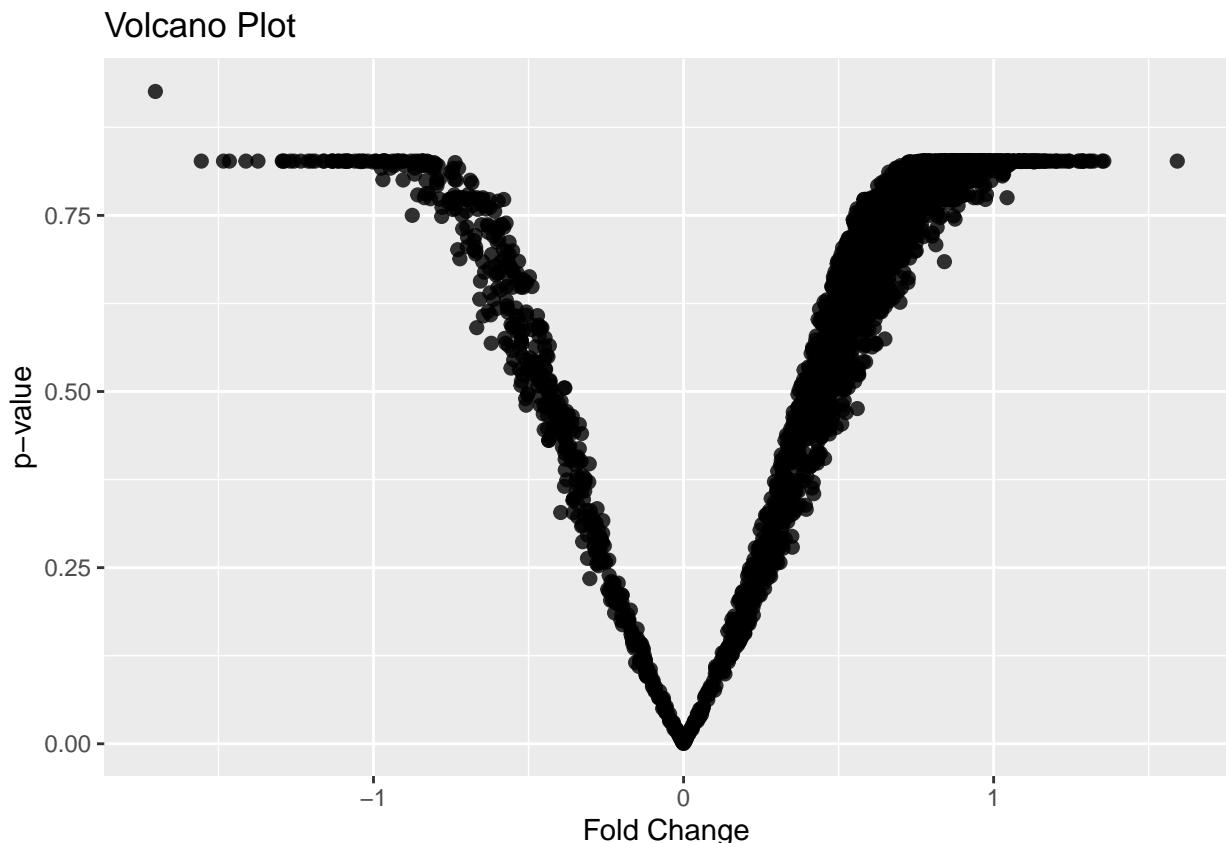
```

THE VOLCANO PLOT FOR CHAMP NOT SO GOOD

```

champ_result$l2fc<-champ_result$Dead_to_Alive.logFC/log(2)
'champ_result$diffexp<-NaN
for(i in 1:nrow(champ_result))
{
  if(champ_result$Dead_to_Alive.adj.P.Val[i]>0.1 & champ_result$l2fc[i] > 0.1)
  {
    champ_result$diffexp[i]<-"UP"
  }
  else if(champ_result$Dead_to_Alive.adj.P.Val[i]>0.1 & champ_result$l2fc[i] < -0.1)
  {
    champ_result$diffexp[i]<-"DOWN"
  }
}
## [1] "champ_result$diffexp<-NaN\nfor(i in 1:nrow(champ_result))\n{\n  if(champ_result$Dead_to_Alive.adj.P.Val[i]>0.1 & champ_result$l2fc[i] > 0.1)\n  {\n    champ_result$diffexp[i]<-"UP"\n  }\n  else if(champ_result$Dead_to_Alive.adj.P.Val[i]>0.1 & champ_result$l2fc[i] < -0.1)\n  {\n    champ_result$diffexp[i]<-"DOWN"\n  }\n}\n"
ggplot(data.frame(champ_result$l2fc,champ_result$Dead_to_Alive.adj.P.Val),aes(x = champ_result$l2fc,y = champ_result$Dead_to_Alive.adj.P.Val))+
  #geom_vline(xintercept = c(-0.025,0.025),col = "red", linetype ='dashed')+
  #geom_hline(yintercept = 0.3,col='blue',linetype='dashed')+
  geom_point(alpha = 0.8, size = 2)+
  #scale_color_manual(values = c("#00AFBB", "grey", "#FFDB6D"),
  #labels = c("Downregulated", "Not significant", "Upregulated"))+
  labs(x = "Fold Change", y = "p-value", title = "Volcano Plot")

```



```
#champ_methyl<-data.frame(methyl_com[as.character(row.names(champ_result)),])
#write.csv(champ_methyl,file = "Champ_methyl_padj0.194.csv")
```

conducting limma analysis for m values of the methylation data

```
'if (!require("BiocManager", quietly = TRUE))
  install.packages("BiocManager")

BiocManager::install("limma")

## [1] "if (!require(\"BiocManager\"), quietly = TRUE))\n      install.packages(\"BiocManager\")\n\nBiocMa

library(limma)

mirna_limma<-as.matrix(methyl_com)

design_matrix<-model.matrix(~ Group, data = sur_com)
normalized_data <- normalizeBetweenArrays(methyl_com, method = "quantile")
fit <- lmFit(normalized_data, design_matrix)
eb_fit <- eBayes(fit)
result_table <- topTable(eb_fit, number = 3000)

## Removing intercept from test coefficients

result_table$adj.P.Val <- p.adjust(result_table$P.Value, method = "BH")
#reslt_final_methy<-data.frame()
```

building the volcano plot to visualize the differentially expressed cg probes

```
result_table$l2fc<-result_table$logFC/log(2)
result_table$diffexp<-NaN
res_gen<-row.names(result_table)
result_table$names<-NaN
for(i in 1:nrow(result_table))
{
  if(result_table$adj.P.Val[i]<0.1 & result_table$l2fc[i] > 1)
  {
    result_table$diffexp[i]<-"UP"
    result_table$names[i]<-res_gen[i]
  }
  else if(result_table$adj.P.Val[i]<0.1 & result_table$l2fc[i] < -1)
  {
    result_table$diffexp[i]<-"DOWN"
    result_table$names[i]<-res_gen[i]
  }
}
```

```
ggplot(data.frame(result_table$l2fc,result_table$adj.P.Val),aes(x = result_table$l2fc,y = -log10(result_
geom_vline(xintercept = c(-1,1),col = "red", linetype ='dashed')+
geom_hline(yintercept = 0.1,col='blue',linetype='dashed')+
```

```

geom_point(alpha = 0.8, size = 2)+  

scale_color_manual(values = c("darkblue", "grey", "darkred"),  

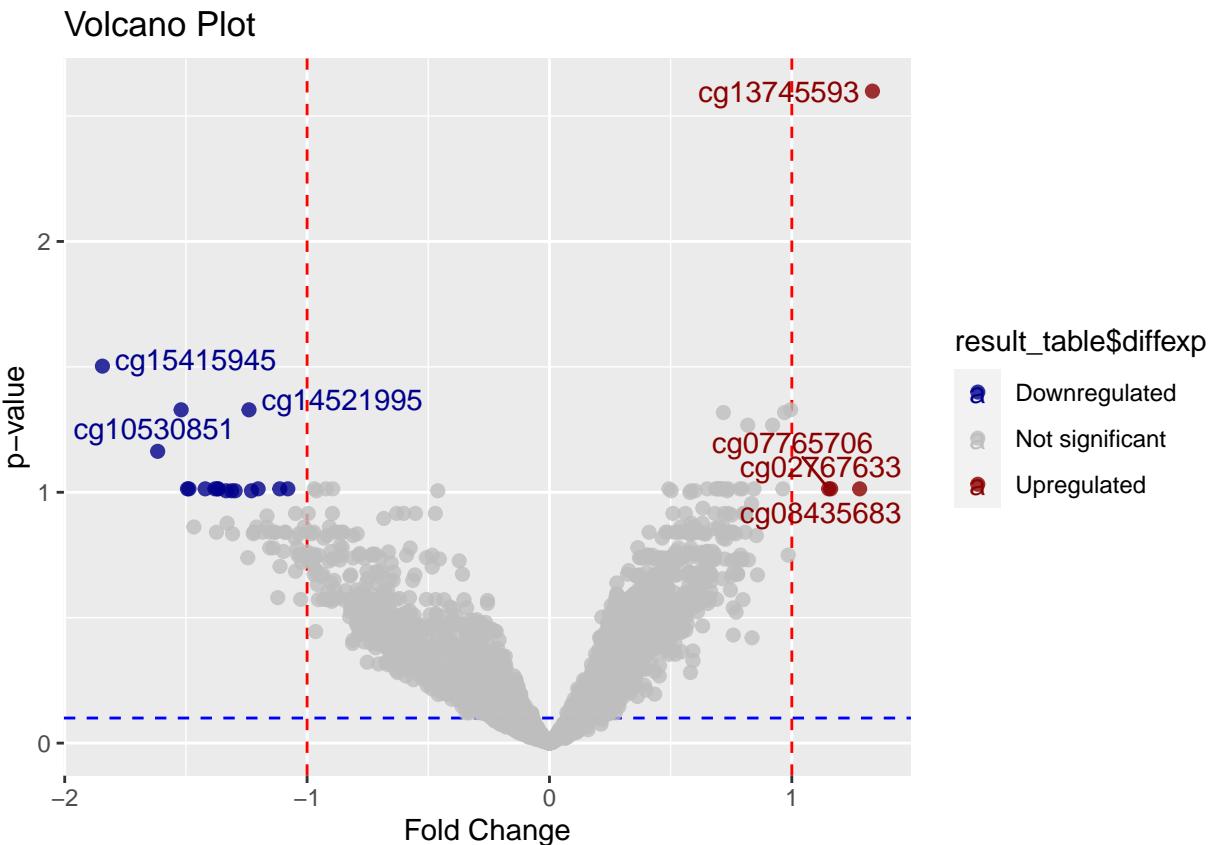
                   labels = c("Downregulated", "Not significant", "Upregulated"))+  

labs(x = "Fold Change", y = "p-value", title = "Volcano Plot")+
geom_text_repel(aes(label = ifelse(result_table$diffexp != "UP" & result_table$diffexp != "DOWN", "",  


```

Warning in geom_text_repel(aes(label = ifelse(result_table\$diffexp != "UP" & :
Ignoring unknown aesthetics: max.overlaps

Warning: ggrepel: 14 unlabeled data points (too many overlaps). Consider
increasing max.overlaps



```

#methyl_sort<-methyl[order(methyl$V1),]  

#row_methyl_com <- order(row.names(methyl_com))  

#row_methyl_com  

# Sort the dataframe based on the row index  

#methyl_com <- df[row_order, ]  

result_table<-rownames_to_column(result_table, var="V1")  

methdata_out<-data.frame(V1=methyl$V1,methyl_com)  

meth_sort<-methdata_out[order(methdata_out$V1),]  

result_table_sort<- result_table[order(result_table$V1),]

```

```

combine_meth<-data.frame(methdata_out,result_table_sort)
meth_dataout<-combine_meth[which(combine_meth$adj.P.Val<0.1 & abs(combine_meth$l2fc) > 1), ]
write.csv(meth_dataout,file = "meth143.csv")

'num<-which(result_table$adj.P.Val<0.1)
for(i in num)
{
  reslt_final_methy<-rbind(reslt_final_methy,result_table[i,])
}
result_methyl<-data.frame(methyl_com[as.character(row.names(reslt_final_methy)),])
write.csv(result_methyl,file = "limma_methylpadj0.1logfc0.05.csv")

## [1] "num<-which(result_table$adj.P.Val<0.1)\nfor(i in num)\n{  reslt_final_methy<-rbind(reslt_final_methy,\n
diff_mir<-fread("C:/Users/bless/OneDrive/MS_Studies/DS/Project pitch/liver/Code/Final/Differ_mirna_padj0.1")
diff_mir<-diff_mir[,2:ncol(diff_mir)]
diff_mrn<-fread("C:/Users/bless/OneDrive/MS_Studies/DS/Project pitch/liver/Code/Final/Differ_mrna_padj0.1")
diff_mrn<-diff_mrn[,2:ncol(diff_mrn)]
diff_meth1<-fread("C:/Users/bless/OneDrive/MS_Studies/DS/Project pitch/liver/Code/Final/Differ_meth_padj0.1")
diff_meth1<-diff_meth1[,2:ncol(diff_meth1)]
#diff_meth2<-fread("C:/Users/bless/OneDrive/MS_Studies/DS/Project pitch/liver/Code/limma_methylpadj0.1logfc0.05")

```

Fetching the similar samples in mirna, mrna and methylation data in reference to survival data

```

options(scipen = 999)

allcom1<-intersect(colnames(diff_mir),colnames(diff_mrn))
#allcom2<-intersect(colnames(diff_meth1),colnames(diff_meth2))
allcom3<-intersect(allcom1,colnames(diff_meth1))
#allcom3
for(i in 1: nrow(sur_com))
{
  sur_com$PatientID[i]<-gsub("\\-", ".", sur_com$PatientID[i])
  #group$sample[i]<-gsub("\\.", "-", group$sample[i])
  #print(colnames(mirna)[i])
}
allcom4<-data.frame(sample=intersect(allcom3,sur_com$PatientID))
#allcom4
diff_meth1_1<-subset(diff_meth1, select = allcom4$sample)
diff_meth1_1<-data.frame(V1=diff_meth1$V1,diff_meth1_1)
write.csv(diff_meth1_1,file = "Diff_methyl.csv")
#diff_meth2_1<-subset(diff_meth2,select = allcom4$sample)
#diff_meth2_1<-data.frame(V1=diff_meth2$V1,diff_meth2_1)
#write.csv(diff_meth2_1,file = "Diff_methyl_limma.csv")
sur_com_1<-sur_com[sur_com$PatientID %in% colnames(diff_meth1_1),]
sur_com_1<-sur_com_1[!duplicated(sur_com_1$PatientID),]
write.csv(sur_com_1,file = "survival_common1.csv")
diff_mir_1<-subset(diff_mir, select = allcom4$sample)
diff_mir_1<-data.frame(V1=diff_mir$V1,diff_mir_1)
write.csv(diff_mir_1,file = "Diff_mirna.csv")
diff_mrn_1<-subset(diff_mrn, select = allcom4$sample)
diff_mrn_1<-data.frame(V1=diff_mrn$V1,diff_mrn_1)
write.csv(diff_mrn_1,file = "Diff_mrna.csv")

```

```

#'arg' should be one of "none", "scale", "quantile", "Aquantile", "Gquantile", "Rquantile", "Tquantile"
#normalized_mir_data <- normalizeBetweenArrays(diff_mir_1, method = "quantile")

#intersect(diff_meth1_1$V1, row.names(reslt_final_methy))

'vv<-colnames(diff_meth1_1)
vv
for(i in 1:nrow(sur_com_1))
{
  for(j in 1:nrow(vv))
  {
    print(sur_com_1$PatientID[i])
  }
}
for(j in 1:nrow(vv))
{
  print(j)
}'
```

[1] "vv<-colnames(diff_meth1_1)\nvv\nfor(i in 1:nrow(sur_com_1))\n{\n for(j in 1:nrow(vv))\n {\n

Note that the `echo = FALSE` parameter was added to the code chunk to prevent printing of the R code that generated the plot.

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