Statistical Methods for High-dimensional Biology

Exploratory Data Analysis, Data visualization, Experimental Design

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Today's lecture: EDA & Exp Design

- **Exploratory Data Analysis**
  - First steps to data analysis
  - Traditional (low-dimensional) approaches
  - High-dimensional methods
  - Tips on how to organize your data/project
- **Experimental Design**
  - Observational vs. Experimental studies
  - Identification of unwanted variation (SVA)
  - Causal inference: matching, stratification, inverse propensity

What is EDA?

Graphing data *is a powerful approach to detecting* [data-specific] *problems. We refer to this as exploratory data analysis (EDA). Many important methodological contributions to existing techniques in data analysis were initiated by discoveries made via EDA.*

Rafael Irizzary

A few questions to ask after you obtained data

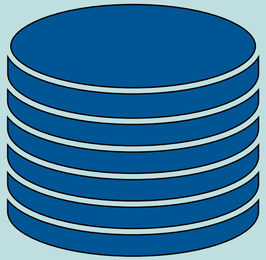
What are the data types?

{0, 1, 2, ...} ?

{-4.2, -3, -2, 0, 1, 2.1, ...}

{0.1, 0.8, 0.2, ...}

How is it stored?

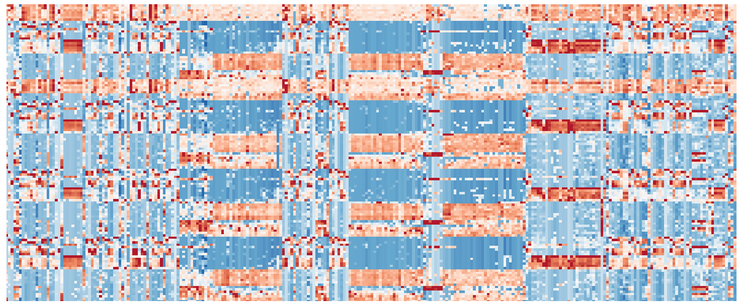


full batch

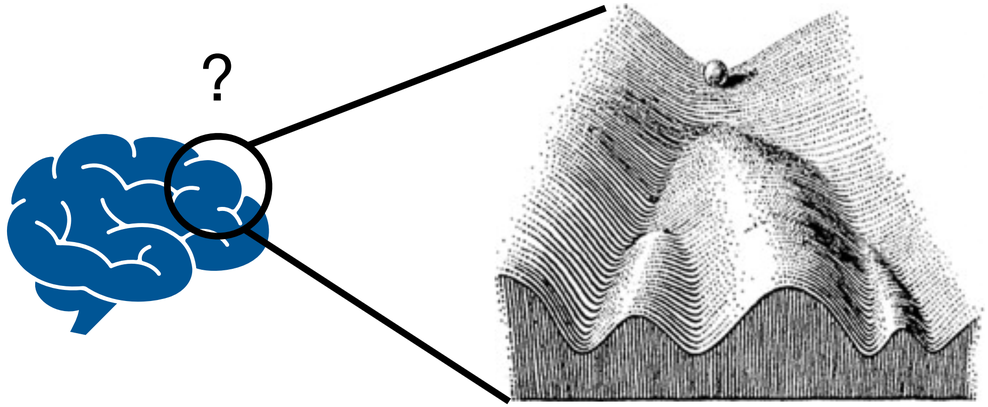
vs.

data steam (online)

How many features? samples?



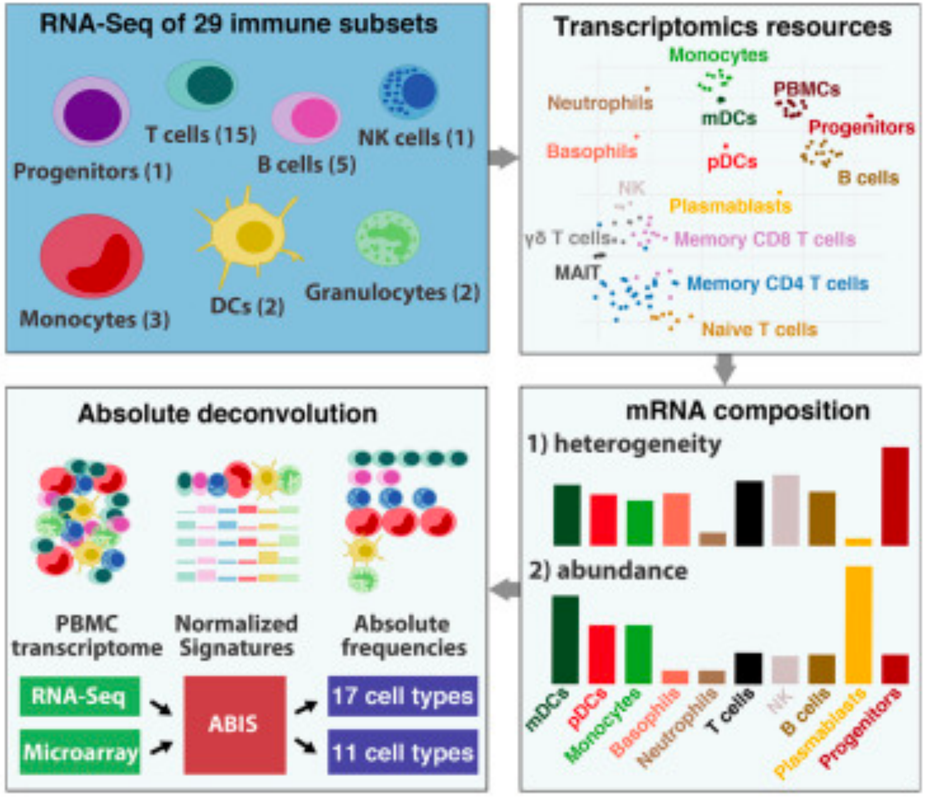
How can I picture it?



Why EDA *before* Data Analysis?

- Reading all the numbers vs. picturing all the numbers
- Modelling assumption vs. data distributions/shapes
- Start your hypothesis emprical, observed properties
- We may not know what to do at first
- Triage to figure out most suitable data analysis methods

A data set to demonstrate the principels of EDA




```r
if (!require("BiocManager", quietly = TRUE)){
    install.packages("BiocManager")
}
if(!require("GEOquery", quietly = TRUE)){
    BiocManager::install("GEOquery")
}
raw.data.file <- "GSE107011/GSE107011_Processed_data_TPM.txt.g
if(!file.exists(raw.data.file)){
    getGEOSuppFiles("GSE107011")
}
raw.data <- fread(raw.data.file)
X <- as.matrix(raw.data[, -1])
rownames(X) <- unlist(raw.data[,1])
```

Monaco + Lee *et al.* Cell Reports (2019)

Code available in our GitHub repo

https://github.com/STAT540-UBC/lectures/blob/main/lect03-eda/eda.Rmd

What do they look like?

```
X[1:5, 1:5]
```

```
##                    DZQV_CD8_naive DZQV_CD8_CM DZQV_CD8_EM DZQV_CD8_TE DZQV_MAIT
## ENSG00000223972.5       0.214321     0.00000  0.00421414  0.00953342 0.0112167
## ENSG00000227232.5       4.759630     3.49280  2.64877000  3.72232000 2.4792700
## ENSG00000278267.1       0.000000     2.61518  2.45976000  0.00000000 4.5861000
## ENSG00000243485.5       0.000000     0.00000  0.00000000  0.00000000 0.0000000
## ENSG00000284332.1       0.000000     0.00000  0.00000000  0.00000000 0.0000000
```

- What do you see?

What are the range of values?

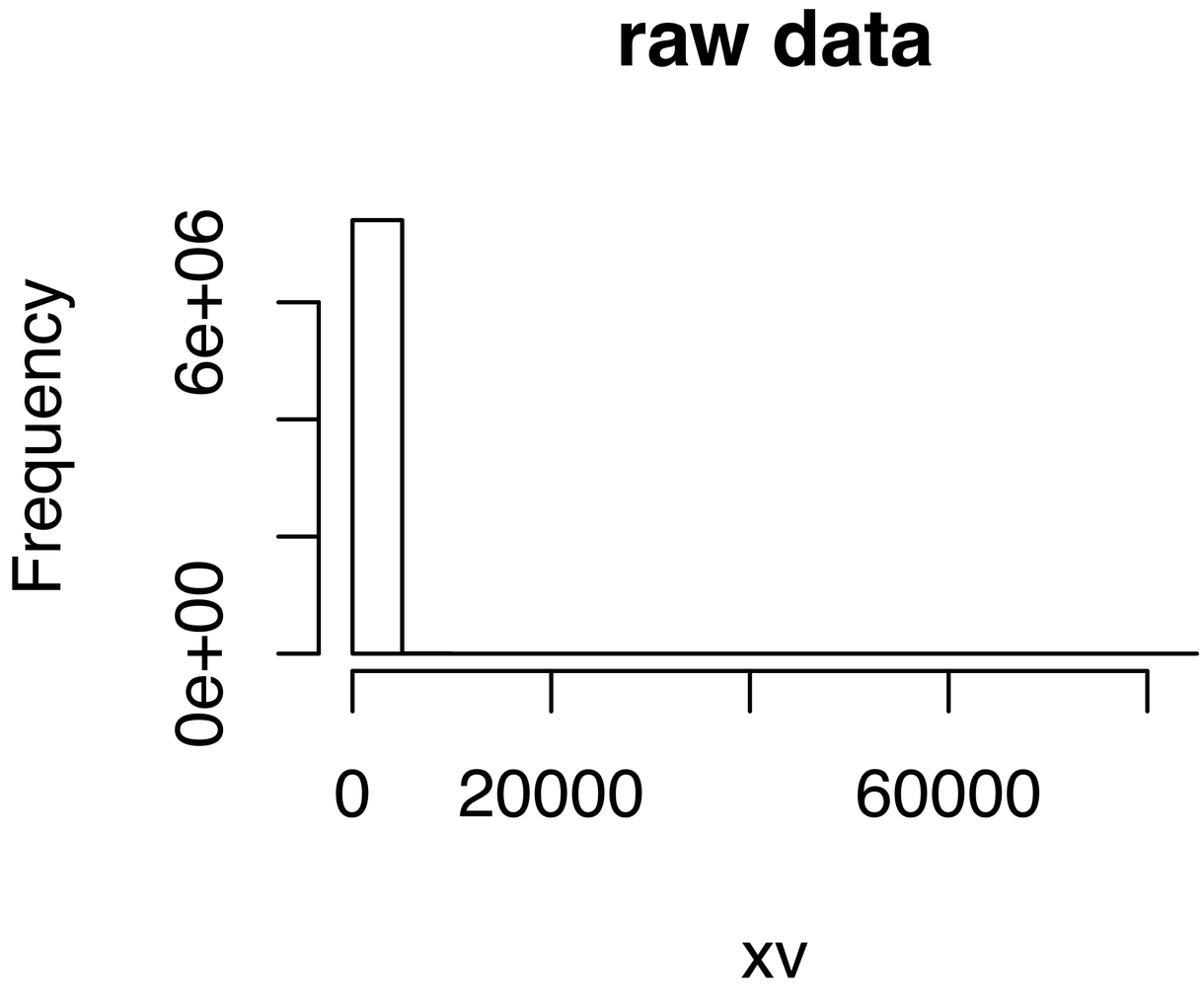
```
xv <- as.vector(X)
range(xv) %>%
    round(digits=2)
```

```
## [1]     0.0 80639.8
```

```
breaks <- c(0.1, 0.25, 0.5, 0.75, 0.9)
quantile(xv, probs=breaks) %>%
    round(digits=2)
```

```
##    10%    25%    50%    75%    90%
##   0.00   0.00   0.00   2.86  24.16
```

Histogram `hist`: Roughly... how are they distributed?



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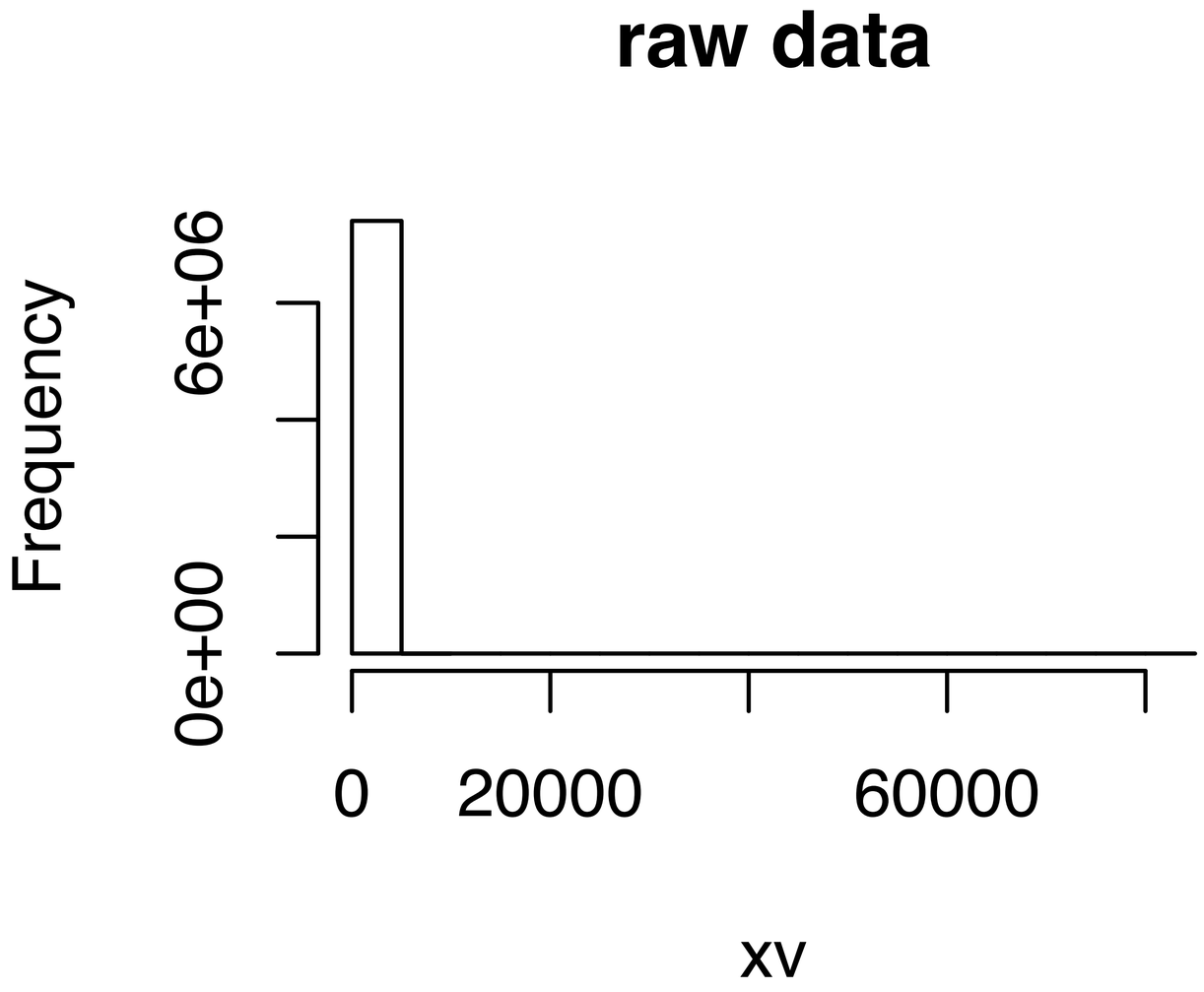
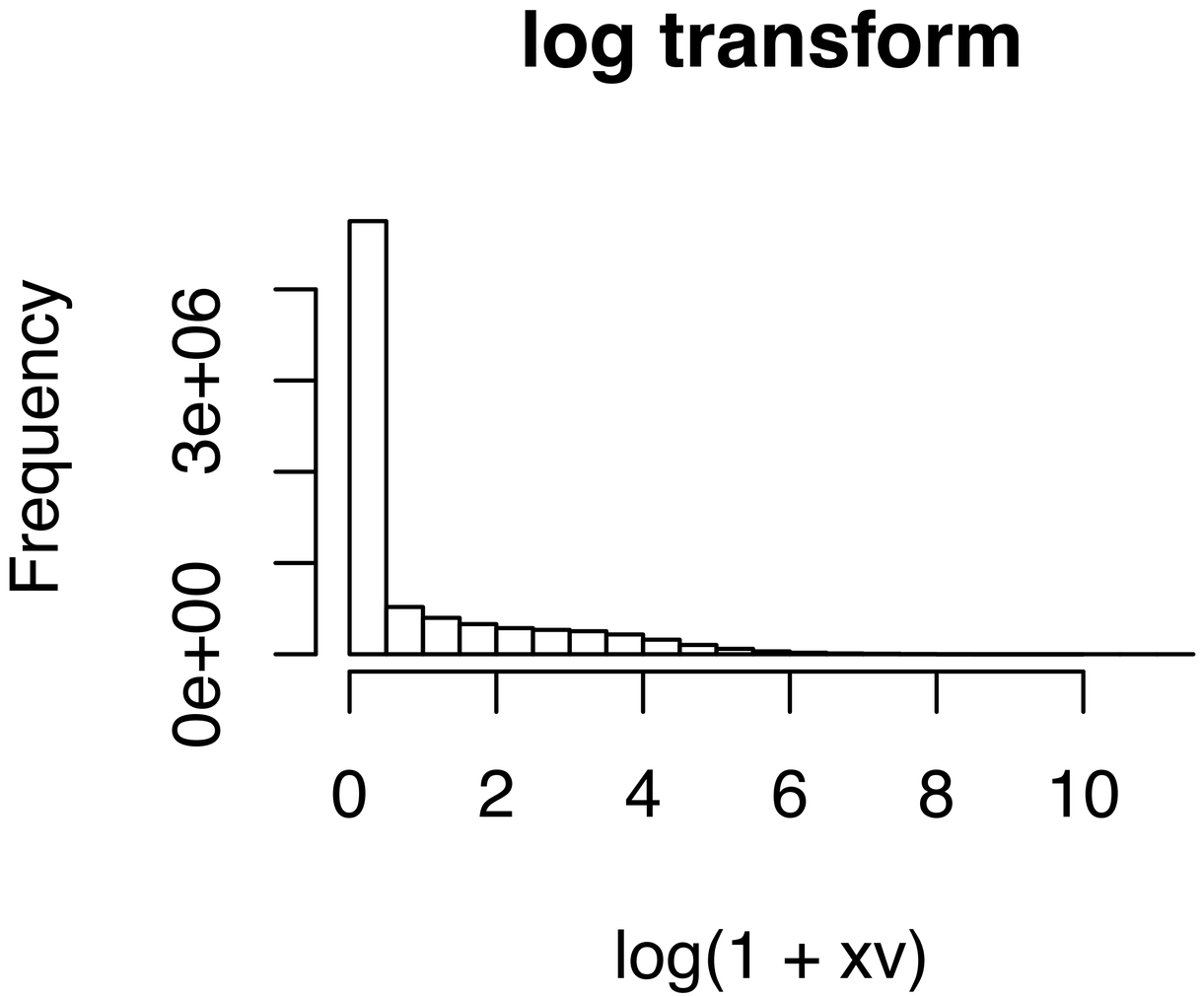
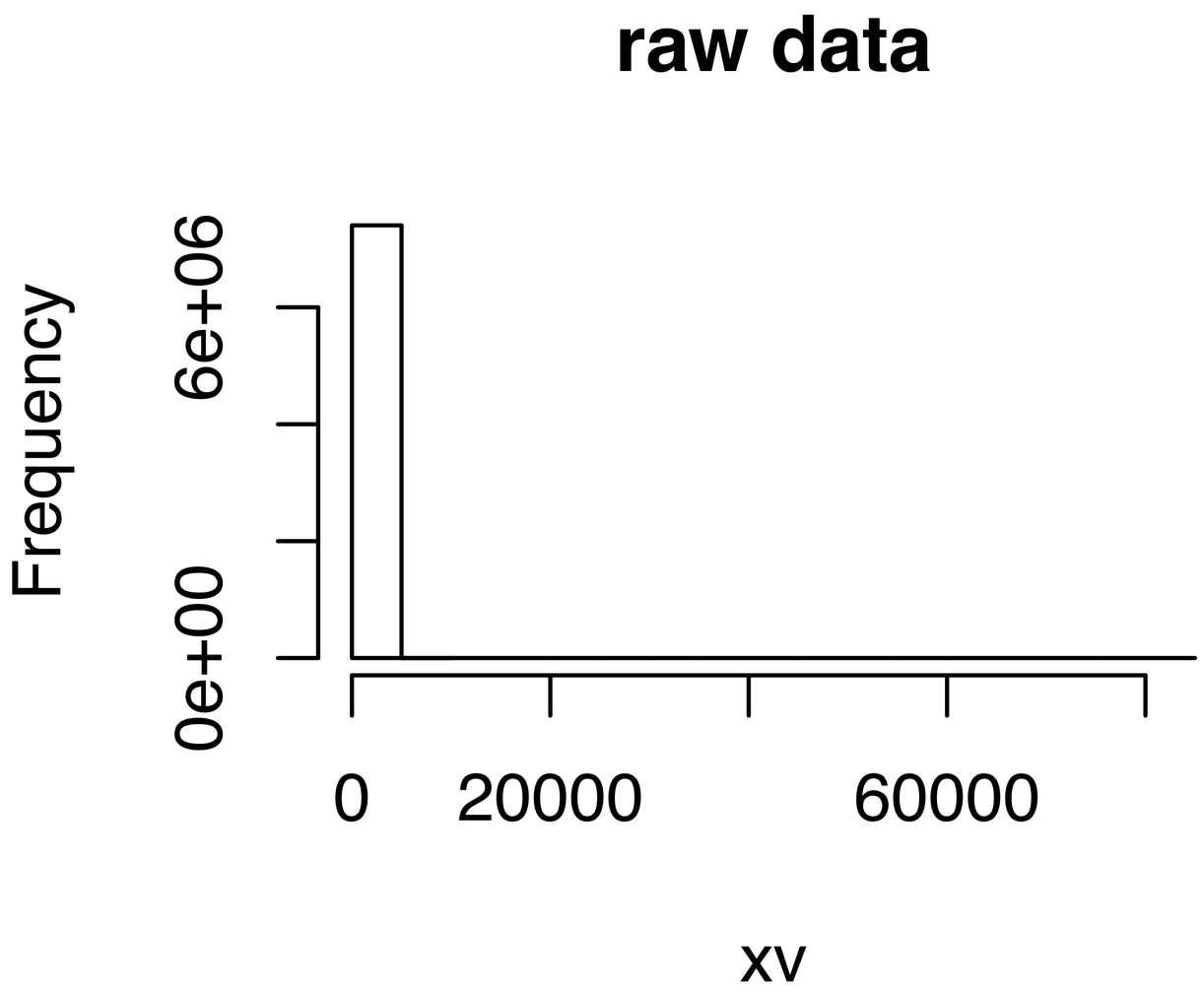
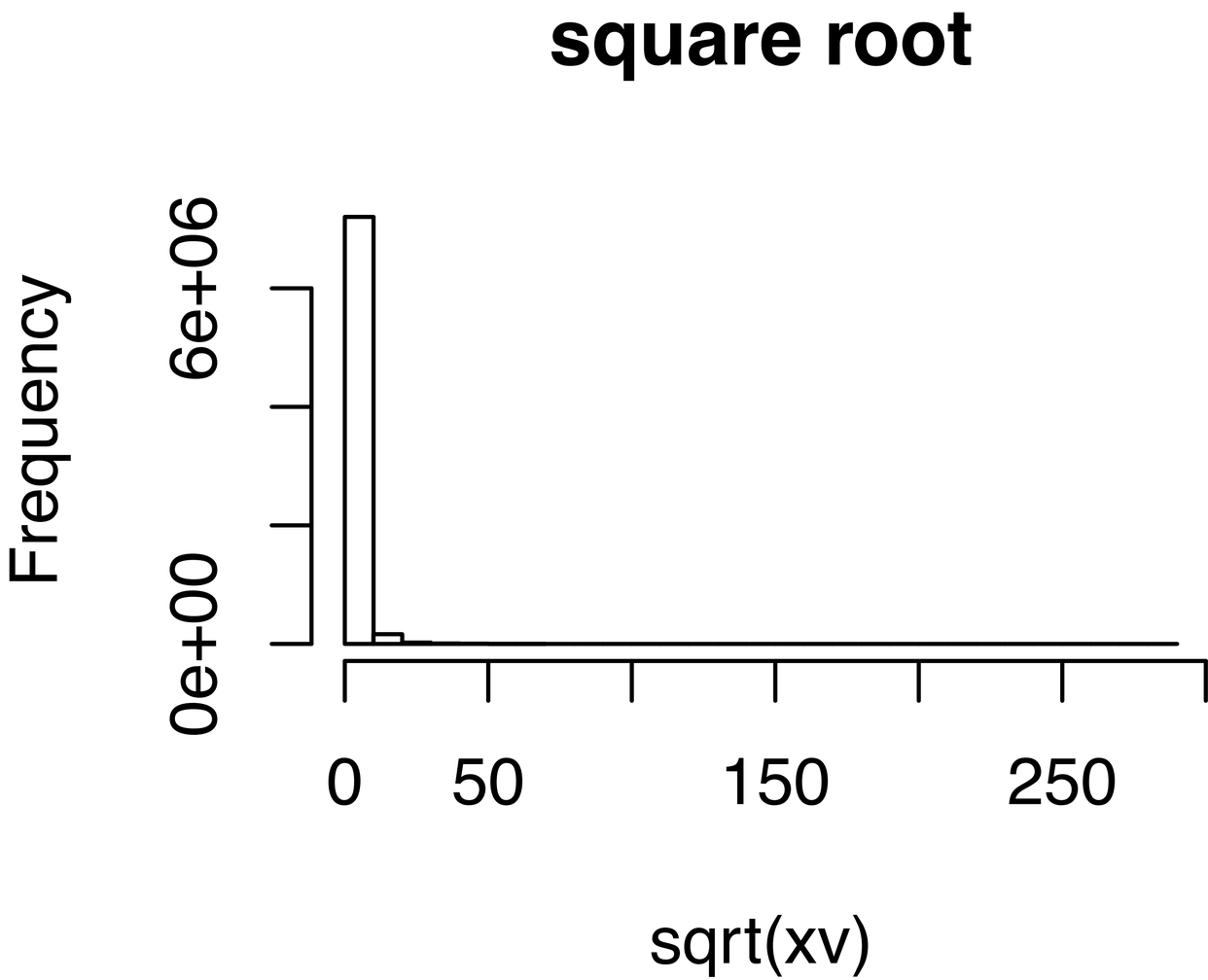




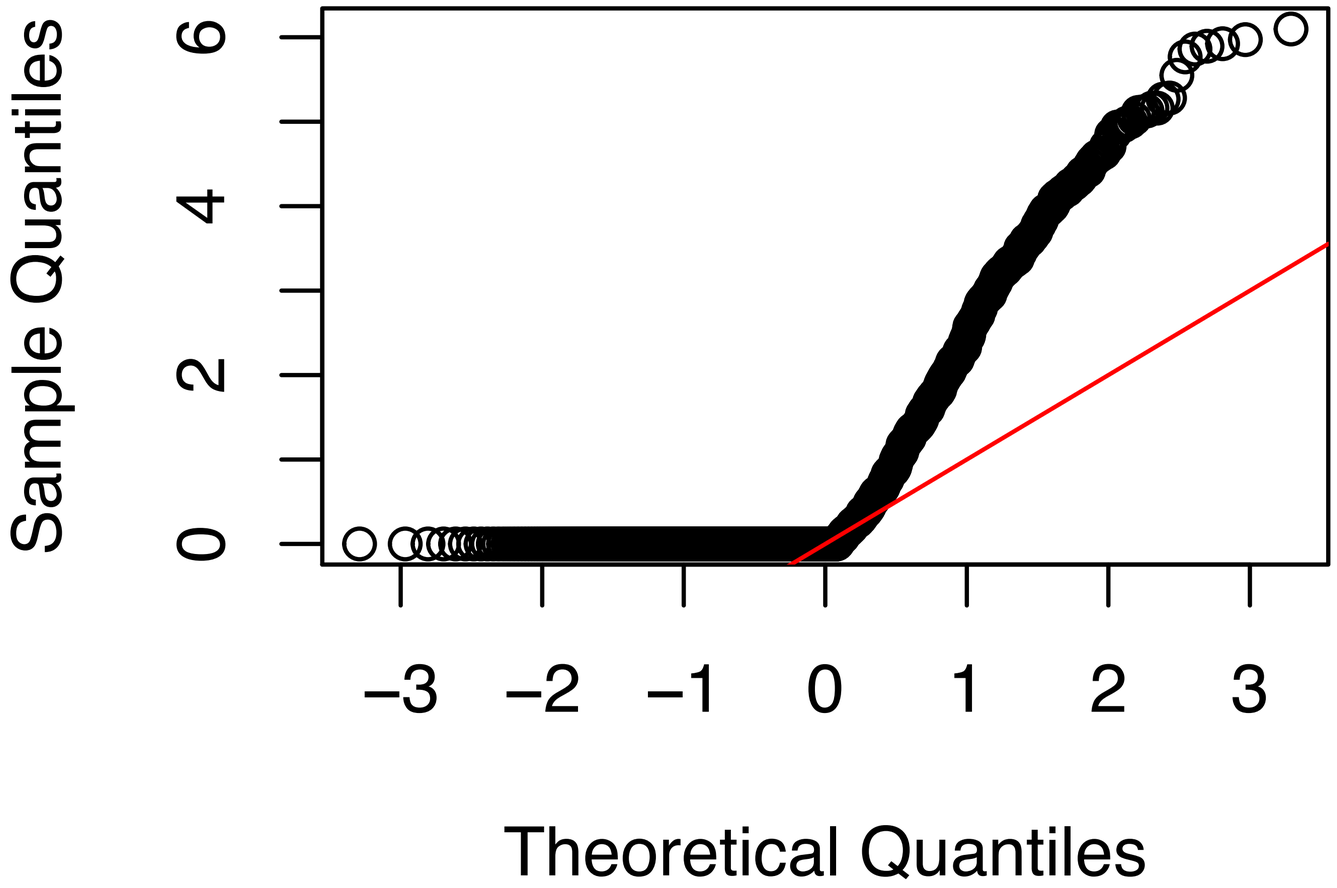
Histogram `hist`: Roughly... how are they distributed?





Quantile-quantile plot against standard Normal

```r
xv.rand <- sample(xv, 1000)       # random 1000 ponits
qqnorm(log(1+xv.rand), main="") # compare with the Normal
abline(a=0,b=1,col=2)             # diagnoal line
```



Side note: Why do many statisticians care about Normality?

- Full understanding of its properties
- Maximum entropy (most random/chaotic) distribution of real numbers
- Defined by first and second moments (mean and $\approx$ var.)
- Central Limit Theorem (will discuss in the next lecture)
- Many statistical methods were built on the Normality assumption.

Let's investigate the data more with ggplot

ggplot and dplyr love fully linearized format.

```
x.melt <- reshape2::melt(X); head(x.melt, 3)
```

```
##                 Var1            Var2    value
## 1 ENSG00000223972.5 DZQV_CD8_naive 0.214321
## 2 ENSG00000227232.5 DZQV_CD8_naive 4.759630
## 3 ENSG00000278267.1 DZQV_CD8_naive 0.000000
```

What are Var1 and Var2?

```
head(rownames(X), 3)
```

```
##                 V11                 V12                 V13
## "ENSG00000223972.5" "ENSG00000227232.5" "ENSG00000278267.1"
```

```
head(colnames(X), 3)
```

```
## [1] "DZQV_CD8_naive" "DZQV_CD8_CM"    "DZQV_CD8_EM"
```

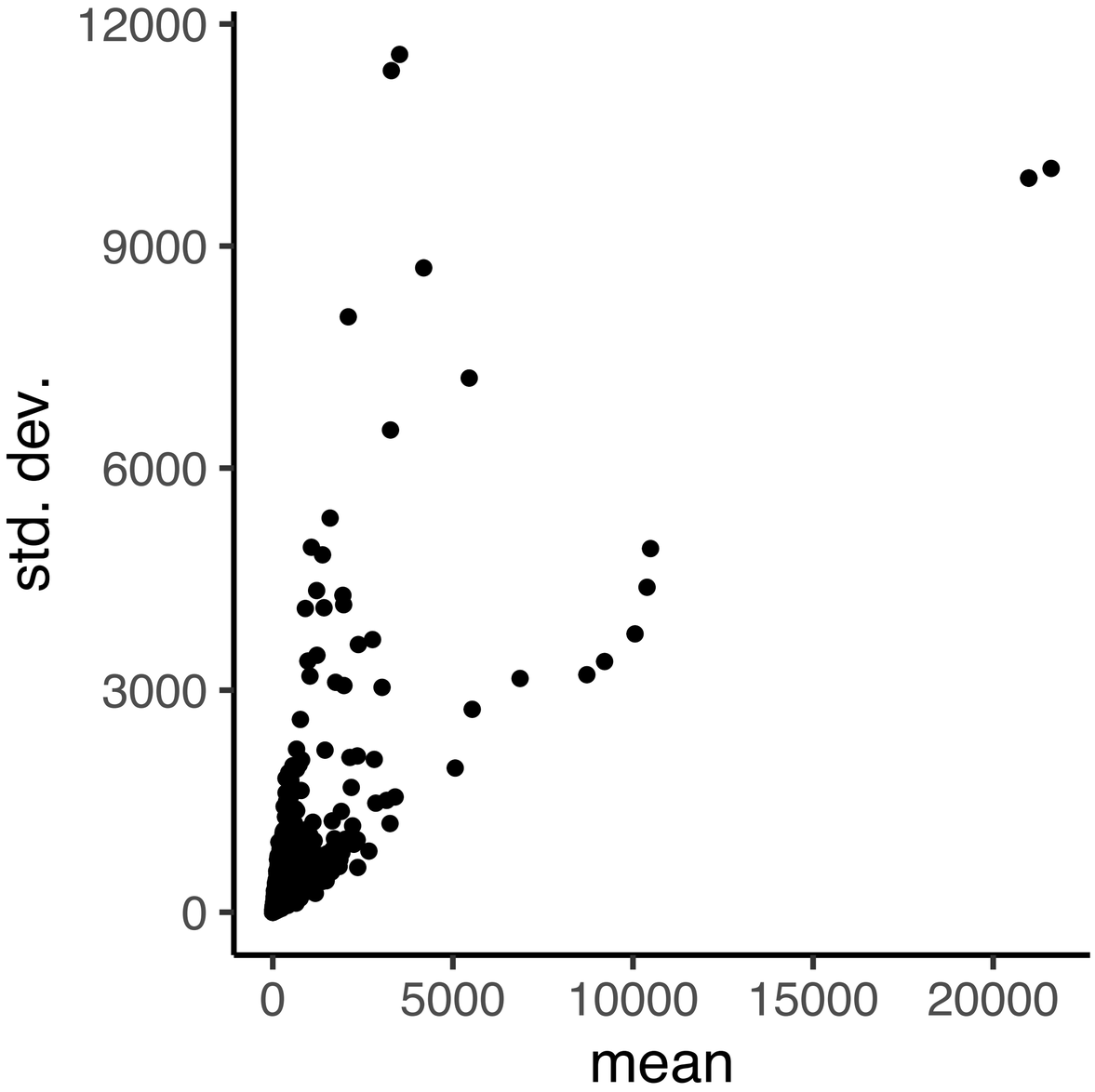
Excess of zeros... Can we zoom-in non-zero values?

```
row.stat <- x.melt %>%
    group_by(`Var1`) %>%
    summarize(m=mean(`value`),
              s=sd(`value`),
              nz=sum(`value` > 0),
              cv=`s`/`m`) %>%
    ungroup()
```

- `m`: the mean of each row (`Var1`)
- `s`: standard deviation
- `nz`: number of non-zeros
- `cv`: coefficient of variation (`s/m`)

```
zero.rows <- row.stat %>% filter(m == 0) %>%
    nrow()
tot.rows <- nrow(row.stat)
```

- 10,326 rows/features (out of 58,311) are just empty



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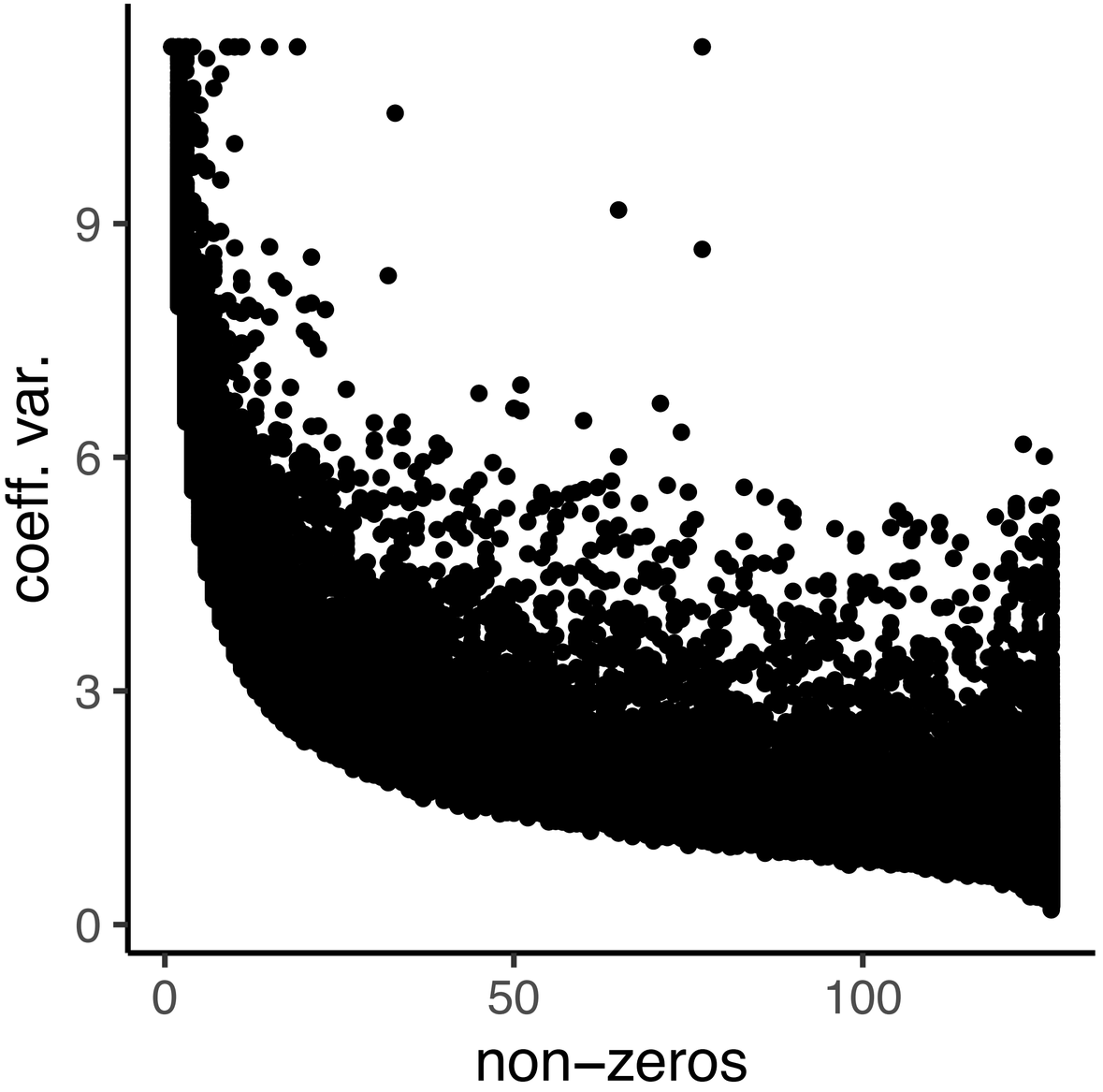

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              nz=sum(`value` > 0),
              cv=`s`/`m`) %>%
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```

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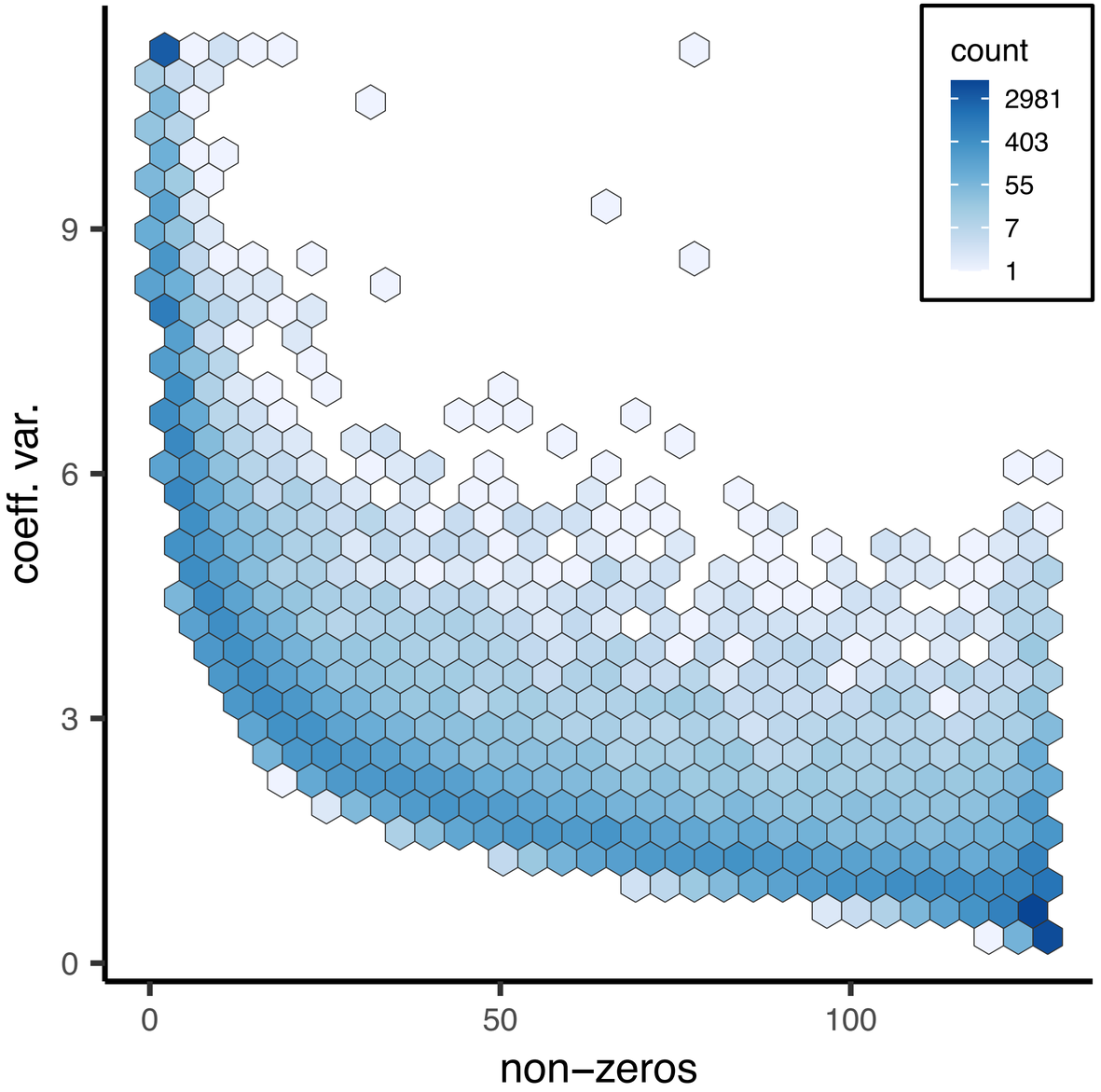


Filter out features (based on some statistics)

```
.df <- row.stat %>%
    filter(nz > 0)

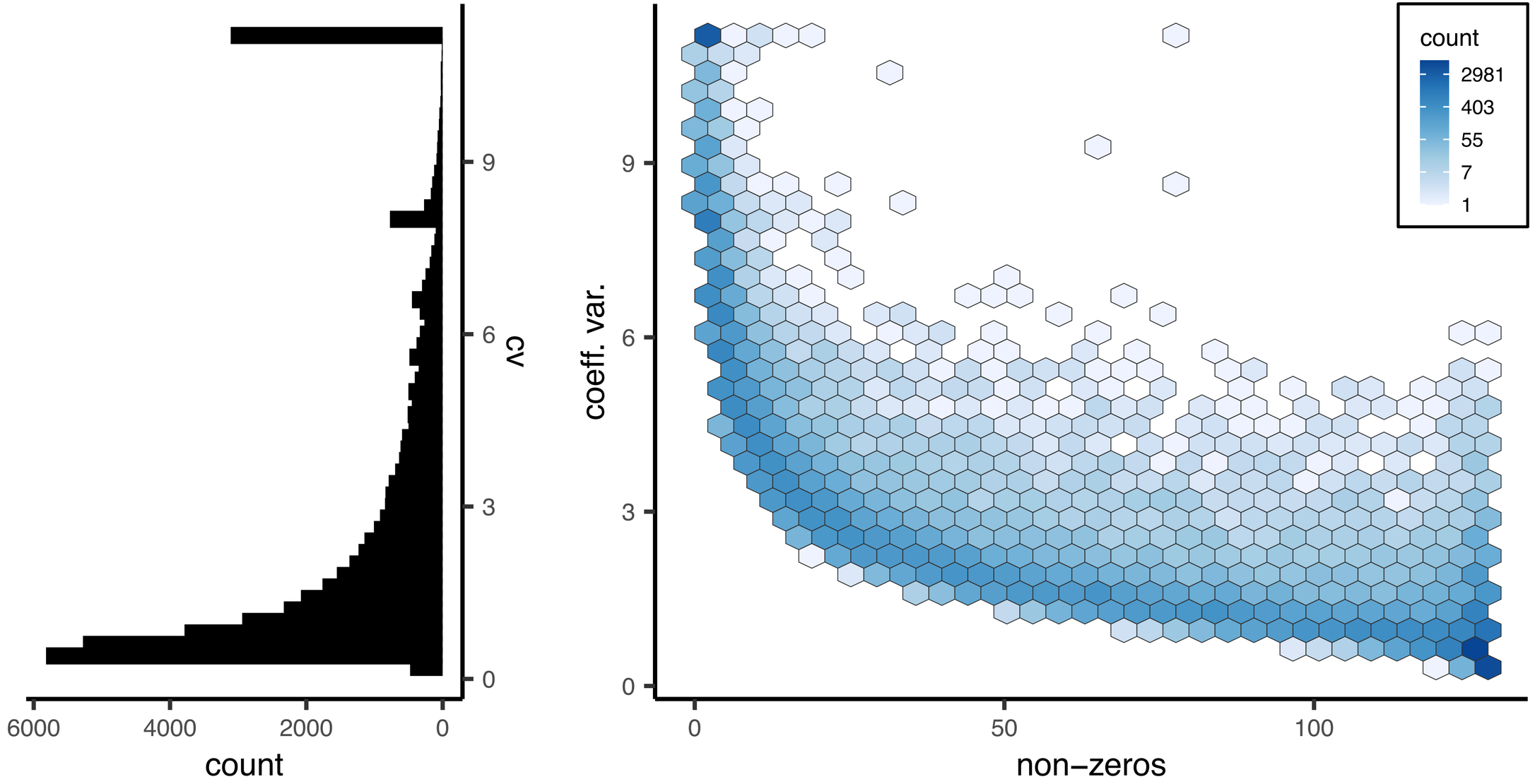
p1 <-
    .gg.plot(.df, aes(nz, cv)) +
    theme(legend.position = c(1,1), legend.justifi
    geom_hex(color="gray20", size=.1) +
    scale_fill_distiller(trans="log", labels=round
    xlab("non-zeros") +
    ylab("coeff. var.")
```

```
.df.cv.hist <- .df %>%
    group_by(cv = round(cv*5)/5) %>%
    summarize(count = n()) %>%
    ungroup()

p0 <-
    .gg.plot(.df.cv.hist, aes(x=0, xend=`count`, y=
    geom_segment(size=2) +
    scale_x_reverse("count") +
    scale_y_continuous(position="right")
```

Filter out features (based on some statistics)

```
wrap_plots(p0, p1, nrow=1, widths=c(2,4))
```



Filter out features (based on some statistics)

```
ub.cv <- quantile(.df$cv, .9) # throw away top 90% of CV
lb.cv <- quantile(.df$cv, .4) # bottom 30% of CV

lb.nz <- 10  # non-zero in at least 10 samples
ub.nz <- round(ncol(X) * .9) # avoid ubiquitously expressed

p1.1 <- p1 +
    geom_hline(yintercept = ub.cv, color="red", lty=2) +
    geom_hline(yintercept = lb.cv, color="red", lty=2) +
    geom_vline(xintercept = ub.nz, color="red", lty=2) +
    geom_vline(xintercept = lb.nz, color="red", lty=2)

p0.1 <- p0 +
    geom_hline(yintercept = ub.cv, color="red", lty=2) +
    geom_hline(yintercept = lb.cv, color="red", lty=2)
```

Filter out features (based on some statistics)

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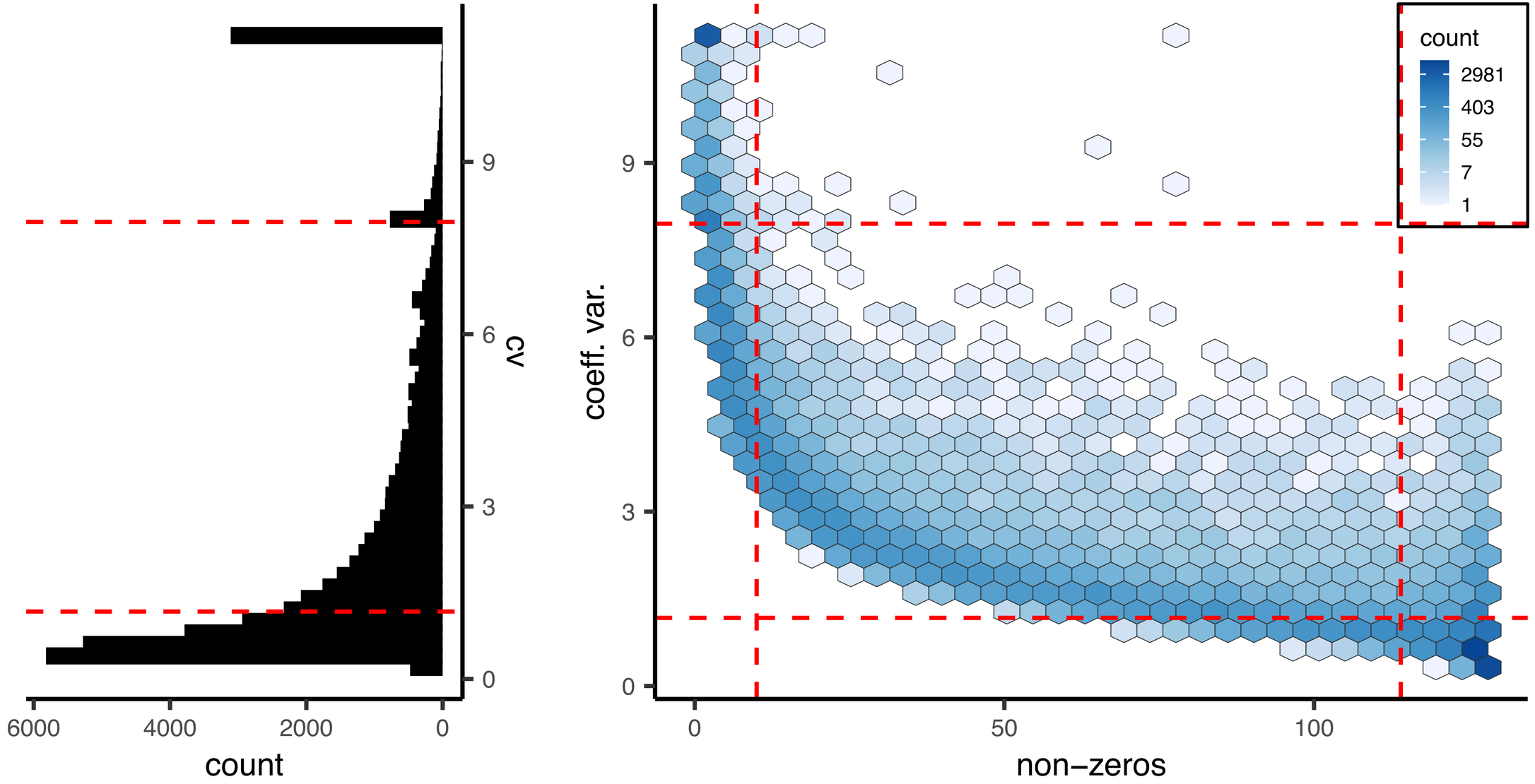
```



How do we find the threshold levels?

- Scientific rationale (based on the sequencing technology)
- Communications with collaborators
- Gut feeling/experience in the field
- Be honest and transparent (never look at the desired outcome, e.g., p-hacking)
- Sensitivity analysis

Let's take a deeper look at the sub-matrix focusing on informative features

Intersection with the full data tuples

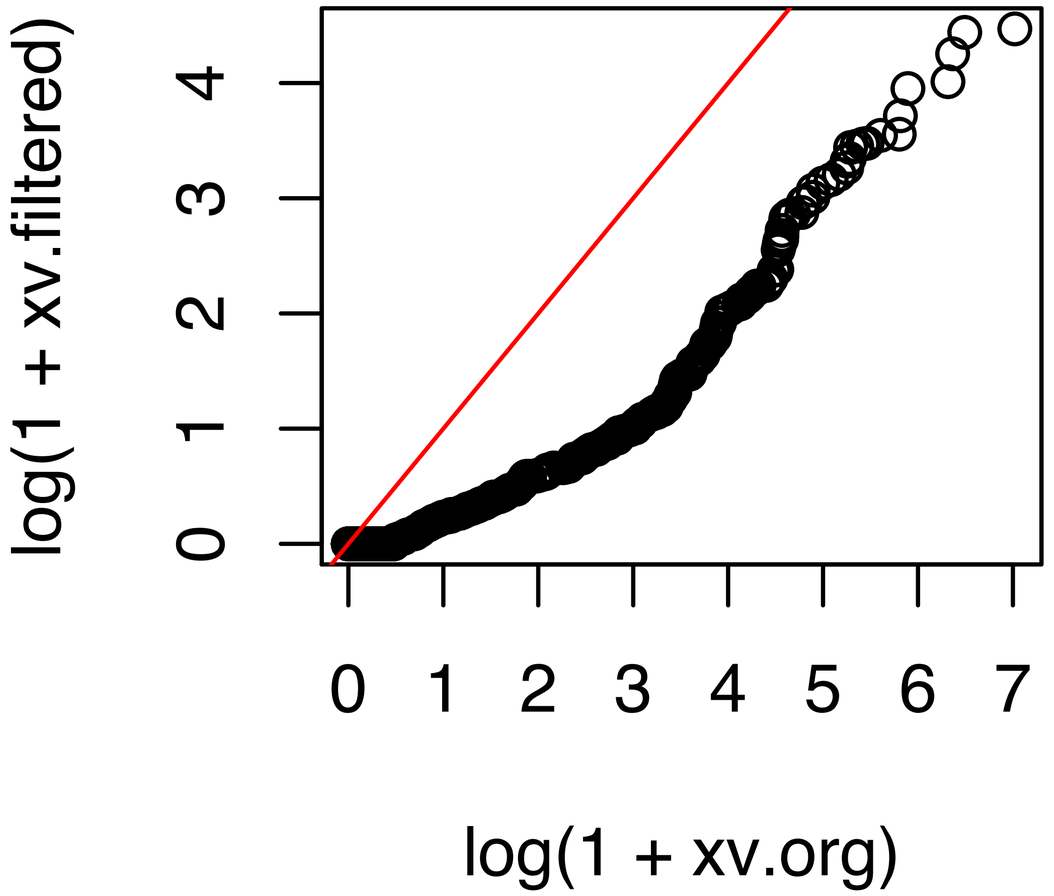
```
valid.rows <-
    row.stat %>%
    filter(`cv` < ub.cv, `cv` > lb.cv) %>%
    filter(`nz` < ub.nz, `nz` > lb.nz) %>%
    select(`Var1`)

x.melt.valid <-
    left_join(valid.rows, x.melt, by = "Var1")
```

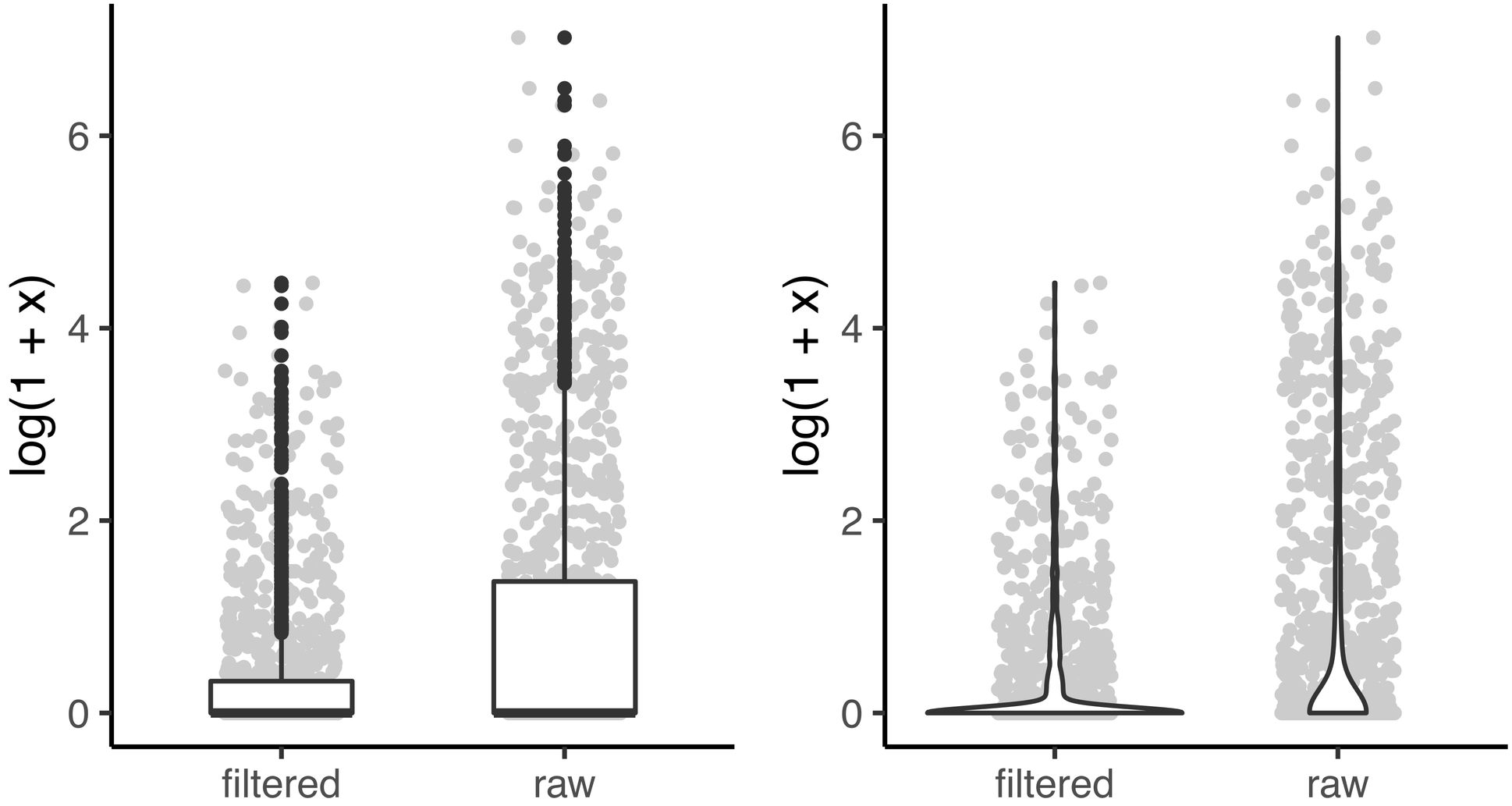
What could happen after the filtering?

```
## random 1000 ponits
xv.org <- sample(xv, 1000)
## random 1000 ponits
## among the retained
xv.filtered <-
    sample(x.melt.valid$value, 1000)
```

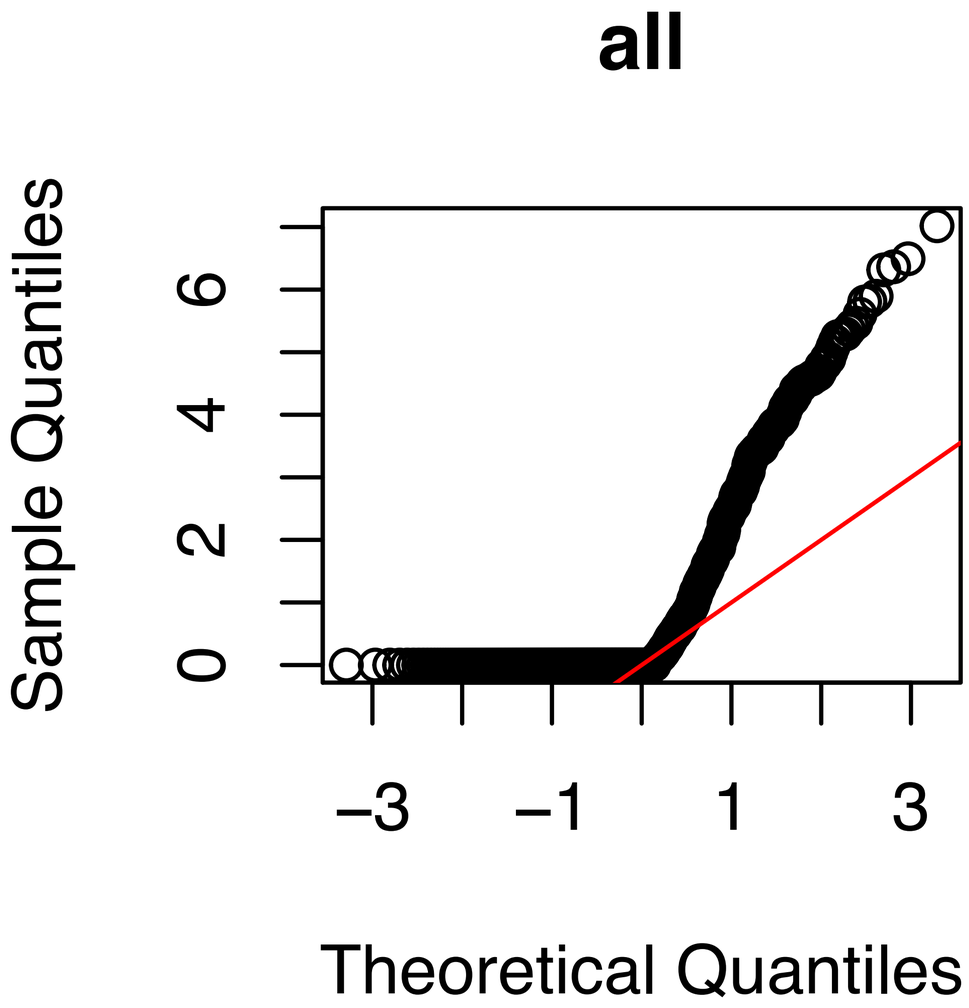
- What have we done?
- Which side is generally bigger?

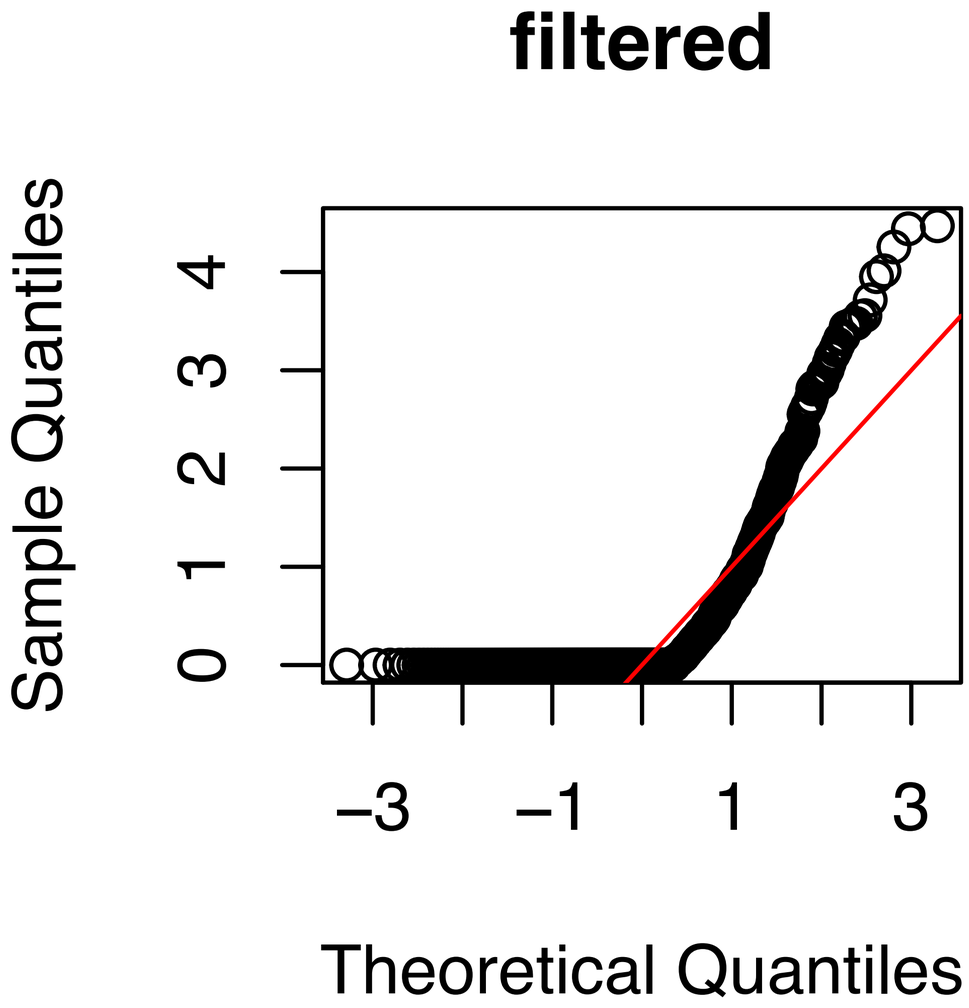


What could happen after the filtering?



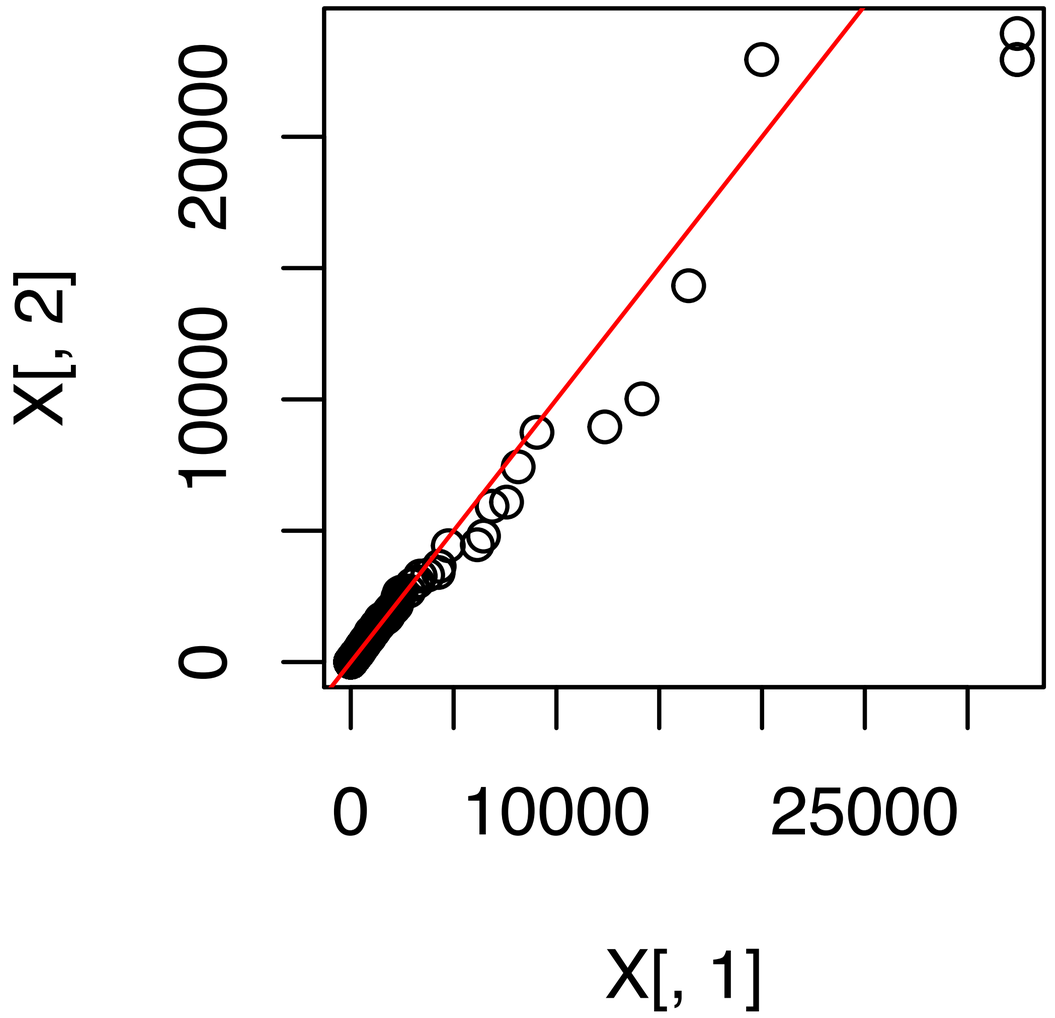
What could happen after the filtering? Normality of "log(1 + x)"



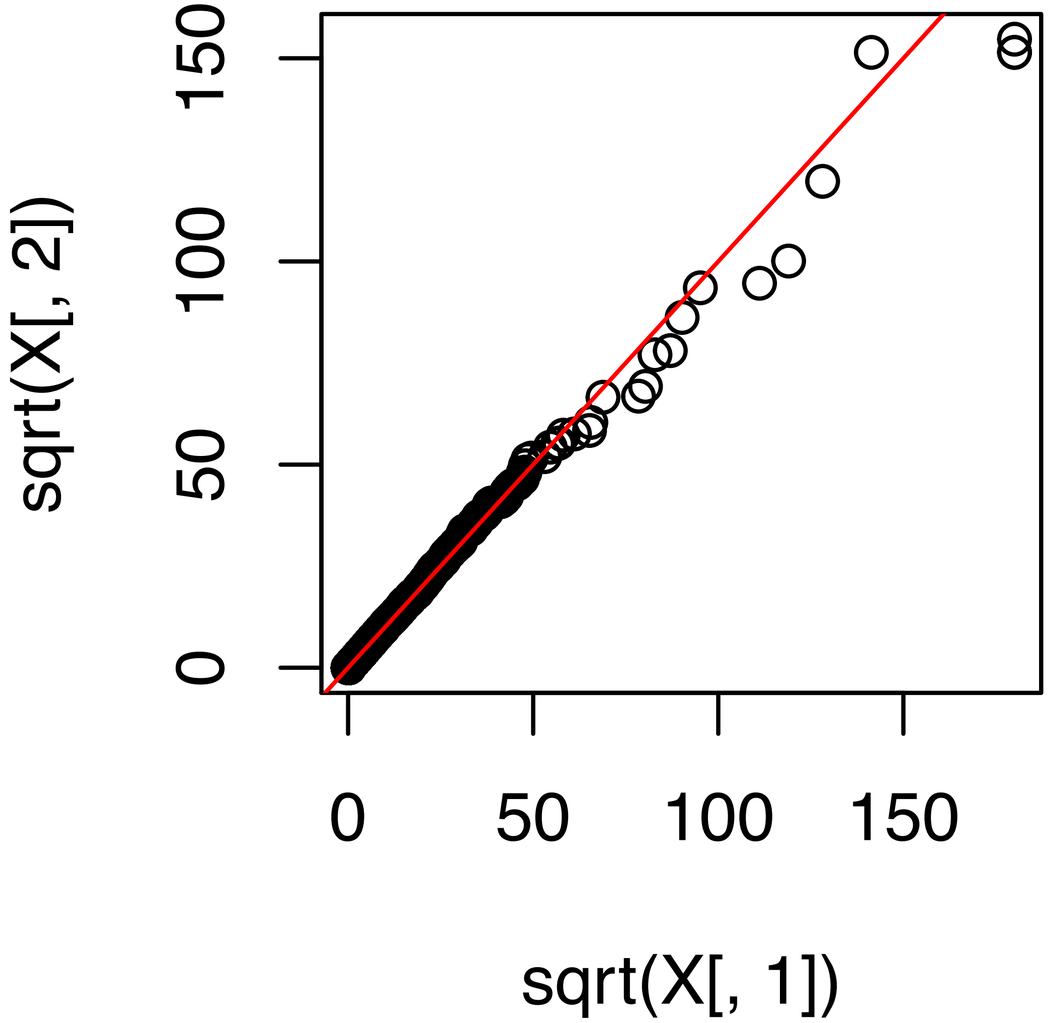


What about relationships between two columns (samples)?

```
qqplot(X[,1], X[,2])    # raw X1 and X2
abline(a=0,b=1,col=2)   # diagnoal line
```




```
qqplot(sqrt(X[,1]), sqrt(X[,2]))
abline(a=0,b=1,col=2)   # diagnoal line
```



Can we compare them in a more systematic way?

```
R.1 <- cor(X, method="pearson")
R.2 <- cor(X, method="spearman")
```

- What is the dimensionality of R?

```
dim(R.1)
```

```
## [1] 127 127
```

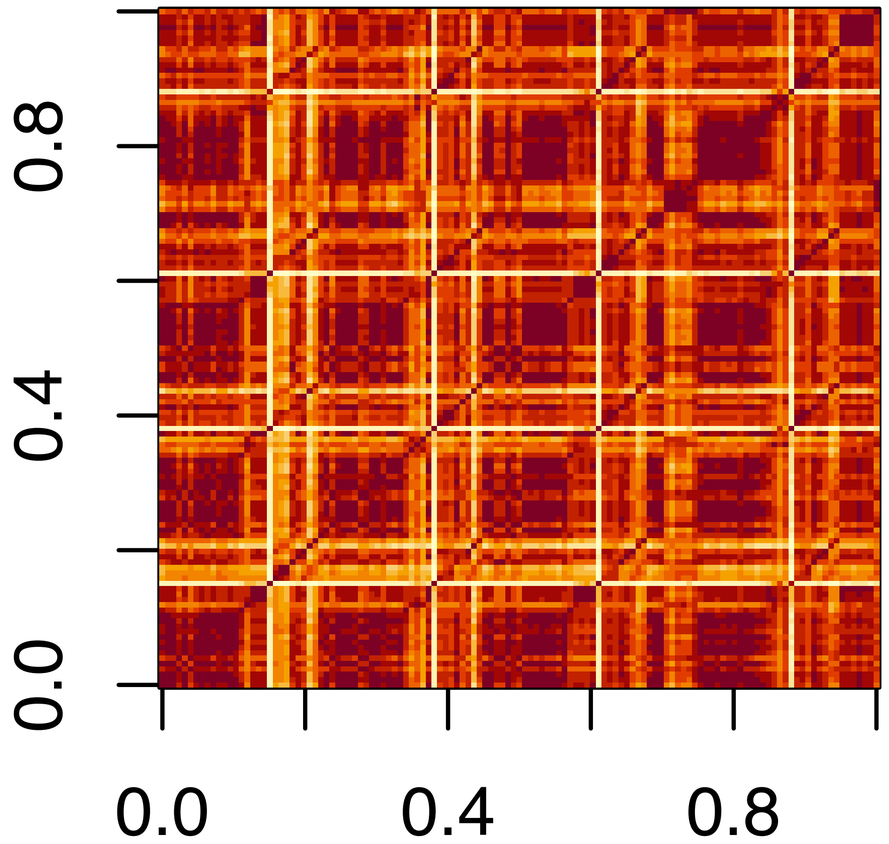
```
R.1[1:3, 1:3]
```

```
##                 DZQV_CD8_naive DZQV_CD8_CM DZQV_CD8_EM
## DZQV_CD8_naive       1.0000000   0.9659527   0.9335116
## DZQV_CD8_CM          0.9659527   1.0000000   0.9767444
## DZQV_CD8_EM          0.9335116   0.9767444   1.0000000
```

- What's the difference between the "pearson" and "spearman" methods?

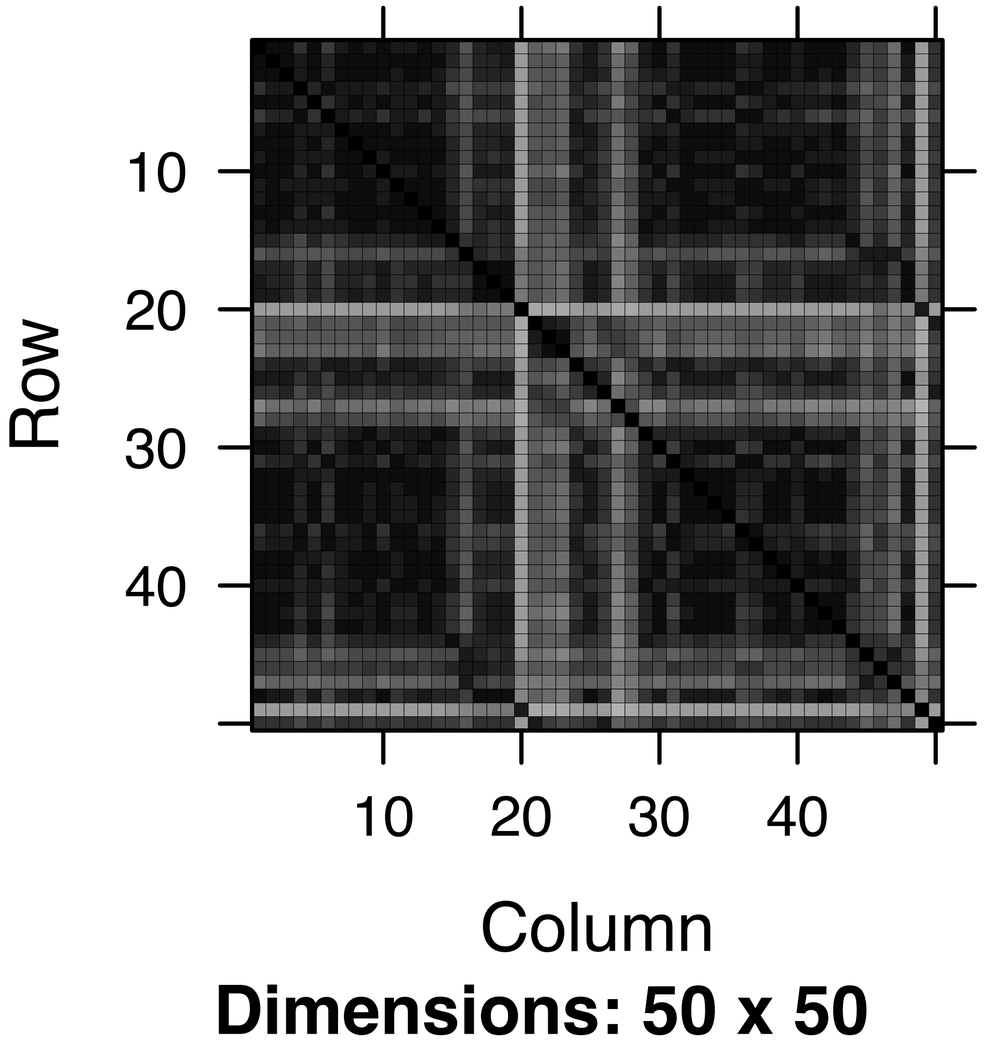
Quick visualization – base version 1

```
image(R.1)
```

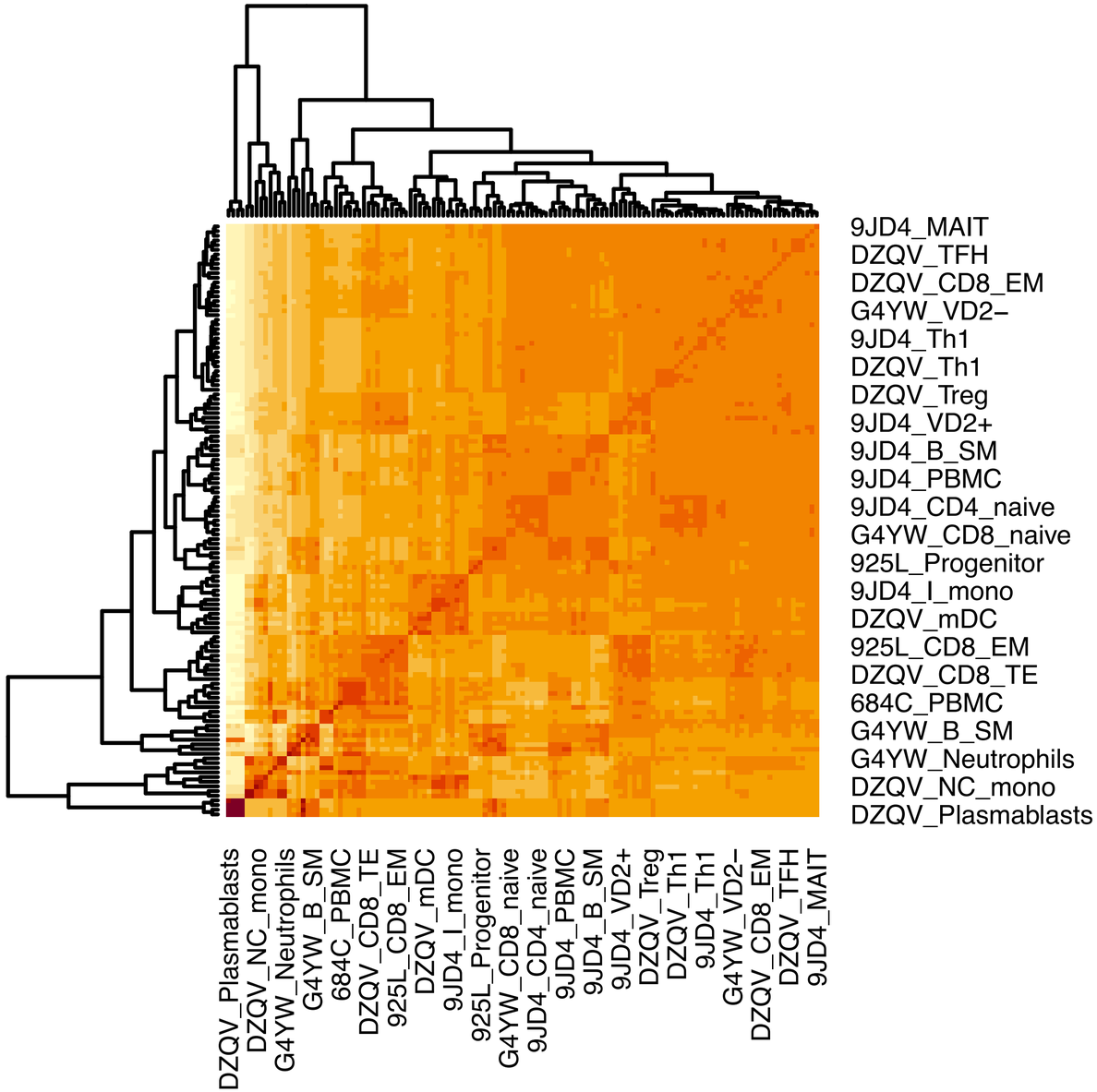


Quick visualization – base version 2

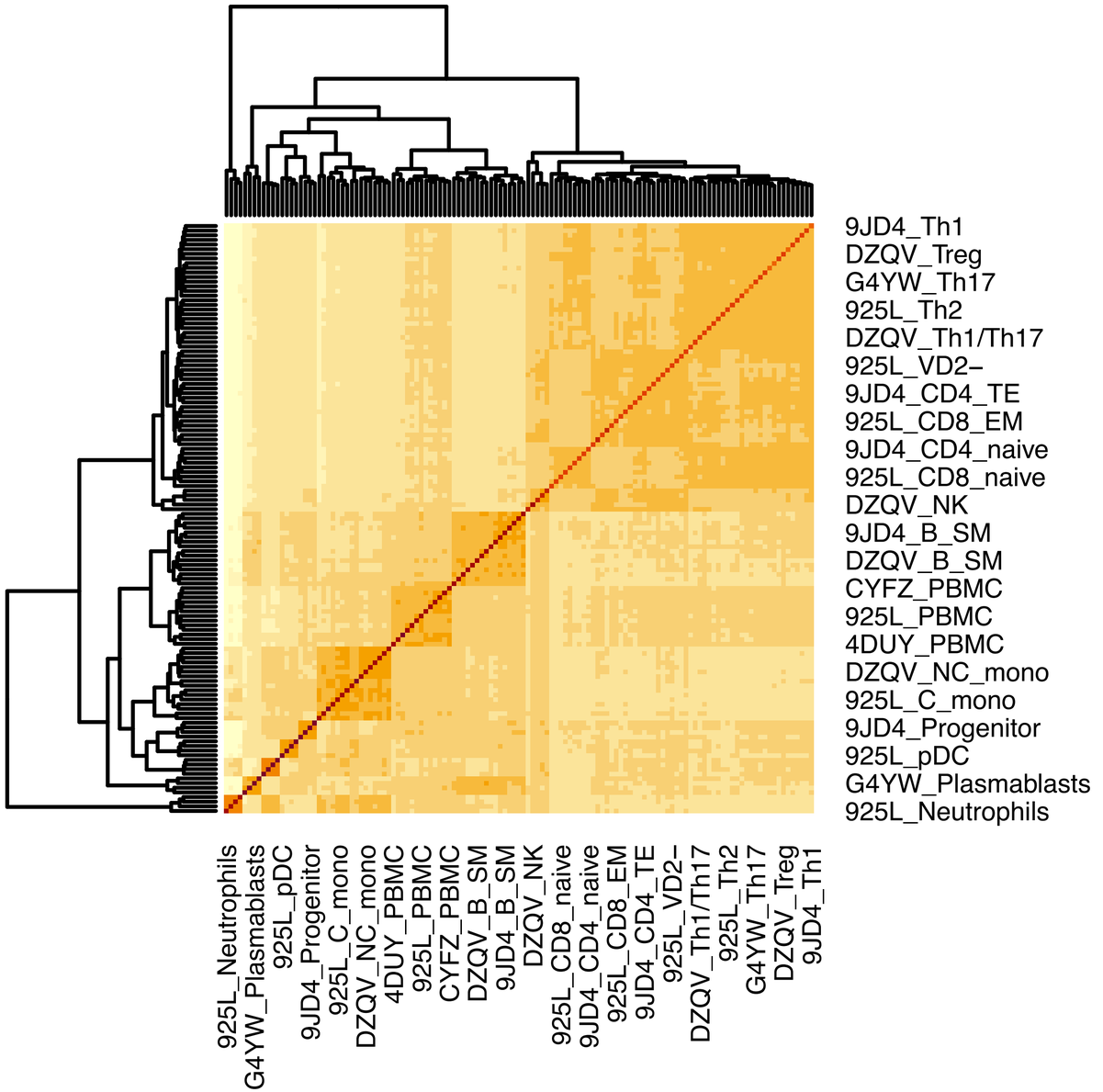
```
image(Matrix::Matrix(R.1[1:50, 1:50]))
```



We may use `heatmap` function for a small matrix (Pearson)



We may use `heatmap` function for a small matrix (Spearman)

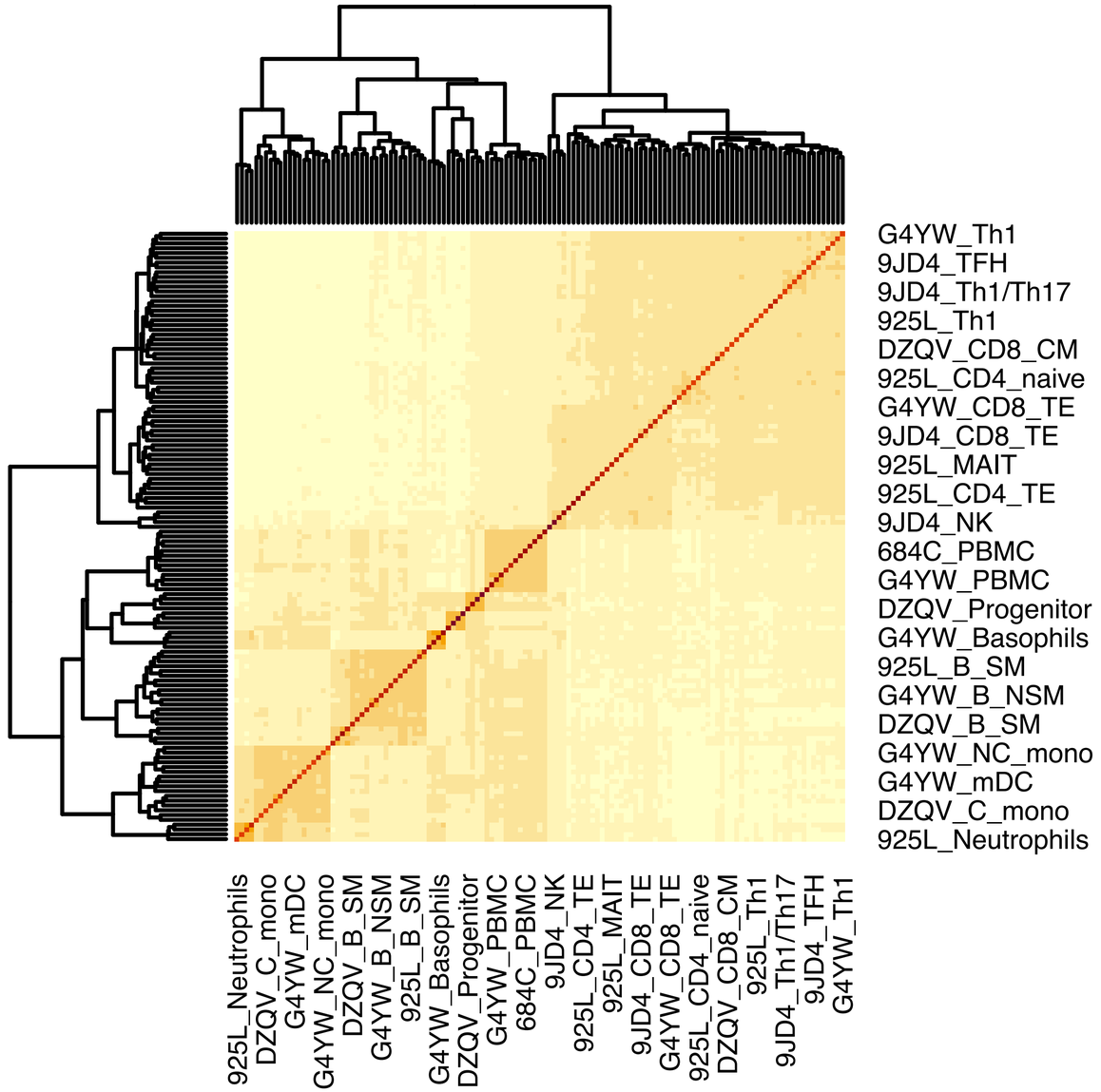


Wait, didn't we filter out some features?

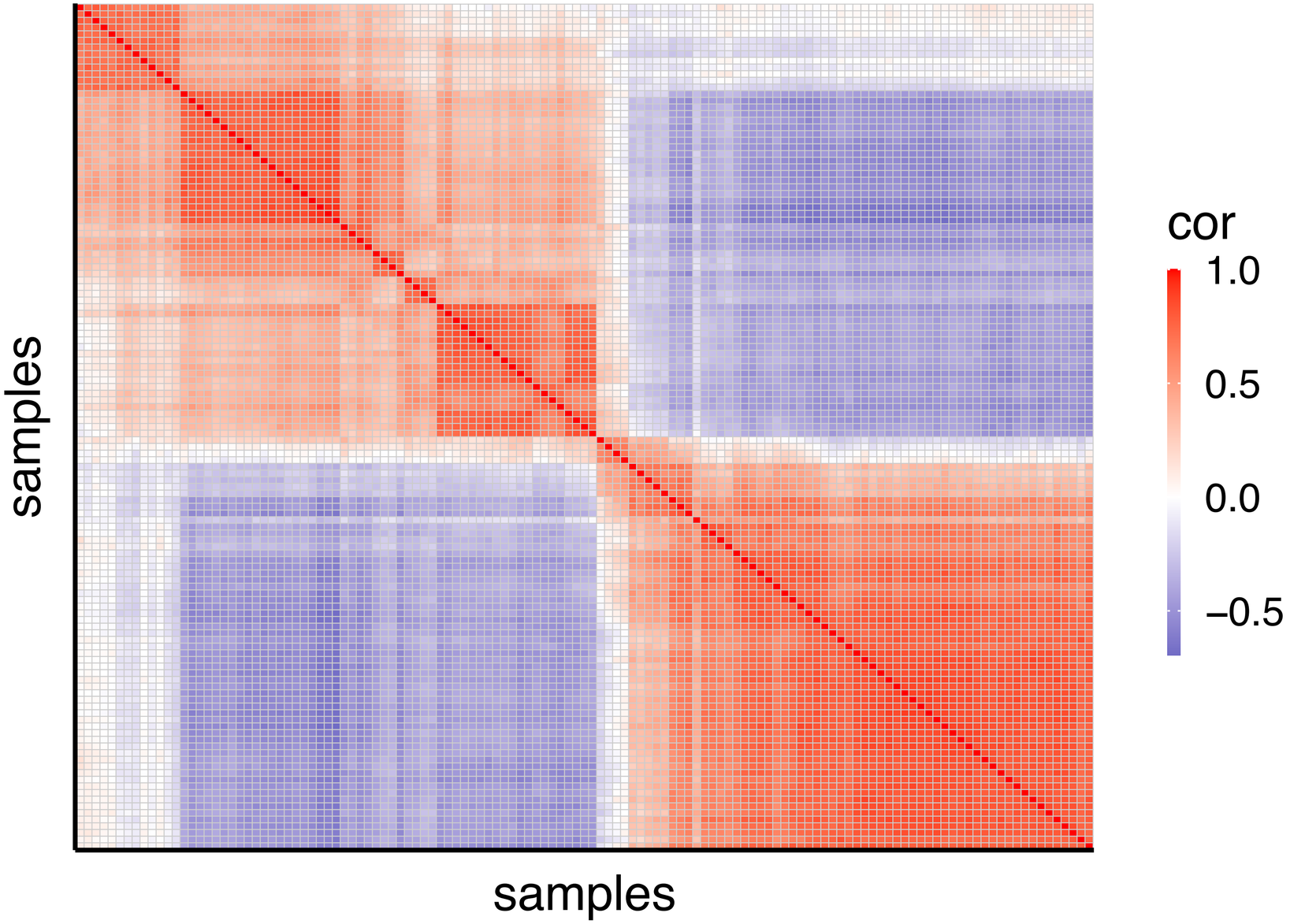
```
x.valid <- X[as.character(unlist(valid.rows)), ]
```

```
R <- cor(x.valid, method="spearman")
```

After removing the list of unwanted features



Just focusing on the top features



Today's lecture: EDA & Exp Design

- **Exploratory Data Analysis**
  - First steps to data analysis
  - Traditional (low-dimensional) approaches
  - High-dimensional methods
  - Tips on how to organize your data/project
- **Experimental Design**
  - Observational vs. Experimental studies
  - Identification of unwanted variation (SVA)
  - Causal inference: matching, stratification, inverse propensity

High-dimensional EDA methods

Clustering

- Group similar features into representative ones
- Group samples
- Lect 15

Dimensionality reduction

- Synthesize new features as a (linear) combination of existing features
- Map high-dim. data points onto latent space (Lect 12-)

What can help us in the high-dimensional setting? Essentially, our only hope is that the data is endowed with ***some form of low-dimensional structure****, one which makes it simpler than the high-dimensional view might suggest.*

Wainwright, High-dimensional Statistics

```
top.vars <-
    x.melt.valid %>%
    group_by(`Var2`) %>%
    top_n(n=15, wt=`value`) %>%
    ungroup() %>%
    select(Var1) %>%
    unique()
```

```
col.names <-
    x.melt.valid %>%
    select(`Var2`) %>%
    unique() %>%
    mutate(type = substr(`Var2`, 6, 99)) %>%
    mutate(m = `type`) %>%
    separate(`m`, c("major.type","remove"), sep="[_-]") %>%
    select(-`remove`)
```

```
head(col.names, 3)
```

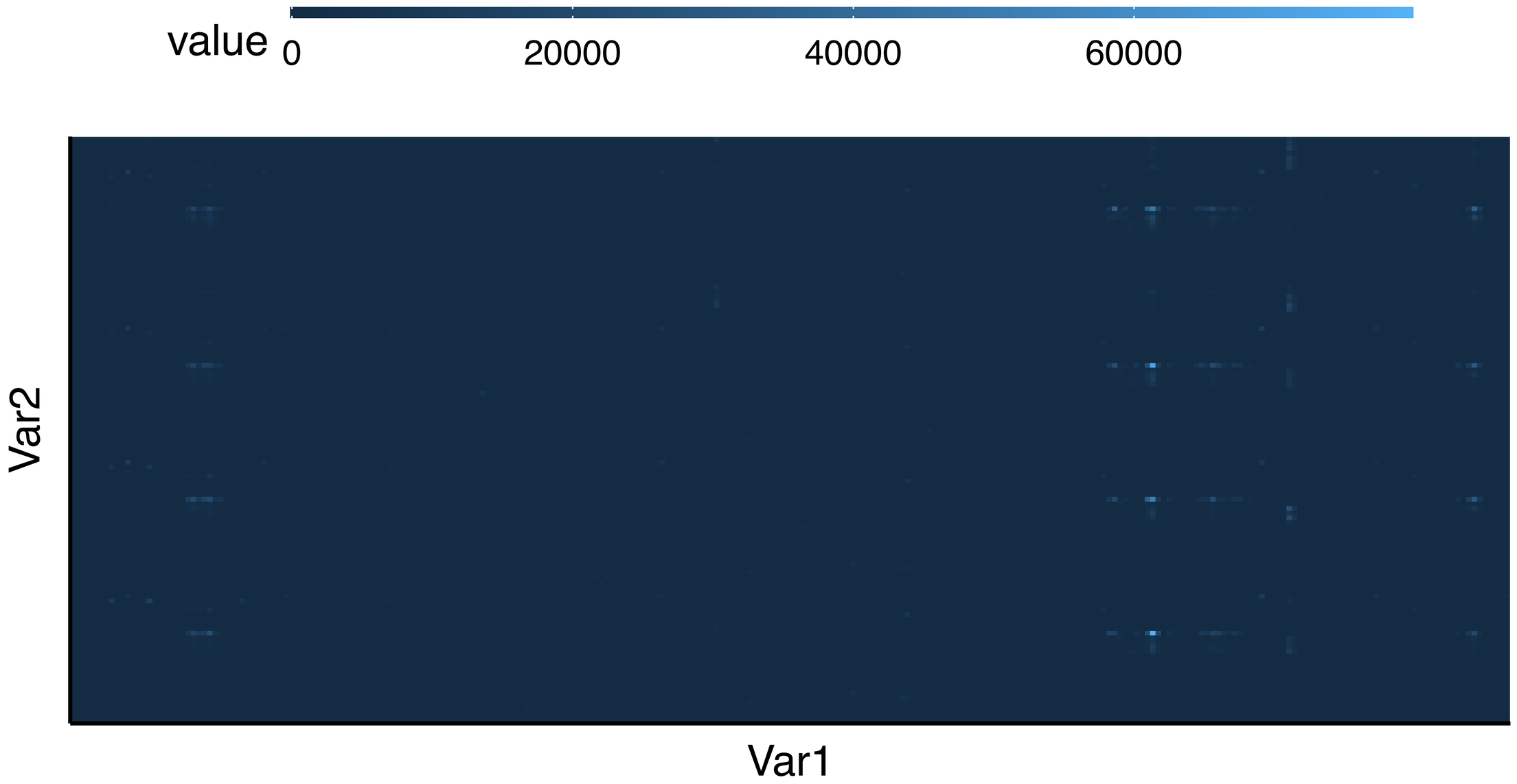
```
## # A tibble: 3 x 3
##   Var2           type      major.type
##   <fct>          <chr>     <chr>
## 1 DZQV_CD8_naive CD8_naive CD8
## 2 DZQV_CD8_CM    CD8_CM    CD8
## 3 DZQV_CD8_EM    CD8_EM    CD8
```

Drawing a heatmap for the top features

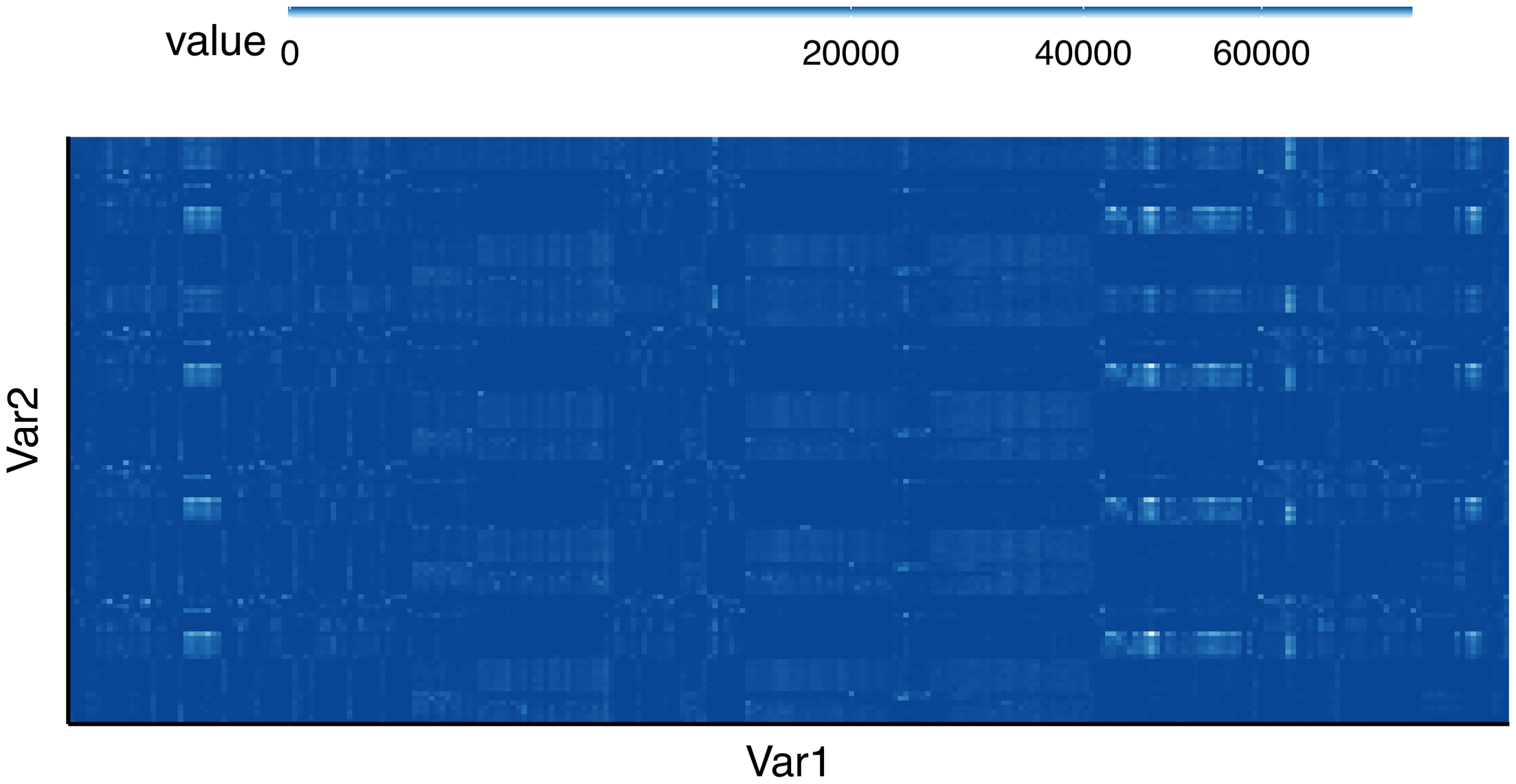
```
heat.df <- top.vars %>%
    left_join(x.melt.valid, by="Var1")
```

```
p0 <-
    ggplot(heat.df, aes(Var1, Var2, fill=value)) +
    geom_tile() +
    theme(axis.text=element_blank(), axis.ticks=element_blank()) +
    theme(legend.position = "top",
          legend.key.height = unit(.2, "lines"),
          legend.key.width = unit(4, "lines"))
```

A vanilla version



A simple transformation will provide a more informative view

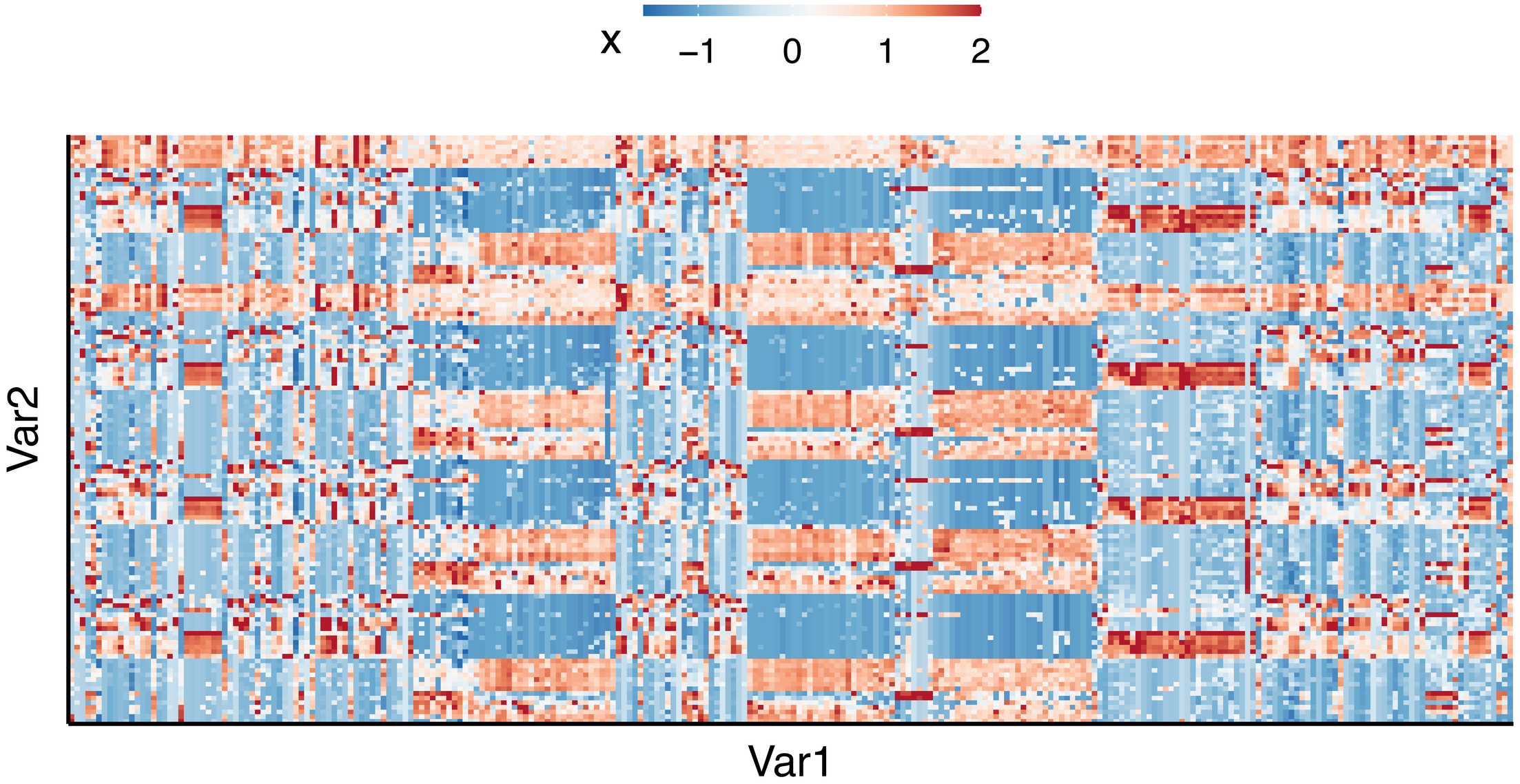


Can we normalize across samples?

```
heat.df <- heat.df %>%
    mutate(x.log = log(1 + `value`)) %>%
    group_by(`Var1`) %>%
    mutate(x.log.std = (x.log - mean(x.log))/sd(x.log)) %>%
    ungroup()
```

```
.aes <- aes(Var1, Var2, fill=pmin(pmax(`x.log.std`, -2), 2))
p1 <-
    ggplot(heat.df, .aes) +
    geom_tile() +
    theme(axis.text=element_blank(), axis.ticks=element_blank()) +
    theme(legend.position = "top",
          legend.key.height = unit(.2, "lines"))
```

Can we normalize across samples



Sorting columns by cell type (Var2)

```
heat.df <- heat.df %>% left_join(col.names)
```

```
v2.order <-
    heat.df %>%
    select(`type`, `Var2`) %>%
    arrange(`type`) %>%
    unique() %>%
    select(`Var2`) %>%
    unlist() %>%
    as.character()
```

```
head(v2.order, 3)
```

```
## [1] "DZQV_B_Ex" "925L_B_Ex" "9JD4_B_Ex"
```

Sorting columns by cell type (Var2)

Recover the data matrix after sorting the rows by v2.order

```
M <- heat.df %>%
    select(Var1, Var2, x.log.std) %>%
    mutate(Var2 = factor(Var2, v2.order)) %>%
    spread(Var1, value=x.log.std, fill = 0)
```

Diagnoalize the order of columns by maximum value positions

```
argmax.v2.index <- apply(M[, -1], 2, which.max)
.order <- order(argmax.v2.index, decreasing=TRUE)
v1.order <- colnames(M)[-1][.order]
```

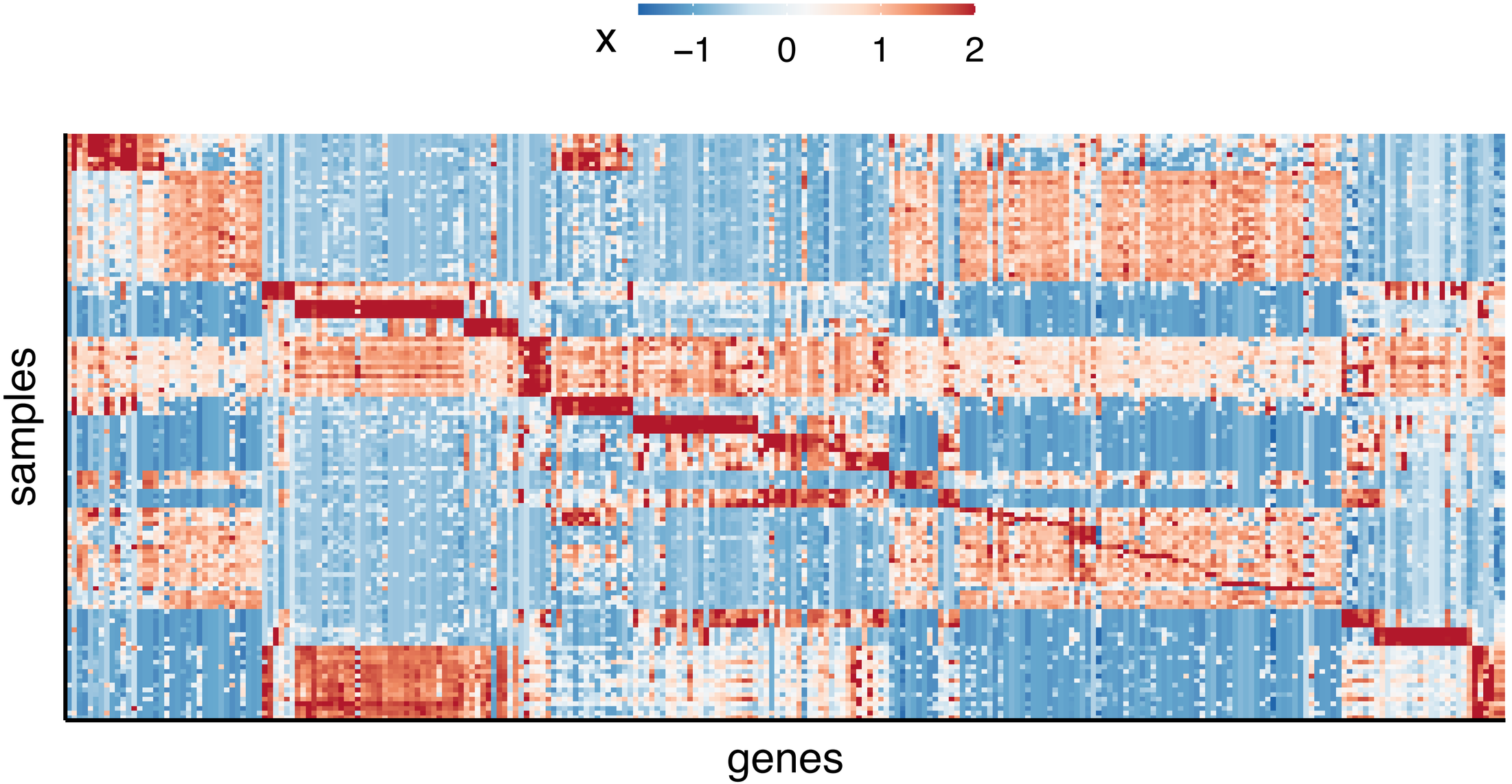
Plotting the heatmap after sorting the rows and columns

```
heat.df <- heat.df %>%
    mutate(v1.sorted = factor(Var1, v1.order)) %>%
    mutate(v2.sorted = factor(Var2, v2.order))

.aes <- aes(v1.sorted, v2.sorted, fill=pmin(pmax(`x.log.std`, -2), 2))

p2 <-
    ggplot(heat.df, .aes) +
    geom_tile() +
    theme(axis.text=element_blank(), axis.ticks=element_blank()) +
    theme(legend.position = "top",
          legend.key.height = unit(.2, "lines"))
```

Plotting the heatmap after sorting the rows and columns



Take one step forward compare ...

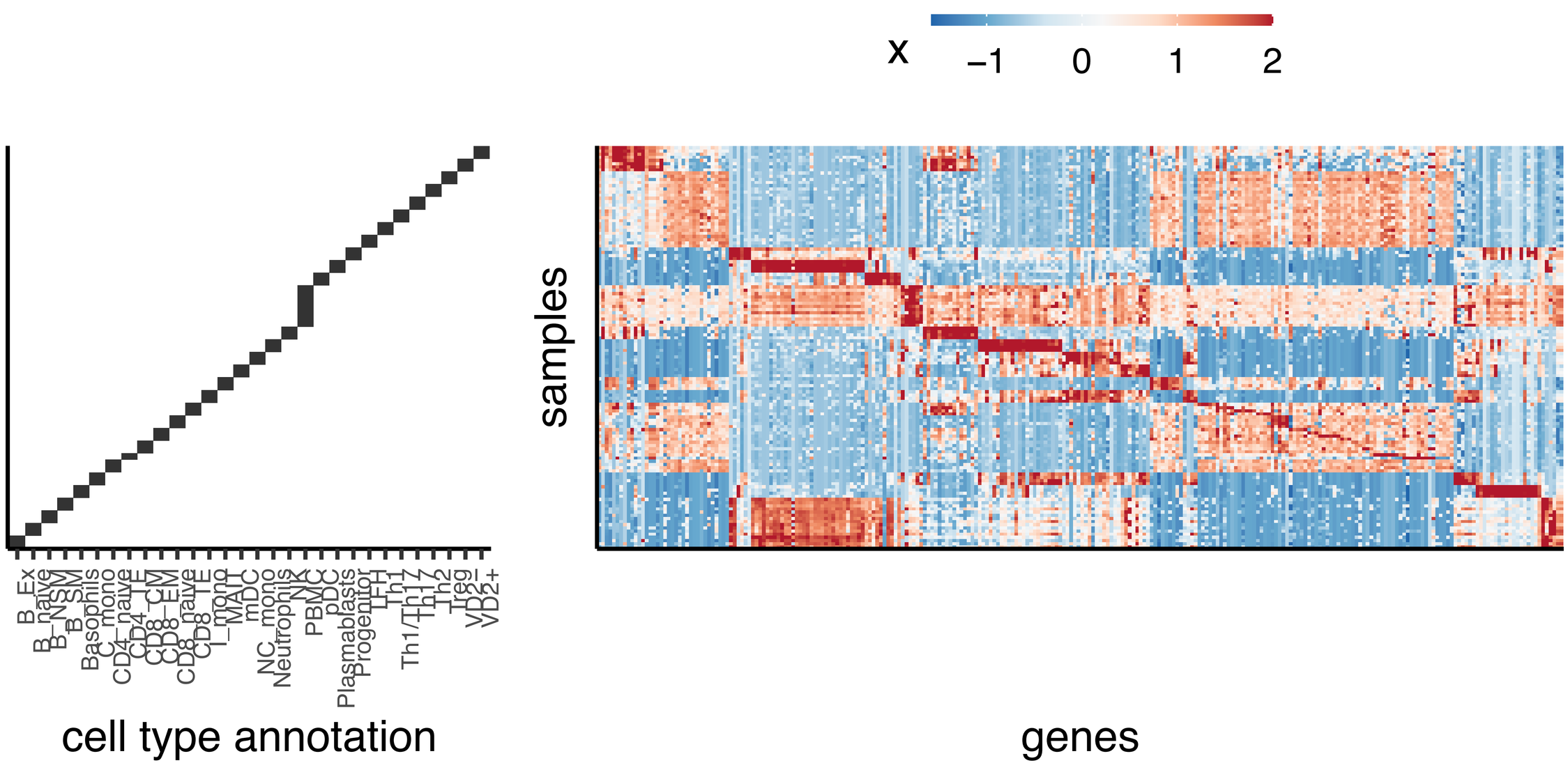
```
annot.df <-
    col.names %>%
    mutate(v1.sorted = factor(type)) %>%
    mutate(v2.sorted = factor(Var2, v2.order))
```

```
.aes <- aes(v1.sorted, v2.sorted)

p2.1 <-
    ggplot(annot.df, .aes) + geom_tile() + xlab("cell type annotation") +
    theme(axis.title.y = element_blank(),
          axis.text.y = element_blank(),
          axis.ticks.y = element_blank(),
          axis.text.x = element_text(size=6, angle=90, vjust=1, hjust=1))

p2.2 <- p2 +
    scale_fill_distiller("x", palette = "RdBu", direction=-1) +
    ylab("samples") + xlab("genes")
```

Compare this heatmap with known cell type annotations



High-dimensional EDA methods

Clustering

- Group similar features into representative ones
- Group samples
- Lect 15

Dimensionality reduction

- Synthesize new features as a (linear) combination of existing features
- Map high-dim. data points onto latent space (Lect 12-)

What can help us in the high-dimensional setting? Essentially, our only hope is that the data is endowed with ***some form of low-dimensional structure****, one which makes it simpler than the high-dimensional view might suggest.*

Wainwright, High-dimensional Statistics

Principal component analysis

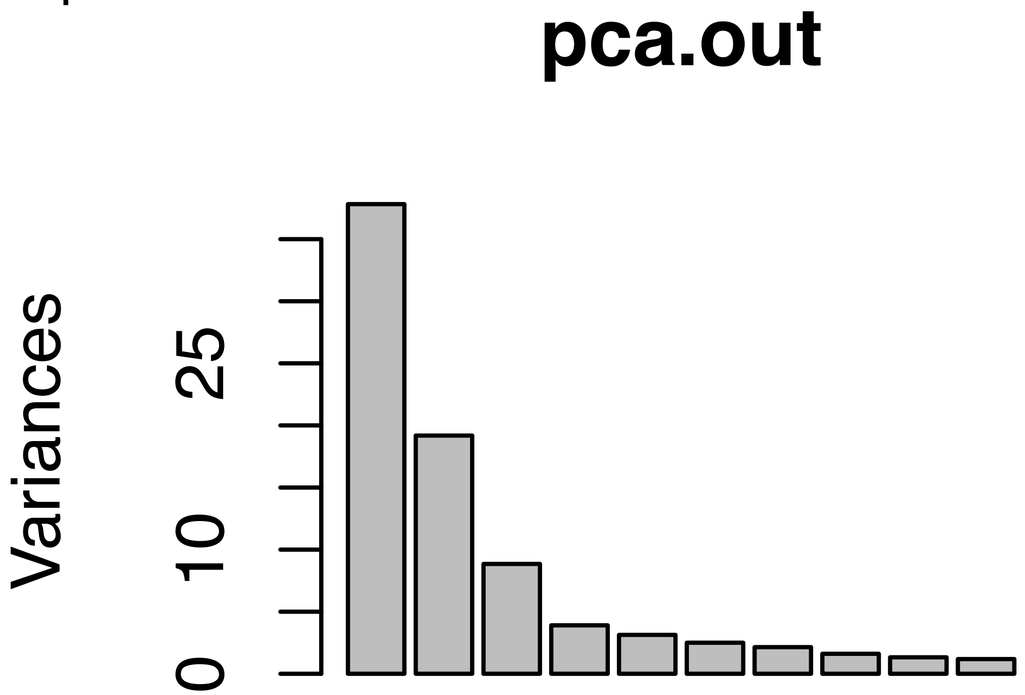
```
xx <- log(1 + x.valid)
## Note: measure PCs for the columns
pca.out <- prcomp(xx, scale.=TRUE)

## Extract the output
pcs <- pca.out$rotation[, 1:3]

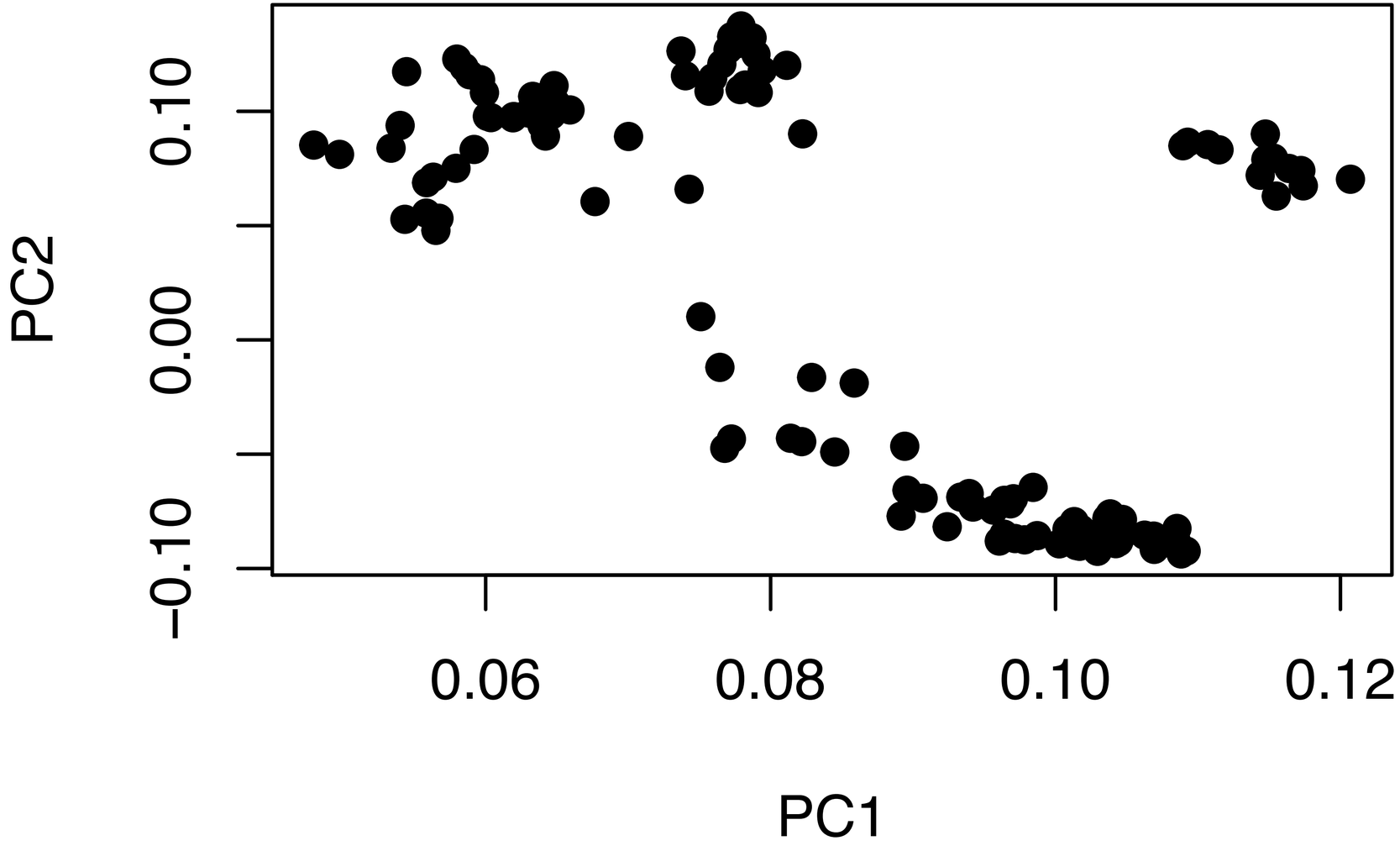
head(pcs, 3)
```

```
##                          PC1          PC2           PC3
## DZQV_CD8_naive 0.09239707 -0.08174110  0.012668092
## DZQV_CD8_CM    0.10112809 -0.08644983  0.005001030
## DZQV_CD8_EM    0.10360903 -0.07807551 -0.001014498
```

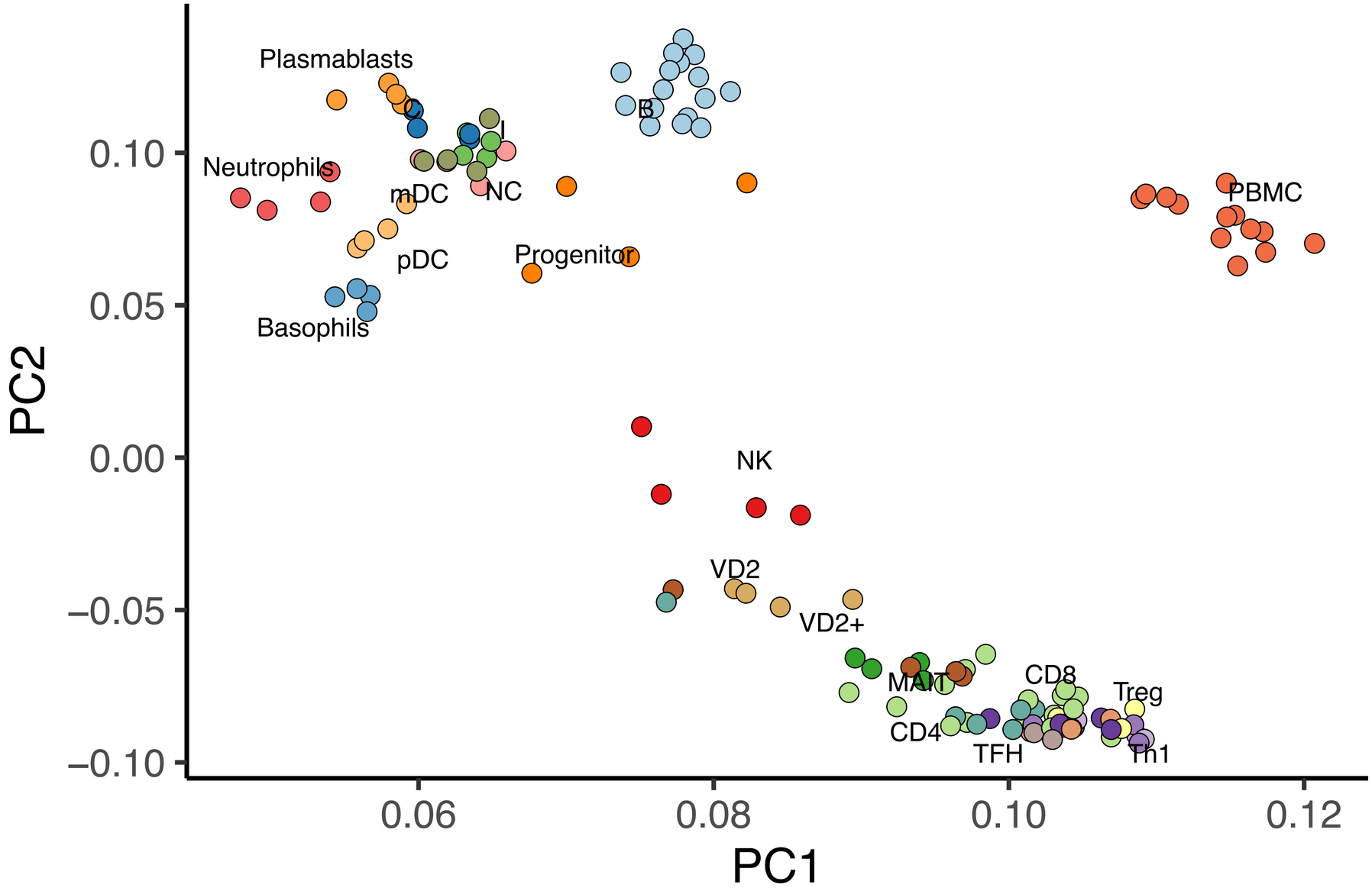
How much variance was explained by each component?



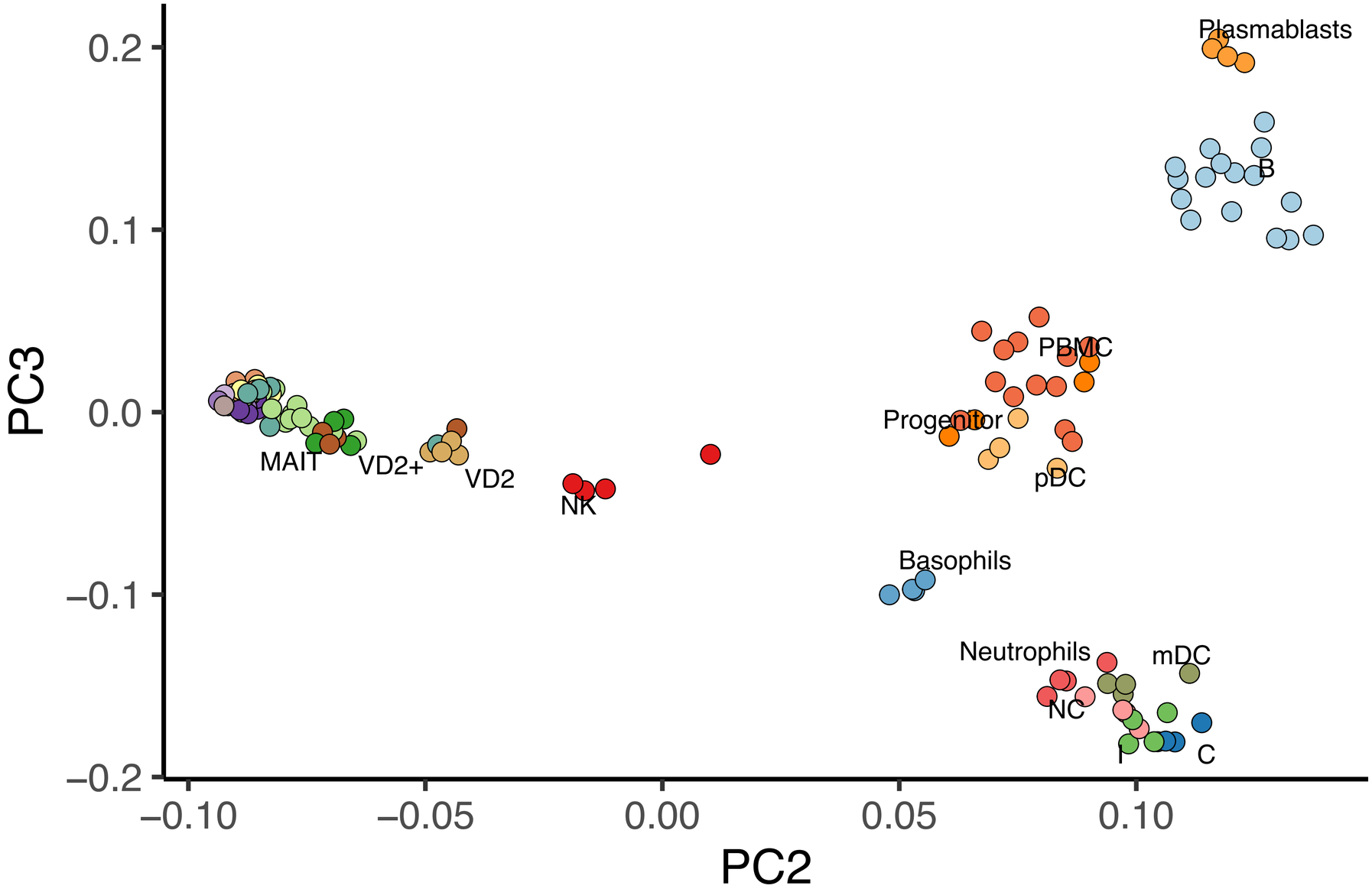
Top principal components



Top principal components



Top principal components



t-SNE: Other dimensionality reduction methods

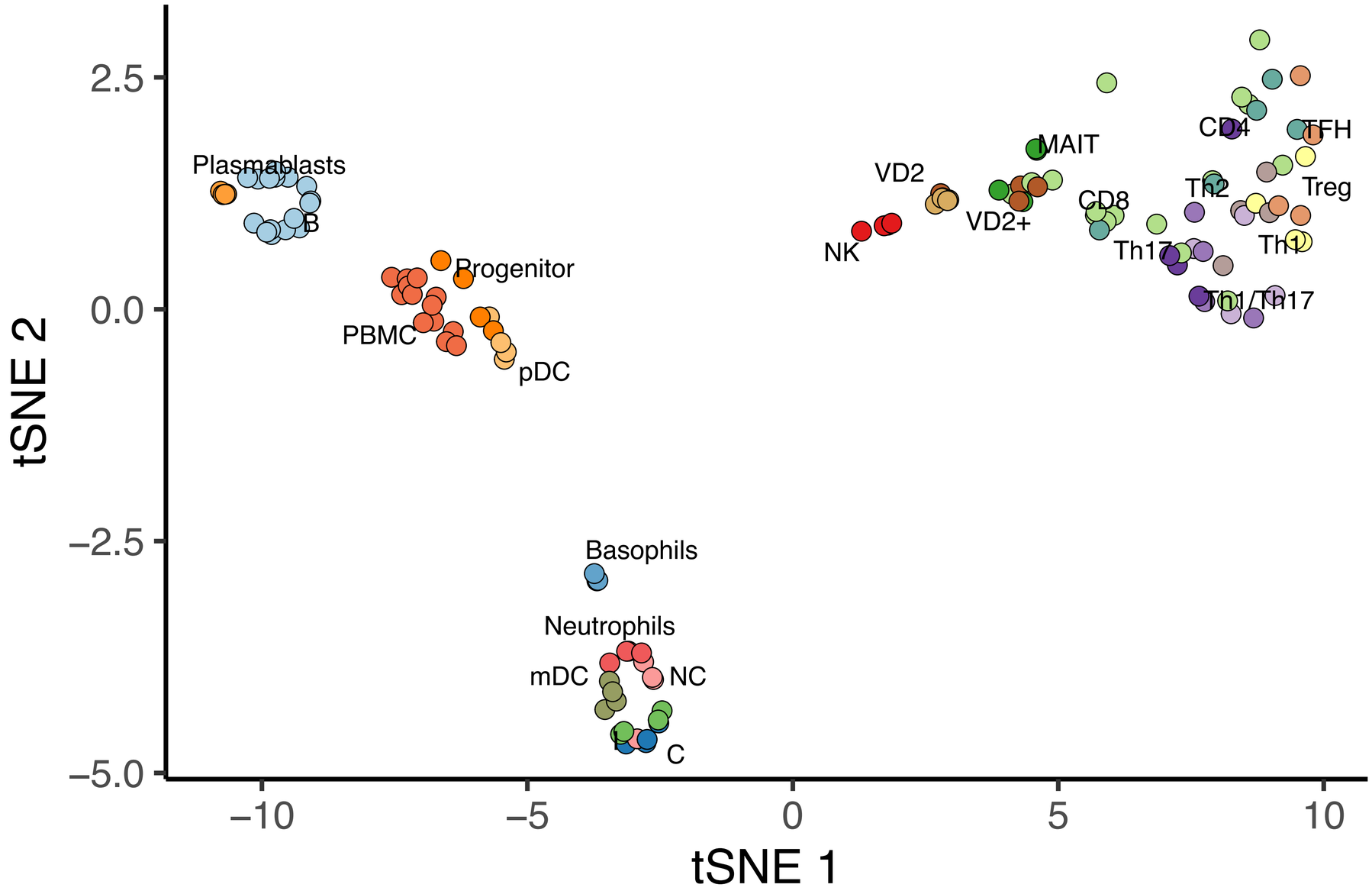
```
tsne <- Rtsne::Rtsne(pcs, dims = 2)

.df <- tsne$Y %>%
    as_tibble() %>%
    mutate(Var2=rownames(pcs)) %>%
    left_join(col.names, by = "Var2")

.centers <- .df %>%
    group_by(major.type) %>%
    summarize(V1=mean(V1), V2=mean(V2)) %>%
    ungroup()
```

We will discuss PCA and tSNE later ...

t-SNE: Other dimensionality reduction methods



Today's lecture: EDA & Exp Design

- **Exploratory Data Analysis**
  - First steps to data analysis
  - Traditional (low-dimensional) approaches
  - High-dimensional methods
  - Tips on how to organize your data/project
- **Experimental Design**
  - Observational vs. Experimental studies
  - Identification of unwanted variation (SVA)
  - Causal inference: matching, stratification, inverse propensity

General rules for organizing your project

- Treat your data sacred (keep them as raw as possible).
- Never manipulate your data points manually!
- Literate programming (variable and function names should make sense)
- Strive to make your working directory organized
- Use one R markdown file for one figure.
- Do not postpone your interpretation until paper writing.
- Separate data analysis from plotting routines.

Tips for visualization

- Ask: What am I trying to show with this picture?
- Generate pictures that you can explain in words.
- Be kind to annotate all the axes' names.
- Additionally, annotate helpful information if needed.
- Avoid 3d or higher dimensional pictures (your paper is 2d)
- Build your own graphing library

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Why do we care about experimental design?

Make the best out of budget

Reduce variability along any unwanted axes/factors

vs.

Magnify variability along relevant axes (e.g., disease)

Causal discovery + validatation

Design your statistical model identifiable!

Measure causal effects of XXX

Observation vs. experimentation

- X and Y are correlated.
- I recovered from a fever (Y) after taking ibuprofen (X) last night.
- We found *BRCA* genes highly expressed in the metastasized breast cancer samples.
- Seeing the results Y given X

- X causes Y.
- Had I not taken medicine (X), I would still have a fever (Y).
- We knocked down *BRCA* genes and mitigated cancer progression in patient-derived xenograft models.
- Doing X to make changes in Y

Code available in our GitHub repo

https://github.com/STAT540-UBC/lectures/blob/main/lect03-eda/causality.Rmd

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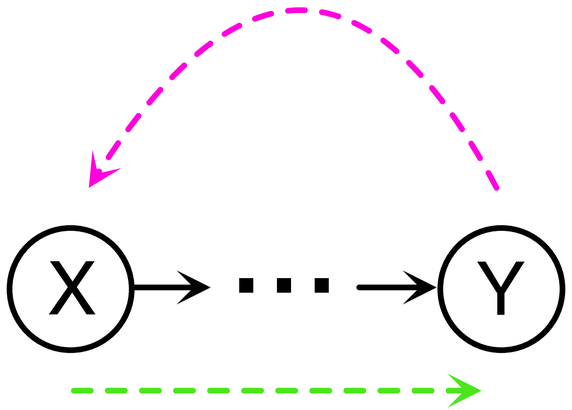
“Backdoor” exercise

Question: Which nodes should be “conditioned” and/or “adjusted” to block a reverse path from Y to X?



“Backdoor” exercise

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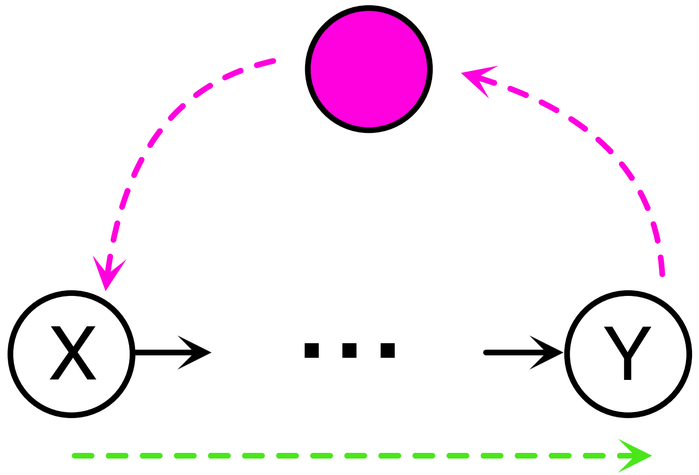
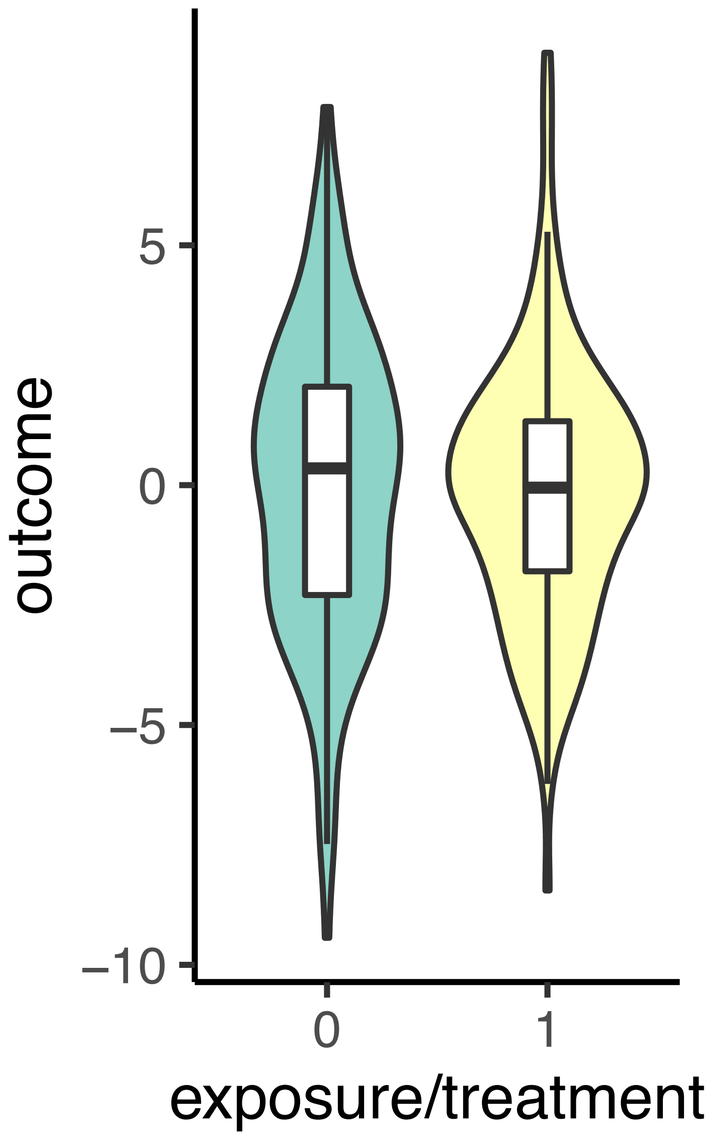


A working example: confounder adjustment in case-control study

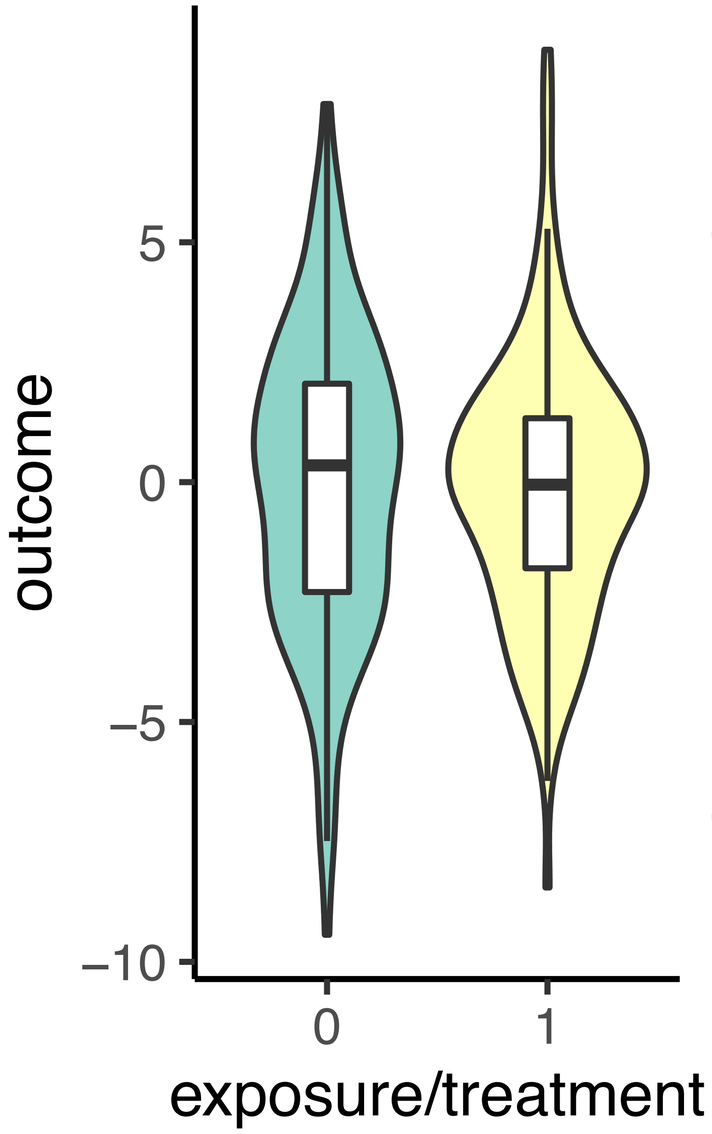


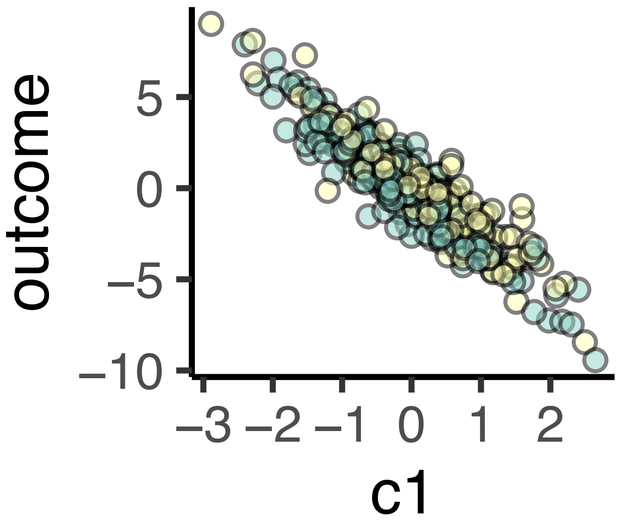
Key question: $X \overset{?}{\rightarrow} Y$

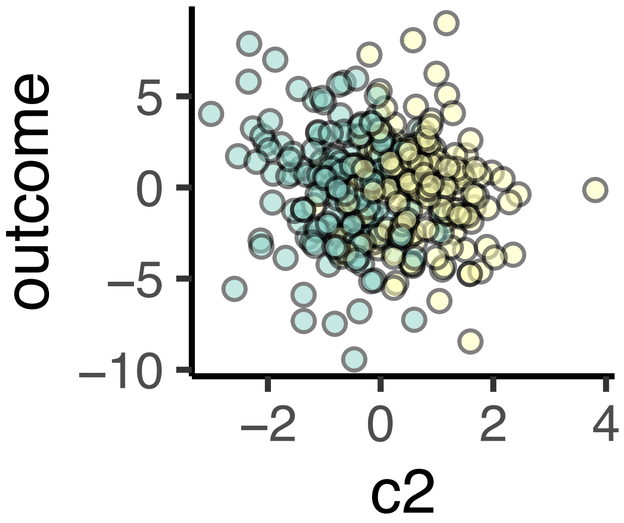
$\mathbf{X}$: exposure variable

$\mathbf{Y}$: outcome variable

A working example: confounder adjustment in case-control study







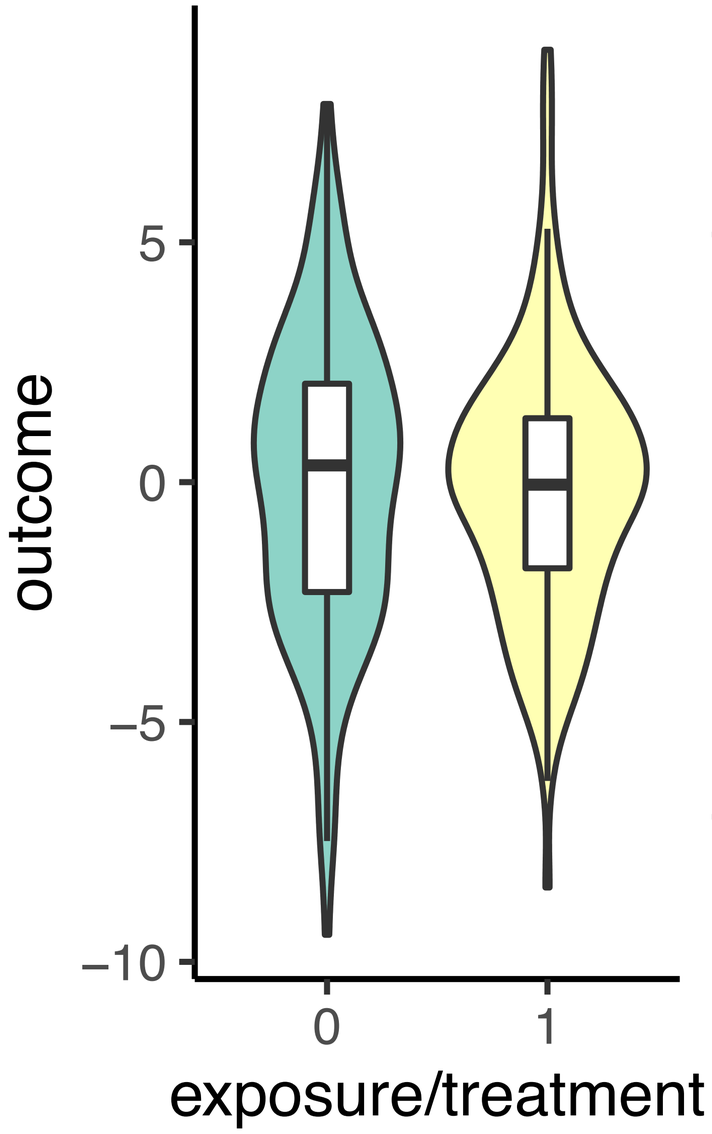
Key question: $X \overset{?}{\to} Y$

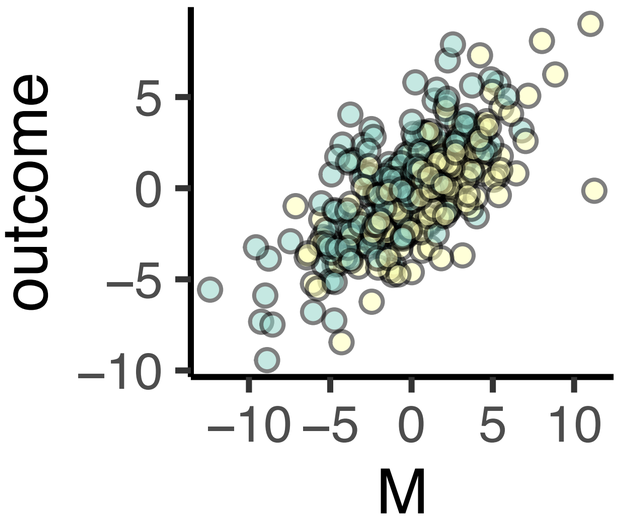
$\mathbf{X}$: exposure variable

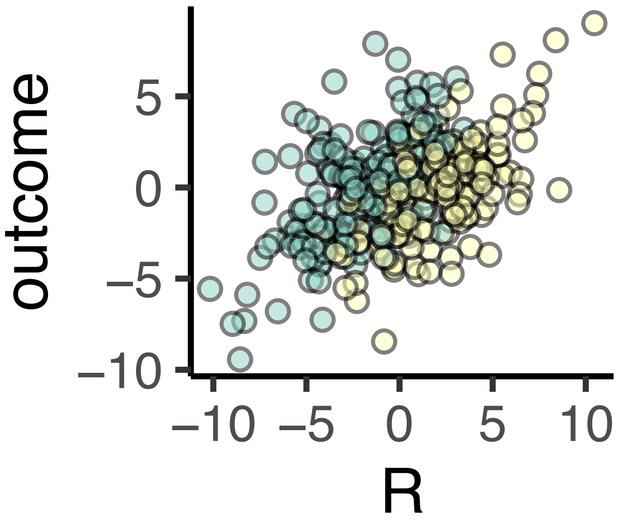
$\mathbf{Y}$: outcome variable

$\mathbf{C_1}$ and $\mathbf{C_2}$: covariates

A working example: confounder adjustment in case-control study







Key question: $X \overset{?}{\rightarrow} Y$

$\mathbf{X}$: exposure variable

$\mathbf{Y}$: outcome variable

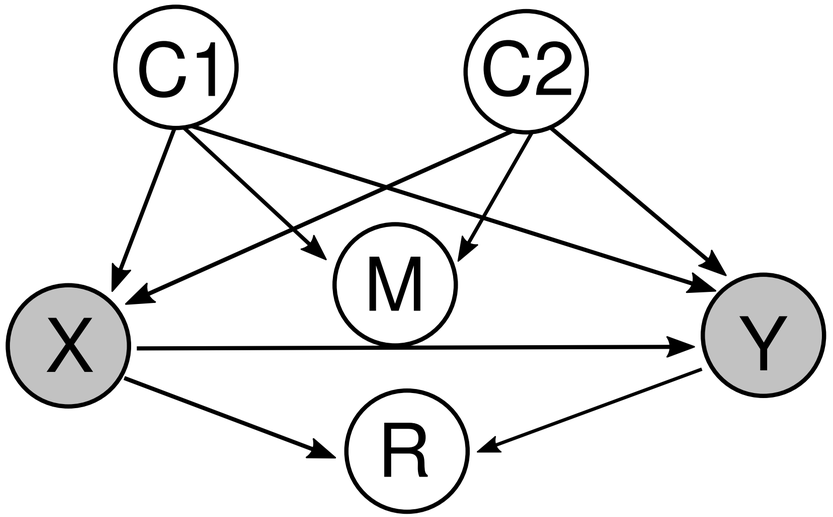
$\mathbf{C_1}$ and $\mathbf{C_2}$: covariates

$\mathbf{M}$: other covariate

$\mathbf{R}$: other covariate

Causal inference with a graphical model

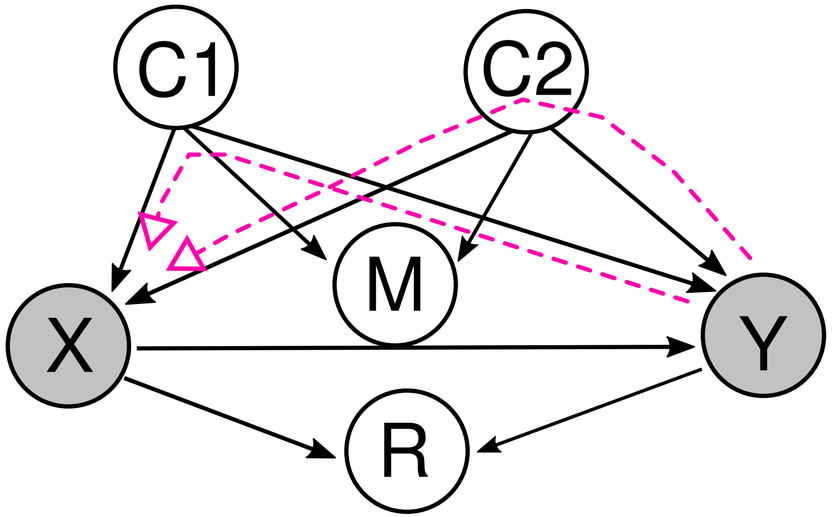
1. Build a causal structural model



What are potential backdoors?

Causal inference with a graphical model

1. Build a causal structural model
2. Identify "back-door" paths/variables (*closing* $Y \to X$, *while opening* $X \to Y$)



How do we close them?

Causal inference with a graphical model

1. Build a causal structural model
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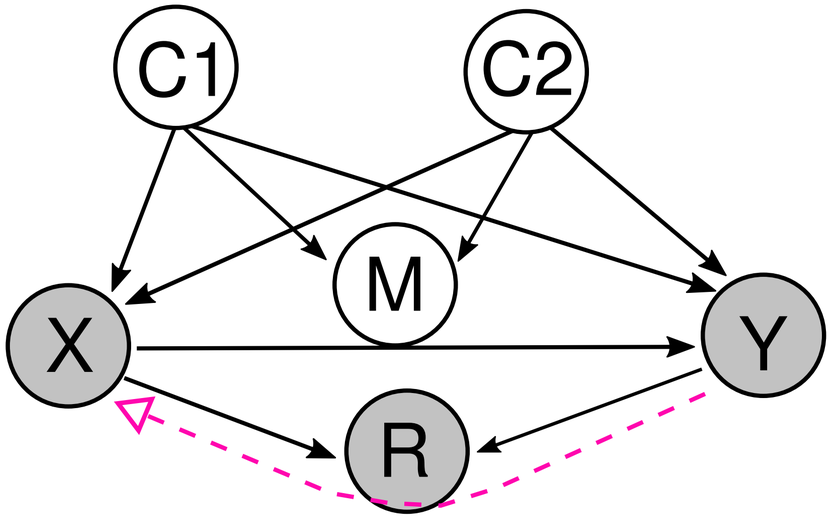

What about this?

Causal inference with a graphical model

1. Build a causal structural model
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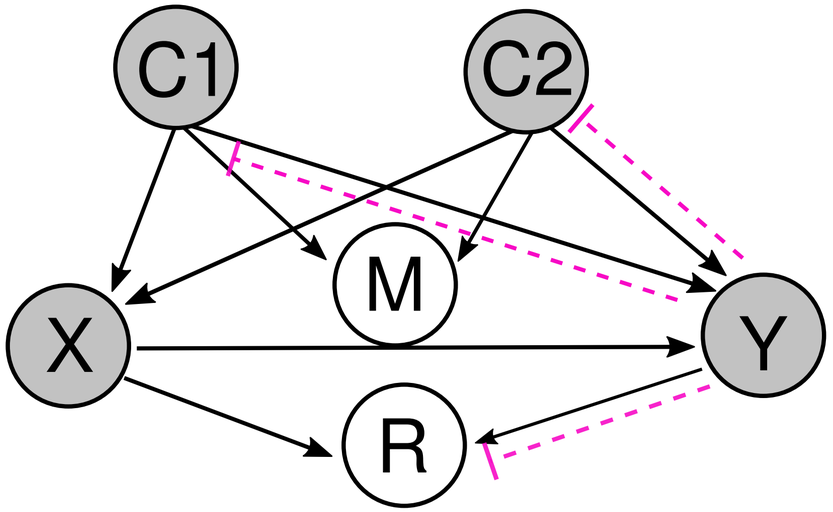


Is this enough?

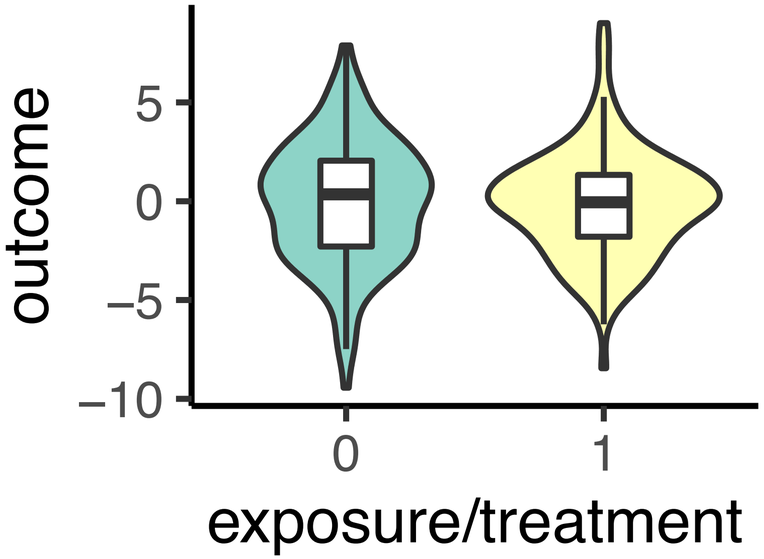
Causal inference with a graphical model

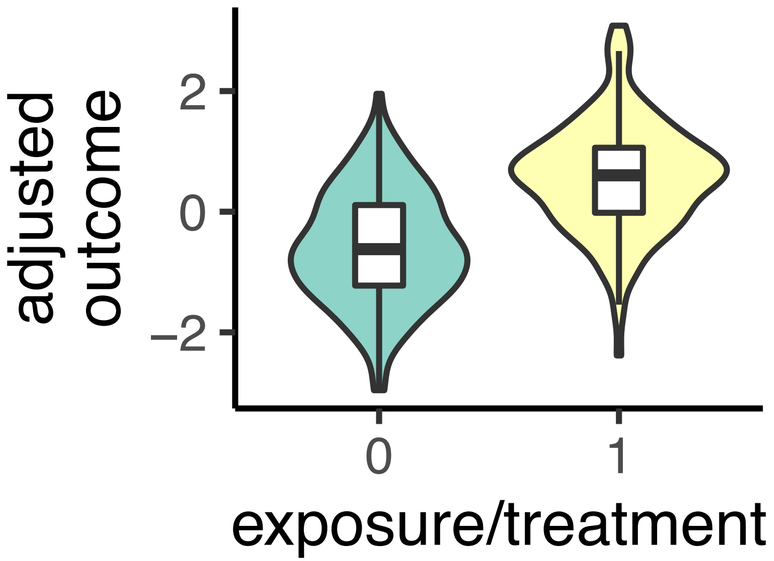
1. Build a causal structural model
2. Identify "back-door" paths/variables (*closing* $Y \rightarrow X$, *while opening* $X \rightarrow Y$)
3. Adjust "back-door" variables
4. Estimate causal effects

$$Y \leftarrow Y - \sum_{k=1}^{2} C_k \hat{\beta}_k$$

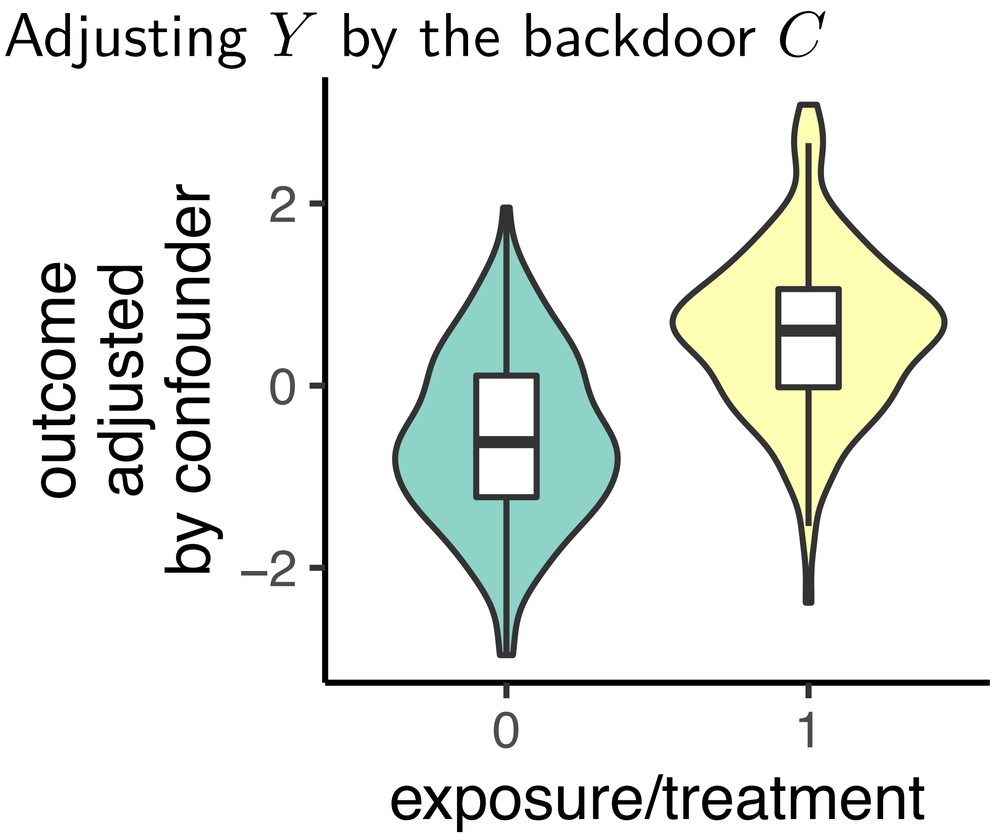
which approximates

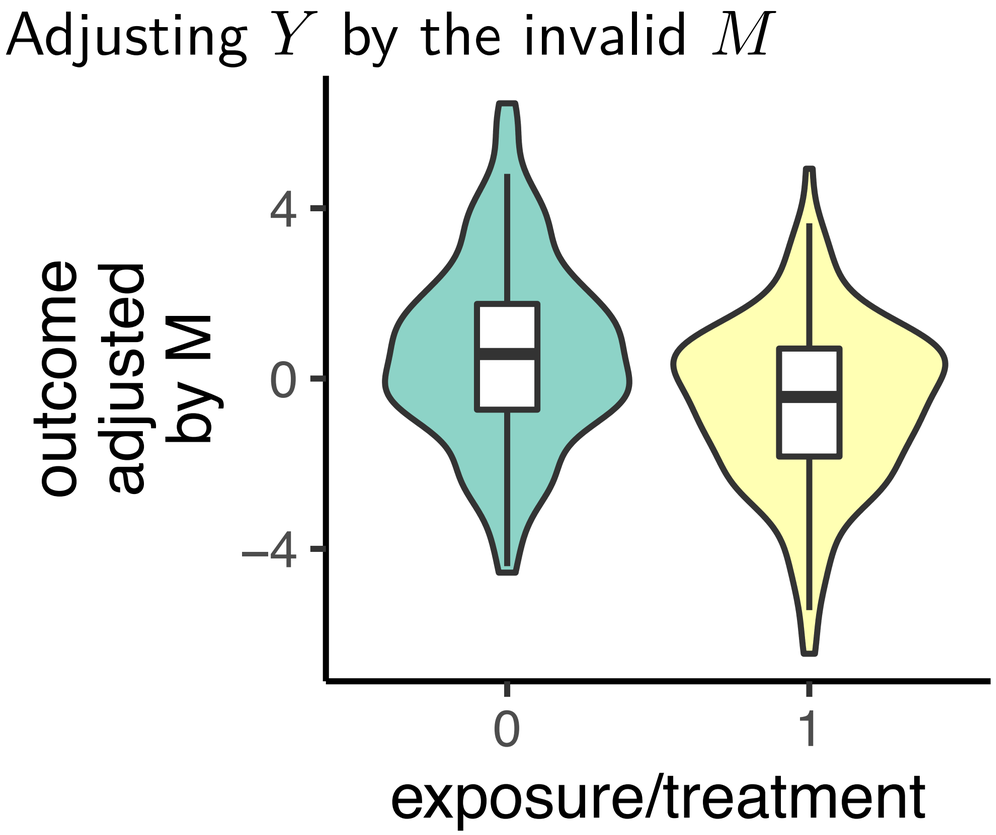
$$p(Y|X) = \int_C p(Y|X, C)p(C)dC$$





What would happen if we close a wrong "backdoor" variable?





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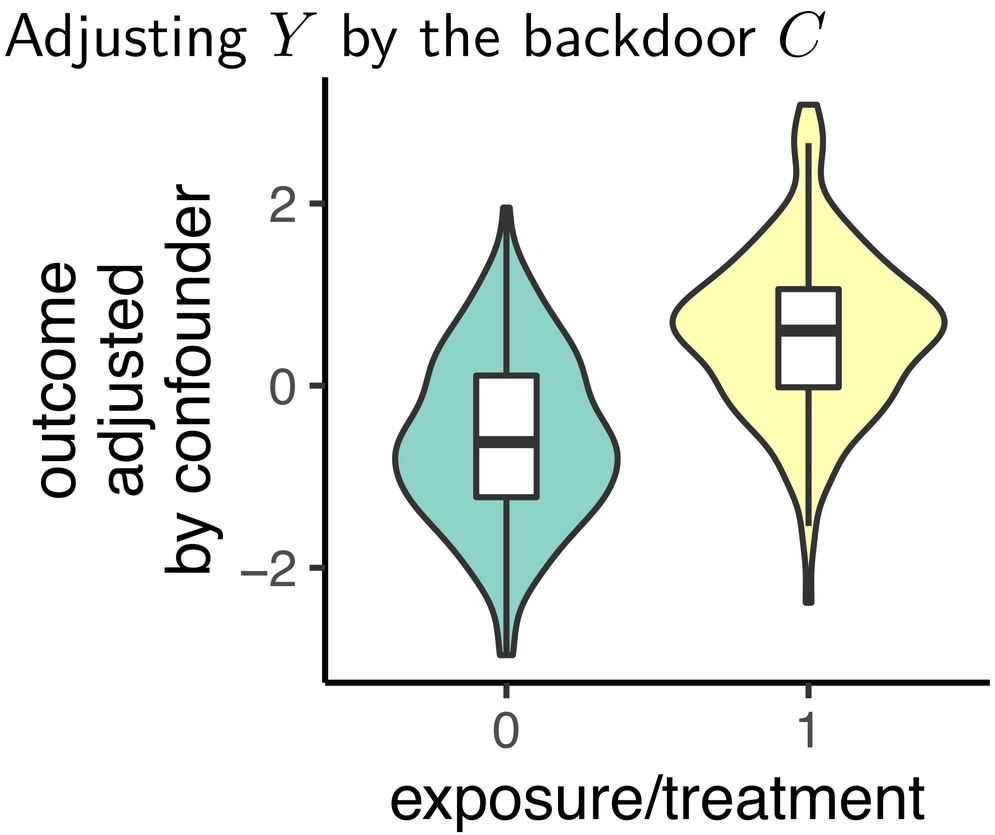

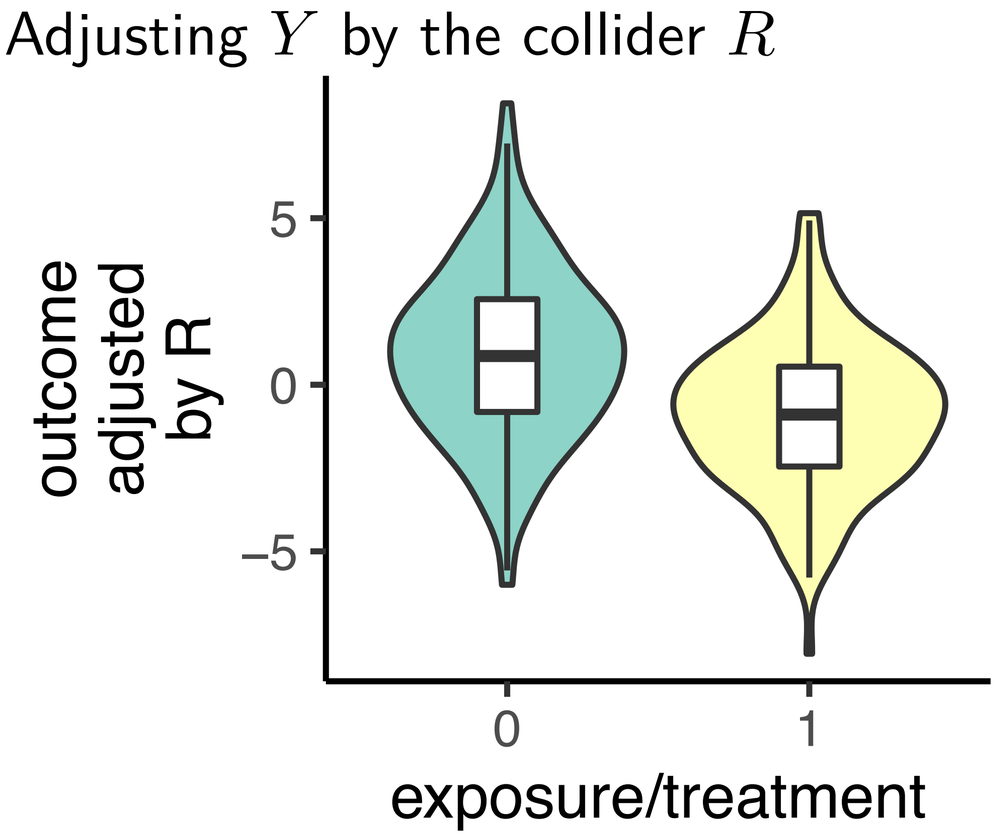

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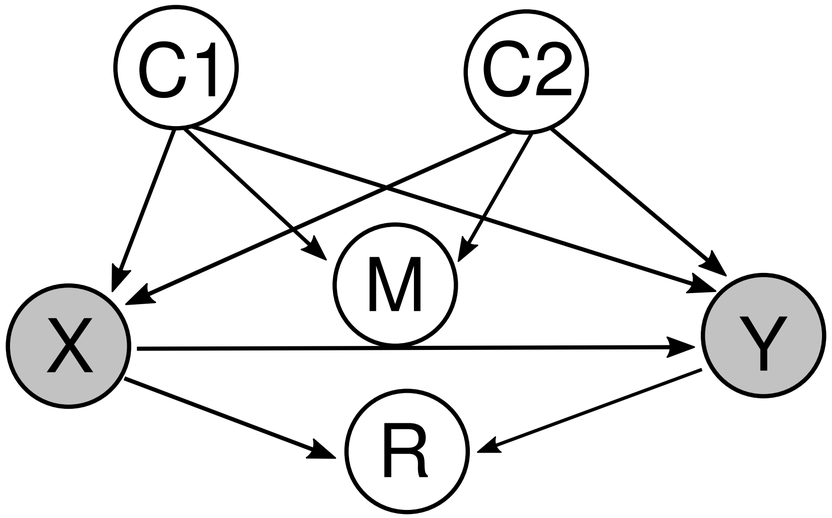
The same example with causal relationship from X to Y

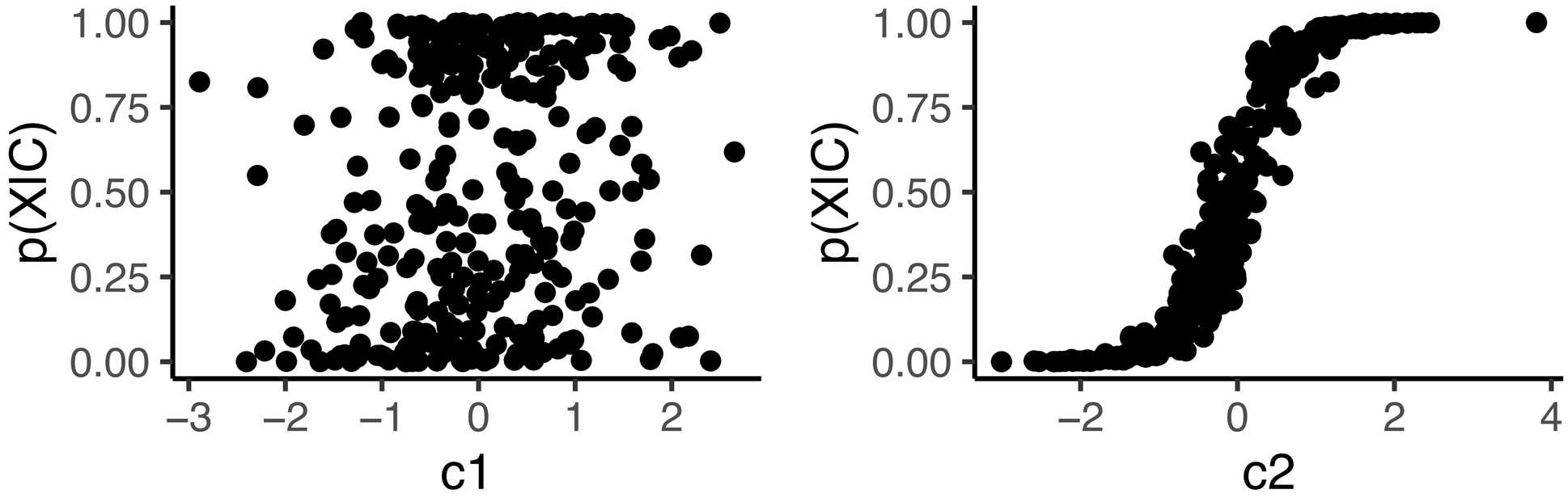


Inverse Propensity Weighting

What is the model for X given confoudners (the backdoor variables)?

Propensity $=$ probability of assignment $X = 1$:

$$p(X|C_1, C_2) \approx \frac{1}{1 + \exp(-\beta_0 - \beta_1 C_1 - \beta_2 C_2)}$$



Horvitz and Thomson, *JASA*, 1952

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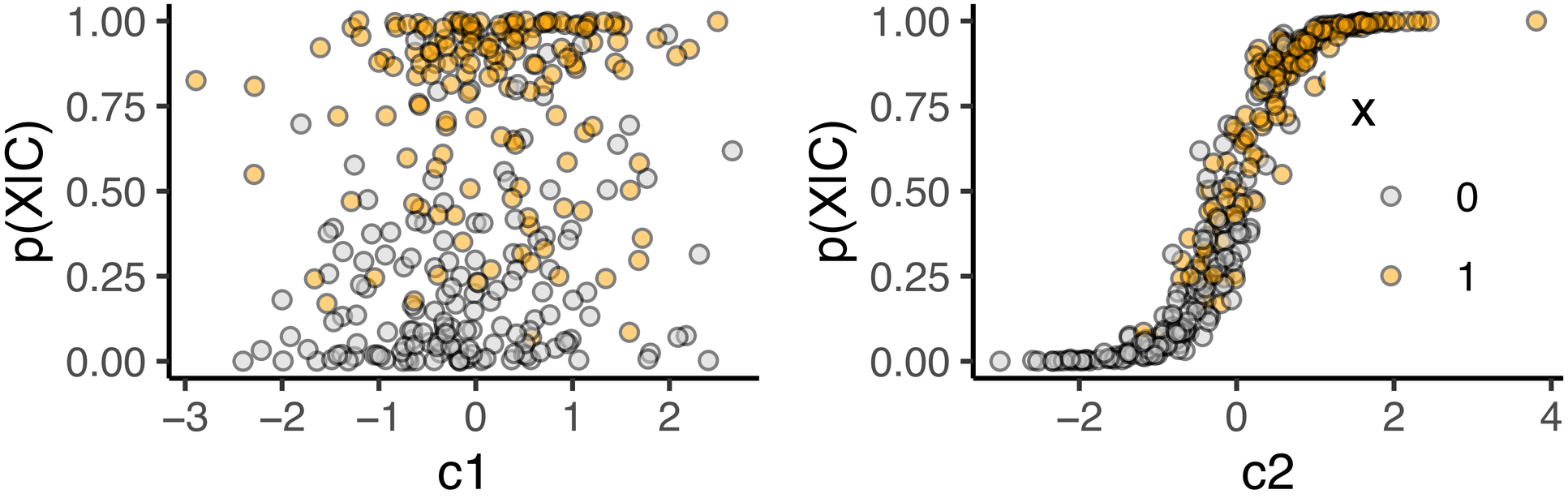
Propensity $=$ probability of assignment $X = 1$:

$$p(X|C_1, C_2) \approx \frac{1}{1 + \exp(-\beta_0 - \beta_1 C_1 - \beta_2 C_2)}$$



Horvitz and Thomson, *JASA*, 1952

Intuition behind IPW

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Likewise, what if samples could be dropped in the overrepresented group?

Inverse Propensity Weighting "inverse" confounded assignment

$$\hat{Y}_i^{(1)} = \frac{X_i Y_i}{\hat{p}(X_i = 1|C_i)}$$

$$\hat{Y}_i^{(0)} = \frac{(1 - X_i) Y_i}{1 - \hat{p}(X_i = 1|C_i)}$$

```
p.xc <-
    glm(x~cc, family="binomial") %>%
    predict() %>%
    sigmoid() %>%
    clamp() # avoid 0 or 1

ww <- x / p.xc + (1-x) / (1-p.xc)
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equivalently give weights for $\forall$ i

$$W_i \propto \begin{cases} 1/p(X_i = 1|C_i) & X_i = 1 \\ 1/p(X_i = 0|C_i) & X_i = 0 \end{cases}$$

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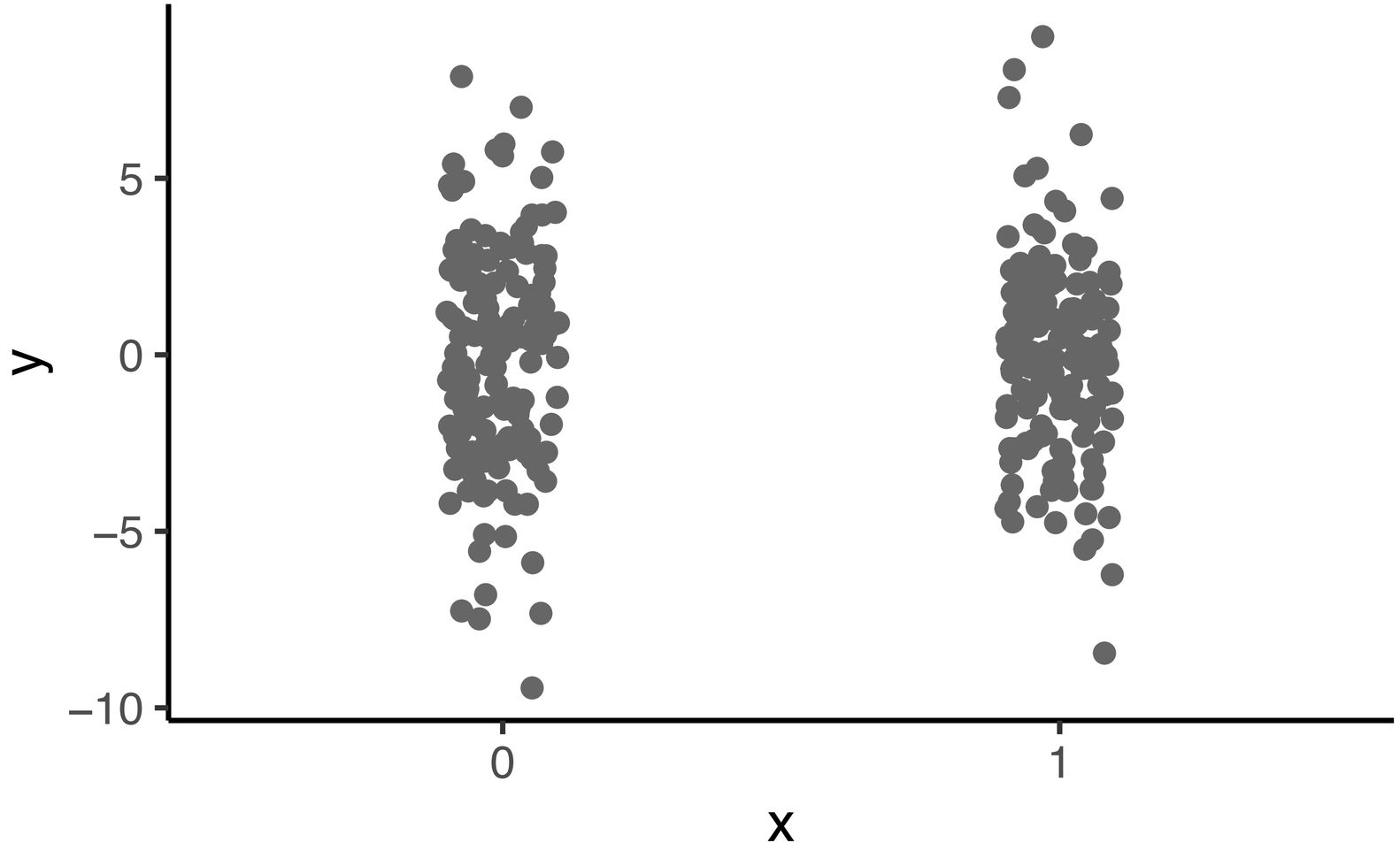
Take samples inversely proportional to propensity



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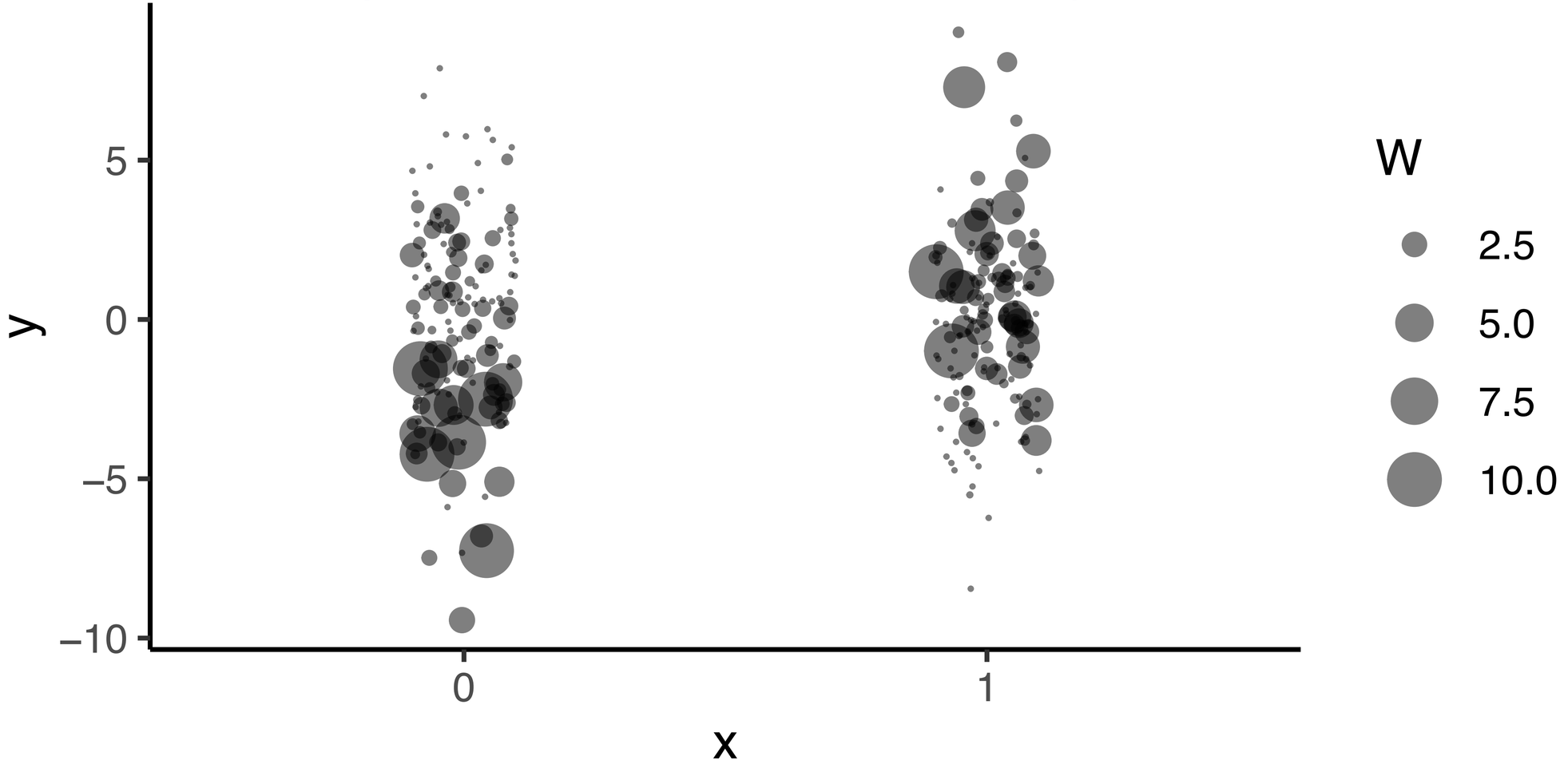

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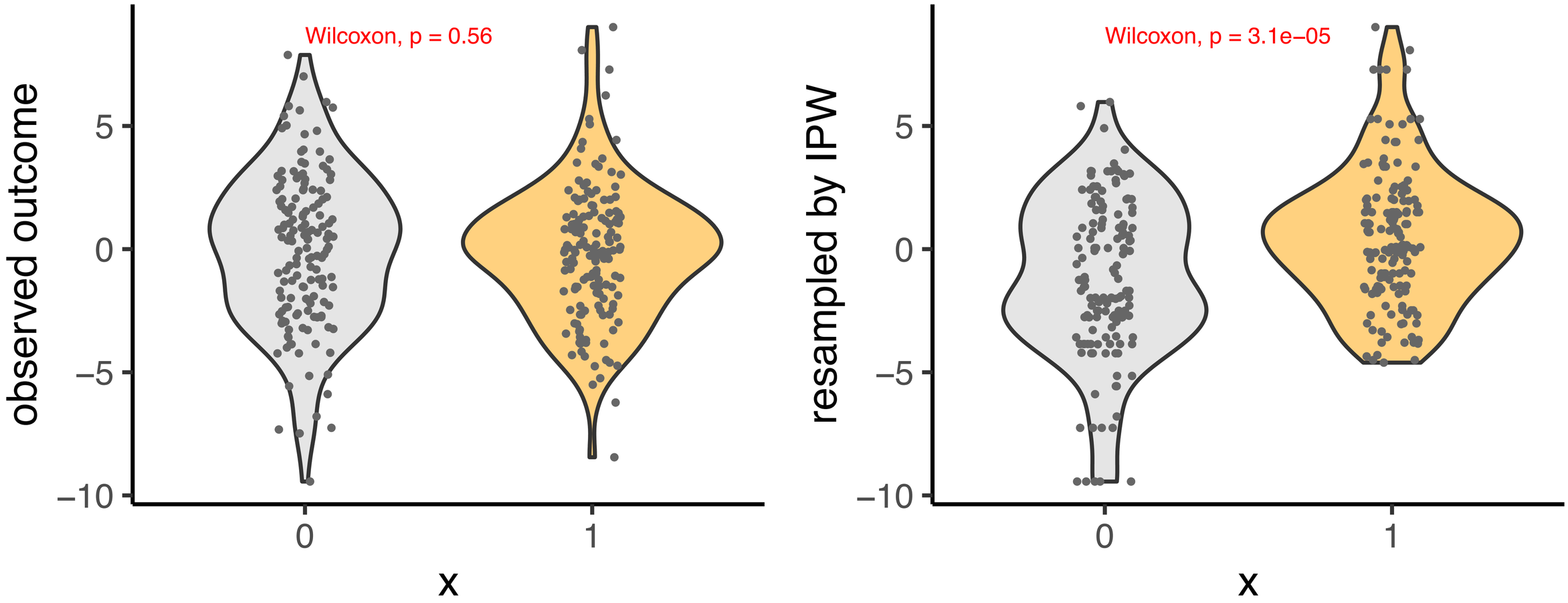

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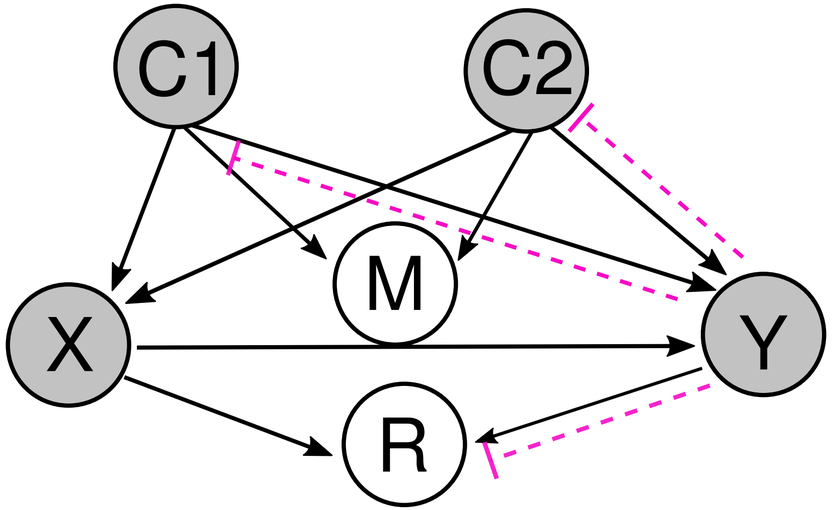
Today's lecture: EDA & Exp Design

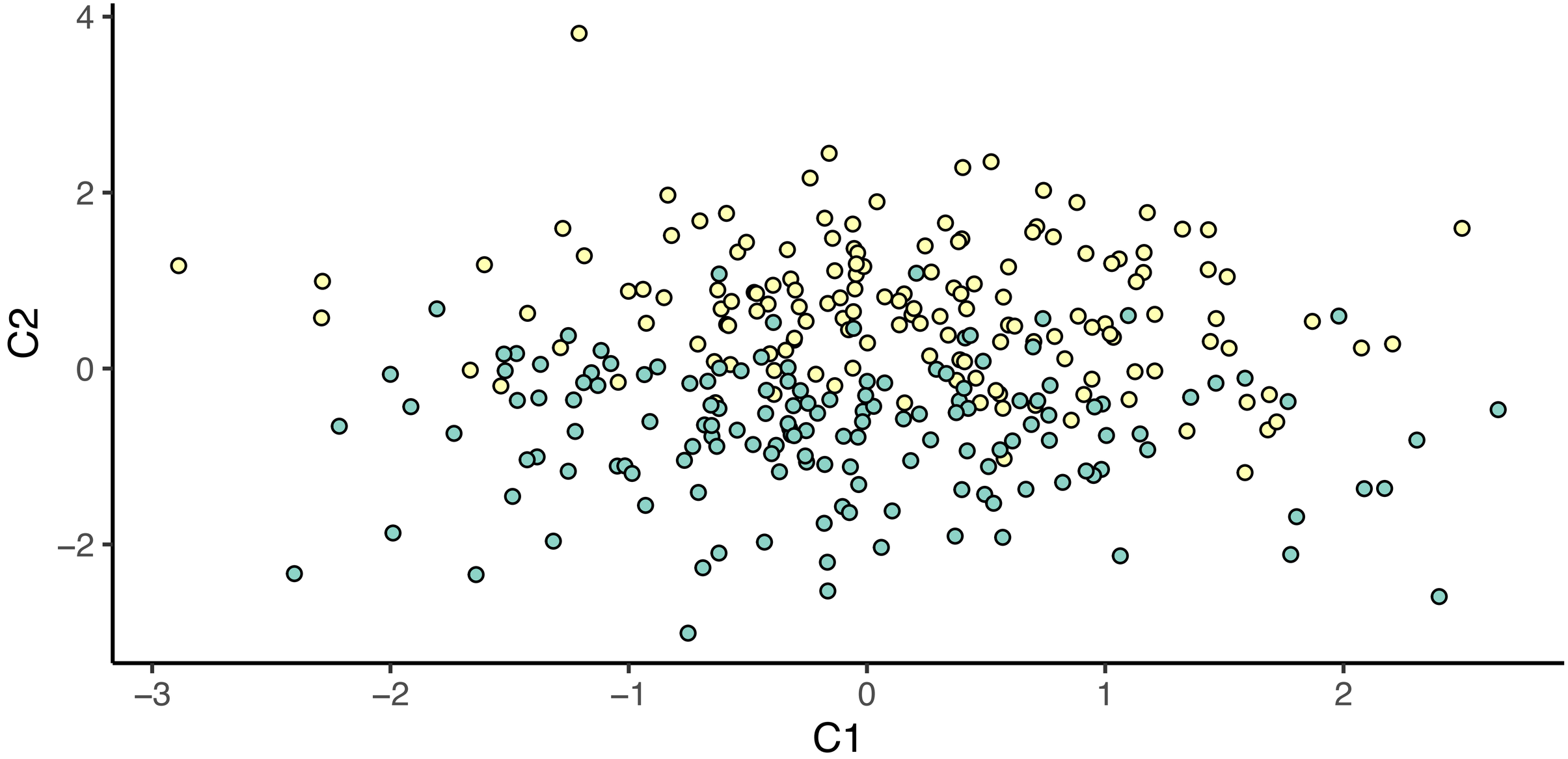
- **Exploratory Data Analysis**
  - First steps to data analysis
  - Traditional (low-dimensional) approaches
  - High-dimensional methods
  - Tips on how to organize your data/project
- **Experimental Design**
  - Observational vs. Experimental studies
  - Identification of unwanted variation
  - Causal inference: matching, stratification, inverse propensity
- **Tips on effective data visualization in science**

Estimating potential outcome by matching



- Estimtae $\mathbb{E}\left[Y_i^{(0)}|C_{i1}, C_{i2}\right]$ for $X_i = 1$ to compare with $\mathbb{E}[Y_i|X_i = 1]$
- Estimtae $\mathbb{E}\left[Y_i^{(1)}|C_{i1}, C_{i2}\right]$ for $X_i = 0$ to compare with $\mathbb{E}[Y_i|X_i = 0]$

Estimating potential outcome by matching



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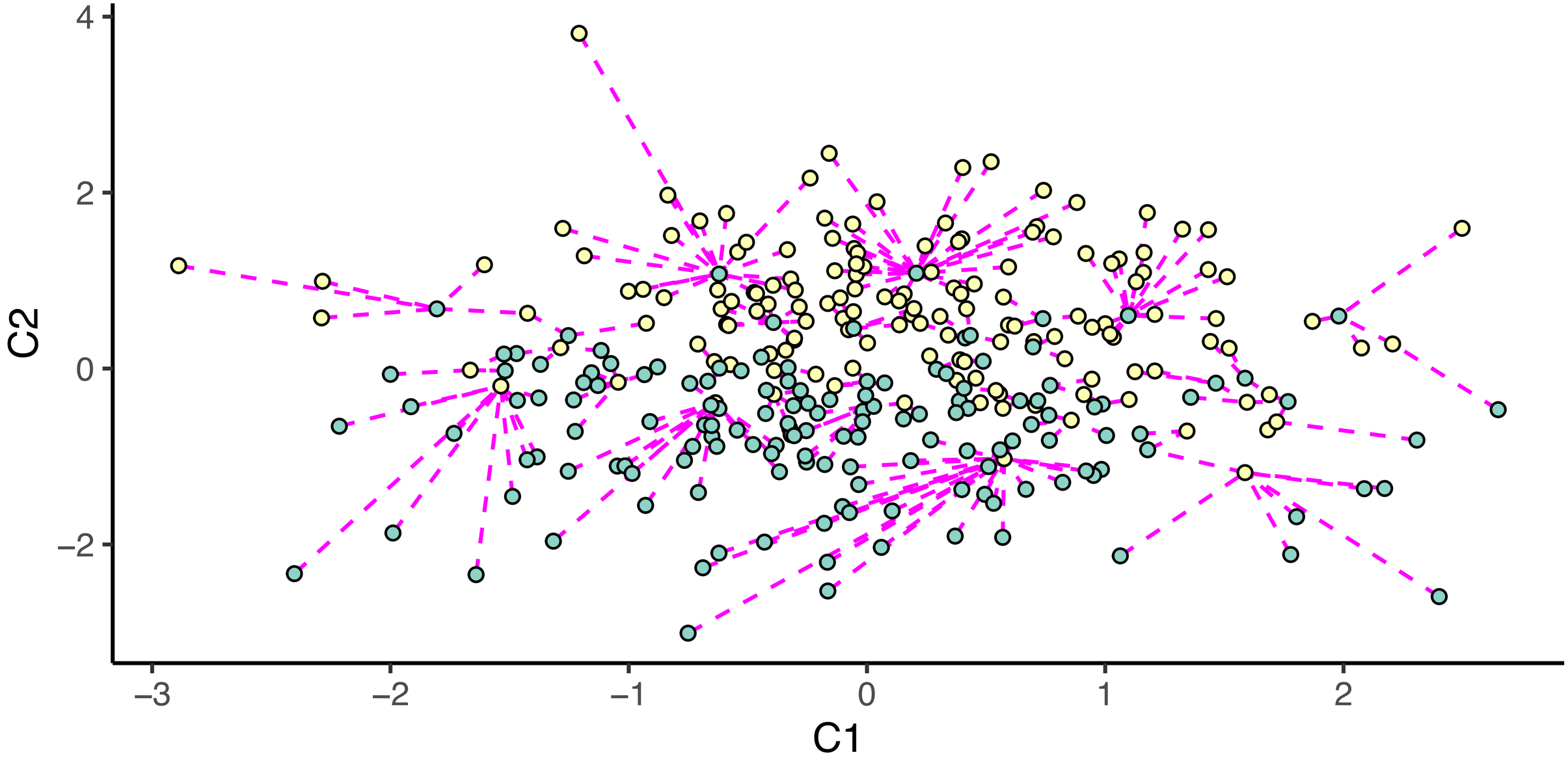

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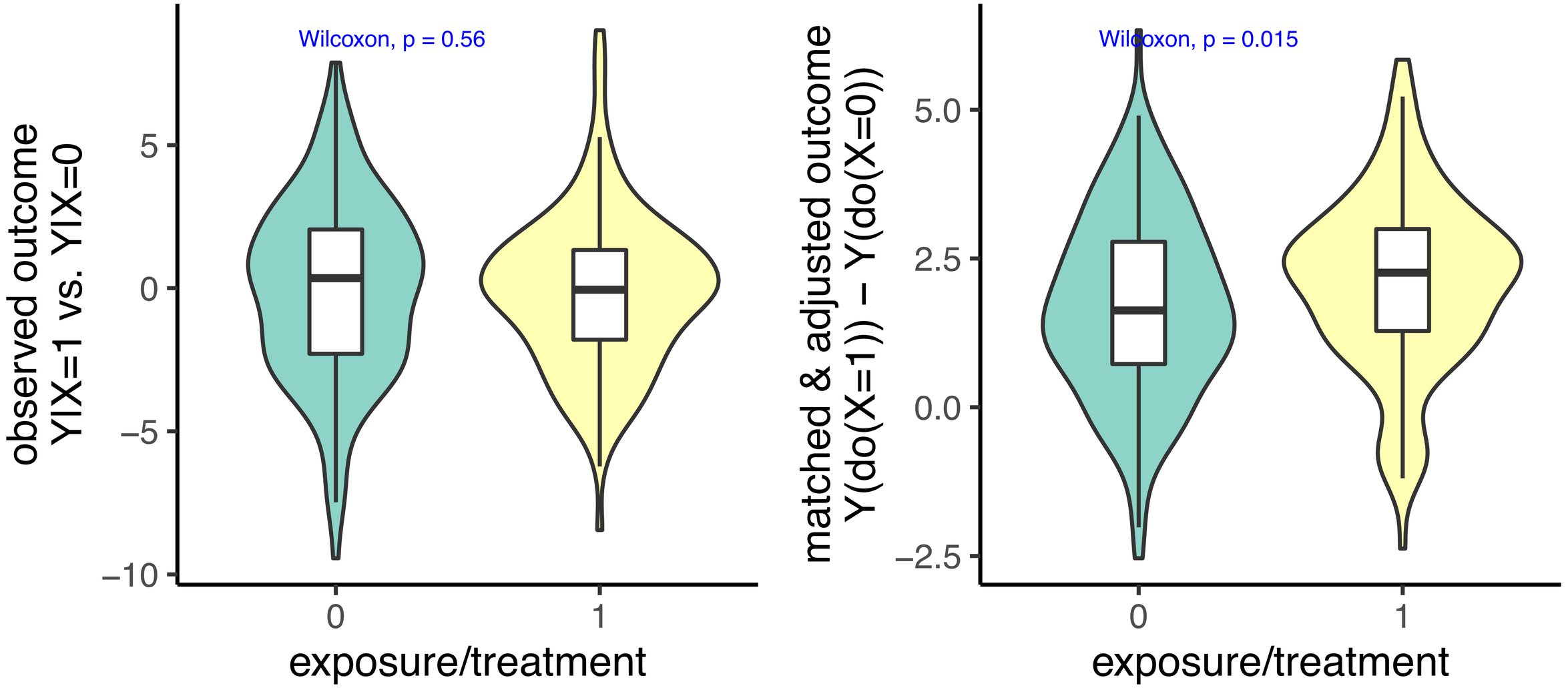


Bayesian Additive Regression Tree (BART) approach

- G-formula $\rightarrow$ outcome regression models
- Regression model for $Y \sim S$ for each $X = 1$ and $X = 0$ using BART

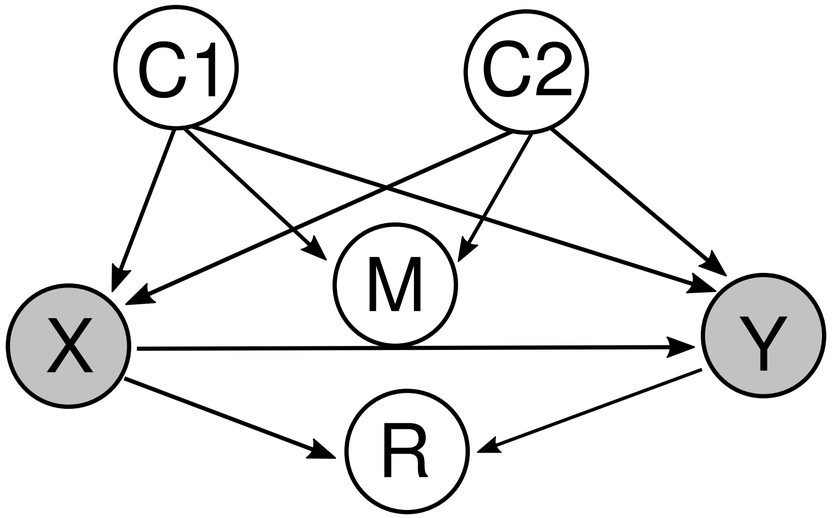
$$\mathbb{E}\left[Y^{(1)}\right] = \int_S \mathbb{E}[Y|X = 1, S]dS$$

$$\mathbb{E}\left[Y^{(0)}\right] = \int_S \mathbb{E}[Y|X = 0, S]dS$$

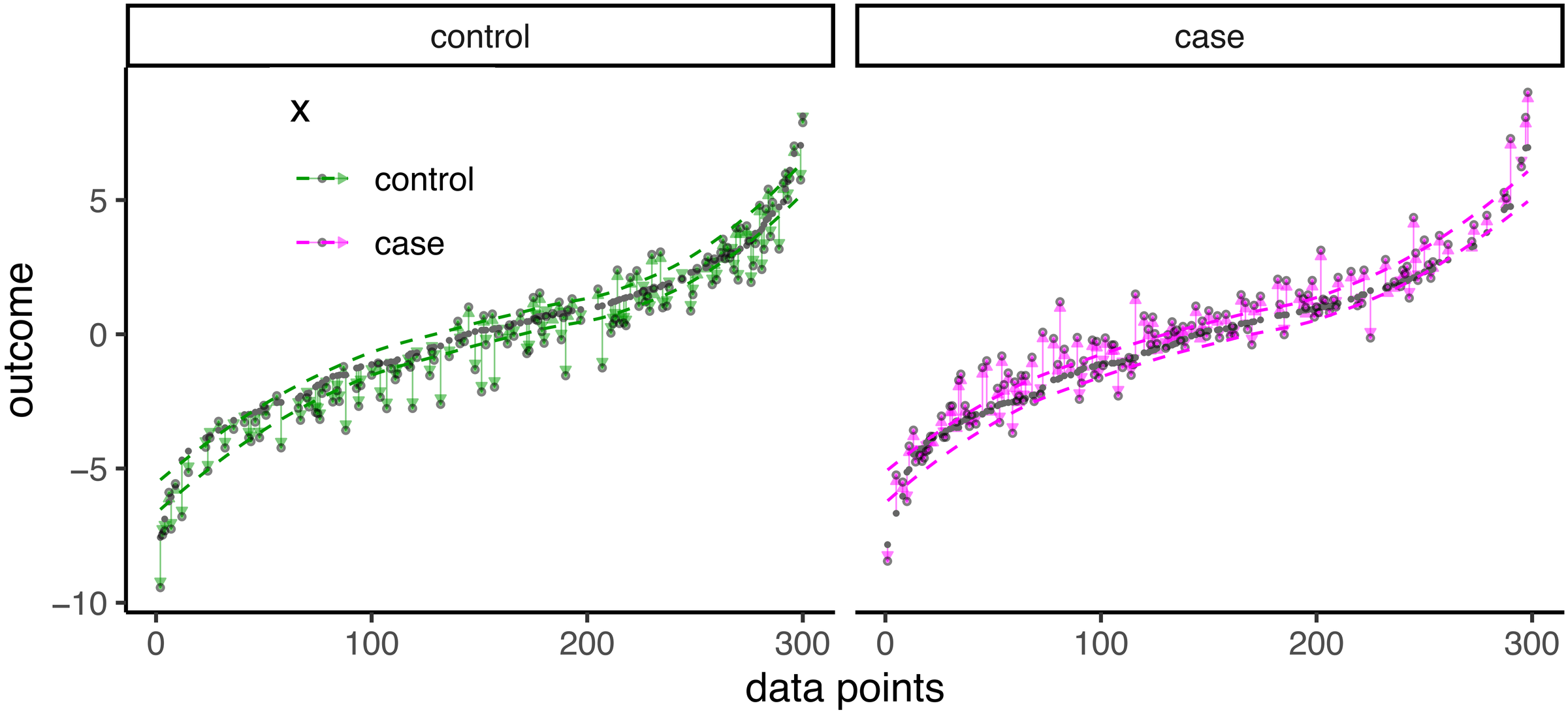
- Estimate causal effect: $\mathbb{E}\left[Y^{(1)}\right] - \mathbb{E}\left[Y^{(0)}\right]$

Hill, *Bayesian Nonparametric Modeling for Causal Inference* (2011)

The same example with causal relationship from X to Y



BART: a regression model to impute potential outcomes



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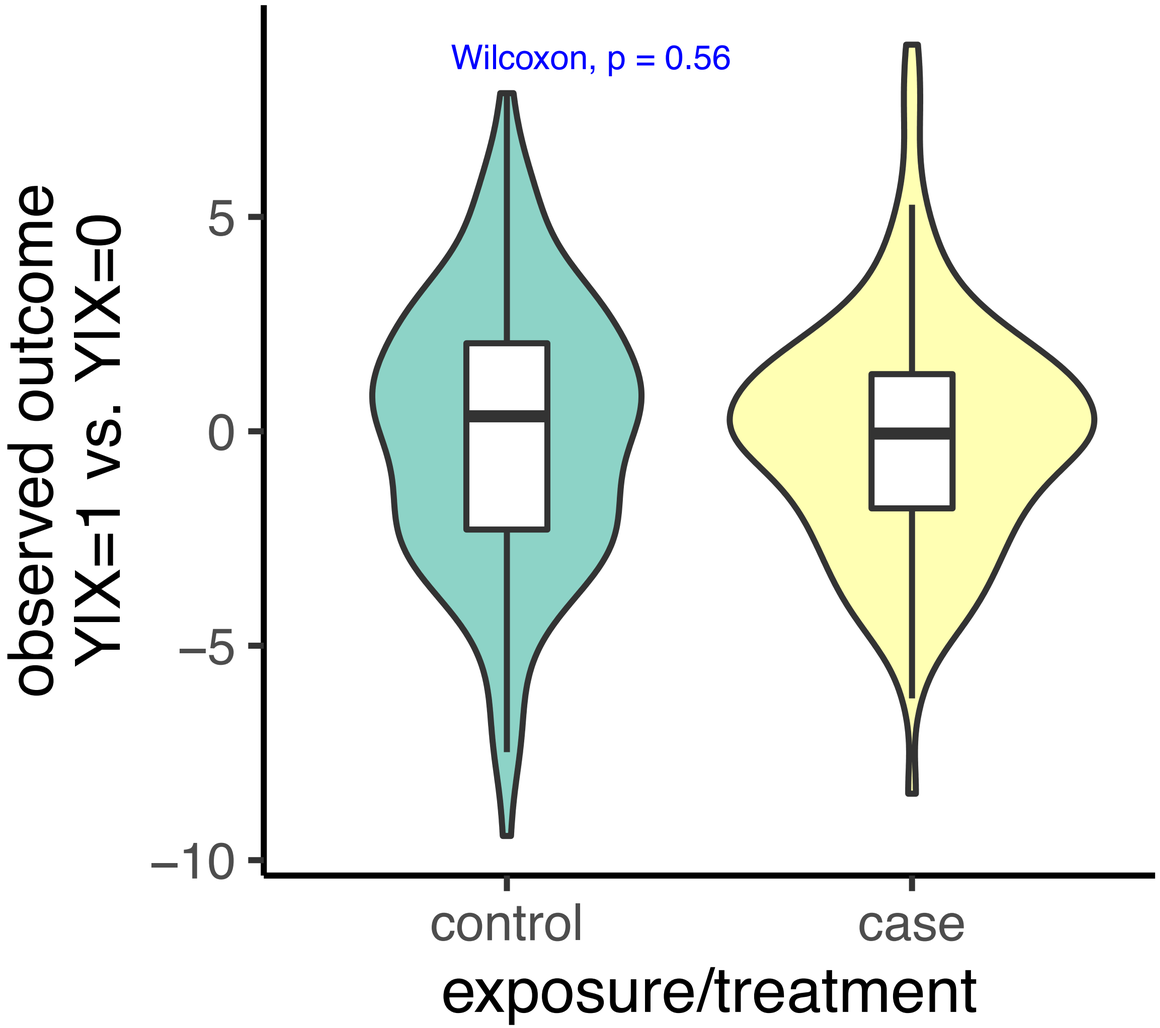

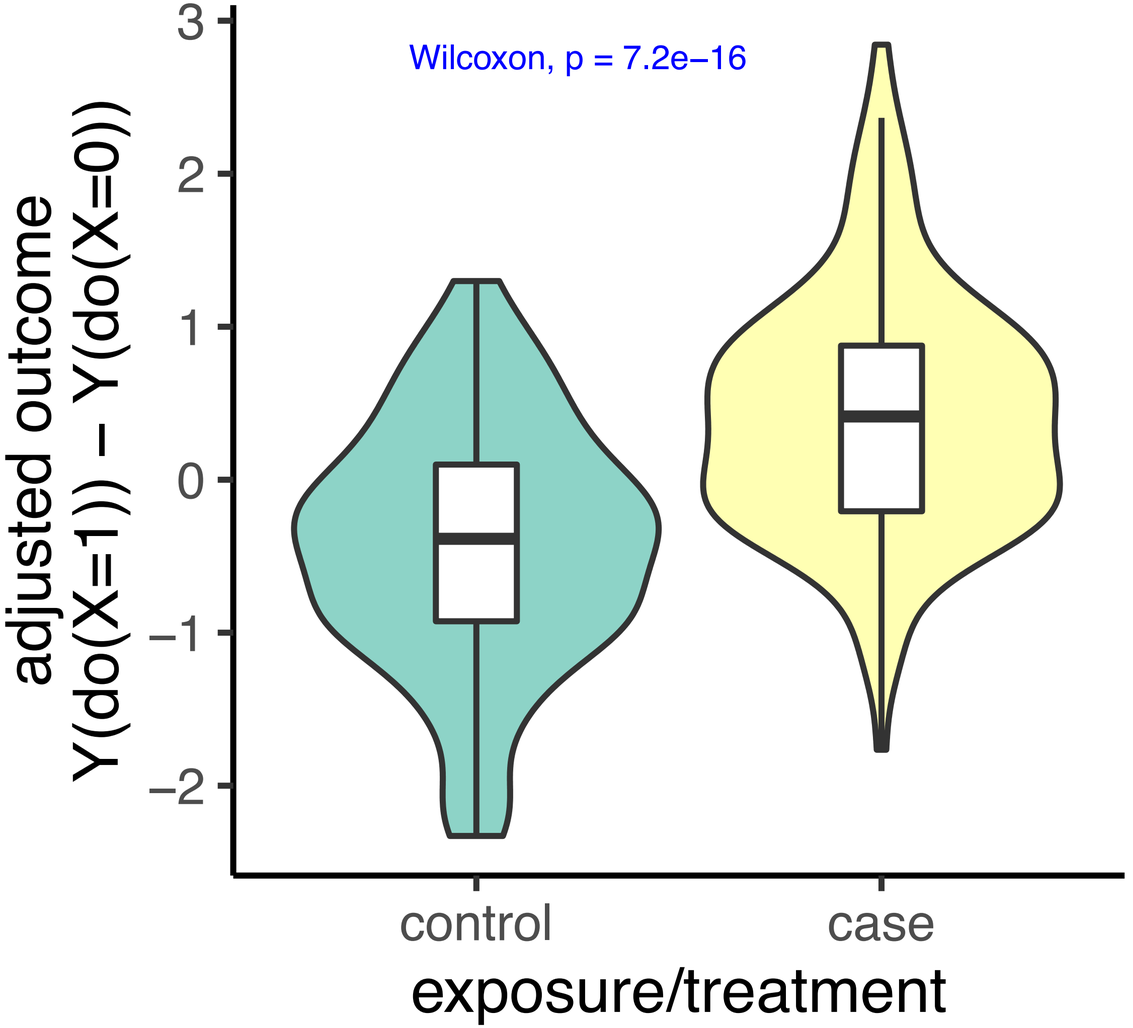

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