



# Planning Experiments and Sample Size Estimations

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## 1 Introduction

In statistics we distinguish two type of study: experimental study versus observational study. An **experimental study** is a study in which the experimenter introduces some *intervention* group(s) and studies the varying effects of these intervention(s) with comparison to a control group on the response variable (outcome/endpoint). As opposed to experimental study, in **observational study** the researcher *merely observes* and records what she sees, there is no intervention.

The purpose of an observational study is to investigate some *association*, while the purpose of an experimental study is typically to investigate a *causal-effect* relationship between the treatment factor and the outcome. Therefore, the environment of an experiment has to be supervised/manipulated/controlled, keeping all the subjects (aka experimental units) similar except the interventions.

**Planning an experiment is an exciting process.** It is also extremely time-consuming that creates a temptation to begin collecting data without giving the experimental design sufficient thought (see [Dean, Angela and Daniel Voss and Danel Draguljic \(2017\) Chapter 2](#)). However, this approach will rarely yield data that is collected in the right way and in sufficient quantity to allow a good analysis with the required precision. In experimentation, careful planning and execution of the plan are the most important steps. If anything can go wrong it will (Murphy's Law), and analysis of data can never compensate for botched experiments.

Statistical **design of experiments** refers to the process of planning the experiment so that appropriate data will be collected and analyzed by statistical methods, resulting in valid and objective conclusion.

An experimental study can be distinguished further into two general goals: *to learn something new* (it is called **exploratory experiment**) or *to confirm a specific hypothesis* (it is called **confirmatory experiment**). The distinction between exploratory and confirmatory is important because it affects the decisions made about the design, the subsequent analysis and the way sample size is calculated (see [Lazic, Stanley \(2016\) Chapter 2](#)).

The following examples are respectively research questions for exploratory and confirmatory experiments.

- Does stress affect rodent behavior (what kind of stress, for how long, on what behavioral tasks)?
- Does fox urine odour (a stressor) affect the amount of food Wistar rats consume during the first 24 hours after exposure?

In the first question we want to learn something new, while the second one is to a specific hypothesis.

There are **two sources of error that are inherent in any experiment**: the random error and the systematic error (aka bias). Large random error will lead to large imprecision and large systematic error will lead to large inaccuracy. The **random error** is almost unavoidable, but it can be improved by increasing the number of **replications of the experimental unit**, that is the sample size. The **systematic error** can be eliminated by **randomization, blinding** and **stratifying** when possible.

Some glossary:

- *Experimental unit (EU)* is the smallest unit that is subjected to the treatment groups.
- *Randomization (aka allocation)* is a process by which each EU has the same chance of being assigned to any of the treatment groups.
- *Blinding* is keeping the identity of the treatment assignment from experimenters administering treatments, experimenters assessing outcome, caregiver, animal facilities staff and others who interact with the animals, whenever possible.
- *Stratifying* is the arranging of experimental units in blocks that are similar/homogeneous to one another in order to reduce variability, but in itself it is not of primary interest to the experimenter.

## 2 Planning an experiment

All studies has a main question/objective. Planning an experiment obviously starts with formulating the **objective of the study** in a clear and compact way. The objective can be formulated with an help of **PICO** framework as a mnemonic. It consist of four elements: the **population** of interest which is the experimental unit (**P**), the **intervention** group(s) (**I**), the **control** group (**C**) and the primary **outcome** or the variable of interest (**O**).

As an example, consider the following objective of a confirmatory experiment: *"To confirm effect of diet-induced obesity by comparing effect of three types of diet (high-fat, low-fat and standard) administered by food in a cage on weight gain (average gr/week) of male B6J mice."*

Here the population is the male B6J mice, the intervention groups are the high-fat diet and the low-fat diet, the control group is the standard diet and the outcome is the average weekly weight gain in gram. Moreover, the **experimental unit** is the cage.

The second step in planning an experiment is **describing the methods and procedures used to collect and analyze data** on the (primary) outcome specified in the objective of the study (aka experimental design).

In the example above the primary outcome of average weight gain in gr/week is a continuous variable and we compare the means of the three groups. Thus, the **appropriate statistical model** to analyze the data is one-way ANOVA model. That is, we use F test with **research hypothesis** that at least two groups have different means and **null hypothesis** that the means of the three groups are the same.

The following keywords are a simplification of a very large number of decisions that need to be made for planning an experiment:

- Type of the experiment,
- Type of the primary response variable (outcome/endpoint),
- Study objective and source of variability,
- Statistical method/model/test,
- Multiple testing,
- Sample size estimation,
- Randomization and blinding.

This list can be seen as a simplified sequence of decisions (questions to answer) in planning an experiment.

### 3 Sample size estimation

One of the first questions facing an experimenter is "How many observations should I take?", or alternatively "Given my limited budget, how can I obtain as much information as possible?". These questions cannot be answered in a couple of sentences, but we will give some examples in the next section.

There are two ways of sample size estimation depending on the type of the experiment (exploratory or confirmatory).

Recall that a confirmatory experiment is to test a specific hypothesis. Thus there is a test. Sample size estimation for confirmatory experiment is then based on the power-to-achieve of the test (aka power calculation). Power is the probability of detecting an effect if there is an effect. Thus, we aim for a large power. Power of a test depends on: (i) the significant level (type I error), (ii) the alternative hypothesis, (iii) the effect size (aka signal), (iv) the variability of the population (aka noise) measured with standard deviation and (v) the sample size. The relationship of these component is an explicit mathematical equation that is solved numerically with a statistical software.

Since there is no test in an exploratory experiment, we cannot – and it does not make sense – use power calculation to calculate sample size. Sample size approximation is therefore derived from pragmatic information of feasibility and resources. For example, time constraints, processing capacity, budget, available manpower, etc. This method is called Fermi's approximation (see [Reynolds, Penny \(2019\)](#)).

For an observational study, one would aim as many as as possible for the sample size.

### 4 Examples

The following examples are sample size estimation for confirmatory and exploratory experiment, including the three types of outcome (continuous, categorical and time-to-event).

The power calculation of sample size of the examples below can also be carried-out using our shiny R interactive application [SampleSizeR](#) (see [Cherneva, Kalina and Reinhard Furrer and Bernadetta Tarigan \(2021\)](#)).

#### 4.1 Confirmatory, continuous outcome, multiple comparisons, $F$ test

##### 4.1.a One treatment factor

###### *Objective*

To confirm an effect of diet-induced obesity administered by food in a cage on weight gain (average gr/week) of male B6J mice, comparing three types of diet: high-fat, low-fat and standard.

###### *Statistical test/model*

Our research hypothesis is that at least one pair out of the three levels of the treatment factor is different, while the null hypothesis is that there is no difference. Thus, we use F test with one factor (aka one-way ANOVA) where the factor has 3 levels/groups. We are interested in comparing all the three possible pairs for the groups.

###### *Power calculation of sample size*

We consider a difference of 4 gr/week of average weight gain among the three groups as meaningful. Previous study shows that the population standard deviation is estimated with 3 gr/week in each group. To count for the three multiple tests we use Bonferroni correction, i.e., taking  $\alpha = 0.05/3 = 0.01667$  for calculating the sample size (see section [Multiple Testing](#)). We use R with the package *daeWR* (see [Lawson, John \(2015\)](#) Chapter 2) as below.

```

library(daewr)
round(Fpower1(alpha = 0.01667, nlev = 3, nreps = 15:20, Delta = 4, sigma = 3), 3)

##      alpha nlev nreps Delta sigma power
## [1,] 0.017   3   15    4     3 0.781
## [2,] 0.017   3   16    4     3 0.815
## [3,] 0.017   3   17    4     3 0.845
## [4,] 0.017   3   18    4     3 0.871
## [5,] 0.017   3   19    4     3 0.893
## [6,] 0.017   3   20    4     3 0.912

```

Thus, 20 cages per group is needed to obtain a power of at least 0.90 with family-wise significant level of 0.05, resulting at  $3 \cdot 20 = 60$  cages in total. Since we use male mice, where a cage contains one male mouse, the total number of animals needed in this study is  $3 \cdot 20 = 60$  male B6J mice.

If we were to use female mice with 3 mice per cage, then the total number of animals we need is  $3 \cdot 3 \cdot 20 = 180$  female B6J mice.

#### *Randomization and blinding*

The experimental unit (i.e., the cage) is completely randomized (balance randomized) with the use of computer randomization process. Given the total sample size of 60 for the 3 groups, we can use the R command as below.

```

set.seed(8057)
sample(rep(c("HFD", "LFD", "SD"), each = 20), 60)

## [1] "LFD" "SD"  "LFD" "HFD" "LFD" "SD"  "SD"  "LFD" "HFD" "LFD" "HFD" "HFD"
## [13] "LFD" "SD"  "SD"  "HFD" "HFD" "LFD" "HFD" "LFD" "HFD" "LFD" "HFD" "SD"
## [25] "SD"  "HFD" "SD"  "SD"  "SD"  "SD"  "SD"  "SD"  "HFD" "LFD" "SD"  "LFD"
## [37] "SD"  "HFD" "LFD" "LFD" "HFD" "SD"  "HFD" "HFD" "LFD" "HFD" "LFD" "HFD"
## [49] "LFD" "SD"  "SD"  "SD"  "LFD" "SD"  "LFD" "HFD" "LFD" "HFD" "LFD" "HFD"

```

Blinding is conducted for experimenters administering treatments, experimenters assessing outcome, caregiver, animal facilities staff and others who interact with the animals.

#### 4.1.b Two treatment factors

We extend the above example by adding another treatment factor, that is an exercise factor with two levels (moderate and sedentary).

#### *Objective*

To confirm an effect of **diet** with 3 levels (high-fat, low-fat and standard) and an effect of **exercise** with 2 levels (moderate and sedentary) on weight gain (average gr/week) of male B6J mice. The diet is administered by food in a cage.

#### *Statistical test/model*

Our research hypothesis is that at least one pair out of the six combined levels of the two treatment factors is different, while the null hypothesis is that there is no difference. Thus, we use F test with two factors (i.e. two-way ANOVA). We are interested in comparing all the three possible pairs of the diet groups for each of the two exercise groups. Thus, in total we have 6 comparisons.

### Power calculation of sample size

We consider a difference of 4 gr/week of average weight gain among the three groups as meaningful. Previous study shows that the population standard deviation is estimated with 3 gr/week in each combined group. To count for the six multiple tests we use Bonferroni correction, i.e., taking  $\alpha = 0.05/6 = 0.00833$  for calculating the sample size (see section [Multiple Testing](#)). We use R with the package *daewr* (see [Lawson, John \(2015\) Chapter 2](#)) as below.

```
library(daewr)
pow <- round(Fpower2(alpha = 0.05/6, nlev = c(3,2), nreps = 8:12, Delta = 4, sigma = 3), 3)
pow

##      alpha a b nreps Delta sigma powera powerb
## [1,] 0.008 3 2     8     4     3  0.731  0.504
## [2,] 0.008 3 2     9     4     3  0.804  0.595
## [3,] 0.008 3 2    10     4     3  0.860  0.676
## [4,] 0.008 3 2    11     4     3  0.902  0.746
## [5,] 0.008 3 2    12     4     3  0.932  0.805
```

Thus, 1 cages per combined group is needed to obtain a power of at least 0.90 with family-wise significant level of 0.05, resulting at  $6 \cdot 11 = 66$  cages in total. Since we use male mice, where a cage contains one male mouse, the total number of animals needed in this study is  $6 \cdot 11 = 66$  male B6J mice.

### Randomization and blinding

The experimental unit (i.e., the cage) is completely randomized (balance randomized) with the use of computer randomization process. Given the total sample size of 66 for the 6 combined groups, we can use the R command as below.

```
set.seed(80)
sample(rep(c("A1B1", "A2B1", "A3B1", "A1B2", "A2B2", "A3B2"), each = 11), 66)

## [1] "A1B1" "A1B2" "A3B1" "A3B2" "A1B1" "A1B2" "A1B2" "A2B2" "A3B2" "A1B2"
## [11] "A2B1" "A1B1" "A1B1" "A3B1" "A2B1" "A3B2" "A2B1" "A2B2" "A1B1" "A3B1"
## [21] "A1B2" "A3B2" "A1B1" "A3B2" "A3B1" "A3B2" "A2B2" "A1B2" "A3B1" "A1B1"
## [31] "A1B2" "A3B1" "A2B1" "A1B2" "A2B2" "A3B2" "A2B1" "A2B2" "A2B2" "A3B2"
## [41] "A2B1" "A2B2" "A2B1" "A2B2" "A2B1" "A3B1" "A2B1" "A3B1" "A1B1" "A2B2"
## [51] "A2B2" "A1B1" "A3B1" "A1B2" "A3B2" "A1B1" "A3B1" "A1B2" "A1B1" "A2B1"
## [61] "A3B1" "A2B1" "A1B2" "A3B2" "A3B2" "A2B2"
```

where A and B respectively denote the **diet** and **exercise** factors and the numeric are the levels.

Blinding is conducted for experimenters administering treatments, experimenters assessing outcome, caregiver, animal facilities staff and others who interact with the animals.

## 4.2 Confirmatory, categorical outcome, one treatment factor, $\chi^2$ test

### 4.2.a Standard case

#### Objective

To confirm an effect in mice of a new drug compared to a standard drug for a certain tumor disease on death vs alive (a mouse is either alive or dead at the end of the experiment).

### Statistical test/model

Our research hypothesis is that the new drug will reduce the proportion of death compare to the standard drug, while the null hypothesis is the two proportions of death are the same. Thus, we use two sample comparison of proportion (relative frequency), using Gaussian distribution as limiting distribution of binomial, with one-sided test.

### Power calculation of sample size

The standard drug is known to have 60% proportion of death ( $p_1 = 0.60$ ). A reduction of 50% for the new drug compare to the standard drug is meaningful for us. That is,  $p_2 = p_1 - (p_1 * 0.50) = 0.60 - (0.60 * 0.5) = 0.60 - 0.30 = 0.30$ . We use R with the function `power.prop.test()` in standard library stats as below.

```
power.prop.test(p1 = 0.60, p2 = 0.30, sig.level = 0.05, power = 0.90, alternative = "two.sided")

##
##      Two-sample comparison of proportions power calculation
##
##              n = 55.68382
##              p1 = 0.6
##              p2 = 0.3
##      sig.level = 0.05
##              power = 0.9
##      alternative = two.sided
##
## NOTE: n is number in *each* group
```

The output is 55.7, rounded up to 56. Thus, 56 mice per group is needed to obtain a power of at least 0.90 with significant level of 0.05. The total number of animals needed in this study is  $2 \cdot 56 = 112$  mice.

### Randomization

The experimental unit (i.e., the mouse) is completely randomized (balance randomized) into the two groups of new drug (NEW) and standard drug (STD) with the use of computer randomization process. We use R with the code below, which is a similar fashion as in the previous example, thus we do not show the output.

```
set.seed(8057)
sample(rep(c("NEW", "STD"), each = 56), 112)
```

## 4.2.b Non-standard case: either probability is close to either one or zero

When either one of the survival-rates, denoted as  $p_1$  for the control group and  $p_2$  for the intervention group, is close to either zero or one, then one should use Fisher's exact test, instead of  $\chi^2$  test. Let  $n$  be the sample size calculated based on the  $\chi^2$  test. The correction for Fisher exact test is to replace  $n$  with

$$n' = \frac{n}{4} \cdot \left( 1 + \sqrt{1 + \frac{4}{n|p_1 - p_2|}} \right)^2$$

as shown by [Wittes, Janet \(2002\)](#) in equation (7C).

As an example we use the above scenario but now we assume that  $p_1 = 0.50$  (instead of 0.60) and that a reduction of 80% (instead of 50%) of the new drug is meaningful. That is,  $p_2 = p_1 - (p_1 * 0.50) = 0.50 - (0.80 * 0.5) = 0.50 - 0.40 = 0.10$  which is close to zero. The output of the  $\chi^2$  test with power of at least 0.90 and significant level of 0.05 would result in sample size of  $n = 26$  per group is shown below.

```
power.prop.test(p1 = 0.50, p2 = 0.10, sig.level = 0.05, power = 0.90, alternative = "two.sided")

##
##      Two-sample comparison of proportions power calculation
##
##              n = 25.43862
##              p1 = 0.5
##              p2 = 0.1
##      sig.level = 0.05
##              power = 0.9
##      alternative = two.sided
##
## NOTE: n is number in *each* group
```

Based on the  $\chi^2$  test we would need  $n = 26$  experimental units in each group. However, we should use the correction above since  $\chi^2$  test is not appropriate but Fisher's exact test is. Plug-in the correction formula

```
n <- 26
p1 <- 0.50
p2 <- 0.10
nprime <- (n/4)*(1+sqrt(1+(4/(n*abs(p1-p2))))))^2
nprime

## [1] 30.79706
```

we calculate  $n' = 31$ . Thus, we should require the total number of animals of  $2 \cdot 31 = 62$  mice.

### 4.3 Confirmatory, time-to-event outcome, one treatment factor, *logrank* test

#### *Objective*

To confirm an effect in mice of a new drug on the time to recurrence of a tumor compare to a conventional drug.

#### *Statistical test/model*

Our research hypothesis is that the new drug would decrease the hazard rate compared to the conventional drug, while the null hypothesis is that the hazard ratio of both groups is one. Thus, we use logrank test (aka Cox test).

#### *Power calculation of sample size*

First we note that two-sided sample size formula of two groups is given by

$$n = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{p_0 p_1 (\ln(\text{HR}))^2} \times \frac{1}{p_0 d_0 + p_1 d_1}$$

with

- $p_0$  and  $p_1$  are proportions of the subjects randomized to respectively control group and intervention group,
- $d_0$  and  $d_1$  are probabilities of the subjects to experience the event in respectively control group and intervention group (which are also called as mortality rates),
- $\alpha$  is the level of the test (probability of type I error),
- $1 - \beta$  is the power of the test.

The details of how this formula is constructed can be seen in [Schoenfeld, David \(1981\)](#) in Section 3.2.

A decrease of 35% hazard rate of the new drug relative to the conventional drug is meaningful for us. Let  $\lambda_1$  and  $\lambda_0$  be the hazard rates of the intervention drug and the control drug, respectively. Thus, the hazard ratio is

$$\text{HR} = \frac{\lambda_1}{\lambda_0} = \frac{\lambda_0 - 0.35\lambda_0}{\lambda_0} = 1 - 0.35 = 0.65 ,$$

for any value of the hazard rate of control group  $\lambda_0$ .

Under the assumption of logrank test (that the underlying survival curve is assumed to be exponential), the mortality rates are  $d_0 = 1 - \exp(-\lambda_0)$  and  $d_1 = 1 - \exp(-\lambda_1)$  respectively for the conventional drug and the new drug. From literature, an estimate of the mortality rate of the conventional drug is  $d_0 = 0.40$ . Therefore,  $\lambda_0 = -\ln(1 - d_0) = -\ln(1 - 0.40) \approx 0.51$ . Furthermore, the mortality rate of the intervention group is

$$d_1 = 1 - \exp(-\lambda_1) = 1 - \exp(-\lambda_0 \cdot \text{HR}) = 1 - \exp(-0.51 \cdot 0.65) = 1 - \exp(-0.33) \approx 0.28 .$$

We further assume an equal sample size for each group. Thus,  $p_0 = p_1 = 1/2$ . Plugging in these values to the sample size formula

```
my_nsize <- function(HR, d0, d1, P0, P1, alpha, beta){
  (qnorm(1-alpha/2) + qnorm(1-beta))^2 /
  (P0*P1*(P0*d0+P1*d1)*(log(HR))^2)
}
n_size <- my_nsize(0.65, 0.40, 0.28, 1/2, 1/2, 0.05, 0.20)
round(n_size, 2)

## [1] 497.59
```

gives us a total sample size of 497.59 for both groups, which we round up to 498 (that is, a balance size of 249 per group), with power of 0.80 and significant level of 0.05.

Further detail on the topic of modeling survival data can be found in [Tarigan, Bernadetta \(2022\)](#).

## 4.4 Exploratory, continuous outcome, one treatment factor

### *Objective*

To explore in male mice the effect of a certain simulation for neural activity compare to no-simulation, with cerebral blood volume (in ml) as primary outcome

### *Fermi's approximation of sample size*

Since the experiment is an exploratory type, we cannot use power analysis for sample size estimation. Instead we apply the Fermi's approximation, based on feasibility and resources. Given the complexity of the experiment and the laboratory constraints we have, as explained previously in the paragraph 29 (of Form A), we choose 9 animals per group. In total we need  $2 \times 9 = 18$  mice.

If we were to use two-sided  $T$  test of two independent samples this choice of sample size would enable us to detect a signal-to-noise ratio of at least  $d = 1.5$ , given  $\alpha = 0.10$  and power of 0.90.

## 5 Multiple Testing

When an  $F$ -test for null hypothesis  $H_0 : \mu_1 = \mu_2 = \dots = \mu_t$  is rejected, it tells us that there are significant differences between at least two of the means. If there are several levels of the treatment factor ( $t \geq 2$ ), the rejection of the  $H_0$  does not necessarily imply that all means are significantly different from each other. Thus,

further investigation should be conducted to find out exactly which means differ. If the comparisons are not planned in advance of running the experiment (unplanned comparison), the investigator might be tempted to choose the comparisons she/he would like to make based on the means of the data. This implicitly means that all possible comparisons have been made.

When testing all possible comparisons, each at the significance level  $\alpha = 0.05$ , the overall significance level can be much higher than 0.05, can even be greater than 0.50, depending on the number of comparisons. This implies that even there is no difference in the means  $\mu_1, \mu_2, \dots, \mu_t$  there could be a high chance of finding one or more comparisons significant when each comparison is tested individually.

This overall significance level is also called family-wise error rate (FWER). The term "family" refers to the collection of null hypotheses. For the  $F$ -test with  $t$  levels, there are  $m = \binom{t}{2}$  null hypotheses (comparing every combination of 2 out of  $t$  means) that are jointly tested. Thus, the probability of committing at least one type I error out of  $m$  tests is

$$\begin{aligned} \text{FWER} &= P(\text{committing at least one type I error in } m \text{ tests}) \\ &= 1 - P(\text{committing no type I error}) \\ &= 1 - (1 - \alpha)^m, \end{aligned}$$

where  $\alpha = P(\text{committing type I error})$  for each individual test.

Consider a case where the treatment factor has five levels/groups ( $t = 5$ ) and we are interested in comparing all possible pairs  $m = \binom{5}{2} = 10$ . In this case with individual  $\alpha = 0.05$  the FWER is  $1 - (1 - 0.05)^{10} = 0.40$ , which is away much larger than the individual error rate. Even with  $t = 3$ , the overall significant level is  $1 - (1 - 0.05)^3 = 0.14$ , triple the individual significant level.

Thus, in the case of multiple comparisons/tests, we should correct the individual significant level in calculating sample size. The Bonferroni method is conservative but the simplest. For the overall error rate of  $\alpha$ , the corrected significant level is  $\alpha/m$  with  $m$  is the number of comparisons that are jointly tested. For example, if we have 3 comparisons, then to achieve an overall significant level of 0.05 the test should be with significant level of  $\alpha = 0.05/3 = 0.017$ .

## References

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- [8] Wittes, Janet. Sample Size Calculations for Randomized Controlled Trials. <https://doi.org/10.1093/epirev/24.1.39>, 07 2002.

## Version Information

v1.1 04.02.2021

v1.2 19.01.2022 add examples, add references & change style

```
print( sessionInfo(), locale=FALSE)

## R version 4.0.2 (2020-06-22)
## Platform: x86_64-pc-linux-gnu (64-bit)
## Running under: Ubuntu 18.04.6 LTS
##
## Matrix products: default
## BLAS: /usr/lib/x86_64-linux-gnu/libf77blas.so.3.10.3
## LAPACK: /usr/lib/x86_64-linux-gnu/atlas/liblapack.so.3.10.3
##
## attached base packages:
## [1] stats graphics grDevices utils datasets methods base
##
## other attached packages:
## [1] daewr_1.2-7 knitr_1.36
##
## loaded via a namespace (and not attached):
## [1] igraph_1.2.6 mathjaxr_1.4-0 magrittr_2.0.1 sfsmisc_1.1-12
## [5] partitions_1.10-2 MASS_7.3-54 scatterplot3d_0.3-41 colorspace_2.0-2
## [9] lattice_0.20-41 conf.design_2.0.0 highr_0.8 stringr_1.4.0
## [13] tools_4.0.2 grid_4.0.2 vcd_1.4-8 xfun_0.26
## [17] lmtest_0.9-38 gmp_0.6-2 numbers_0.7-5 evaluate_0.14
## [21] stringi_1.4.6 compiler_4.0.2 FrF2_2.2-2 combinat_0.0-8
## [25] DoE.base_1.2 polynom_1.4-0 pkgconfig_2.0.3 zoo_1.8-9
```