Statistical Genetics

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Contents

Chapter 1

Prerequisites

Elementary probability theory and linear algebra will be sufficient. However, topics regarding theoretical genetics requires knowledge about stochastic processes and measure theory.

Reference on advanced mathematics can be found in Rudin (1986), Durrett (2019) and Durrett (2008).

Chapter 2

Introduction

You can label chapter and section titles using `{#label}` after them, e.g., we can reference Chapter 2. If you do not manually label them, there will be automatic labels anyway, e.g., Chapter **??**.

Figures and tables with captions will be placed in `figure` and `table` environments, respectively.

```
par(mar = c(4, 4, .1, .1))
plot(pressure, type = 'b', pch = 19)
```

Reference a figure by its code chunk label with the `fig:` prefix, e.g., see Figure 2.1. Similarly, you can reference tables generated from `knitr::kable()`, e.g., see Table 2.1.

```
knitr::kable(
  head(iris, 20), caption = 'Here is a nice table!',
  booktabs = TRUE
)
```

You can write citations, too. For example, we are using the **bookdown** package (Xie, 2018) in this sample book, which was built on top of R Markdown and **knitr** (**?**).

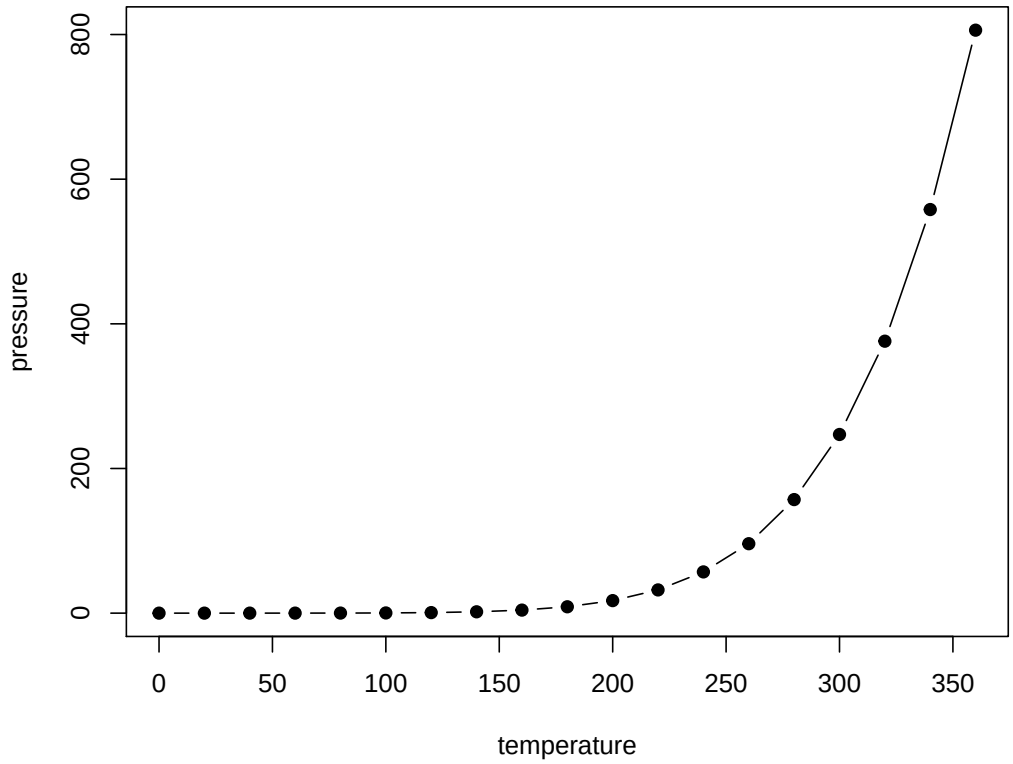

Figure 2.1: Here is a nice figure!

Table 2.1: Here is a nice table!

Sepal.Length	Sepal.Width	Petal.Length	Petal.Width	Species
5.1	3.5	1.4	0.2	setosa
4.9	3.0	1.4	0.2	setosa
4.7	3.2	1.3	0.2	setosa
4.6	3.1	1.5	0.2	setosa
5.0	3.6	1.4	0.2	setosa
5.4	3.9	1.7	0.4	setosa
4.6	3.4	1.4	0.3	setosa
5.0	3.4	1.5	0.2	setosa
4.4	2.9	1.4	0.2	setosa
4.9	3.1	1.5	0.1	setosa
5.4	3.7	1.5	0.2	setosa
4.8	3.4	1.6	0.2	setosa
4.8	3.0	1.4	0.1	setosa
4.3	3.0	1.1	0.1	setosa
5.8	4.0	1.2	0.2	setosa
5.7	4.4	1.5	0.4	setosa
5.4	3.9	1.3	0.4	setosa
5.1	3.5	1.4	0.3	setosa
5.7	3.8	1.7	0.3	setosa
5.1	3.8	1.5	0.3	setosa

Chapter 3

Linkage Disequilibrium Score Regression (LDSC)

Linkage Disequilibrium Score Regression (LDSC) is a popular method in statistical genetics with a wide range of application. It is used to measure confounding due to population structure, computing genetic correlation and heritability. Most of all, the method can be performed soley on summary statistics rather than the full data which reduces memeory and computation requirements tremendously.

3.1 Univariate LDSC

The original from of LDSC (here we call it Univariate LDSC) can be used to estimate SNP heritability and confounding effects of population structure (Bulik-Sullivan et al., 2015). I refer the supplementary notes of Bulik-Sullivan et al. (2015) for the notations.

Definition 3.1 (LD score)**.** Define the **LD Score** of variant j as

$$l_j = \sum_{k=1}^{M} r_{jk}^2$$

Then for a homogenous sample without population structure, the following holds.

Theorem 3.1 (LDSC without structure)**.** *In a sample without population structure*

$$\mathbb{E}[\chi_j^2] = \frac{Nh_g^2}{M} l_j + 1$$

holds.

If a population structure (measured by the fixation index F_{ST}) exists, a non-zero constant is added to .

Theorem 3.2 (General LDSC)**.** *In a sample with population structure*

$$\mathbb{E}[\chi_j^2] = \frac{Nh_g^2}{M} l_j + 1 + aNF_{ST}$$

holds.

Proof.

$$\begin{aligned} \mathrm{Var}[\hat{\beta}_j] &= \mathbb{E}[\mathrm{Var}[\hat{\beta}_j|X]] + \mathrm{Var}[\mathbb{E}[\hat{\beta}_j|X]] \\ &= \mathbb{E}[\mathrm{Var}[\hat{\beta}_j|X]] + 0 \end{aligned}$$

The second term vanishes since $\mathbb{E}[\hat{\beta}_j|X] = X_j^T/N \cdot \mathbb{E}[\phi] = 0$.

Inspecting the first term,

$$\begin{aligned}
\mathrm{Var}[\hat{\beta}_j|X] &= \frac{1}{N^2}\mathrm{Var}[X_j^T\phi|X] \\
&= \frac{1}{N^2}X_j^T\mathrm{Var}[\phi|X]X_j \\
&= \frac{1}{N^2}\left(\frac{h_g^2}{M}X_j^T X X^T X_j + N(1-h_g^2)\right)
\end{aligned}$$

□

Chapter 4

Mendelian Randomization

Mendelian Randomization (MR) is a special case of the Instrumental Variable (IV) which is widely used in econometrics. MR employs genetic variants (e.g. SNP) as IVs since genotypes are automatically randomized in the gametic phase of cell division.

4.1 Simple MR

4.2 Two-sample MR

4.3 MR-Egger

4.4 Weighted Median MR

4.5 Modal Based MR

Bibliography

Bulik-Sullivan, B. K., , Loh, P.-R., Finucane, H. K., Ripke, S., Yang, J., Patterson, N., Daly, M. J., Price, A. L., and Neale, B. M. (2015). LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nature Genetics*, 47(3):291–295.

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