UNIVERSITÉ GRENOBLE-ALPES

THÈSE

Pour obtenir le grade de

DOCTEUR DE L'UNIVERSITÉ DE GRENOBLE-ALPES

Spécialité : **Modèles, méthodes et algorithmes en biologie, santé et environnement**
Arrêté ministériel : ?

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Écrire le titre de la thèse ici

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Préface

This is an example of a thesis setup to use the reed thesis document class (for LaTeX) and the R bookdown package, in general.

Table des matières

Liste des tableaux

Table des figures

$->$

Remerciements

Je remercie ...

Cette thèse est dédiée à ...

Résumé

The preface pretty much says it all.
Second paragraph of abstract starts here.

Abstract

The preface pretty much says it all.
Second paragraph of abstract starts here.

Chapitre 1

Introduction

1.1 Structure et fonction du spermatozoïde

1.1.1 La spermatogénèse

La spermatogenèse des mamifères est un processus long et complexe controllé par plusieurs mécanismes étroitement liés ((Gnessi, Fabbri, & Spera, 1997, Kierszenbaum (1994)),**Sharpe1994 à trouver ! ! !**).C'est au cours de celle-ci que, à partir de cellules germinales, seront produits les spermatozoïdes matures. Ce processus est divisé en trois phases principales : La phase de multiplication, la phase de division (appelée la méiose) et la phase de maturation. Chez les hommes, ces tapes se déroulent en continue dans la paroi des tubes séminifères du testicules depuis la pubertés jusqu'à la mort et implique trois types de cellules germinales : les spermatogonies, les spermatocytes et les spermatides. Le temps nécessaire pour obtenir un spermatozoïde mature à partir de cellules germinales est d'environs 30 à 40 jours (Y Clermont, 1972) et la production quotidienne de spermatozoïde est d'environ 45 million par testicules (Johnson, Petty, & Neaves, 1980).

Rappels sur le testicule

Les testicules sont les organes sexuels masculins. Ils possèdes deux fonctions principales plus ou moins exprimés selon les période de la vie de l'individu : une fonction endocrine caractérisé par la synthèse des hormones stéroïdes sexuelles masculines (la stéroïdogenèse) et une fonction exocrine au cours de laquelle seront produits les gamètes masculins. Chez un individu adulte en bonne santé, celui-ci présente une forme ovoïde ayant un volume moyen de 18 cm^3 par testicule. Comme chez la plupart des mammifères terrestres, ils sont sous le pénis dans dans une poche de peau appelée scrotum et reliés à l'abdomen par le cordon spermatique (Figure : **??**). Cette externalisation des testicules permet leur maintien à une température plus basse que celle du reste du corps nécessaire à la spermatogenèse.
L'intérieur du testicule contient des tubes séminifères enroulés ainsi que du tissu entre les tubules appelé espace interstitiel. Les tubes séminifères sont de longs tubes compactés sous forme de boucles et dont les deux extrémités débouchent sur le *rete*

testis (Figure : **??**). C'est le long des parois du tube séminifère que se dérouleront l'ensemble des étapes de la spermatogenèse.

La phase de multiplication

La phase de multiplication est la phase au cours de laquelle les spermatogonies se divisent par mitoses pour aboutir au stade de spermatocytes primaires. Les spermatogonies sont des cellules dploïdes à l'origine de k'ensemble des autres cellules germinales humaines. Pour cela, elle vont s'auto-renouveller par mitose successive afin de maintenir une production continue de spermatozoïdes tout au long de la vie de l'individu. Ces cellules sont localisées dans le compartiment basal des tubes séminifères. Elles présentent un noyau ovoïde ainsi qu'un cytoplasme dense contenant un petit appareil de Golgi, quelques mitochondrie ainsqi que plusieurs ribosomes libres. Les analyses histologiques ont permis de distinguer trois types de spermatogonies en fonction de leur contenu en heterochromatine ((Yves Clermont, 1963, Yves Clermont (1966), Goossens & Tournaye (2013))) :

1. Les spermatogonies de type A dark (ou Ad)
2. Les spermatogonies de type A pale (ou Ap)
3. Les spermatogonies de type B

Dans le modèle le plus communément accepté, les spermatogonies Ad vont au cours d'une première mitose former un spermatogonie Ad et un spermatogonie Ap (**Figure :** 1.1). Cette propriété permet à la fois de se différencier en spermatocytes tout en constituant un compartiment de réserve de spermatogonies Ad permettant d'assurer la production permanente de spermatozoïdes. Les spermatogonies Ap ainsi formés se diviseront ensuite par mitose pour former deux spermatogonies B qui elles-mêmes se diviseront en deux spermatocytes primaires diploïdes (**Figure :** 1.1).

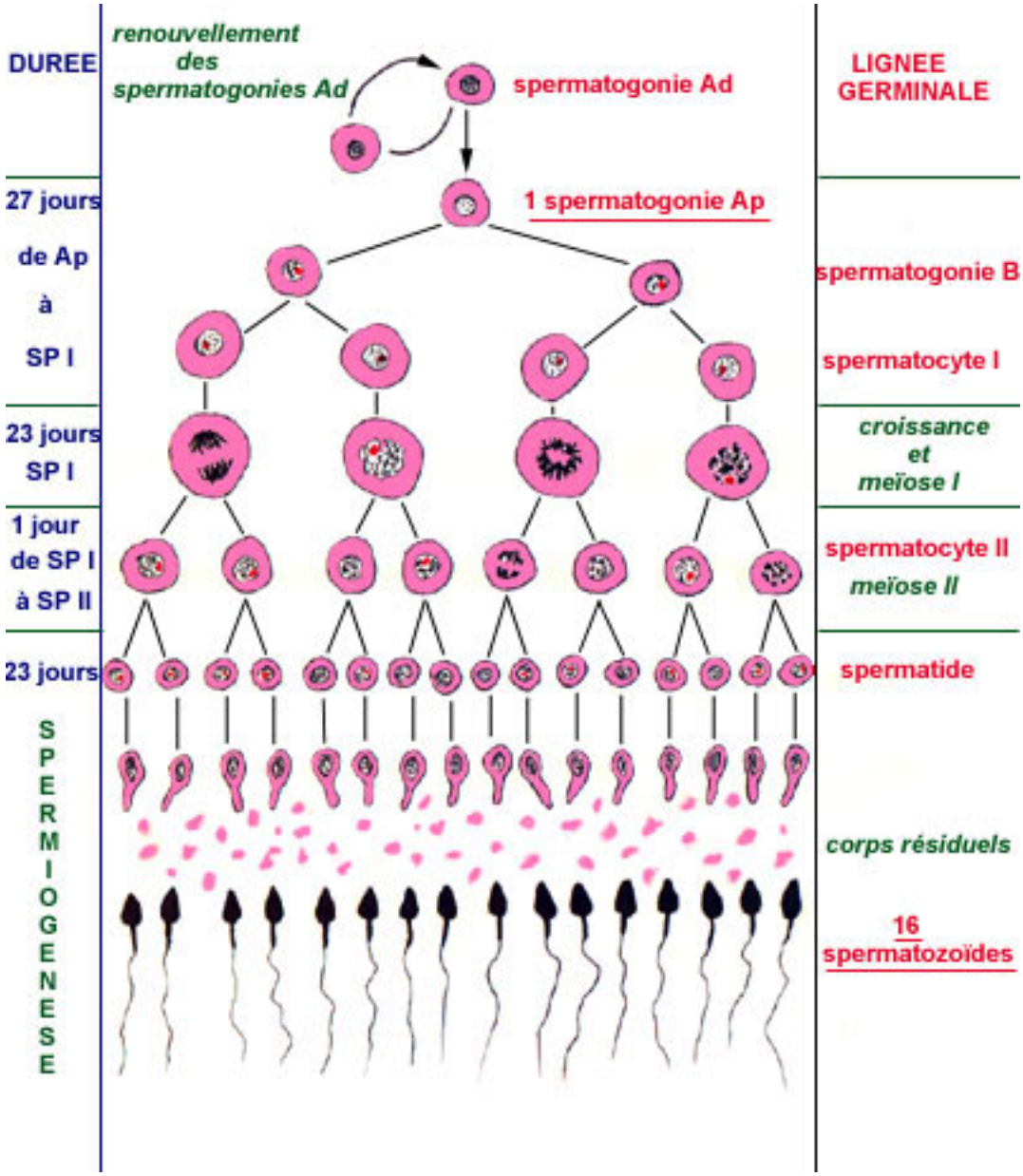
DUREE
renouvellement des spermatogonies Ad
spermatogonie Ad
LIGNEE GERMINALE
27 jours
de Ap
à
SP I
1 spermatogonie Ap
spermatogonie B
spermatocyte I
23 jours
SP I
croissance et meïose I
1 jour
de SP I
à SP II
spermatocyte II
meïose II
23 jours
spermatide
SPERMIOGENESE
corps résiduels
16
spermatozoïdes

FIGURE 1.1 – :

La méïose

La spermiogénèse

1.1.2 Anatomie du spermatozoïde

La tête

Le flagelle

1.1.3 Fonction du spermatozoïde

1.2 L'infertilité masculine

L'organisation mondiale de la santé définie l'infertilité comme étant : "*une pathologie du système reproductif définie par l'échec d'une grossesse clinique après 12 mois ou plus de rapports sexuels réguliers non protégés*" (`Who.int. 2013-03-19. Retrieved 2013-06-17`). Environ 10-15% des couples humains sont considérés infertiles. On estime que dans la moitié des cas, la cause sous-jacente est masculine. Les facteurs causaux sous-jacents de l'infertilité masculine peuvent être attribués à des toxines environnementales, des troubles systémiques tels que la maladie hypothalamo-hypophysaire, les cancers testiculaires et l'aplasie des cellules germinales. Les facteurs génétiques, y compris les aneuploïdies et les mutations de gènes uniques, contribuent également à l'infertilité masculine. Cependant, aucune cause n'est identifiée dans 10-20% des cas.

1.2.1 Les différents phénotypes d'infertilité masculine

Liée à la quantité

liée à la forme

liée à la mobilitée

1.2.2 La génétique de l'infertilité

Les causes fréquentes

Les microdélétions du chromosome Y

Anomalies chromosomiques

Mutations CFTR

Les nouveaux gènes

1.3 Les techniques d'analyses génétiques

1.3.1 Les puces

1.3.2 Le séquençage

Le Sanger

Le NGS

1.4 L'analyse bioinformatique

1.4.1 L'analyse des données brut

L'alignement

L'appel des variants

1.4.2 La priorisation des variants

Chapitre 2

Investigation génétique et physiologique de la globozoospermie

2.1 Math

2.2 Chemistry 101 : Symbols

Chemical formulas will look best if they are not italicized. Get around math mode's automatic italicizing in LaTeX by using the argument `$\mathrm{formula here}$`, with your formula inside the curly brackets. (Notice the use of the backticks here which enclose text that acts as code.)

So, $Fe_2^{2+}Cr_2O_4$ is written `$\mathrm{Fe_2^{2+}Cr_2O_4}$`.
Exponent or Superscript : O^-
Subscript : CH_4

To stack numbers or letters as in Fe_2^{2+}, the subscript is defined first, and then the superscript is defined.
Bullet : $CuCl \bullet 7H_2O$
Delta : Δ
Reaction Arrows : $\longrightarrow$ or $\xrightarrow{solution}$
Resonance Arrows : $\leftrightarrow$
Reversible Reaction Arrows : $\rightleftharpoons$

2.2.1 Typesetting reactions

You may wish to put your reaction in an equation environment, which means that LaTeX will place the reaction where it fits and will number the equations for you.

$$C_6H_{12}O_6 + 6O_2 \longrightarrow 6CO_2 + 6H_2O \tag{2.1}$$

We can reference this combustion of glucose reaction via Equation (2.1).

2.2.2 Other examples of reactions

$$\mathrm{NH_4Cl_{(s)} \rightleftharpoons NH_{3(g)} + HCl_{(g)}}$$

$$\mathrm{MeCH_2Br + Mg \xrightarrow[below]{above} MeCH_2 \bullet Mg \bullet Br}$$

2.3 Physics

Many of the symbols you will need can be found on the math page `http://web.reed.edu/cis/help/latex/math.html` and the Comprehensive LaTeX Symbol Guide (`http://mirror.utexas.edu/ctan/info/symbols/comprehensive/symbols-letter.pdf`).

2.4 Biology

You will probably find the resources at `http://www.lecb.ncifcrf.gov/~toms/latex.html` helpful, particularly the links to bsts for various journals. You may also be interested in TeXShade for nucleotide typesetting (`http://homepages.uni-tuebingen.de/beitz/txe.html`). Be sure to read the proceeding chapter on graphics and tables.

Chapitre 3

Tables, Graphics, References, and Labels

3.1 Tables

In addition to the tables that can be automatically generated from a data frame in **R** that you saw in [R Markdown Basics] using the `kable` function, you can also create tables using *pandoc*. (More information is available at `http://pandoc.org/README.html#tables`.) This might be useful if you don't have values specifically stored in **R**, but you'd like to display them in table form. Below is an example. Pay careful attention to the alignment in the table and hyphens to create the rows and columns.

Table 3.1 – Correlation of Inheritance Factors for Parents and Child

Factors	Correlation between Parents & Child	Inherited
Education	-0.49	Yes
Socio-Economic Status	0.28	Slight
Income	0.08	No
Family Size	0.18	Slight
Occupational Prestige	0.21	Slight

We can also create a link to the table by doing the following : Table 3.1. If you go back to [Loading and exploring data] and look at the `kable` table, we can create a reference to this max delays table too : Table **??**. The addition of the `(\#tab:inher)` option to the end of the table caption allows us to then make a reference to Table `\@ref(tab:label)`. Note that this reference could appear anywhere throughout the document after the table has appeared.

3.2 Figures

If your thesis has a lot of figures, *R Markdown* might behave better for you than that other word processor. One perk is that it will automatically number the figures accordingly in each chapter. You'll also be able to create a label for each figure, add a caption, and then reference the figure in a way similar to what we saw with tables earlier. If you label your figures, you can move the figures around and *R Markdown* will automatically adjust the numbering for you. No need for you to remember ! So that you don't have to get too far into LaTeX to do this, a couple **R** functions have been created for you to assist. You'll see their use below.

In the **R** chunk below, we will load in a picture stored as `reed.jpg` in our main directory. We then give it the caption of "Reed logo", the label of "reedlogo", and specify that this is a figure. Make note of the different **R** chunk options that are given in the R Markdown file (not shown in the knitted document).

FIGURE 3.1 – Reed logo

Here is a reference to the Reed logo : Figure 3.1. Note the use of the `fig:` code here. By naming the **R** chunk that contains the figure, we can then reference that figure later as done in the first sentence here. We can also specify the caption for the figure via the R chunk option `fig.cap`.

Below we will investigate how to save the output of an **R** plot and label it in a way similar to that done above. Recall the `flights` dataset from Chapter. (Note that we've shown a different way to reference a section or chapter here.) We will next explore a bar graph with the mean flight departure delays by airline from Portland for 2014. Note also the use of the `scale` parameter which is discussed on the next page.

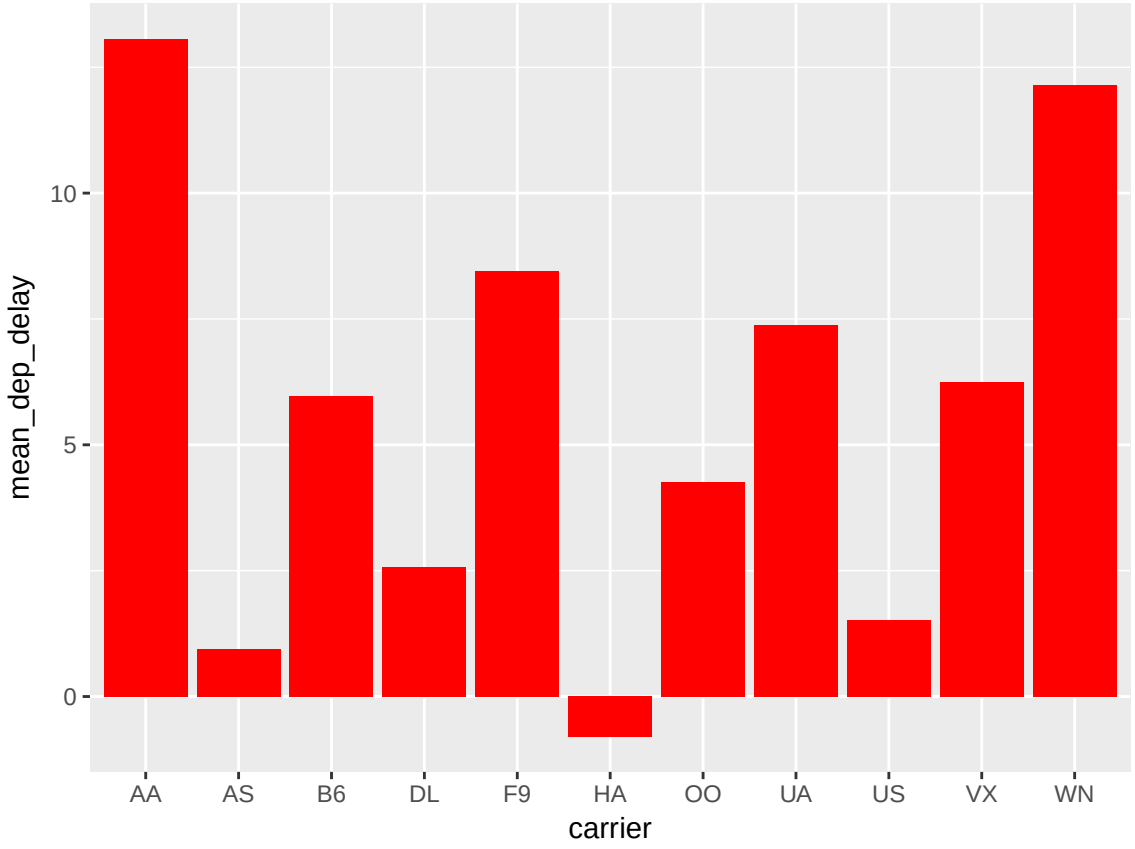

FIGURE 3.2 – Mean Delays by Airline

Here is a reference to this image : Figure 3.2.

A table linking these carrier codes to airline names is available at `https://github.com/ismayc/pnwflights14/blob/master/data/airlines.csv`.

Next, we will explore the use of the `out.extra` chunk option, which can be used to shrink or expand an image loaded from a file by specifying `"scale= "`. Here we use the mathematical graph stored in the "subdivision.pdf" file.

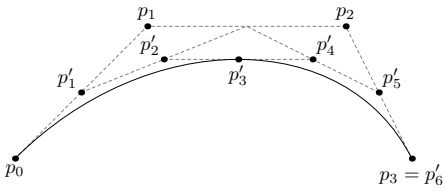

FIGURE 3.3 – Subdiv. graph

Here is a reference to this image : Figure 3.3. Note that `echo=FALSE` is specified so that the **R** code is hidden in the document.

More Figure Stuff

Lastly, we will explore how to rotate and enlarge figures using the `out.extra` chunk option. (Currently this only works in the PDF version of the book.)

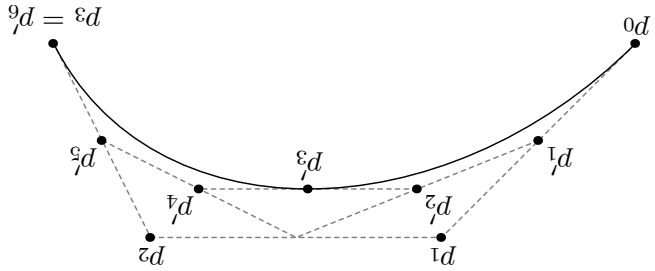

FIGURE 3.4 – A Larger Figure, Flipped Upside Down

As another example, here is a reference : Figure 3.4.

3.3 Footnotes and Endnotes

You might want to footnote something.[1] The footnote will be in a smaller font and placed appropriately. Endnotes work in much the same way. More information can be found about both on the CUS site or feel free to reach out to `data@reed.edu`.

3.4 Bibliographies

Of course you will need to cite things, and you will probably accumulate an armful of sources. There are a variety of tools available for creating a bibliography database (stored with the .bib extension). In addition to BibTeX suggested below, you may want to consider using the free and easy-to-use tool called Zotero. The Reed librarians have created Zotero documentation at `http://libguides.reed.edu/`

1. footnote text

`citation/zotero`. In addition, a tutorial is available from Middlebury College at `http://sites.middlebury.edu/zoteromiddlebury/`.

R Markdown uses *pandoc* (`http://pandoc.org/`) to build its bibliographies. One nice caveat of this is that you won't have to do a second compile to load in references as standard LaTeX requires. To cite references in your thesis (after creating your bibliography database), place the reference name inside square brackets and precede it by the "at" symbol. For example, here's a reference to a book about worrying : (**???**). This `Molina1994` entry appears in a file called `thesis.bib` in the `bib` folder. This bibliography database file was created by a program called BibTeX. You can call this file something else if you like (look at the YAML header in the main .Rmd file) and, by default, is to placed in the `bib` folder.

For more information about BibTeX and bibliographies, see our CUS site (`http://web.reed.edu/cis/help/latex/index.html`) [2]. There are three pages on this topic : *bibtex* (which talks about using BibTeX, at `http://web.reed.edu/cis/help/latex/bibtex.html`), *bibtexstyles* (about how to find and use the bibliography style that best suits your needs, at `http://web.reed.edu/cis/help/latex/bibtexstyles.html`) and *bibman* (which covers how to make and maintain a bibliography by hand, without BibTeX, at `http://web.reed.edu/cis/help/latex/bibman.html`). The last page will not be useful unless you have only a few sources.

If you look at the YAML header at the top of the main .Rmd file you can see that we can specify the style of the bibliography by referencing the appropriate csl file. You can download a variety of different style files at `https://www.zotero.org/styles`. Make sure to download the file into the csl folder.

Tips for Bibliographies

- Like with thesis formatting, the sooner you start compiling your bibliography for something as large as thesis, the better. Typing in source after source is mind-numbing enough ; do you really want to do it for hours on end in late April ? Think of it as procrastination.
- The cite key (a citation's label) needs to be unique from the other entries.
- When you have more than one author or editor, you need to separate each author's name by the word "and" e.g. `Author = {Noble, Sam and Youngberg, Jessica},`.
- Bibliographies made using BibTeX (whether manually or using a manager) accept LaTeX markup, so you can italicize and add symbols as necessary.
- To force capitalization in an article title or where all lowercase is generally used, bracket the capital letter in curly braces.
- You can add a Reed Thesis citation [3] option. The best way to do this is to use the phdthesis type of citation, and use the optional "type" field to enter "Reed thesis" or "Undergraduate thesis."

2. (**???**)
3. (**???**)

3.5 Anything else ?

If you'd like to see examples of other things in this template, please contact the Data @ Reed team (email `data@reed.edu`) with your suggestions. We love to see people using *R Markdown* for their theses, and are happy to help.

Conclusion

If we don't want Conclusion to have a chapter number next to it, we can add the `{-}` attribute.

More info

And here's some other random info : the first paragraph after a chapter title or section head *shouldn't be* indented, because indents are to tell the reader that you're starting a new paragraph. Since that's obvious after a chapter or section title, proper typesetting doesn't add an indent there.

Annexe A

The First Appendix

This first appendix includes all of the R chunks of code that were hidden throughout the document (using the `include = FALSE` chunk tag) to help with readibility and/or setup.

In the main Rmd file

In Chapter 3 :

```
# This chunk ensures that the thesisdown package is
# installed and loaded. This thesisdown package includes
# the template files for the thesis and also two functions
# used for labeling and referencing
if(!require(devtools))
  install.packages("devtools", repos = "http://cran.rstudio.com")
if(!require(dplyr))
    install.packages("dplyr", repos = "http://cran.rstudio.com")
if(!require(ggplot2))
    install.packages("ggplot2", repos = "http://cran.rstudio.com")
if(!require(ggplot2))
    install.packages("bookdown", repos = "http://cran.rstudio.com")
if(!require(thesisdown)){
  library(devtools)
  devtools::install_github("ismayc/thesisdown")
  }
library(thesisdown)
flights <- read.csv("data/flights.csv")
```

Annexe B

The Second Appendix, for Fun

References

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