# Hierarchical Spatial Structure in Compartmental Epidemiological models

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# Sections

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# Abstract

Epidemiological modelling is essential to understand and predict the spread of infectious diseases and plan effective interventions. Disease spread is an inherently spatial process, particularly in diseases that spread through contact with body fluids, and spatially structured epidemiological models provide an opportunity to incorporate a wealth of geographical information into the modelling process. Here, we present a compartmental meta-population model encoding the hierarchical spatial structure of the Australian Statistical Geography Standard (ASGS). Relationships between spatial groupings are represented in a mixing matrix, which influences the spread of infection between patches (i.e. Patches in the same spatial grouping are more likely to spread disease to each other compared to patches outside this grouping). As an example, we model the Greater Melbourne Statistical Area (SA) with patches representing SA2, SA4, and SA4 level groupings, and stochastically simulate the course of an epidemic as a Continuous Time Markov Chain (CTMC). We compare the results of simulations with varying influence of the spatial relationships between patches (through the construction of the mixing matrix), different levels of spatial resolution (which level of the spatial hierarchy is represented by compartmental patches), and different infectious disease parameters (e.g. $R_0$), as well as with the results of a spatial compartmental model incorporating an alternative source of geographic information (i.e. empirically derived mobility data). We conclude by speculating on the potential use of such geographically informed epidemiological models in the management of infectious diseases.

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The contribution in sec-litreview of this thesis was presented in the International Symposium on Nonsense held in Dublin, Ireland, in July 2022.

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This thesis is written using Quarto with renv (Ushey, 2022) to create a reproducible environment. All materials (including the data sets and source files) required to reproduce this document can be found at the Github repository `github.com/SusanSu/thesis`.

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# Acknowledgements

I would like to thank my pet goldfish for …

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# 1 Introduction

# Part I

# Background

# 2 Compartmental Models

"Compartmental models are the most frequently used type of epidemic model. In this class of models, individuals can be in a finite number of discrete states. Some of these states are simply labels that specify the various traits of individuals. Of these, some will be changing with time, such as age class, and others will be fixed, such as sex or species. Other states indicate the progress of an infection: for example, an individual can upon becoming infected, typically first enter a state of latency, then progress to a state of infectiousness, and then lose infected status to progress to a recovered/immune state. With each state one can associate the subpopulation of individuals who are in that particular state at the given time (e.g. a female in a latent state of infection). Often the same symbol is used as a label for a state and to denote the corresponding subpopulation size, either as a fraction or as a number (e.g. I or Y for individuals in an infectious state)" - (**diekmann2010?**)

### 2.0.1 The SIR compartmental model

The simplest comparmental model of infectious disease spread is the SIR Compartmental Model, with three compartments: S - for individuals *susceptible* to the disease; I - for *infected* individuals; and R - for previously infected individuals who have *recovered* (or been otherwise *removed* from that compartment). With the simplifying assumption of a constant population size, $N$, i.e.

$$N = S + I + R \tag{2.1}$$

Individuals move between compartments in a fixed set of ways, they may either become infected (moving from S -> I), or recover from infection (I -> R).

At each time unit an infected individual can come into contact with, on average, $k\frac{S}{N}$ Susceptible individuals. $\pi$ is the probability of infecting somebody on coming in contact, so $\beta = k\pi$ is the average rate at which an infected indivudual will infect a susceptible. Infected individuals recover at the constant rate, $\gamma$, with $1/\gamma$ the mean recovery time.

| Parameter | Interpretation |
|---|---|
| $\beta$ | Transmission rate |
| $\gamma$ | Recovery rate |

Thus, an SIR model can be represented by the schematic

## 2.1 SIR Dynamics

### 2.1.1 ODE representation

Given the rate parameters defined above, the change in compartment composition over time can be described by the system of differential equations

$$\begin{aligned} \frac{dS}{dt} &= -\beta I \frac{S}{N} \\ \frac{dI}{dt} &= \beta I \frac{S}{N} - \gamma I \\ \frac{dR}{dt} &= \gamma I \end{aligned} \tag{2.2}$$

Importantly, if the total population size is known, given Equation 2.1, R = N - S + I and the entire system can be described by two of the equations in Equation 2.2.

EXAMPLE

#### Limitations of Deterministic ODE

While Equation 2.2 provides a neat solution for the expected behaviour of a epidemic, it fails to caputure the variability inherent in a complex process like disease spread.

# 3 Compartmental models as stochastic processes

## 3.1 Stochastic processes

A Stochastic Process is a collection of random variables, $X(t)$. In the case of a compartmental SIR model **?@sec-ref**, the state of the model at time $t$ can be represented by the number of individuals in the Susceptible and Infected compartments, i.e.

$$X(t) = S(t) + I(t)$$

Where $S(t), I(t) \in \{0, 1, 2, \dots, N\}$, $S(t) + I(t) \leq N$, and $t \in [0, \infty)$

We can represent the probability of a transitioning one particular state $x = (s, i)$[1] to another $x = (s + k, i + j)$ (i.e. due to infection or recovery) after a time $\Delta t > 0$, as

$$P(X(t + \Delta t) = (s + k, i + j) \mid (S(t), I(t)) = (s, i))$$

We will make two assumptions about the probability of states, $P(X(t))$:

1. Time Homogeneity

   $$P\left(X(t + \Delta t) = j \mid X(t) = i\right) = P\left(X(t) = j \mid X(0) = i\right)$$

   Which states that the transition probabilities depend on the time between events, $\Delta t$, but not on the specific time $t$.

2. Memorylessness (Markov Property)

   $$P(X(t + \Delta t) = j \mid X(t) = i, X(u) = k, 0 \leq u < t) = P(X(t + \Delta t) = j \mid X(t) = i)$$

   Which states that the probability of transitioning from a state $i$ at time $t$ to a state $j$ at time $(t + \Delta t)$ depends on the state at $t$ and not on any previous state.

[1] lower case letters (e.g. $s$, $i$) represent specific values of the random variables ($S(t)$ and $I(t)$)

Representing our compartmental model as such a 'Time Homogeneous Markov Chain' means that we can succinctly describe the probabilities of possible state transitions ('events') because they only depend on the intervening time ($\Delta t$) and the current state $x_t = (s_t, i_t)$.

Table 3.1: Transition events in a SIR time homogeneous markov chain

| Event | Change ($\Delta S$ , $\Delta I$) | Probability |
|---|---|---|
| Infection | $(-1, +1)$ | $\beta i \frac{s}{N} \Delta t + o(\Delta t)$ |
| Recovery | $(0, -1)$ | $\gamma i \Delta t + o(\Delta t)$ |

Time homogeneity and the markov property allow us to define the 'transition function' $p_{ij}(t)$, which gives the probabilty of transitioning from state $i$ to state $j$ after time $t$

$$p_{ij} = P(X(t) = P(X(t) = j \mid X(0) = i)$$

and represent the possible state transition probabilities for our SIR model as

$$p_{(s,i),(s+k,i+j)}(\Delta t) = \begin{cases} \beta i \frac{s}{N} \Delta t + o(\Delta t), & (k,j) = (-1,+1) \\ \gamma i \Delta t + o(\Delta t), & (k,j) = (0,-1) \\ 1 - (\beta i \frac{s}{N} + \gamma i)\, \Delta t & \\ \quad + o(\Delta t), & (k,j) = (0,0) \\ 0(\Delta t), & \text{otherwise.} \end{cases} \tag{3.1}$$

Moreover, if we consider the state space of $X(t)$, (e.g. containing all possible comninations of numbers of susceptible and infected individuals $(s, i)$,

$$\mathbb{S} = \{s, i : 0 \leq s, i; s + i \leq N\}.$$

For a particular ordering of this space[2] (e.g. $(s, i) \in \{(N, 0), (N - 1, 1), \ldots, (0, 0)\}$), $P(t)$ can be represented as a matrix specifying the probability of every state transition at time $t$. Our bivariate SIR state space contains $(N + 1)(N + 2)/2$ elements, and therefore P(t) corresponds to a $(N + 1)(N + 2)/2 \times (N + 1)(N + 2)/2$ matrix.

We can now consider the derivative of the transition function, $p'_{i,j}(t)$, which has two forms known as the forward (Equation 3.2) and backward (Equation 3.3) Kolmogorov equations

$$\frac{dp_{i,j}(t)}{dt} = \sum_{k \neq i} p_{i,k}(t) q_{k,j} - q_{i,i} p_{i,j}(t) \tag{3.2}$$

[2]Note that while the ordering of state space is arbitrary, it is not without consequence Black & Ross (2015)

$$\frac{dp_{i,j}(t)}{dt} = \sum_{k \neq i} q_{i,k} p_{k,j}(t) - q_{i,i} p_{i,j}(t) \tag{3.3}$$

where $q_{k,j}$,$q_{i,i}$, and $q_{i,k}$ are the transition *rates* defined in Equation 3.1, i.e. for our SIR model, the forward Kolmogorov equations are

$$\frac{dp_{a,(s,i)}(t)}{dt} = p_{a,(s+1,i-1)}(t)\frac{\beta}{N}(s+1)(i-1) + p_{a,(s,i+1)}(t)\gamma(i+1) - p_{a,(s,i)}(t)\left[\frac{\beta}{N}si + \gamma i\right].$$

and the backward Kolmogorov equations are

$$\frac{dp_{(s,i),b}(t)}{dt} = \frac{\beta si}{N} p_{(s-1,i+1),b}(t) + \gamma i p_{(s,i-1),b}(t) - \left[\frac{\beta}{N}si + \gamma i\right] p_{(s,i),b}(t).$$

We can simplify (Equation 3.2) and (Equation 3.3), by considering the matrix $Q$ specifying the rates of all transitions $q_{ij}$ for $i, j \in \mathbb{S}$.Similarly to the transition probability matrix $P(t)$, $Q$ has dimension $(N+1)(N+2)/2 \times (N+1)(N+2)/2$ .

The system of equations Equation 3.2 and Equation 3.3, can now be written as $dP(t)/dt = P(t)Q$ and $dP(t)/dt = QP(t)$, respectively. Considering$p'(t) = qp(t)$, where $p$ is a differentiable function and $q$ is a constant, when $p(0) = 1$, there is a unique solution $p(t) = e^{tq}$, we can similarly solve the Kolmogorov Equation 3.2 and Equation 3.3 as as $P(t) = e^{Qt}$ and $P(t) = e^{tQ}$ (when $P(0) = I$), respectively.

Thus, the theoretically and empirically derived event rates presented in Equation 3.1, along with the assumptions of time homogeneity and memorylessness, allow us to compute the probability of any state transition at time $t$. This technique can be used, for example, to derive important statistics about an epidemic, such as its mean final size and the effects of vaccination programs Teo (2017), Teo et al. (2021). However, "computing the matrix exponential is often numerically challenging. Finding accurate and eficient algorithms is still a topic of current research" Dobrow (n.d.)

## 3.2 Stochastic simulation

Instead of analytically deriving the marginal probability of a particular series of events by the method outlined above, we can simulate instantiations of the continuous time markov chain ("sample paths") numerically. There are several stochastic simulation algorithms Simoni et al. (2019), but in this thesis, we will use only the original 'Direct-method' algorithm put forward by Gillespie (1976).

Originally a method for simulating chemical reaction networks, the Gillespie direct algorithm is applicable to many domains of stochastic simulation with discrete state spaces, continuous time, and known rate equations.

In general, the core of the Gillespie algorithm takes in the possible state changes in a system, and a 'propensity function' for each state change. Random number generation is used to select a particular state change, $u$ and a time interval, $\tau$, which can be used to update the state of the system $X(t) = i \rightarrow X(t + \tau) = i + u$ ( Algorithm 1 ).

**Algorithm 1** Gillespie Direct Method

**Input:** $v$, $a$

**Output:** $\mu$, $\tau$

set $a_{net} = 0$
**for all** j **do**
    compute $a_j$
    update $a_{net} = a_{net} + a_j$
**end for**
generate two random numbers $r_1$, $r_2$ in $\mathcal{U}(0, 1)$
select $\mu$ such that $\sum_{j=1}^{\mu} a_j \leq r_1 a_0$
compute $\tau \leftarrow \frac{1}{a_0} \ln(1/r_2)$
update $X \leftarrow X + v_\mu$
set $t \leftarrow t + \tau$

In particular, two random numbers $r_1$ and $r_2$ are used to compute $mu$ and $\tau$, respectively

- $r_1$ is used to calculate $mu$ by cumulatively adding the values of the propensity function to each other. mu gets the largest value which is smaller than $r_1$
- $r_2$ is used to calculate $\tau$ by taking advantage of the fact that in a Continuous time markov proces $\Delta t \sim \lambda e^{-\lambda t}$, where lambda is the sum of the rates for all possible events.

In the case of our SIR model, the state change vector is given by Table 3.1 column two, and the propensity function vector is given in column 3.We can include the core stochastic event step in a loop which updates the state and time of our SIR model simulate the progression of an epidemic @alg-SIR_CTMC.

As an example, **?@fig-GMelb_SIR_Sim** 100 sample trajectories of an SIR CTMC comprising N = 4976157, the population of the Greater Melbourne region. In this example, $I_0 = 10$, $\beta = 1.4$, and $\gamma = 1.0$, though clearly variation in these parameter values can be explored.

The Greater Melbourne Region presents large geographical region which highlights the important assumption of homogeneous mixing, which we will explore relaxing in the next chapter.

**Algorithm 2** Stochastic simulation of SIR Compartmental Model CTMC

**Input:**$N$, $I_0$, $\beta$, $\gamma$ **Output:**

Initialise time $t \leftarrow 0.0$ and $S \leftarrow N - I_0$, $I \leftarrow I_0$
state change vector $v = [(-1, 1), (0, -1)]$
propensity vector $a = [(\beta I \frac{S}{N}), (\gamma I)]$
**while** $I > 0$ **do**
    **for all** j **do**
        compute $a_j$
        update $a_{net} = a_{net} + a_j$
    **end for**
    generate two random numbers $r_1, r_2 \sim \mathcal{U}(0, 1)$
    select $\mu$ such that $\sum_{j=1}^{\mu} a_j \leq r_1 a_0$
    compute $\tau \leftarrow \frac{1}{a_0} \ln(1/r_2)$
    update $X \leftarrow X + v_\mu$
    set $t \leftarrow t + \tau$
**end while**

# 4 Metapopulation Models

## 4.1 Motivation

Multi-patch, 'subdivided' models

- Wilson & Worcester (1945), Haskey (1957)
- Within patch mixing is random, between patch mixing is limited.
- assumptions Sattenspiel (1987)
  - Constant size
    - equal birth deaths
  - constant recovery parameter $\gamma$
  - No permanent movement of individuals between patches
  - Disease spread can occur on contact between susceptible individuals
    - "the total number of new cases is a proportion, $\beta$, of the number of contacts"
    - "The number of new cases is a proportion $\sigma$ of the total number of contacts between susceptible and infective individuals, corrected by a factor a, for differences in population size and density among the groups." Sattenspiel & Simon (1988)
  - Proportionate mixing Sattenspiel & Simon (1988)
    - "where the number of encounters is proportional to the size of the subpopulations involved"
    - "The mixing matrices used are chosen to fit known patterns of incidence, rather than on theoretical grounds; and there is no exploration of the importance of variation in the mixing patterns to the transmission of infection through the population."

Mixing matrix

- Migration matrix Bodmer & Cavalli-Sforza (1968)

  - "These models use a backward stochastic migration matrix, in which the elements m, j give the probabilitiesthat the parents of individuals in population i came from population j"

- Mixing (contact) matrix Sattenspiel (1987)
  - "the probability of two individuals from different neighborhoods coming into contact. This matrix is a forward stochastic migration matrix, with each element m„giving the probability that an individual from population i moves topopulation j." Sattenspiel & Simon (1988)

## 4.2 Formulation

### 4.2.1 Patches

- each region $i$ has its own N and $S$ $I$ and $R$ compartments
- sinlge $\beta$ and $\gamma$ values

### 4.2.2 Mixing matrix

- $m_{ij}$represent the probability that a susceptible individual who lives in neighborhood $i$ comes into contact with an infectiveindividual who lives in nieghborhood $j$.
  - Therefore, $0 \leq m_{ij} \leq 1$ and $\sum_j m_{ij} = 1$
  - M is a stochastic matrix

### 4.2.3 Force of infection

Moss et al. (2019)

- FOI in region $i$ exerted by infectious individuals who reside in patch$j$ ($\beta_{ij}$)

$$\beta_{ij} = \beta \cdot I_j \cdot M'_{j,i}$$

- total FOI in patch $i$ ($\Lambda_i$)

$$\Lambda_i = \sum_{j=1}^{r} \beta_{ij}$$

- and the FOI vector

$$\Lambda = \beta \cdot I \times M'$$

### 4.2.4 Dynamics

$$\begin{aligned}
\frac{dS_i}{dt} &= -\Lambda_i \cdot \frac{S_i}{N_i} \\
\frac{dE_i}{dt} &= \Lambda_i \cdot \frac{S_i}{N_i} - \sigma E_I \\
\frac{dI_i}{dt} &= \sigma E_I - \gamma I_i \\
\frac{dR_i}{dt} &= \gamma I_i
\end{aligned}$$

Jacquez et al. (1988)

## 4.3 Implimentation

- We impliment the metapopulation model as a CTMC in an analogous way to **?@sec-SIR_CTMC**, but with a few key differences
- Following Moss et al. (2019)

### 4.3.1 Patches

- `The GMGCCSA is partitioned into 40 subpopulations, based on the @2023AustralianStatistica`
- `The population of each patch is given in appendix_n and shown in @figGMelbSA3Pop`

### 4.3.2 Initial conditions

- At the beginning of a simulation, all patches are composed of entirely susceptivle individuals.
- a number, $I_0$, of individuals in a randomly selected patch, $\alpha$, become infected.
- i.e

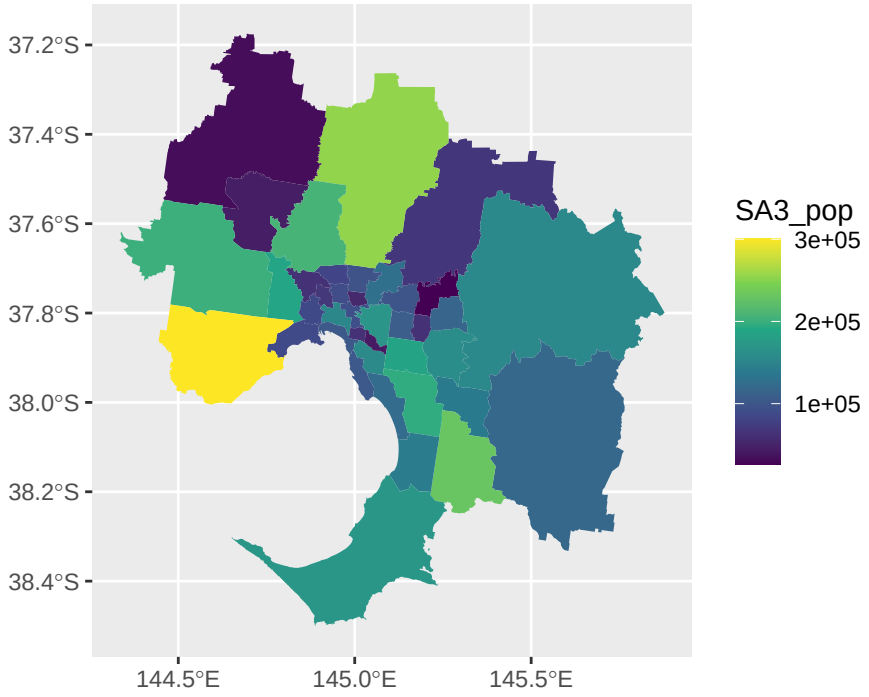



Figure 4.1: **?(caption)**

$$\alpha \sim \mathcal{U}\{1, r\}$$

$$S_i(0) = \begin{cases} N_i & \text{if } i \neq \alpha \\ N_i - E_0 & \text{if } i = \alpha \end{cases}$$

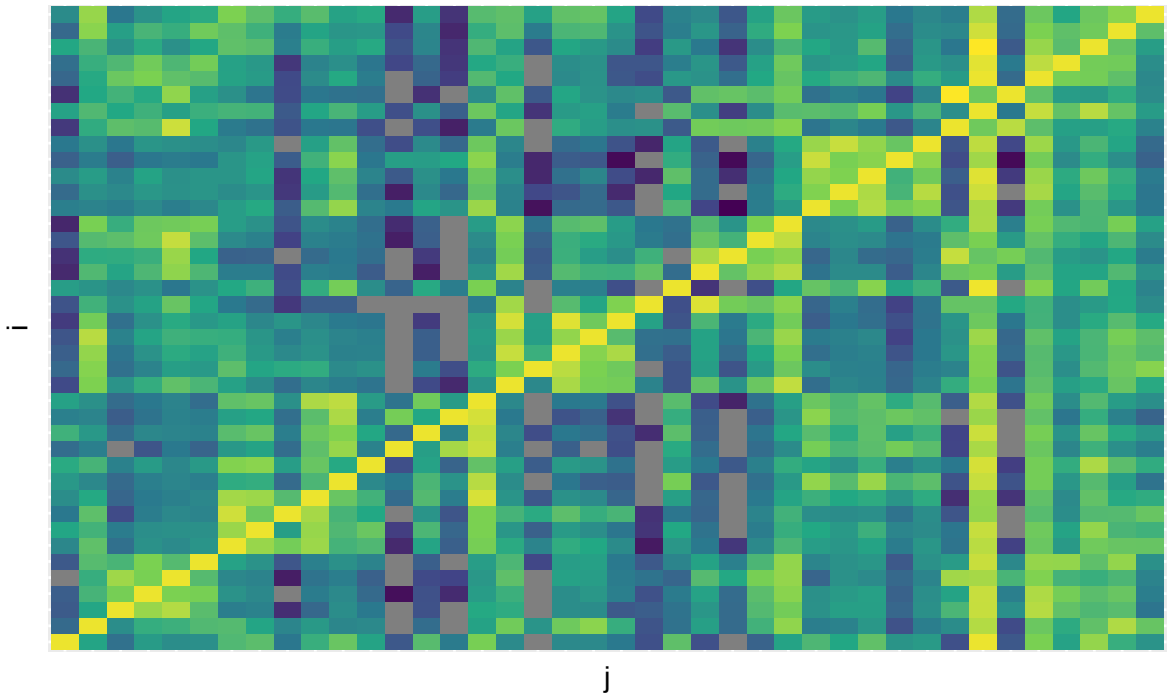
$$E_i(0) = \begin{cases} 0 & \text{if } i \neq \alpha \\ E_0 & \text{if } i = \alpha \end{cases}$$

$$R_i(0) = 0$$

### 4.3.3 Mixing

- The mixing matrix was defined after Moss et al. (2019)
- Empirically informed Origin Destination (OD) matrix
  - Derived from the 2016 Census data
    - usual residence X place of work matrix
    - Determines contact *between regions* but not *within* the region of residence
  - $$F = \begin{pmatrix} f_{1,1} & f_{1,2} & \cdots & f_{1,r} \\ f_{2,1} & f_{2,2} & \cdots & f_{2,r} \\ \vdots & \vdots & \ddots & \vdots \\ f_{r,1} & f_{r,2} & \cdots & f_{r,r} \end{pmatrix}$$
  - $$f_{i,i} = 0$$
    $$\sum_{j=1}^{r} f_{i,j} = 1 \quad \forall i \in [1..r]$$
- Within patch mixing is given by a parameter $\delta_i^H$, the remaining mixing proportion, $\delta_r^* = 1 - \delta_i^H$ is distributed among the non-local patches

$$M = \begin{pmatrix} \delta_1^H & \delta_1^* f_{1,2} & \cdots & \delta_1^* f_{1,r} \\ \delta_2^* f_{2,1} & \delta_2^H & \cdots & \delta_2^* f_{2,r} \\ \vdots & \vdots & \ddots & \vdots \\ \delta_r^* f_{r,1} & \delta_r^* f_{r,2} & \cdots & \delta_r^H \end{pmatrix}$$




### 4.3.4 Simulation

- As per **?@sec-SIR_sim**
- detlta t will be the sum of exponentially distributed times (expt(sum.rates))
- State change will involve event type (as in single patch), and event location
  - State change vector is now 2*n patch long

# Part II

# Current Study

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# A Additional stuff

You might put some computer output here, or maybe additional tables. It is possible to have multiple appendices. Just list them in the appropriate place within `_quarto.yml`.