Mathematical modeling
The dynamics of infection

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Overview

1. Prologue
   - Introduction
   - Discrete time models
   - The basic reproduction number

2. Who acquires infection from whom?
   - How it all started . . .
   - The social contact approach
   - Research based on social contact data

3. Epilogue
   - Further research
   - Discussion
Mathematical Modelling of Infectious Diseases

**Purposes:**

- **prediction**: requires the inclusion of known complexities and population-level heterogeneity
- **understanding**: investigating the factors that drive dynamics

**Building a model presents a trade-off:**

- **accuracy**: reproduce what is observed and predict future dynamics
- **transparency**: ability to understand how model components influence the dynamics and interact
- **flexibility**: ease of adapting the model to new situations
Mathematical Modelling of Infectious Diseases

- Limitations:
  - models present a simplification of reality
  - chance events of infectious disease transmission hinder perfect prediction

- A good model:
  - suited to its purpose: simple as possible, but no simpler
  - balance accuracy, transparency, flexibility
  - parametrisable from available data
Mathematical Modelling of Infectious Diseases

- Daniel Bernoulli was the first to present a mathematical model for smallpox in 1760.
- Since then many people have developed models to describe infectious disease dynamics, see e.g. Bailey (1975); Anderson and May (1991); Grenfell and Dobson (1995); Daley and Gani (1999); Hethcote (2000).
- Historical perspectives by Klaus Dietz.
Contacts between individuals

- Predicting the number of infections at time \( t + 1 \) based on the circumstance at time \( t \)
- The force of infection \( \lambda \)
  - the per capita rate at which a susceptible individual contracts infection
  - it is assumed proportional to the number of infectious persons at time \( t \) and depending on how the contact structure is assumed to change with population size \( N \) it is given by:

\[
\lambda_t = \beta I_t \\
\lambda_t = \beta I_t / N_t
\]
Contacts between individuals

- The **number of new infections at time** $t + 1$ is given by $\lambda_t S_t$ and thus:
  
  $I_{t+1} = \beta S_t I_t$
  
  $I_{t+1} = \frac{\beta S_t I_t}{N_t}$

  This is referred to as the **mass action principle**

- **density-dependent transmission:** $I_{t+1} = \beta S_t I_t$:
  
  - as the population size increases, so does the contact rate
  - mostly applicable to plant and animal diseases (homogeneity)

- **frequency-dependent transmission:** $I_{t+1} = \frac{\beta S_t I_t}{N_t}$:
  
  - the contact rate is assumed constant regardless of a change in population size
  - mostly applicable to human and vectorborne diseases (heterogeneity)
Contacts between individuals

Heterogeneity

- airborne infections: age - example: children at school have more contacts with children of the same age
- sexually transmitted infections: age and sexual behavior
- temporal heterogeneity
  - seasonality,
  - week vs weekend,
  - holiday vs non-holiday, . . .
- . . .
Modeling Frameworks

- **compartmental** models
  - the population is subdivided into broad subgroups (compartments)
  - individuals are tracked *collectively*
  - roughly either **deterministic** or **stochastic** (probabilistic)
    - deterministic models describe what happens ‘on average’ in a population
    - stochastic models allow the number of individuals who move between compartments to vary through chance
  - **transmission dynamic** or **static** models
- **microsimulation** or **agent-based** models
- **network** models
- **metapopulation** models
Discrete time deterministic models

- SIR compartmental model
- Equations:

\[
S_{t+1} = S_t - \lambda_t S_t \\
I_{t+1} = I_t + \lambda_t S_t - \nu I_t \\
R_{t+1} = R_t + \nu I_t
\]

with \( N_{t+1} = S_{t+1} + I_{t+1} + R_{t+1} = S_t + I_t + R_t = N_t \).

- \( \lambda_t = \beta I_t \) and \( \nu \) are risks
- risks are related to rates as follows:

\[
\text{risk} = 1 - e^{-\text{rate}}
\]
Discrete time stochastic models

- The number of newly infected cases arises from a stochastic process with mean $\beta I_t S_t$
- The number of newly recovered individuals arises from a stochastic process with mean $\nu_t I_t$
- Our best option: the binomial distribution
Discrete time models

- When do you expect the number of new infections to decrease?
- Focus on the second equation:

\[ I_{t+1} = I_t + \beta I_t S_t - \nu I_t \]

clearly \( I_{t+1} = I_t \) if \( \beta S_t = \nu \)

- The epidemic will
  - die out if \( S_t < \nu/\beta \)
  - continue if \( S_t > \nu/\beta \)
- At the start of an epidemic in a susceptible population: \( S_0 = N \)
- The epidemic will
  - die out if \( N\beta/\nu < 1 \)
  - take of if \( N\beta/\nu > 1 \)
The basic reproduction number

- Consider the total number of new infections in the population between time $t$ and $t+1$:
  \[ \beta I_t S_t \]

- At the start of an epidemic, say $t = 0$: $I_0 = 1$ and $S_0 = N$ and thus the total number of new infections between $t = 0$ and $t = 1$ equals
  \[ \beta N \]

- By the end of the infectious period of duration $D = 1/\nu$ time units, the infectious person would have infected $\beta N D$ individuals.

- $N \beta D$ is called the basic reproduction number $R_0$.

- Therefore $R_0$ is the number of secondary cases caused by a single infective introduced into a wholly susceptible population of size $N$ during the infective’s infectious period.
The basic reproduction number

- $R_0$ constitutes a threshold:
  - if $R_0 > 1$ then the epidemic can grow
  - if $R_0 \leq 1$ then the epidemic will die out

- Using $R_0$, one defines the number of effective contacts by each person per unit time by

  $$c_e = \frac{R_0}{D}.$$ 

- Therefore $\beta = \frac{c_e}{N}$ is the “per capita number of effective contacts made by a given individual per unit time”, or equivalently “the per capita rate at which two specific individuals come into effective contact per unit time”

- For a given pathogen, it is difficult to define an effective contact
The herd immunity threshold

- The epidemic will die out if $S_t < \nu/beta$:
- Equivalently $s_t R_0 < 1$, where $s_t = S_t/N$
- $R_e = s_t R_0$ is called the effective reproduction number
- Monitoring an epidemic is best done using $R_e$
- Vaccination: lowering $s_t \rightarrow$ control: $R_e < 1$
- Critical vaccination coverage

$$p_c = 1 - 1/R_0.$$  

- Examples:
  - Measles: $R_0 = 20 \rightarrow p_c = 0.95,$
  - Varicella $R_0 = 8 \rightarrow p_c = 0.875$

- But issues of primary and secondary vaccine failure complicate matters
Who Acquires Infection From Whom?

Many infections are transmitted by contact or air

Influenza, Varicella, Measles, Parvovirus B19, …

The transmission rate $\beta$ depends on

- person-to-person contact $c$
- the probability of transmission given a contact $q$

but this is not the same for everyone

$$\beta \equiv \beta(a, a') = q(a, a') \times c(a, a')$$

Two decades ago math. convenient WAIFW-structures

(Anderson and May, 1991)
Who Acquires Infection From Whom?

Heterogeneity: Age

The age-heterogeneous mass action principle:

$$\lambda(a) = \frac{ND}{L} \int_{A}^{L} \beta(a, a') \lambda(a') \exp \left( - \int_{A}^{a'} \lambda(s) ds \right) da'$$

with life expectancy $L$, population size $N$ and mean infectious period $D$ and age $A$ the age of maternal antibody loss

The Next Generation Operator

The operator that defines the next generation of infected individuals

$$g(a, a') = \frac{ND}{L} \beta(a, a')$$
Who Acquires Infection From Whom?

Basic reproduction number $R_0$

The dominant eigenvalue of the ‘next generation operator’

Initial Spread

- Simulate the initial epidemic phase by iterating the next generation operator
- Identical to the right eigenvector of that operator
The Traditional ‘WAIFW’ approach

- Discretization into several age-categories
- Anderson and May (1991): mixing patterns
  - impose mixing pattern on $\beta_{ij}$
  - constrain $\#$ distinct elements
  - based on prior knowledge of social mixing behaviour
The Traditional ‘WAIFW’ approach

- Discretization into several age-categories
- Anderson and May (1991): mixing patterns

\[
\begin{array}{cccc}
\text{age class 1} & \text{age class 2} & \text{age class 3} & \text{age class 4} \\
\downarrow & \downarrow & \downarrow & \downarrow \\
\beta_1 & \beta_4 & \beta_4 & \beta_4 \\
\beta_4 & \beta_2 & \beta_4 & \beta_4 \\
\beta_4 & \beta_4 & \beta_3 & \beta_4 \\
\beta_4 & \beta_4 & \beta_4 & \beta_4 \\
\end{array}
\]
The Traditional ‘WAIFW’ approach

- Discretization into several age-categories
- Anderson and May (1991): mixing patterns

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<th>age class 1</th>
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The Traditional ‘WAIFW’ approach

- Anderson and May (1991): mixing patterns
  → disadvantages:
    - low dimensional matrices
    - non-realistic discontinuities
    - choice age classes: ad hoc

- Farrington and Whitaker (2005): continuous contact surface
  → both methods rely on strong parametric assumptions

- Wallinga et al. (2006): use data on social contacts to inform estimation of age-dependent transmission rates
Social Contact hypothesis

Social contact hypothesis (Wallinga et al., 2006)

\[ \beta(a, a') = q \cdot c(a, a') \]

- Proportionality constant
  - Estimation from serological survey
- Contact rate
  - Estimation from social contact survey
Social Contact Approach

Alternative approach:

Using data on social contacts to estimate age-specific transmission parameters for respiratory-spread infectious agents.

Objectives

- Disentangle contact behaviour from transmission process
- Get insights in predictiveness of social contact data
- Get new insights in the transmission process
Social Contact Survey

- Wallinga et al. (2006): Utrecht
- POLYMOD
  - pilot study: Beutels et al. (2006)
  - main study: Mossong et al. (2008)

Social Contacts and Mixing Patterns Relevant to the Spread of Infectious Diseases

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(WoK: 400 citations)
Social Contact Survey

- Part of POLYMOD project
- Period March - May 2006
- 750 participants, selected through random digit dialing
- Diary-based questionnaire
- Two main types of contact: non-close and close contacts
- Total of 12775 contacts (~ 16 contacts per person per day)

Hens et al. (2009a,b)
**Mixing Patterns**

- Assortative mixing with clear (grand)parent-(grand)child components
- Divergence for work contacts
EU mixing patterns

- common structure
- note the converging off-diagonals: parents get older
Serology and social contacts

- Using social contact surveys in statistical and mathematical models
- Hens et al. (2012) →
- Varicella
  - Ogunjimi et al. (2009)
  - Goeyvaerts et al. (2010)
School Closure

- most effective social distancing measure
- previous analyses were based on assumptions or sentinel data
  (see e.g. Cauchemez et al., 2008)
- use contact data to quantify the reduction in $R_0$
  - POLYMOD data
  - use the holiday period as a proxy for school closure: 17% reduction
  - use the weekend as a proxy for social distancing: 21% reduction

Hens et al. (2009a)

- school closure: huge economic impact
  Keogh-Brown et al. (2010a,b)
**School Closure**

- **global school closure** and its impact on the health care system
  
  Cauchemez et al. (2009)

- Could **reactive school closure** alleviate the burden upon the NHS critical care capacity during the H1N1 influenza pandemic?
  
  - mathematical influenza model
  
  - UK contact data (holiday pattern as a proxy)
  
  - timing is crucial!
  
  - in the most realistic situation 12% over maximum capacity

House et al. (2011)
Contact patterns during illness

- **Van Kerckhove et al. (2013):** study in the UK
- People were asked to record their contacts
  - When ill (H1N1-diagnosis - lab-confirmed)
  - When healthy (few weeks later)
Contact patterns during illness
Contact patterns during illness

- assuming 1/3-2/3 asymptomatic individuals (Carrat et al., 2008)
Contact patterns during illness

- fitted to age-specific relative ILI incidence during exponential phase of the 2009 A/H1N1 pandemic in the UK
- results:
  - symptomatic individuals are 3 to 12 times as infectious
  - symptomatic individuals cause 66% of all infections

![Graph showing age distribution of cases in the early stages of the 2009 A/H1N1 pandemic](image1)

![Graph showing age distribution from general practitioners' consultation data](image2)
Preferential transmission

- Account for
  - pre-clinical subclinical infectious period
  - subclinical/asymptomatic infections
- Investigate the role of carrying over high viral loads
  - viral load $\sim$ infectiousness (intranasal dose: Keitel et al., 1990)
  - viral load $\sim$ symptoms (Carrat et al., 2008)
  - transfer?
    supported indirectly by challenge studies & empirical evidence for other infections
- Simplistic approach: compartmental models
  - (a)symptomatic infections (Ejima et al., 2013)
  - preferential transmission
Preferential transmission

Who acquires infection from whom?

Research based on social contact data

Figure 2 shows a schematic diagram of the preferential compartmental transmission model. Superscripts indicate clinical status of the infectee: symptomatic (s) or asymptomatic (a). Subscripts indicate whether the infector was symptomatic (s) or not (a).

In this paper it is assumed that $\lambda_a = \lambda_s = \gamma_s = \gamma_a$ and $\phi_a = \phi_s = \sigma_s = \sigma_a$.

Under these assumptions, the preferential transmission model simplifies to the non-preferential transmission model if $\phi = 1 - \varphi$.

In Section 2.2, a social contact network between different age groups is introduced which allows using social contact data of ill and healthy people to describe the social mixing patterns of symptomatic and asymptomatic individuals, respectively.
Preferential transmission: results

- Non-preferential transmission if \( \phi = 1 - \tilde{\phi} \)
  - \( \tilde{\phi} = 0.4209 \) (95% CI: 0.3258, 0.5222)
  - \( 1 - \phi = 0.1618 \) (95% CI: 0.1227, 0.2103)

- Sensitivity analysis
  - 12 scenarios (estimated - referenced values)
  - best scenario \( (\gamma, \theta, \sigma^a, \sigma^s) = \{(1.5, 0.5, 1, 5.6)\text{days}\}^{-1} \)
    - \( \tilde{\phi} = 0.5706 \) (95% CI: 0.4784, 0.6583)
    - \( 1 - \phi = 0.2664 \) (95% CI: 0.2187, 0.3203)

- Outcome
  - rel. trans. of symptomatic individuals is 2.87 (95% CI: 2.20, 3.73)
  - evidence suggests preferential transmission is possible
Preferential transmission: control strategies

Isolation (at home)
Susceptibility patterns for H1N1 in Vietnam

- household-based survey in rural Vietnam
- 264 households
Susceptibility patterns for H1N1 in Vietnam

- serial seroprevalence $\rightarrow$ H1N1 incidence estimate
- ratio of incidence and eigenvector $\rightarrow q(a)$
Comparative analysis of the spread of H1N1 in Europe

- relative incidence
- example UK:
## Comparative analysis of the spread of H1N1 in Europe

- based on the European contact data
- estimating the relative susceptibility
- meta-analysis over countries

<table>
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<th>Countries</th>
<th>Cl 95%</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>0.48 (0.27,0.77)</td>
<td>7.2%</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>1.37 (0.89,2.08)</td>
<td>8.6%</td>
</tr>
<tr>
<td>England</td>
<td>0.5 (0.48,0.52)</td>
<td>13.1%</td>
</tr>
<tr>
<td>France</td>
<td>0.31 (0.19,0.46)</td>
<td>8.3%</td>
</tr>
<tr>
<td>Germany</td>
<td>0.69 (0.66,0.72)</td>
<td>13.1%</td>
</tr>
<tr>
<td>Italy</td>
<td>1.52 (0.43,4.44)</td>
<td>2.7%</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>0.63 (0.46,0.83)</td>
<td>10.5%</td>
</tr>
<tr>
<td>Netherlands</td>
<td>0.71 (0.41,1.11)</td>
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<tr>
<td>Portugal</td>
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<tr>
<td>Romania</td>
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<tr>
<td>Slovakia</td>
<td>4.23 (0.52,16.35)</td>
<td>1.1%</td>
</tr>
<tr>
<td>Spain</td>
<td>0.32 (0.27,0.37)</td>
<td>12.3%</td>
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<tr>
<td><strong>Pooled estimate</strong></td>
<td><strong>0.61 (0.5–0.76)</strong></td>
<td><strong>100%</strong></td>
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</table>
Inferring networks from egocentric data

- households of size 4
- egocentric data
- latent network
- 64 possible networks

- 63 parameters
- \(4 \times 2^3 = 32\) observations
- penalized likelihood approach

Potter and Hens (2013)
Further research

- **Serology-contact papers**
  - Goeyvaerts et al. (2011): *immunological processes* for B19
  - Santermans et al. (2014): *inferring infectivity from serology*
  - Hens et al. (2009c); Abrams et al. (2014): *frailty* models

- **Other contact-related work**
  - Willem et al. (2012): *Weather & contacts*
  - Grijalva et al. (2014): *Contact Patterns in Peru*
  - Goeyvaerts et al. (in prep): *Household contact survey* in Flanders
  - Van Kerckhove et al. (in prep): *Spatial networks* of social contacts
  - Luca et al. (in prep): *A spatio-temporal* model of social contacts
  - Béraud et al. (in prep): *Social contacts in France: temporal effects*
  
  ...
Discussion

- Infectious disease dynamics
  - mass action principle
  - contact data prove to be useful
  - new epidemiological hypotheses
- Bruges 2015: 7-11 September 2015:
  - 2nd network course by Martina Morris and colleagues
  - 6th SIMID course (www.simid.be; Hens et al. (2012))
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  - Gail Potter *(University of Washington, US)*
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Selected references I


Selected references II


