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Which mathematical models for antimicrobial resistance?

Niel Hens:

Better models?

A bird's eye view

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Overview

- Mathematical Modeling
  - Daniel Bernoulli & Jean le Rond d'Alembert
  - Sir Ronald Ross
- Statistical Modeling
- Model Issues
  - Design
  - Identifiability
- Model Tools
- Design
- Discussion & Conclusion

Mathematical Modelling

- Daniel Bernoulli (1700-1782)
  - first mathematical model for smallpox (1760) → vaccination
  - mean life expectancy would increase from 26.6 yrs to 29.7 yrs
- Jean Le Rond d'Alembert (1717-1783)
  - personal rivalry
  - individual vs social decision making (vaccination implied risk of mortality) – life expectancy is not the best rational decision criterion for an individual (1761)
  - distinguishing between what is metaphysically possible and physically possible

Dietz and Heestzerbeek (Math BioSc 2002)
Colombo and Diamanti (Lett Mat Int, 2015)

Mathematical Modelling

- Since then a lot of work has been done …
- The superspreader event of modelling:

A Contribution to the Mathematical Theory of Epidemics.

By W. O. Kermack and A. G. McKendrick.

(Communicated by Sir Gilbert Walker, F.R.S.—Received May 13, 1927.)

Kermack and McKendrick (1927)

Mathematical Modelling

- 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

- 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 (see Guillaume and Lulla)

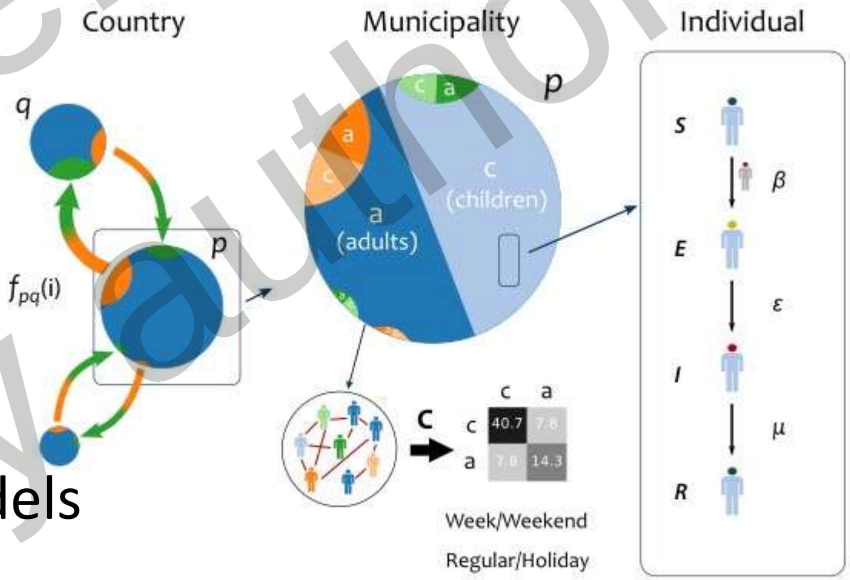
Mathematical Modelling

- Problem solving principle by William of Ockham (1287-1347)
- Heuristic guide to developing theoretical models
  - preference for simplicity based on falsifiability: simple models are more testable
  - 'shaving away' unnecessary assumptions or cutting apart two similar conclusions
  - John Punch: 'Occam's Razor'
- This is different from the principle of parsimony

Encyclopædia Britannica (2010)

Mathematical Modelling

- Deterministic or *compartmental* models (SIR model -> Guillaume)
- Stochastic models
- Meta-population models
- Network models
- Agent-based models
- Within and/or between-host models



Statistical and Mathematical Models

- Sir Ronald Ross (1857-1932): Nobel Prize for Medicine (1902) for his malaria research.

Quote: 'The whole subject is capable of study by **two distinct methods** which are used in other branches of sciences, which are **complementary of each other**, and which would **converge towards the same results** – the **a posteriori** and the **a priori** methods. In the former we commence with observed statistics, endeavor to fit analytical laws to them and so work backwards to the underlying cause (as done in much **statistical work** of the day); and in the latter we assume a knowledge of causes, **construct our differential equations** on that supposition, follow up the logical consequences, and finally test the calculated results by comparing them with the observed statistics.'

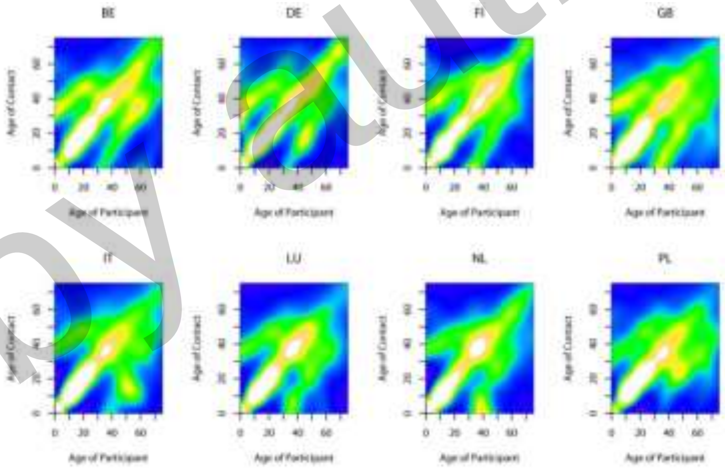
- Take Home Message: Uniting statistical and mathematical approaches

Statistical Modelling

- association ≠ causation
- observational intervention studies
  - uncontrolled before-after designs
  - bad practice because of (time-varying) confounders
- RCT as a gold standard
  - often affected by clustering (including sparseness; e.g. at the country, district, hospital or physician level)
  - stepped wedge designs
- quasi-experimental designs as a workable alternative
  - interrupted time series analyses (need for replication)
  - inclusion of a control arm
  - time-varying confounders still constitute an issue

Statistical Modelling

- infectious diseases: herd immunity which statistical models alone do not capture → integrating mathematical concepts
- Who acquires infection/resistance from whom?
  - (bipartite) networks of contacts (hospital setting, MRSA, etc)
  - general population: mixing patterns →

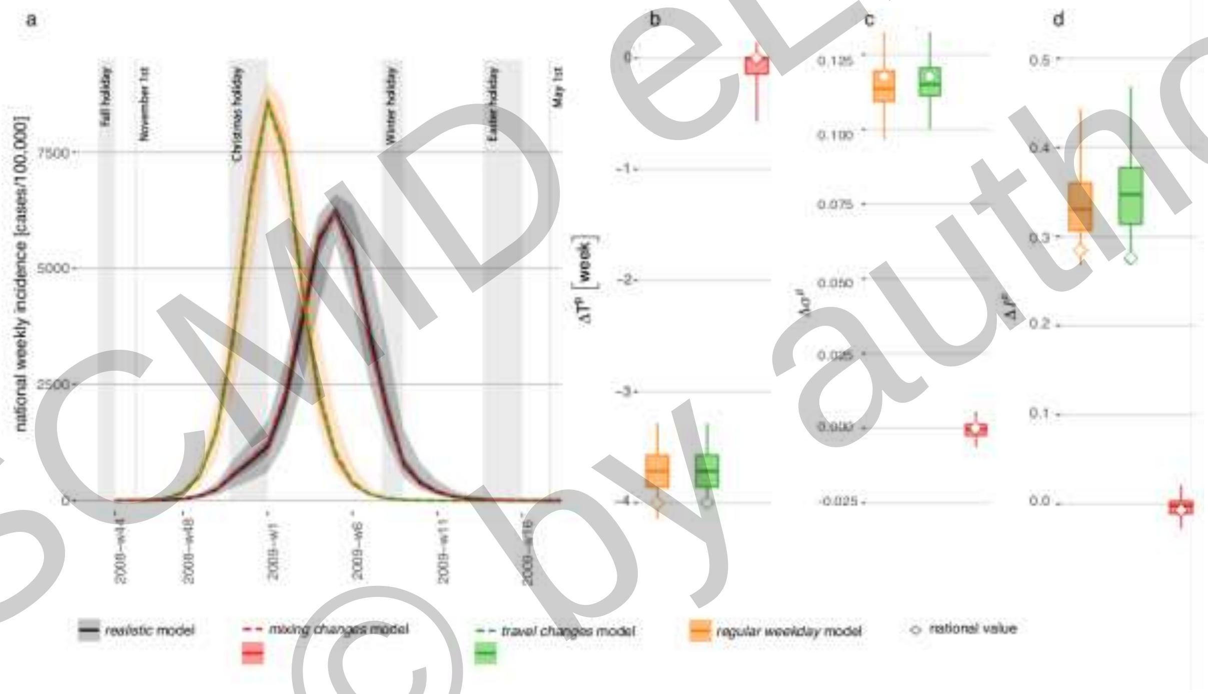


Mossong et al. (PLoS Medicine, 2008)

Intermezzo: Social Encounters

- Predictive for the spread of infectious diseases?
  - Pandemic H1N1, seasonal influenza and vaccination programs, … 👍
  - Hepatitis A , … 👎
  - Bacterial infections:
    - hospital setting 👍
    - community setting 💪
- Invitation to use mixing data: ERC TransMID grant

Intermezzo: Social Encounters



De Luca et al. (submitted)

Model Issues: Identifiability (statistics)

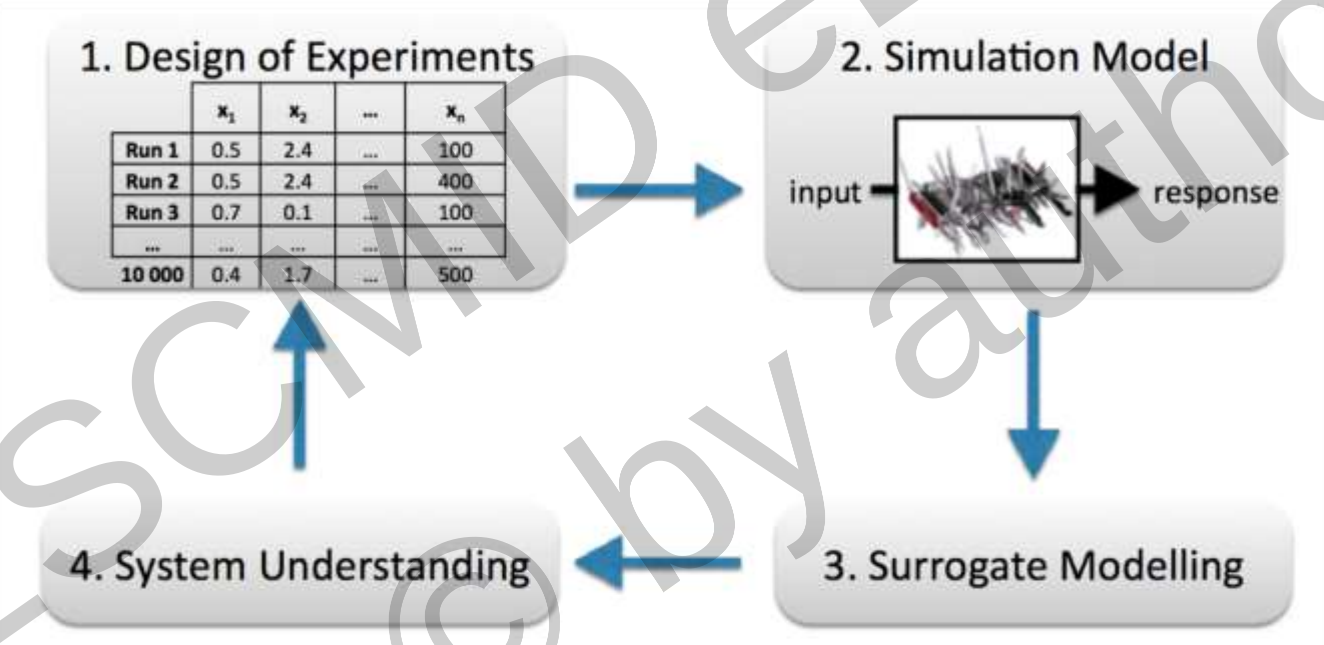
- Identifiability: lack of data or too complex model
- Assessing (quasi-) identifiability is not easy unless models exhibit a simple structure
- General purpose methods do exist:
  - profiling
  - parameter redundancy measures
  - emulators
- Raise new hypotheses to be tested with data

Catchpole and Morgan (Biometrics, 1997)

Model Issues: Biological plausibility

- ≠ detailed and complex
- informing models by parameters estimated from data & informing models by estimating/calibrating the model to data
- don't put your eggs in one basket
- question the literature
  - the bodyguard principle (known in statistics)
  - assumptions

Model Tools: Emulators



Willem et al. (PLoS Comp Bio, 2014)

Model Tools: Uncertainty

- model selection uncertainty - model averaging
- simple stochastic versus complex deterministic methods
  – Stocks et al. (submitted) vs Weidemann et al. (2014) on rotavirus dynamic modelling
- taking 'multiple datasets' uncertainty in account through sampling
  – meta-analytic estimates
  – literature estimates
- …

Burnham & Anderson (2002)

Model Tools: Proper use of measurements?

- Definition of resistance?
  - use of thresholds
  - underlying distribution?
  - limits of detection
  - …
- Antibiotic use:
  - DID and/or PID and/or prescriptions?
  - …
- Statistical literature is rich, mathematical models are being developed

Bruyndonckx et al. (JAC, 2014)

Model Tools: Proper use of measurements?

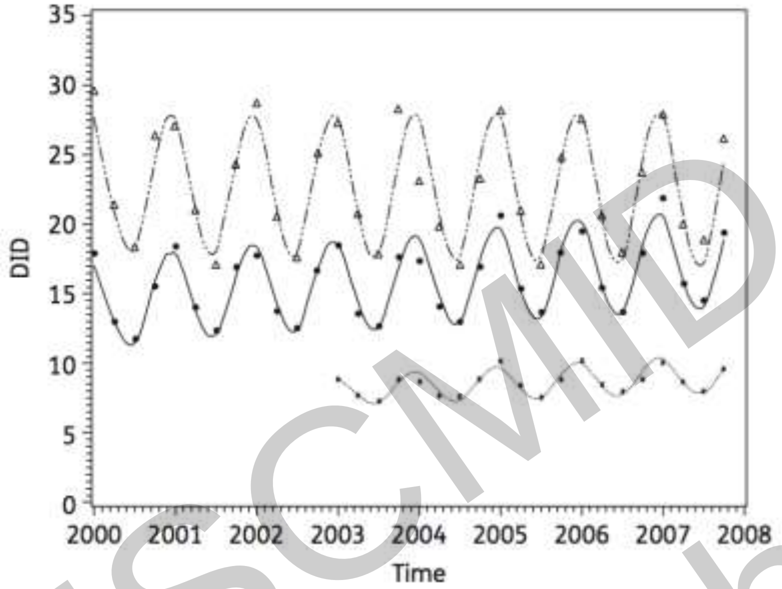


Figure 1. Total outpatient antibiotic use expressed in DID. Predicted average (solid line), predicted country-specific [Belgium (dashed line) and the Netherlands (dotted line)] and observed (circles, triangles and stars, respectively).

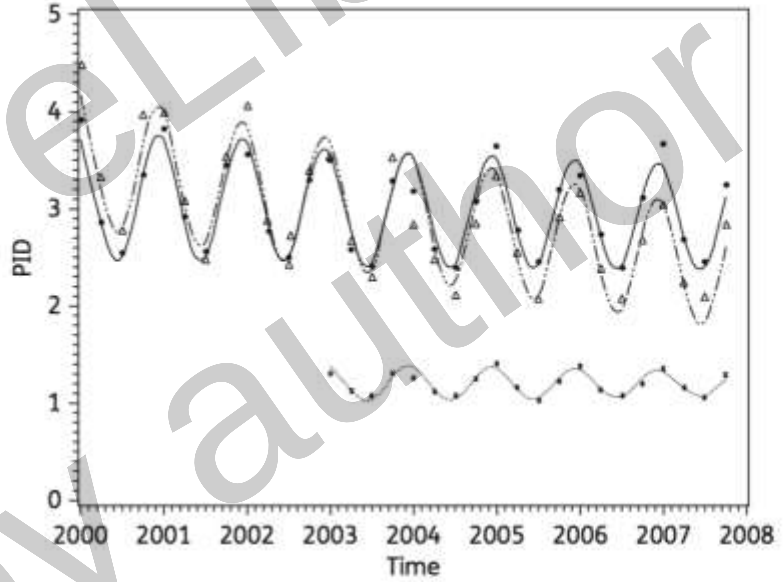


Figure 2. Total outpatient antibiotic use expressed in PID. Predicted average (solid line), predicted country-specific [Belgium (dotted line) and the Netherlands (dashed line)] and observed (circles, triangles and stars, respectively).

Bruyndonckx et al. (JAC, 2014)

Model Tools: Proper use of measurements?

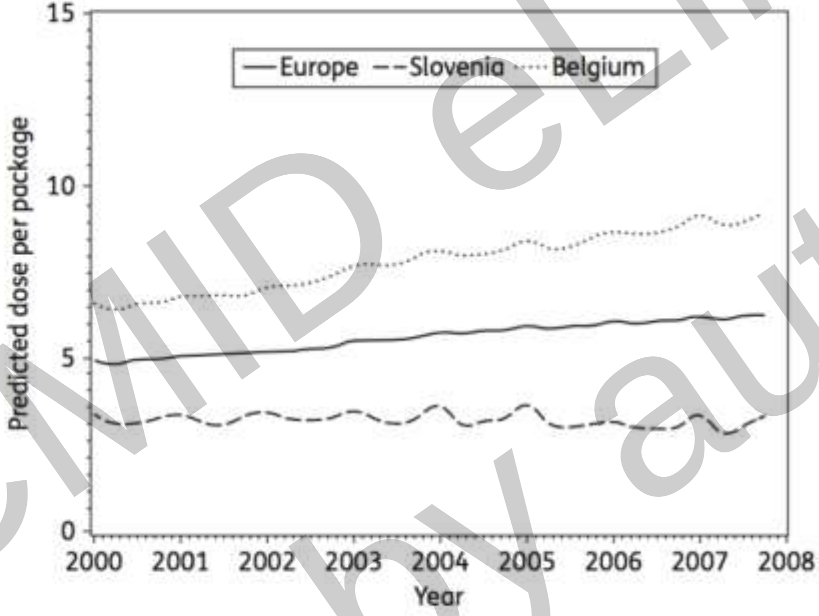
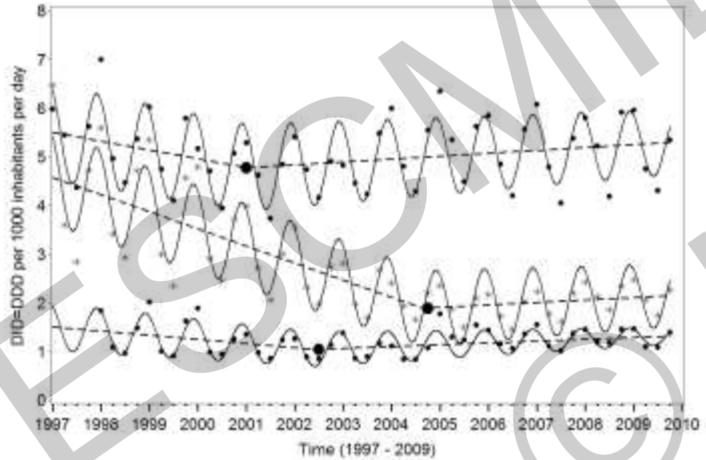


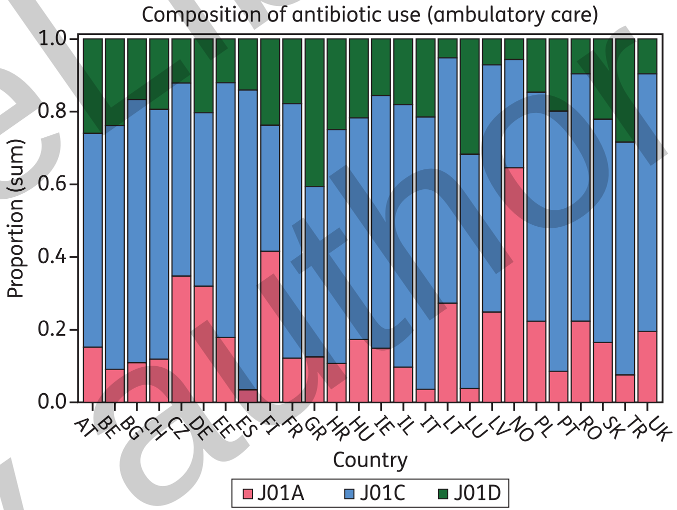
Figure 1. Trends in the number of DDDs per package for total outpatient antibiotic consumption.[4]

Coenen et al. (JAC, 2014)

Model Tools: Proper data generating mechanisms?

- Changepoint analysis
  - – continuous versus abrupt
  - – lags and distributed lags





- Compensation behaviour
  - compositional data analysis

Faes et al. (JAC, 2009)
Minalu et al. (Stat. Modelling, 2009)

Study Design

- Protocols
  - EPOC, ORION (ITS), CONSORT (RCT), …
- Future:
  - designs based on mathematical modelling acknowledging mathematical epidemiological features
  - combine mathematical and statistical approaches e.g. acknowledging outcome dependent sampling

Herzog et al. (BMC ID, 2015)
Stone et al. (TLID, 2007)

Conclusion & discussion

- Mathematical and statistical models, if properly used, offer valuable instruments to understand mechanisms of antibiotic use and resistance
- Interdisciplinary research
  - Example: Methusalem grant awarded to Herman Goossens (Vaxinfectio, UAntwerpen) and Geert Molenberghs (CenStat, UHasselt)
- Lulla Opatowski will present several examples

Opatowski et al. (Current Opinion in ID, 2011)

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Additional Reading

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- The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. Austin DJ, Kristinsson KG, Anderson RM. Proc Natl Acad Sci U S A. 1999 Feb 2;96(3):1152-6. PMID:9927709
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- Social contacts and mixing patterns relevant to the spread of infectious diseases. Mossong J, Hens N, Jit M, Beutels P, Auranen K, Mikolajczyk R, Massari M, Salmaso S, Tomba GS, Wallinga J, Heijne J, Sadkowska-Todys M, Rosinska M, Edmunds WJ. PLoS Med. 2008 Mar 25;5(3):e74. doi: 10.1371/journal.pmed.0050074. PMID: 18366252
- Contribution of mathematical modeling to the fight against bacterial antibiotic resistance. Opatowski L, Guillemot D, Boëlle PY, Temime L. Curr Opin Infect Dis. 2011 Jun;24(3):279-87. doi: 10.1097/QCO.0b013e3283462362. Review. PMID: 21467930
- Active learning to understand infectious disease models and improve policy making. Willem L, Stijven S, Vladislavleva E, Broeckhove J, Beutels P, Hens N. PLoS Comput Biol. 2014 Apr 17;10(4):e1003563. doi: 10.1371/journal.pcbi.1003563. eCollection 2014 Apr 17. PMID: 24743387