Dynamic Bayesian Markov models for health economic evaluations of interventions in infectious disease

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Joint work with Gianluca Baio and Ardo van den Hout

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Outline of presentation

1. Aim of the research
2. Compartmental models in health economics
   - Ordinary differential equation models
   - Markov models
3. Dynamic Bayesian Markov models
4. Example of fictional chronic sexually transmitted infection
   - Prevalence estimation
   - Cost-effectiveness analysis
5. Application to human papillomavirus modelling
6. Conclusions
Aim of the research

- ODE systems are standard tools in infectious disease modelling
- Health economic evaluations require characterising uncertainty
  - Possible impact on decision making process
- ODE systems sometimes fail to account for uncertainty
- Dynamic Bayesian Markov models are introduced as alternative
- Application of methodology to identify the most cost-effective vaccination strategy against human papillomavirus
Modelling for health economic evaluations

• Bayesian framework is most suitable
  – Parameters incorporate a high amount of uncertainty
    • Clinical trials of pathogen transmission ethically impracticable
    • Contacts between susceptible and infectious individuals not always traceable or reported incorrectly (e.g. sexual contacts)
  – Probabilistic sensitivity analysis conducted straightforwardly

• Compartmental models differ in
  – Temporal resolution
  – Accounting for population dynamics and herd immunity
  – Suitability to incorporate parameter uncertainty

• Ordinary differential equation models are industry standard
  – Continuous-time approach
  – Dynamic force of infection accounts for time-dependent prevalence
  – Bayesian ODE systems induce extremely high computational effort

• Markov models are frequently applied
  – Continuous- and discrete-time approaches
  – Dynamic changes in prevalence and herd immunity not considered
  – Computational effort in a Bayesian framework manageable
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Parameter uncertainty in ODE systems

- ODE systems in health economics commonly deterministic
  - Likely to result in biased model outcome
  - Scenario analysis through minimum/maximum values or quantiles
  - Difficulties in conducting PSA (Elbasha et al.\(^1\), Zechmeister et al.\(^2\))
    - Monte Carlo or Latin Hypercube Sampling

- Incorporation of probability distributions on parameters
  - Markov Chain Monte Carlo (MCMC) samplers
    - WinBUGS interface WBDiff computationally intensive
    - Stan may struggle in "stiff" regions of ODE systems; recent improvements in ODE solvers

- Computational effort mainly increased through
  - Long observation time horizon
  - High number of ODEs and distributions on parameters

Complex ODE-based models including distributions on each parameter are rare exceptions in the health economics literature.

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Markov models in health economics

- Disease progression models of non-communicable conditions
  - Cardiovascular diseases
  - Cancer
  - Auto-immune diseases
- Well-known to clinicians and decision makers
- Commonly include static force of infection
  - Ignore time-dependent changes in population prevalence
  - Do not account for the effects of herd immunity
  - Result in biased model outcome
    - Mainly underestimate vaccine-induced benefits and related cost-effectiveness
    - May not recognize undesired effects of vaccines (e.g. shift in age of varicella infection)

To the best of our knowledge, Markov models in the health economics literature do not include a dynamic force of infection - possibly due to their common application for non-communicable diseases.
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## Static versus dynamic models

<table>
<thead>
<tr>
<th></th>
<th>Static</th>
<th>Dynamic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Force of infection</td>
<td>Predefined</td>
<td>Depends on prevalence</td>
</tr>
<tr>
<td>Contact rates</td>
<td>–</td>
<td>✓</td>
</tr>
<tr>
<td>Pathogen transmission</td>
<td>✓</td>
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</tr>
<tr>
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<td>Vaccine implications</td>
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<td>Recognized</td>
</tr>
<tr>
<td>Model outcome</td>
<td>Possibly biased</td>
<td>Unbiased</td>
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Dynamic Bayesian Markov models

- Dynamic force of infection $\lambda_t$ is function of
  - Probability of pathogen transmission $\beta$
  - Rate of contacts $\omega$ between susceptible and infectious people
  - Time-dependent pathogen prevalence $\psi_t = \frac{I_t}{N_t}$

$$\lambda_t = \beta \omega \psi_t$$

- Transformation into transition probability for discrete-time model
- Assumption of uniformity of $\lambda_t$ within each discrete time interval
  $$\pi_{1,2,t} = 1 - \exp^{-\lambda_t}$$

- Accounting for high amount of uncertainty in $\beta$ and $\omega$ essential
- Probability distributions assigned in Bayesian setting
- Distribution on force of infection automatically generated
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Limitations and advantages

Limitations

- transitions between states only once per discrete time interval
  - suitable Markov cycle length and half-cycle correction reduce bias
- accounting for disease history induces rapid increase in number of states
  - inclusion of so-called tunnel states
  - individual-based (e.g. microsimulation) model might be preferable

Advantages in comparison to ODE systems

- no numerical approximations to solutions necessary
- inclusion of exclusively probabilistic model parameters computationally feasible

A Bayesian framework enables

- propagating parameter uncertainty through the model
- combining several sources of data through evidence synthesis
- conducting probabilistic sensitivity analysis straightforwardly
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Example: chronic STI

- Prevalence estimation and health economic evaluation of vaccine compared to STI screening through
  - Deterministic ODE-based model
  - Bayesian ODE-based model
  - Dynamic Bayesian Markov model

- Transition parameters $\phi_{r,s}$
  - $r$ is the original state
  - $s$ is the target state
  - $\phi_{1,2}$ represents dynamic force of infection

- Transition parameters are
  - Transition rates $\rho_{r,s}$ in continuous-time ODE systems
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Force of infection of chronic STI

- Random mixing
- Heterosexual relationships
  - People of sex $v$ mix with people of opposite sex $v'$
- Low- and high-risk sexual behaviour groups

Sex-, behavioural- and time-specific force of infection

$$\rho_{v,b,1,2}(t) = \beta \omega_{vb} \overline{\psi}_{v'}(t)$$

- $\beta$ is the STI transmission probability per partnership
- $\omega_{vb}$ is the sex- and behavioural-specific partner acquisition rate
- $\overline{\psi}_{v'}(t)$ is the population prevalence
  - Weighted average of prevalence in both risk groups
  - Weight is estimated through probabilities of selecting a partner from one of the two groups
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Workshop on infectious disease modelling
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### Overview on model parameters

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<th>Description</th>
<th>Mean</th>
<th>95% CI</th>
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<tbody>
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<td>$\omega_{MH}$</td>
<td>Partner acquisition rate (high-risk males)</td>
<td>9.10</td>
<td>[8.70;9.50]</td>
</tr>
<tr>
<td>$\omega_{ML}$</td>
<td>Partner acquisition rate (low-risk males)</td>
<td>1.80</td>
<td>[1.76;1.84]</td>
</tr>
<tr>
<td>$\omega_{FH}$</td>
<td>Partner acquisition rate (high-risk females)</td>
<td>7.50</td>
<td>[7.11;7.90]</td>
</tr>
<tr>
<td>$\omega_{FL}$</td>
<td>Partner acquisition rate (low-risk females)</td>
<td>1.10</td>
<td>[1.06;1.14]</td>
</tr>
<tr>
<td>$\chi$</td>
<td>Proliferation parameter</td>
<td>0.01</td>
<td>[0.01;0.01]</td>
</tr>
<tr>
<td>$\beta$</td>
<td>STI transmission probability per partnership</td>
<td>0.15</td>
<td>[0.14;0.16]</td>
</tr>
<tr>
<td>$\pi_{2,3}$</td>
<td>Transition parameter from state 2 to state 3</td>
<td>0.80</td>
<td>[0.79;0.81]</td>
</tr>
<tr>
<td>$\pi_{3,4}$</td>
<td>Transition parameter from state 3 to state 4</td>
<td>0.09</td>
<td>[0.09;0.09]</td>
</tr>
<tr>
<td>$\pi_{4,5}$</td>
<td>Transition parameter from state 4 to state 5</td>
<td>0.04</td>
<td>[0.04;0.04]</td>
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<tr>
<td>$\pi_{1,5}$</td>
<td>Transition parameter from state 1 to state 5</td>
<td>&lt;0.01</td>
<td>[&lt;0.01;&lt;0.01]</td>
</tr>
<tr>
<td>$\tau$</td>
<td>Probability of STI diagnosis</td>
<td>0.90</td>
<td>[0.81;0.99]</td>
</tr>
<tr>
<td>$\xi$</td>
<td>Screening probability</td>
<td>0.90</td>
<td>[0.80;1]</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>Vaccine coverage parameter</td>
<td>0.90</td>
<td>[0.88;0.92]</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Vaccine efficacy parameter</td>
<td>0.90</td>
<td>[0.88;0.92]</td>
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<tr>
<td>$c_{\text{screen}}$</td>
<td>Unit cost of screening in £</td>
<td>25.39</td>
<td>[5.19;77.53]</td>
</tr>
<tr>
<td>$c_{\text{vac}}$</td>
<td>Unit cost of vaccination in £</td>
<td>150.02</td>
<td>[147.14;152.98]</td>
</tr>
<tr>
<td>$c_{\text{test}}$</td>
<td>Unit cost of STI test in £</td>
<td>20.01</td>
<td>[18.83;21.19]</td>
</tr>
<tr>
<td>$c_{\text{blood}}$</td>
<td>Unit cost of blood test in £</td>
<td>30</td>
<td>[28.26;31.79]</td>
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<tr>
<td>$c_{\text{treat}}$</td>
<td>Unit cost of treatment in £</td>
<td>4999.78</td>
<td>[4853.56;5149.24]</td>
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<tr>
<td>$c_{\text{dis}}$</td>
<td>Unit cost of disease treatment in £</td>
<td>9999.95</td>
<td>[9802.97;10198.10]</td>
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<tr>
<td>$c_{\text{gp}}$</td>
<td>Unit cost of visit to general practitioner in £</td>
<td>50.01</td>
<td>[48.08;52.01]</td>
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<tr>
<td>$u_2$</td>
<td>Health utility of infected (min=0, max=1)</td>
<td>0.70</td>
<td>[0.68;0.72]</td>
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<tr>
<td>$u_3$</td>
<td>Health utility of asymptomatic (min=0, max=1)</td>
<td>0.60</td>
<td>[0.58;0.62]</td>
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<td>Health utility of morbid (min=0, max=1)</td>
<td>0.30</td>
<td>[0.28;0.32]</td>
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</table>
Prevalence results

Estimated STI prevalence under screening (higher variability)

- Mean prevalence output of Bayesian Markov model and Bayesian ODE-based model basically identical
- More conservative outcome of Bayesian models in comparison to deterministic ODE-based model
- Results of scenario analysis show wider range than 95% credible intervals
- Final conclusion not possible without calibration to simulated data
Model calibration

Calibration involves the comparison of model outputs (e.g. prevalence) with empirical data, leading to the identification of model parameter values that achieve a good fit (Vanni et al., 2011).

- Visual comparison of output to data and parameter adjustment
- Frequentist probabilistic calibration
  - Creating large number of parameter sets through forward sampling
  - Calculating goodness-of-fit statistics (e.g. sum of mean squared errors, $\chi^2$ statistics, log-likelihood)
  - Select parameter set with GOF statistic indicating best fit to data
- Advantages of Bayesian calibration
  - Updating output directly (in one step) by assigning suitable distributions to data on output parameters
  - Evidence synthesis if only data on surrogate output parameters or subpopulations are available, for example
    - seroconversion studies to estimate incidence
    - hepatitis C prevalence in heroine users to estimate overall prevalence
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Cost-effectiveness analysis

• Comparison of costs generated by interventions to induced benefits

• Costs generated by
  – Screening
  – Vaccination
  – Visit at the general practitioner
  – Diagnostic tests
  – Disease treatment

• Quality of life in certain state described by utilities
  – Typically ranging between 0 and 1
  – Representing death and perfect health
  – Decreasing values for more severe states
  – Quality-adjusted life years (QALYs): Time spent in state multiplied by utility
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- Costs generated by
  - Screening
  - Vaccination
  - Visit at the general practitioner
  - Diagnostic tests
  - Disease treatment
- Quality of life in certain state described by utilities
  - Typically ranging between 0 and 1
  - Representing death and perfect health
  - Decreasing values for more severe states
  - Quality-adjusted life years (QALYs): Time spent in state multiplied by utility
Overall costs and utilities

\[
C_i = \sum_{t=1}^{T} \sum_{s=1}^{S} \frac{c_{si} n_{sti}}{(1 + \delta)^{t-1}} \\
U_i = \sum_{t=1}^{T} \sum_{s=1}^{S} \frac{u_{s} n_{sti}}{(1 + \delta)^{t-1}}
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- \(c_{si}\) are unit costs in state \(s\) under intervention \(i\)
- \(u_{s}\) are unit utilities in state \(s\)
- \(n_{sti}\) are number of people in state \(s\) at time \(t\) receiving intervention \(i\)
- \(\delta\) is yearly discount rate of 3%

Rescaling into population averages

\[
\mu_{ci} = \frac{C_i}{n_i} \quad \mu_{ei} = \frac{U_i}{n_i}
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Incremental Cost-Effectiveness Ratio

\[
\text{ICER} = \frac{\text{Increment in population average costs}}{\text{Increment in population average benefits}}
\]

- Amount of money spent on reference intervention to increase benefits by one QALY
- Comparison of interventions STI screening and vaccination
- Threshold of cost-effectiveness of £20,000 - £30,000 per QALY gained
Comparison of ICER results

Comparing STI vaccination versus the status-quo results in ICERs of

- £13,704 in deterministic ODE-based model
  - £2.5% quantile at £-13,660
  - £97.5% quantile at £133,620
- £7,084 in Bayesian Markov model
- £6,800 in Bayesian ODE-based model

- All ICERs indicate that vaccination is cost-effective
- ICER of deterministic ODE-based model is nearly twice as high due to corresponding lower STI prevalence estimate
Joint distributions of cost- and effectiveness differentials of both Bayesian models comparable

- Vaccination less expensive and more effective than status-quo (STI screening)
- Vast majority of points within sustainability area
- Vaccination cost-effective at threshold of £25,000
CEACs reach values of only around 30% at break-even points of £7,084 (Bayesian Markov model) and £6,800 (Bayesian ODE-based model)
- 80% cost-effectiveness is reached at around £40,000

EVI results in values of around £23 per individual in both models
- Value for additional research is limited

Amount of uncertainty in both models is basically identical
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Extensions

- To update priors into corresponding posteriors, integrate simulated data on
  - number of partners
  - transitions between states
  - STI transmission

- Calibrate model outputs to simulated time series data on number of people in states
  - Frequentist probabilistic calibration approach in deterministic ODE-based model
    - Assign suitable distributions to model parameters
    - Create 50,000 sets of input parameter combinations
    - Calculate least squared error between data and outputs
  - Bayesian calibration approach in Bayesian models
    - Assign Poisson distributions to simulated count data on output
    - Event rate $\lambda$ is directly represented by expectation on model output
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Example: human papillomavirus

- Application of dynamic Bayesian Markov model to cost-effectiveness analysis of human papillomavirus vaccination
- Comparison of universal (including both sexes) to female-only vaccination strategies
- Cervical screening at age-specific rates in both interventions
Human papillomavirus

- Mainly sexually transmitted
- Necessary cause of cervical cancer
- Contributory cause of anal, vaginal, vulvar, penile and head/neck cancers
- Considerably high HPV prevalence
  - 20.7% in females
  - 17.4% in males
- Heavy economic impact
  - £17 million for genital warts treatment
  - £157 million for cervical cancer treatment
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| Multiple sources of data, contradictory data or lack of information        | Bayesian evidence synthesis  
Probabilistic sensitivity analysis                                      |
Example: HPV transmission probability

- Crucial parameter with limited and inconclusive evidence
  - Uniform distribution in [0;1] (Korostil et al., 2012)
  - Per sex act $\sim 40\%$ with a range of 5-100\% (Dunne et al., 2006)
  - Per partnership $\sim 42\%$ with a range of 36-47\% (Burchell al., 2011)
- Affected by risk factors such as previous STIs and smoking
- Inclusion of expert opinion in a Bayesian setting
$S_f = 36$ states in females and $S_m = 22$ states in males
Cervical cancer compartment

- Infection
- Clearance
- Reinfection

Cervical cancer
- CIN I
- CIN II
- CIN III

Year 1 → Year 2 → Year 3
Universal versus female-only vaccination

Cost effectiveness plane
Universal vs Female-only

Cost differential
0 200000 400000
0 600000
Effectiveness differential
0 200000 600000

Expected Incremental Benefit
Willingness to pay
0 0 50000 100000
0 0 150000000

Cost Effectiveness
Acceptability Curve
Probability of cost effectiveness
0 0.2 0.4 0.6 0.8 1.0
0 10000 30000 50000

Expected Value of Information
Willingness to pay
0 0 10000 30000 50000
0 0 250000000

ICER = 11516.63
k* = 11600
Conclusions

- A fully probabilistic approach (ideally Bayesian) is essential in infectious disease modelling
  - Propagating parameter uncertainty through the model
  - Conducting probabilistic sensitivity analysis straightforwardly
- Bayesian ODE systems are the “gold standard”
  - Modelling under a continuous-time approach
  - Recent developments to reduce computational effort of Bayesian ODE systems (e.g. through more flexible ODE solvers in Stan)
- Dynamic Bayesian Markov models as reasonable alternative to Bayesian ODE systems
  - Level of temporal resolution is lower (discrete-time approach)
  - To date, implementation, computation and conducting PSA is faster
Thank you very much for your attention.