# SIS models for recurrent infections

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Instructors: Vladimir Minin, Kari Auranen, Elizabeth Halloran

# Outline

- Recurrent infections
- A simple SIS model without transmission
  - Complete-data likelihood
- Model extensions
  - Several subtypes of a pathogen
  - Transmission in small mixing groups
- Incomplete observations
  - Discrete-time Markov transition models
  - Continuous-time Markov processes with Bayesian data augmentation and reversible jump MCMC
- A computer class exercise of an SIS model without transmission and with completely observed data

# Background

- Many infections can be considered recurrent, i.e., occurring as an alternating series of presence and absence of infection
  - Nasopharyngeal carriage of *Streptococcus pneumoniae* (Auranen et al.; Cauchemez et al.; Melegaro et al.)
  - Nasopharyngeal carriage of *Neisseria meningitidis*
  - multi-resistant *Staphylococcus aureus* (Cooper et al.)
  - HPV (human papilloma virus) infection
  - some parasitic infections (e.g. Nagelkerke et al.)
- Many of the above infections are asymptomatic, which means that observation requires active sampling of the underlying epidemiological states
- Exact acquisition and clearance times often remain unobserved $\Rightarrow$ incompletely observed data

# A binary Markov process

A simple model for a recurrent infection is the binary Markov process:

- The state of the individual alternates between "susceptible" (state 0) and "infected" (state 1)
- Hazard of acquiring infection is $\beta$:

  $$\mathrm{P}(\text{acquisition in } [t, t+dt[ \mid \text{ susceptible at time } t-) \simeq \beta dt$$

- Hazard of clearing infection is $\mu$:

  $$\mathrm{P}(\text{clearance in } [t, t+dt[ \mid \text{infected at time } t-) \simeq \mu dt$$

# Complete data

- For each individual $i$, the complete data include the times of acquisition and clearance during the observation period $[0, T]$:
  - Denote the ordered acquisition times for individual $i$ during $]0, T[$ by $\boldsymbol{t}^{(i)} = (t_{i1}, \ldots, t_{iN_{01}^{(i)}})$
  - Denote the ordered clearance times for individual $i$ during $]0, T[$ by $\boldsymbol{r}^{(i)} = (r_{i1}, \ldots, r_{iN_{10}^{(i)}})$
  - Denote the ordered acquisition and clearance times together as $u_{i1} = 0, u_{i2}, \ldots, u_{i,N^{(i)}} = T$
    - Note: these include times 0 and $T$ (so that $N^{(i)} = N_{01}^{(i)} + N_{10}^{(i)} + 2$)

# Keeping track who is susceptible

- The binary indicators for individual $i$ to be susceptible or infected at time $t$ are denoted by $Y_0^{(i)}(t)$ and $Y_1^{(i)}(t)$, respectively
  - For the simple binary model, $Y_1^{(i)}(t) = 1 - Y_0^{(i)}(t)$ for all times $t \geq 0$, i.e. the individual is always either susceptible or infected
  - Both indicators are taken to be *predictable*, i.e., their values at time $t$ are determined by their initial values and the complete data observed up to time $t-$
  - In practice, this means that the values of $Y_0^{(i)}(t)$ and $Y_1^{(i)}(t)$ can be calculated from the observed data and these indicators can be used as shorthand when writing the likelihood function

# Process of acquisitions

- In each individual, acquisitions (i.e. infections) occur with intensity $\beta Y_0^{(i)}(t)$
  - The intensity is $\beta$ when the individual is in state 0 (susceptible) and 0 when the individual is in state 1 (infected)
- The probability density of the acquisition events is proportional to

$$\prod_{k=1}^{N^{(i)}} \left[ \beta^{1(u_k \text{ is time of acq.})} e^{-\beta Y_0^{(i)}(u_k)(u_k - u_{k-1})} \right]$$

$$\propto \beta^{N_{01}^{(i)}} \times \exp\{-\beta \overbrace{\sum_{k=1}^{N^{(i)}} Y_0^{(i)}(u_k)(u_k - u_{k-1})}^{\text{total time susceptible}}\}$$

# Process of clearances

- In each individual, clearances occur with intensity $\mu Y_1^{(i)}(t)$
  - The intensity is $\mu$ when the individual is in state 1 (infected) and 0 when then individual is in state 0 (susceptible)
- The probability density of the clearance events is proportional to

$$\prod_{k=1}^{N^{(i)}} \left[ \mu^{1(u_k \text{ is time of clearance})} e^{-\mu Y_1^{(i)}(u_k)(u_k - u_{k-1})} \right]$$

$$= \mu^{N_{10}^{(i)}} \times \exp\{-\mu \overbrace{\sum_{k=1}^{N^{(i)}} Y_1^{(i)}(u_k)(u_k - u_{k-1})}^{\text{total time infectd}}\}$$

# Complete data likelihood

- The likelihood function of parameters $\beta$ and $\mu$, based on the complete data from individual $i$:

$$\overbrace{L_i(\beta, \mu; \boldsymbol{t}^{(i)}, \boldsymbol{r}^{(i)})}^{f(\boldsymbol{t}^{(i)}, \boldsymbol{r}^{(i)} | \beta, \mu)}$$

$$= \beta^{N_{01}^{(i)}} \mu^{N_{10}^{(i)}} \times e^{-\sum_{k=1}^{N^{(i)}} (\beta Y_0^{(i)}(u_k) + \mu Y_1^{(i)}(u_k))(u_k - u_{k-1})}$$

$$= \beta^{N_{01}^{(i)}} \mu^{N_{10}^{(i)}} \times \exp\left( - \int_0^T \{\beta Y_0^{(i)}(u) + \mu Y_1^{(i)}(u)\} du \right)$$

- Likelihood based on all $M$ individuals is $\prod_{i=1}^{M} L_i(\beta, \mu; \boldsymbol{t}^{(i)}, \boldsymbol{r}^{(i)})$

# Model extension 1: Several subtypes of infection

- If the pathogen has $K$ subtypes/strains, infections with each can be modelled as separate states
- Let the hazards from making a transition from state $s$ to state $r$ be $\alpha_{sr}$, $s, r \in \{0, \ldots, K\}$
  - This means that infection for a susceptible occurs with rate $\alpha_{0r}$, $r = 1, \ldots, K$
  - Also direct transitions from infection with type $s$ to infection with type $r$ are possible if we allow $\alpha_{sr} > 0$ also when $s > 0$
- Transitions for each individual are now modelled as follows:

$$\text{P(individual } i \text{ makes transition from } s \text{ to } r \text{ in } [t, t + dt) \simeq \alpha_{sr} Y_s^{(i)}(t) dt$$

# Model extension 2: Modelling transmission

- The hazard of infection may depend on the presence of infected individuals in the family, day care group, school class etc.
  - The statistical unit is defined by the relevant mixing group
- Denote $H_t^{(i,fam)}$ the joint infection status of all members in the mixing group (e.g. family) of individual $i$ at time $t-$
- For a single-type pathogen, infections are modeled as follows:

$$\mathrm{P}(\text{infection for } i \text{ in } [t, t+dt[ | H_{t-}^{(i,\mathrm{fam})}) \simeq \alpha_{01}^{(i)}(t) Y_0^{(i)}(t) dt \equiv \frac{\beta C^{(i)}(t)}{M_{\mathrm{fam}}^{(i)} - 1} Y_0^{(i)}(t) dt$$

where $C^{(i)}(t)$ is the number of infected individuals in $i$'s family (of size $M_{fam}^{(i)}$) at time $t-$; note that $C^{(i)}(t)$ can be calculated from the state-indicator variables of $i$'s family members

# Complete data likelihood: the general expression

- For $M$ individuals followed from time 0 to time $T$, the *complete data* record all transitions between states $s$ and $r$:

$$x_{\text{complete}} = \{ T_{sr}^{(ik)};\ s, r = 0, 1\ (s \neq r),\ k = 1, \ldots, N_{sr}^{(i)}(T),\ i = 1, \ldots, M \}$$

- The likelihood of the rate parameters $\theta$, based on the complete (event-history) data

$$\overbrace{L(\theta; x_{\text{complete}})}^{f(x_{\text{complete}}|\theta)} = \prod_{i}^{N} \prod_{r \neq s} \prod_{k}^{N_{sr}^{(i)}(T)} \left[ \alpha_{sr}^{(i)}(T_{sr}^{(ik)}) \times \exp\left( - \int_0^T \alpha_{sr}^{(i)}(u) Y_s^{(i)}(u) du \right) \right]$$

# Remarks

- Although the likelihood expression was written as a product of individual likelihood contributions, it is valid even if the individual processes are dependent on the infection outcomes of *other* individuals (as when modeling transmission)
- The likelihood is correctly normalized with respect to any number of events occurring between times 0 and $T$
  - This is crucial when performing MCMC computations through data augmentation with an unknown number of events
- These results are somewhat non-trivial and require the theory of counting processes (Andersen et al.)

# Incomplete observations

- Usually we do not observe complete data (= all infection and clearance times)
- Instead, the status (infection stage) $X_j^{(i)}$ of each individual is observed at pre-defined times $t_j^{(i)}$
  - This creates *incomplete data*: the process is only observed at discrete times (panel data)
  - The observed data likelihood is now a complicated function of the model parameters
- How to estimate the underlying continuous process from discrete observations?
  - (A) Discrete-time Markov transition model
  - (B) Continous-time Markov transition model with Bayesian data augmentation

# (A) Markov transition models

- Treat the problem as a discrete-time Markov transition model
- For simplicity, assume equal-length ($= \Delta$) time steps indexed by $t = 1, 2, 3, \ldots$, and time-homogeneous one-time-step transition probabilities:

$$p_{sr} \equiv \mathrm{P}(X_{t+1}^{(i)} = r | X_t^{(i)} = s) \quad \text{for } t = 1, 2, \ldots; s, r = 0, \ldots, K$$

- This defines matrix $P_\Delta$ of one-step transition probabilities with entries $[P_\Delta]_{sr} = p_{sr}$, where $\sum_r p_{sr} = 1$ for each $s = 0, \ldots, K$

# Likelihood function under the discrete model

- Denote the observed numbers of one-step transitions in all study subjects by $N_{sr}$, $s, r = 0, \ldots, K$
- The likelihood of the unknown transition probabilities (i.e. the elements of matrix $P_\Delta$)) is now particularly simple:

$$L(P_\Delta) = \prod_{s,r} [p_{sr}(\Delta)]^{N_{sr}(T)} = \prod_{s,r} [P_\Delta]_{sr}^{N_{sr}(T)}$$

- When observation are actully made at intervals $k\Delta$ (e.g. $\Delta =$ day and $k = 28$), the likelihood is

$$L(P_\Delta) = \prod_{s,r} [P_\Delta^k]_{sr}^{N_{sr}(T)}$$

# Modeling transmission

- In a mixing group of size $M$, the state space is $\chi \times \chi \times \ldots \chi$, where $\chi$ is the state space for one individual
  - In a binary infection model, the individual state space is $\{0, 1\}$
  - In a family of three individuals the state space is then $\{(0,0,0),(1,0,0),(0,1,0),(0,0,1),(1,1,0),(1,0,1),(0,1,1),(1,1,1)\}$
  - For $M$ individuals, the dimension of the state space is $2^M$
- Application to pneumococcal carriage in families (Melegaro et al.)
  - The transition probability matrix in a family of 3 (next page), assuming the same probabilities (per day) for each family member
  - Notation: $q_{ii}$ = 1 - (sum of the non-diagonal elements on the $i$th row)

# Transition probability matrix

$$
P_\Delta = \begin{array}{c}
\begin{matrix} (0,0,0) & (1,0,0) & (0,1,0) & (0,0,1) & (1,1,0) & (1,0,1) & (0,1,1) & (1,1,1) \end{matrix} \\
\begin{pmatrix}
q_{11} & \kappa & \kappa & \kappa & 0 & 0 & 0 & 0 \\
\mu & q_{22} & 0 & 0 & \beta/2+\kappa & \beta/2+\kappa & 0 & 0 \\
\mu & 0 & q_{33} & 0 & \beta/2+\kappa & 0 & \beta/2+\kappa & 0 \\
\mu & 0 & 0 & q_{44} & 0 & \beta/2+\kappa & \beta/2+\kappa & 0 \\
0 & \mu & \mu & 0 & q_{55} & 0 & 0 & \beta+\kappa \\
0 & \mu & 0 & \mu & 0 & q_{66} & 0 & \beta+\kappa \\
0 & 0 & \mu & \mu & 0 & 0 & q_{77} & \beta+\kappa \\
0 & 0 & 0 & 0 & \mu & \mu & \mu & q_{88}
\end{pmatrix}
\end{array}
$$

# Potential problems

- The dimension of the state space
  - With $M$ individuals and $K+1$ types of infection, the dimension of the state space is $(K+1)^M$
  - With 13 serotypes and 25 individuals (see Hoti et al.), the dimension is $\sim 4.5 \times 10^{28}$
- Non-Markovian sojourn times
  - e.g. a Weibull duration of infection may be more realistic than the exponential one
- Handling of varying observation intervals and individuals with completely missing data are still cumbersome

# (B) Bayesian data augmentation

- If we retain the continuous-time model formulation, unobserved event times of acquisition and clearance can be taken as additional model unknowns (parameters)
- Statistical inference on all model unknowns (parameters $\theta$ and event times $x_{\text{complete}}$)

$$\overbrace{f(x_{\text{observed}}|x_{\text{complete}})}^{\text{observation model}} \overbrace{f(x_{\text{complete}}|\theta)}^{\text{complete data likelihood}} \overbrace{f(\theta)}^{\text{prior}}$$

- The observed data $x_{observed}$ contain only the current status of infection in each study subject at predefines time points
- The observation model often only ensures agreement with the observed data (as an indicator function)
- The computational problem:
  how to sample from $f(x_{\text{complete}}|x_{\text{observed}}, \theta)$?

# Sampling algorithm

- Initialize the model parameters and the latent processes (i.e. the unobserved event times)
- For each individual, update the unobserved event times
  - Update the current iterates of the event times using standard MH
  - Add/delete episodes of infection and non-infection using reversible jump MH
    - with 0.5 probability propose to add a new episode
    - with 0.5 probability propose to delete an existing episode
- Update the model parameters using single-step MH
- Iterate the above updating steps for a given number of MCMC iterations

# Adding/deleting episodes

- Choose one interval at random from among the $K$ sampling intervals (see page+2)
- Choose to add an episode (delete an existing episode) within the chosen interval with probability $\pi_{\text{add}} = 0.5$ ($\pi_{\text{delete}} = 0.5$)
  - If 'add', choose random event times $\bar{t}_1 < \bar{t}_2$ uniformly from $\Delta$ (= the length of the sampling interval). These define the new episode.
  - If 'delete', delete the two event times
- The 'add' move is accepted with probability (Metropolis-Hastings acceptance ratio)

$$\min\left(\frac{f(x_{\text{observed}}|x^*_{\text{complete}})f(x^*_{\text{complete}}|\theta)q(x_{\text{complete}}|x^*_{\text{complete}})}{f(x_{\text{observed}}|x_{\text{complete}})f(x_{\text{complete}}|\theta)q(x^*_{\text{complete}}|x_{\text{complete}})}, 1\right)$$

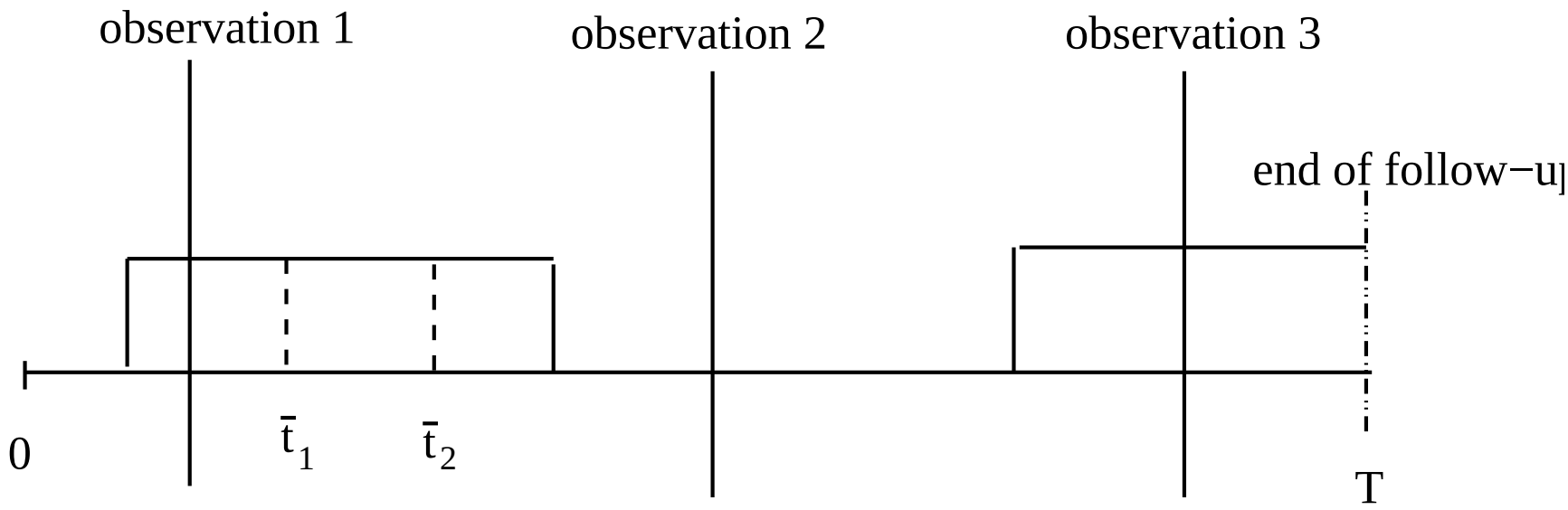
# Adding/deleting episodes cont.

- The ratio of the proposal densities is

$$\frac{q(x_{\text{complete}}|x^*_{\text{complete}})}{q(x^*_{\text{complete}}|x_{\text{complete}})} = \frac{\pi_{\text{delete}} \frac{1}{K} \frac{1}{L}}{\pi_{\text{add}} \frac{1}{K} \frac{1}{L} \frac{2}{\Delta^2}} = \frac{\Delta^2}{2}$$

- The ratio of the proposal densities in the 'delete' move is the inverse of the expression above
- Technically, the add/delete step relies on so called reversible jump MCMC (see page+2)
- Reversible jump types should be devised to assure irreducibility of the Markov chain
- For a more complex example, see e.g. Hoti et al.

# Adding/deleting latent processes cont.




The number of sampling intervals K= 4
The number of 'sub−episodes' within the second interval L = 2

# Reversible jump MCMC

- "When the number of things you don't know is one of the things you don't know"
- For example, under incomplete observation of the previous (Markov) processes, the exact number of events is not observed
- This requires a joint model over 'sub-spaces' of different dimensions
- And a method to do numerical integration (MCMC sampling) in the joint state space

# References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