SIS models for recurrent infections

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Outline

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- ▶ 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 β:

  P(acquisition in $[t, t + dt[|$ susceptible at time $t-) \simeq \beta dt$

- ▶ Hazard of clearing infection is μ:

  P(clearance in $[t, t + dt[|$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 β 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 μ 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 β and μ, 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 α_{sr}, $s, r \in \{0, \ldots, K\}$
  - This means that infection for a susceptible occurs with rate α_{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:

P(individual i makes transition from s to r 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:

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

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 θ, 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 <u>discrete-time</u> 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:

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

- ▶ This defines matrix P_Δ 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_Δ)) 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 χ 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 ith row)

Transition probability matrix

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

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 θ and event times x_{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 Δ ($=$ 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

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

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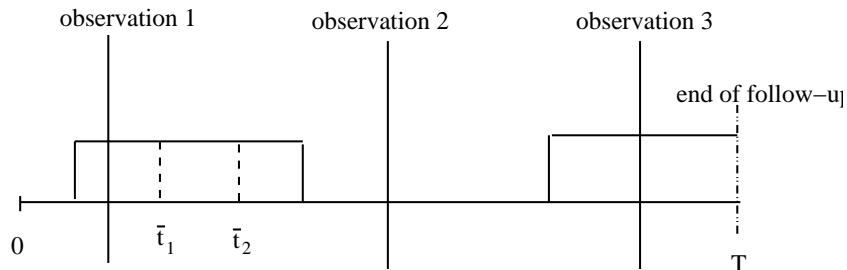
The number of sampling intervals K= 4
The number of 'sub-episodes' within the second interval L = 2

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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