SIS models for recurrent infections

SISMID/July 11–13, 2018

Instructors: Vladimir Minin, Kari Auranen, Elizabeth Halloran

Outline

- Background: recurrent infections
- Binary Markov processes and their generalizations
- Counting process likelihood
- Incomplete observations
  - discrete-time transition models
  - Bayesian data augmentation and reversible jump MCMC
- A computer class exercise

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 menigitidis*
  - multi-resistant *Staphylococcus aureus* (Cooper et al.)
  - some parasitic infections (e.g. Nagelkerke et al.)
- Observation of these processes requires active sampling of the underlying epidemiological states
- 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)
- The hazard of acquiring infection is β:

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

- The hazard of clearing infection is μ:

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

The 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 indicators for individual i to be susceptible or infected at time t are denoted by $S_i(t)$ and $I_i(t)$, respectively
  - Both indicators are taken to be *predictable*, i.e., they values at time t are determined by the initial value $S_i(0)$ and the complete data observed up to time $t-$
  - Note that $I_i(t) = 1 - S_i(t)$ for all times $t \geq 0$

The process of acquisitions

- In each individual, acquisitions occur with intensity $\beta S_i(t)$
  - 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

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

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

The process of clearances

- In each individual, the clearances occur with intensity $\mu I_i(t)$
  - 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

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

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

The complete data likelihood

- The likelihood function of parameters β and μ, based on the complete data from individual i:

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

$$= \beta^{N_{01}^{(i)}} \mu^{N_{10}^{(i)}} \times \exp^{-\sum_{k=1}^{N^{(i)}} (\beta S_i(u_k) + \mu I_i(u_k))(u_k - u_{k-1})}$$

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

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

More complex models

- In the following six slides, the binary model is formulated as a process of counting transitions "$0 \to 1$" (acquisitions) and "$1 \to 0$" (clearances)
- More complex models can then be defined, allowing e.g.
  - different (sero)types/strains of infection
  - taking into account exposure from other individuals in the relevant mixing groups, e.g., modelling transmission in households

A counting process formulation

- For individual i, the binary process can be described in terms of two counting processes (jump processes):
  - $N_{01}^{(i)}(t)$ counts the number of acquisitions for individual i from time 0 up to time t
  - $N_{10}^{(i)}(t)$ counts the number of clearances for individual i from time 0 up to time t
- Specify the initial state: (e.g.) $N_{01}^{(i)}(0) = N_{10}^{(i)}(0) = 0$
- Denote $H_t^{(i)}$ the history of the processes up to time t: $H_t^{(i)} = \{N_{01}^{(i)}(s), N_{10}^{(i)}(s); 0 \leq s \leq t\}$

Stochastic intensities

- The two counting processes can be specified in terms of their stochastic intensities:

$$\mathrm{P}(dN_{01}^{(i)}(t) = 1 | H_{t-}^{(i)}) = \alpha_{01}^{(i)}(t) Y_0^{(i)}(t) dt$$

$$\mathrm{P}(dN_{10}^{(i)}(t) = 1 | H_{t-}^{(i)}) = \alpha_{10}^{(i)}(t) Y_1^{(i)}(t) dt$$

- Here, $Y_j^{(i)}(t)$ is indicator for individual i being in state j at time $t-$
- In the simple Markov model, $\alpha_{01}^{(i)}(t) = \beta$, $\alpha_{10}^{(i)}(t) = \mu$, $Y_0^{(i)}(t) = S_i(t)$, and $Y_1^{(i)}(t) = I_i(t)$

Several types of infection

- The infection can involve a "mark", e.g. the serotype of the infection
  - $N_{0j}^{(i)}(t)$ counts the number of times that individual i has acquired infection of type j from time 0 up to time t
  - $N_{j0}^{(i)}(t)$ counts the number of times that individual i has cleared infection of type j from time 0 up to time t
  - Stochastic intensities can be defined accordingly for all possible transitions between the states. For example, for K serotypes, $\alpha_{rs}^{(i)}(t) Y_r^{(i)}(t), \quad r, s = 0, \ldots, K$

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 the relevant mixing group
- Denote $H_t^{(i,fam)}$ the joint history of all members in the mixing group (e.g. family) of individual i:

$$\mathrm{P}(dN^{(i)}(t) = 1 | H_{t-}^{(i,\mathrm{fam})}) = \alpha_{01}^{(i)}(t) S_i(t) dt \equiv \frac{\beta C^{(i)}(t)}{M_{\mathrm{fam}}^{(i)} - 1} S_i(t) dt$$

where $C^{(i)}(t) = \sum_{j=1}^{M_{fam}^{(i)}} I_j^{(i)}(t)$ is the number of infected individuals in the family of individual i at time $t-$

The counting process likelihood

- For M individuals followed from time 0 to time T, the *complete data* record all transitions between states 0 and 1 (equivalent to observing all jumps in the counting processes):

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

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

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

Remarks

- The likelihood is valid even when the individual processes are dependent on the histories of *other* individuals, e.g. in the case of modelling transmission (cf. Andersen et al)
- The likelihood is correctly normalized with respect to any number of events occurring between times 0 and T (cf. Andersen et al)
  - This is crucial when performing MCMC computations through data augmentation with an unknown number of events

Incomplete observations

- Usually, we do not observe complete data
- Instead, the status $y_j^{(i)}$ 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
  - Bayesian data augmentation

Markov transition models

- Treat the problem as a discrete-time Markov transition model
- This is parameterized in terms of transition probabilities $\mathrm{P}(X^{(i)}(t) = s | X^{(i)}(u) = r)$ for all r, s in the state space χ, and for all times $t \geq u \geq 0$
- In a time-homogeneous model the transition probabilities depend only on the time difference:

$$p_{rs}(t) = \mathrm{P}(X^{(i)}(t) = s | X^{(i)}(0) = r)$$

- This defines a transition probability matrix P_t with entries $[P_t]_{rs} = p_{rs}(t)$, where $\sum_s p_{rs}(t) = 1$ for all r and all $t \geq 0$

The likelihood

- When observations $y_j^{(i)}$ are made at equal time intervals (Δ), the likelihood is particularly simple

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

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

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

Modeling transmission

- In a mixing group of size M, the state space is $\chi_1 \times \chi_2 \times \cdots \chi_M$
  - For example, in a family of three the states then are: (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: $q_{ii} = 1$ - the sum of the ith row

Transition probability matrix

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

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

Bayesian data augmentation

- Retaining the continuous-time model formulation, the unknown event times are taken as additional model unknowns (parameters)
- Statistical inference on all model unknowns (θ and y_{complete})

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

- The observation model often only ensures agreement with the observed data (as an indicator function)
- The computational problem:
  how to sample from $f(y_{\text{complete}}|y_{\text{observed}}, \theta)$?

The sampling algorithm

- Initialize the model parameters and the latent processes
- For each individual, update the latent processes
  - Update the event times using standard MH
  - Add/delete episodes 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 updating steps for a given number of MCMC iterations
  - See the computer class exercise

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 ("acceptance ratio")

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

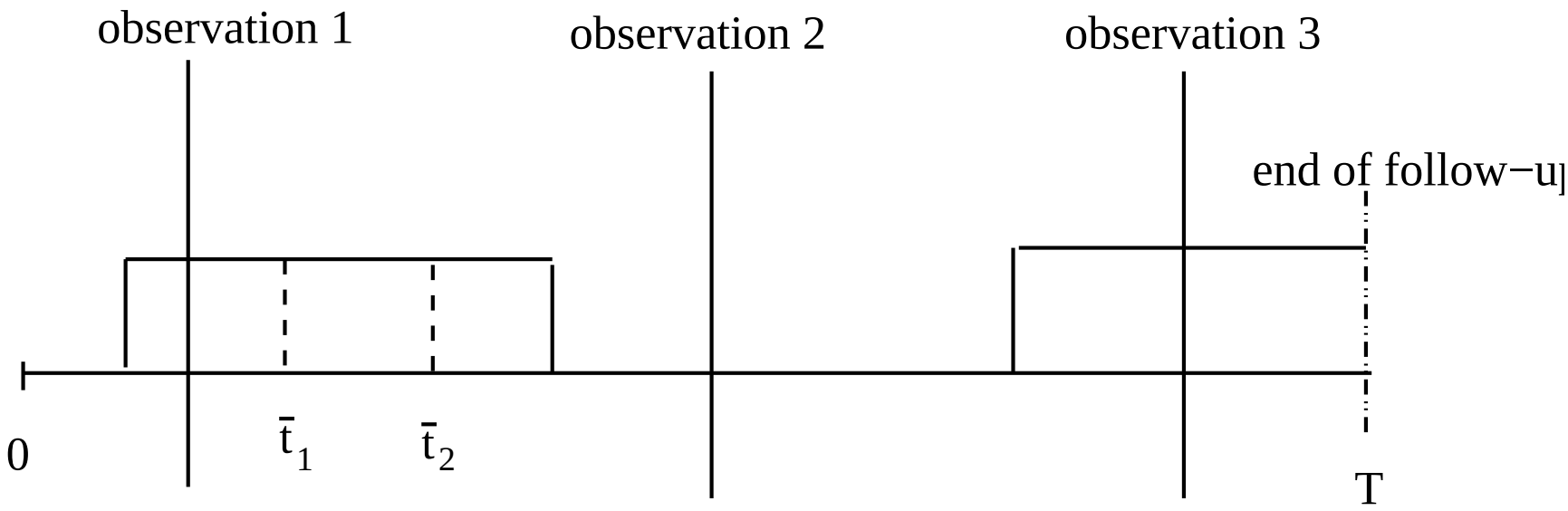
Adding/deleting episodes cont.

- The ratio of the proposal densities is

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

- 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 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

[1] Andersen et al. "Statistical models based on counting processes", Springer, 1993
[2] Auranen et al. "Transmission of pneumococcal carriage in families – a latent Markov process model for binary data. J Am Stat Assoc 2000; 95:1044-1053.
[3] Melegaro et al. Estimating the transmission parameters of pneumococcal carriage in families. Epidemiol Infect 2004; 132:433-441.
[4] Cauchemez et al. Streptococcus pneumoniae transmission according to inclusion in cojugate vaccines: Bayesian analysis of a longitudinal follow-up in schools. BMC Infectious Diseases 2006, 6:14.
[5] Nakelkerke et al. Estimation of parasitic infection dynamics when detectability is imperfect. Stat Med 1990; 9:1211-1219.
[6] Cooper et al. "An augmented data method for the analysis of nosocomial infection data. Am J Epidemiol 2004; 168:548-557.
[7] Bladt et al. "Statistical inference for disceretly observed Markov jump processes. J R Statist Soc B 2005; 67:395-410.
[8] Andersen et al. Multi-state models for event history analysis. Stat Meth Med Res 2002; 11:91-115.
[9] Hoti et al. Outbreaks of Streptococcus pneumoniae carriage in day care cohorts in Finland – implications to elimination of carriage. BMC Infectious Diseases, 2009 (in press)
[10] Green P. Reversible jump Markov chain Monte Carlo computation and Bayesianmodel determination. Biometrika 1995; 82:711-732.