Multi-state Models: A Review

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1. Constructing event history models

Event histories involve the times between events.

These may be recurrent events such as migraine, fits, or infections, or they may involve moves between distinct states, such as catching a disease, being hospitalized, recovering, or dying.

A subject is said to change *state* and the event is called a *transition* between the states.

Sometimes we are mainly interested in the states, and sometimes in the transition events:

being ill versus catching an illness.

Several special cases are particularly important.

- Mortality: two states of which the second is absorbing (classical survival analysis).

- Competing risks: transition from one state to any one of several others.

- Recurrent events (the first example mentioned above).

- Alternance between two states.

- Disability: transition through a series of irreversible states (the second example mentioned, if death must be the final result).

Several of these may need to be combined to describe the complete history of subjects.

Model construction depends greatly on how the series of states for individuals is defined.

Generally, there is no unique structure.

Where they are possible, certain assumptions will facilitate model building.

A model is *progressive* if all states, except the first, have only one transition into them.

Then, the current state defines what states were previously occupied and in what order, but not when the changes occurred.

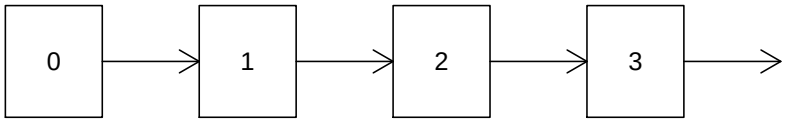
A transition probability is *Markovian* if it only depends on the present state and not on the previous history of the individual.

However, it may depend on time.

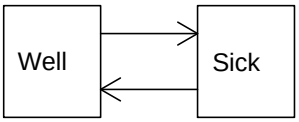
An extension is to allow it to depend on the time since the last event, a special case being the semi-Markov model.

Generally, it useful to clarify ideas by constructing a diagram for the states and possible transitions between them.

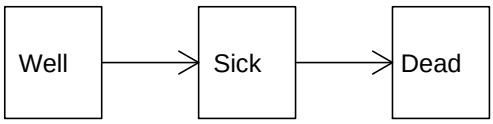
Recurrent events



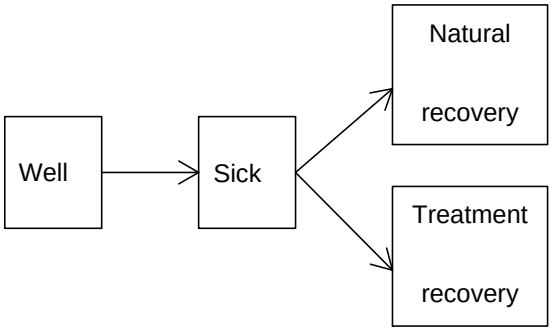
Alternating events



Progressive events



Alternative outcomes



A multi-state model must never have several transition routes from one state to another.

Instead several different states must be defined.

For example, suppose that subjects in the state of having a given disease may recover either by natural body defenses or by medical treatment.

Then, these must be defined either as two different recovery states, as in the alternative outcomes model, or they must not be distinguished at all.

For recurrent events, it is especially important to establish a zero time point.

If this is birth, then the time to the first event will generally be quite distinct from subsequent repetitions of the event.

Often, it is convenient to start the process from the time of the first event.

If this is unknown, the possible models that can be fitted may be limited.

For example, a birth process is usually unreasonable because the actual number of previous events is unknown.

2. Counting processes

The cumulated number, N_t, of events up to time, t, in a point process is known as a *counting process*.

Let the intensity of transition from state j to state k be $\omega_{jk}(t|\mathcal{F}_{t-})$, defined by

$$\begin{aligned}\omega_{jk}(t|\mathcal{F}_{t-})dt &= \Pr(\text{the event in } (t, t+dt)|\mathcal{F}_{t-}) \\ &= \Pr(dN_t = 1|\mathcal{F}_{t-})\end{aligned}$$

where $\mathcal{F}_{t-}$ is the complete history up to, but not including, t.

If

$$\begin{aligned}\mathrm{E}[M_t] &< \infty \\ \mathrm{E}[M_{t+k} - M_t|\mathcal{F}_{t-}] &= 0\end{aligned}$$

$\forall t, 0 < k < \infty$, then, M_t is called a *martingale*.

For a counting process,

$$M_t = N_t - \int_0^t \omega_{jk}(t|\mathcal{F}_{t-})dt$$

fulfils this condition.

3. Likelihood function

The kernel of the log likelihood function for observation over the interval $(0, T]$ is

$$\log[\mathrm{L}(\boldsymbol{\beta})] = \int_0^T \log[\omega_{jk}(t|\mathcal{F}_{t-}; \boldsymbol{\beta})] dN_t - \int_0^T \omega_{jk}(t|\mathcal{F}_{t-}; \boldsymbol{\beta}) \mathrm{I}(t) dt$$

where $\mathrm{I}(t)$ is an indicator function.

In any empirical situation, even a continuous-time process will only be observed at discrete time intervals, once an hour, once a day, once a week.

Suppose that these are sufficiently small so that at most one event is observed to occur in any interval.

(There will be a finite non-zero theoretical probability of more than one, unless the event is absorbing or a transition to another state.)

With R intervals of observation, not all necessarily the same size, this equation becomes, by numerical approximation,

$$\log[\mathrm{L}(\boldsymbol{\beta})] \doteq \sum_{t=1}^{R} \log[\omega_{jk}(t|\mathcal{F}_{t-};\boldsymbol{\beta})]\Delta N_t - \sum_{t=1}^{R} \omega_{jk}(t|\mathcal{F}_{t-};\boldsymbol{\beta})\mathrm{I}(t)\Delta_t$$

where Δ_t is the width of the tth observation interval and ΔN_t is the change in the count during that interval, with possible values zero and one.

This is the kernel of the log likelihood for the Poisson distribution of ΔN_t, with mean $\omega(t|\mathcal{F}_{t-};\boldsymbol{\beta})\Delta_t$.

Conditional on the filtration, it is the likelihood for a Poisson process.

4. Examples of intensity functions

Important simplifications occur when the intensity depends only on the complete history through N_t: $\omega_{jk}(t|N_t)$. Special cases include:

- the ordinary homogeneous *Poisson process*, with

  $$\omega(t|N_t) = \omega$$

  where the intensity is always the same (the only counting process with stationary independent increments);

- the *nonhomogeneous Poisson process*, with

  $$\omega(t|N_t) = \omega(t)$$

  where the intensity is a function of time;

- the *pure birth* or *Yule process*, with

$$\omega(t|N_t) = N_t\omega$$

where the intensity is proportional to the number of previous events;

- the *nonhomogeneous birth process*, with

$$\omega(t|N_t) = N_t\omega(t)$$

where the intensity, proportional to the number of previous events, is also a function of time;

- the *renewal process*, with

$$\omega(t|N_t) = \omega(t - t_{N_t})$$

where the intensity depends on the time since the last recurrent event, starting afresh after each event;

- the *semi-Markov* or *Markov renewal process*, with

$$\omega_{jk}(t|N_t) = \omega_{jk}(t - t_{N_t})$$

  where the form of the intensity function depends on the time since the last event, with the process changing state at each event.

Those processes with an intensity depending on time are non-stationary.

This dependence may be on the elapsed time, either total or since the previous event, or on the number of previous events, or both.

In more complex cases, it may also depend on other time-varying covariates.

5. Intensity and probability transition matrices

The intensity transition matrix, say $\mathbf{\Omega}(t)$, is a matrix with elements, $\omega_{jk}(t)$, the transition intensity from state j to state k, off diagonal and $-\sum_j \omega_{jk}(t)$ on diagonal.

Thus, rows sum to zero.

The probability transition matrix, say $\mathbf{T}(t)$, is a matrix with elements, $\pi_{jk}(t)$, the transition probability from state j to state k, including $\pi_{jj}(t)$.

Thus, rows sum to unity.

6. Transition probabilities

The transition probabilities can be found from the transition intensities.

They are defined as

$$\pi_{jk}(t-,t) = \mathsf{Pr}(Y_t = k | Y_{t-} = j, \mathcal{F}_{t-})$$

the probability of being in state k at time t given the previous history up until that time, including the previous state(s), the immediately preceding one being j.

These satisfy

$$\pi_{jk}(t_1,t_3) = \sum_l \pi_{jl}(t_1,t_2)\pi_{lk}(t_2,t_3)$$

for $t_1 \leq t_2 \leq t_3$.

They can be obtained from the set of differential equations,

$$\frac{d\mathbf{T}(t-,t)}{dt} = \mathbf{T}(t-,t)\mathbf{\Omega}(t)$$

where $\mathbf{T}(t-,t)$ is the matrix of transition probabilities, $\pi_{jk}(t-,t)$, to and from all possible states.

These are the forward recurrence equations.

They can only easily be solved for homogeneous Markov processes where none of the transition intensities either vary with time or depend on time-varying covariates.

Then, matrix exponentiation can be used, defined by

$$\mathrm{e}^{\mathbf{A}t} = \mathbf{I} + \frac{\mathbf{A}t}{1!} + \frac{(\mathbf{A}t)^2}{2!} + \cdots$$

However, a preferable way to calculate the exponential is by spectral decomposition.

If $\mathbf{V}$ is a column matrix of the eigenvectors of $\mathbf{A}$ and $\mathbf{D}$ is a diagonal matrix containing the corresponding eigenvalues, then

$$\mathbf{A} = \mathbf{V}\mathbf{D}\mathbf{V}^{-1}$$

and

$$\mathrm{e}^{\mathbf{A}t} = \mathbf{V}\mathrm{e}^{\mathbf{D}t}\mathbf{V}^{-1}$$

If the eigenvalues of $\mathbf{T}$ are all distinct, the solution will be of the form

$$\pi_{jk}(t_1, t_2) = \sum_l \beta_{jkl} \mathrm{e}^{-E_l(t_1 - t_2)}$$

where E_l are the eigenvalues.

In such cases,

$$\pi_{jk}(t_1, t_2) = \pi_{jk}(0, t_2 - t_1)$$

The boundary conditions are $\pi_{jj}(t, t) = 1$ and $\pi_{jk}(t, t) = 0$ for $j \neq k$.

Otherwise, polynomials will also be involved.

If there are inputs to the system, the set of linear differential equations for a strictly progressive model will be

$$\frac{d\boldsymbol{\pi}(t)}{dt} = \boldsymbol{\Omega}\boldsymbol{\pi}(t) + \mathbf{b}(t)$$

where $\boldsymbol{\pi}(t)$ is the vector of probabilities and $\mathbf{b}(t)$ defines the inputs.

The general solution is then

$$\boldsymbol{\pi}(t) = \boldsymbol{\pi}(0)\mathrm{e}^{\boldsymbol{\Omega}t} + \int_0^t \mathrm{e}^{\boldsymbol{\Omega}(t-u)}\mathbf{b}(u)du$$

where integration is component-wise.

Example

Suppose that an individual can move in either direction between healthy (1) and sick (2) states and can die (state 3) while in either other state i, with intensities, ω_i.

The intensity matrix is

$$\mathbf{\Omega} = \begin{pmatrix} -\omega_1 - \omega_{12} & \omega_{12} & \omega_1 \\ \omega_{21} & -\omega_2 - \omega_{21} & \omega_2 \\ 0 & 0 & 0 \end{pmatrix}$$

However, the absorbing death state 3 can be deleted without affecting the solution, yielding the intensity matrix

$$\mathbf{\Omega}^* = \begin{pmatrix} -\omega_1 - \omega_{12} & \omega_{12} \\ \omega_{21} & -\omega_2 - \omega_{21} \end{pmatrix} \qquad (1)$$

where ω_{ij} is the rate of transfer between states i and j and ω_i is the rate of output of state i from the system.

$\mathbf{\Omega}^*$ has eigenvalues, $E_i = -[\omega_1 + \omega_2 + \omega_{12} + \omega_{21} \pm \sqrt{(\omega_1 - \omega_2 + \omega_{12} - \omega_{21})^2 + 4\omega_{12}\omega_{21}}\,]/2$.

The entries of the matrix, $\exp(\mathbf{\Omega}^* t)$, are

$$\Omega^*_{11} = \frac{(E_1 + \omega_2 + \omega_{21})\mathrm{e}^{E_1 t} - (E_2 + \omega_2 + \omega_{21})\mathrm{e}^{E_2 t}}{E_1 - E_2}$$

$$\Omega^*_{22} = \frac{(E_1 + \omega_2 + \omega_{21})\mathrm{e}^{E_2 t} - (E_2 + \omega_2 + \omega_{21})\mathrm{e}^{E_1 t}}{E_1 - E_2}$$

$$\Omega^*_{12} = \frac{\omega_{12}(\mathrm{e}^{E_1 t} - \mathrm{e}^{E_2 t})}{E_1 - E_2}$$

$$\Omega^*_{21} = \frac{(E_1 + \omega_2 + \omega_{21})(E_2 + \omega_2 + \omega_{21})(\mathrm{e}^{E_2 t} - \mathrm{e}^{E_1 t})}{\omega_{12}(E_1 - E_2)}$$

Results such as these can be obtained from symbolic algebra computer programs or from standard texts on compartment models.

(A model in which the rows of the intensity matrix do not sum to zero, as for the two states here, is called defective because there is a net flow out of those two states.)

7. Epidemics: the SIR model

Suppose that a non-fatal infectious disease confers immunity upon recovery.

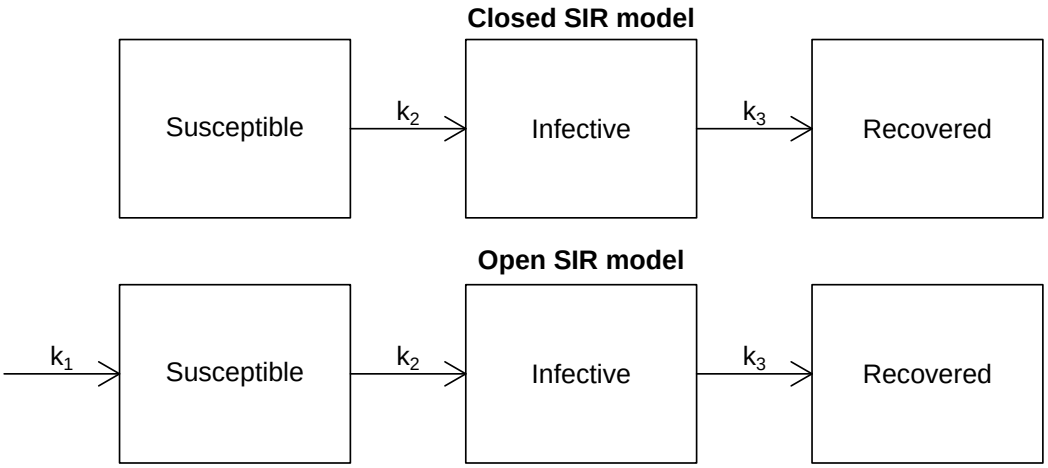
We can then divide a given population into three distinct categories:

1. susceptibles (S) who can catch the disease;

2. infectives (I) who have the disease and are contagious so that they can transmit it;

3. recovered (R), who have had the disease and are now immune.

The stages can then be described by a compartment model



This is called the (closed) SIR model.

Let us assume that

- the intensity (ω_{12}) of exit from the susceptible category and entry to the infective category is proportional to the present numbers of infectives and susceptibles;

- the intensity (ω_{23}) of exit from the infective category and entry to the recovered category is proportional to the present number of infectives;

- each category of people is uniformly mixed so that every pair of individuals has the same probability of meeting; and

- the population is of constant size.

Then, the model can be defined by the differential equations

$$\begin{aligned}
\frac{dS(t)}{dt} &= -\omega_{12} S(t) I(t) \\
\frac{dI(t)}{dt} &= \omega_{23} S(t) I(t) - \omega_{23} I(t) \\
\frac{dR(t)}{dt} &= \omega_{23} I(t)
\end{aligned}$$

with initial conditions, $S(0) = S_0 > 0$, $I(0) = I_0 > 0$, and $R(0) = 0$.

If $S_0 < \omega_{23}/\omega_{12}$, the infection eventually dies out and no epidemic occurs.

If the population is not closed so that susceptibles are born or can immigrate at the constant intensity ω_{01}, the stages are now given by the compartment model in the bottom panel.

The first equation becomes

$$\frac{dS(t)}{dt} = \omega_{01} - \omega_{12} S(t) I(t)$$

This is an open SIR model.

The system will reach an endemic level or equilibrium at $S_\infty = \omega_{23}/\omega_{12}$ and $I_\infty = \omega_{01}/\omega_{23}$, obtained by setting the above equations equal to zero.

However, with stochastic variability, there will be damped oscillations around the equilibrium starting after each disturbance.

If the deviations from the equilibrium values are small, the appropriate functions can be derived.

Generally, information is only available on infectives.

The resulting function will be

$$I(t) = I_\infty \left[1 + \kappa \mathrm{e}^{-t/(2\sigma)} \cos(\xi t)\right]$$

where $\sigma = \frac{\omega_{23}}{\omega_{12}\omega_{01}}$ and $\xi = \sqrt{\frac{\omega_{12}}{\sigma} - \frac{1}{4\sigma^2}}$.

The maximum magnitude of the oscillations from the equilibrium value is given by κ and the period by $2\pi/\xi$.

If the stochastic disturbances occur frequently enough, damping will not have had time to take effect, so that

$$I(t) = I_\infty \left[1 + \kappa \cos(\xi t)\right]$$

From this function, we can no longer obtain estimates of all three intensities because they now only relate to two parameters, I_∞ and ξ.

In both cases, oscillations are symmetric about I_∞.