Multi-state Models for Intermittently Observed Data

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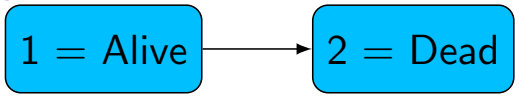
INSERM Workshop
Recent advances in statistical analysis of survival data

Contents

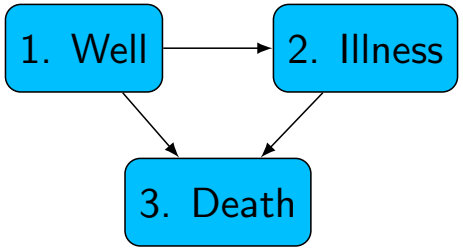
Examples of multi-state models

General discrete(finite)-state, continuous-time stochastic process

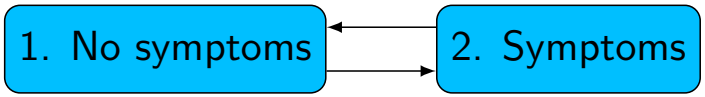
Survival model



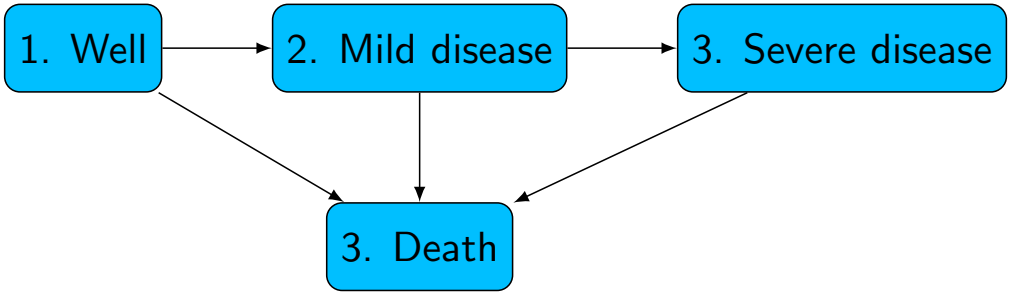
Illness-death model



Relapsing and remitting non-fatal condition



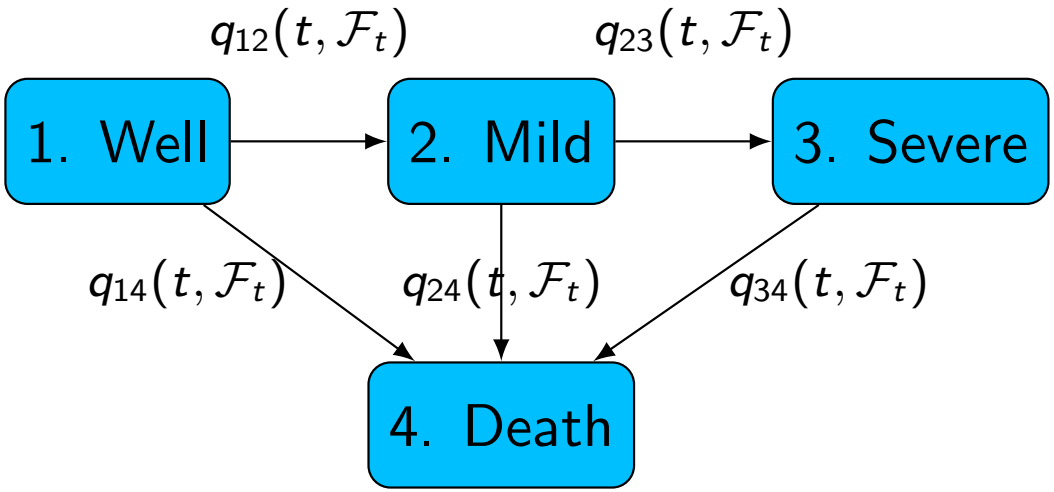
Staged disease progression model



- Many situations where we represent a disease as a multi-state process
- States chosen from clinical convention, or corresponding to measured data, though disease severity may be continuous

Contents

Transition intensities

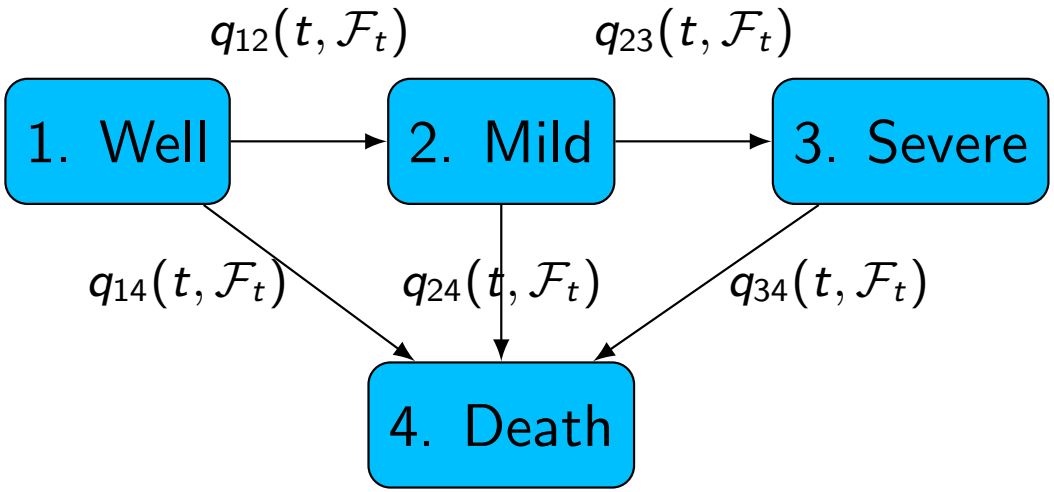


Multi-state models are fully specified by their transition intensities $q_{rs}(t, \mathcal{F}_t) : r \neq s, r, s = 1, ..., R$.
Rate of transition to state s for someone currently in state r.

$$q_{rs}(t; \mathcal{F}_t) = \lim_{\delta t \to 0} \frac{P(X(t + \delta t) = s | X(t) = r, \mathcal{F}_t)}{\delta t}, r \neq s, r, s = 1, ..., R$$

- Not a probability but a rate
- May depend on current time t and also the history $\mathcal{F}_t$

Transition intensities



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- Not a probability but a rate
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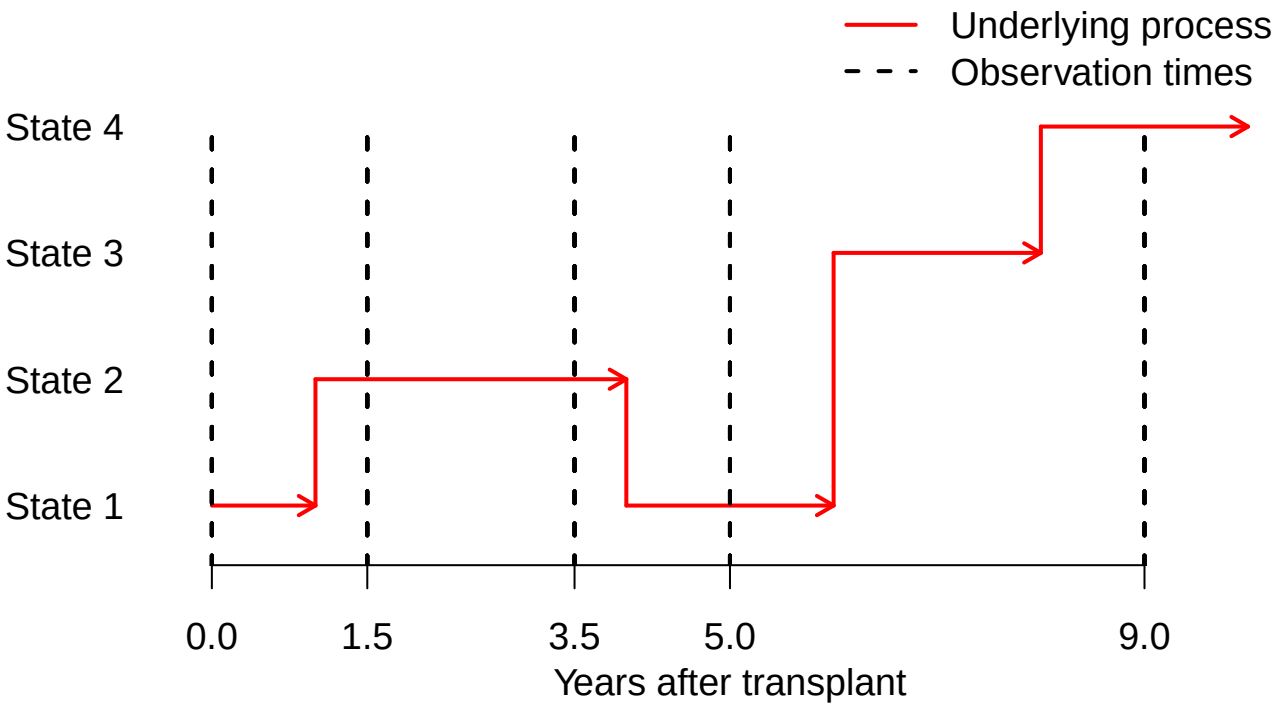
Context for this talk (previous sessions)

Previous talks dealt with fitting multi-state models to data where:

- we know the state at all times
- that is, the process is continuously observed
- Data can be represented as times to events
  - or times from one event to another
  - potentially with censoring
- Multi-state modelling methods can be constructed as generalisations of survival analysis.

Context for this talk



Instead, this talk will mainly deal with intermittently observed data

- Only know the state at a finite series of times

To be able to fit the models to data, first we'll need some more probability theory...

Contents

Markov processes

If $q_{rs}(t; \mathcal{F}_t) = q_{rs}(t)$ where t is time since start of process
i.e. no dependence on history $\mathcal{F}_t$:

- time spent in the current state
- states visited previously by the individual and time spent in them

then the process is a (continuous-time) Markov process, or Markov model

Extensive theory developed for continuous-time Markov models, e.g. textbooks

- Cox & Miller *Theory of Stochastic Processes*
- Norris *Markov Chains*
- Kulkarni *Modeling and Analysis of Stochastic Systems*

Other special cases and variants

Semi-Markov model $q_{rs}(t; \mathcal{F}_t)$ depends only on $\mathcal{F}_t$ through time since entered current state,

- Most general non-Markov model considered in this talk.

Time-homogeneous Markov model $q_{rs}(t; \mathcal{F}_t) = q_{rs}$

- transition rate is constant (over some time period)
- piecewise-constant models are important with intermittent observation...

Dependence on covariates $\mathbf{z}(t)$: $q_{rs}(\mathbf{z}(t); \mathcal{F}_t)$

- covariates could be constant or time-varying
- proportional hazards common
  $q_{rs}(\mathbf{z}(t); \mathcal{F}_t) = q_{rs}^{(0)}(t, \mathcal{F}_t) \exp(\beta' \mathbf{z}(t))$

Transition intensity matrix in a time-homogeneous Markov model

Transition intensity matrix $\mathbf{Q}$: r, s entry equals the intensity q_{rs}

$$\begin{bmatrix} \cdot & q_{12} & q_{13} & \cdots & q_{1n} \\ q_{21} & \cdot & q_{23} & \cdots & q_{2n} \\ q_{31} & q_{32} & \cdot & \cdots & q_{3n} \\ \vdots & & & \ddots & \vdots \end{bmatrix}$$

Additionally define the diagonal entries $q_{rr} = -\sum_{s \neq r} q_{rs}$, so that rows of Q sum to zero. Then we have:

- Sojourn time T_r (spent in state r before moving) has exponential distribution
  - rate $-q_{rr}$, i.e. mean $-1/q_{rr}$.
  - Pr(still in state r in t units' time) $P(T > t)$? $\exp(q_{rr} t)$
- Pr(next state is s | in r now)? $-q_{rs}/q_{rr} = q_{rs} / \sum_{j \neq r} q_{rj}$

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Transition probability matrix $P(t)$

Probability of being in some state at a specific time in the future

$$p_{rs}(t_0, t) = P(\text{state } s \text{ at time } t_0 + t \mid \text{state } r \text{ at time } t_0)$$

$P(t_0, t)$: matrix with r, s entry $p_{rs}(t_0, t)$, solves the Kolmogorov forward equation in terms of intensities $Q(t)$

$$\frac{dP(t_0, t)}{dt} = P(t_0, t)Q(t_0 + t) \quad \text{with} \quad P(t_0, t_0) = I$$

If Q is time-homogeneous over desired time interval

- where $Q(t) = Q$ and $p_{rs}(t_0, t) = p_{rs}(t)$ is independent of t_0
- explicit solution using the matrix exponential

$$P(t) = Exp(tQ) = \sum_{n=0}^{\infty} \frac{t^n}{n!} Q^n$$

(can be computed with specialised numerical methods, or element-wise solution for each $p_{rs}(t)$ for some simpler models)

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Time-varying transition intensities

Transition intensities $Q(t)$ commonly not constant with t .

If they can be modelled as piecewise constant

- Compute $P(t_0, t) = P(t_0, t_1)P(t_1, t_2) \dots P(t_{n-1}, t_0 + t)$ over n intervals where Q is constant

More generally if $Q(t)$ not constant, compute $P(t_0, t)$ by solving the Kolmogorov equation numerically

$$\frac{dP(t_0, t)}{dt} = P(t_0, t)Q(t + t_0) \quad \text{with} \quad P(t_0, t_0) = I$$

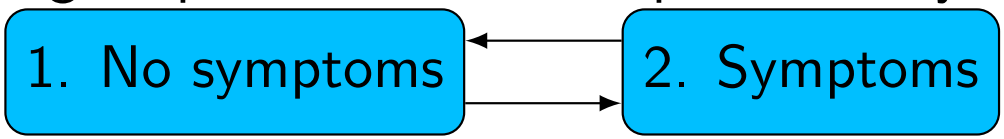
- e.g. Titman, Biometrics 67:780–7, 2011
- `deSolve` R package

Quantities of interest in a multi-state model

e.g. for person in state r at current time $t = 0$, total time they are expected to spend in state s before time t is

$$E\left\{\int_0^t I_{X(u)=s}\,du\right\} = \int_0^t p_{rs}(u)\,du$$

e.g. expected total time spent with symptoms over 10 years in



Other quantities of interest, e.g.

- expected first passage time (time to reach particular state)
- expected number of visits to a state

straightforward functions of transition probabilities or intensities.

van Loan (1978) IEEE Trans Automatic Control 23(3)395–404
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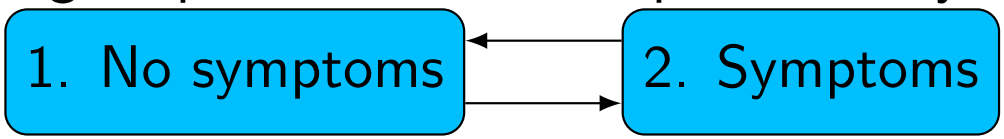

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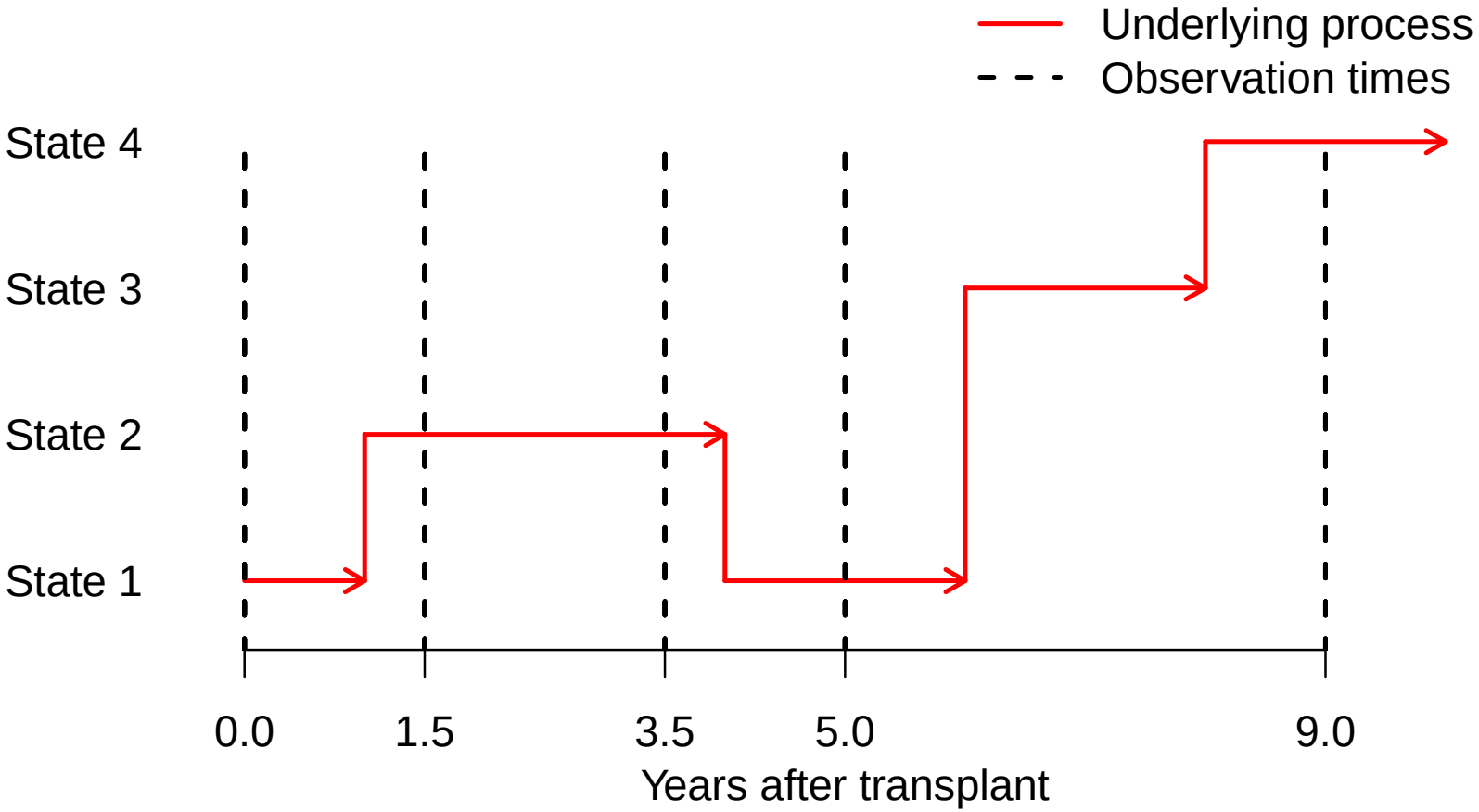
"Panel data" or intermittent observation



- For each patient $i = 1, \ldots, N$, only observe state at a finite series of times. Common in chronic disease modelling.

Likelihood for panel data

(Kalbfleisch and Lawless, JASA 1985)

- Data $\mathbf{x}$: states $(x_{i1}, \ldots, x_{in_i})$ at times $(t_{i1}, \ldots, t_{in_i})$ for person i
  Conditional on state at $t_{i0} = 0$ (e.g. $x_{i0} = 1$)
- Parameters: $\boldsymbol{\theta} = \{q_{rs}\}$: transition intensities of Markov model

Likelihood contribution for person i is product of transition probabilities

$$\begin{aligned} L_i(\boldsymbol{\theta}|\mathbf{x}_i) &= p(x_{i1}|x_{i0})p(x_{i2}|x_{i1})\ldots p(x_{in_i}|x_{i,n_i-1}) \\ &= \prod_{j=1}^{n_i} p_{x_{i,j-1},x_{ij}}(t_{i,j-1}, t_{ij}|\boldsymbol{\theta}) \end{aligned}$$

- Markov assumption $\rightarrow x_{i,j+1}|x_{i,j}$ indep. of $x_{i,1}\ldots x_{i,j-1}$
- Intensities constant within each interval $(t_{i,j-1}, t_{i,j})$: each transition probability is a closed form function of $\boldsymbol{\theta}$.

Maximum likelihood estimation

- Maximise the likelihood as a function of transition intensities (and covariate effects on these, see later)
- Then we can compute quantities of interest as functions of intensities:
  - transition probabilities
  - expected total time spent in a state
  - etc.... for different covariate values
- Confidence intervals can be computed by simulation, given the Hessian at the maximum likelihood
- All models from this section implemented in the `msm` package for R (see practical course in September)

Several variants of this basic data and model...

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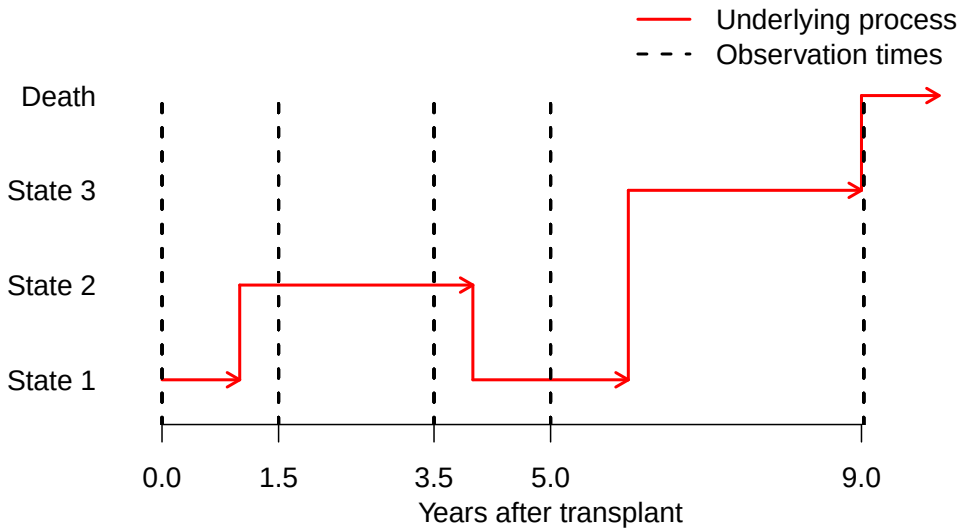
Panel data with exact death time observed



- For patients who die, day of death known, so assume death time known exactly, but state s at previous instant is unknown
- Get likelihood contribution for final time interval (t_{i,n_i-1}, t_{i,n_i}) by summing over "alive" states s:

$$\sum_s p_{r,s}(t_{in_i} - t_{i,n_i-1})q_{sD}, \qquad r = x_{i,n_i-1}$$

Data with all transition times known?

We could accumulate the likelihood from terms that look like

- P(move out of state r at a time t_{rs} after entering state r)
- P(this move is to state s)

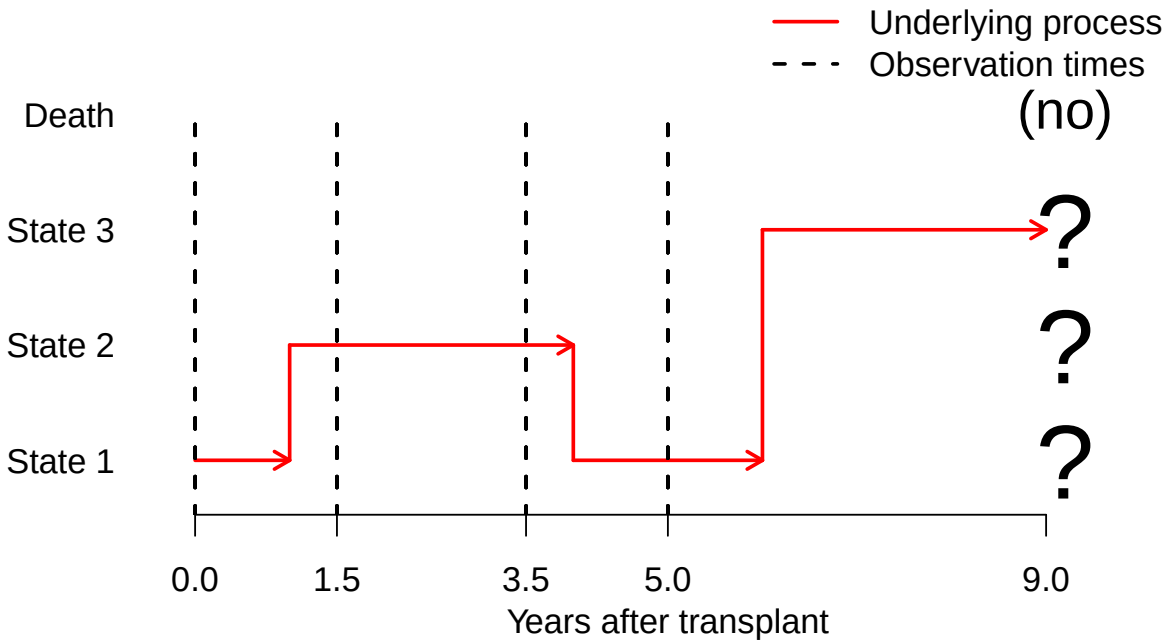
or equivalent formulations.

But these can be calculated easily from any parametric survival distribution — no need to assume piecewise-constant intensities

See framework from other talks based on survival modelling / competing risks ideas.

For fully-parametric modelling of this kind of data, see e.g. `flexsurv` R package, or Stata `multistate` package.

Likelihood with partially-known ("censored") state



- Suppose patient i known to be alive at final time t_{in_i}, but in an unknown disease state x_{in_i}
- Then likelihood contribution for the final transition is $\sum_{s \neq D} p_{r,s}(t_{in_i} - t_{i,n_i-1}) = 1 - p_{r,D}(t_{in_i} - t_{i,n_i-1}), \quad r = x_{i,n_i-1}$
- Generalises easily to partially-known intermediate states

Covariates

Intensities typically given log-linear model

$$q_{rs}(\mathbf{z}_i) = q_{rs}^{(0)} \exp\left(\sum_{m=1}^{M} \beta_m z_{ijm}\right)$$

- $\exp(\beta_m)$ is hazard ratio for mth covariate for ith individual's jth observation
- Covariates could be constant for all times j for individual i
- Any time-varying covariates assumed piecewise-constant:
  - Easiest if constant within each observation interval $(t_{i,j-1}, t_{i,j})$
  - Or if state unknown at a time when covariate changes: integrate over this state using "censored state" likelihood (previous slide)

Time-dependent transition intensities

Covariates could include time itself, giving a time-inhomogeneous model, e.g.

- as a categorical variable, with different intensity estimated for a series of time periods
- through a piecewise-constant approximation to a standard parametric hazard function, e.g. in

$$q_{rs}(\mathbf{z}_i) = q_{rs}^{(0)} \exp\left(\sum_{m=1}^{M} \beta_m z_{ijm}\right)$$

setting $\left.\begin{array}{lcl} z_{ijm} & = & log(t_{ij}) \\ z_{ijm} & = & t_{ij} \end{array}\right\}$ approximates a $\left\{\begin{array}{l} \text{Weibull} \\ \text{Gompertz} \end{array}\right.$ model for the time of transition from state r to s[1]

More general, non piecewise-constant models, possible in principle, though not in `msm` (would need numerical ODE solvers).

[1] van den Hout (2017) *Multi-State Survival Models for Interval-Censored Data*.

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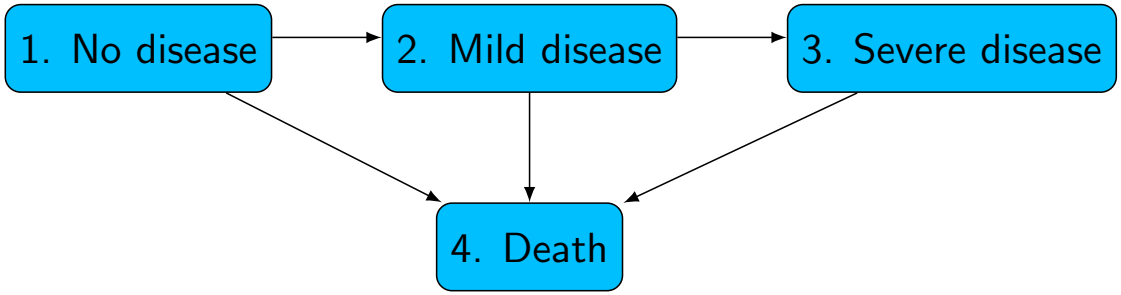
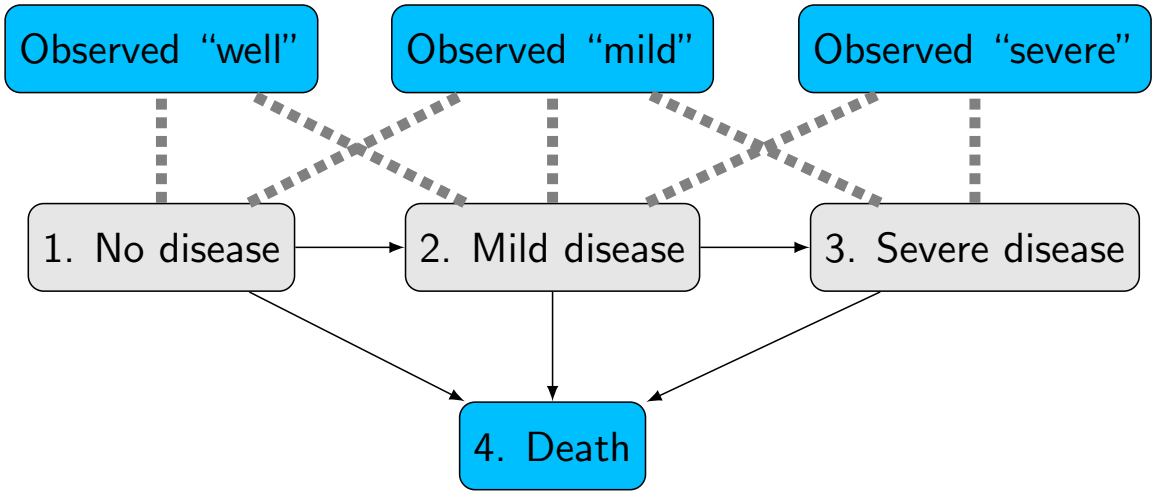
Hidden Markov models: misclassification of states



- What if disease is known to be an irreversible process...
- ...but transitions from worse to better states observed?
- Screening test may be subject to misclassification

Hidden Markov models: misclassification of states



e.g, could assume
$e_{13} = e_{31} = 0$

- What if disease is known to be an irreversible process...
- ...but transitions from worse to better states observed?
- Screening test may be subject to misclassification

Assume observed state $O(t)$ generated with error given true states $X(t)$

$$e_{rs} = P(O(t) = s | X(t) = r), \qquad e_{rr} = 1 - \sum_{s!=r} e_{rs}$$

True states follow a hidden multi-state model (e.g. hidden Markov)

Misclassification likelihood

Individual i, observed states O_{ij} at time t_{ij}, likelihood contribution is summed over all possible pathways through true states X

$$L_i = P(O_{i0}, \ldots, O_{in_i}) = \sum_{\{X\}} P(O_{i0}, \ldots, O_{in_i} | X_{i0}, \ldots, X_{in_i}) P(X_{i0}, \ldots, X_{in_i})$$

If the $O_{ij}|X_{ij}$ conditionally independent and true process is Markov

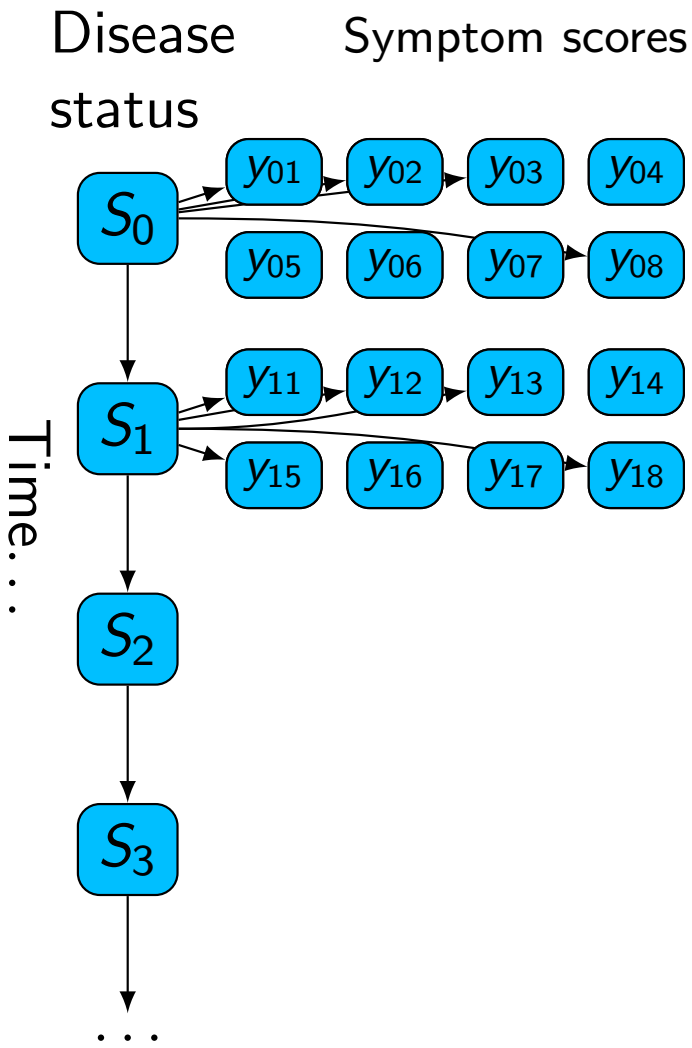
$$L_i = \sum_{X_{i0}} P(O_{i0}|X_{i0}) P(X_{i0}) \sum_{X_{i1}} P(O_{i1}|X_{i1}) P(X_{i1}|X_{i0}) \ldots \sum_{X_{in_i}} P(O_{in_i}|X_{in_i}) P(X_{in_i}|X_{i,n_i-1})$$

Maximise likelihood as a function of transition rates Q, misclassification probabilities $\mathbf{e}$, any covariate effects

- Initial true state probabilities $P(X_{i0})$ can also be estimated, or fixed. For example, could know $X_{i0} = 1$: everyone disease-free at start

Jackson et al (Statistician 2003), after Satten and Longini (Appl. Stat 1997),

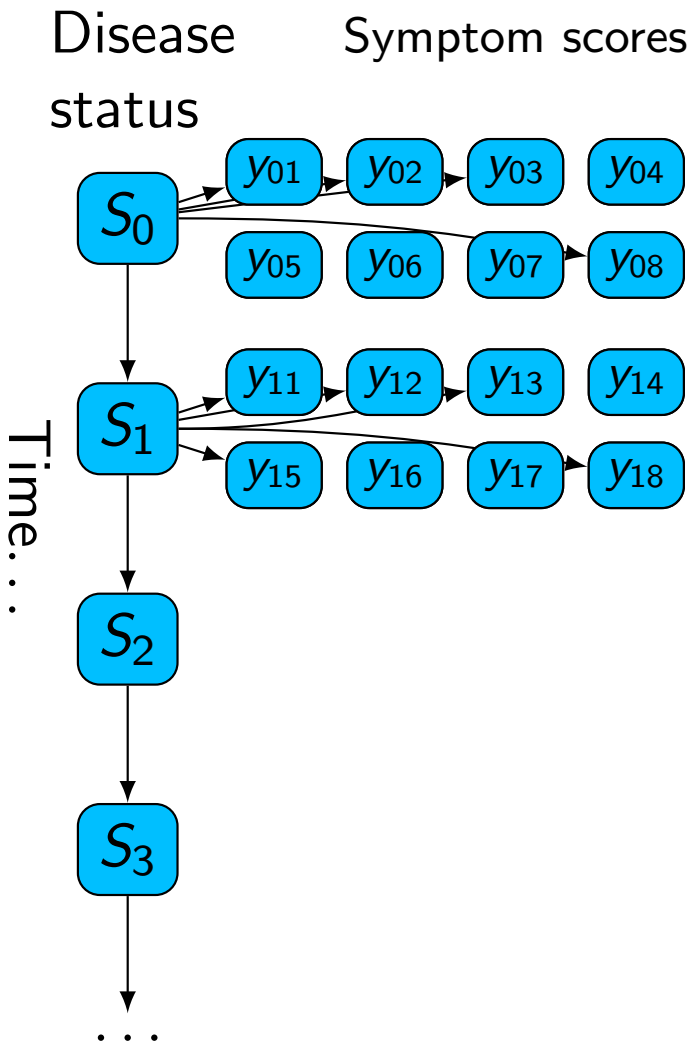
Hidden Markov model with any/multiple outcomes



- Clinical interest in a discrete, latent disease process
  - following a multi-state model
- Vector $\mathbf{y}_{ij}$ of observations, from each person i, at times j
  - e.g. multiple symptoms, biomarkers
- Specify joint distribution of $(\mathbf{y}_{ij}|S)$ for each potential hidden state S
- Likelihood similar to misclassification model
- Usually need constraints for identifiability
  - state known at some times
  - constraints on state-specific parameters

Satten and Longini (Appl. Stat 1997), Jackson and Sharples (Stat Med 2002) for HMM with general outcome
Jackson, Su, Gladman & Farewell (Arthritis Care and Research 2017) for multiple outcomes

Hidden Markov model with any/multiple outcomes



- Clinical interest in a discrete, latent disease process
  - following a multi-state model
- Vector $\mathbf{y}_{ij}$ of observations, from each person i, at times j
  - e.g. multiple symptoms, biomarkers
- Specify joint distribution of $(\mathbf{y}_{ij}|S)$ for each potential hidden state S
- Likelihood similar to misclassification model
- Usually need constraints for identifiability
  - state known at some times
  - constraints on state-specific parameters

Satten and Longini (Appl. Stat 1997), Jackson and Sharples (Stat Med 2002) for HMM with general outcome
Jackson, Su, Gladman & Farewell (Arthritis Care and Research 2017) for multiple outcomes

Contents

Semi-Markov models for intermittently-observed data

Markov models: transition rates independent of

- previous states visited
- time in current state

Semi-Markov models for intermittently-observed data

Semi-Markov models: transition rates

- depend on time in current state, but not previous states

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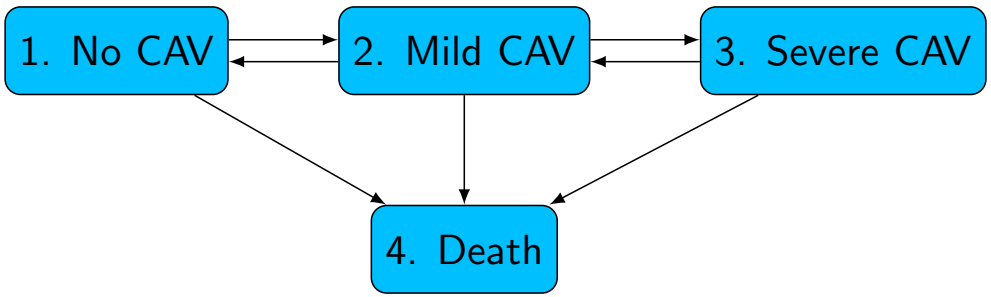
Semi-Markov models: transition rates

- depend on time in current state, but not previous states

Phase-type model

- E.g.: transition rate from state 2 depends on time spent there
- Replace state 2 by a series of hidden "phases".
- Expanded state structure follows a Markov process.



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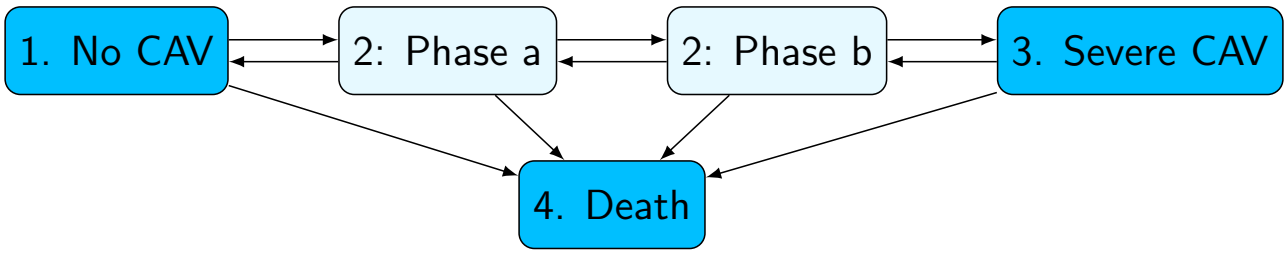

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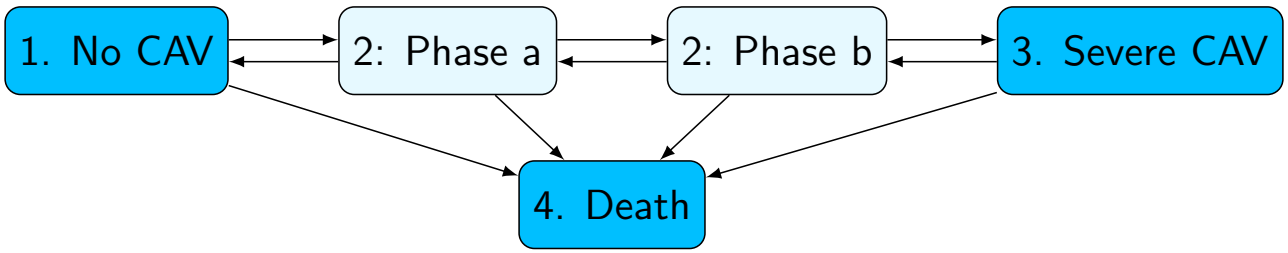


Likelihood the same as that for a hidden Markov model on the expanded state structure $\rightarrow$ can use `msm`.

- See Titman and Sharples (2010) Biometrics 66
- `phase.states` option to `msm()` function

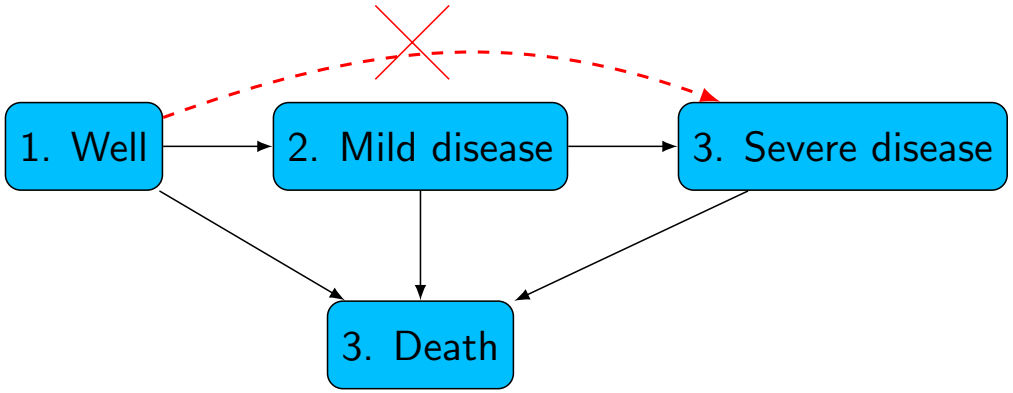
Practical concerns with modelling intermittent observations

It can be tempting to make the model too big

- $\rightarrow$ non-identifiable models, or flat/awkward likelihood function that can't be maximised.

Careful of, e.g.

- choice of state structure. If states are ordered (e.g. disease severity) should only allow transitions between adjacent states. Jumps not plausible in continuous time.



- if several covariates, affecting different transitions in different ways – may need to restrict/constrain effects.
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Random effects or hierarchical multi-state models

- "Frailties" shared between groups of individuals, or between different transition types within an individual
- Difficult to distinguish individual frailties from dependence on history (Cook & Lawless 2012)

Implementation and examples:

- Maximum marginal likelihood (e.g. O'Keeffe, Tom & Farewell, JRSSC 2011; Yiu, Farewell & Tom, JRSSC 2018; Cook et al, Biometrics 2004)
- Bayesian methods
  - See e.g. van den Hout, *Multi-state Survival Models for Interval Censored Data* CRC 2017
  - MCMC estimation
  - JAGS and Stan have matrix exponential, allowing general panel data likelihood

Other advanced models for intermittent data (b)

Informative observation times

- When data are observed intermittently, observation time may depend on status at that time
- Jointly model observation process and outcome process, e.g.
  - Lange et al., Biometrics 2015
  - Sweeting, Farewell & De Angelis, Stat. Med. 2010

Joint models for multistate and other longitudinal data

e.g.

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Model checking and comparison

(Titman & Sharples, "Model diagnostics for multi-state models" SMMR, 2010)

- Fit elaborated model with questionable assumption relaxed, then compare using e.g. likelihood ratio, AIC.
- Intermittent data makes it hard to check absolute fit
  - e.g compare fitted transition probabilities $p(t)$ to observed prevalence of a state at time t
  - what if not everyone measured at time t?
  - Current approaches `msm` use imputations/approximations of observed state
- If death times observed, could compare parametric estimates of survival against Kaplan-Meier estimates.
- Pearson-type goodness-of-fit tests have been proposed
  - low power, sensitive to how data grouped to construct the test
  - hard to interpret: what part of the model is most wrong?

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Multi-state models for aggregate data

Age	Disease prevalence	Mortality from disease
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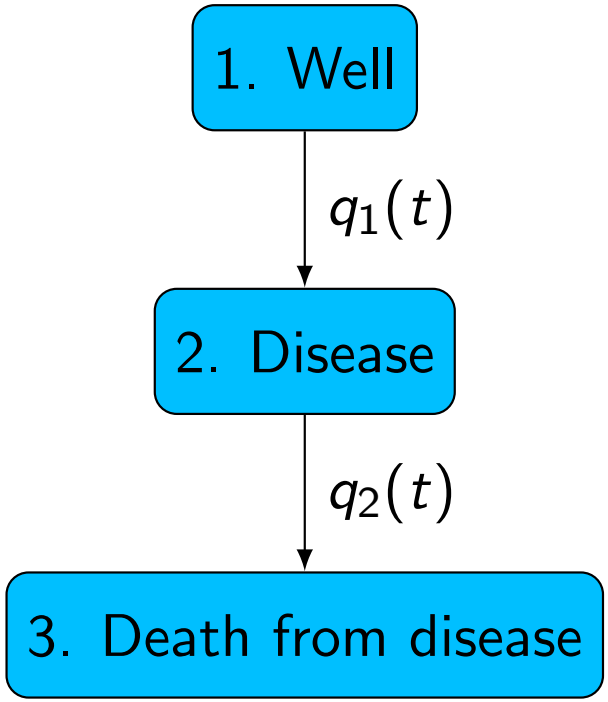
...		
40	r_1/n_1	s_1/m_1
45	r_2/n_2	s_2/m_2
50	r_3/n_3	s_3/m_3
...		



- Survey of n_i people by age i gives disease prevalence r_i/n_i
- Mortality data: s_i/m_i people die from disease at each age i
- Infer disease incidence $q_1(t)$ and case fatality $q_2(t)$

$$r_i \sim Bin(n_i, p_{12}(0, t_i)), \qquad s_i \sim Bin(m_i, p_{23}(t_{i-1}, t_i))$$

- $p_{rs}(.,.)$: transition probability from the multi-state model
  - function of $q_1(t), q_2(t)$ through Kolmogorov equation

(Ongoing work: `github.com/chjackson/disbayes`, Bayesian, in Stan)

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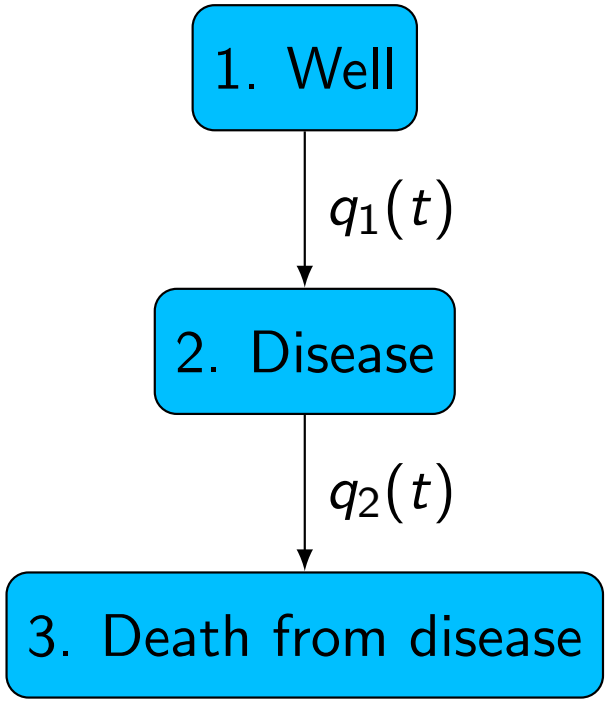

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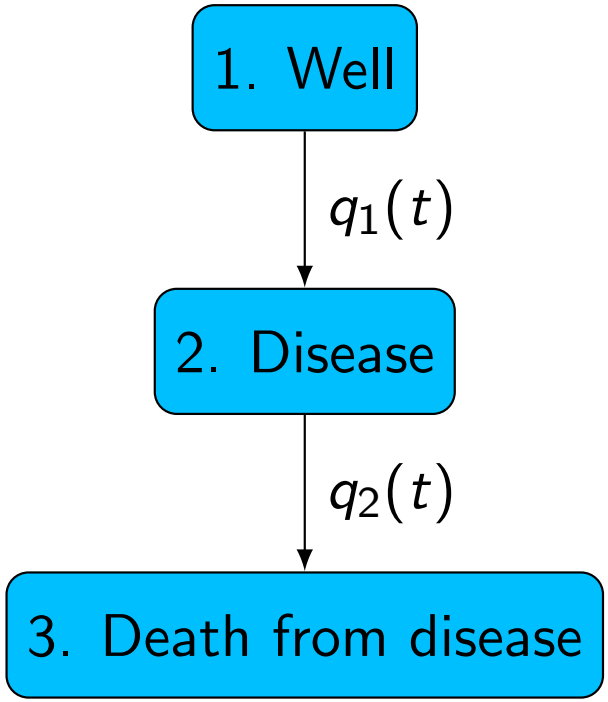

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- Cook, R. J., & Lawless, J. F. (2018). Multistate models for the analysis of life history data. CRC Press.
  Multi-state models for both continuously-observed and intermittently-observed data, mathematical detail, range of examples in medicine. Advanced topics, e.g. nonparametric methods, informative observation, random effects, mixture, hidden Markov models.
- Jackson, C. H. (2011). Multi-state models for panel data: the msm package for R. Journal of Statistical Software, 38(8), 1-29.
  Review of methods for intermittent observation and worked examples of implementing in R

See you in September, hopefully, for more about this package!

Thanks for listening!

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