Semi-Markov multi-state models for panel data

Making them accessible and stable

Christopher Jackson

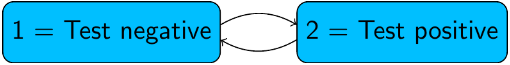
Symposium on Innovation in Multi-state Models, VU Amsterdam

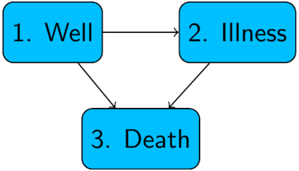
2025-10-17

MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Multi-state models





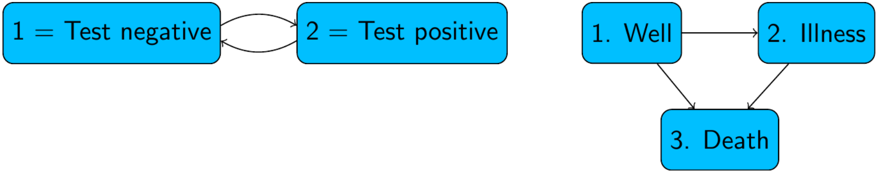
... or any other state and transition structure

Parameters: continuous-time models with transition intensities / rates / hazards
$q_{rs} = \exp(\beta_{rs}\mathbf{x})$, or $q_{rs}(t) = \exp(\beta_{rs}\mathbf{x}(\mathbf{t}))$

Estimate:, e.g.,

- expected time spent in a state (e.g. duration of an infection)
- probabilities of transition between states, over periods of time ...

Multi-state models



. . . or any other state and transition structure

Parameters: continuous-time models with transition intensities / rates / hazards
$q_{rs} = \exp(\beta_{rs}\mathbf{x})$, or $q_{rs}(t) = \exp(\beta_{rs}\mathbf{x}(\mathbf{t}))$

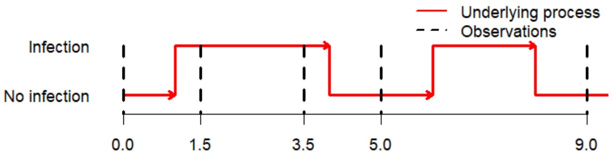
Estimate:, e.g.,

- expected time spent in a state (e.g. duration of an infection)
- probabilities of transition between states, over periods of time . . .

Data

Multi-state models get applied to a wide range of data structures

Continuous-time models, but intermittent observations: In our applications, we only know the state at a finite set of times — e.g. when person is tested for infection



Don't know transition times between states:

- e.g. when someone got the infection, when it cleared

Some infections may be completely unobserved for people in the data

Model estimation and challenges

Standard framework based on maximum likelihood estimation (Kalbfleisch and Lawless, JASA 1985) `msm` R package (CRAN, Jackson 2011 J. Stat. Soft.) widely used.

Consequences of intermittent observation:

Strong model assumptions

- Markov assumption: exponentially-distributed *sojourn* time (since state entry)
- Hazard is constant or piecewise-constant function of time (since start of process)

Estimation challenges:

- lots of parameters, hard to tell which are informed by data $\rightarrow$
- model fitting prone to non-convergence. "Is my model wrong for data, or can the estimation be tweaked until it works??"

Model estimation and challenges

Standard framework based on maximum likelihood estimation (Kalbfleisch and Lawless, JASA 1985) `msm` R package (CRAN, Jackson 2011 J. Stat. Soft.) widely used.

Consequences of intermittent observation:

Strong model assumptions

- Markov assumption: exponentially-distributed *sojourn* time (since state entry)
- Hazard is constant or piecewise-constant function of time (since start of process)

Estimation challenges:

- lots of parameters, hard to tell which are informed by data $\rightarrow$
- model fitting prone to non-convergence. "Is my model wrong for data, or can the estimation be tweaked until it works??"

Model estimation and challenges

Standard framework based on maximum likelihood estimation (Kalbfleisch and Lawless, JASA 1985) `msm` R package (CRAN, Jackson 2011 J. Stat. Soft.) widely used.

Consequences of intermittent observation:

Strong model assumptions

- Markov assumption: exponentially-distributed *sojourn* time (since state entry)
- Hazard is constant or piecewise-constant function of time (since start of process)

Estimation challenges:

- lots of parameters, hard to tell which are informed by data $\rightarrow$
- model fitting prone to non-convergence. "Is my model wrong for data, or can the estimation be tweaked until it works??"

Approaches to relaxing the Markov assumption

Integrate over unknown times of state entry to get likelihood (e.g. Wei and Kryscio (2016), Aastveit et al (2023), Akwiwu et al BMC Med Res Meth (2022))

- computation scales badly with more states and more unknown times
- does not generalise to cyclic structures.

Nonparametric approach (Gu et al, Biometrika 2024, JASA 2025)

- cyclic structures not supported, code not provided

Simulate pathways through states to approximate the likelihood (Aralis & Brookmeyer, SMMR (2019); Barone & Tancredi, Stat Med (2022)).

- MCMC or EM-type algorithm: needs custom software

Approaches to relaxing the Markov assumption

Integrate over unknown times of state entry to get likelihood (e.g. Wei and Kryscio (2016), Aastveit et al (2023), Akwiwu et al BMC Med Res Meth (2022))

- computation scales badly with more states and more unknown times
- does not generalise to cyclic structures.

Nonparametric approach (Gu et al, Biometrika 2024, JASA 2025)

- cyclic structures not supported, code not provided

Simulate pathways through states to approximate the likelihood (Aralis & Brookmeyer, SMMR (2019); Barone & Tancredi, Stat Med (2022)).

- MCMC or EM-type algorithm: needs custom software

Approaches to relaxing the Markov assumption

Integrate over unknown times of state entry to get likelihood (e.g. Wei and Kryscio (2016), Aastveit et al (2023), Akwiwu et al BMC Med Res Meth (2022))

- computation scales badly with more states and more unknown times
- does not generalise to cyclic structures.

Nonparametric approach (Gu et al, Biometrika 2024, JASA 2025)

- cyclic structures not supported, code not provided

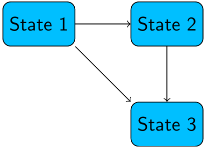
Simulate pathways through states to approximate the likelihood (Aralis & Brookmeyer, SMMR (2019); Barone & Tancredi, Stat Med (2022)).

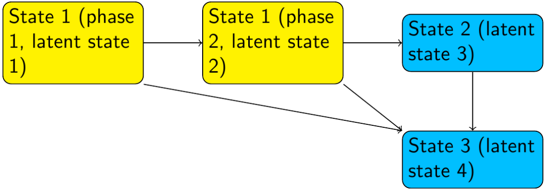
- MCMC or EM-type algorithm: needs custom software

Semi-Markov "phase-type" model

(Titman and Sharples Biometrics 2012).

Allows the rate of transition out of some state to change with the time spent in that state. Example:





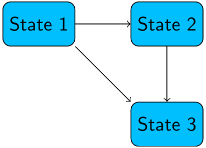
Replace an observable state (state 1 in this picture) with a set of latent states ("phases"). Latent states follow a Markov model

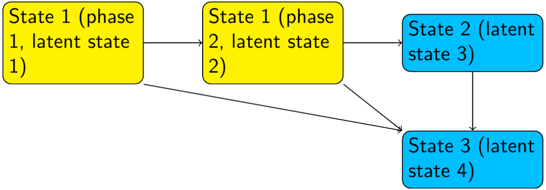
Hidden Markov model: hence likelihood calculation tractable. Sum over potential pathways among the S states, equivalent to a product (over observations) of $S \times S$ matrices

Semi-Markov "phase-type" model

(Titman and Sharples Biometrics 2012).

Allows the rate of transition out of some state to change with the time spent in that state. Example:





Replace an observable state (state 1 in this picture) with a set of latent states ("phases"). Latent states follow a Markov model

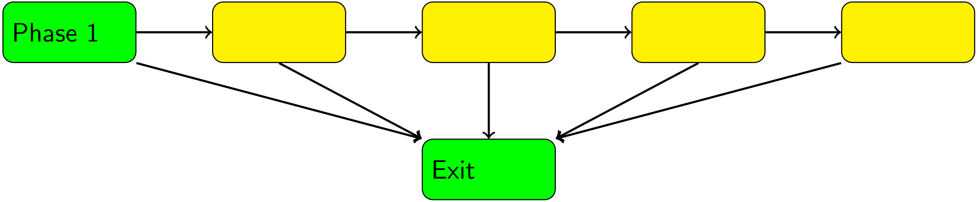
Hidden Markov model: hence likelihood calculation tractable. Sum over potential pathways among the S states, equivalent to a product (over observations) of $S \times S$ matrices

Phase-type sojourn distributions

In a Markov model, the sojourn time in every state is exponentially distributed

In this semi-Markov model, the sojourn time in some state follows a "phase-type" sojourn distribution

Time from entering state 1 to reaching the "Exit" state in a continuous-time Markov model structure like this:



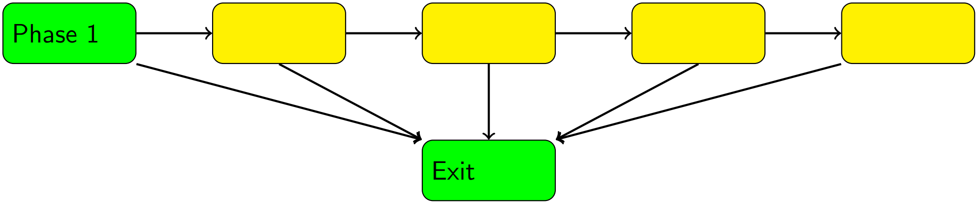
- More latent phases and transitions → more flexible sojourn distribution ... more estimation challenges, particularly with coarse data

Phase-type sojourn distributions

In a Markov model, the sojourn time in every state is exponentially distributed

In this semi-Markov model, the sojourn time in some state follows a “phase-type” sojourn distribution

Time from entering state 1 to reaching the “Exit” state in a continuous-time Markov model structure like this:



- More latent phases and transitions → more flexible sojourn distribution ... more estimation challenges, particularly with coarse data

Phase-type approximations to common distributions

Motivation:

- Want to fit a more stable / parsimonious distribution than the phase-type, e.g. Gamma, Weibull
- Hard to calculate likelihood of Gamma, Weibull directly
- Phase-type models infinitely flexible, can calculate their likelihood...

Approximate the Weibull or Gamma (shape a, scale b) with a phase-type family with rate $\boldsymbol{\lambda} = b\mathbf{h}(a)$ (Titman, Stat Comp 2014)

Phase-type approximations to common distributions

Motivation:

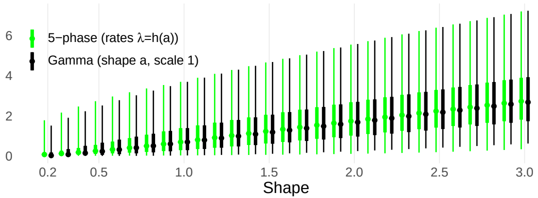
- Want to fit a more stable / parsimonious distribution than the phase-type, e.g. Gamma, Weibull
- Hard to calculate likelihood of Gamma, Weibull directly
- Phase-type models infinitely flexible, can calculate their likelihood...

Approximate the Weibull or Gamma (shape a, scale b) with a phase-type family with rate $\boldsymbol{\lambda} = b\mathbf{h}(a)$ (Titman, Stat Comp 2014)

Motivation:

- Want to fit a more stable / parsimonious distribution than the phase-type, e.g. Gamma, Weibull
- Hard to calculate likelihood of Gamma, Weibull directly
- Phase-type models infinitely flexible, can calculate their likelihood...

Approximate the Weibull or Gamma (shape a, scale b) with a phase-type family with rate $\boldsymbol{\lambda} = b\mathbf{h}(a)$ (Titman, Stat Comp 2014)



Find a function $\mathbf{h}()$ that maps shape a to parameters $\boldsymbol{\lambda}$ of best-matching phase type

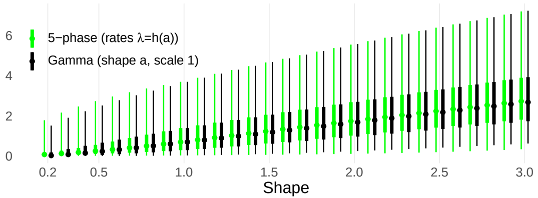
Lets us compute the likelihood as a function of a (and b, via scaling time t)

Phase-type approximations to common distributions

Motivation:

- Want to fit a more stable / parsimonious distribution than the phase-type, e.g. Gamma, Weibull
- Hard to calculate likelihood of Gamma, Weibull directly
- Phase-type models infinitely flexible, can calculate their likelihood...

Approximate the Weibull or Gamma (shape a, scale b) with a phase-type family with rate $\boldsymbol{\lambda} = b\mathbf{h}(a)$ (Titman, Stat Comp 2014)



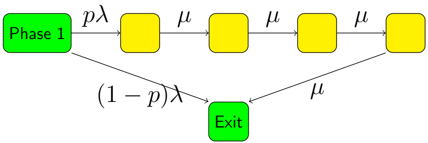
Find a function $\mathbf{h}()$ that maps shape a to parameters $\boldsymbol{\lambda}$ of best-matching phase type

Lets us compute the likelihood as a function of a (and b, via scaling time t)

Phase-type approximations by moment matching

Titman (2014) did a complicated spline fitting to find the mapping $h()$

Easier way: for phase-type distributions of this form, there is an analytic formula for λ, μ, p that give a particular mean, variance and skewness



(Bobbio et al. Stochastic Models 2005)

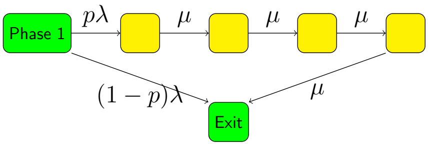
So to approximate Gamma (or Weibull), given shape and scale,

- Calculate first three moments of the Gamma (or Weibull)
- $\rightarrow$ determine matching phase parameters λ, p, μ

With more phases n, can match a wider range of the target distribution. Example...

Titman (2014) did a complicated spline fitting to find the mapping $h()$

Easier way: for phase-type distributions of this form, there is an analytic formula for λ, μ, p that give a particular mean, variance and skewness



(Bobbio et al. Stochastic Models 2005)

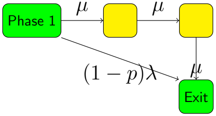
So to approximate Gamma (or Weibull), given shape and scale,

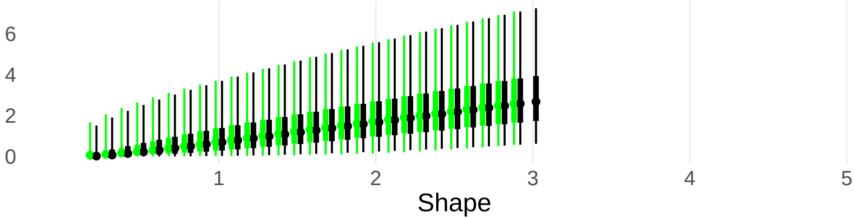
- Calculate first three moments of the Gamma (or Weibull)
- $\rightarrow$ determine matching phase parameters λ, p, μ

With more phases n, can match a wider range of the target distribution. Example...

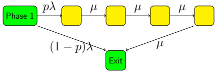
Example

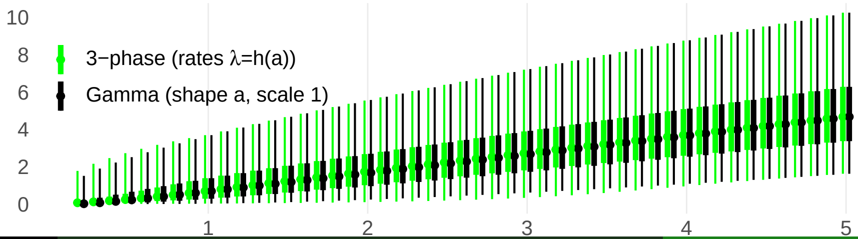
Gamma with shapes 0 to 3 can be moment-matched to 3-phase distributions





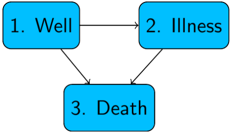
Gamma with shapes up to 5 can be moment-matched to 5-phase distributions

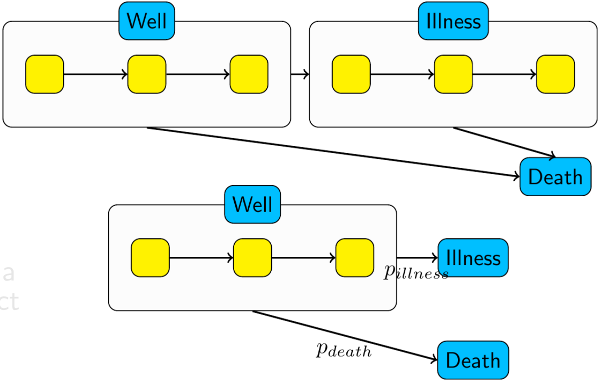




Building multi-state models with "phase-type" states

One or more states r can have a "phase-type approximation" sojourn distribution with shape a, scale b



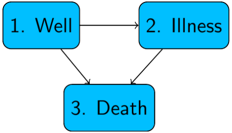


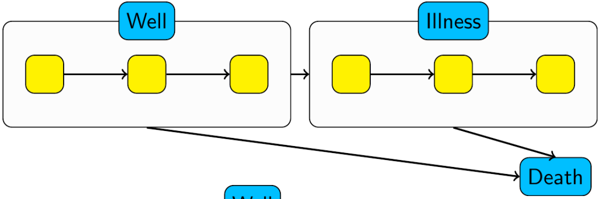
Covariates: can modify the scale b

Or if 2+ "competing risks" on leaving a "phase-type" state: covariates can affect probability of competing state (assumed independent of sojourn time)

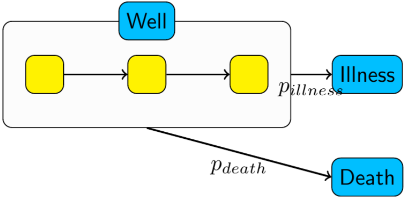
Building multi-state models with "phase-type" states

One or more states r can have a "phase-type approximation" sojourn distribution with shape a, scale b





Covariates: can modify the scale b



Or if 2+ "competing risks" on leaving a "phase-type" state: covariates can affect probability of competing state (assumed independent of sojourn time)

Computation

Bayesian inference, maximum likelihood or approximate Bayes (Laplace around posterior mode), using "off-the-shelf" algorithms in the **Stan** software

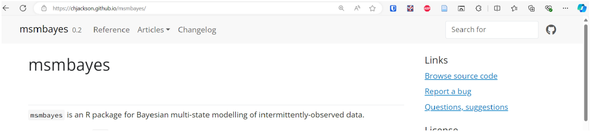
Identifiability/stability

- Weakly informative prior/penalty from background information recommended
- Pure MLE often fails with infrequently-observed data
- What if no information in data? Get posterior where all information comes from the prior. More useful than convergence failure

Scalability: With number of distinct covariate values / observation times, size of the latent state space...

msmbayes R package

Extends the `msm` package for Markov models to do Bayesian inference and phase-type semi-Markov models

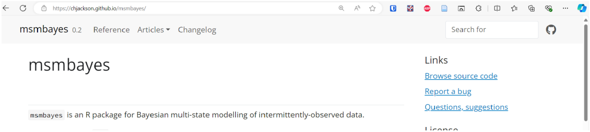


Familiar interface, like common R modelling packages

```
Q <- rbind(c(0, 1),
           c(1, 0)) # 2-state transition structure
priors <- list(
  msmprior("time(1,2)", median=10,  upper=30),
  msmprior("time(2,1)", median=0.5, upper=1)
)
mod <- msmbayes(data = infsim, state="state", time="months",
                subject="subject", qmatrix=q, priors=priors,...)
summary(mod)
```

msmbayes R package

Extends the `msm` package for Markov models to do Bayesian inference and phase-type semi-Markov models



Familiar interface, like common R modelling packages

```
Q <- rbind(c(0, 1),
           c(1, 0)) # 2-state transition structure
priors <- list(
  msmprior("time(1,2)", median=10,  upper=30),
  msmprior("time(2,1)", median=0.5, upper=1)
)
mod <- msmbayes(data = infsim, state="state", time="months",
                subject="subject", qmatrix=q, priors=priors,...)
summary(mod)
```

Simulation-based calibration study (as in Talts et al. 2018)

Assess correctness of Bayesian computation procedure:

- Simulate many datasets from prior predictive distribution
- Fit models to them: average of resulting posteriors should match the prior

Designed here around infection duration example (2 or 3-state).

Results:

- MCMC estimation accurate under a range of model structures, but slow
- Laplace approximation is mildly biased / underestimates uncertainty, but allows scalability

Simulation-based calibration study (as in Talts et al. 2018)

Assess correctness of Bayesian computation procedure:

- Simulate many datasets from prior predictive distribution
- Fit models to them: average of resulting posteriors should match the prior

Designed here around infection duration example (2 or 3-state).

Results:

- MCMC estimation accurate under a range of model structures, but slow
- Laplace approximation is mildly biased / underestimates uncertainty, but allows scalability

Computational stability and scalability

Stability

- `msm` did not converge in majority of simulated datasets due to weak identifiability
- Bayesian estimation always produced a valid posterior — strongly influenced by prior, but more helpful than "it didn't work".
- Phase-type shape-scale approximation works where fitting the phase-type distribution directly doesn't

Scalability

- expanding the state space makes likelihood harder, due to need to calculate matrix exponential.
- Stan "black-box" auto-differentiation particularly memory intensive here

Computational stability and scalability

Stability

- `msm` did not converge in majority of simulated datasets due to weak identifiability
- Bayesian estimation always produced a valid posterior — strongly influenced by prior, but more helpful than “it didn’t work”.
- Phase-type shape-scale approximation works where fitting the phase-type distribution directly doesn’t

Scalability

- expanding the state space makes likelihood harder, due to need to calculate matrix exponential.
- Stan “black-box” auto-differentiation particularly memory intensive here

Computational stability and scalability

Stability

- `msm` did not converge in majority of simulated datasets due to weak identifiability
- Bayesian estimation always produced a valid posterior — strongly influenced by prior, but more helpful than "it didn't work".
- Phase-type shape-scale approximation works where fitting the phase-type distribution directly doesn't

Scalability

- expanding the state space makes likelihood harder, due to need to calculate matrix exponential.
- Stan "black-box" auto-differentiation particularly memory intensive here

Applications

(a) Estimating infection duration and incidence

Cohort of people tested intermittently.
Start / end times of person's infection unknown.

(b) Cancer screening

No cancer → detectable precursor → clinical cancer ....
Incidence, time to progression not exponentially distributed.
Choose optimal screening interval. (e.g. Akwiwu et al. BMC Med Res Meth 2022)

(c) Cognitive function

Longitudinal studies of ageing, observations every 2 years.
Dynamics of decline in cognitive function, and mortality

Applications

(a) Estimating infection duration and incidence

Cohort of people tested intermittently.
Start / end times of person's infection unknown.

(b) Cancer screening

No cancer $\rightarrow$ detectable precursor $\rightarrow$ clinical cancer ....
Incidence, time to progression not exponentially distributed.
Choose optimal screening interval. (e.g. Akwiwu et al. BMC Med Res Meth 2022)

(c) Cognitive function

Longitudinal studies of ageing, observations every 2 years.
Dynamics of decline in cognitive function, and mortality

Applications

(a) Estimating infection duration and incidence

Cohort of people tested intermittently.
Start / end times of person's infection unknown.

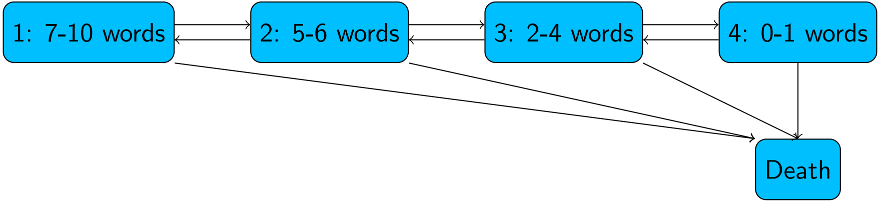
(b) Cancer screening

No cancer → detectable precursor → clinical cancer ....
Incidence, time to progression not exponentially distributed.
Choose optimal screening interval. (e.g. Akwiwu et al. BMC Med Res Meth 2022)

(c) Cognitive function

Longitudinal studies of ageing, observations every 2 years.
Dynamics of decline in cognitive function, and mortality

Realistically-complex illustrative application



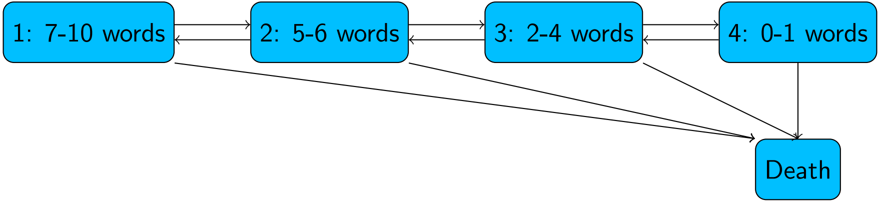
English Longitudinal Study of Ageing. Cognitive function test: how many words from a list of 10 recalled after a few minutes. $\approx$ 5000 observations from people aged 50+, every 2 years.

Semi-Markov model on all four states: 21 latent "phases"

Predictors of transitions: age, gender, education

MCMC not feasible for semi-Markov, use Laplace approximation to posterior

Realistically-complex illustrative application



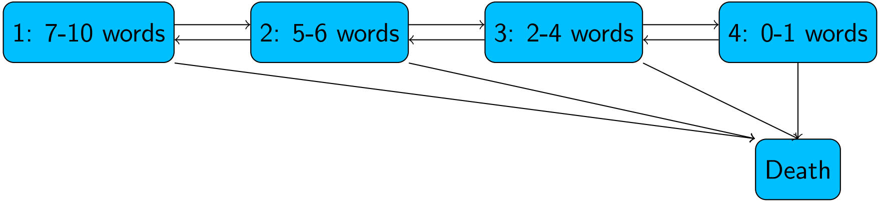
English Longitudinal Study of Ageing. Cognitive function test: how many words from a list of 10 recalled after a few minutes. $\approx$ 5000 observations from people aged 50+, every 2 years.

Semi-Markov model on all four states: 21 latent "phases"

Predictors of transitions: age, gender, education

MCMC not feasible for semi-Markov, use Laplace approximation to posterior

Realistically-complex illustrative application



English Longitudinal Study of Ageing. Cognitive function test: how many words from a list of 10 recalled after a few minutes. $\approx$ 5000 observations from people aged 50+, every 2 years.

Semi-Markov model on all four states: 21 latent “phases”

Predictors of transitions: age, gender, education

MCMC not feasible for semi-Markov, use Laplace approximation to posterior

Priors, model choice

- Strong priors on mortality rates from national statistics
- Markov model, specify judgements about mean sojourn time and hazard ratios: e.g. 95% credible interval (1/7, 7)
- Semi-Markov model: shape and scale of sojourn distribution, next-state probabilities?
  - Covariates affect both, so harder to give prior judgements
  - Ad hoc procedure of simulation/checking/modifying

Compare models via maximised log posterior — formal cross-validation / absolute goodness-of-fit challenging with intermittent data

Priors, model choice

- Strong priors on mortality rates from national statistics
- Markov model, specify judgements about mean sojourn time and hazard ratios: e.g. 95% credible interval (1/7, 7)
- Semi-Markov model: shape and scale of sojourn distribution, next-state probabilities?
  - Covariates affect both, so harder to give prior judgements
  - Ad hoc procedure of simulation/checking/modifying

Compare models via maximised log posterior — formal cross-validation / absolute goodness-of-fit challenging with intermittent data

Priors, model choice

- Strong priors on mortality rates from national statistics
- Markov model, specify judgements about mean sojourn time and hazard ratios: e.g. 95% credible interval (1/7, 7)
- Semi-Markov model: shape and scale of sojourn distribution, next-state probabilities?
  - Covariates affect both, so harder to give prior judgements
  - Ad hoc procedure of simulation/checking/modifying

Compare models via maximised log posterior — formal cross-validation / absolute goodness-of-fit challenging with intermittent data

Priors, model choice

- Strong priors on mortality rates from national statistics
- Markov model, specify judgements about mean sojourn time and hazard ratios: e.g. 95% credible interval (1/7, 7)
- Semi-Markov model: shape and scale of sojourn distribution, next-state probabilities?
  - Covariates affect both, so harder to give prior judgements
  - Ad hoc procedure of simulation/checking/modifying

Compare models via maximised log posterior — formal cross-validation / absolute goodness-of-fit challenging with intermittent data

Results

"Covariate effect parameters" hard to interpret. Instead:

Calculate expected total amount of time spent with no/mild cognitive impairment over next 10 years

Compare this between categories of one covariate (standardised over others)

Discussion

Made semi-Markov models for intermittently-observed data practicable

Software to make Bayesian inference in general Markov and semi-Markov models accessible

Challenges: computational scalability, prior specification, model checking, more practical experience...

`https://chjackson.github.io/msmbayes`

Paper on ArXiV linked from there, with full details of the studies described here