A discrete semi-Markov model for the effect of need-based treatments on the disease states

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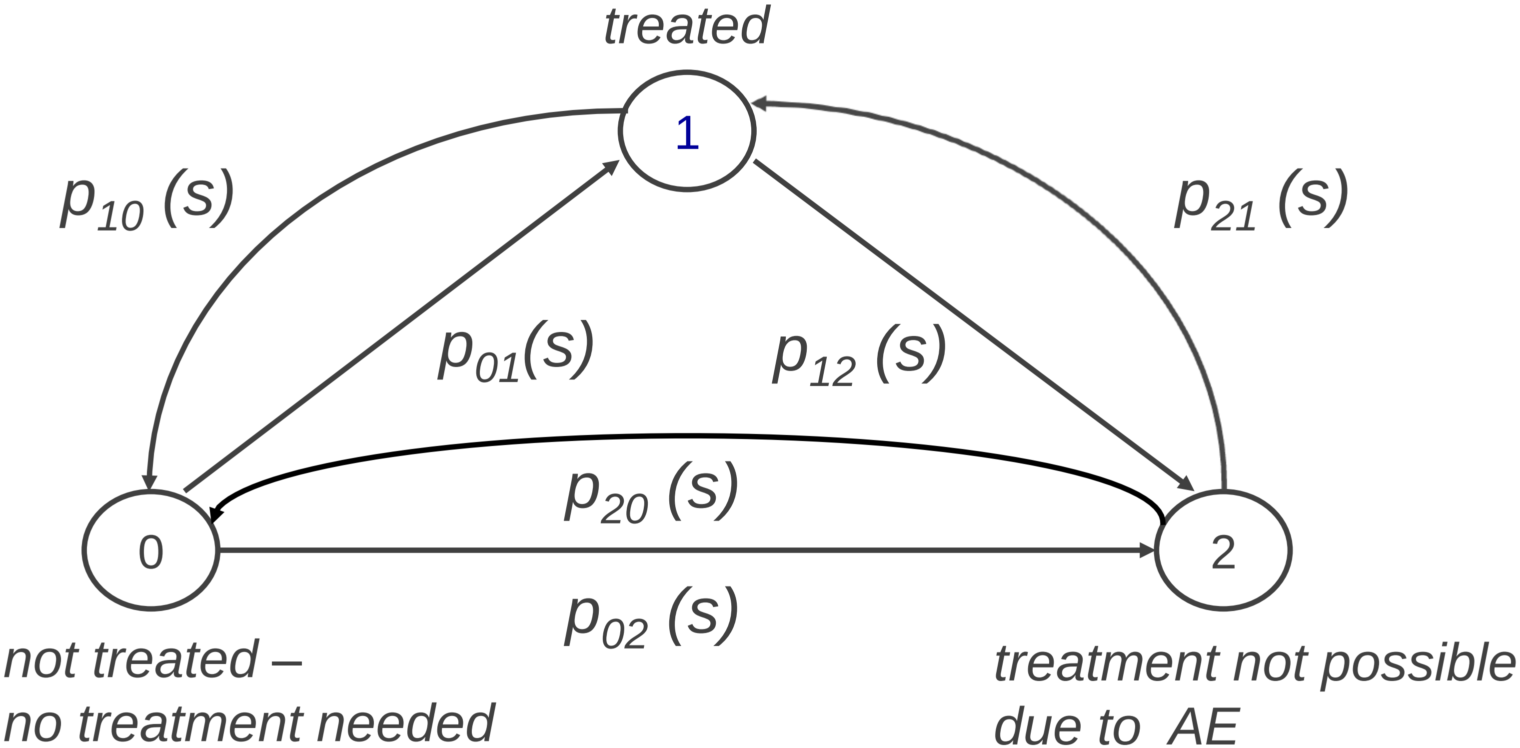
Agenda

1. Semi-Markov models
2. Layout of the analysed study
3. Quantities of interest from this model and how to calculate them
4. Application to study and experiences with implementation

Discrete semi-Markov model

- Transition Graph for a multi-state semi-Markov stochastic process
- Model the probabilities of outcomes



Application of this model to a clinical study

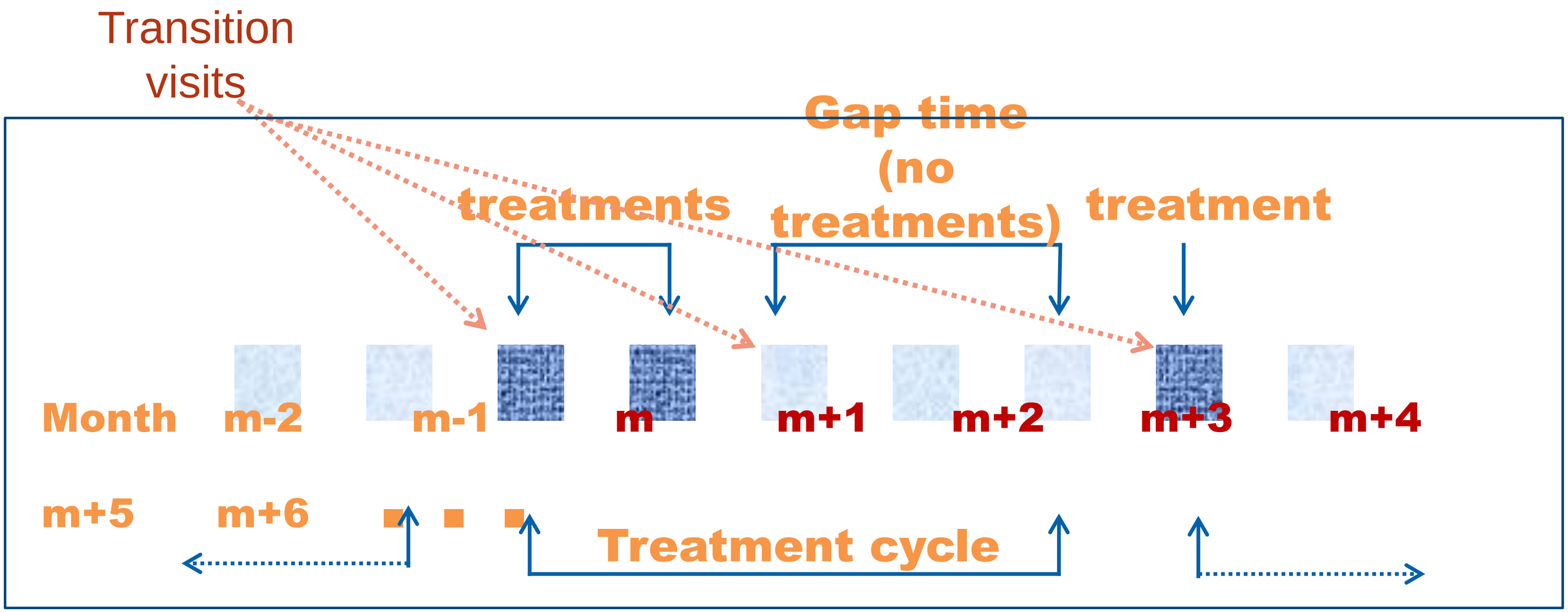
- Pro-re-nata ("as needed") treatment
- At every visit, decide if the patient needs / does not need or cannot tolerate treatment
- Design: double blind, active controlled
- Treatments = injections
  - 1: Experimental drug
  - 2: combination of experimental and standard treatment
  - 3: Standard treatment (active control)
- 12 scheduled monthly visits: <u>discrete time</u>
  - Baseline
  - 3 initiation treatment visits (treatment is given)
  - 9 treatment visits (treatment decision made based on need)

Potential quantities of interests

- Gap time between treatment episodes
- Expected number of consecutive treatments
- Expected length of a treatment cycle
- Probability of needing a treatment at each visit
- ...

Gap time and treatment cycles

Example of a patient history:



sojourn time = number of consecutive visits in a state

path = sequence of states a patient visits (e.g. 11012100...)

Model for transition probabilities

A natural model for this:

- Baseline logit model (e.g. Agresti, 2013): $logit(\mathbf{x}, s, s^*, t) = \log\left(\frac{p_{ss^*}(\mathbf{x},t)}{p_{ss}(\mathbf{x},t)}\right)$ models the probability of leaving state *s* after sojourn time *t* into state *s**≠ *s*
  x vector of additional covariates (treatment and others)
- Linear model for the logit of patient *i* with additional continuous covariate x_i :
- $\mu_{ss*} + \beta_{s2} \cdot I_i(trt = 2) + \beta_{s3} \cdot I_i(trt = 3) + \gamma_s \cdot t + \delta_s \cdot x_i$
- Effects of sojourn time *t* and covariate x_i linear on logit.
- *s** only influences parameter μ_{ss*}

Model for transition probabilities

- At every patient-visit (i, t), the distribution for the next state is multinomial $Mult\left(1, (p_{ss^*}(\mathbf{x}_i, t))_{s^*=0,1,2}\right)$
- We could have added a random effect for patient here (but we did not)
- Assuming that patients are stochastically independent, the loglikehood is easily written out.
- To avoid a positive probability of staying in a state forever, we imposed the additional model restriction $p_{ss^*}(\mathbf{x}_i, t) = p_{ss^*}(\mathbf{x}_i, 5)$ for $t \geq 5$.

Data

- 359 patients (119 / 124 / 116 per treatment)
- 3150 visits in total
- 2 visits off-schedule (treated as if on schedule)

Table of state by nextstate				
	nextstate			
state	0	1	2	Total
0	1110	246	5	1361
1	475	1222	21	1718
2	10	4	28	42
Total	1595	1472	54	3121
Frequency Missing = 29				

Additional assumptions

- Missed visits in a treatment-free period were assumed to be state 0 ("no treatment needed")
- All other missings were loss to follow-up
- These were assumed to be missing at random
  → patients contribute to the likelihood for as long as they are in the study
- Initially, every patient had 3 visits with injections
  → We modelled only from visit 4 onwards, assuming all patients are in state 1 ("under treatment") at visit 3 with sojourn time 3 (also gave the best fit among initial sojourn times 1 to 5)

Computer implementation

- Likelihood coded up in SAS PROC NLMIXED.
- Transition probabilities are written out into a dataset.
- Make a list of all transition paths in a year.
- Calculate the path probability for every possible path.
- Calculate quantities of interest from this.
- For confidence intervals: bootstrap this:
  1. Produce 1000 lists of the number of times every patient is represented in a bootstrap sample.
  2. Append to analysis dataset.
  3. Loop over boostrap samples using the number from 1. as a multiplier of the likelihood contribution of an individual patient in NLMIXED.

Quantities of interest calculated

- expected number of consecutive visits in every state (corresponds to expected sojourn time)
- median number of consecutive visits in every state (median sojourn time)
- expected number of injections in a year
- expected number of state switches in a year
- expected number of switches into "no treatment needed"

Quantities of interest calculated

- expected mean and median sojourn time do not require path probabilities:
  e.g. expected sojourn time in state 2:

$$E(T, \mathbf{x}) = \sum_{t=1}^{\infty} t \cdot (1 - p_{22}(\mathbf{x}, t)) \prod_{k=0}^{t-1} p_{22}(\mathbf{x}, k)$$

  has an explicit solution using the standard formulas for geometric and power series

- expected switches and visit numbers require path probabilities:
  e.g. expected number of injections in a year:

$$\sum_{t=1}^{12} E(W_t) \cdot P(X_t = 1, X_0 = 1)$$

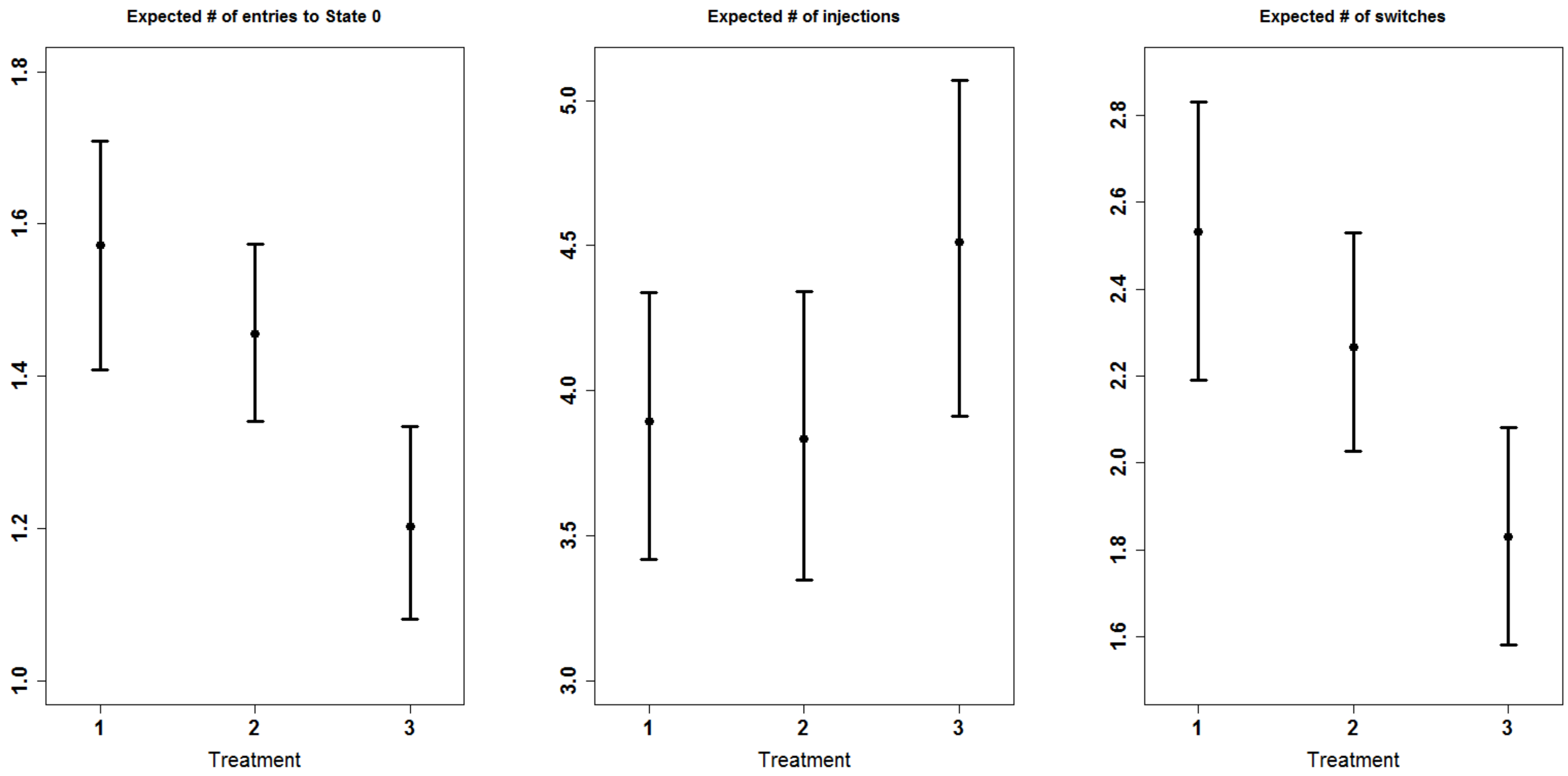
$E(W_i)$ expected dose at visit t if patient needs treatment,
$P(X_t = 1, X_0 = 1)$ sum of path probabilities

Experience from implementation

- Bootstrap worked quite well:
  less than 0.5% of bootstrap runs did not converge
  (most frequent reason: a predicted transition probability got too close to 0 or 1, leading to a parameter estimate converging to $+\infty$ or $-\infty$).
- A scenario with 1000 bootstrap samples takes approx. 2 hours on my laptop, <1 hour on the high-performance cluster
- NLMIXED takes practically all of that time, the rest (bootstrap sampling, calculating path probabilities, calculating quantities of interest) is negligible.

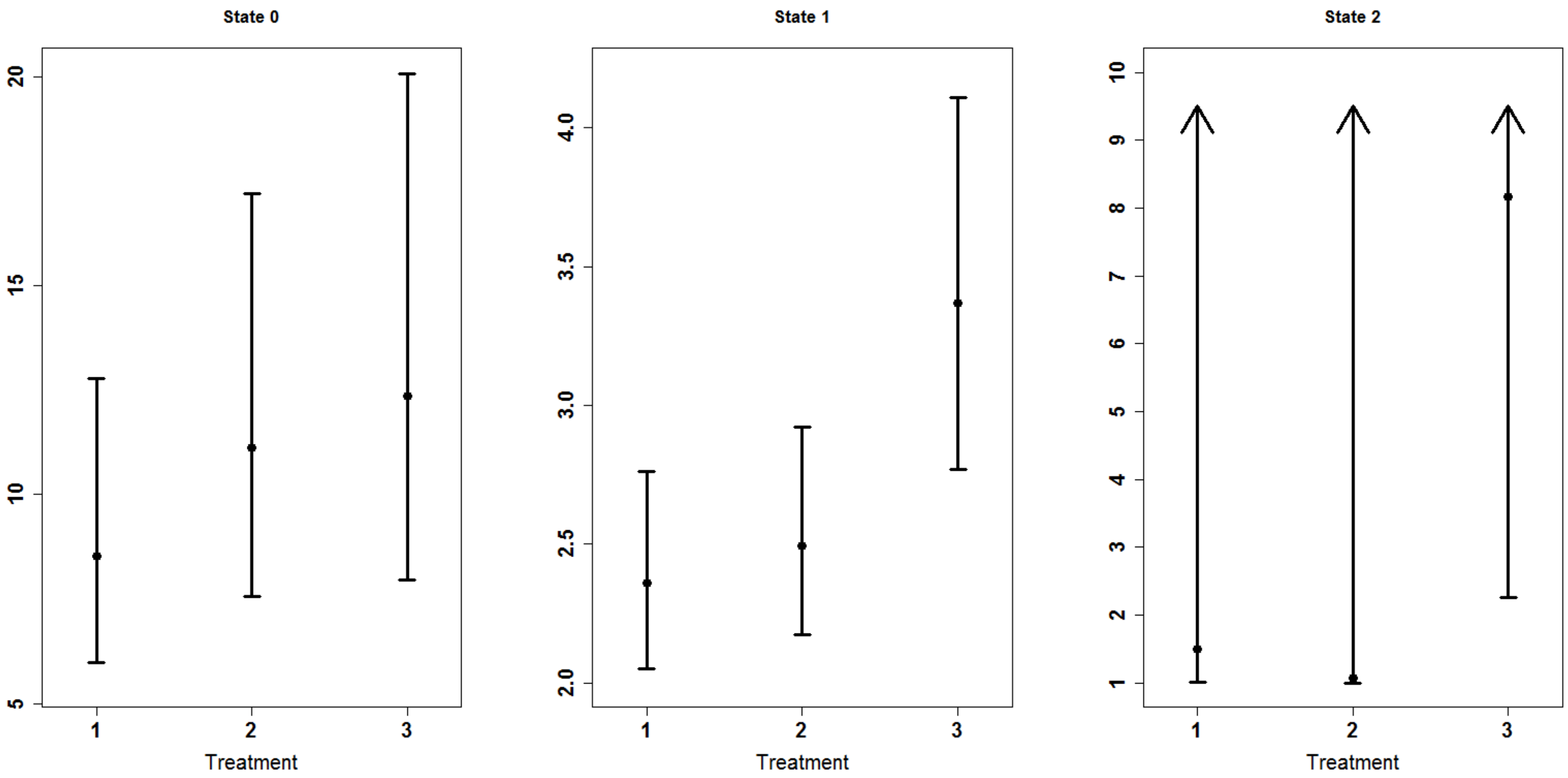
Results

Covariate value = 40



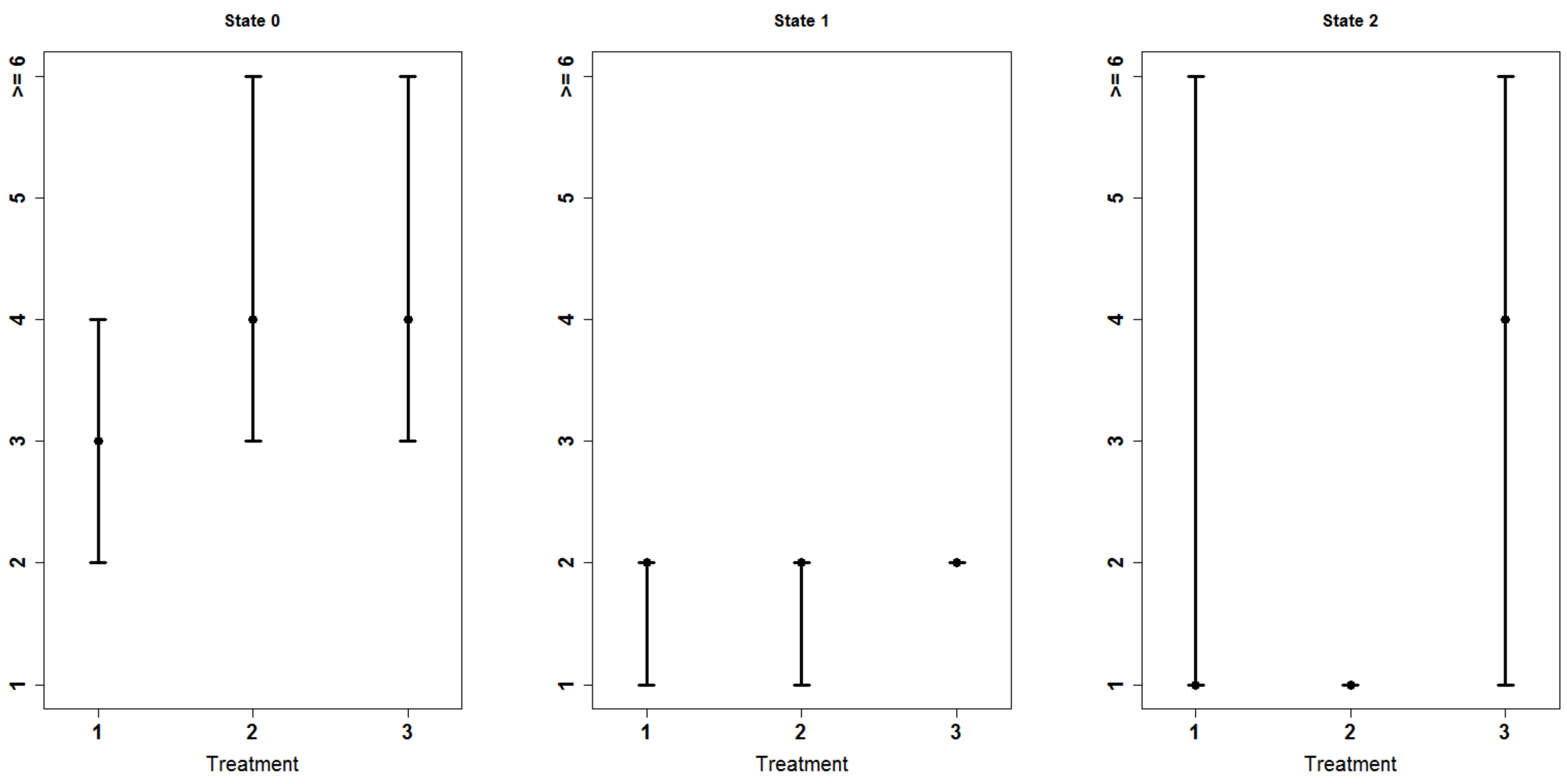
Results

expected sojourn times per state, covariate value = 40



Results

median sojourn times per state, covariate value = 40



Result interpretation

- Not much difference between treatment 1 and combination treatment 2
- Treatment 3 seems inferior by most measures (number of injections, reaching state 0), but not all (sojourn time in state 0)
- Looking at isolated aspects can be misleading:
  - E.g. number of injections is largest for treatment 3, but injection-free sojourn time is longest for treatment 3
- Caveat: The fact that all patients started in state 1 may bias the results, time series may not be long enough to eliminate the impact of starting value

Summary

- Multistate semi-Markov models offer a very flexible framework
- More versatile than modelling aspects like number of injections, recurrent events, ... in isolation
- computationally tractable, but still demanding
- This application was simplified by
  - (almost) no unscheduled visits
  - time frame of only 1 year
  - plausible reduction to three states possible

Thank you