Multistate Semi-Markov Modeling in R

Devin Incerti

October 3, 2020

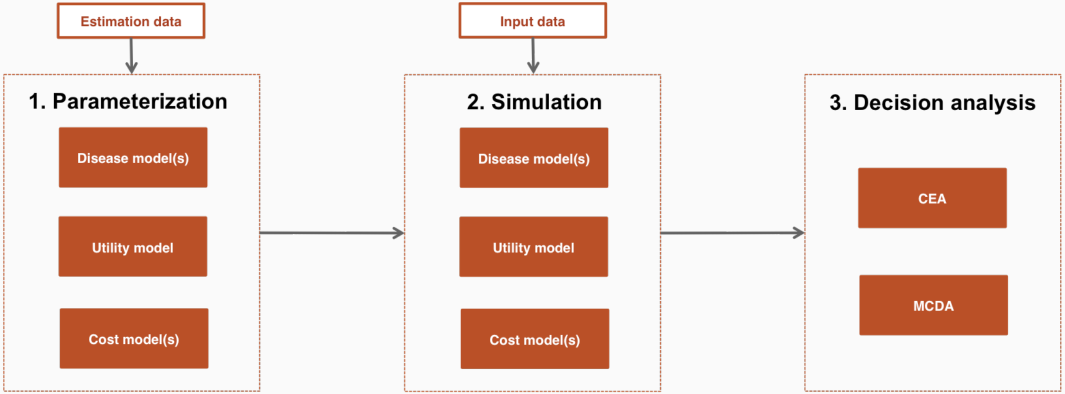
Introduction

- Markov models are the most commonly used models for economic evaluation of health technologies
- Due to the Markov assumption, it is not straightforward (requires tunnel states) to incorporate time dependency
- Semi-Markov models can model time dependency in a very flexible manner but require individual patient simulation, which is computationally expensive
- The `hesim` package provides a general framework for simulating semi-Markov models very quickly and using them to perform cost-effectiveness analysis (CEA)

What is `hesim`?

- A modular and computationally efficient `R` package for health economic simulation modeling and decision analysis that provides a general framework for integrating statistical analyses with economic evaluation
- Supports both cohort and **individual-level** state transition models
- Parameterized by fitting a statistical model (e.g., multi-state model) or creating a custom parameter object
- Nearly all simulation code written in `C++` under the hood

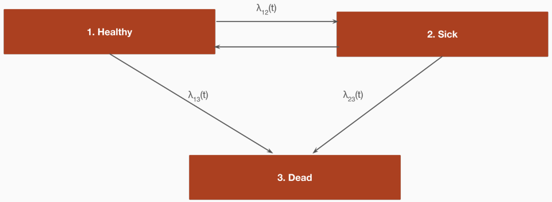
hesim integrates the entire modeling process



Parameterization with multi-state models

- Multi-state models can be used to parameterize the disease model
- Estimate hazard functions for each possible transition while properly accounting for censoring

Reversible illness death model

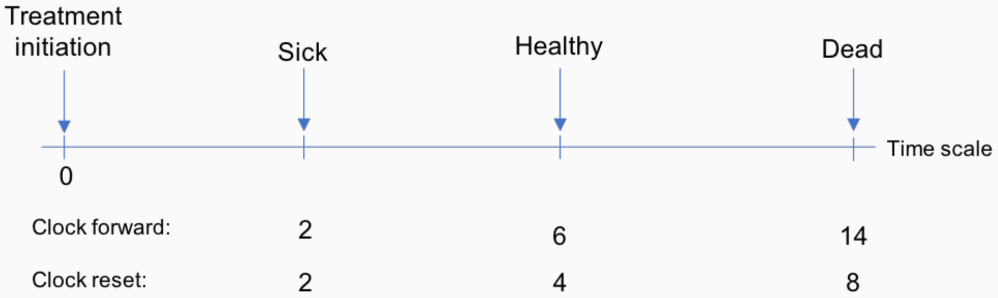


Fitting multi-state models in R

Statistical method	R package	Data
Parametric and spline models	flexsurv	Continuously observed processes
Non-parametric and semi-parametric models	mstate	Continuously observed processes
Exponential and piecewise exponential models	msm	Panel data
Multi-state network meta-analysis	rjags/rbugs/rstan	Summary data from RCTs

Timescales

- **Markov (i.e., "clock forward")** implies that the hazard function is based on time since entering the initial state
- **semi-Markov (i.e., "clock reset")** implies that the hazard function is based on time since entering each state (i.e., the clock resets to 0 after each transition)



Parameter estimation of clock-reset model with `flexsurv`

```r
for (i in 1:4)){ # 4 transitions in reversible illness-death model
  wei_fits_cr[[i]] <- flexsurvreg(Surv(years, status) ~ factor(strategy_id),
                                   data = mstate_data,
                                   subset = (trans == i),
                                   dist = "weibull")
}
wei_fits_cr <- flexsurvreg_list(wei_fits_cr)
```

Parameters in `hesim` can also be created without fitting a model in `R`

```r
transmod_params <- params_surv_list(
  # 1. Healthy -> Sick
  params_surv(coefs = list(rate = healthy_to_sick_rate),
              dist = "exp"),

  # 2. Healthy -> Dead
  params_surv(coefs = list(rate = healthy_to_dead_rate),
              dist = "exp"),

  # 3. Sick -> Dead
  params_surv(coefs = list(shape = sick_to_dead_shape,
                           scale = sick_to_dead_scale),
              dist = "weibullPH")
)
```

Simulating disease progression

- Individual patient simulation (IPS) is required to simulate clock-reset models; can also be used for clock-forward models
- IPS works by simulating trajectories through the multi-state model with random number generation for a large number of patients
- Purpose of IPS is to compute expected values, which is operationalized by averaging over a large number of simulatd patients

Individual patient simulation for multi-state models

- Simulate times to all competing health state and transition to state with smallest sampled time

Individual patient simulation for multi-state models

- Simulate times to all competing health state and transition to state with smallest sampled time
- In **clock-reset** models sampling can be performed using standard survival distributions; in a **clock-forward** model sampling must be performed from truncated distributions since time does not reset

Individual patient simulation for multi-state models

- Simulate times to all competing health state and transition to state with smallest sampled time
- Let’s consider a clock-reset simulation

Individual patient simulation for multi-state models

- Simulate times to all competing health state and transition to state with smallest sampled time
- Let's consider a clock-reset simulation

$$\begin{tikzcd}
& \text{Sick} \\
\text{Healthy} \arrow[ur, "3"] \arrow[dr, dash dot, "8"] & \\
& \text{Dead}
\end{tikzcd}$$

Individual patient simulation for multi-state models

- Simulate times to all competing health state and transition to state with smallest sampled time
- Let's consider a clock-reset simulation

$$\begin{tikzcd}
 & & \text{Dead} \\
 & \text{Sick} \arrow[ur, "4"] \arrow[dr, dashed, "5"] & \\
\text{Healthy} \arrow[ur, "3"] & & \text{Healthy}
\end{tikzcd}$$

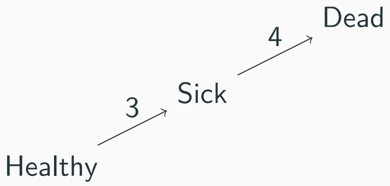
Individual patient simulation for multi-state models

- Simulate times to all competing health state and transition to state with smallest sampled time
- Let’s consider a clock-reset simulation

$$\begin{tikzcd} & & \text{Dead} \\ & \text{Sick} \arrow[ur, "4"] & \\ \text{Healthy} \arrow[ur, "3"] & & \end{tikzcd}$$

Individual patient simulation for multi-state models

- Simulate times to all competing health state and transition to state with smallest sampled time
- Let's consider a clock-reset simulation



- Patient transitions from (i) healthy to sick at year 3 and (ii) from sick to death at year 7

Computational efficiency

- `hesim` uses `C++` to vectorize over treatment strategies, patients, and PSA iterations.
- Simulation is very fast if efficient random number generation functions have been implemented in base `R` or a closed-form expression exists for the quantile function (all parametric distributions)
- If not (e.g., splines, fractional polynomials), simulation is slower. There are a couple of options:
    - Compute quantile function numerically and use inverse CDF method
    - Use discrete time approximation and sample from Bernoulli distribution

Simulating disease progression with `hesim`

```r
transmod_cr <- create_IndivCtstmTrans(wei_fits_cr, input_data,
                                      trans_mat = tmat, n = 1000,
                                      clock = "reset",
                                      start_age = patients$age)
econmod_cr <- IndivCtstm$new(trans_model = transmod_cr)
econmod_cr$sim_disease()
```

```
##    sample strategy_id patient_id grp_id from to final time_start  time_stop
## 1:      1           1          1      1    1  2     0  0.0000000  0.4426233
## 2:      1           1          1      1    2  1     0  0.4426233  0.8347335
## 3:      1           1          1      1    1  3     1  0.8347335 10.1059473
## 4:      1           1          2      1    1  3     1  0.0000000  2.3750032
## 5:      1           1          3      1    1  2     0  0.0000000  1.0297401
## 6:      1           1          3      1    2  1     0  1.0297401  5.1060423
```

Simulating costs and QALYs

- Costs and QALYs are computed using the continuous time present value given a flow of state values

$$\sum_{m=1}^{M} \int_{t_m}^{t_m+1} z_{hm} e^{-rt} dt = \sum_{m=1}^{M} z_{hm} \left(\frac{e^{-rt_m} - e^{-rt_{m+1}}}{r} \right)$$

- The present value for health state h, z_h, can be predicted from a statistical model or predefined; can vary by treatment strategy, patient, and/or time.
- IPS is advantageous because state values can reset (e.g., costs in oncology can depend on time in progressed state due to changes in chemotherapy cycles)

Parameterizing costs and QALYs with `hesim`

```r
utility_tbl <- stateval_tbl(
  data.table(state_id = c(1, 2),
             mean = c(1, .7),
             se = c(0, .2)),
  dist = "beta",
  hesim_data = hesim_dat)
```

```
##    state_id mean se
## 1:        1 1.0  0.0
## 2:        2 0.7  0.2
```

Simulating costs and QALYs and performing CEA with `hesim`

```r
# Construct utility and cost modes
utilitymod <- create_StateVals(utility_tbl, n = 1000)
econmod_cr <- IndivCtstm$new(trans_model = transmod_cr,
                             utility_model = utilitymod,
                             cost_models = costmods)

# Simulate cost and QALYs
econmod_cr$sim_qalys(dr = c(0,.03))
econmod_cr$sim_costs(dr = 0.03)

# Perform cost-effectiveness analysis
ce <- econmod_cr$summarize()
cea(ce, dr_qalys = .03, dr_costs = .03)
cea_pw(ce_sim, comparator = 1, dr_qalys = .03, dr_costs = .03)
```

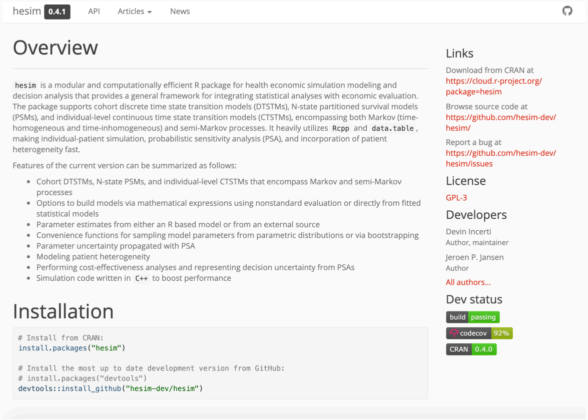
Speed tests

- Comparison of `$sim_disease()` to `mstate::mssample()` using Weibull 6-state model
  - 1,000 patients, 100 PSA iterations: `hesim`= .44 seconds, `mstate` = 34 minutes
  - 1,000 patients, 1,000 PSA iterations: `hesim` = 5 seconds, `mstate` = N/A
- Comparison of `hesim` IPS (1,000 patients) to `heemod` cohort model
  - 100 PSA iterations:
  - 1,000 PSA iterations:

What's next?

- Allow users to pass functions to update data as a function of simulation output after each transition
- Multi-state network meta-analysis
- Support for parallelization

https://hesim-dev.github.io/hesim/



Overview

`hesim` is a modular and computationally efficient R package for health economic simulation modeling and decision analysis that provides a general framework for integrating statistical analyses with economic evaluation. The package supports cohort discrete time state transition models (DTSTMs), N-state partitioned survival models (PSMs), and individual-level continuous time state transition models (CTSTMs), encompassing both Markov (time-homogeneous and time-inhomogeneous) and semi-Markov processes. It heavily utilizes `Rcpp` and `data.table`, making individual-patient simulation, probabilistic sensitivity analysis (PSA), and incorporation of patient heterogeneity fast.

Features of the current version can be summarized as follows:

- Cohort DTSTMs, N-state PSMs, and individual-level CTSTMs that encompass Markov and semi-Markov processes
- Options to build models via mathematical expressions using nonstandard evaluation or directly from fitted statistical models
- Parameter estimates from either an R based model or from an external source
- Convenience functions for sampling model parameters from parametric distributions or via bootstrapping
- Parameter uncertainty propagated with PSA
- Modeling patient heterogeneity
- Performing cost-effectiveness analyses and representing decision uncertainty from PSAs
- Simulation code written in `C++` to boost performance

Installation

```
# Install from CRAN:
install.packages("hesim")

# Install the most up to date development version from GitHub:
# install.packages("devtools")
devtools::install_github("hesim-dev/hesim")
```

Links

Download from CRAN at https://cloud.r-project.org/package=hesim

Browse source code at https://github.com/hesim-dev/hesim/

Report a bug at https://github.com/hesim-dev/hesim/issues

License

GPL-3

Developers

Devin Incerti
Author, maintainer

Jeroen P. Jansen
Author

All authors...

Dev status