

Multistate Semi-Markov Modeling in R

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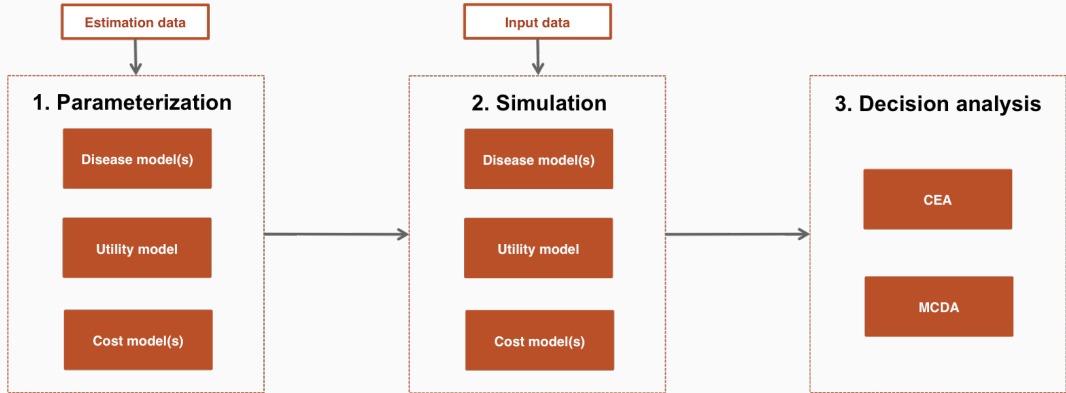
October 7, 2020

- 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 (IPS), 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 building simulation models for economic evaluation
- Supports both cohort and **individual-level** state transition models
- Parameterization 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

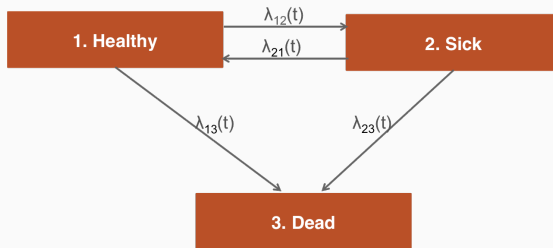
hesim integrates the entire modeling process



Parameterization with multi-state models

- Multi-state models can be used to parameterize a 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

```
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

```
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

- 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 is to compute expected values, which is operationalized by averaging over a large number of simulated 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

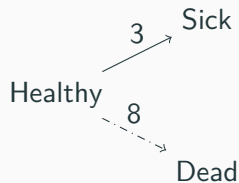
- Simulate times to all competing health state and transition to state with smallest sampled time
- In **clock-reset** models sampling can be performed using standard survival distributions; in a **clock-forward** model sampling must be performed from truncated distributions since time does not reset

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

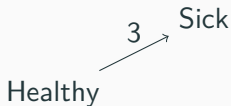
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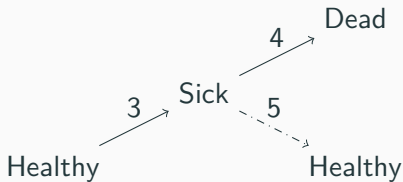
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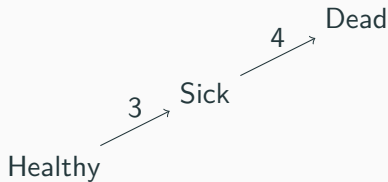
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Individual patient simulation for multi-state models

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- 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. Must either:
 - Compute quantile function numerically and use inverse CDF method
 - Use discrete time approximation and sample from Bernoulli distribution

Simulating disease progression with hesim

```
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      2  1  1      0  0.4426233  0.8347335  
## 3:      1             1           1      1  3  1      1  0.8347335 10.1059473  
## 4:      1             1           2      1  3  1      1  0.0000000  2.3750032  
## 5:      1             1           3      1  2  0      0  0.0000000  1.0297401  
## 6:      1             1           3      2  1  0      1  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

```
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

```
# Construct utility and cost models
```

```
utilitymod <- create_StateVals(utility_tbl, n = 1000)  
econmod_cr <- IndividCtstm$new(trans_model = transmod_cr,  
                              utility_model = utilitymod,  
                              cost_models = costmods)
```

```
# Simulate costs 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)
```

- **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 (60 annual cycles) used to model two treatment strategies with the time-inhomogeneous Markov model from the *Decision Modeling for Health Economic Evaluation* textbook
 - 1,000 PSA iterations: `hesim` = 9 seconds, `heemod` = 85 seconds ¹

¹Run time for an equivalent cohort model in `hesim` was ≈ 1 second.

Summary

- Semi-Markov models are flexible because they can track patient history; hazards, costs, and/or utility can all depend on time in state (not just model time)
- Although they can only be simulated in a general manner with IPS, `hesim` eliminates concerns about slow run times
- In addition to simulating disease progression, `hesim` can be used to (i) simulate cost/QALYs and (ii) perform CEA
- Some potential features to add: (i) function to update covariates during IPS, (ii) integration with multi-state network meta-analysis, and (iii) support for parallel computing.
- Learn more and see new updates at <https://hesim-dev.github.io/hesim/>