Multistate Semi-Markov Modeling in R

Devin Incerti

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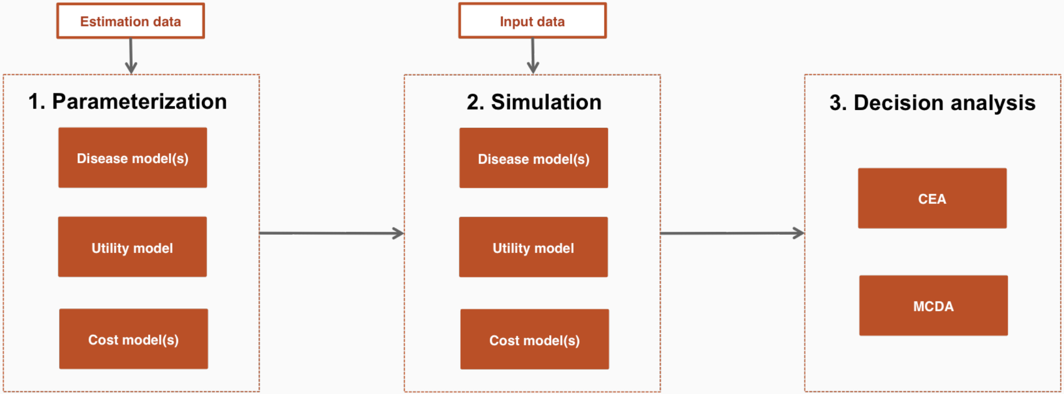
Introduction

- 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 (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

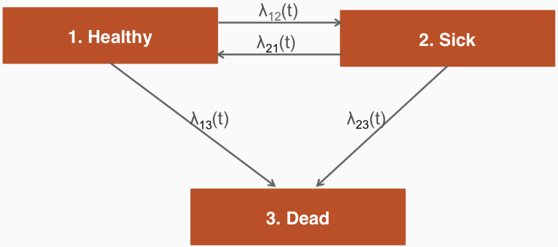
hesim integrates the entire modeling process



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

```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

- 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 samples must be drawn from truncated distributions since time does not reset

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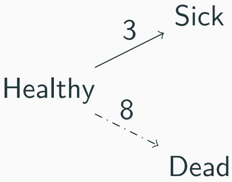

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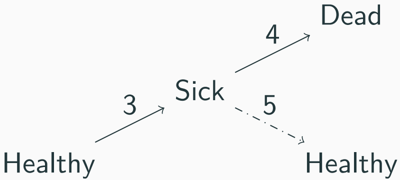

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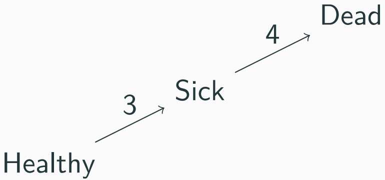

- Patient transitions from (i) healthy to sick at year 3 and (ii) sick to death at year 7

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

```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 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`

```r
# Construct cost and utility models
utilitymod <- create_StateVals(utility_tbl, n = 1000)
econmod_cr <- IndivCtstm$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)
```

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` individual-level (1,000 patients) to `heemod` cohort-level (60 annual cycles) when evaluating 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]

[1] Run 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/