hesim: Health Economic Simulation Modeling and Decision Analysis

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Abstract

Health economic models simulate the costs and effects of health technologies for use in health technology assessment (HTA) to inform efficient use of scarce resources. Models have historically been developed using spreadsheet software (e.g., Microsoft Excel) and while use of R is growing, general purpose modeling software is still limited. **hesim** helps fill this gap by facilitating parameterization, simulation, and analysis of economic models in an integrated manner. Supported model types include cohort discrete time state transition models (cDTSTMs), individual continuous time state transition models (iCTSTMs), and partitioned survival models (PSMs), encompassing Markov (time-homogeneous and time-inhomogeneous) and semi-Markov processes. A modular design based on **R6** and S3 classes allows users to combine separate submodels for disease progression, costs, and quality-adjusted life years (QALYs) in a flexible way. Probabilistic sensitivity analysis (PSA) is used to propagate uncertainty in model parameters to model outputs. Simulation code is written in C++ so complex simulations such as those combining PSA and individual simulation can be run much more quickly than previously possible. Decision analysis within a cost-effectiveness framework is performed using simulated costs and QALYs from a PSA.

Keywords: health economic evaluation, cost-effectiveness analysis, simulation, multi-state models, R.

1. Introduction

Health technology assessment (HTA) is a systematic approach for comparing competing health technologies to inform the efficient use of health care resources. Publicly funded health systems such as those in Australia, Canada, and the United Kingdom, among others, use HTA to help maximize health gains for the population given a fixed budget. HTA is also commonly used by private payers to guide coverage decisions and the adoption of new technologies (Trosman, Van Bebber, and Phillips 2011). Such assessments usually rely heavily on cost-effectiveness analysis (CEA) so that decisions can be made on the basis of a formal evaluation of costs and effects (Dakin, Devlin, Feng, Rice, O'Neill, and Parkin 2015). CEA is made feasible by development of health economic models that simulate costs and effects over relevant time horizons using the totality of available evidence.

The most commonly used economic models are Markov state transition models (STMs) that simulate transitions between mutually exclusive health states. When the Markov assumption holds so that transition probabilities are either constant over time or depend only on model

time, a cohort-level model can be used (Briggs and Sculpher 1998). If the Markov assumption is relaxed—e.g., with a semi-Markov model so that transition probabilities depend on time in an intermediate health state—then individual-level models are required in most cases (Brennan, Chick, and Davies 2006; Fiocco, Putter, and van Houwelingen 2008). Individual-level models afford considerably more flexibility and allow patient history to be tracked over time.

Decisions informed by economic models and CEA are subject to uncertainty. One source of decision uncertainty stems from uncertainty in the underlying model parameters. Parameter uncertainty is typically quantified using probabilistic sensitivity analysis (PSA), which involves randomly sampling the model parameters from suitable probability distribution and simulating the model for each sampled parameter set (Claxton, Sculpher, McCabe, Briggs, Akehurst, Buxton, Brazier, and O'Hagan 2005). When combined with individual-level simulation, PSA can take an appreciable amount of time to run (O'Hagan, Stevenson, and Madan 2007).

Estimation of model parameters should ideally be performed using statistical models that are aligned with the structure of the economic model. For instance, when patient-level data is available, a multi-state model can be used to parameterize all possible transitions in a STM while accounting for censoring and competing risks (Williams, Lewsey, Briggs, and Mackay 2017). Similarly, in oncology, partitioned survival models (PSMs) can be parameterized from estimates of progression-free survival (PFS) and overall survival (OS). In other cases, parameters might be combined from disparate sources, such as within a single Bayesian model (Baio 2012). When the clinical evidence base is not limited to a single study, a formal evidence synthesis, such as a network-meta analysis (NMA), might even be performed (Dias, Ades, Welton, Jansen, and Sutton 2018).

Despite their computational demands and foundations in statistics, health economic models have historically been developed with specialized commercial software (e.g., TreeAge) or more commonly with a spreadsheet (almost always Microsoft Excel). The limitations of such software relative to programming languages like R have been increasingly emphasized in the literature (Baio and Heath 2017; Incerti, Thom, Baio, and Jansen 2019; Jalal, Pechlivanoglou, Krijkamp, Alarid-Escudero, Enns, and Hunink 2017). It is therefore no surprise that a number of related R packages have recently been developed, such as **BCEA** (Baio, Berardi, and Heath 2017), **SAVI** (Strong, Oakley, and Brennan 2014), **survHE** (Baio 2020), and **heemod** (Filipović-Pierucci, Zarca, and Durand-Zaleski 2017). Still, of the available packages, only **heemod** provides a general purpose framework for developing simulation models and it is limited to cohort Markov models.

hesim is an R package that advances the functionality and performance of the existing software. Multiple model types are supported including cohort discrete time state transition models (DTSTMs), N-state PSMs, and individual-level continuous time state transition models (CTSTMs), encompassing both Markov (time-homogeneous and time-inhomogeneous) and semi-Markov processes. To maximize flexibility and faciliate integration of the statistical methods and economic model, parameters can be estimated either by fitting a model in R or by inputting parameters obtained from external sources. So that individual-level simulation and PSA can be run quickly, **Rcpp** and **data.table** are heavily utilized. After simulating costs and quality-adjusted life-years (QALYs) from a PSA, decision analysis can be performed within a cost-effectiveness framework.

2. Model taxonomy

STMs simulate transitions between mutually exclusive health states. A common assumption is that the STM is a Markov model, meaning that transitions to the next health state can only depend on the present health state. In a time homogeneous Markov model transition probabilities are constant over time, whereas in a time inhomogeneous model they can depend on time since the start of the model. A semi-Markov model relaxes the Markov assumption and allows transitions to depend on time since entering an intermediate state.

Markov and semi-Markov models can be formulated in either continuous or discrete time, at either the cohort or individual level. In health economics, Markov cohort models tend to be formulated in discrete time (i.e., as cDTSTMs), although state probabilities can be computed in continuous time models using the Aalen-Johansen estimator (Aalen and Johansen 1978). While tunnel states can be used to approximate a semi-Markov model using a cohort approach, they can only be simulated in a general fashion using individual level models. Discrete time individual simulation is possible, but we use a continuous time models (i.e., iCTSTMs) because they do not require specification of model cycles and can be run considerably faster.

PSMs are specialized models that can be parameterized using survival curves and are especially useful in oncology where PFS and OS are commonly reported. They are "area under the curve" models, although they can also be formulate as STMs by using the survival curves to construct transition probabilities.

2.1. Cohort discrete time state transition models

cDTSTMs simulate the probability that a cohort of patients is in each of H health states over time. Time is measured at discrete times with each time point known as a model cycle. A $1 \times H$ state vector that stores the probability of being in each health state at time t is written as $x_t = (x_{1t}, x_{2t}, \ldots, x_{Ht})$ where $\sum_i x_{ht} = 1$. A transition probability matrix is denoted by P_t where the (r, s)th element represents a transition from state r to state s between times t and $t + 1$. The state vector at time $t + 1$ for each of T model cycles is given by,

$$x_{t+1}^T = x_t^T P_t, \quad t = 0, \ldots, T. \tag{1}$$

Costs and QALYs are computed by assigning (potentially time-varying) values to each health state. Utility, a measure of preference for a health state that normally ranges from 0 (dead) to 1 (perfect health), is used when computing QALYs (Torrance 1986). Assuming model time is in years, state values for costs are estimated by annualizing costs. In a Markov model, state values, like transition probabilities, can depend on time since the start of the model but not on time since entering an intermediate health state.

Expected values are computed by integrating the "weighted" probability of being in each state, where weights are a function of the discount factor and state values. That is, for a time horizon T, discounted costs and QALYs in health state h are computed as,

$$\int_0^T z_h(t) e^{-rt} P_h(t) dt, \tag{2}$$

where $z_h(t)$ is the predicted cost or utility value at time t, r is the discount rate, and $P_h(t)$ is the probability of being in a given health state.

In a discrete time, the integral is approximated with

$$\sum_{j=1}^{T} f(t_j^*)\Delta t_j \tag{3}$$

where $\Delta t_j = t_j - t_{j-1}$, $t_j^* \in [t_{j-1}, t_j]$, and $f(t_j^*) = z_h(t_j^*)e^{-rt_j^*}P_h(t_j^*)$. Three methods can be used to estimate $f(t_j^*)$. First, a left Riemann sum uses values at the start of each time interval $f(t_j^*) = f(t_{j-1})$. Second, a right Riemann sum uses values at the end of each time interval $f(t_j^*) = f(t_j)$. Finally, the trapezoid rule averages values at the start and end of each interval $f(t_j^*) = \frac{1}{2}\Delta t_j[f(t_{j-1}) + f(t_j)]$.

2.2. Individual continuous time state transition models

iCTSTMs simulate individual trajectories between health states using random number generation. Trajectories are simulated for multiple patients and costs and QALYs are computed by averaging across the simulated patients. A reasonably large number of patients must be simulated to ensure that expected values are stable (O'Hagan *et al.* 2007).

In continuous time, a patient is in state $X(t)$ at time t. State transitions are modeled using a multi-state modeling framework (Putter, Fiocco, and Geskus 2007) where the probability of a transition from state r to state s is governed by the hazard function,

$$h_{rs}(t) = \lim_{\Delta t \to 0} \frac{\mathsf{P}(X(t + \Delta t) = s | X(t) = r)}{\Delta t}. \tag{4}$$

Simulated disease progression is characterized by J distinct jumps between health states $D = \{(t_0, X(t_0)), (t_1, X(t_1)), \dots (t_J, X(t_J))\}$ with a patient remaining in a health state from time t_j until transitioning to the next state at t_{j+1}. Jumps between health states are simulated using parametric and flexible parametric survival models as implemented in the **flexsurv** package (Jackson 2016). Specifically, if a patient enters state r at time t_j, then a probability density function for the time-to-event t^* for the $r \to s$ transition is,

$$f_{rs}(t^* | \theta(z), t_j), \quad t^* \geq 0, \tag{5}$$

where parameters $\theta = (\theta_1, \theta_2, \dots, \theta_p)$ may depend on covariates z_p through the link function $g(\theta_p) = z_p^T\gamma$ and γ is a vector of regression coefficients. In a time inhomogeneous Markov model, time $t^* = t_{j+1}$ is conditional on not experiencing event s until time t_j (i.e., it is left-truncated at time t_j). In a semi-Markov model, time-to-event is expressed in terms of $t^* = t_{j+1} - t_j$ and a patient enters state s at time $t_j + t^*$.

A survival distribution is specified for each permitted transition in the multi-state model. A trajectory through the model can then be simulated as described in Algorithm 1. While the algorithm repeats until a patient dies, it can also be stopped at a specified time t or when a patient reaches a maximum age. In the latter scenario, death is assume to occur at the maximum age.

Costs and QALYs are computed using the continuous time present value given a flow of state values, which change as patients transition between health states or as costs vary as a function of time. The state values can be partitioned into M time intervals indexed by $m = 1, \dots, M$

Algorithm 1 Simulation of individual continuous time state transition model

1. Let r be the state entered at time t_j. The number of permitted transitions from state r is given by n_r. If $j = 0$, then $t_j = 0$.
2. Simulate times $\mathcal{T} = \{t_{1,j+1}, t_{2,j+1}, \dots t_{n_r,j+1}\}$ to each of the n_r permitted transitions.
3. Set the time of the transition t_{j+1} equal to the minimum simulated time in $\mathcal{T}$ and the next state s to the state with the minimum simulated time.
4. Set $r = s$ and $t_j = t_{j+1}$. If the patient is still alive, repeat the previous steps until death.

where interval m contains times t such that $t_m \leq t \leq t_{m+1}$ and values for state h are equal to z_{hm} during interval m. z_{hm} will equal zero during time intervals in which a patient is not in state h. Discounted costs and QALYs for health state h are then given by,

$$\sum_{m=1}^{M} \int_{t_m}^{t_m+1} z_{hm} e^{-rt} dt = \sum_{m=1}^{M} z_{hm} \left(\frac{e^{-rt_m} - e^{-rt_{m+1}}}{r} \right), \tag{6}$$

where $r > 0$ is again the discount rate. If $r = 0$, then the present value simplifies to $\sum_{m=1}^{M} z_{hm}(t_{m+1} - t_m)$.

Note that while state values in cohort models can depend on time since the start of the model, state values in individual-level models can depend on either time since the start of the model or time since entering the most recent health state. Individual-level models consequently not only afford more flexibility than cohort models when simulating disease progression, but when simulating costs and/or QALYs as well.

2.3. Partitioned survival models

PSMs are conceptually similar to STMs in that they are characterized by mutually exclusive health states. They differ, however, in that state probabilities are not computed via matrix multiplication or individual simulation, but from a set of non-mutually exclusive survival curves (Glasziou, Simes, and Gelber 1990; Woods, Sideris, Palmer, Latimer, and Soares 2018). Each survival curve represents time to transitioning to that state or to a more severe health state.

In N-state model, $N-1$ non-mutually exclusive survival curves are required. The cumulative survival function, $S_n(t)$, represents the probability that a patient survives to health state n or to a lower indexed state beyond time t. The probability that a patient is in health state 1 is $S_1(t)$. State membership in health states $2, \dots, N-1$ is computed as $S_n(t) - S_{n-1}(t)$. Finally, the probability of being in the final health state n (i.e., the death state) is $1 - S_{N-1}(t)$, or one minus overall survival function.

Survival functions are estimated by fitting parametric or flexible parametric survival models as described in Section 2.2. The nth fitted survival model with density $f_n(t)$ has cumulative density function $F_n(t)$, survivor function $1 - F_n(T)$, cumulative hazard $H_n(t) = -\log S_n(t)$, and hazard $h_n(t) = f_n(t)/S_n(t)$. State probabilities for each health states can be computed

for an arbitrarily fine grid of time points to produce the health state vector x_t for each time t in the grid. Costs and QALYs are then computed in the same manner as in the cohort model described in Section 2.1.

3. Framework

The **hesim** coding framework aims to follow three main tenets. First, it should be possible to seamlessly integrate parameter estimation with simulation. Second, modular code show allow for models to be built in a flexible manner. Finally, code should be computationally efficient.

Each economic model consists of separate statistical models of disease progression, costs, and utilities. All analyses proceed in 4 steps. The first step is to setup the model by defining the model structure, target population, and treatment strategies of interest. This is implemented in **hesim** with the `hesim_data` class as will be illustrated in the examples below.

The actual analysis is performed in the next three steps as shown in Figure 1. First, a statistical models for disease progression, costs, and utilities are parameterized using "estimation" datasets. Next, the statistical models are combined to construct an economic model. For a given model structure, disease progression, QALYs, and costs are simulated from "input data", based on the target population and treatment strategies of interest. Finally, the simulated outcomes are used to perform decision analysis, currently limited to CEA.

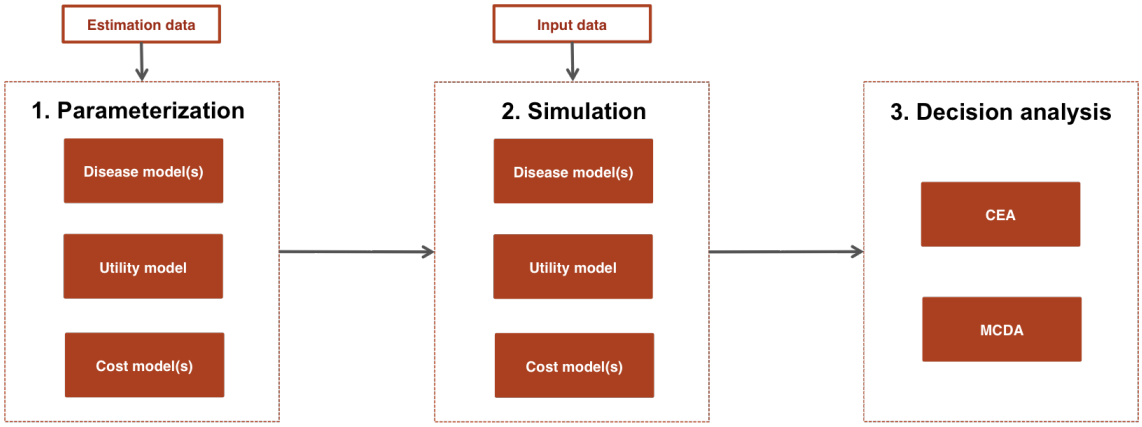

Figure 1: Economic modeling process

The three economic models described in Section 2 are implemented as the **R6** classes `CohortDtstm`, `IndivCtstm`, and `Psm`. Methods are provided within each class for simulating disease progression, costs, and QALYs. These methods are made possible by separate **R6** classes for disease progression, costs, and utility, which comprise the full economic model. Below, we describe this modular design in more detail.

3.1. Parameterization

Disease progression

The statistical model used to parameterize the disease model component of an economic model varies by the type of economic model. For example, multinomial logistic regressions

Table 1: Parameterization of disease models

Economic model	Statistical model	Parameter object	Model fit object
`CohortDtstm`	Custom	`tparams_transprobs`	`define_model()`
	Multinomial logistic regressions	`params_mlogit`	`multinom_list`
`IndivCtstm`	Multi-state model (joint likelihood)	`params_surv`	`flexsurv::flexsurvreg`
	Multi-state model (transition-specific)	`params_surv_list`	`flexsurvreg_list`
`Psm`	Independent survival models	`param_surv_list`	`flexsurvreg_list`

can be used to parameterize a cDTSTM, a set of N-1 independent survival models are used to parameterize an N-state partitioned survival model, and multi-state models can be used to parameterize an iCTSTM (Table 1).

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