Markov Models for Health Economic Evaluations: The R Package heemod

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Abstract

Health economic evaluation studies are widely used in public health to assess health strategies in terms of their cost-effectiveness and inform public policies. We developed an R package for writing Markov models for health economic evaluations which implements the modelling and reporting features described in reference textbooks and guidelines: deterministic and probabilistic sensitivity analysis, heterogeneity analysis, time dependency on state-time and model-time (semi-Markov and non-homogeneous Markov models), etc. In this paper we illustrate the features of heemod by building and analysing an example Markov model. We then explain the design and the underlying implementation of the package.

Keywords: health economic evaluation, Markov models, R.

1. Introduction

Health economic evaluation studies are widely used in public health to assess healthcare strategies in terms of their cost-effectiveness and inform public policies (Russell et al. 1996). In order to account for the long-term consequences of healthcare strategies, models are needed to extrapolate results to a longer time frame (Sonnenberg and Beck 1993; Eddy et al. 2012).\(^1\) These models estimate the repartition of a population in various health states (e.g. healthy, sick, dead) and how its health is affected by different strategies. Costs (e.g. medical or drug costs) and outcomes (e.g. life years or quality of life) are attached to each distinct health status, allowing to estimate the cost and effectiveness expected for every studied strategy.

By representing health status as states and health changes over time as transitions probabilities between states this process can be modelled with Markov chains, using a Markov model. Transition probabilities between states can be described by a square 2-dimensional transition matrix \(T\), where element \(i, j\) is the transition probability between state \(i\) and \(j\). The probability of being in a given state at time \(t\) is given by:

\[
X \times T^t
\]

\(^1\)Usually the entire target population lifetime.
Where $X$ is a vector giving the probability of being in a given state at the start of the model, and $T^t$ is the product of multiplying $t$ matrices $T$. The use of Markov models in health economic evaluation have been thoroughly described in Beck and Pauker (1983), Sonnenberg and Beck (1993) and Briggs and Sculpher (1998).

In order to best inform the decision process, Markov models should incorporate a wide range of information to account for all the available evidence at a given time (Briggs and Sculpher 1998). Results from various sources can be combined, such as estimated drug efficacy from clinical trials, disease evolution from epidemiological cohorts, quality of life values from population-level studies, transition probabilities from life-tables, etc. An implementation of Markov models should be flexible enough to receive all these sources of data.

Most Markov models are built using basic spreadsheet software such as Microsoft Excel (Microsoft Corp. 2016) or commercial packages such as TreeAge (TreeAge Software Inc. 2017), which has drawbacks: analyses are hard to reproduce and lack transparency, errors are difficult to spot, track and correct, and graphic capabilities are lacking (Williams et al. 2016a). The R language (R Core Team 2016) can overcome these issues through script-based approaches: there is a written record of what was done, the calculations are transparent, modification can be easily applied to the model, traceability is guaranteed, and the code just needs to be run again to reproduce the analysis (Williams et al. 2016a). Despite these advantages, usage of R in health economic modelling has been limited by the significant challenge of programming Markov models from scratch and the lack of packages providing a comprehensive set of tools for developing such models.

Our objective was to develop an R package for writing Markov models for health economic evaluations, using a simple declarative syntax, which implements the modelling and reporting features described in reference textbooks (Drummond et al. 2005; Briggs et al. 2006) and guidelines (Eddy et al. 2012; Husereau et al. 2013). We named the package heemod, standing for Health Economic Evaluation MODelling. The package is available from the Comprehensive R Archive Network (CRAN) at http://CRAN.R-project.org/package=heemod.

In Section 2 we illustrate the possibilities of heemod by building and analysing an example Markov model. For completeness we then present in Section 3 the features that were not used in the previous example. In Section 4 we detail the mathematical implementation of some functionalities. Finally in Section 5 we explain the design and the back-end of the package.

2. Building and analysing a model: an example

In this section we use a simplified example to illustrate how and why Markov models are used in health economic evaluation studies. We introduce theoretical concepts and methods along as they are encountered, present the production of results with the heemod package, and their interpretation. In this article we used heemod version 0.9.0.9001.

2.1. Description of the question

For this example we will model the imaginary disease called shame, which is still a terminal disease in some parts of the Galaxy (Adams 1979). At the onset the disease is asymptomatic:
patients are quite unashamed, they do not feel sick, have a good quality of life, and are not likely to die of shame. But patients are at risk of being ashamed: that marks the entry into the symptomatic phase of the disease, with frequent hospital stays, deteriorated quality of life and a high risk of dying of shame. The probability to revert to the asymptomatic unashamed state is unfortunately quite low, and there is no cure known to work reliably: to be effective shame therapy should thus be provided during the initial asymptomatic state, to prevent being ashamed in the first place.

2.2. Compared strategies

Three strategies are proposed to prevent being ashamed:

**Base strategy** *(base)*: Do nothing, this is the natural evolution of the disease.

**Medical treatment** *(med)*: Patients with asymptomatic disease are treated with a *ashaminib*, a highly-potent shame inhibitor, until progression to symptomatic state in order to lower the risk of being ashamed.

**Surgical treatment** *(surg)*: Patients with asymptomatic disease undergo *shamectomy*, a surgical procedure that lowers the risk of being ashamed. The procedure needs to be performed only once.

Medical treatment is effective in preventing symptomatic disease, but the drug is expensive. Surgical treatment is a one-time cost, but its effect decreases with time. The increased probability of dying of shame once in the symptomatic disease state does not depend on the treatment used before, when the disease was asymptomatic.

2.3. States

From the description of the disease we can define 3 states:

**Asymptomatic state** *(pre)*: Before the symptomatic state, when treatment can still be provided.

**Symptomatic state** *(symp)*: Symptomatic disease, after being ashamed. With degraded health, high hospital costs and increased probability of dying of shame.

**Death** *(death)*: Death by natural causes or because of shame.

2.4. Model parameters

In this section we define parameters that will be called later in the analysis (e.g. in the transition matrix or the state values). Because we said in the disease description that some probabilities and values vary with time, we need to introduce some concepts regarding time-dependency before we can define the parameters.

Transition probabilities or state values may change with time (e.g. the protecting effect of surgery may decrease with time after the procedure, probability of all-causes death may increase as the population gets older, hospital costs may change with disease evolution). It is
thus important to account for time-dependency in order to build accurate models. In Markov models values may depend on 2 distinct measurements of time (Hawkins et al. 2005): time elapsed since the start of the model (called model time), and time spent in a given state (called state time). Both situations can co-exist in a same model.

In heemod time-dependency is specified with 2 variables: model_time and state_time. These package-reserved names return sequential values starting from 1, corresponding to time spent in the model for model time and time spent in a given state for state time. They can be used in any user-defined expression or function.

In our case the probability of all-cause death depends on age. Because age increases with time spent since the beginning of the model, the all-cause death probability is model time dependent. On the other hand the probability of dying of shame depends on the time elapsed after being ashamed (i.e. time spent in the symp state): this probability is state time dependent. The probability of being ashamed after surgery, the cost of surgery, and the hospital costs in the symptomatic state also depend on the time spent in their respective state.

In this model we will use a cycle duration of 1 year: we must take care that all transitions probabilities, values attached to states, and discount rates are calculated on this time-frame.

We can now create the global parameters with define_parameters():

```r
R> par_mod <- define_parameters(
  R+ age_base = 20,
  R+ age_cycle = model_time + age_base)
```

The age of individuals for a given cycle age_cycle is the age at the beginning of the model (age_base), plus the time the model has run (model_time).

```r
R> par_mod <- modify(
  R+ par_mod,
  R+ sex_indiv = "MLE", # MLE => male in the WHO database
  R+ p_death_all = get_who_mr(
    R+ age = age_cycle,
    R+ sex = sex_indiv,
    R+ country = "GBR",
    R+ local = TRUE))
```

The death probability p_death_all, as a function of age and sex, is fetched from the World Health Organisation database with get_who_mr(), here for a British population.

```r
R> par_mod <- modify(
  R+ par_mod,
  R+ p_death_disease = compute_surv(
    R+ fit_death_disease,
    R+ markov_cycle).5
```

---

4Or its alias markov_cycle.

5Relying on the rgho package (Filipovic-Pierucci 2017).

6We specify the use of local data cached in heemod with local = TRUE to avoid adding overhead query time.
The probability of dying of shame when the disease is symptomatic $p_{\text{death_disease}}$ is extracted with the `get_probs_from_surv()` function from `fit_death_disease`, a model fitted with the `flexsurv` package (Jackson 2016). Because this probability depends on time spent in the disease state, the `state_time` model variable is used to specify time. Here we use non-parametric Kaplan-Meier estimates for the first 5 years instead of model-fitted values with `km_limit = 5`.

The parametric survival model `fit_death_disease` used to compute $p_{\text{death_disease}}$ is fitted with the following code:

```R
R> fit_death_disease <- flexsurv::flexsurvreg(
R+   survival::Surv(time, status) ~ 1,
R+   dist = "weibull",
R+   data = tab_surv)
```

Where `tab_surv` is a data-frame containing survival data.

```R
R> dput(tab_surv)
structure(list(time = c(0.4, 8.7, 7, 5.1, 9.2, 1, 0.5, 3.3, 1.8,
3, 6.7, 3.7, 1.1, 5.9, 5.1, 10, 10, 10, 10, 10, 10, 10, 10, 10, 10,
10), status = c(1L, 1L, 1L, 1L, 1L, 1L, 1L, 1L, 1L, 1L, 1L, 1L,
1L, 1L, 1L, 0L, 0L, 0L, 0L, 0L, 0L, 0L, 0L)), .Names = c("time",
"status"), row.names = c(NA, -25L), class = "data.frame")
```

The death probability in the symptomatic state $p_{\text{death_symp}}$ is the probability to die either from old age ($p_{\text{death_all}}$) or from the disease ($p_{\text{death_disease}}$). Assuming those probabilities are independent, we use the `combine_probs()` to combine them with the formula $P(A \cup B) = 1 - (1 - P(A)) \times (1 - P(B))$.

```R
R> par_mod <- modify(
R+   par_mod,
R+   p_dedeath_symp = combine_probs(
R+     p_dedeath_all,
R+     p_dedeath_disease))
```

The probability of disease under medical treatment $p_{\text{disease_med}}$ is the base probability of disease $p_{\text{disease_base}}$ times the protecting effect of the treatment, $\text{med_effect}$.

```R
R> par_mod <- modify(
R+   par_mod,
R+   p_disease_base = 0.25,
R+   med_effect = 0.5,
R+   p_disease_med = p_disease_base * med_effect)
```
The probability of disease after surgery is extracted with `get_probs_from_surv()` from a parametric Weibull survival model defined with `define_survival()`. For reason explained in Section 2.10 parameters `scale` and `shape` are not written in the `define_survival()` call, but defined separately.

Because surgery is only performed once at the beginning of the pre state, the time-dependant variable `state_time` was used to limit surgery costs to the first cycle in the pre state.

After `n_years` in the symptomatic state the symptoms become milder and hospital costs decrease (from `cost_hospit_start` to `cost_hospit_end`). We used the time-dependant variable `state_time` to condition the hospital costs `cost_hospit` on `n_years`.

```r
R> par_mod <- modify(
R+ par_mod,
R+  shape = 1.5, # We will see later why we need
R+  scale = 5, # to define these 2 parameters here.
R+  p_disease_surg = define_survival(
R+    distribution = "weibull",
R+    shape = shape,
R+    scale = scale) %>%
R+    compute_surv(time = state_time))

R> par_mod <- modify(
R+ par_mod,
R+  cost_surg = 20000,
R+  cost_surg_cycle = ifelse(state_time == 1, cost_surg, 0))

R> par_mod <- modify(
R+ par_mod,
R+  cost_hospit_start = 11000,
R+  cost_hospit_end = 9000,
R+  n_years = 9,
R+  cost_hospit_cycle = ifelse(
R+    state_time < n_years,
R+    cost_hospit_start,
R+    cost_hospit_end))

R> par_mod <- modify(
R+ par_mod,
R+  p_cured = 0.001,
R+  cost_med = 5000,
R+  dr = 0.05,
R+  qaly_disease = 0.5)
```
Finally we define \( p_{\text{cured}} \) the probability to spontaneously revert to the asymptomatic unashamed state, \( \text{cost}_{\text{med}} \) the drug costs, \( \text{dr} \) the discount rate for a year and \( \text{qaly}_{\text{disease}} \) the QALY for one year in the symptomatic state.

### 2.5. Transitions

We define a transition matrix for the base strategy with the `define_transition()` function. We can reference parameters defined in the previous section.

```r
mat_base <- define_transition(
  state_names = c("pre", "symp", "death"),
  C, p_disease_base, p_death_all,
  p_cured, C, p_death_symp,
  0, 0, 1)
```

A transition matrix, 3 states.

```
  pre symp death
pre C p_disease_base p_death_all
symp p_cured C p_death_symp
death 1
```

\( p_{\text{disease base}} \) is the probability of being ashamed in the base strategy, \( p_{\text{death all}} \) the all cause probability of death (not caused by the disease) and \( p_{\text{death symp}} \) the death probability in the symptomatic state (greater than \( p_{\text{death all}} \)). \( p_{\text{cured}} \) is the unlikely probability to revert to the asymptomatic unashamed state. \( p_{\text{cured}}, p_{\text{death symp}} \) and \( p_{\text{death all}} \) do not depend on the strategy. The value of these parameters will be defined later. \( C \) is an alias for the probability complement, 1 minus the sum of probabilities in a given row. Death was
modelled as an absorbing health state (i.e. the probability of transitioning from death to other health states was set to zero). The resulting transition diagram is presented in Figure 1.\

Similarly, transitions can be defined for the other 2 strategies. In our case only the name of the probabilities change: \texttt{p\_disease\_base} becomes \texttt{p\_disease\_med} or \texttt{p\_disease\_surg} (those parameters will also be defined later).

\begin{verbatim}
R> mat_med <- define_transition(
  R+   state_names = c("pre", "symp", "death"),
  R+   C, p\_disease\_med, p\_death\_all,
  R+   p\_cured, C, p\_death\_symp,
  R+   0, 0, 1)

R> mat_surg <- define_transition(
  R+   state_names = c("pre", "symp", "death"),
  R+   C, p\_disease\_surg, p\_death\_all,
  R+   p\_cured, C, p\_death\_symp,
  R+   0, 0, 1)
\end{verbatim}

2.6. State values

Next we define the values associated with states using the \texttt{define\_state} function. An arbitrary number of values can be attached to a state, here we define: \texttt{cost\_treat} the treatment cost (drug costs for the \texttt{med} strategy or surgery costs for the \texttt{surg} strategy, there is no treatment in the \texttt{base} strategy), \texttt{cost\_hospit} the hospitalization costs, \texttt{cost\_total} the total cost, and \texttt{qaly} the health-related quality-adjusted life years (QALY), where 1 stands for one year in perfect health and 0 stands for death (Torrance and Feeny 1989). In the following code we define the state \texttt{pre}:

\begin{verbatim}
R> state_pre <- define_state(
  R+   cost\_treat = dispatch\_strategy(
  R+       base = 0, # no treatment => no treatment cost
  R+       med = cost\_med,
  R+       surg = cost\_surg\_cycle),
  R+   cost\_hospit = 0, # good health => no hospital expenses
  R+   cost\_total = discount(cost\_treat + cost\_hospit, r = dr),
  R+   qaly = 1)
\end{verbatim}

To dispatch the cost of treatment according to the strategy we used the \texttt{dispatch\_strategy()} function, with arguments named as strategies (we will define the strategy names in Section 2.8). Another approach would have been to define 3 versions of \texttt{state\_pre}, one per strategy, and in the next section use the corresponding version in each distinct \texttt{define\_strategy()} call.

\footnote{Generated by plot(mat\_base).}
The total cost is discounted with the `discount()` function at a given rate (`dr`). The QALY attached to 1 year in this state are set to 1, corresponding to 1 year in perfect health. The variables `dr`, `cost_med` and `cost_surg_cycle` will be defined later.

The other 2 states are defined similarly:

```r
R> state_symp <- define_state(
R+   cost_treat = 0,
R+   cost_hospit = cost_hospit_cycle,
R+   cost_total = discount(cost_treat + cost_hospit, r = dr),
R+   qaly = qaly_disease)
```

```r
R> state_death <- define_state(
R+   cost_treat = 0,
R+   cost_hospit = 0,
R+   cost_total = 0,
R+   qaly = 0)
```

Patients have a degraded quality of life and are hospitalized during the symptomatic disease phase, we need to define specific QALYs (`qaly_disease`) and hospital costs (`cost_hospit_cycle`) for this state. These variables will be defined later. Finally dead patients have QALYs at 0, and they do not cost anything to the healthcare system.

### 2.7. Strategies

All the information (states and transitions) is now available to define the strategies. For this purpose we use the `define_strategy()` function. Only the transition objects differ between `strat_base`, `strat_med` and `strat_surg`.

```r
R> strat_base <- define_strategy(
R+   transition = mat_base,
R+   pre = state_pre,
R+   symp = state_symp,
R+   death = state_death)
```

```r
R> strat_med <- define_strategy(
R+   transition = mat_med,
R+   pre = state_pre,
R+   symp = state_symp,
R+   death = state_death)
```

```r
R> strat_surg <- define_strategy(
R+   transition = mat_surg,
R+   pre = state_pre,
R+   symp = state_symp,
R+   death = state_death)
```
2.8. Running the model

The model can then be run with `run_model()`:

```r
R> res_mod <- run_model(
R+   parameters = par_mod,
R+   base = strat_base,
R+   med = strat_med,
R+   surg = strat_surg,
R+   cycles = 10,
R+   cost = cost_total,
R+   effect = qaly,
R+   method = "life-table")
```

base: detected use of 'state_time', expanding states: pre, symp.

Fetching mortality data from package cached data.

Using cached data from year 2015.

Fetching mortality data from package cached data.

Using cached data from year 2015.

med: detected use of 'state_time', expanding states: pre, symp.

surg: detected use of 'state_time', expanding states: pre, symp.

Strategy names are defined at that point by using the argument names provided by the user.\(^8\)

We define `cost_total` and `qaly` as the respective cost and effectiveness result. The model is run for 10 cycles (i.e. 10 years), and state membership counts are corrected using the life-table method (Barendregt 2009). By default the starting population is made of 1,000 patients in the first state, and no patient in the other states.

---

\(^8\)Strategy names are used in the results, and by functions such as `dispatch_strategy()`. 
2.9. Results interpretation

How do the strategies compare to each other with regard to their relative cost and effectiveness?

The answer is given by calculating the total expected cost and effectiveness of all strategies, and then computing the incremental cost-effectiveness ratio (ICER) between them (Drummond et al. 2005). The ICER between strategies A and B is defined as:

\[
\frac{C_B - C_A}{E_B - E_A}
\]

Where \( C \) is the total expected cost of a strategy and \( E \) its total expected effect (e.g. sum of life-years of the population). Thus the ICER is the cost of an incremental unit of effectiveness. The most cost-effective strategy is (1) the most effective strategy (2) among the strategies having an ICER no higher than a threshold. This ICER threshold is the maximal willingness to pay for an additional unit of effectiveness: it is a political choice that depends on multiple factors (Claxton et al. 2015).

The strategies can be presented on a cost-effectiveness plane (Figure 2),\(^9\) were we see that both med and surg are more effective than base, but more costly.

R> summary(res_mod, threshold = c(1000, 5000, 15000))

3 strategies run for 10 cycles.

Initial state counts:

pre = 1000L

\(^9\)Generated by plot(res_mod, type = "ce").
symp = 0L
death = 0L

Counting method: 'life-table'.

Values:

|          | cost_treat | cost_hospit | cost_total | qaly |
|----------|------------|-------------|------------|------|
| base     | 0          | 54214446    | 42615142   | 5792.258 |
| med      | 27619456   | 37181168    | 52246211   | 7224.085 |
| surg     | 10074777   | 47429243    | 46220058   | 6553.701 |

Net monetary benefit difference:

|        | 1000 | 5000 | 15000 |
|--------|------|------|-------|
| 1      | 8199.241 | 2471.932 | 0.000 |
| 2      | 5355.769 | 2674.230 | 7816.725 |
| 3      | 0.000   | 0.000  | 11846.341 |

Efficiency frontier:

base \rightarrow surg \rightarrow med

Differences:

|      | Cost Diff. | Effect Diff. | ICER | Ref. |
|------|------------|--------------|------|------|
| surg | 3604.915   | 0.7614427    | 4734.322 | base |
| med  | 6026.153   | 0.6703846    | 8989.098 | surg |

From the printed model output presented above we see in the ICER column of the Differences section that surg is more cost-effective than base if one is willing to pay 4,734 more per QALY gained. Furthermore med is more cost-effective than surg if one is willing to pay 8,989 more per QALY gained.

A net monetary benefit analysis (Stinnett and Mullahy 1998) is run by specifying thresholds ICER values in the summary() function with the threshold argument. We see in the Net monetary benefit section that at a threshold ICER of 1,000 the strategy with the highest net monetary benefit is base, at 5,000 surg and at 15,000 med.

Figure 3 gives us more information about what happens in our model: the effect of surgery seems to wear down with time compared to the medical treatment. Surgery delays the outcome, reporting degraded health status and hospital costs further in time. After a few years the hospital costs of the surgery strategy reach similar levels to the base strategy. Nevertheless these increased hospital costs do not outweigh the important treatment costs associated with the medical therapy.

\[10\]Generated by plot(res_mod, type = "counts", panel = "by_state") and plot(res_mod, type = "values", panel = "by_value").
2.10. Uncertainty analysis

What is the uncertainty of these results? What strategy is probably the most cost-effective?

Uncertainty of the results originate from uncertainty regarding the true value of the input parameters (e.g. treatment effect, cost of hospital stays, quality of life with the disease, survival probabilities). The effect of this uncertainty can be assessed by varying the parameter values and computing the model results with these new inputs. While multiple methods exist to study uncertainty (Briggs et al. 1994), deterministic and probabilistic sensitivity analysis (DSA and PSA) are the most widely used (Briggs et al. 2006).

In a DSA, parameter values are changed one by one, usually to a low and high value (e.g. the lower and upper bounds of the parameter confidence interval). Model results are plotted on a tornado plot to display how a change in the value of one parameter impacts the model results. A DSA gives a good sense of the relative impact of each parameter on the uncertainty of the model outcomes, but does not account for the total uncertainty over all the parameters, for skewed or complex parameter distribution, nor for correlations between the errors of different parameter estimates (Briggs et al. 1994).

We define the DSA with define_dsa() by specifying a lower and upper bound for each parameter of interest.

```R
R> def_dsa <- define_dsa(
R+   age_base, 15, 30,
R+   p_disease_base, 0.2, 0.3,
R+   p_cured, 0.005, 0.02,
R+   med_effect, 0.3, 0.7,
R+   shape, 1.4, 1.6,
R+   scale, 4, 6,
R+   cost_med, 4000, 6000,
R+   cost_surg, 8000, 12000,
R+   cost_hospit_start, 5000, 15000,
R+   dr, 0, 0.1,
R+   qaly_disease, 0.3, 0.7,
R+   n_years, 8, 10)
```

```R
R> res_dsa <- run_dsa(res_mod, dsa = def_dsa)
```

Running DSA on strategy 'base'...

Running DSA on strategy 'med'...

Running DSA on strategy 'surg'...

Only parameters (e.g. state values, transition probabilities) defined with define_parameters() can be modified in a DSA (or a PSA). Accordingly, many state values, transition probabilities, and the shape and scale parameters used in our example were defined as parameters, thus allowing them to be varied in sensitivity analyses. Once defined, the analysis can be run using run_dsa().
Figure 3: Evolution over time of counts by state (A) and of values (B).

Figure 4: Tornado plot presenting uncertainty of the cost for the med strategy. Each line shows how setting the parameter to its low and high value impacts costs. The bars are centred around baseline costs.
Figure 4 shows the impact of varying each parameter individually on total cost for the \textit{med} strategy.\textsuperscript{11} The results demonstrate that the discount rate and hospital costs have a greater impact than other parameters. Unsurprisingly parameters used only in the surgery strategy and parameters unrelated to costs have no effect on the cost of the \textit{med} strategy.

In a PSA, the model is re-run for a given number of simulations with each parameter being re-placed with a value re-sampled from a user-defined probability distribution. These results are then aggregated, allowing us to obtain the probability distribution of model outputs (Critchfield \textit{et al.} 1986).

We define the parameter distributions with \texttt{define_psa()}, and optionally their correlation structure with \texttt{define_correlation()}.

\begin{verbatim}
R> def_psa <- define_psa(
  R+ age_base ~ normal(mean = 20, sd = 5),
  R+ p_disease_base ~ binomial(prob = 0.25, size = 500),
  R+ p_cured ~ binomial(prob = 0.001, size = 500),
  R+ med_effect ~ lognormal(mean = 0.5, sd = 0.1),
  R+ shape ~ normal(mean = 1.5, sd = 0.2),
  R+ scale ~ normal(mean = 5, sd = 1),
  R+ cost_med ~ gamma(mean = 5000, sd = 1000),
  R+ cost_surg ~ gamma(mean = 20000, sd = 3000),
  R+ cost_hospit_start ~ gamma(mean = 11000, sd = 2000),
  R+ dr ~ binomial(prob = 0.05, size = 100),
  R+ qaly_disease ~ normal(mean = 0.5, sd = 0.1),
)
\end{verbatim}

\textsuperscript{11}Generated by \texttt{plot(res_dsa, result = "cost", strategy = "med")}.  

Figure 5: Uncertainty of the incremental cost and effect of strategies on the cost-effectiveness plane, taking the \texttt{base} strategy as a reference.
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\begin{verbatim}
R> n_years ~ poisson(mean = 9),
R+ correlation = define_correlation(
R+ shape, scale, -0.5,
R+ age_base, p_disease_base, 0.3))

R> res_psa <- run_psa(res_mod, psa = def_psa, N = 1000)

Resampling strategy 'base'...

Resampling strategy 'med'...

Resampling strategy 'surg'...

We then run the PSA with \texttt{run_psa()}, here for 1,000 re-samplings. The results can be plotted as uncertainty clouds on the cost-effectiveness plane (Figure 5).

The probability of a strategy being cost effective can be plotted for various willingness to pay values on a cost-effectiveness acceptability curve (Van Hout et al. 1994; Fenwick and Byford 2005). In Figure 6A we see that with a threshold ICER below 1,000 the \texttt{base} strategy is probably the most cost-effective. Above 50,000, \texttt{med} is probably the most cost-effective strategy. Between those 2 values the decision is less clear.

It is possible to compute the expected value of perfect information (EVPI) depending on the willingness to pay (Claxton and Posnett 1996; Felli and Hazen 1997). This is a quantification of the cost of potentially choosing the wrong strategy, and thus conversely the price one is ready to pay to reduce the risk of incorrect decisions by obtaining more information (e.g. by conducting more studies). In Figure 6B we see the EVPI peaks between 1,000 and 10,000, where the uncertainty is high. It also increases for higher willingness to pay, because even though the uncertainty is not as high, the costs of a wrong decision become higher.

The EVPI can indicate whether conducting more research is cost-effective. But it does not inform on the value of getting more information on particular parameters (Briggs et al. 2006). The expected value of perfect information for parameters (EVPPI) is very similar to the EVPI, but returns values by parameters (Ades et al. 2004). Unfortunately its computation is not trivial. PSA results can be exported to compute EVPPI with the Sheffield Accelerated Value of Information SAVI software (Strong et al. 2014) with \texttt{export_savi()}.

The individual contribution of parameter uncertainty on the overall uncertainty (Briggs et al. 2006) is illustrated by Figure 6C. We can see that, depending on the strategy, different parameters generate the uncertainty on costs and effect. In all cases \texttt{dr}, \texttt{cost_hospit_start} and \texttt{qaly_disease} explain a high part of variability for all strategies. Unsurprisingly the effect of \texttt{scale} (the scale of the post-surgery Weibull survival function), \texttt{med_effect} and \texttt{cost_med} are limited to the \texttt{surg} or \texttt{med} strategies.

\footnotesize

\textsuperscript{12}A similar plot can be generated with \texttt{plot(res_psa, type = "ce")}.

\textsuperscript{13}Generated by \texttt{plot(res_psa, type = "ac")}.

\textsuperscript{14}Generated by \texttt{plot(res_psa, type = "evpi")}.

\textsuperscript{15}Generated by \texttt{plot(res_psa, type = "cov")}. We could also perform the same analysis on the difference between strategies with the option \texttt{diff = TRUE}.\normalsize
Figure 6: A: Cost-effectiveness acceptability curve; B: Expected value of perfect information; C: Covariance analysis of PSA results.
In addition, average model values can be computed on the results and presented in a summary similar to the run_model() output. Because of non-linearities in Markov models, averages over the PSA output distribution are more accurate than point estimates (Briggs et al. 2006). In our case the ICERs changed from 4,734 to 6,453 and 8,989 to 7,059 for the surg and med strategies respectively.

2.11. Heterogeneity analysis

*How does the cost-effectiveness of strategies vary depending on the characteristics of the population?*

If population characteristics are available, model results can be computed on the different sub-populations to study the heterogeneity of the resulting model outputs (Briggs et al. 2006). Furthermore, average population-level results can be computed from these distributions.

The model we ran in Section 2.9 computed results for a cohort of males aged 20. To assess how population characteristics affect model results we can run a heterogeneity analysis. We use the update() function to run the model on a table containing population data.\(^{16}\)

\begin{verbatim}
R> head(tab_pop)

  age_base sex_indiv .weights
1     10      MLE      0.04242889
2     10     FMLE      0.86696571
3     15      MLE      0.69960873
4     15     FMLE      0.51253057
\end{verbatim}

\(^{16}\)In this example we use a table with population characteristics, here named tab_pop, with an optional column .weights giving the relative population weight of each strata.
5  20  MLE 0.91723545
6  20  FMLE 0.09685623

R> pop_mod <- update(res_mod, newdata = tab_pop)

Updating strategy 'base'...

Updating strategy 'med'...

Updating strategy 'surg'...

The summary of the updated model gives the distribution of the values of interest in the population, and the average model values over the entire population. Here the average ICERs in the population are 5,052 and 9,150 for the surg and med strategies respectively, quite similar to the values computed in Section 2.9 (4,734 and 8,989). We can also plot the distribution of model results (e.g. the intervention effects in Figure 7).\footnote{Generated by plot(pop_mod, result = "effect", bins = 15).}

\subsection*{2.12. Budget impact analysis}

What would be the total cost of a strategy for the health system?

So far we mostly worked on model results at the scale of the individual (e.g. cost per person). If we want to implement a strategy at a health system level we also need to know the total cost over a given time horizon, in order to assess whether the strategy is sustainable. This is called a budget impact analysis (BIA). The main differences with the classic model are (1) the patient counts at the model start should reflect the population statistics, and (2) additional patients may enter the model every year (new disease cases).

We use the init and inflow arguments of \texttt{run\_model()} to implement BIA, here for the med strategy. The inflow of new patients is defined with \texttt{define\_inflow()}. Inflow counts can depend on model time (state time dependency is meaningless in this context).

R> res_bia <- run_model(
R+  parameters = par_mod,
R+  med = strat_med,
R+  cycles = 10,
R+  cost = cost_total,
R+  effect = qaly,
R+  method = "life-table",
R+  init = c(
R+    pre = 25000,
R+    symp = 5000,

\footnote{Generated by plot(pop_mod, result = "effect", bins = 15).}
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\begin{verbatim}
R+ death = 0),
R+ inflow = define_inflow(
R+ pre = 8000,
R+ symp = 0,
R+ death = 0))
\end{verbatim}

med: detected use of 'state_time', expanding states: pre, symp.

At the start of the model there are 25,000 patients with asymptomatic shame and 5,000 with a symptomatic form of the disease in the population. Every year 8,000 additional cases of shame are added to the model, starting the disease in the asymptomatic state.

\begin{verbatim}
R> summary(res_bia)
1 strategy run for 10 cycles.
Initial state counts:
pre = 25000
symp = 5000
death = 0
Counting method: 'life-table'.
Values:

   cost_treat cost_hospit cost_total    qaly
  med 1942366603  2621681008 3531335211 508495.2
\end{verbatim}

The total cost of strategy med over a 10-year time horizon will be 3.5 billions.

3. Other features and extensions

This section introduces features and extensions that were not presented in the previous example.

3.1. Survival analysis

The heemod package provides a number of ways to estimate transition probabilities from survival distributions. Survival distributions can come from at least three different sources:

- User-defined parametric distributions created using the define_survival() function.
- Fitted parametric distributions with \texttt{flexsurv::flexsurvreg()} (Jackson 2016).
- Fitted Kaplan-Meiers with \texttt{survival::survfit()} (Therneau 2015; Therneau and Grambsch 2000).
Once defined, each of these types of distributions can be combined and modified using a standard set of operations. Treatment effects can be applied to any survival distribution:

- Hazard ratio: `apply_hr()`.
- Odds ratio: `apply_or()`.
- Acceleration factor: `apply_af()`.

In addition, distributions can be combined:

- Join one (or more) survival distributions together: `join()`.
- Pool two (or more) survival distributions: `pool()`.
- Combine two (or more) survival distributions as independent risks: `add_hazards()`.

The transition or survival probabilities are computed with `compute_surv()`. Time (usually `model_time` or `state_time`) needs to be passed to the function as a `time` argument.

All these operations can be chained with the `%>%` piping operator (Bache and Wickham 2014), e.g.:

```r
R> fit_cov %>%
R+ apply_hr(hr = 2) %>%
R+ join(
R+ fitcov_poor,
R+ at = 3) %>%
R+ pool(
R+ fitcov_medium,
R+ weights = c(0.25, 0.75)) %>%
R+ add_hazards(
R+ fit_w) %>%
R+ compute_surv(time = 1:5)
```

### 3.2. Convenience functions

For reproducibility and ease of use we implemented convenience functions to perform some of the most common calculations needed in health economic evaluation studies (e.g converting incidence rates, odds ratios, or relative risks to transition probabilities with `rate_to_prob()`, `or_to_prob()`, or `rr_to_prob()` respectively). Probabilities and discount rates can be rescaled to fit different time frames (generally the duration of a cycle) with `rescale_prob()` and `rescale_discount_rate()`.

### 3.3. Cluster computing

PSA and heterogeneity analyses can become time-consuming since they consist in iteratively re-running the model with new parameter inputs. Because this workload is *embarrassingly parallel* (Herlihy and Shavit 2012), i.e. there is no dependency or need for communication
between the parallel tasks, it can easily be run on a cluster relying on the parallel (R Core Team 2016) package. This is done by calling the `use_cluster()` function. This function can either take as an argument:

1. A number: a local cluster with the given number of cores will be created.
2. A cluster object defined with the `makeCluster()` function from parallel: the user-defined cluster will be used (e.g. to use more complex clusters with non-local hosts).

### 3.4. Alternative interfaces

To facilitate the use of `heemod` by users not familiar with R we developed a shiny (Chang et al. 2017) graphical user interface. Similarly, for users that require the use of spreadsheet models (such as health regulatory agencies), a model can be specified in spreadsheet files and run by `heemod`. To keep the traceability, transparency and reproducibility advantages provided by written source code it is possible to export models built from these interfaces to R source code files.

These alternative interfaces are needed in a context where (1) Markov models are already widely used and implemented on spreadsheet software, (2) a significant proportion of the modellers are not R users, and (3) health regulatory agencies from several countries require models to be in spreadsheet format. We believe that to gain acceptance in a field such as health economic evaluation where habits are already ingrained one must adapt to existing user requirements, as long as the final outcome is to help develop transparency and reproducibility in the domain.

### 3.5. Extension to other types of model

Even though the main focus of `heemod` is to compute Markov models, other methods that model state changes can be included in the package: only the `transition` argument of `define_strategy()` and the associated evaluation methods need to be extended.

For example partitioned survival models (Williams et al. 2016b) were added to the package recently. These models can be computed by passing an object defined by `define_part_surv()` to `transition`.

In theory most modelling methods that return state counts over time could be integrated into `heemod`, e.g. dynamic models for infectious diseases (Keeling and Rohani 2011; Snedecor 2012).

### 4. Mathematical implementation

In this section we detail the mathematical implementation of most of the features of `heemod`.

#### 4.1. Parameter correlation in PSA

Correlation of parameters in PSA was implemented with the following steps:

1. A correlation structure is define with `define_correlation()` (see Section 2.10).
2. Values are sampled from a multi-normal distribution having the required correlation structure with `mvnfast` (Fasiolo 2016).

3. The sampled values are then mapped to the target distributions on a quantile by quantile basis.

This approach described in Briggs et al. (2006) is an approximation that allows to define correlations between arbitrary distributions. The final Pearson correlation coefficients between the target distributions may differ slightly from the ones initially defined by the user. That issue is mostly true if the target distributions are too dissimilar, e.g. a gamma and a binomial distribution.

### 4.2. Time-dependency implementation

A throughout description of time-dependency in Markov models is given by Hawkins et al. (2005), with solutions for the computation of both non-homogeneous and semi-Markov models. These methods were implemented in the `heemod` package. Markov models with model time dependency are usually called non-homogeneous Markov models, and models with state time dependency are called semi-Markov models.

**Model time** (non-homogeneous Markov models) was implemented by using a 3-dimensional transition matrix \( U \). As in the 2-dimensional matrix \( T \) described in Section 1 the indices of the first 2 dimensions \( i, j \) encode the transition probability between state \( i \) and \( j \). In addition the third dimension index \( k \) corresponds to the number of cycles the model has run so far, so that element \( i, j, k \) of matrix \( U \) corresponds to the transition probability between state \( i \) and \( j \) at time \( k \). The probability of being in a given state at time \( t \) is given by a simple extension of Equation 1:

\[
X \times \prod_{k=1}^{t} U_k
\]

Where \( X \) is a vector\(^{18}\) giving the probability of being in a given state at the start of the model, \( \prod \) stands for matrix multiplication, and \( U_k \) is a 2-dimensional slice of the 3-dimensional transition matrix \( U \), giving the transition probabilities at time \( k \).

**State time** (semi-Markov models) was implemented with the tunnel-state method, described in Hawkins et al. (2005). A tunnel state is a state that can be occupied for only 1 cycle, it represents at the same time the health state a person is in and the number of cycles previously spent in this state. A state \( A \) with state-time dependency is expanded in \( t \) tunnel states \( A_1, A_2, \ldots, A_t \) (where \( t \) is the total number of cycles). For example consider the following transition matrix:

\[
\begin{bmatrix}
P(A \rightarrow A) = f(s) & P(A \rightarrow B) = C \\
P(B \rightarrow A) & P(B \rightarrow B)
\end{bmatrix}
\]

Where \( P(A \rightarrow B) \) is the transition probability between state \( A \) and \( B \), \( s \) the number of cycles spent in state \( A \), \( f \) an arbitrary function returning a transition probability, and \( C \) the probability complement (1 minus the sum of probabilities in a given row). \( P(B \rightarrow A) \) and \( P(B \rightarrow B) \) are arbitrary probabilities that do not depend on state time.

---

\(^{18}\)Of length equal to the number of states.
The matrix in Equation 3 can be expanded to the following matrix when the model is run for $t$ cycles:

$$
\begin{bmatrix}
0 & P(A_1 \rightarrow A_2) = f(1) & 0 & \cdots & 0 & 0 & P(A_1 \rightarrow B) = C \\
0 & 0 & P(A_2 \rightarrow A_3) = f(2) & \cdots & 0 & 0 & P(A_2 \rightarrow B) = C \\
0 & 0 & 0 & \cdots & 0 & 0 & P(A_3 \rightarrow B) = C \\
\vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\
0 & 0 & 0 & \cdots & 0 & P(A_{t-1} \rightarrow A_t) = f(t-1) & P(A_{t-1} \rightarrow B) = C \\
0 & 0 & 0 & \cdots & 0 & P(A_t \rightarrow A_t) = f(t) & P(A_t \rightarrow B) = C \\
& P(B \rightarrow A) & 0 & 0 & \cdots & 0 & 0 & P(B \rightarrow B) \\
\end{bmatrix}$$

(4)

The semi-Markov model described in Equation 3 is now rearranged as a classic Markov model. It can be noticed that if we were to run this model for more than $t$ cycles then $P(A \rightarrow A)$ would remain constant after time $t$, at a value of $f(t)$. This property is useful in situations where $f(s)$ become roughly constant when $s \geq t$: in that case we can stop the state expansion at $t$ tunnel states in order to limit the final matrix size, and thus the computational burden. This approximation is implemented in heemod with the state_cycle_limit option of run_model().

In practice in heemod any state where state time dependency is detected is implicitly converted internally to a sequence of tunnel states. Counts and values are internally computed for each tunnel state, and then internally re-aggregated before being returned to the user as a single state. The transformation to a sequence of tunnel states is thus invisible for the user, except for a message informing of the implicit state expansion.

4.3. Implementing budget impact analysis

The main technical difficulty to implement budget impact analyses is that new individuals may enter the model at any point in time. The classic Markov model computation described in Equation 1 cannot be used any more. Instead the probability of being in a given state at time $k$ is given by the following sequence:

$$
a_0 = Y \\
a_k = a_{k-1} \times T + Z
$$

(5)

Where $Y$ is a vector of the number of individuals in a given state at the start of the model, $T$ a 2-dimensional transition matrix, and $Z$ a vector\(^{19}\) giving the number of new individuals entering the model at each new cycle.

Equation 5 can be adapted to allow (1) for model time dependency of transition probabilities as described in Equation 2 and (2) for time-dependency of the number of individual entering the model at each new cycle, in this way:

$$
a_0 = Y \\
a_k = a_{k-1} \times U_k + Z_k
$$

(6)

Where $U_k$ is a 2-dimensional slice of the 3-dimensional transition matrix $U$, and $Z_k$ a vector giving the number of new individuals entering the model at cycle $k$.

Finally, state time dependency by tunnel state expansion can be integrated without any change to Equation 6.

\(^{19}\)Of length equal to the number of states.
5. Package design and back-end

In this section we explain the ideas underlying the design of the package, the general structure, and the validation process. The entire workflow is summarised in a chart presented in Figure 8. We then present the package back-end and how most of the features were actually implemented.

5.1. Package design and workflow

The package was focused on reproducibility of analyses and ease of use. Both those objectives could be reached by making the functions unambiguous and easily readable by humans. We tried to rely on Hadley Wickham’s *tidy manifesto* to design our package in that direction (Wickham 2017).

We divided health economic evaluation modelling into distinct and sequential tasks, and wrote simple *verb* functions corresponding to the most common tasks (e.g. `define_*`, `run_*`), detailed in Figure 8.

We tried to keep functions as simple as possible: each function should do one thing, each task should have its own function. By simplifying the options we hoped to simplify how the user thinks about modelling, hence making it easier not only to build models, but more importantly for another user to read and understand someone else’s model. This last point is of particular importance if we want more research transparency and reproducibility in health economic evaluation studies.

To paraphrase Hal Abelson, we think that models must be written for people to read, and only incidentally for machines to execute.

5.2. Validation

We validated the package by reproducing the exact result of 2 analyses described in the reference textbook by Briggs *et al.* (2006): the HIV therapy and the total hip replacement model. In both case we found identical results (total values, patient counts and ICERs).

To ensure the results remain correct when the package is updated or when a dependency is upgraded multiple tests were written with the *testthat* package (Wickham 2011). We verify that functions produce the expected output, that incorrect inputs generate errors, and that results from published models are reproduced. The tests are run as soon as a modification is made to the code: when a change introduces a bug a warning is raised and remains until the issue is fixed.

5.3. Back-end

The *heemod* package syntax relies heavily on the non-standard evaluation features offered by *lazymeval* (Wickham 2016). This allows the user to define parameters, state values, and transition probabilities as a sequence of expressions to be evaluated at runtime. In addition to being familiar to users of the *dplyr* package (Wickham and Francois 2016), this results has the advantage of resembling spreadsheet formulae and making heemod more approachable, while keeping namespace collisions in check.\(^{20}\)

\(^{20}\)A usual pitfall of non-standard evaluation in R.
Figure 8: **heemod** package workflow. Drawn with yEd (yWorks 2016).
Figure 9: Example of plot customization.

More generally, most of heemod’s core functions rely on the dplyr package: the objects, data, and results are stored as tbl_df objects, the dplyr implementation of data frames. This is another principle of the tidy manifesto (Wickham 2017): reuse existing data structures. This allows the use of powerful base functions, efficient computation by limiting copy creation, and iterative model re-computation for PSA or heterogeneity analyses with the `dplyr::do()` function.

Relying on another package instead of writing package-specific functions has the drawback that slightly ill-fitting data structures may sometimes be used. But we think this drawback is outweighed by the multiple advantages of piggybacking a widely used package such as dplyr. We benefit from the code quality control and the constantly improving features of a popular package, letting us focus our development time on actually implementing Markov models. Even more importantly our internal code is easier to understand by anyone familiar with dplyr. This last point reduces barriers to entry for potential contributors.

The plotting functions rely on the ggplot2 package (Wickham 2009), and can be easily customized using the + operator. The following code is used to produce Figure 9:

```r
R> library(ggplot2)
R+ plot(res_psa, type = "ce") +
R+ scale_color_brewer(name = "Treatment", palette = "Set1") +
R+ facet_wrap(~ .strategy_names) +
R+ xlab("Incremental QALYs") + ylab("Incremental Costs") +
R+ geom_hline(yintercept = 0, linetype = "dashed") +
R+ geom_vline(xintercept = 0, linetype = "dashed")
```

The plotting of transition matrices as directed diagrams is performed by the diagram package (Soetaert 2014), the covariance analysis of PSA relies on the mgcv package (Wood 2011), and the weighted summary of the results is computed with the Hmisc package (Harrell and Dupont 2016).

The running time of some functions is not negligible (e.g. `get_who_mr()`). While half a second is not an issue when a function is run only once, it becomes a major hurdle during re-sampling where the function may be called thousands of times. We used the memoisation features of the memoise package (Wickham et al. 2016) to shorten execution time: when a
function is called the result is kept in memory alongside the values of the calling arguments. If the function is called again with the same argument values then the function body is not evaluated, but the memoised result is instantly returned instead. The use of memoisation is particularly efficient in re-sampling because in most cases the values of the arguments of most functions remain identical, resulting in the same outputs.

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