INNOVATION AND VALUE INITIATIVE

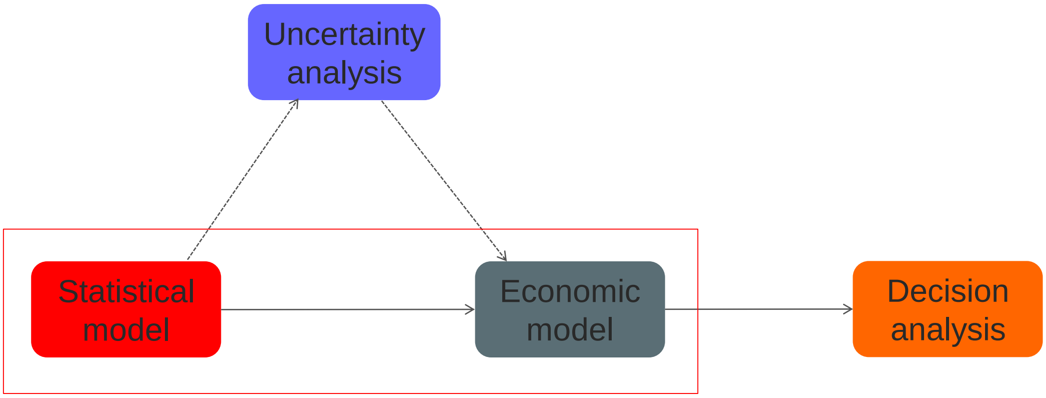
Developing relevant economic models with R for health technology assessment

Devin Incerti

What is a relevant model?

- Based on available clinical evidence
- Quantifies decision uncertainty
- Transparent and reproducible
- Reusable and adaptable

Building an economic model for decision analysis



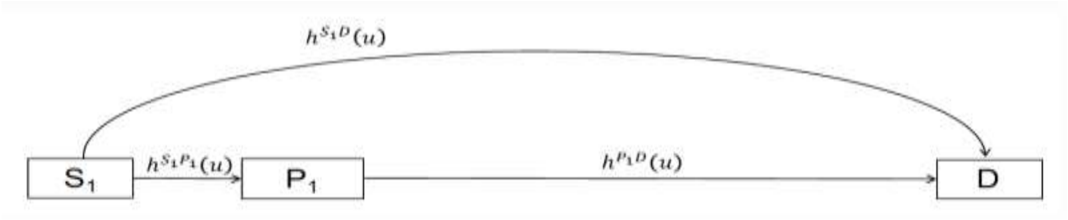
Uncertainty analysis

Statistical model

Economic model

Decision analysis

Example: a multi-state model in oncology

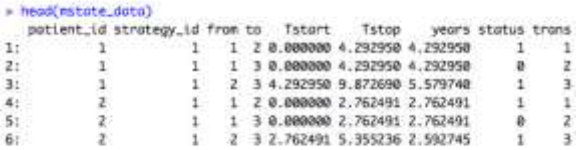


- 3 health states
  1. S1: Stable disease
  2. P1: Progressed disease
  3. D: Death
- 3 transitions where $h^{rs}(u)$ is the time-varying hazard for transitions from state r to s as a function of time u
  1. Stable -> Progression
  2. Stable -> Death
  3. Progression -> Death

Parameterizing multi-state models

Statistical method	R package	Data
Network meta-analysis	`rjags/rbugs/rstan`	Summary data from RCTs
Parametric & 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 data with continuously observed processes



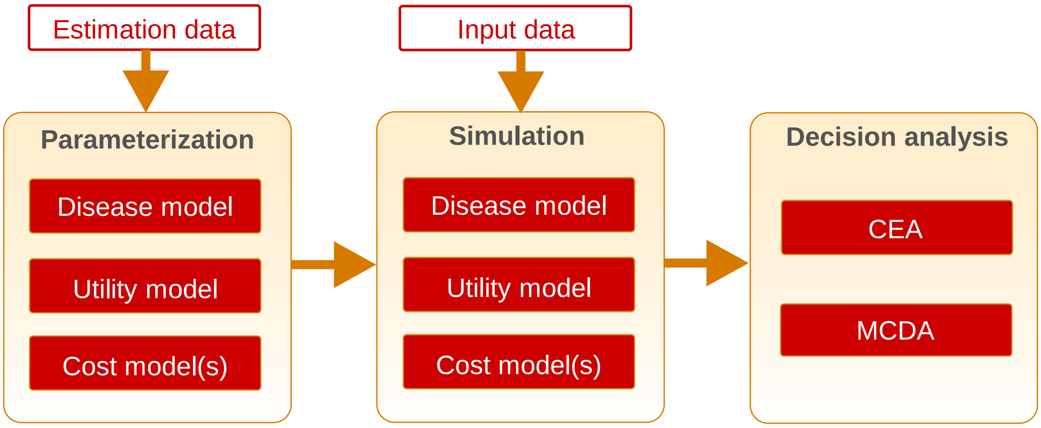
```
> head(mstate_data)
   patient_id strategy_id from to   Tstart    Tstop    years status trans
1:          1           1    1  2 0.000000 4.292950 4.292950      1     1
2:          1           1    1  3 0.000000 4.292950 4.292950      0     2
3:          1           1    2  3 4.292950 9.872690 5.579740      1     3
4:          2           1    1  2 0.000000 2.762491 2.762491      1     1
5:          2           1    1  3 0.000000 2.762491 2.762491      0     2
6:          2           1    2  3 2.762491 5.355236 2.592745      1     3
```

Fitting a multi-state Weibull model with flexsurv

```
fit_wei <- flexsurv::flexsurvreg(Surv(years, status) ~
                                 factor(strategy_id) * trans +
                                 shape(trans),
                                 data = mstate_data,
                                 dist = “weibull”)
```

A “clock reset” model

`hesim`: a new R package for integrating statistical and economic models for decision analysis



Estimation data

Input data

Parameterization

- Disease model
- Utility model
- Cost model(s)

Simulation

- Disease model
- Utility model
- Cost model(s)

Decision analysis

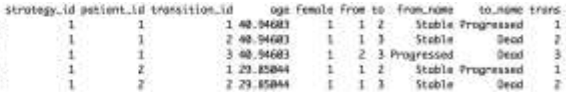
- CEA
- MCDA

Economic models are constructed by combining statistical models for disease progression, utility, and costs. Disease progression, QALYs, and costs are simulated, which are used for decision analysis

Simulating an economic model

- Individual continuous time state transition models (*iCTSTMs*) can be used to simulate “clock-reset” multi-state models in `hesim`
- Disease progression, utilities and costs simulated as function of *input data* and *parameters*

Input data for disease model

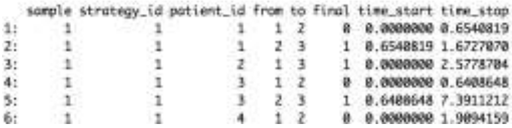


```
   strategy_id patient_id transition_id      age female from to  from_name    to_name trans
1:           1          1             1 40.94683      1    1  2     Stable Progressed     1
2:           1          1             2 40.94683      1    1  3     Stable       Dead     2
3:           1          1             3 40.94683      1    2  3 Progressed       Dead     3
4:           1          2             1 29.85044      1    1  2     Stable Progressed     1
5:           1          2             2 29.85044      1    1  3     Stable       Dead     2
```

Parameters for disease model

```
Estimates:
                            data mean  est      L95%     U95%     se       exp(est)  L95%     U95%
shape                            NA    0.8274   0.7001   0.9779   0.0706        NA        NA        NA
scale                            NA    5.2865   3.9219   7.1258   0.8053        NA        NA        NA
factor(strategy_id)2         0.4834    0.2004  -0.2959   0.6966   0.2532   1.2218    0.7438    2.0070
trans2                       0.3992    0.9847   0.4685   1.5010   0.2634   2.6771    1.5976    4.4861
trans3                       0.2016   -0.2770  -0.6554   0.1014   0.1831   0.7581    0.5192    1.1067
factor(strategy_id)2:trans2  0.2035   -0.9044  -1.5706  -0.2381   0.3399   0.4048    0.2079    0.7881
factor(strategy_id)2:trans3  0.0763   -0.4157  -1.0671   0.2357   0.3324   0.6599    0.3440    1.2658
shape(trans2)                0.3992    0.6986   0.3698   1.0275   0.1678   2.0110    1.4474    2.7939
shape(trans3)                0.2016    0.4015   0.1488   0.6543   0.1290   1.4941    1.1604    1.9238
```

Simulated disease progression



```
   sample strategy_id patient_id from to final time_start time_stop
1:      1           1          1    1  2     0  0.0000000 0.6540819
2:      1           1          1    2  3     1  0.6540819 1.6727070
3:      1           1          2    1  3     1  0.0000000 2.5778704
4:      1           1          3    1  2     0  0.0000000 0.6408648
5:      1           1          3    2  3     1  0.6408648 7.3911212
6:      1           1          4    1  2     0  0.0000000 1.9094159
```

Uncertainty in parameters propagated to uncertainty in disease progression via PSA

R code is a wrapper for underlying C++, which makes PSA with microsimulation fast

R facilitates script based analyses

- Economic model combines disease model (i.e., transition model for iCTSTM), utility model, and cost models

```
econmod <- IndivCtstm$new(trans_model = transmod,
                          utility_model = utilmod,
                          cost_models = costmods)
```

- Which is used to simulate costs and quality-adjusted life-years (QALYs)

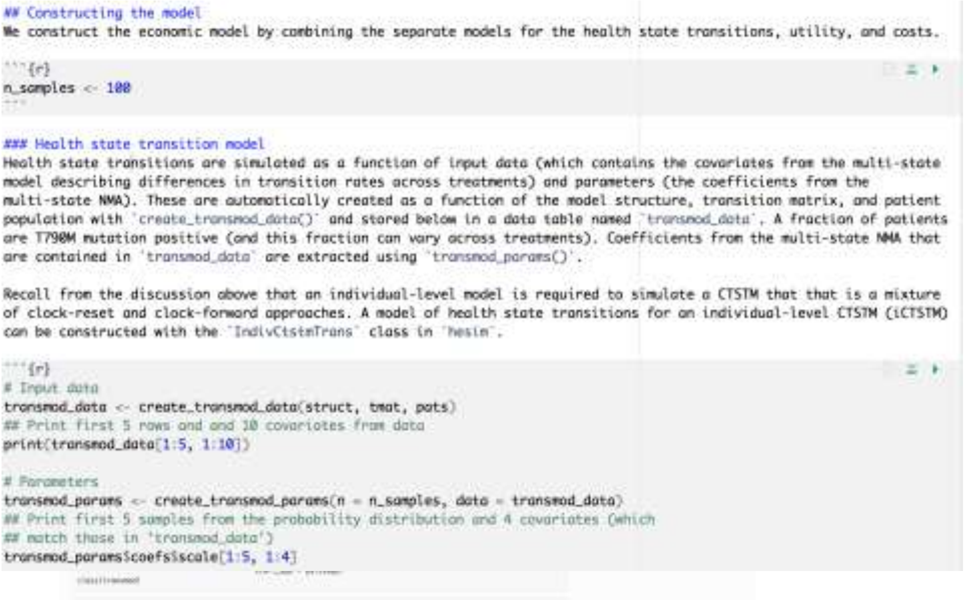
```
econmod$sim_disease()
econmod$sim_qalys(dr = .03)
ecpnmod$sim_costs(dr = .03)
```

- And can be used for cost-effectiveness analysis

```
# with hesim
ce <- econmod$summarize()
icea <- icea(ce, dr = .03)
icea_pw <- icea_pw(ce, dr = 0.03,
                   comparator = 2
```

```
# with BCEA
qalys_mat <- matrix(ce$qalys$qalys, nrow = n_samples,
                    byrow = TRUE)
costs_mat <- matrix(ce$costs$costs, nrow = n_samples,
                    byrow = TRUE)
bcea <- BCEA::bcea(e = qalys_mat, c = costs_mat,
                   ref = 2)
```

Making models reproducible with R Markdown



~~~
## Constructing the model
We construct the economic model by combining the separate models for the health state transitions, utility, and costs.

```{r}
n_samples <- 100
~~~

Health state transition model
Health state transitions are simulated as a function of input data (which contains the covariates from the multi-state
model describing differences in transition rates across treatments) and parameters (the coefficients from the
multi-state NMA). These are automatically created as a function of the model structure, transition matrix, and patient
population with `create_transmod_data()` and stored below in a data table named `transmod_data`. A fraction of patients
are T790M mutation positive (and this fraction can vary across treatments). Coefficients from the multi-state NMA that
are contained in `transmod_data` are extracted using `transmod_params()`.

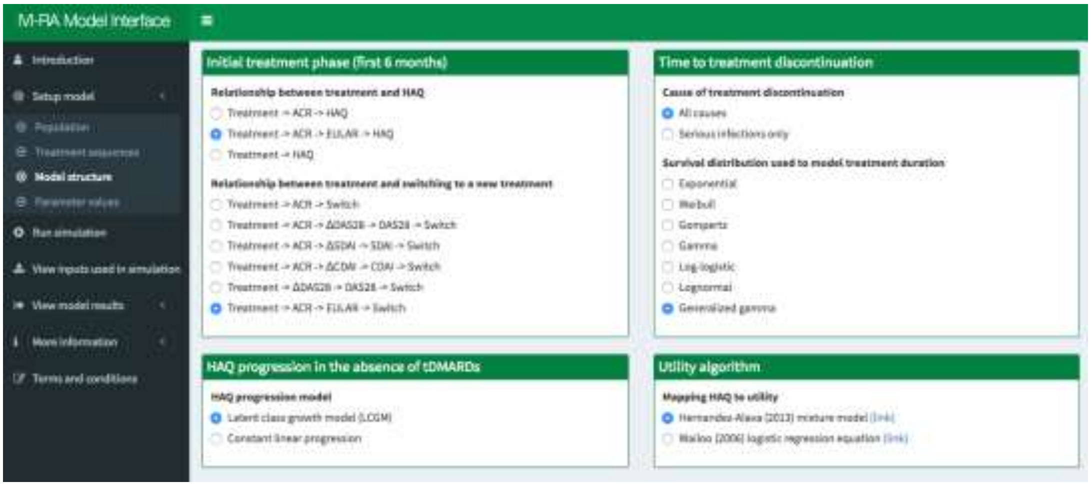
Recall from the discussion above that an individual-level model is required to simulate a CTSTM that that is a mixture
of clock-reset and clock-forward approaches. A model of health state transitions for an individual-level CTSTM (iCTSTM)
can be constructed with the `IndivCtstmTrans` class in `hesim`.

```{r}
# Input data
transmod_data <- create_transmod_data(struct, tmat, pats)
## Print first 5 rows and and 10 covariates from data
print(transmod_data[1:5, 1:10])

# Parameters
transmod_params <- create_transmod_params(n = n_samples, data = transmod_data)
## Print first 5 samples from the probability distribution and 4 covariates (which
## match those in 'transmod_data')
transmod_params$coefs$scale[1:5, 1:4]
```

Increasing transparency with web apps

- Web apps can be built using R Shiny or by embedding R code into JavaScript
- Allows users to run custom analyses without any knowledge of R



Initial treatment phase (first 6 months)

Relationship between treatment and HAQ
○ Treatment → ACR → HAQ
● Treatment → ACR → EULAR → HAQ
○ Treatment → HAQ

Relationship between treatment and switching to a new treatment
○ Treatment → ACR → Switch
○ Treatment → ACR → ΔDAS28 → DAS28 → Switch
○ Treatment → ACR → ΔSDAI → SDAI → Switch
○ Treatment → ACR → ΔCDAI → CDAI → Switch
○ Treatment → ΔDAS28 → DAS28 → Switch
● Treatment → ACR → EULAR → Switch

Time to treatment discontinuation

Cause of treatment discontinuation
● All causes
○ Serious infections only

Survival distribution used to model treatment duration
○ Exponential
○ Weibull
○ Gompertz
○ Gamma
○ Log-logistic
○ Lognormal
● Generalized gamma

HAQ progression in the absence of tDMARDs

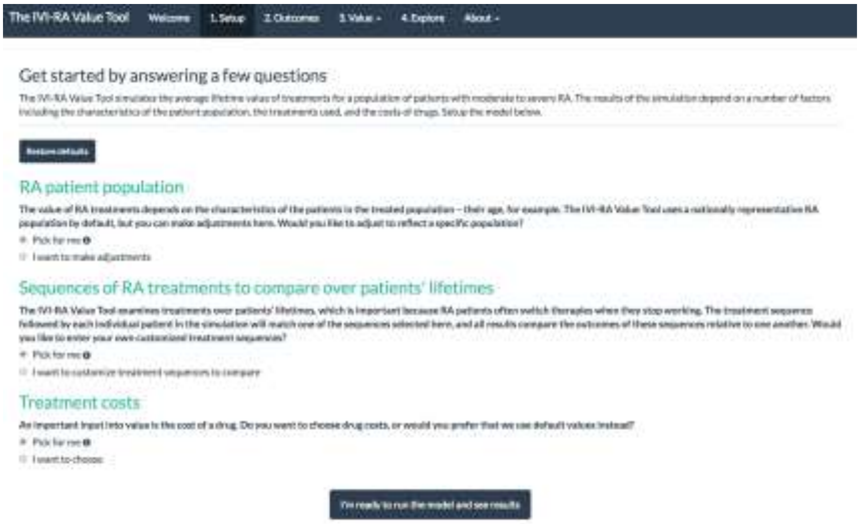
HAQ progression model
● Latent class growth model (LCGM)
○ Constant linear progression

Utility algorithm

Mapping HAQ to utility
● Hernandez-Alava (2013) mixture model (link)
○ Wailoo (2006) logistic regression equation (link)

Tailoring web apps to different audiences

> Web app for rheumatoid arthritis decision model aimed at general audience



Get started by answering a few questions

The IVI-RA Value Tool simulates the average lifetime value of treatments for a population of patients with moderate to severe RA. The results of the simulation depend on a number of factors including the characteristics of the patient population, the treatments used, and the costs of drugs. Setup the model below.

RA patient population

The value of RA treatments depends on the characteristics of the patients in the treated population – their age, for example. The IVI-RA Value Tool uses a nationally representative RA population by default, but you can make adjustments here. Would you like to adjust to reflect a specific population?

● Pick for me
○ I want to make adjustments

Sequences of RA treatments to compare over patients' lifetimes

The IVI-RA Value Tool examines treatments over patients' lifetimes, which is important because RA patients often switch therapies when they stop working. The treatment sequence followed by each individual patient in the simulation will match one of the sequences selected here, and all results compare the outcomes of these sequences relative to one another. Would you like to enter your own customized treatment sequences?

● Pick for me
○ I want to customize treatment sequences to compare

Treatment costs

An important input into value is the cost of a drug. Do you want to choose drug costs, or would you prefer that we use default values instead?

● Pick for me
○ I want to choose

So why R?

> A comprehensive ecosystem for fitting statistical models

> Computational efficiency

> Reproducible research

> Web apps

> Unit testing

Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: Following our presentations, how much more likely are you to start using R for decision modelling?

Resources

- Gianluca’s R packages
  - https://github.com/giabaio
  - http://www.statistica.it/gianluca/page_software/
- Toy decision tree model
  - https://github.com/Bogdasayen/Depression-toy-decision-tree-in-R
- hesim
  - https://innovationvalueinitiative.github.io/hesim/
- IVI-RA Web apps
  - Expert (https://innovationandvalueinitiative.shinyapps.io/ivi-ra-expert/)
  - General audience (https://innovationandvalueinitiative.shinyapps.io/ivi-ra/)

IVI INNOVATION AND VALUE INITIATIVE

Location

11100 Santa Monica Blvd Suite 500
Los Angeles, CA 90025

Devin Incerti
devin.incerti@thevalueinitiative.org

www.thevalueinitiative.org