EXCEL WITH YOUR ECONOMIC MODELS IN R

IVI INNOVATION AND VALUE INITIATIVE

PRECISION XTRACT

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

Today's speakers

- Jeroen P Jansen PhD
  - Precision; Innovation & Value Initiative
- Joseph Levy PhD
  - John Hopkins University
- Devin Incerti PhD
  - Precision; Innovation & Value Initiative

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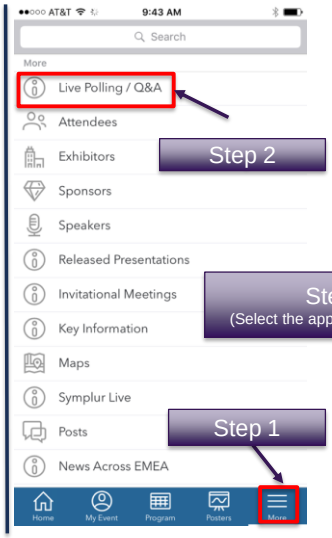

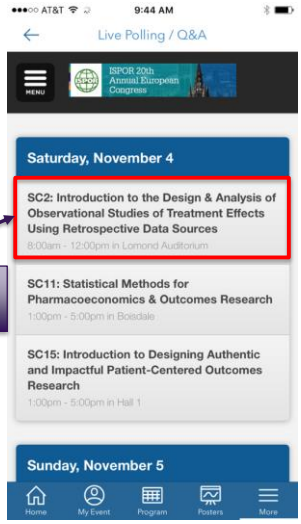

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Live Content Slide

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Poll: What software do you mostly use for cost-effectiveness analysis?

Live Content Slide

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

Poll: Do you think R is better for cost-effectiveness modeling and analysis than Excel?



Rationale



Criteria that economic models should strive to meet

- Clinical realism
  - A model should reflect the state of evidence, the current understanding of the disease, and be accepted by clinical experts.
- Quantifying decision uncertainty
  - A model should be capable of quantifying decision uncertainty and informing prioritization of future research.
- Transparency and reproducibility
  - Resources should exist so that a model can be completely understood, reproduced, and pressure tested.
- Reusability and adaptability
  - It should be possible to easily update a model to reflect new clinical evidence or adapt it for a new market, indication, or intervention.
- *Many of these are unobtainable without the use of modern software*

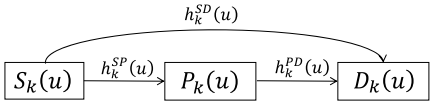
Common practice – 2-step approach

- Input parameter estimation (by means of evidence synthesis) with statistical software
- Forward simulation to calculate expected outcomes (e.g. QALYs, costs, NMBs, etc.) with economic model implemented in MS Excel

Plugging in model input parameter estimates

Oncology

Preferred economic model structure: multi-state model



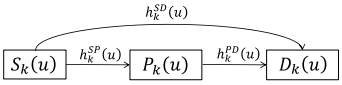
Common practice

Economic model
- Partitioned survival model

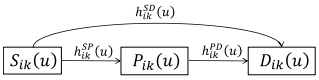
Evidence synthesis
- Typical source data: KM curves, hazard ratios
- Meta-analysis of baseline hazard function for PFS and OS
- Network meta-analysis of (time-varying) hazard ratios for PFS and OS

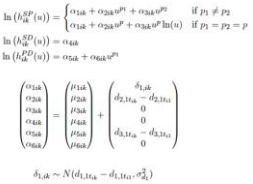
Why not this?

Economic model

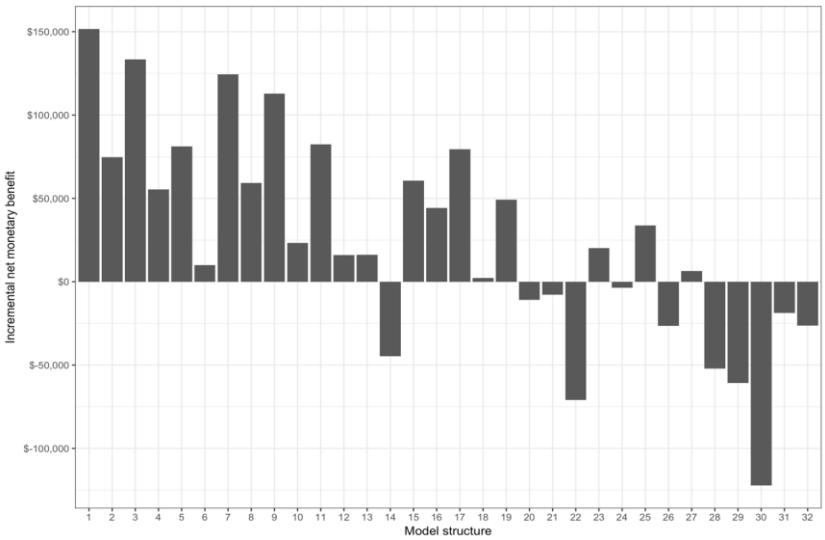


Evidence synthesis

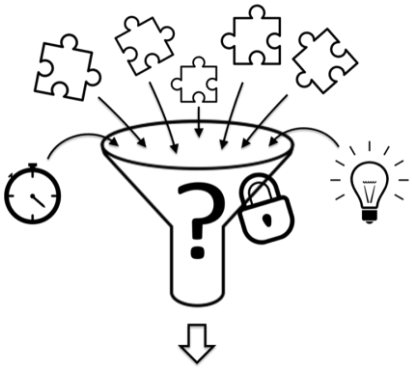




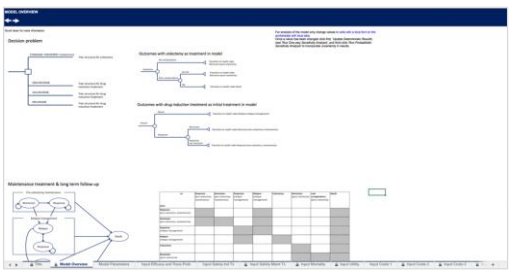
Quantifying decision uncertainty as a function of parameter uncertainty and structural uncertainty

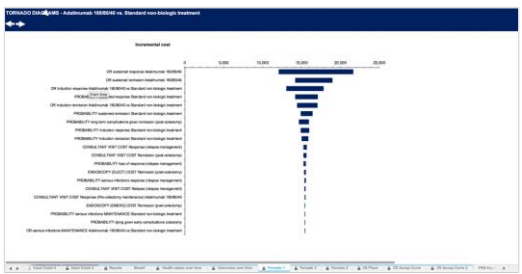


Transparency & reproducibility

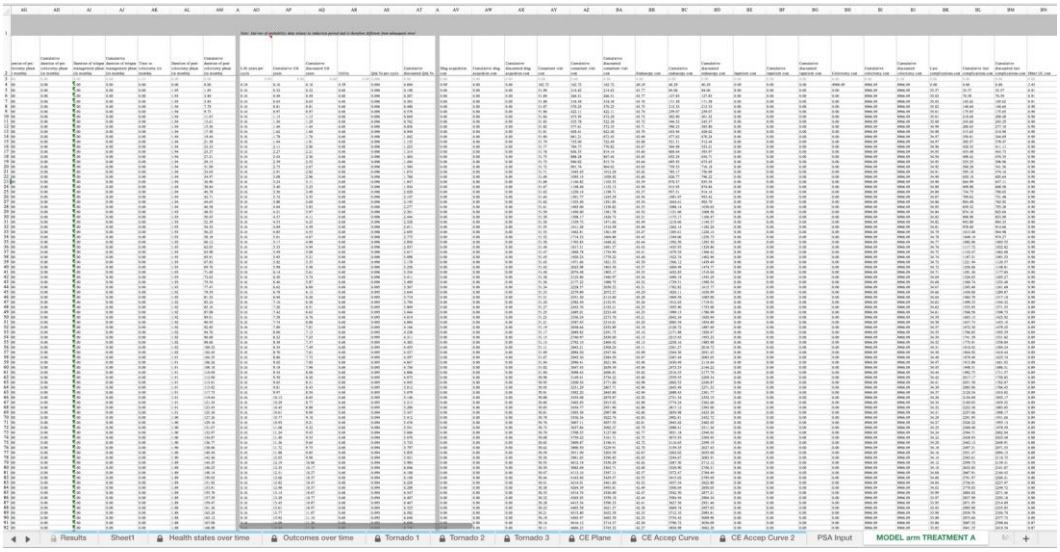


Excel-based models





Excel-based models



What do we mean with model transparency?

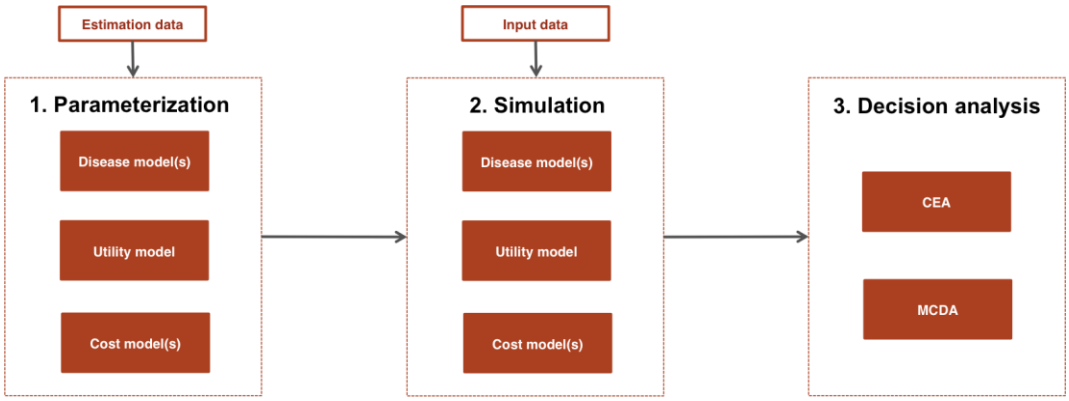
- Concept, math
- Face validity
- Implementation/programming
- Open-source, open-access

- *Familiarity with software?*

Alternative

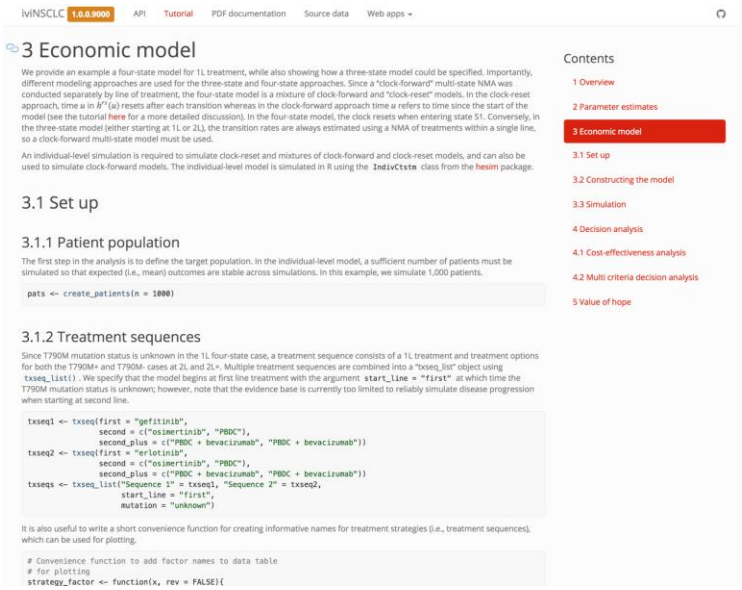
BCEA HEEMOD HESIM …

`hesim`

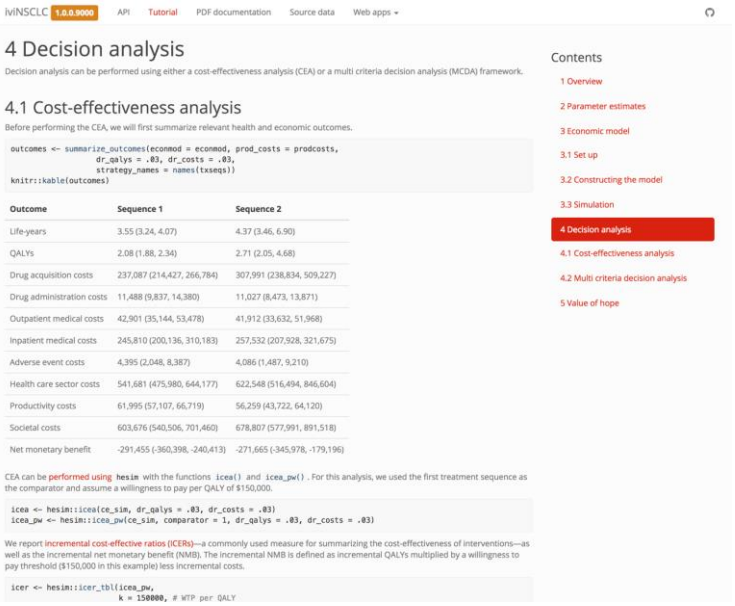


http://hesim-dev.github.io/hesim/

Increasing transparency with reproducible scripts



Increasing transparency with reproducible scripts



ivINSCLC 1.0.0.9000 API Tutorial PDF documentation Source data Web apps

4 Decision analysis

Decision analysis can be performed using either a cost-effectiveness analysis (CEA) or a multi criteria decision analysis (MCDA) framework.

4.1 Cost-effectiveness analysis

Before performing the CEA, we will first summarize relevant health and economic outcomes.

```
outcomes <- summarize_outcomes(econmod = econmod, prod_costs = prodcosts,
                               dr_qalys = .03, dr_costs = .03,
                               strategy_names = names(txseqs))
knitr::kable(outcomes)
```

Outcome	Sequence 1	Sequence 2
Life-years	3.55 (3.24, 4.07)	4.37 (3.46, 6.90)
QALYs	2.08 (1.88, 2.34)	2.71 (2.05, 4.68)
Drug acquisition costs	237,087 (214,427, 266,784)	307,991 (238,834, 509,227)
Drug administration costs	11,488 (9,837, 14,380)	11,027 (8,473, 13,871)
Outpatient medical costs	42,901 (35,144, 53,478)	41,912 (33,632, 51,968)
Inpatient medical costs	245,810 (200,136, 310,183)	257,532 (207,928, 321,675)
Adverse event costs	4,395 (2,048, 8,387)	4,086 (1,487, 9,210)
Health care sector costs	541,681 (475,980, 644,177)	622,548 (516,494, 846,604)
Productivity costs	61,995 (57,107, 66,719)	56,259 (43,722, 64,120)
Societal costs	603,676 (540,506, 701,460)	678,807 (577,991, 891,518)
Net monetary benefit	-291,455 (-360,398, -240,413)	-271,665 (-345,978, -179,196)

CEA can be performed using `hesim` with the functions `icea()` and `icea_pw()`. For this analysis, we used the first treatment sequence as the comparator and assume a willingness to pay per QALY of $150,000.

```
icea <- hesim::icea(ce_sim, dr_qalys = .03, dr_costs = .03)
icea_pw <- hesim::icea_pw(ce_sim, comparator = 1, dr_qalys = .03, dr_costs = .03)
```

We report incremental cost-effective ratios (ICERs)—a commonly used measure for summarizing the cost-effectiveness of interventions—as well as the incremental net monetary benefit (NMB). The incremental NMB is defined as incremental QALYs multiplied by a willingness to pay threshold ($150,000 in this example) less incremental costs.

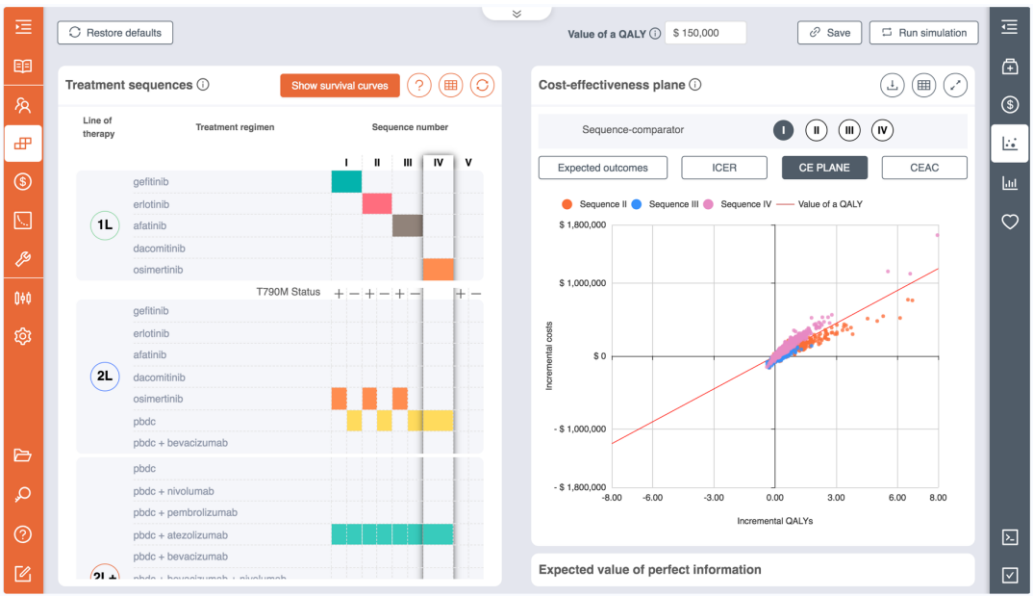
```
icer <- hesim::icer_tbl(icea_pw,
                        k = 150000, # WTP per QALY
```

Contents

1 Overview
2 Parameter estimates
3 Economic model
3.1 Set up
3.2 Constructing the model
3.3 Simulation
4 Decision analysis
4.1 Cost-effectiveness analysis
4.2 Multi criteria decision analysis
5 Value of hope

User friendly interfaces

https://innovationvalueinitiative.github.io/IVI-NSCLC/



User friendly interfaces

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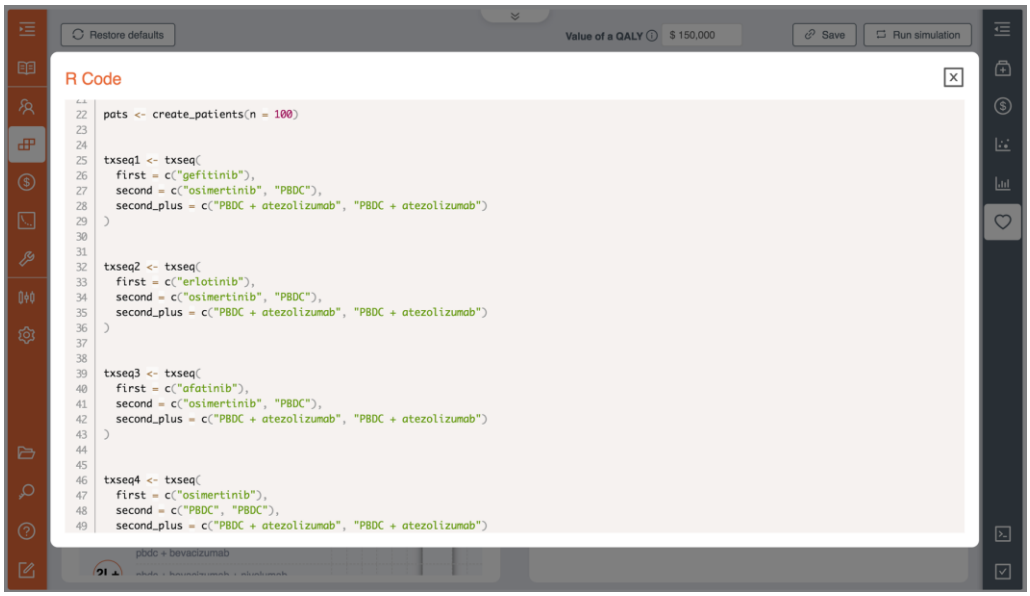
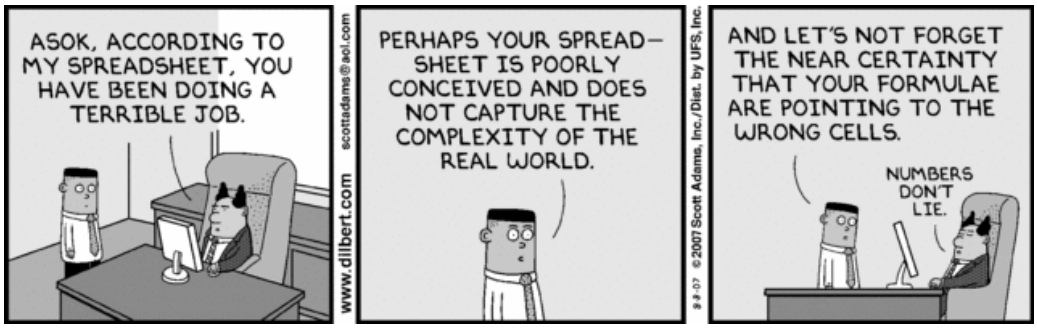


Code testing

- Unit tests can be performed to ensure units of source (e.g. functions) produce correct results
- Enhance code adaptability because developers can test that modifications or new features do not create unintended errors
- R packages (testhat, Runit) facilitate unit testing

Time to change?



Using R for health economic modeling

Modeling in Excel

- Excel has been dominant software platform used by modelers forever, especially for HTA submissions
- Reasons are not surprising:
  - (practically) Everyone with a computer has access to Excel
  - Does not require that you learn a new programming language
- Many users consider its “transparency” to be an attribute
- With models in Excel, you can follow calculations that are being performed in every single cell of every single worksheet

Modeling in Excel

- Virtually all textbooks use it
- And for simple models, it is transparent and fast to build
- However……

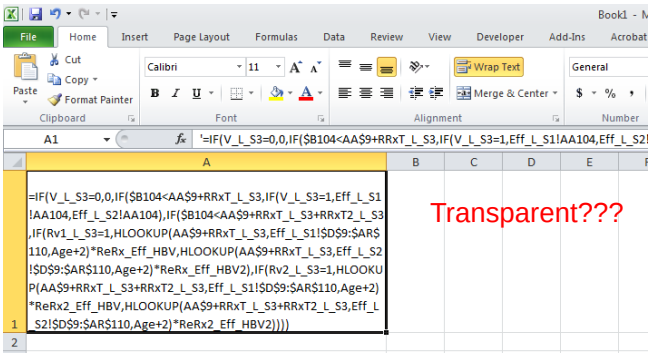


Table 1a. Probability of Clinical Events

Strategy	Description	Variable Name	Base Case value	Uncertainty	Draw (look at equation)
IF	Pr Complications	p_comp_if	0.7	beta(mean=0.7,0.15)	0.69898813
IF	Pr No Complications	pr_no_comp_if	0.3	1-	0.30101187
IF	Pr Regain	p_regain_if	0.55	beta(mean=0.55,sd=0.1)	0.553535031
IF	Pr No Regain	pr_no_regain_if	0.45	1-	0.446464969
ERF	Pr Complications	p_comp_erf	0.35	beta(0.35,0.25)	0.360783336
ERF	Pr No Complications	pr_no_comp_erf	0.65		0.639216664
ERF	Pr Regain	p_regain_erf	0.8	beta(mean=0.8, sd=0.2)	0.965500747
ERF	Pr No Regain	pr_no_regain_erf	0.2	1-	0.034499253

d

Table 1b. Treatment Costs

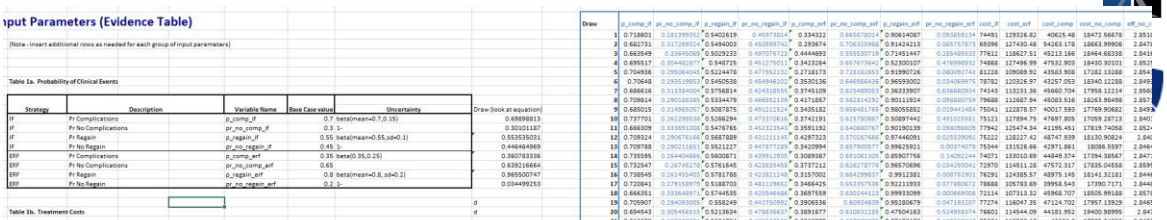
d

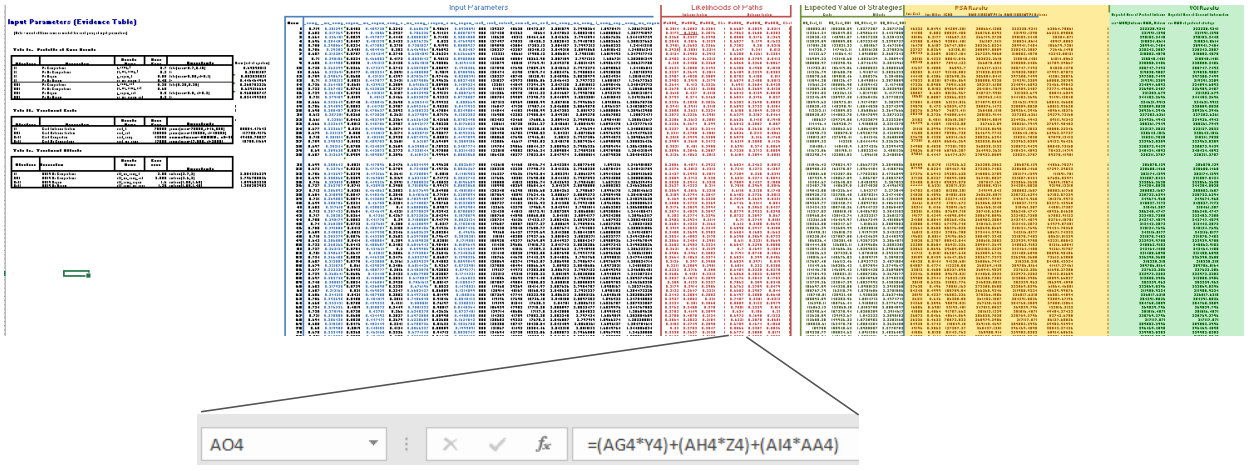
v

Strategy	Description	Variable Name	Base Case value	Uncertainty	
IF	Cost Internal Fixation	cost_if	75000	gamma(mean=75000,sd=16,500)	80804.47642
ERF	Cost External Fixation	cost_erf	120000	gamma(mean=120000, sd=45000)	117708.9176
Both	Cost Complication	cost_comp	42500	**gamma(mean=45000, sd=15000)**	49408.75537
Both	Cost No Complications	cost_no_comp	17500	gamma(mean=17,500, sd=2000)	18750.11669

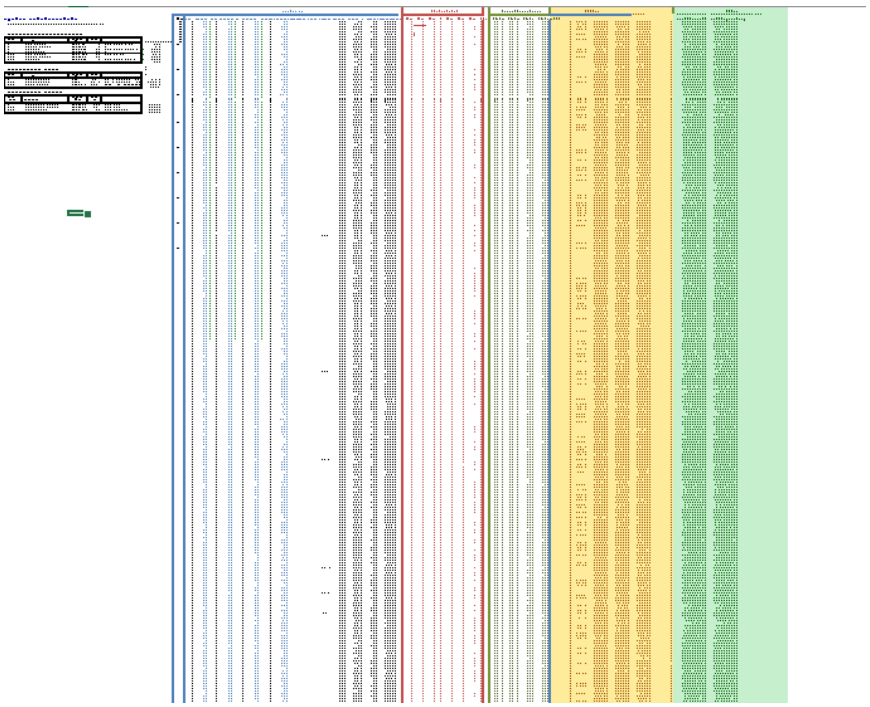
Table 1c. Treatment Effects

Strategy	Description	Variable Name	Base Case value	Uncertainty	
IF	QALY No Complications	eff_no_comp_if	2.85	uniform(2.7,3)	2.854326339
ERF	QALY No Complications	eff_no_comp_erf	2.800	uniform(2.6,3)	2.796758536
Both	QALY Regain	eff_comp_regain	1.6	uniform(1.55,1.65)	1.599653238
Both	QALY No Regain	eff_comp_no_regain	1.25	uniform(1.05,1.45)	1.258252952



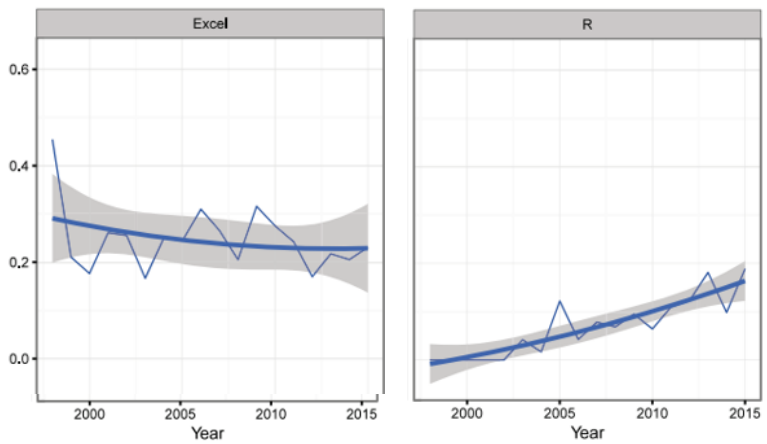

Input Parameters (Evidence Table)
Input Parameters
Likelihoods of Paths
Expected Value of Strategies
PSA Results
VOI Results

AO4
=(AG4*Y4)+(AH4*Z4)+(AI4*AA4)



Criticisms

- Really hard to check, models can be validated by building second one from scratch, this is rarely done due to budget and time constraints
- Complex procedures generally require VBA knowledge
- Increasingly more data and other models, inform CEA. Excel cannot do all of these things
- Slow performance with large and complex models



An Overview of R in Health Decision Sciences

Hawre Jalal, MD, PhD, Petros Pechlivanoglou, MSc, PhD, Eline Krijkamp, MSc, Fernando Alarid-Escudero, MSc, Eva Enns, MS, PhD, M. G. Myriam Hunink, MD, PhD

As the complexity of health decision science applications increases, high-level programming languages are increasingly adopted for statistical analyses and numerical computations. These programming languages facilitate sophisticated modeling, model documentation, and analysis reproducibility. health decision science methodology as well as the visualization and communication of results. Although R's popularity is increasing among health decision scientists, methodological extensions of R in the field of decision analysis remain isolated. The purpose of this article is to provide an overview

An Overview of R in Health Decision Sciences Jalal et al. (Med Decis Making 2017;37: 735–746)

What is R

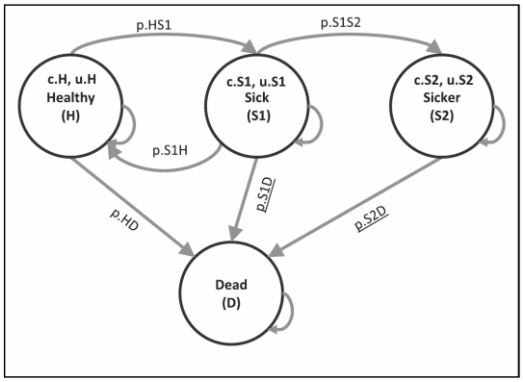
- Statistical programing language and environment for statistical computing
- Totally free to use (open source, user developed packages that are completely transparent)
- Very good for regression analysis, hypothesis testing, data management, visualization and cleaning (and many, many other things)
- All parts of an analysis can exist in one file (code)
- CEA models can be coded from ‘scratch’ using r core or via convenient and improving packages

Programing in R

- Everything is an object or function
- Code can be highly customized or generalized to suit purposes
- Packages are shareable bundles of code, data and documentation that allow for reproducible analysis
- Built for statistical analysis, contains many functions relevant for CEA
- There are many ways to do the same thing

Programing a Markov model in

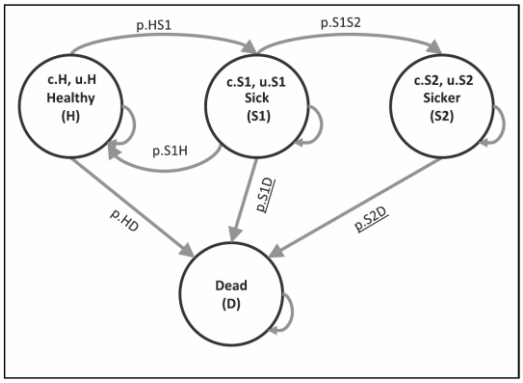
Example: Sick Sicker Markov



Adapted from Krijkamp, Eline M., et al. "Microsimulation Modeling for Health Decision Sciences Using R: A Tutorial." *Medical Decision Making* 38.3 (2018): 400-422.

- Compare Treatment to No Treatment
- 4 State Model
- Treatment Modifies Cost of Sick, Sicker and Utility of Sick
- Transitions Probabilities are the Same between treatment groups
- Time horizon: 5 years

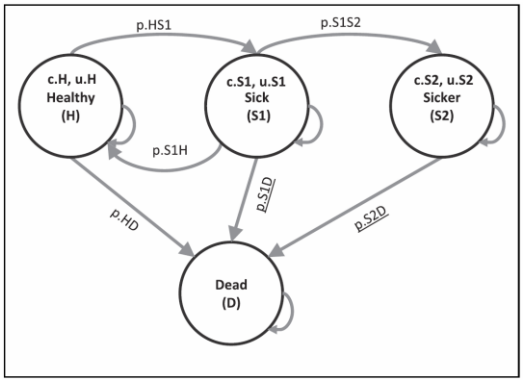
Example: Sick Sicker Markov



Krijkamp, Eline M., et al. "Microsimulation Modeling for Health Decision Sciences Using R: A Tutorial." *Medical Decision Making* 38.3 (2018): 400-422.

Parameter	No Treat	Treat
p.HS1	0.15	0.15
p.S1S2	0.105	0.105
p.S1H	0.5	0.5
p.HDie	0.005	0.005
p.S1Die	0.01492512	0.01492512
p.S2Die	0.04888987	0.04888987
cost.H	2000	2000**+12000**
cost.S1	4000	4000**+12000**
cost.S2	15000	15000**+12000**
utility.H	1	1
utility.S1	0.75	**0.95**
Utility.S2	0.5	0.5
Discount Rate	3%	3%

Example: Sick Sicker Markov

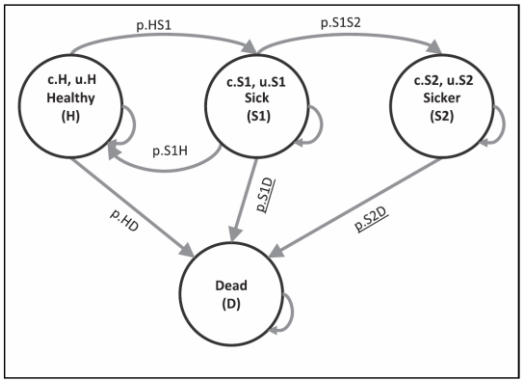


Krijkamp, Eline M., et al. "Microsimulation Modeling for Health Decision Sciences Using R: A Tutorial." *Medical Decision Making* 38.3 (2018): 400-422.

$$
\begin{array}{c} \\ H \\ S1 \\ S2 \\ D \end{array}
\begin{array}{c}
\begin{array}{cccc} H & S1 & S2 & D \end{array} \\
\begin{pmatrix} c & p.HS1 & 0 & p.HD \\ p.S1H & c & p.S1S2 & p.S1D \\ 0 & 0 & c & p.S2D \\ 0 & 0 & 0 & 1 \end{pmatrix}
\end{array}
$$

c = complement of row (i.e. 1-row_sum)

Example: Sick Sicker Markov



Krijkamp, Eline M., et al. "Microsimulation Modeling for Health Decision Sciences Using R: A Tutorial." *Medical Decision Making* 38.3 (2018): 400-422.

$$\begin{array}{c} \\ H \\ S1 \\ S2 \\ D \end{array} \begin{array}{c} \begin{array}{cccc} H & S1 & S2 & D \end{array} \\ \begin{pmatrix} c & 0.15 & 0 & 0.005 \\ 0.5 & c & 0.105 & 0.01492512 \\ 0 & 0 & c & 0.04888987 \\ 0 & 0 & 0 & 1 \end{pmatrix} \end{array}$$

c = complement of row (i.e. 1-row_sum)

State Occupancy (Matrix Arithmetic)

- Define Transition Matrix

```
> transition_matrix<-matrix(c((1-.15-0.005),.15,0,.005,
+                             .5,(1-.5-.105-0.01492512),.105,0.01492512,
+                             0,0,(1-0.04888987),0.04888987,
+                             0,0,0,1),nrow=4,byrow=T)
> transition_matrix
      [,1]      [,2]      [,3]       [,4]
[1,] 0.845 0.1500000 0.0000000 0.00500000
[2,] 0.500 0.3800749 0.1050000 0.01492512
[3,] 0.000 0.0000000 0.9511101 0.04888987
[4,] 0.000 0.0000000 0.0000000 1.00000000
```

State Occupancy (Matrix Arithmetic)

- Define Initial Population

```
> initial<-matrix(c(1000,0,0,0),nrow=1)
> initial
     [,1] [,2] [,3] [,4]
[1,] 1000    0    0    0
```

- Multiply

```
> #After Year 1
> initial%*%(transition_matrix%^%1)
     [,1] [,2] [,3] [,4]
[1,]  845  150    0    5
> #After Year 5
> initial%*%(transition_matrix%^%5)
         [,1]     [,2]    [,3]     [,4]
[1,] 713.8373 180.7036 69.2586 36.20055
```

Compute Costs (Brute Force)

```
> #Cost after time 1
> initial%*%(transition_matrix%^%1)*matrix(c(12000+2000,12000+4000,12000+15000,0),nrow=1)
         [,1]    [,2] [,3] [,4]
[1,] 11830000 2400000    0    0
>
> costTreat<-matrix(c(12000+2000,12000+4000,12000+15000,0),nrow=1)
>
> #Cost after time 5
> Treat_Cost<-
+   sum(
+     initial%*%(transition_matrix%^%1)*costTreat+
+       initial%*%(transition_matrix%^%2)*costTreat+
+       initial%*%(transition_matrix%^%3)*costTreat+
+       initial%*%(transition_matrix%^%4)*costTreat+
+       initial%*%(transition_matrix%^%5)*costTreat
+   )
> Treat_Cost
[1] 72624336
```

Compute Effects (Function)

```
> makeTraceEffect<-function(initialpop,trans,t,util){
+     trace=matrix(rep(NA, ncol(trans)* t), nrow=t)
+     for(i in 1:t){
+     trace[i,]<-initialpop%*%(trans%^%i)*util
+ }
+     return(trace)
+
+ }
> treatEffect<-matrix(c(1,0.95,0.5,0),nrow=1)
> UtilTreaT<-
makeTraceEffect(trans=transition_matrix,t=5,util=treatEffect,initialpop=initial)
> UtilTreaT
         [,1]     [,2]     [,3] [,4]
[1,] 845.0000 142.5000  0.00000    0
[2,] 789.0250 174.5732  7.87500    0
[3,] 758.6067 178.7869 17.13746    0
[4,] 735.1211 176.0539 26.17994    0
[5,] 713.8373 171.6684 34.62930    0
> sum(UtilTreaT)
[1] 4770.994
```

ICER

```
> controlEffect
     [,1] [,2] [,3] [,4]
[1,]    1 0.75  0.5    0
> UtilControl<-
makeTraceEffect(trans=transition_matrix,t=5,util=controlEffect,initialpop=initial)
> #Compute ICER
> (Treat_Cost-Control_Cost)/(sum(UtilTreaT)-sum(UtilControl))
[1] 331170.1
```

$331,170.1…….but

Can we rely on others to do this for us?

- Yes. There are **packages** that have been built with convenient functions to do virtually any type of health economic model.
- Tested and open source
- Trivializes: discounting, time dependency, trace, probabilistic sensitivity analysis, graphics, voi
- No one catch all package

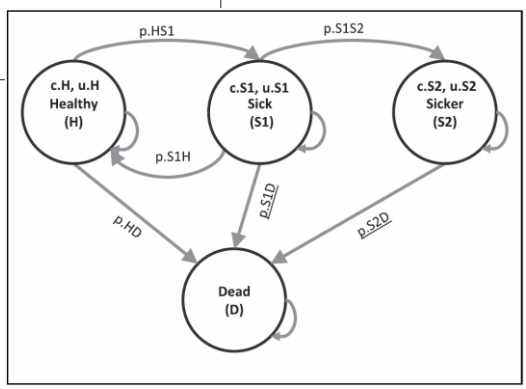
Package: heroMod (Health Economic Evaluation Modeling)

- Gives structure to build and evaluate markov (or partitioned survival) model, requires you to learn their syntax, learning curve not steep if you use R
- Packages in R contain pre built functions to do particular things
  - c = complement of row probability
  - prob_rr()
  - cycleTime
  - stateTime
  - discount(amount, rate)

https://github.com/PolicyAnalysisInc/heRoMod

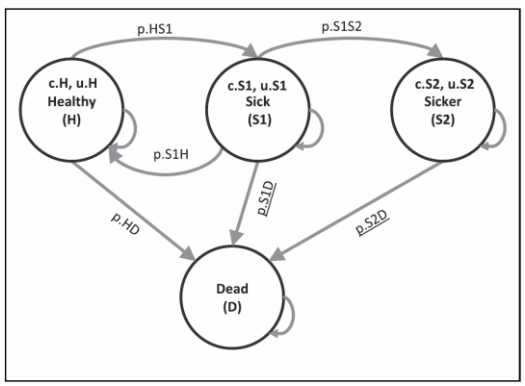
define_transition

```
> library(heRomod)
> transition_Treat<- define_transition(state_names = c("healthy","sick","sicker","dead"),
+                                      1-p.HS1-p.HD    ,p.HS1,0      ,p.HD,
+                                      p.S1H,1-p.S1H-p.S1S2-p.S1D    ,p.S1S2,p.S1D,
+                                      0    ,0    ,1-p.S2D      ,p.S2D,
+                                      0    ,0    ,0      ,1)
> transition_Treat
A transition matrix, 4 states.

        healthy          sick                        sicker    dead
healthy 1 - p.HS1 - p.HD p.HS1                                 p.HD
sick    p.S1H            1 - p.S1H - p.S1S2 - p.S1D p.S1S2    p.S1D
sicker                                              1 - p.S2D p.S2D
dead                                                           1
```



define_state

```
>   healthy_t<-define_state(cost=discount(c.H+c.Trt,dr),utility=discount(u.H,dr))
>   sick_t<-define_state(cost=discount(c.S1+c.Trt,dr),utility=discount(u.Trt,dr))
>   sicker_t<-define_state(cost=discount(c.S2+c.Trt,dr),utility=discount(u.S2,dr))
>
>   healthy<-define_state(cost=discount(c.H,dr),utility=discount(u.H,dr))
>   sick<-define_state(cost=discount(c.S1,dr),utility=discount(u.S1,dr))
>   sicker<-define_state(cost=discount(c.S2,dr),utility=discount(u.S2,dr))
>
>   dead<-define_state(cost=0,utility=0)
```



define_parameters

```
param<-define_parameters(
  dr=0.03,
  p.HD = 0.005, # probability to die when healthy
  p.HS1 = 0.15, # probability to become sick when healthy
  p.S1H =  0.5, # probability to become healthy when sick
  p.S1S2 = 0.105, # probability to become sicker when sick
  rr.S1 = 3 , # rate ratio of death when sick vs healthy
  rr.S2 = 10,  # rate ratio of death when sicker vs healthy
  r.HD = -log(1 - p.HD), # rate of death when healthy
  r.S1D = rr.S1 * r.HD, # rate of death when sick
  r.S2D = rr.S2 * r.HD, # rate of death when sicker
  p.S1D = 1-exp(-r.S1D), # probability to die when sick
  p.S2D = 1-exp(-r.S2D), # probability to die when sicker

  # Cost and utility inputs
  c.H = 2000, # cost of remaining one cycle healthy
  c.S1 = 4000 ,# cost of remaining one cycle sick
  c.S2 = 15000 ,# cost of remaining one cycle sicker
  c.Trt = 12000, # cost of treatment (per cycle)
  u.H = 1,
  u.S1 = .75,
  u.S2 = .5,
  u.Trt = .95
  )
```

Parameter	No Treat	Treat
p.HS1	0.15	0.15
p.S1S2	0.105	0.105
p.S1H	0.5	0.5
p.HDie	0.005	0.005
p.S1Die	0.01492512	0.01492512
p.S2Die	0.04888987	0.04888987
cost.H	2000	2000+12000
cost.S1	4000	4000+12000
cost.S2	15000	15000+12000
utility.H	1	1
utility.S1	0.75	0.95
Utility.S2	0.5	0.5
Discount Rate	3%	3%

```
>   model_ss<-run_model(control=strat_ctrl, treat=strat_trt, cycles=5, method="beginning",
+                       cost=cost, effect=utility,parameters = param, init = c(1000L,0L,0L,0L))
```

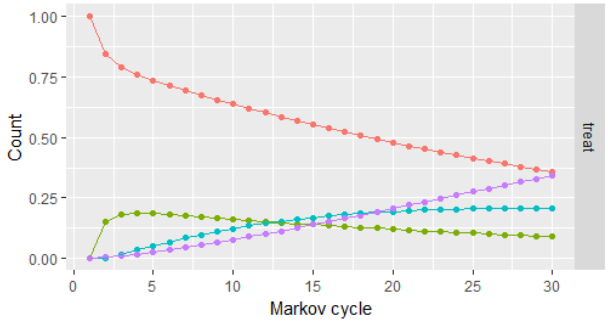
Run_model

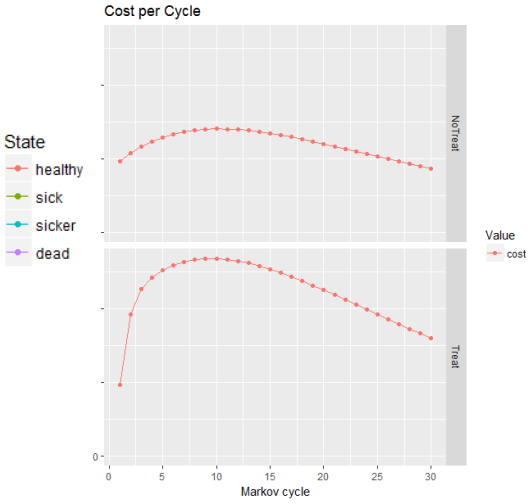
```
>   model_ss
2 strategies run for 5 cycles.

Initial state counts:

healthy = 1000L
sick = 0L
sicker = 0L
dead = 0L

Counting method: 'beginning'.

Values:

            cost  utility
control 13809757 4593.398
treat   72624336 4770.994

Efficiency frontier:

control -> treat

Differences:

      Cost Diff. Effect Diff.     ICER    Ref.
treat   58814.58    0.1775963 331170.1 control
```

```
param<-define_parameters(
  dr=0.03,
```

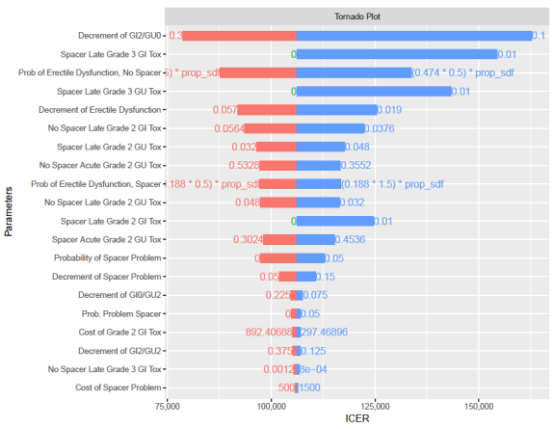
```
>   model_ss
2 strategies run for 5 cycles.

Initial state counts:

healthy = 1000L
sick = 0L
sicker = 0L
dead = 0L

Counting method: 'beginning'.

Values:

            cost  utility
control 12965715 4338.566
treat   68478655 4505.756

Efficiency frontier:

control -> treat

Differences:

      Cost Diff. Effect Diff.     ICER    Ref.
treat   55512.94    0.1671898 332035.4 control
```

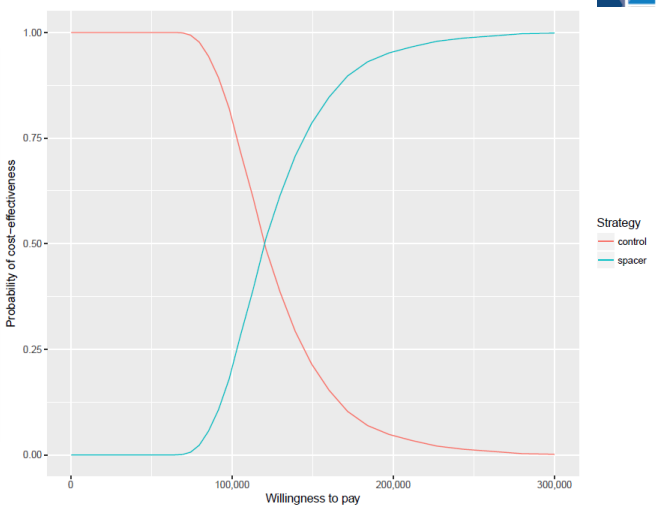
Built in Graphics





Built in Graphics





So why R?

- One platform to do everything
- Your problems are rarely unique
- Easier to share and review
- More complex analysis and microsimulation …..



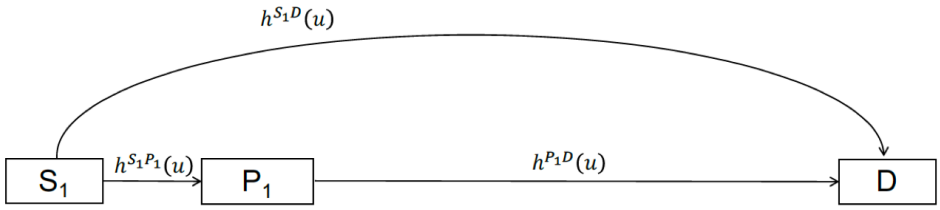


Integrating statistical and economic models with `hesim`

Economic modeling

- Economic models are constructed by combining statistical models for disease progression, costs, and utilities
  - The disease progression models simulate health state occupancy probabilities
  - The utility and cost models predict utility and costs in each health state
- Uncertainty in the parameters from the statistical models is propagated throughout the economic model and decision analysis with *probabilistic sensitivity analysis (PSA)*
- Supported economic models include N-state *partitioned survival models (PSMs)* and *continuous time state transition models (CTSTMs)*

Example CTSTM in oncology (the IVI-NSCLC model)



S_1= Progression-free (stable disease) with 1L treatment

P_1= Progression with 1L treatment, captures the survival with 2L and 2L+ without making a distinction between progression free and progression phases

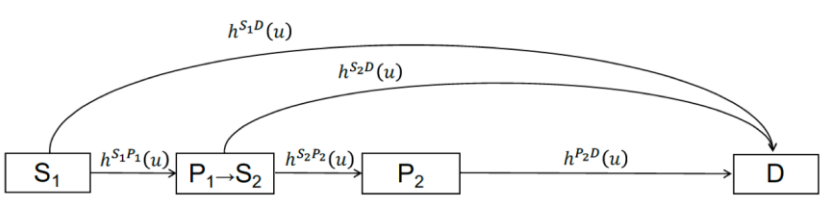
D= Dead

$h^{S_1P_1}(u)$= hazard for transitioning from progression-free to progression with 1L treatment at time *u*

$h^{S_1D}(u)$= hazard for transitioning from progression-free to dead with 1L treatment at time *u*

$h^{P_1D}(u)$= hazard for transitioning from progression on 1L to dead at time *u*

Expanding the standard 3-state oncology model to 4-states



S_1= Progression-free (stable disease) with 1L treatment

P_1= Progression with 1L treatment

S_2= Progression-free (stable disease) with 2L treatment

P_2= Progression with 2L treatment, captures the survival with 2L+ without making a distinction between a progression free and progression phase

D= Dead

$h^{S_1P_1}(u)$= hazard for transitioning from progression-free to progression with 1L treatment at time u

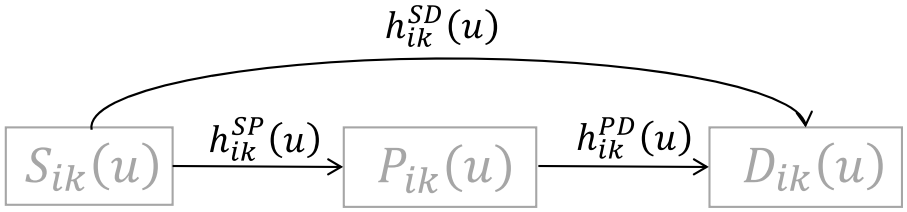
$h^{S_1D}(u)$= hazard for transitioning from progression-free to dead with 1L treatment at time u

$h^{S_2P_2}(u)$= hazard for transitioning from progression-free to progression with 2L treatment at time u

$h^{S_2D}(u)$= hazard for transitioning from progression-free to dead with 2L treatment at time u

$h^{P_2D}(u)$= hazard for transitioning from progression on 2L to dead at time u

Parameterization using multi-state network meta-analysis conducted separately by line (1L, 2L)



$S_{ik}(u)$= progression -free (stable disease) in study i, treatment arm k at time u

$P_{ik}(u)$= progressed disease in study i, treatment arm k at time u

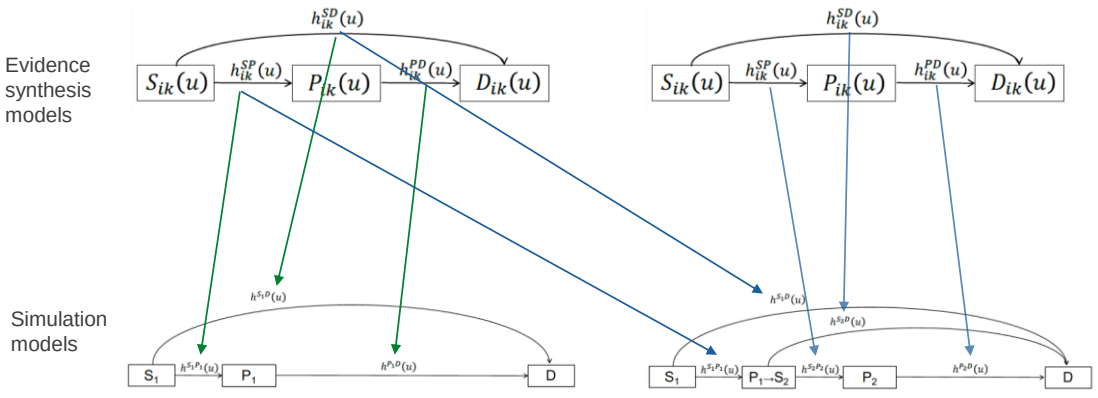
$D_{ik}(u)$= dead in study i, in treatment arm k at time u

$h_{ik}^{SP}(u)$= hazard rate for disease progression in study i, in treatment arm k at time u

$h_{ik}^{PD}(u)$= hazard rate for dying post-progression in study i, in treatment arm k at time u

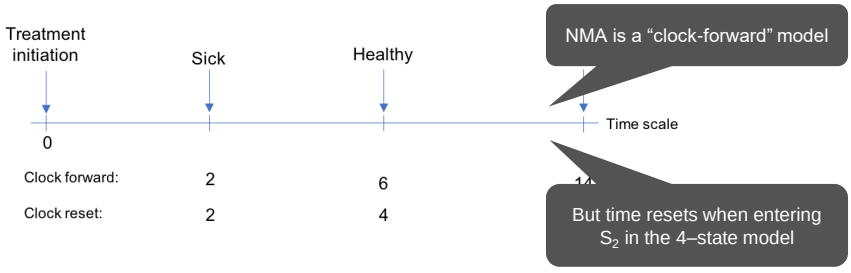
$h_{ik}^{SD}(u)$= hazard rate for dying pre-progression in study i, in treatment arm k at time u

Integration of statistical and economic models



Time scales for multi-state models

1. Markov (i.e., “clock-forward”) implies that the hazard function is based on time since initiating 1L treatment
2. Semi-Markov (i.e., “clock-reset”) implies that the hazard function is based on time since entering each state



Two methods for simulating multi-state models

1. Cohort simulation (Aalen-Johansen estimator)
   - Matrix version of the Kaplan-Meier estimator that can compute state occupancy probabilities
   - Only applicable to clock-forward models
2. Individual-level simulation
   - Simulate trajectories through multi-state model with random number generation for a large number of patients
   - Compute expected values by averaging over simulating patients
   - Applicable to both clock-forward and clock-reset models

Simulating a simplified 3-state NSCLC model with `hesim` using an individual-level simulation

Treatment strategies

- For simplicity, we will compare 2 treatment strategies

```
strategies <- data.table(strategy_id = 1:2,
                         strategy_name = c("gefitinib", "erlotinib")
print(strategies)
```

```
   strategy_id strategy_name
1:           1     gefitinib
2:           2     erlotinib
```

Target population

- Economic evaluations are conducted for a target population of interest
- Here we rely completely on summary-level RCT data so patients are identical (i.e., no covariates), but we will simulate 1,000 of them so that expected values are stable

```
patients <- data.table(patient_id = 1:1000)

patients[1:3]
```

```
   patient_id
1:          1
2:          2
3:          3
```

Model structure (health states)

- The simplified NSCLC model has 3 health states, 2 of which are non-death states

```
states <- data.table(state_id = 1:2,
                     state_name = c("Stable", "Progression")
print(states)
```

```
   state_id  state_name
1:        1      Stable
2:        2 Progression
```

Model structure (health state transitions)

- The model has 3 transitions, which are summarized with a transition table

```
tmat <- rbind(c(NA, 1, 2),
              c(NA, NA, 3),
              c(NA, NA, NA))

colnames(tmat) <- rownames(tmat) <- c("Stable", "Progression", "Dead")
transitions <- create_trans_dt(tmat)
print(transitions)
```

```
   transition_id from to   from_name     to_name
1:             1    1  2      Stable Progression
2:             2    1  3      Stable        Dead
3:             3    2  3 Progression        Dead
```

hesim data

- Information on the treatment strategies, target population, and model structure can be combined into a *hesim_data* object, which will later be used to create *input data* for the simulation

```
hesim_dat <- hesim_data(patients = patients,
                        strategies = strategies,
                        states = states,
                        transitions = transitions)
```

Constructing a model for health state transitions

- The transition model consists of parameters from the multi-state (Weibull) NMA and *input data* used for prediction

```
transmod <- create_IndivCtstmTrans(object = params_mstate_nma_wei,
                                   input_data = transmod_data,
                                   trans_mat = tmat,
                                   clock = "forward")
```

Parameters

	gef_s1p1_a0	gef_s1d_a0	gef_p1d_a0	d_erl_s1p1_a0
[1,]	-3.784340	-5.366895	-3.731685	-0.43446666
[2,]	-3.761110	-6.825649	-2.966205	-2.03816144
[3,]	-3.528427	-8.245599	-2.532110	-0.27728178
[4,]	-3.719523	-17.194142	-3.235055	-0.91764059
[5,]	-3.837291	-6.222580	-3.728116	-0.92859578
[6,]	-3.601048	-9.385497	-2.368913	0.09399997

Input data

	strategy_id	patient_id	transition_id	gef_s1p1_a0	gef_s1d_a0	gef_p1d_a0	d_erl_s1p1_a0
1:	1	1	1	1	0	0	0
2:	1	1	2	0	1	0	0
3:	1	1	3	0	0	1	0
4:	1	2	1	1	0	0	0
5:	1	2	2	0	1	0	0
6:	1	2	3	0	0	1	0

Note: The Weibull distribution used for the NMA is a reparameterization of the standard Weibull distribution that depends on 2 parameters, a_0 and a_1, which are functions of the standard shape and scale parameters

Constructing models for costs and utilities

- The easiest way to model utilities and costs is from a *stateval_tbl*

```
utility_tbl <- stateval_tbl(data.table(state_id = 1:2,
                                       mean = c(0.7540, 0.6532),
                                       sd = c(0, 0.02223000)),
                            dist = "norm",
                            hesim_data = hesim_dat)

print(utility_tbl)
```

```
   state_id   mean      sd
1:        1 0.7540 0.00000
2:        2 0.6532 0.02223
```

- Which are, in turn, used to construct a “state values” model

```
utilitymod <- create_StateVals(utility_tbl, n = 1000)
```

Creating an economic model by adding costs and utility models

- The CTSTM is constructed by combing the transition, utility, and cost models

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

Simulating health state transitions

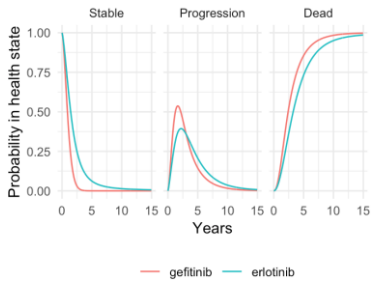
- In the individual-level CTSTM, unique trajectories through the multi-state model are simulated for each patient, treatment strategy, and PSA sample

```
econmod$sim_disease()
econmod$sim_stateprobs(t = seq(0, 20 , 1/26))
```

Disease progression

	sample	strategy_id	patient_id	from	to	final	time_start	time_stop
1:	1	1	1	1	2	0	0.0000000	0.2159427
2:	1	1	1	2	3	1	0.2159427	4.5955250
3:	1	1	2	1	2	0	0.0000000	1.6311646
4:	1	1	2	2	3	1	1.6311646	1.7369871
5:	1	1	3	1	2	0	0.0000000	1.3226559
6:	1	1	3	2	3	1	1.3226559	1.5715098

State probabilities



Simulating QALYs and costs

- By default, mean QALYs and costs are simulated by treatment strategy, patient, health state, and PSA sample

```
econmod$sim_qalys(dr = c(0, .03))
econmod$sim_costs(dr = .03)
```

QALYs

	sample	strategy_id	state_id	dr	qalys	lys
1:	1	1	1	0	0.7268540	0.9639974
2:	1	1	2	0	1.3746284	2.0465449
3:	1	2	1	0	2.2017992	2.9201580
4:	1	2	2	0	1.1798833	1.7566087
5:	2	1	1	0	0.7472271	0.9910173
6:	2	1	2	0	1.3231991	2.0574506

Costs

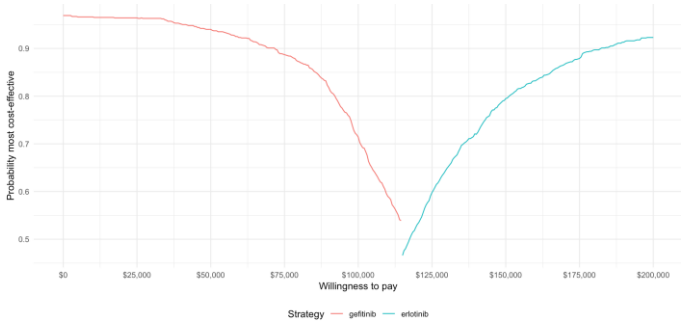
	sample	strategy_id	state_id	dr	category	costs
1:	1	1	1	0.03	Hospital	1222.653
2:	1	1	2	0.03	Hospital	9405.282
3:	1	2	1	0.03	Hospital	3510.894
4:	1	2	2	0.03	Hospital	7658.533
5:	2	1	1	0.03	Hospital	1347.405
6:	2	1	2	0.03	Hospital	12091.954

Cost-effectiveness analysis

- Summaries of costs and QALYs (i.e., estimates by treatment strategy and PSA sample) are used to perform a (potentially “individualized”) CEA

```
ce_sim <- econmod$summarize()
icea_out <- icea(ce_sim, dr_qalys = .03, dr_costs = .03)
icea_pw_out <- icea_pw(ce_sim, comparator = 1, dr_qalys = .03, dr_costs = .03)
```

Cost-effectiveness acceptability frontier



So why R?

- A comprehensive ecosystem for fitting statistical models
- Computational efficiency
- Reproducible research
- Web apps
- Unit testing

Resources

- `hesim`
  - https://github.com/hesim-dev/hesim
  - https://github.com/hesim-dev/hesim-presentations
- IVI-NSCLC model
  - https://innovationvalueinitiative.github.io/IVI-NSCLC/

Live Content Slide

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

Poll: Do you think R is better for cost-effectiveness modeling and analysis than Excel?

Live Content Slide

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

Pre/Post Comparison: Do you think R is better for cost-effectiveness modeling and analysis than Excel?