Decision Modeling for Publich Health

Exercises – Calibration

The DARTH workgroup

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- Krijkamp EM, Alarid-Escudero F, Enns EA, Jalal HJ, Hunink MGM, Pechlivanoglou P. Microsimulation modeling for health decision sciences using R: A tutorial. Med Decis Making. 2018;38(3):400–22. https://journals.sagepub.com/doi/abs/10.1177/0272989X18754513

- Krijkamp EM, Alarid-Escudero F, Enns E, Pechlivanoglou P, Hunink MM, Jalal H. A Multidimensional Array Representation of State-Transition Model Dynamics. BioRxiv 670612 2019.https://www.biorxiv.org/content/10.1101/670612v1

Exercise: Calibration of a Sick-Sicker Model

In this exercise, we will calibrate a model of a hypothetical Sick-Sicker disease. A Markov model of the Sick-Sicker disease has been implemented using four health states: Healthy (H); two disease states, Sick (S1) and Sicker (S2); and Dead (D). A state transition diagram is shown in Figure 1. All individuals start in the Healthy state (H). Over time, healthy individuals may develop the disease and can progress to S1. Individuals in S1 can recover (return to state H), progress further to S2 or die. Once in S2, individuals cannot recover (i.e. cannot transition back to either S1 or H). Individuals in H have a baseline probability of death, while individuals in S1 and S2 have an increased mortality rate compared to healthy individuals, modeled as a hazard ratio applied to the baseline mortality rate.

Unfortunately, while we can identify those who are afflicted with the illness through obvious symptoms, we can't easily distinguish those in the S1 state from the those in the S2 state. Thus, we can't directly estimate state-specific mortality hazard ratios, nor do we know the transition probability of progressing from S1 to S2. We do have some idea of the plausible ranges for these unknown parameters; these ranges are listed in Table 1. All other model parameters are known and are also listed in Table 1.

There are three calibration targets to be used in this example: (1) observed survival of a cohort over time; (2) disease prevalence in a cohort over time; and (3) among sick patients (S1+S2), the proportion who are in the S1 state at three points in time. The first two targets came from an observational study of a typical cohort of individuals. The third target was obtained by subjecting ill patients to an invasive procedure which can determine disease stage but can't be used routinely due to its invasiveness. The calibration target values are provided in the data file "SickSicker_CalibTargets.RData", which contains a list with three data frames: Surv, Prev, and PropSick.

Tasks

1. Use the `R` script `SickSicker_CalibTemplate.R` as a starting point to code the calibration of the Sick-Sicker.

- Load and plot the calibration target data stored in `SickSicker_CalibTargets.RData`.

- Source the file, `SickSicker_MarkovModel_Function.R`, which contains the Sick-Sicker model function, `run_sick_sicker_markov()`. This function takes in a vector of three parameters, `c(p_S1S2, hr_S1, hr_S2)`, and returns model outputs corresponding to the calibration targets. Try using the model function and look at the output.

2. Implement the calibration of the Sick-Sicker model using random search with 1000 random samples. Copy code from the calibration of the 3-state model, modifying where necessary. Remember that the Sick-Sicker model needs to be calibrated to three different targets (instead of one) by varying three different inputs (instead of two).

- Explore the top-fitting input sets (e.g. top 10, top 100). To visualize the best-fitting sets, use `pairs.panels()` and `scatterplot3d()` functions. Type "?scatterplot3d" for function documentation.

- Plot the model-predicted output at the best-fitting parameter set overlaid over each of the three types of calibration targets (extend the plotting code in the 3-state model calibration script).

3. Save a new copy of your Sick-Sicker model calibration code. Change the implementation from random search to Nelder-Mead, using 100 random starting points. Where do you need to make changes? Use the Nelder-Mead calibration of the 3-state model as a guide.

- Explore the top-fitting input sets (e.g. top 10) using `pairs.panels()` and `scatterplot3d()`. How does it compare to the best-fitting sets from random search?

- Plot the model-predicted output at the best-fitting parameter set overlaid over each of the three types of calibration targets.

4. Save a new copy of your Sick-Sicker model calibration code. Use the Bayesian calibration of the 3-state model as a guide and modify your Sick-Sicker calibration code to implement the IMIS calibration method.

- Sample 1,000 parameter sets from the calibrated posterior distribution. Visualize these parameter sets using `scatterplot3d()` and `pairs.panels()`.

- Plot the model-predicted output at the maximum aposteriori parameter set overlaid over each of the three types of calibration targets.

Table 1: Input parameters for the time dependent Sick-Sicker Microsimulation

| Parameter	R name	Value
Time horizon	n_t	30 years
Cycle length		1 year
Names of simulated individuals	n_i	1000
Names of health states	v_n	H, S1, S2, D
Annual discount rate (costs/QALYs)	d_r	3%
Annual transition probabilities		
- Disease onset (H to S1)	p_HS1	0.15
- Recovery (S1 to H)	p_S1H	0.5
- Disease progression (S1 to S2)	p_S1S2	To be calibrated; range: 0.01 - 0.50
Annual mortality		
- All-cause mortality (H to D)	p_HD	0.005
- Hazard ratio of death in S1 vs H	hr_S1	To be calibrated; range: 1.0 - 4.5
- Hazard ratio of death in S2 vs H	hr_S2	To be calibrated; range: 5 - 15
Annual costs		
- Healthy individuals	c_H	$2,000
- Sick individuals in S1	c_S1	$4,000
- Sick individuals in S2	c_S2	$15,000
- Dead individuals	c_D	$0
- Additional costs of sick individuals treated in S1 or S2	c_trt	$12,000
Utility weights		
- Healthy individuals	u_H	1.00
- Sick individuals in S1	u_S1	0.75
- Sick individuals in S2	u_S2	0.50
- Dead individuals	u_D	0.00
Intervention effect		
- Utility for treated individuals in S1	u_trt	0.95
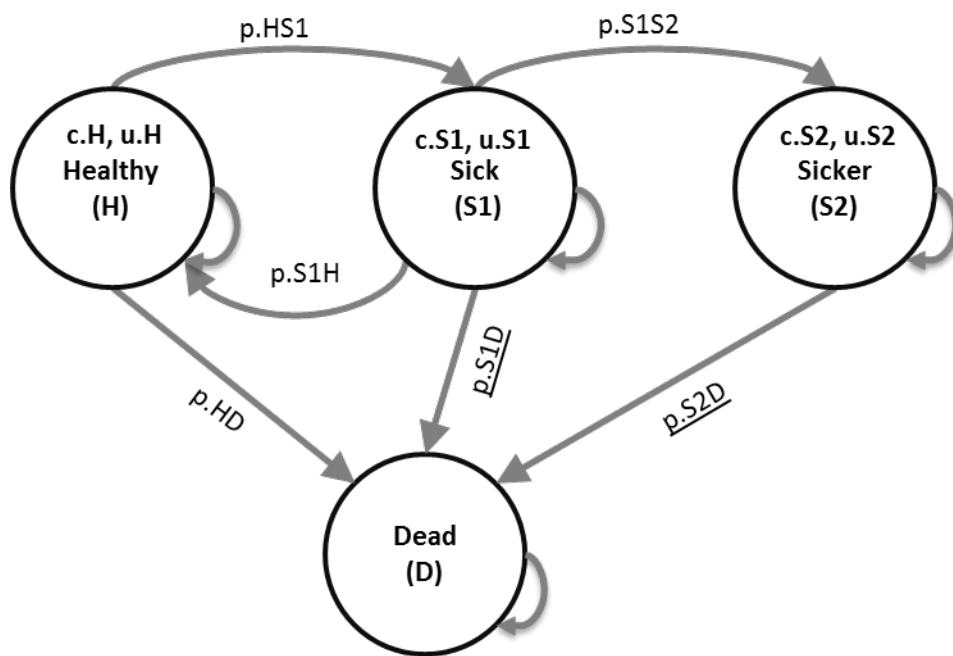
Figure 1: Schematic representation of the Sick-Sicker model