RDS 285 – LAB 4

MODEL CALIBRATION

We will use the 4-state breast cancer Markov model developed in Lab 2 (Tutorial #2: Markov Model Analysis in TreeAge Pro); a copy of this complete model is now posted on the Week 5 Canvas page as "lab 4_model_calibration_2023.trex".

Manual Calibration

In this lab, you will first manually calibrate an uncertain model input: the probability of recurrence (pBCA1) under usual care. Although this probability was assumed in the base case to be 2% per year, several clinical studies have reported estimates ranging from 1.2% to 5.7%. A recent study by the National Breast Cancer Institute (NBCI) reported the following prevalence estimates for non-metastatic and metastatic recurrent disease among women under usual care, by age:

Age	**Non-metastatic BCA (Recur state)** Mean (95% CI)	**Metastatic BCA (Mets state)** Mean (95% CI)
60	0.036 (0.033, 0.040)	0.062 (0.055, 0.065)
65	0.055 (0.049, 0.060)	0.058 (0.050, 0.064)
70	0.063 (0.057, 0.071)	0.049 (0.038, 0.056)

To start, using the TreeAge model as-is (i.e., before doing any calibration), generate a Markov trace of the usual care strategy under the base case probability of 2% per year. Then, open the Excel file "lab4_Calibration Worksheet_2023.xlsx", available on Canvas, and paste the results from the trace into the Base Case sheet.

(1) Graphically compare your model's estimate of age-specific prevalence of non-metastatic recurrent disease with those from the NBCI study. Do the same for the age-specific prevalence of metastatic recurrent disease.

Next, repeat the process above using different values for the probability of recurrence, and paste the results into the Calibration sheet in the Excel file.

(2) What is a reasonable estimate of the probability of recurrence (pBCA1) under usual care, based on the new study data above (you can assume it is constant over time and that all other model parameters are unchanged)?

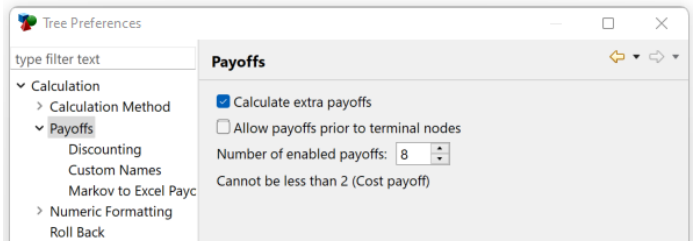
Automated Calibration in TreeAge

In recent years TreeAge Pro has added a built-in calibration feature to perform automated calibration. Calibration in TreeAge automatically adjusts model inputs, so that the resulting model outputs match to calibration targets. Now we will use this TreeAge feature to calibrate pBCA1. Note how pBCA1 is re-defined locally and globally in the TreeAge file "lab4_model_calibration_2023.trex" to allow us to calibrate for pBCA1.

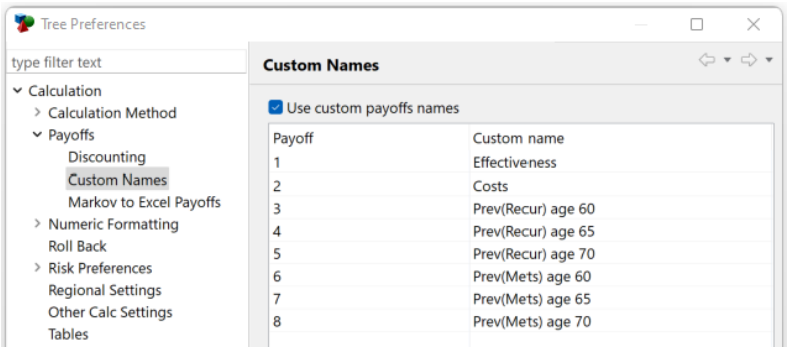
Setting up model outputs

For the purposes of calibration, we need the prevalence estimates for non-metastatic and metastatic recurrent disease among women under usual care (at age 60, 65 and 70) to be independent outcomes of the model. Therefore, we need to create new payoffs to specifically return those values when the model is analyzed.

Go to the PAYOFFS window (under EDIT→TREE PREFERENCES → CALCULATION→PAYOFFS), check the "Calculate extra payoffs" box, and change the number of enabled payoffs to 8. This allows the model to generate 6 extra outputs beyond the primary ones (cost and effectiveness), which correspond to our 6 calibration target values.



Change the payoff names (under PAYOFFS→CUSTOM NAMES) so we can identify what each payoff represents. Note that Payoffs 3-5 represent the prevalence of the Recur state at age 60, 65, and 70, respectively, and Payoffs 6-8 represent the prevalence of the Mets state at age 60, 65, and 70. In addition, change the numerical formatting of the payoffs in the NUMERIC FORMATTING window. Assign "5" for the number of decimal places in the window for Payoffs 3-8 and check that SHOW NUMBERS indicates "Exactly", and UNIT indicates "None".



Finally, we will need to assign values/formulas to these payoffs in the model. In the figure below, you see the MARKOV→HEALTH STATES tab for the USUAL CARE Markov node. Note that under Rewards (Additional Sets), the incremental reward for the Recur state in payoff "Prev(Recur) age 60" is the formula *if(_stage=5; 1; 0)*. This formula returns 1 only at _stage = 5, which is 5 annual cycles into the future. The "1" (in the if statement) is multiplied by the cohort% in that state at that time, such that the output is the cohort%. Therefore, the payoff is only updated with the cohort% in state Recur at 5 years, resulting in the prevalence of the Recur state at age 60 (as the starting age is 55).

Markov Node | Health States | Transition Rewards | PartSA

Markov node: Usual Care

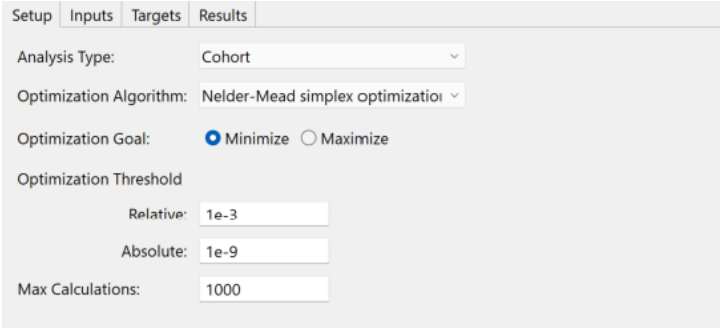
Element	Local	Recur	Mets	Dead
› Rewards (Active Sets)				
⌄ Rewards (Additional Sets)				
Init Prev(Recur) age 60	0	0	0	0
Incr Prev(Recur) age 60	0	if(_stage = 5; 1; 0)	0	0
Final Prev(Recur) age 60	0	0	0	0
Init Prev(Recur) age 65	0	0	0	0
Incr Prev(Recur) age 65	0	if(_stage = 10; 1; 0)	0	0
Final Prev(Recur) age 65	0	0	0	0
Init Prev(Recur) age 70	0	0	0	0
Incr Prev(Recur) age 70	0	if(_stage = 15; 1; 0)	0	0
Final Prev(Recur) age 70	0	0	0	0
Init Prev(Mets) age 60	0	0	0	0
Incr Prev(Mets) age 60	0	0	if(_stage = 5; 1; 0)	0
Final Prev(Mets) age 60	0	0	0	0
Init Prev(Mets) age 65	0	0	0	0
Incr Prev(Mets) age 65	0	0	if(_stage = 10; 1; 0)	0
Final Prev(Mets) age 65	0	0	0	0
Init Prev(Mets) age 70	0	0	0	0
Incr Prev(Mets) age 70	0	0	if(_stage = 15; 1; 0)	0
Final Prev(Mets) age 70	0	0	0	0
› Initial Probabilities and Tunnel Max				

Calibration View

The CALIBRATION view is used to set up and run the calibration process. You can open it via the VIEWS menu in the toolbar.

Setup (Optimization Algorithm)

In the SETUP tab, choose "cohort" as the ANALYSIS TYPE. For now, choose "Nelder-Mead simplex optimization" as the OPTIMIZATION ALGORITHM. You can keep the other options as their default value.



Inputs

The CALIBRATION VIEW - INPUTS Tab is used to select the input parameters that can be modified by the calibration process.

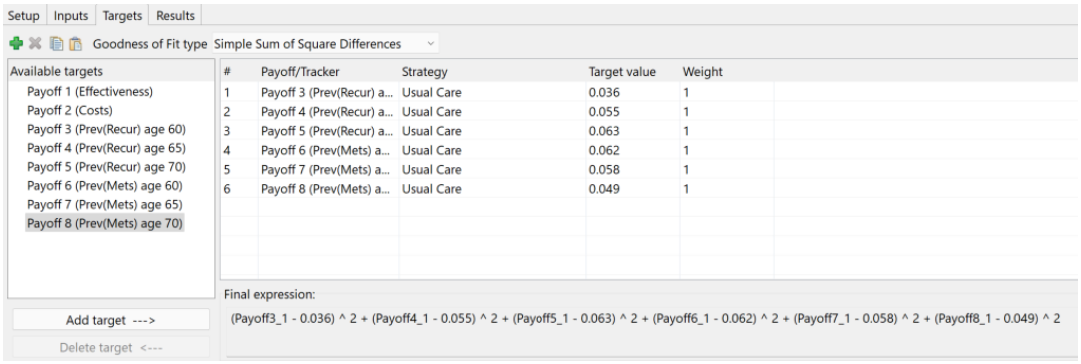
Select "pBCA1" from the AVAILABLE INPUTS list and click "Add variable →" (or double click on "pBCA1") to add pBCA1 to the calibration inputs list on the right. Since pBCA1 has a base-case value of 2% and a plausible range of 1.2% to 5.7%, we will set up the options for pBCA1 as below:

- Initial Value: 0.02
- Initial Step: 0.005 (This is the step size of the first iteration in the calibration process)
- Lower Bound: 0.002
- Upper Bound: 0.057

Targets

The CALIBRATION VIEW - TARGETS Tab is used to select model outputs and the target values for those outputs.

Choose "Simple Sum of Square Differences" as the GOODNESS OF FIT TYPE. Select "Payoff 3 (Prev(Recur) age 60)" from the AVAILABLE TARGETS list and click "Add target --->" (or double click on "Payoff 3 (Prev(Recur) age 60)") to add it to the calibration targets list. Add Payoffs 4-8 to the calibration targets list as well. For each calibration target, use "Usual Care" as the STRATEGY and their mean estimate from the study data table as the TARGET VALUE.



The FINAL EXPRESSION at the bottom shows the formula for the goodness-of-fit score based on your selection of goodness-of-fit type and calibration targets.

(3) Once the SETUP, INPUTS and TARGETS are ready, click the "Run" button at the bottom of the CALIBRATION View. The RESULTS Tab will then be selected automatically. What is the calibrated probability of recurrence (pBCA1) under usual care, using this built-in TreeAge calibration procedure?

(4) Using this calibrated estimate of pBCA1 in your model. Once the calibration stops, under the RESULTS tab, click on 'Use inputs in model' to re-define the variable pBCA1 with the best fitted value from the calibration. Does your conclusion on the cost-effectiveness of the Treat strategy change from the base case? Remember that the original cost-effectiveness results using the base value for pBCA1=0.02 (from lab 2) was $17,538 per QALY.