



EQUIVALENCE OF PARTITIONED SURVIVAL AND MARKOV MODELS

TreeAge Pro 2020 R1.0

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Al Chrosny
Chief Scientific Officer
TreeAge Software, Inc.
achrosny@treeage.com

Andrew Munzer
Director, Product Management & Training
TreeAge Software, Inc.
amunzer@treeage.com



INTRODUCTION

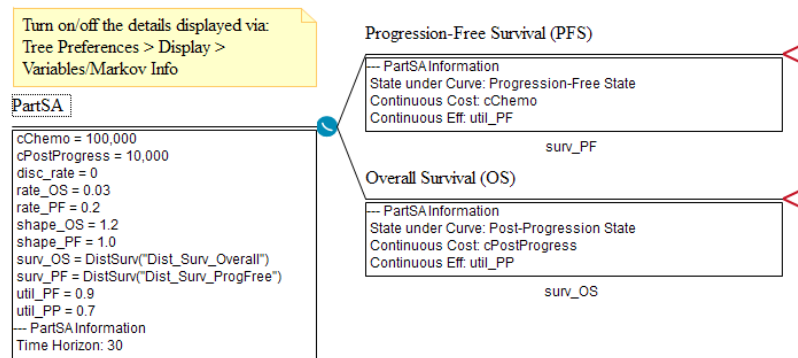
TreeAge Pro 2020 R1.0 introduced two important capabilities which shed some light on the important topic of creating Partitioned Survival Analysis (PartSA) Models and corresponding Markov Models.

First, TreeAge Pro can now convert a simple PartSA model (with 2 or 3 survival curves) into a Markov model. The results from the PartSA and Markov models can then be compared. Second, TreeAge Pro can now calibrate both Markov and PartSA models to obtain results which match the reference model data.

This paper will demonstrate the conversion process, then discuss the subtle but fundamental differences between the assumptions of PartSA and Markov Models.

PartSA Model with 2 Survivor Curves

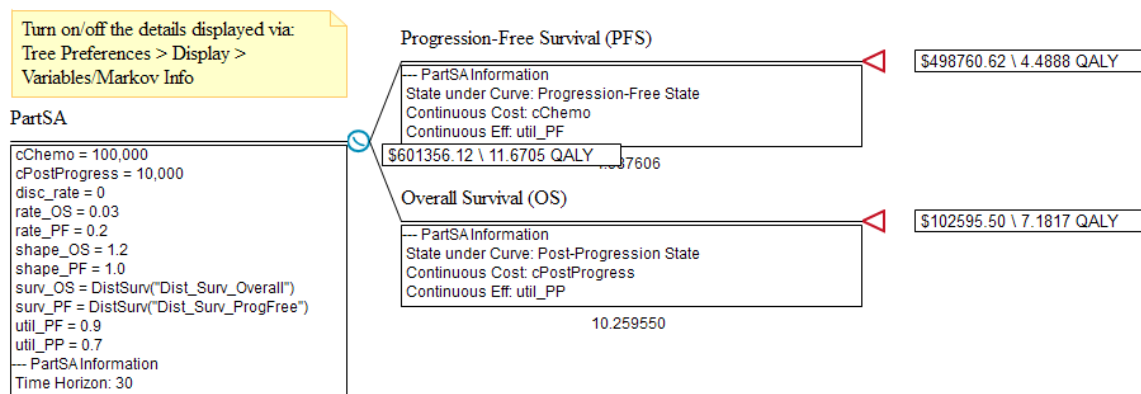
The Partitioned Survival model “PartSA-Reference1.trex” shown below can be found in the accompanying zipped models folder.



The model has two survival curves with each defined by a Weibull distribution:

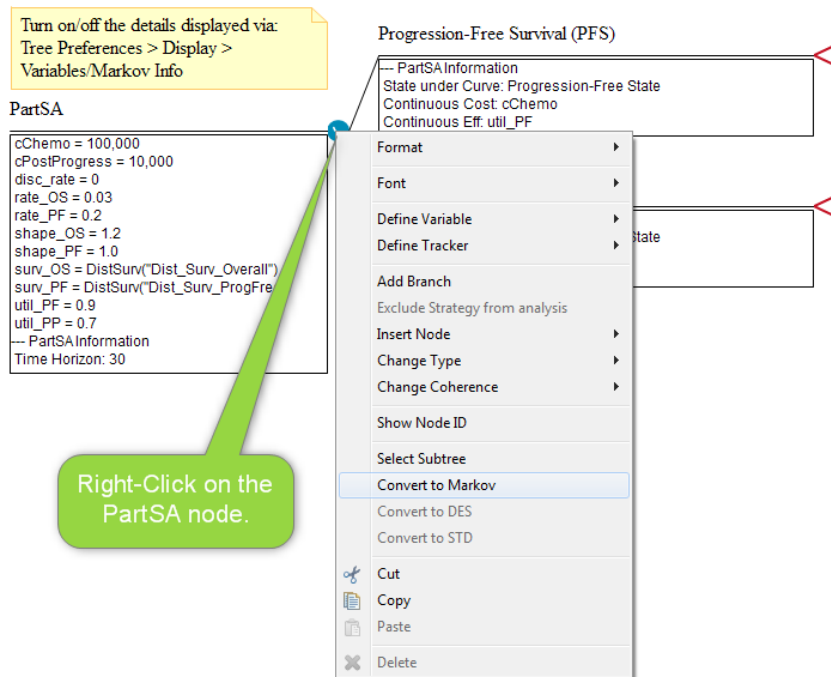
- “Dist_Surv_ProgFree” with parameters rate_PF and shape_PF
- “Dist_Surv_Overall” with parameters rate_OS and shape_OS

Performing RollBack or other Partitioned Survival Analyses generates the reports and charts required to examine the model. The RollBack results from this model are presented below.

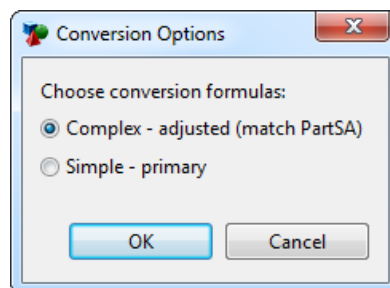


The primary outputs cost and Quality Adjusted Life Years (QALYs) are accumulated continuously using PartSA assumptions based on the areas under the survival curves. The total values accumulated over 30 years are \$601,356.12 and 11.6705 QALY, respectively.

We can quickly convert this model to a fully executable Markov model by Right-clicking on the PartSA node and choosing “Convert to Markov” from the context menu.



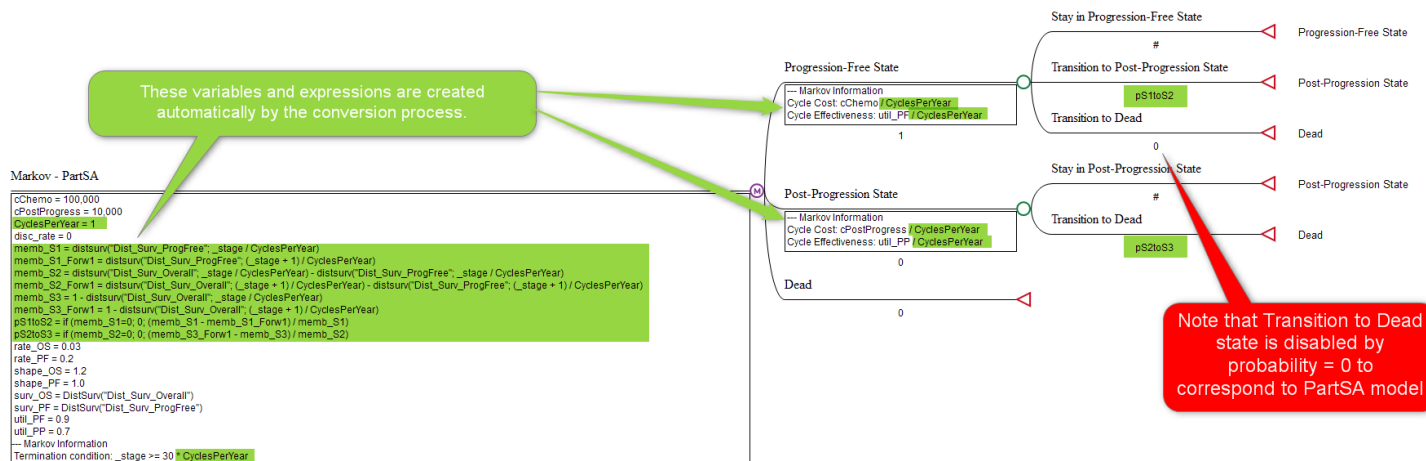
In the Conversion Options dialog shown below, choose Complex and click Ok.



The *complex* option generates special transition probability equations for 2 and 3 curve PartSA models that attempt to match the original PartSA curves. The *simple* option creates more straightforward

formulas, so it is more useful for experimenting with transition probabilities in the Markov model. See more notes on simple conversion formulas at the end of this chapter.

When the conversion is complete, a model editor tab will open with a Markov model shown below:

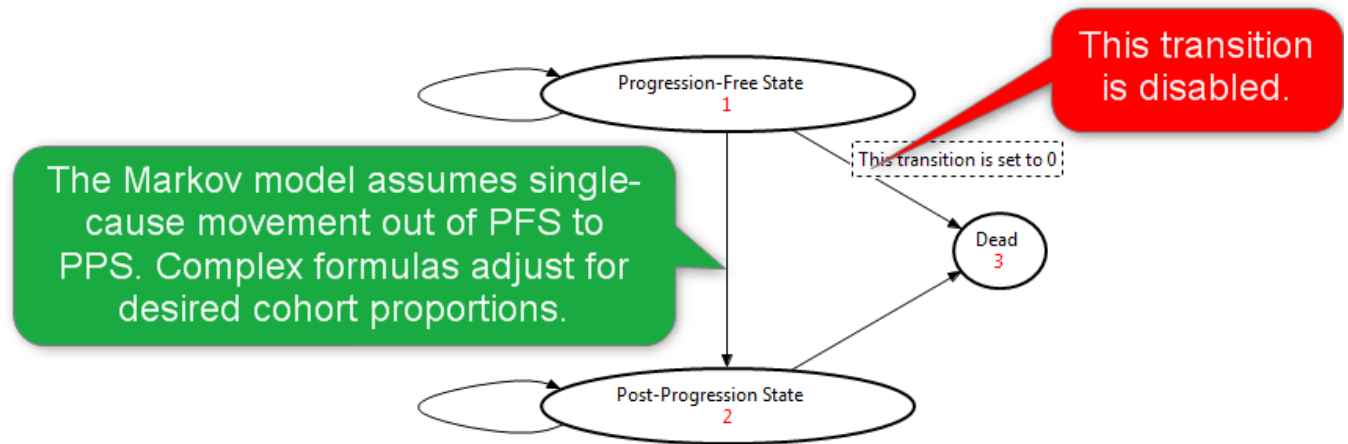


The transition probability expressions $pS1toS2$ and $pS2toS3$ are generated automatically.

Typically, Markov model transitions that represent single-cause risks, while PartSA models represent multi-cause survival functions. In the absence of information on how to split the multi-cause survival functions into separate individual risks, the converted Markov model imposes the constraint that patients only transition from each state to the next sicker state. Conceptually, each expression derives time-dependent transition probabilities by computing the percentage of the cohort in its associated state at time N and at time N+1. The transition probability for each cycle adjusts the cohort membership from time N to time N+1. These probability expressions use the multi-cause survivor functions of the Part SA model to compute “single-cause” transition probabilities for the Markov model that result in equivalent cohort proportions at corresponding times.

For example, the OS curve represents the combination of Background Mortality and Excess disease mortality. Likewise, the Progression Free Survival curve represents proportion of the cohort that moved out from the PFS state due to progression, disease mortality and background mortality.

Here is the State Transition Diagram of the Markov model that allows transition probabilities from the multi-cause survival data.



We see that structurally there are only strict forward transitions to “sicker” states are allowed (in addition to staying in the same state). This structural constraint enables the multi-cause PartSA survival data to be used in the context of the Markov “single-cause” transitions.

Transition from Progression Free State to Dead is disabled. We will later examine how this transition can be used in a more realistic modelling case.

The following three features of the Markov model are important to understanding its equivalence to the original PartSA model:

1. PartSA conversion equations.
2. Within Cycle Correction (WCC) Markov option.
3. Adjustable Markov cycle length.

PartSA Conversion Equations

As mentioned above, transition probability expressions p_{S1toS2} and p_{S2toS3} capture the multi-cause risks of the PartSA survival data and transform them into “single-cause” Markov model transition probabilities. This moves the cohort in a way that mimics the PartSA survival curves.

It should be clear that the conversion is a brute force mechanism to make the Markov model equivalent to the original PartSA model. However, it is intended only for demonstration purposes and to highlight the differences between the modelling techniques. The complex conversion is an interesting solution, but ultimately the simple conversion with additional work on “missing” single-cause transitions will enable the user to create a more realistic Markov model.

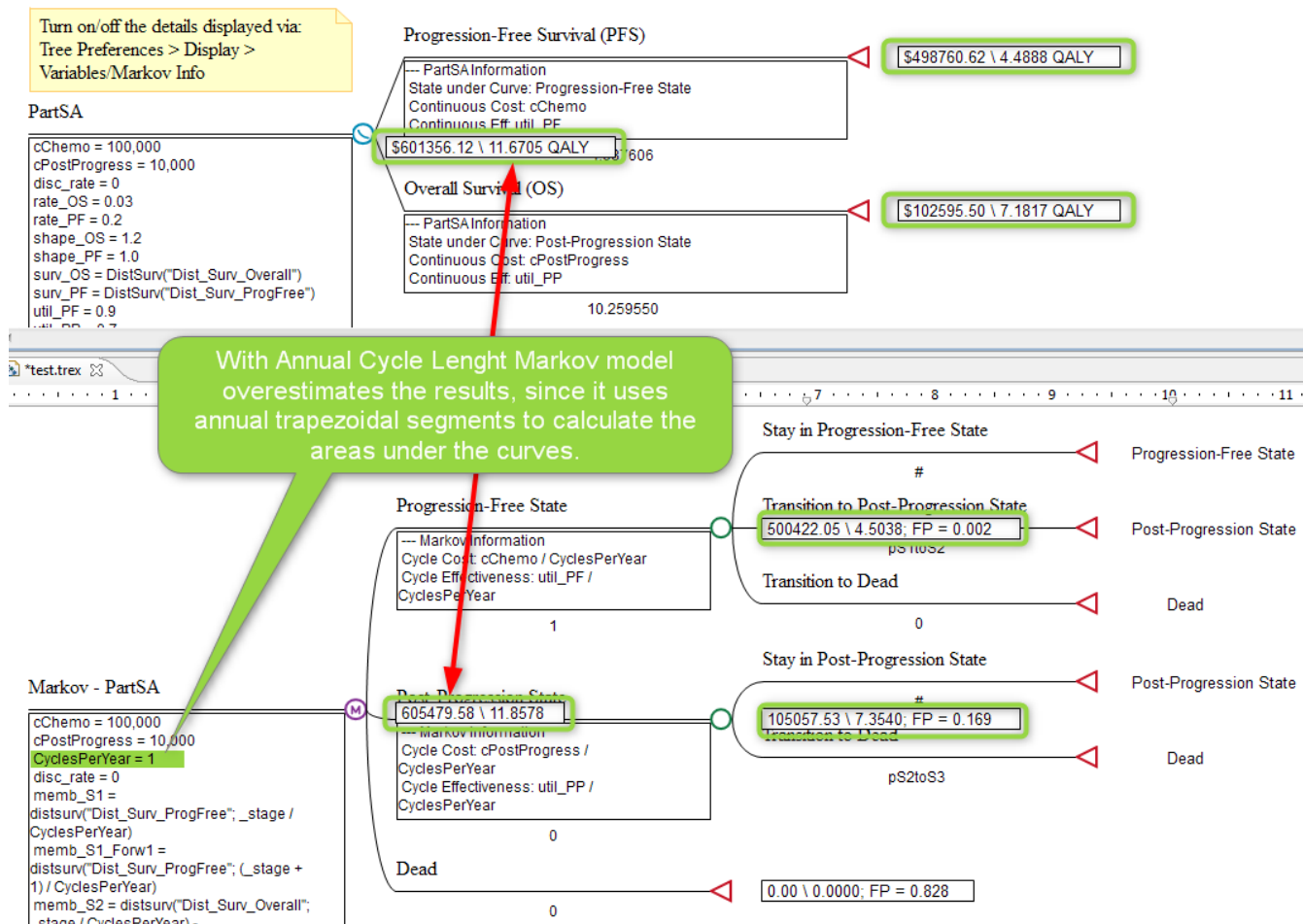
Within-Cycle Correction (WCC)

The Markov model is configured to use Within-Cycle Correction (WCC) option rather than Half Cycle Correction. The reward entries in WCC models are simpler and more directly correspond to the continuous rewards in PartSA model. Note that only continuous rewards in PartSA model are converted to Markov model.

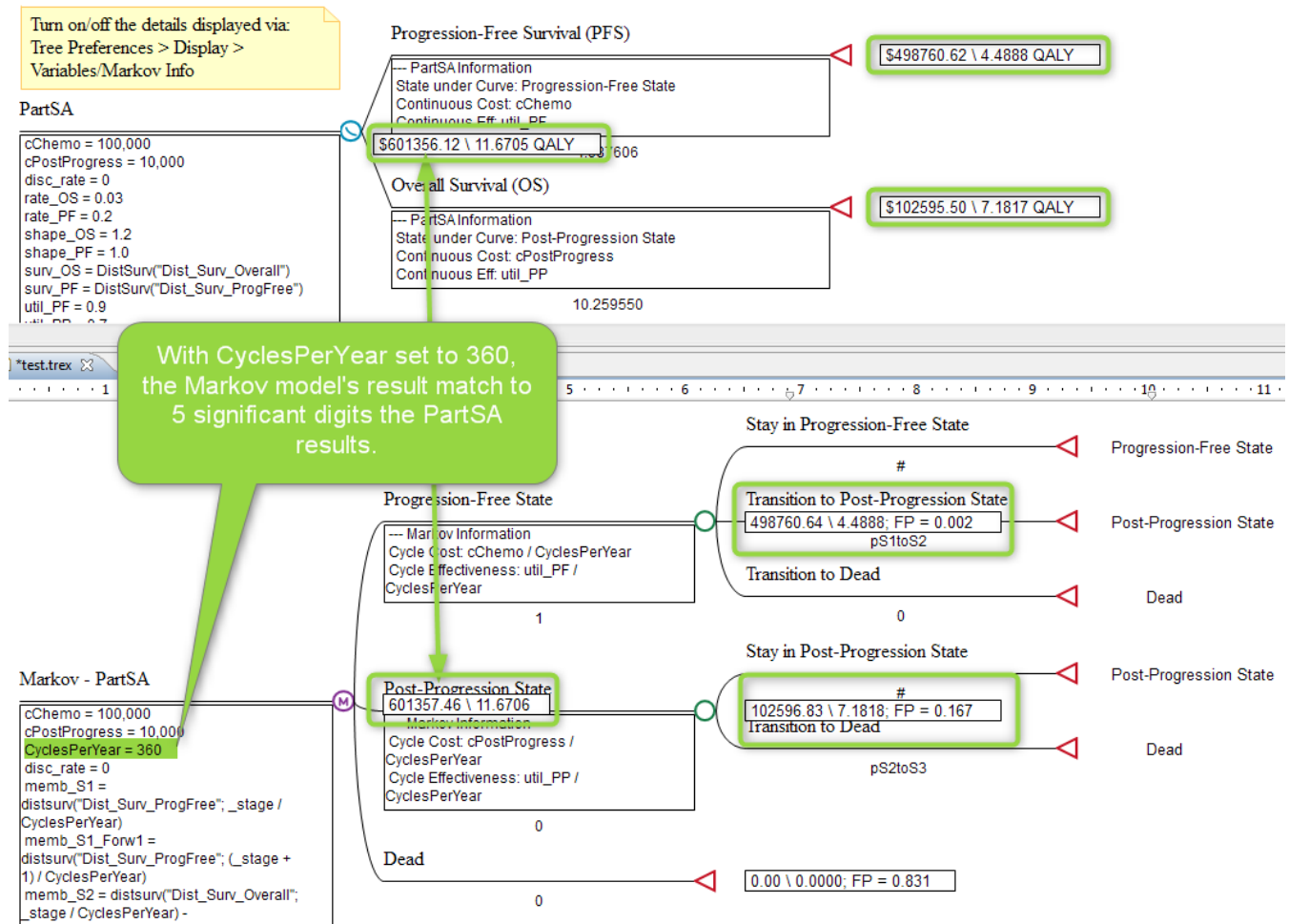
Adjustable Markov Cycle Length

The converted Markov model includes a new parameter *CyclesPerYear*. This parameter is used to change the Markov model’s cycle length. Increasing *CyclesPerYear* shortens the cycle length and improve the accuracy of the results with respect to the original PartSA model. The *CyclesPerYear* value affects transition probability calculations in the complex expressions. Annual Costs and Utilities from the PartSA model are divided by *CyclesPerYear* to generate appropriate values for the cycle length. Also, the Time horizon entry from the PartSA model is multiplied by *CyclesPerYear* to run a sufficient number of cycles based on the cycle length.

If we run RollBack on both models, we see that Markov Model with *CyclesPerYear* = 1 overestimates the rewards:



If we change the CyclesPerYear to 360 the results become quite close.



We noted earlier that only continuous rewards are converted from the PartSA to the Markov model. The modeler can introduce additional rewards (startup, exit, interval, discrete, exit) manually after being satisfied that the continuous rewards are computed correctly.

If the original PartSA model contains survival curves that cross-over, this will generate run-time errors in the converted Markov model. PartSA model analyses can re-allocate the cross-over region to the sicker state (see Cross-Over report), but the Markov model will fail because the transition probability formulas will generate negative values at the cross-over points. Also, LogNormal and LogLogistic

distributions cannot be evaluated at time = 0, requiring a small time adjustment to avoid run-time errors in the Markov model.

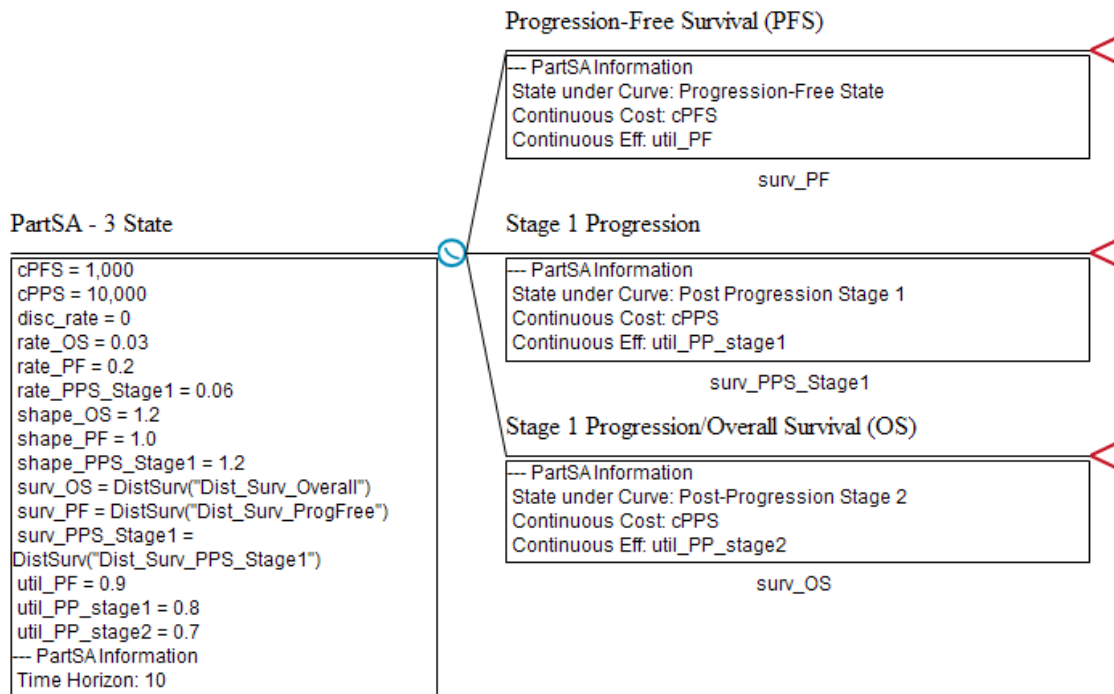
The simple conversion will try to use existing distributions in the converted Markov model, but that may not always be possible. You may encounter function call (specifically if you use an expression with `_time` to represent the survival or hazard function explicitly):

```
DistTransProb("AppropriateDistribution";_stage/CyclesPerYear;1/CyclesPerYear)
```

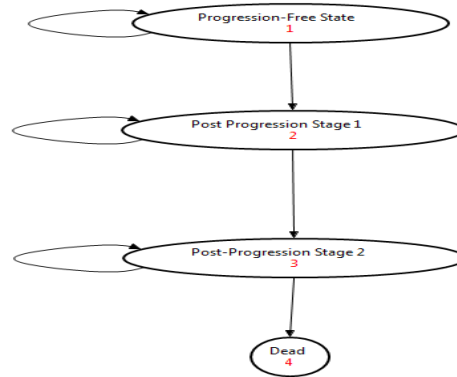
You will need to define an appropriate distribution and then replace the “AppropriateDistribution” with the reference to your newly defined distribution. Alternatively you might define the transition probabilities directly from a survival function.

PartSA Model with 3 Survivor Curves

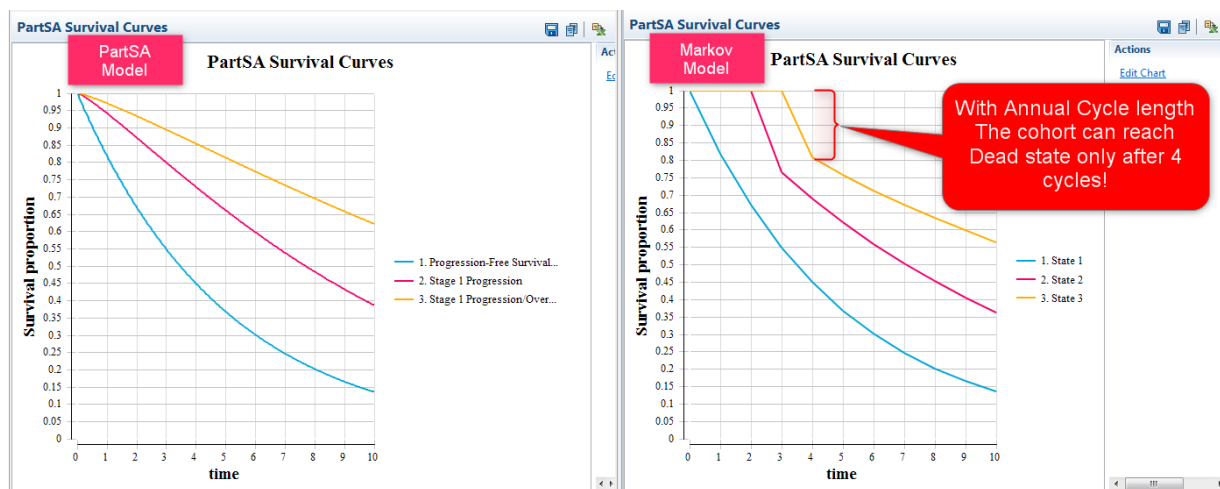
TreeAge Pro can convert models with 3 survivor curves, but the corresponding Markov models have even more complicated formulas and additional nuances. We will demonstrate these complications with survival graphs generated from the second example model “PartSA-Reference2.trex”.



As with 2 curve model, the multi-cause survival curves are used to calculate transition probabilities based on the assumption of direct transition to the next sicker state. These transitions are highlighted in the state transition diagram below:



Notice the effect of the 4-cycle delay in reaching Dead state.



If you increase the *CyclesPerYear* parameter to reduce cycle length, this reduces the impact of the transition delay and yields results closer to the PartSA model.

Conversion of 4 curve models would result in even more complicated equations and has not been implemented in the conversion process.

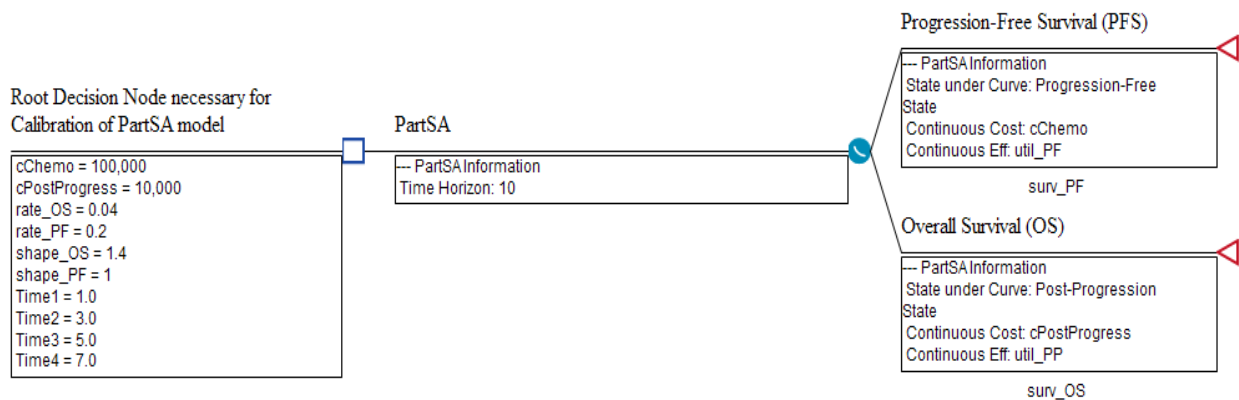
In summary, PartSA models use survival curves for which state exit is a combination of multiple causes. For example the OS curve represents the exit from alive to dead, but death could be from this disease or other causes. Markov models are typically built with transition probabilities derived from single cause events (e.g. separate transitions for disease mortality vs. background mortality). Given the divergent assumptions, conversion from one model type to the other requires assumptions about single-cause transitions as well as complex calculations.

In the next section, we will explore using model calibration as a method that can bridge Markov and PartSA modelling methods without the need to introduce arbitrary restrictions on Markov models.

CALIBRATION OF MARKOV MODEL TO MATCH PARTITIONED SURVIVAL MODEL

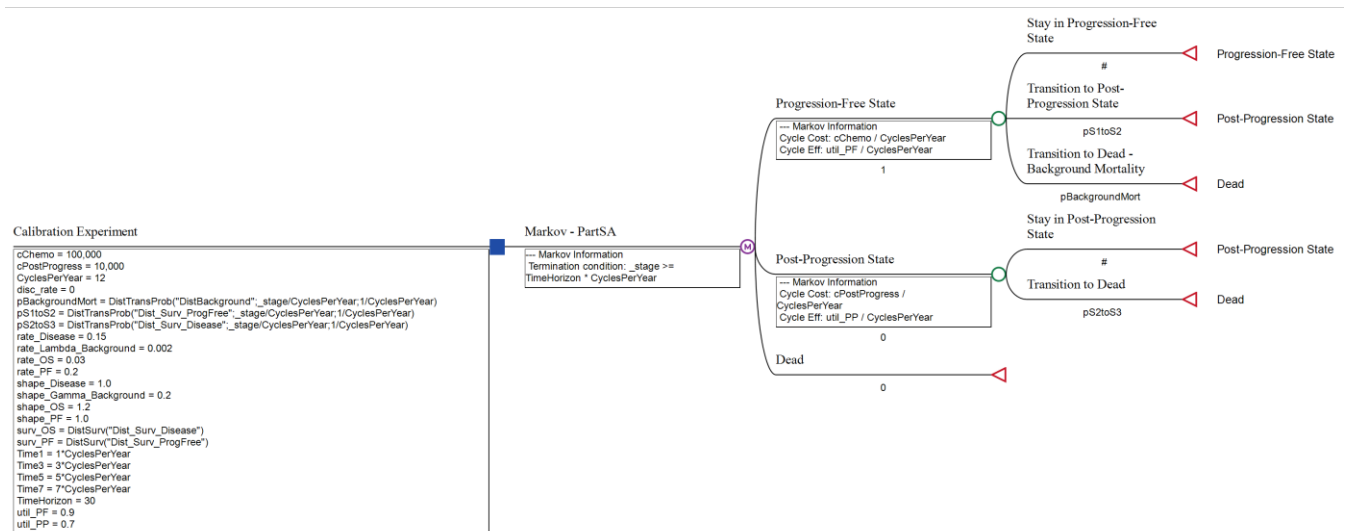
We may have data for survival curves which can be used in PartSA model directly. However, if we want to build a Markov model, we need to separate the PartSA multi-cause survival functions into single-cause Markov transition probabilities. When separating the causes, we must make assumptions about the Markov transition probabilities and their underlying survival or hazard functions. Therefore, we should then use calibration to look for the best set of Markov model parameters that best match the PartSA model outputs.

Starting with the same 2 curve PartSA model “PartSA-Reference1.trex” we would like to find a corresponding Markov model parameters.



Conversion of the PartSA model above generated the Markov model “Markov for Calibration to PartSA.trex” using the *simple* transition probability option. The formulas for single-cause transition

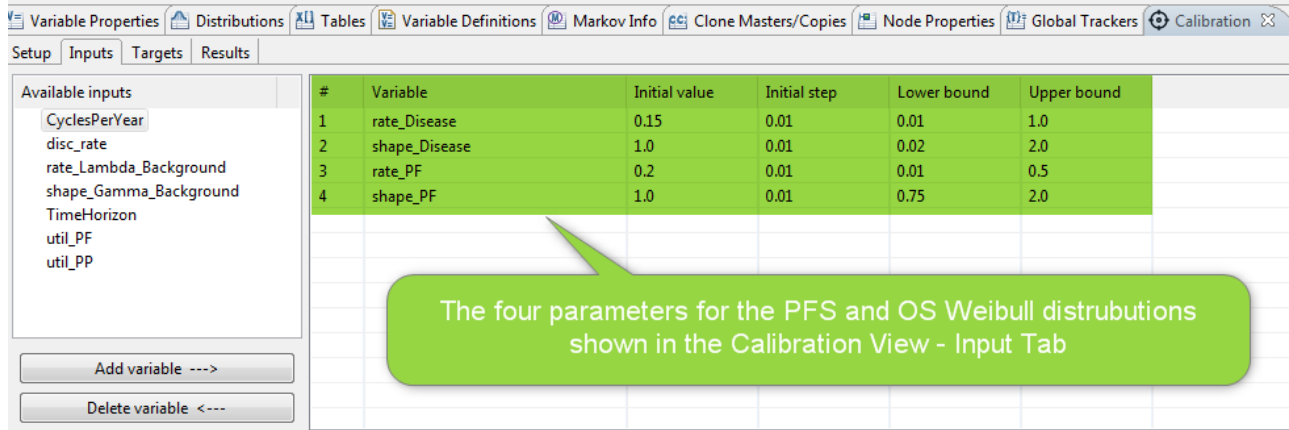
probabilities use the DistTransProb function, which calculates time-dependent probabilities from the original survival function distributions in the PartSA model.



To generate a more accurate Markov model, we will no longer restrict transitions to direct progression from one state to the next sicker state. Note that the transition from the PFS to Dead is no longer zero. Instead, we will assume that background mortality transition $tp_PFSToDead$ is a function of a Gompertz distribution (DistBackground) that was obtained from other population survival studies and should be applied to our PFS cohort. Mortality data including tabular data could be used for this transition probability.

Introduction of this additional risk of death in the PFS state necessarily changes the other transition probabilities generated by the conversion process – $tp_PFSToPPT$ and $tp_PPTToDead$. We will assume that those transitions are functions of Weibull distributions with unknown parameters which we can refine through calibration.

Specifically, we will use the calibration process to refine the underlying distributions to best fit the original survival data by adjusting the rate and shape of each Weibull distribution. The distribution parameters are shown below in the Calibration View's Input Tab.



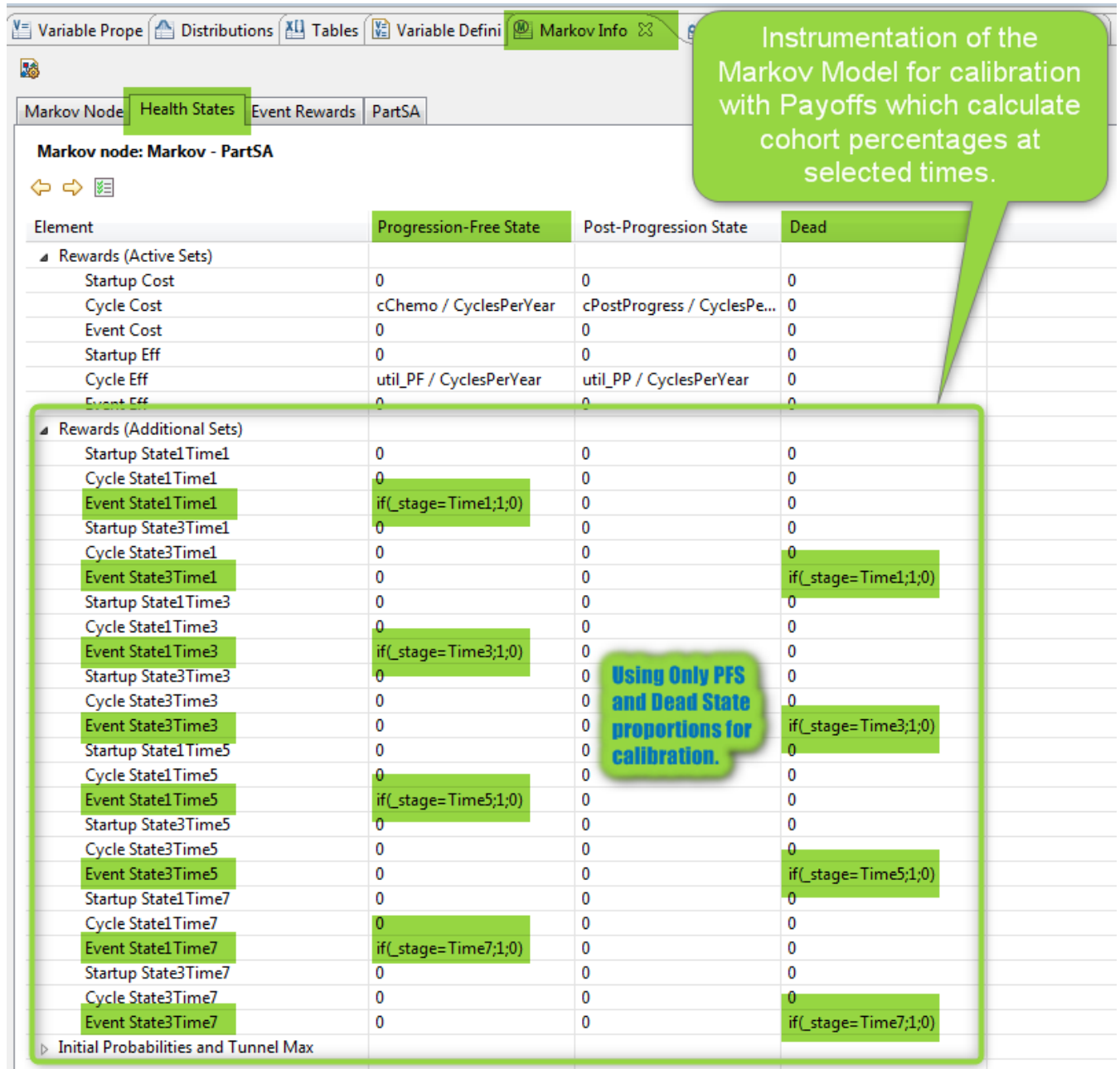
#	Variable	Initial value	Initial step	Lower bound	Upper bound
1	rate_Disease	0.15	0.01	0.01	1.0
2	shape_Disease	1.0	0.01	0.02	2.0
3	rate_PF	0.2	0.01	0.01	0.5
4	shape_PF	1.0	0.01	0.75	2.0

The four parameters for the PFS and OS Weibull distributions shown in the Calibration View - Input Tab

For calibration, we also need target data to measure the fit to the original PartSA survival data. Specifically, we will use the proportions of people in the PFS state and the Dead state from the PFS and OS survival functions at selected times of 1, 3, 5 and 7 years.

Note that we should choose a “sufficient” number of targets for the number of unknown parameters. This is similar to algebraic systems of equations where we need at least as many independent equations as we have unknown variables. Although we could have chosen target proportions at 2 different times (four target values) for four inputs, our calibration results might not match the survivor curves at times further into the future. In general fitting and calibrating is subject to some assumptions (e.g. the type of distributions to use, selection of target time), it is important to try different assumptions and verify how robust are the resulting model outputs.

The next step is to prepare the model for calibration by creating independent model outputs to match against the target values. Specifically, we need to generate outputs that represent state membership in both PFS and Dead states at the times described earlier. This model contains 8 additional payoffs for these outputs. They are instrumented as shown below in the following Markov Info View.



Instrumentation of the Markov Model for calibration with Payoffs which calculate cohort percentages at selected times.

Using Only PFS and Dead State proportions for calibration.

Element	Progression-Free State	Post-Progression State	Dead
Rewards (Active Sets)			
Startup Cost	0	0	0
Cycle Cost	cChemo / CyclesPerYear	cPostProgress / CyclesPe...	0
Event Cost	0	0	0
Startup Eff	0	0	0
Cycle Eff	util_PF / CyclesPerYear	util_PP / CyclesPerYear	0
Event Eff	0	0	0
Rewards (Additional Sets)			
Startup State1Time1	0	0	0
Cycle State1Time1	0	0	0
Event State1Time1	if(_stage= Time1;1;0)	0	0
Startup State3Time1	0	0	0
Cycle State3Time1	0	0	0
Event State3Time1	0	0	if(_stage= Time1;1;0)
Startup State1Time3	0	0	0
Cycle State1Time3	0	0	0
Event State1Time3	if(_stage= Time3;1;0)	0	0
Startup State3Time3	0	0	0
Cycle State3Time3	0	0	0
Event State3Time3	0	0	if(_stage= Time3;1;0)
Startup State1Time5	0	0	0
Cycle State1Time5	0	0	0
Event State1Time5	if(_stage= Time5;1;0)	0	0
Startup State3Time5	0	0	0
Cycle State3Time5	0	0	0
Event State3Time5	0	0	if(_stage= Time5;1;0)
Startup State1Time7	0	0	0
Cycle State1Time7	0	0	0
Event State1Time7	if(_stage= Time7;1;0)	0	0
Startup State3Time7	0	0	0
Cycle State3Time7	0	0	0
Event State3Time7	0	0	if(_stage= Time7;1;0)
Initial Probabilities and Tunnel Max			

The next step is to use the Calibration View's Targets Tab to specify the appropriate model outputs and their corresponding target values as shown below.

Setup Inputs **Targets** Results

Goodness of Fit type: Simple Sum of Square Differences

Available targets

- Payoff 1 (Cost)
- Payoff 2 (Eff)
- Payoff 3 (State1Time1)
- Payoff 4 (State3Time1)
- Payoff 5 (State1Time3)
- Payoff 6 (State3Time3)
- Payoff 7 (State1Time5)
- Payoff 8 (State3Time5)
- Payoff 9 (State1Time7)
- Payoff 10 (State3Time7)

#	Payoff/Tracker	Strategy	Target value	Weight
0	Payoff 3 (State1Time1)	Markov - PartSA	0.832490612611603	1
0	Payoff 4 (State3Time1)	Markov - PartSA	0.0266636542222264	1
0	Payoff 5 (State1Time3)	Markov - PartSA	0.558035145770047	1
0	Payoff 6 (State3Time3)	Markov - PartSA	0.102721558300423	1
0	Payoff 7 (State1Time5)	Markov - PartSA	0.374062144602083	1
0	Payoff 8 (State3Time5)	Markov - PartSA	0.183580685159439	1
0	Payoff 9 (State1Time7)	Markov - PartSA	0.250741353989858	1
0	Payoff 10 (State3Time7)	Markov - PartSA	0.263237972109244	1

Calibration Targets for State1 and State3 at different times.

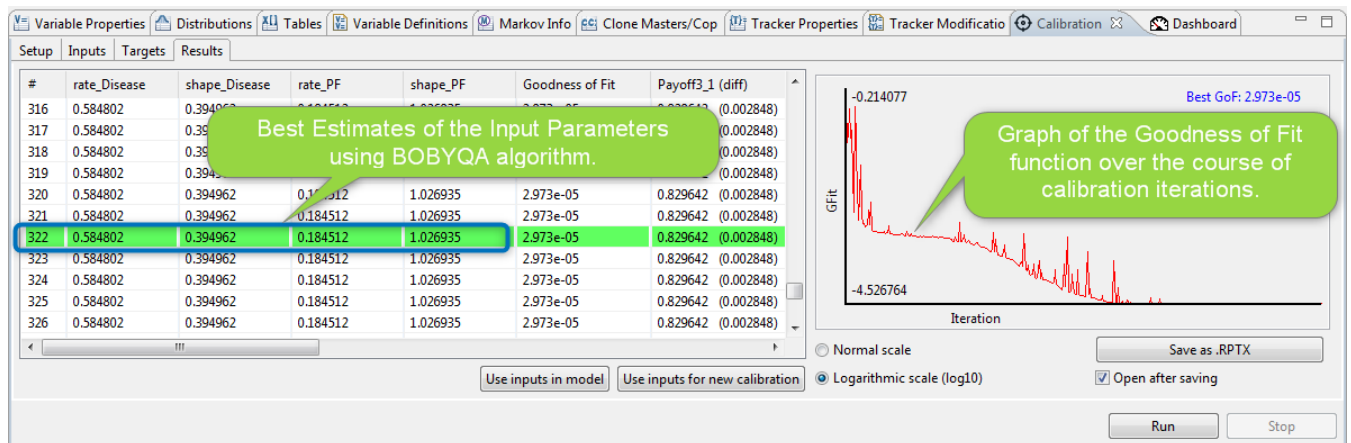
Final expression:

$$(\text{Payoff3_1} - 0.832490612611603)^2 + (\text{Payoff4_1} - 0.0266636542222264)^2 + (\text{Payoff5_1} - 0.558035145770047)^2 + (\text{Payoff6_1} - 0.102721558300423)^2 + (\text{Payoff7_1} - 0.374062144602083)^2 + (\text{Payoff8_1} - 0.183580685159439)^2 + (\text{Payoff9_1} - 0.250741353989858)^2 + (\text{Payoff10_1} - 0.263237972109244)^2$$

Add target ---> Delete target <---

Run Stop

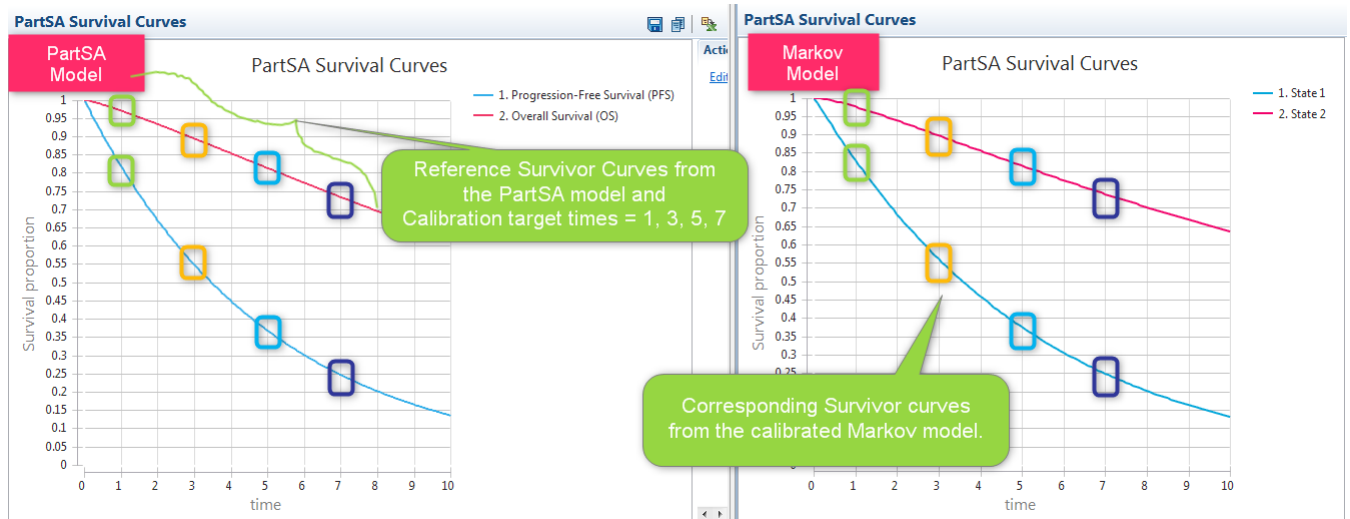
Now we are ready to run the Calibration process. Press the “Run” button and observe the real-time output. Each row consists of a model calculation using a set of input parameter values and shows the calculated target values and the Goodness of Fit demonstrating how close we are to the target values.



Notice that the calibration process identified best fit input values for the model. The parameter estimates for the PFS transition probability distribution are a rate of 0.185 and a shape of 1.027, which are not exactly the same as the original PartSA PFS curve (parameters rate = 0.2 and shape = 1.0). They were adjusted because in the Markov model exit from PFS state is implemented with two different single-cause transitions. The combination of these two paths has to match the PartSA PFS curve.

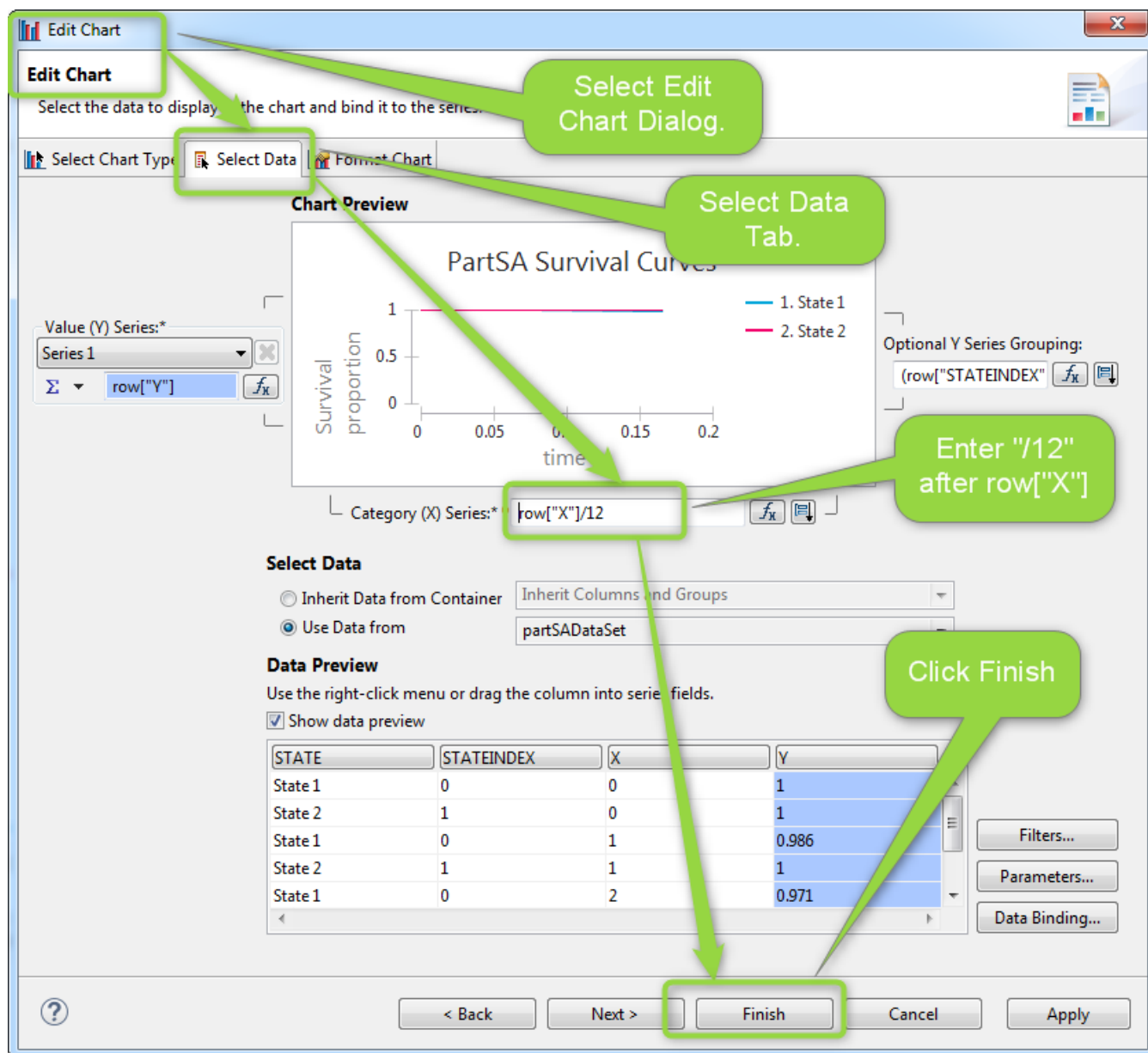
The Weibull distribution “Dist_Surv_Disease” for Death from Disease has the rate estimate of 0.584 and shape = 0.395 (decreasing risk!). The fact that this distribution has decreasing risk is a result that we are trying to match the PartSA OS curve (Weibull with rate = 0.04 and shape = 1.4) with a combination of the Gompertz distribution with increasing risk and a Weibull distribution that has to compensate for the increasing risk.

The PartSA model will generate Survival Curves graph, for a selected PartSA node, from Analysis menu -> Partitioned Survival Analysis -> Survival Curves. In Markov model running Cohort Analysis on a selected Markov node will provide a link to report Markov PartSA report. The final result can be seen in this Survivor Curve graphs generated by PartSA model and calibrated Markov model:



Note that the TimeHorizon variable for these graphs was decreased to 10 years, so we can focus on the calibration time interval. You can extend the time horizon to 30 years to assess the effects of extrapolation of the calibrated survival curves.

Also, note that the Markov Model time axis was adjusted to years. This can be done within the Edit Chart dialog as shown below:



Edit Chart

Select the data to display in the chart and bind it to the series.

Select Chart Type **Select Data** **Format Chart**

Chart Preview

PartSA Survival Curves

Survival proportion

time

1. State 1

2. State 2

Value (Y) Series:

Series 1

Σ row["Y"] f_x

Optional Y Series Grouping:

$(\text{row["STATEINDEX"]})$ f_x

Category (X) Series:

$\text{row["X"]}/12$ f_x

Select Data

☐ Inherit Data from Container

☒ Use Data from

Inherit Columns and Groups

partSADataset

Data Preview

Use the right-click menu or drag the column into series fields.

☒ Show data preview

STATE	STATEINDEX	X	Y
State 1	0	0	1
State 2	1	0	1
State 1	0	1	0.986
State 2	1	1	1
State 1	0	2	0.971

Click Finish

Finish

It should be noted that we could have used other distribution types for the Markov model (e.g. Gamma or Generalized Gamma), which can be more “flexible” than Weibull. We also could have created a model with more complicated Markov structure, while still trying to generate the PFS and OS curves from such a model. A more complicated Markov structure might be appropriate given

understanding of the underlying biology. Calibration could also estimate a larger number of parameters; however, it is important to provide sufficient number of reference target values.

CONCLUSION

TreeAge Pro includes a feature to convert a simple 2 or 3 curve Partitioned Survival Analysis (PartSA) model to an equivalent and executable Markov model. The converted Markov model uses the survival data from PartSA and assumes strict forward progression in the mathematical calculations of transition probabilities based on the original PartSA survival functions. The converted Markov model, while calculating the same values as PartSA reference model, highlights the fundamental difference in structure and transition probability derivation between the two modeling techniques.

The calibration feature can be used to further explore equivalence between Markov models and PartSA models. Calibration demonstrates that different survival functions must to be used in PartSA and Markov model if the strict forward progression within Markov model is relaxed.

APPENDIX

PartSA calculations.

PartSA uses a continuous time and a differential equation solver algorithm with a default integration step equal to 1/360 of a Year. The algorithm used in the solver is a standard 4th-order Runge-Kutta algorithm, which better approximates areas under the curve than Markov WCC trapezoidal approach. You can change PartSA integration step to 1/3600 or smaller and assess the impact on the results. However, it will be true that Markov model with a similar cycle length to PartSA will have less accurate reward results.