Tech Note #13
Discrete Event Simulation

Microsimulation, Parallel Trials, and “Queuing” Models in TreeAge Pro 2008

TreeAge Software, Inc.

Outline

- Simulation and Discrete Simulation
- Microsimulation in TreeAge Pro
- Illustrate Parallel Trials Applications:
  - Resource Competition, other DES aspects
  - Modeling Open/Dynamic “Populations”
- Compare dynamic simulation models to dynamic cohort models

Discrete Event Simulation

- We'll look at options for discrete simulation in TreeAge:
  - Sequential (independent) microsimulation trials is traditional …
  - … But <u>parallel</u> (interacting/competing) trials an option since v2004
  - "Closed population" of indeterminate size is traditional …
  - … But parallel trials allow for <u>open</u> population and <u>dynamic sizing</u> (in v2008)
    - Note: Dynamic/open option with Markov **cohort** (i.e., non-simulation) models available since '04

- But first, the background…

Discrete Event Simulation

- Simulation is, for our purposes:
  - Using a mathematical computer model,
  - to imitate a system (e.g., a patient and/or population),
  - so that we can perform experiments.

- In TreeAge Pro, called "microsimulation"
  - Traditionally used to simulate variability in individual patients (or trials), get mean and other statistics as part of decision analysis
  - Slides don't cover very basics of microsimulation
  - Presentation looks at microsimulation modeling/analysis in the context of "Discrete Event Simulation"

Discrete Event Simulation

- More Resources (beyond these slides):
  - Many useful simulation model publications, e.g.:
  - Start with:

    Le Lay, et al. "Can discrete event simulation be of use in modelling major depression?" Cost Eff Resour Alloc. 2006; 4: 19.

    http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1762026

    Thorough discussion of Discrete Event Simulation and microsimulation in TreeAge Pro

  - BRAM model, NHS monograph 811

    Shown later in the slides… monograph includes thorough model discussion

Discrete Event Simulation

- Discrete event = discrete change model
  - “**State** changes only when **events** occur, [in turn causing] **time** advances.”

    Discrete Event Simulation: A Practical Approach (1992)

  - **Time** may be modeled either as stochastic jumps or fixed increments (i.e., cycle length)

- *Continuous* background change models are as a rule not a feature in computer simulations

Discrete Event Simulation

- Discrete simulation defined…
  - Discrete change (vs. continuous vs. hybrid)
  - Stochastic (vs. deterministic)
  - Dynamic/time-dependent (vs. static)
  - *This defines microsimulation*, *too*

- DES software tools… is TreeAge one?
  - Discrete events ← microsimulation
  - Parallel processes ← can run "parallel trials"
  - Dynamic creation of "objects" ← v2008 enabled "on-the-fly" creation of trials

Discrete Event Simulation

- Simulation software…
  - Simulation languages evolved over 40 years
    - GPSS, Simula67, …
  - Graphical environments specific to DES, last 20 years
    - Arena, …

- TreeAge Pro
  - Simulation evolved in context of decision analysis (CEA, health economics, PSA, etc.)

Discrete Event Simulation

- Terminology of DES-only (i.e., Arena-like) tools or languages:
  - System model; Entities (permanent or transitory); Entity attributes; Activity (cause change); Transactions;
  - Scheduling: Activity scanning; Event orientation; Process orientation. Time management: Periodic scan (fixed increment); Event scan (variable increment).

- TreeAge microsimulation
  - Couched in Markov terms, instead of traditional discrete simulation terminology
  - But not limited to Markov/semi-Markov assumptions

Discrete Event Simulation

- Microsimulation is term from economics originally
  - Model “agents” individually
  - Simulate changes in **state**, attributes, behavior
  - Examine aggregate & average outcomes
  - Also examine distribution
  - Agents **sequentially** processed …
    - So, in theory/strictly defined, doesn’t deal with system/population interactions
    - To model agent (i.e., entity) interactions – for example, resource competition, force of infection – need to run microsimulation trials in <u>parallel</u>

Discrete Event Simulation

- What are options for discrete simulation in TreeAge?
  - Sequential (independent) trials are traditional
    - Many such published patient-level simulation studies
  - Parallel (interacting) trials newer option ('04)
  - Closed population/static size is traditional
  - Open population, dynamic sizing in microsimulation very new ('08)

TreeAge Simulation Models

- TreeAge simulation models, standard elements:
  - Markov node (to create event loop)
  - Monte Carlo microsimulation (1^{st}-order trials)
  - Trackers (to keep track of private state)

TreeAge Simulation Models

- Options (beyond standard elements):
  - **Parallel trials** to allow interaction…
  - 1st-order **distributions** to sample time-to-event, patient state, etc.
  - **GlobalN( )** matrixes for global/public state
  - **Non-coherent probabilities** tree preference for open/dynamic population (v2008)
  - **{T} _CLOCK** for synchronizing trials if stochastic time advance (v2008)
  - **Python**, user-defined functions for complex algorithms (e.g., search/sorting)
    - http://www.treeage.com/support/python.html

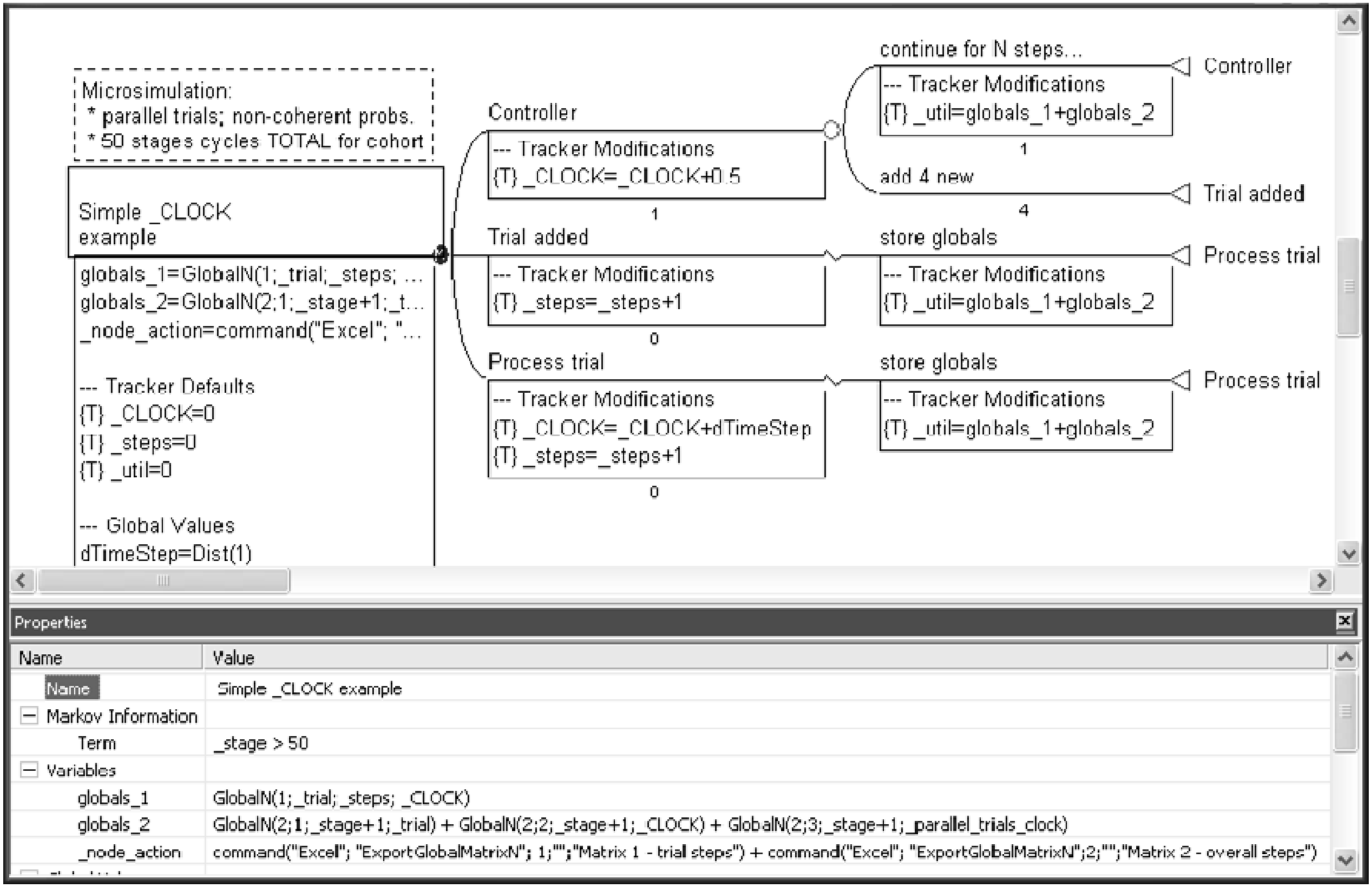
Discrete Event Simulation

- Examples (going beyond just using trackers):
  - "_CLOCK example.tre"
    - Simplistic, abstract model (doesn't solve a problem)
    - Use to describe core DES-related features **in detail**
  - "Organ allocation.pkg"
    - **Quick** illustration of a more complex model than simple "_CLOCK example", plus a realistic issue
    - Download to dig into the details and try simulations
  - "BRAM simulation.pkg"
    - Replicates published, well-documented model from NHS study; regular microsimulation
    - See the NHS monograph for extensive model description
    - Trackers/distributions for time-to-event simulation (i.e., variable cycle length, no use of _stage)

Discrete Event Simulation

- Example #1:
  - "_CLOCK example.tre"
  - Abstract model, doesn't solve a problem.
    Only function is to illustrate…
- Using subset of mentioned sim tools, e.g.:
  - Microsimulation, individual-level simulation
  - Trackers for private state info (like time/age)
  - Distributions, for sampling time-to-event …
    - Effectively stochastic "cycle length"
  - Parallel trials for competition/interaction
  - Using {T} _CLOCK tracker to synchronize trials
  - GlobalN( ) for public/shared state info (versus *private* trackers)
    - Also for more detailed reporting
  - Non-coherent probabilities, for open/dynamic population

Discrete Event Simulation



_CLOCK example

Discrete Event Simulation

_CLOCK example

- Key model element #1a:
  - Cycle length: _stage **not** used to keep patient time
  - Fixed cycle length not an assumption in our model
  - “Time” instead progresses independently for each trial in stochastic jumps (e.g. based on sampled time-to-event)
  - Patient time stored in a tracker

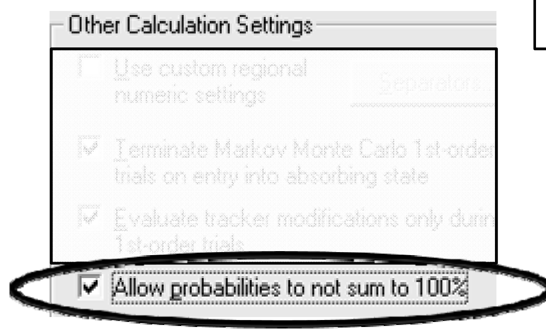
- Key model element #1b:
  - Patient time stored in tracker specifically called {T} _CLOCK, so that trials are synchronized …
  - … Only works if trials run in parallel (versus default/sequential)
  - So, if parallel trials and {T} _CLOCK exists:
    - Trial with lowest _CLOCK time runs next cycle/event
    - Use a different {T} tracker name for patient time to avoid synchronization (e.g., for speed)
  - NOTE:
    - Patient-time tracker **not** required with parallel trials
    - Can still be _stage-based

Discrete Event Simulation

_CLOCK example

- Key model element #2:
  - "States" not really health states, rather events (for system or individual) or event generators
  - E.g., trial #1 in "Controller" state is not an individual

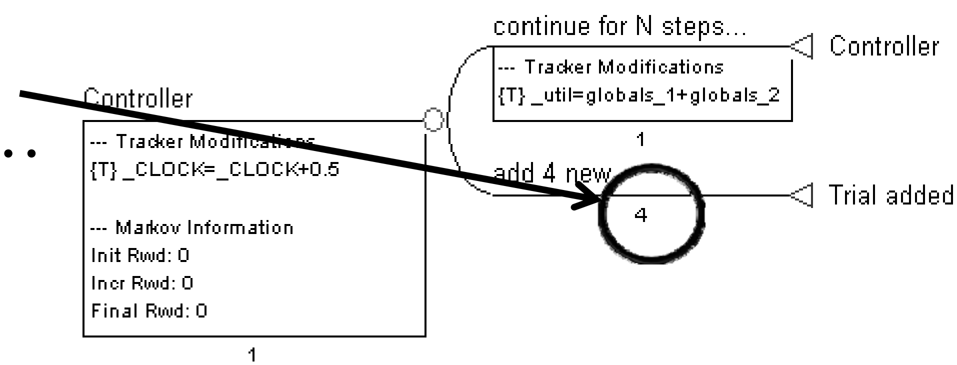
- Key model element #3:
  - Dynamic creation of (parallel) trials using **non-coherent** transition probabilities
    - This is purpose of "Controller" state
  - Although initial probabilities are coherent in this example, <u>they don't need to be</u>
    - In parallel dynamic trials, sum of initial probabilities determines starting # of "trials" (integer >= 1)



Discrete Event Simulation

_CLOCK example

- "Controller" state
  - Initial probability = 1, and trial #1 starts here at initial cycle (**t_0**)
    - If init. prob. instead = 2, then 2 trials would start here
  - Transition probabilities are non-coherent:
    - $p_{Continue} = 1 \quad + \quad p_{Add} = 4 \quad \rightarrow \quad p_{Total} = 5$
  - "continue…" branch
    - <u>Current trial always follows top/first 1.0</u> of p_{Total}
    - **So trial #1 stays in "Controller"**
    - {T} _util → performs a reporting/debugging function
  - "add 4 new" generates trials…



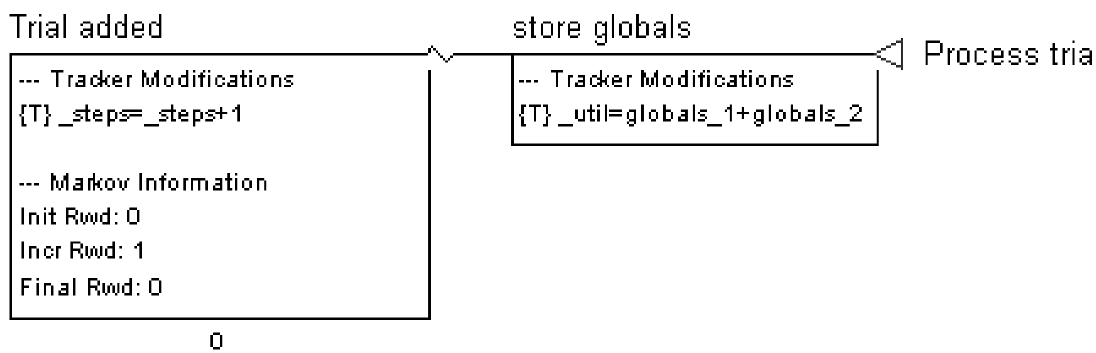
Discrete Event Simulation

- "Controller" state (continued)
  - "add…" event injects new trials
  - Parent trial's {T} _CLOCK increment effectively means trials added every 0.5 time units
  - New trial's {T} _CLOCK initialized equal to parent trial's
  - New trial will start its random walk at "add 4 new" (e.g., executing any tracker modifications, or subsequent chance events)

_CLOCK example

Discrete Event Simulation

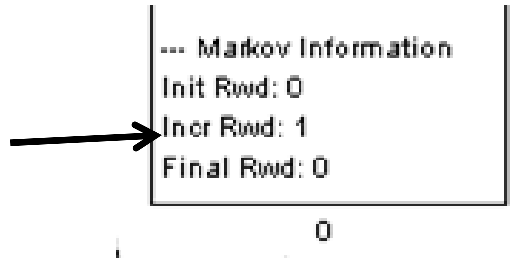
- "Trial added" state
  - Zero initial probability (no trials here at $\mathbf{t_0}$)
  - New trials sent here; temporary state
  - {T} _steps → not a time counter
    - Counts # cycles (events?) for each trial/individual
    - But cycles have no particular length; not clinically meaningful, more for debugging
  - {T} _util: stores clock "history" in Global matrix



_CLOCK example

Discrete Event Simulation

- “Trial added” state (continued)
  - Incremental reward doesn’t do much
    - Each trial added gets a single incr. reward =1



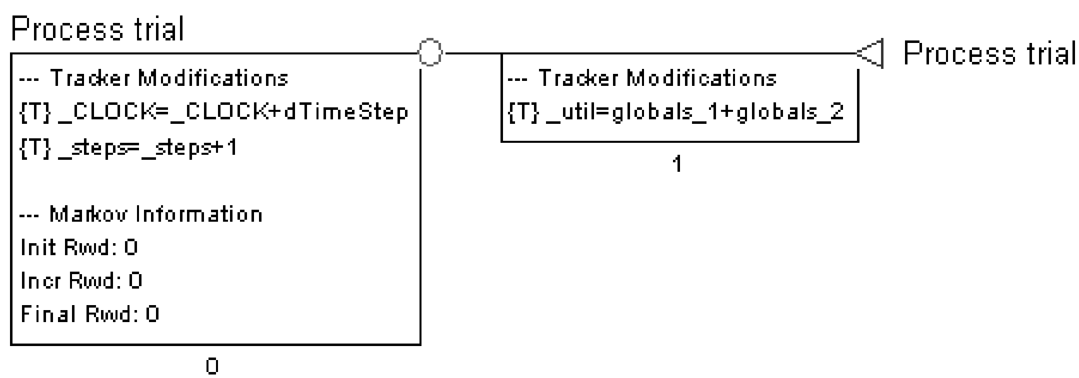
    - Total final cohort reward equals size (# trials added)
    - State is temporary; every trial continues to “processing”

_CLOCK example

Discrete Event Simulation

_CLOCK example

- "Process trial" state
  - Trial with lowest _CLOCK time runs a cycle/event
    - At start, each trial samples its dTimeStep (i.e., "cycle length"); _CLOCK advances by dTimeStep
    - Effectively running in parallel, but simulation processing one at a time
  - In example, termination based on _stage (which is NOT per trial, but total cycles across all trials)



Discrete Event Simulation

- Reporting/debugging trials:
  - Uses Global matrices to mimic report similar to full cohort trace

_CLOCK example

Variable	Definition	Notes
globals_1	GlobalN(1;_trial;_steps; _CLOCK)	Matrix #1 records trials' _clock changes
globals_2	GlobalN(2;1;_stage+1;_trial) + GlobalN(2;2;_stage+1;_CLOCK) + GlobalN(2;3;_stage+1;_parallel_trials_clock)	Matrix #2 record per _stage: _trial; trial's _CLOCK; low _CLOCK
globals_2_titles	Command("GlobalMatrixN"; 2; "ColumnLabels“; "Stg0“;"Stg1“;"Stg2“;"Stg...")	Set some column titles
_node_action	command("Excel"; "ExportGlobalMatrixN"; 1; ""; "Matrix 1 - trial steps") + command("Excel"; "ExportGlobalMatrixN"; 2; ""; "Matrix 2 - overall steps")	Output matrices (to Excel in this case). Linked to:

Discrete Event Simulation

_CLOCK example

- Reporting/debugging output to Excel:
  - Matrix #1:
    - No column titles here
    - Row for trial 1 (controller) isn't filled in; real trials each record their _CLOCK change
    - Groups of 4 new trials added starting at $t_{0.5}$ and every 0.5 time units
    - Their _CLOCK's indicate their sampled "cycle length"

File Edit View Insert Format Tools Data Window

A1 fx C1

	A	B	C	D	E
1	C1	C2	C3	C4	C5
2	0	0	0	0	0
3	0.5	1.077355	1.65471	2.232065	0
4	0.5	0.976082	1.452165	1.928247	2.40433
5	0.5	1.29464	2.08928	0	0
6	0.5	0.979427	1.458855	1.938282	2.41771
7	1	1.593773	2.187545	0	0
8	1	1.496316	1.992633	2.488949	0
9	1	1.617029	2.234059	0	0
10	1	1.745709	2.491418	0	0

Matrix 2 - overall steps / **Matrix 1 - trial steps**

  - Matrix #2:
    - Under titles, first row shows order in which trials processed

	A	B	C	D	E	F	G	H
1	Stg0	Stg1	Stg2	Stg...	C5	C6	C7	C8
2	1	1	2	2	3	3	4	4
3	0.5	1	0.5	1.077355	0.5	0.976082	0.5	1.29464
4	0	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Matrix 2 - overall steps / Matrix 1 - trial steps / Sheet1

Discrete Event Simulation

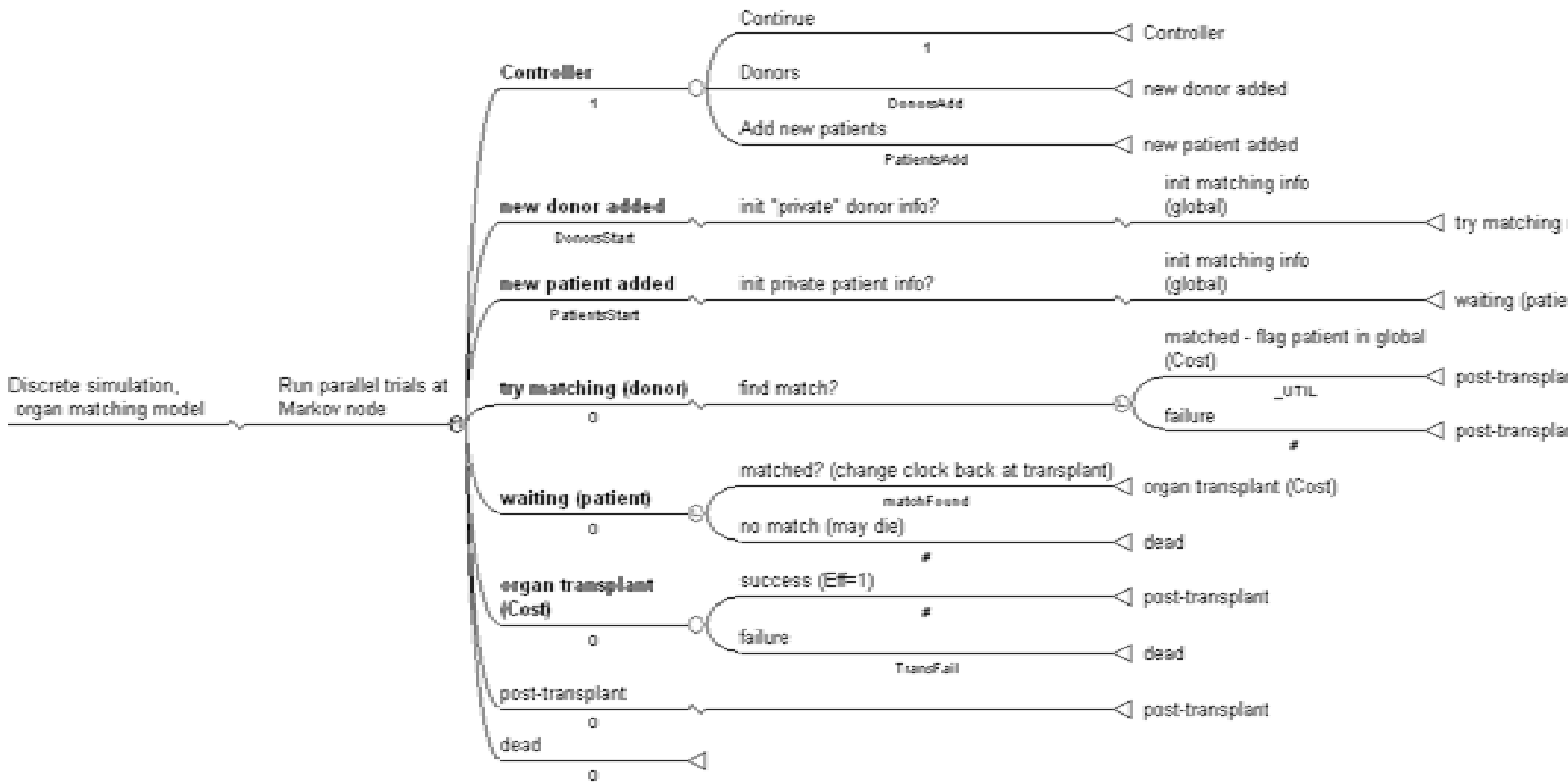
- Global matrices:
  - Can also use for public/shared “state”
  - Next example demonstrates this (in context of competing for limited resources, e.g. organ transplant)

Discrete Event Simulation

- Queueing/competition example
  - "Organan allocation.pkg"
    - Less abstract model, real problem…
  - Uses all the mentioned "DES" tools, e.g.:
    - Microsimulation for trackers (private)
    - Parallel trials, for competition/interaction
      - {T} _CLOCK synchronization
    - GlobalN( ) for public, global state
    - Non-coherent probabilities, to allow for open, dynamic population
    - Python (e.g., for sorting/prioritizing list of recipients by characteristics)

Discrete Event Simulation

Organ allocation example



Discrete Event Simulation

- New features (v2008):
  - Dynamic-sized microsimulation (based on existing parallel trials feature)
    - Illustrates non-coherent initial probabilities
  - "Managed" {T} _CLOCK tracker variable, for triggering events
    - Trial ignored until "system time" catches up to individual _CLOCK
  - Other supporting changes:
    - New functions; keywords; efficiencies added to GlobalN( ) matrixes; Python user-defined functions

Discrete Event Simulation

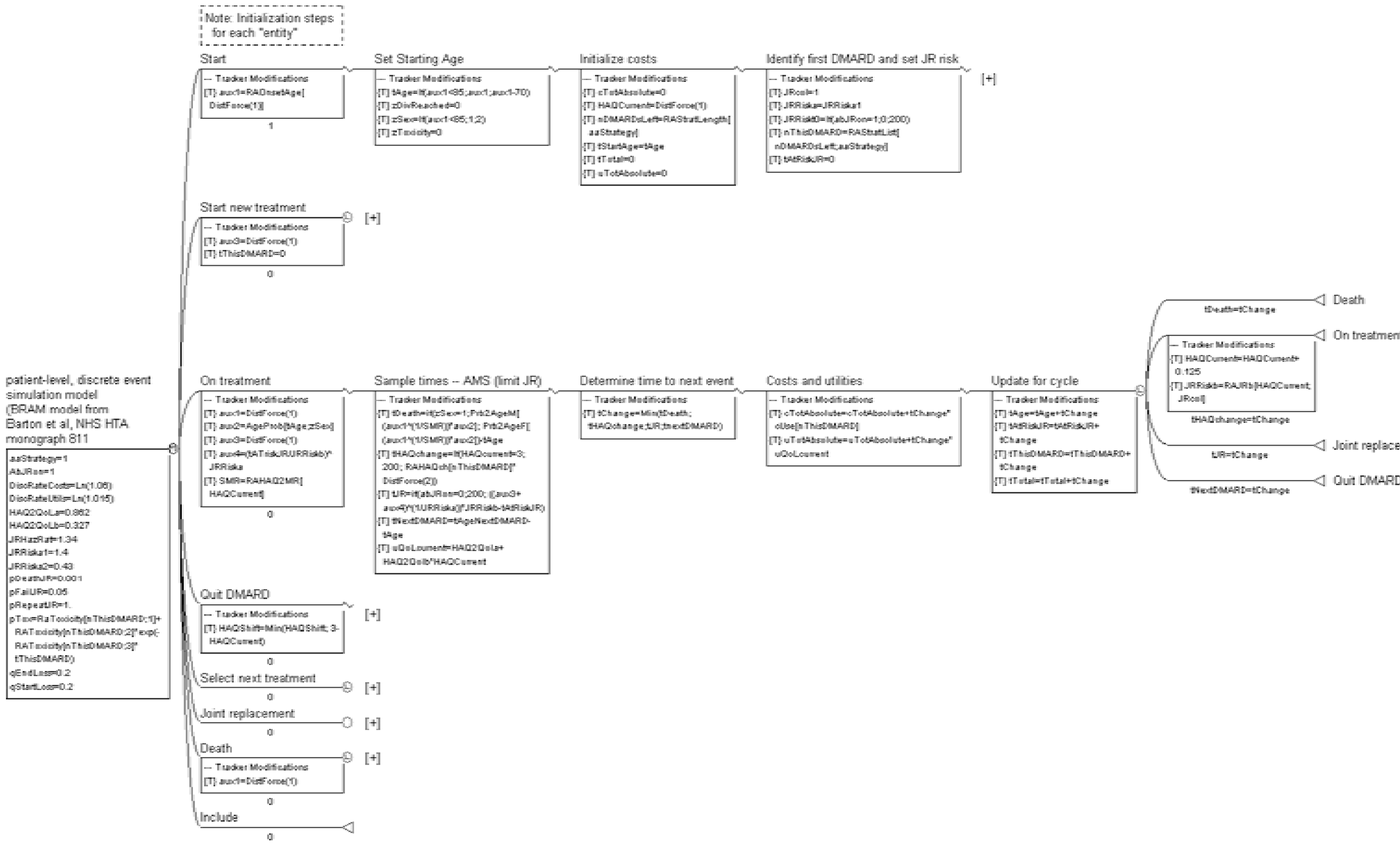
- Download example
  - Run microsimulation (parallel trials will be default) at the Markov node
  - Click on _node_action button to export resulting global matrices/simulation trace outputs to Excel

Discrete Event Simulation

- Sequential, event-advance example
  - BRAM (Birmingham UK Rheumatoid Arthritis Model) simulation
  - Study done c.2003 using DATA Pro (pre-TreeAge Pro speed-ups, features)
  - Not parallel trials (no need for “agent” interaction)
- Discrete Event Simulation using microsimulation
  - Competing risks using sampled times to events
  - So, continuous time jumps to next event
  - Keep patient time in a {T} tracker)
- Lots of trackers (in addition to time)

Discrete Event Simulation

BRAM simulation example



Discrete Event Simulation

- See NHS monograph #811 for complete details on their model

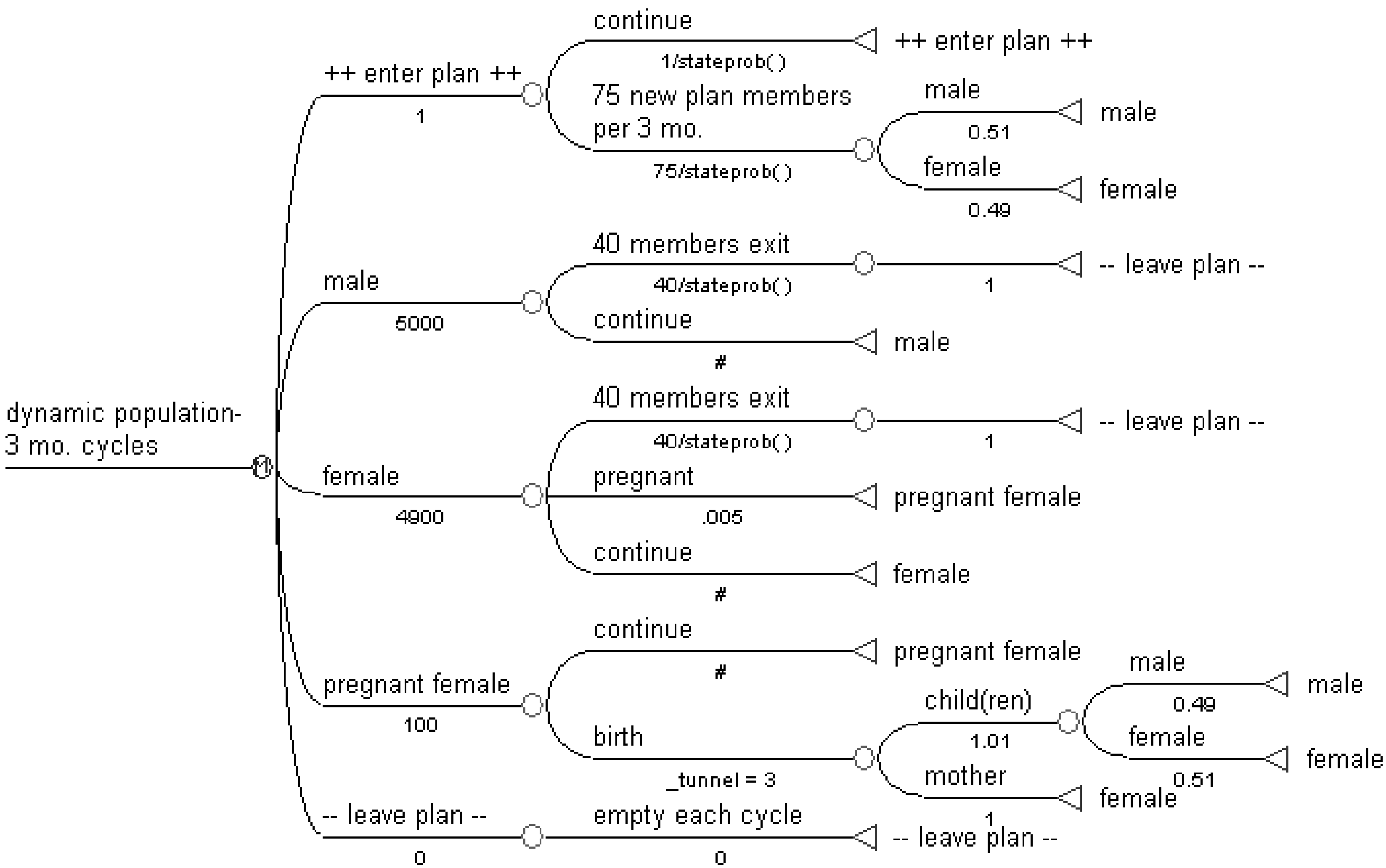
Dynamic **Cohort** Models

- Switching gears for a moment…
- Using dynamic cohorts models
  - If you don't need {T} trackers, and _stage and fixed cycle length are fine...
  - But you do need:
    - "Agent" interaction; and/or
    - Open/dynamic-sized cohort

Dynamic **Cohort** Models

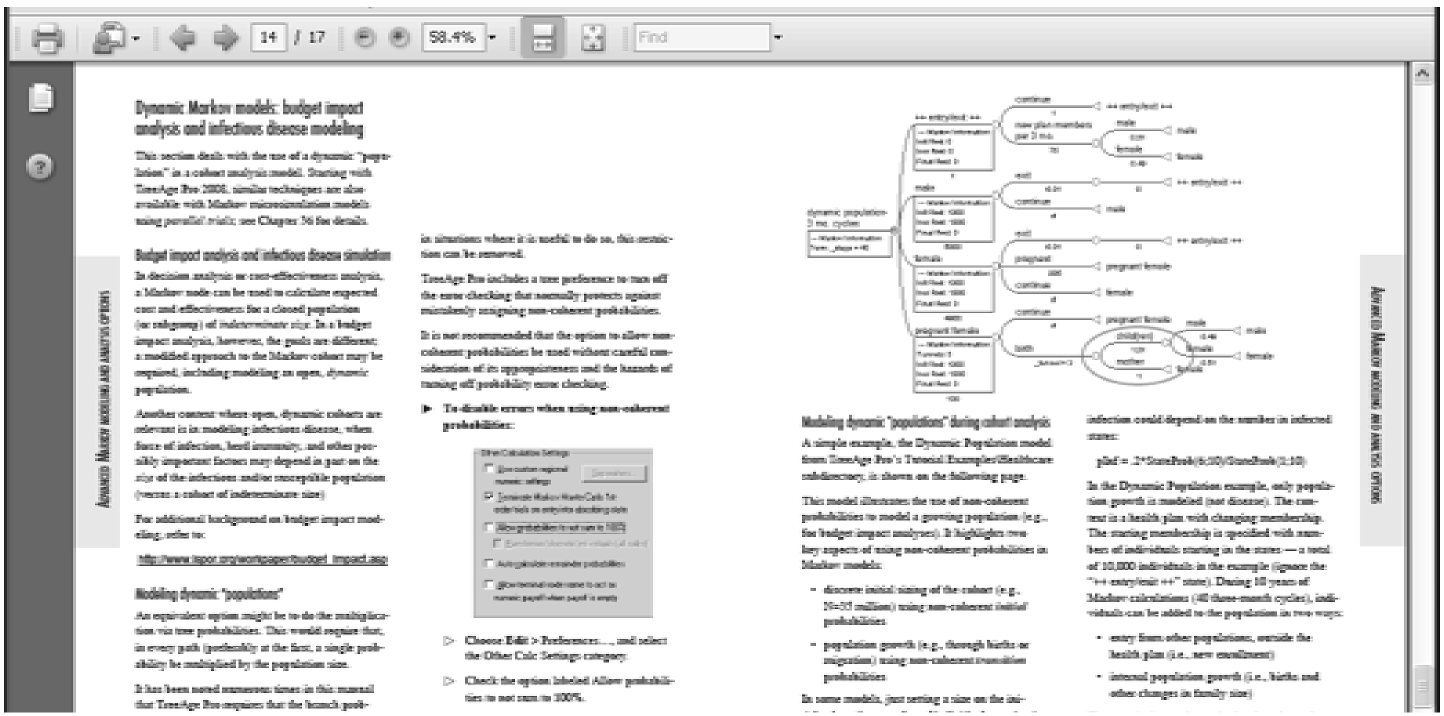
- Dynamic cohorts models
  - Epidemiology
    - Modeling infectious disease
    - Use of StateProb(n) function in determining force of infection (based on counts in Susceptible, Infectious, etc.)
  - Budget-impact analysis
    - Modeling changing size of treatment population
  - Dynamic cohort analysis models useful
  - In microsimulation, parallel trials important
    - Use instead of sequential, to support StateProb() function
    - Model dynamic/open population via non-coherent probabilities (parallel trials allow “creation” of trials)

Dynamic **Cohort** Models



Dynamic **Cohort** Models

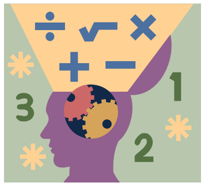
- Model functionality described elsewhere
  - Chapter 35, TreeAge Pro PDF user's manual; "*Modeling dynamic populations during cohort analysis …*"



Dynamic **Cohort** Models

- Final note:
  - Translating a cohort model using a dynamic/open population or StateProb() …
  - … Into a microsimulation model:
    - Parallel trials are required, instead of sequential, to support StateProb() function and/or resource competition, time synchronization
    - Can model dynamic/open population via non-coherent probabilities

Summary

- Questions? 
  - Send an e-mail to support@treeage.com
  - Search Google for more TreeAge simulation/DES models…

Webinar Series

- Material originally presented as part of TreeAge Software webinar series

- Webinar schedule and materials available at:

http://server.treeage.com/treeagepro/training/webinars.asp