
Contents

Abbreviations	xi
Preface.....	xiii
Acknowledgments	xvii
Authors	xix
1. Introduction.....	1
1.1 HTA Context.....	6
1.2 What Is Discrete Event Simulation?	8
1.3 How Does DES Compare to Other Techniques Commonly Used in HTA?.....	10
1.4 When Is Discrete Event Simulation Useful?	15
1.5 Acceptance of Discrete Event Simulation.....	17
1.5.1 Stochastic Behavior.....	18
1.5.2 Data Needs.....	19
1.5.3 Execution Speed	19
1.5.4 Law of the Instrument.....	20
1.5.5 Transparency	21
2. Central Concepts.....	23
2.1 Events.....	23
2.1.1 Types of Events.....	25
2.1.2 Event Consequences	28
2.2 Event Occurrence	29
2.2.1 Time-to-Event Approach.....	30
2.2.2 Periodic Checking.....	32
2.2.3 Event Ordering.....	35
2.3 Entities	35
2.3.1 Why Individuals?.....	35
2.3.2 Types of Entities	38
2.3.3 Creation and Removal of Entities.....	40
2.4 Attributes	41
2.4.1 Attribute Values	42
2.4.2 Types of Attributes	44
2.4.3 What Information Should Be Stored as an Attribute?.....	47
2.4.4 Memory	49
2.5 Time	49
2.6 Resources and Queues	52
2.7 Global Information	56

2.8	Distributions.....	59
2.8.1	Specifying a Distribution.....	59
2.8.2	Commonly Used Distributions.....	62
2.9	Using Influence Diagrams	63
3.	Implementation.....	65
3.1	Control Logic	66
3.1.1	Branching.....	67
3.2	Using Distributions.....	69
3.2.1	Selecting a Distribution	70
3.2.2	Incorporating the Distribution	71
3.2.3	Selecting Values from a Distribution	74
	3.2.3.1 Assigning Sociodemographic Characteristics and Disease Status	79
	3.2.3.2 Sampling Time to an Event.....	81
3.3	Event Handling	82
3.3.1	Event Calendar	84
3.3.2	Entity-Level Event Lists	86
3.4	Specifying Events.....	88
3.4.1	Use of Submodels.....	90
3.4.2	Monitoring and Treatment Change Events.....	91
3.4.3	Specialized Modeling Events	91
	3.4.3.1 Events to Assign Values.....	91
	3.4.3.2 Events to Prompt Input and Output.....	94
	3.4.3.3 Events to End the Simulation	94
3.4.4	Event Sequences.....	95
3.4.5	Composite Events.....	97
3.4.6	Duration of Events	97
3.5	Creating the Population	101
3.5.1	Dynamic Creation.....	102
3.5.2	Using Super-Entities	103
3.5.3	Creating Other Entity Types	104
3.5.4	Agents.....	105
3.6	Assigning Attributes	106
3.6.1	Using Summary Characteristics.....	106
3.6.2	Using Real People	108
3.6.3	Duplication of Entities.....	110
3.6.4	Updating Values and Retaining History	111
3.6.5	Handling Quality of Life	112
3.6.6	Other Values	113
3.7	Handling Time	113
3.7.1	Advancing the Clock Using Time-to-Event	114
3.7.2	Advancing the Clock in Fixed Steps	117

3.7.3	Recording Times.....	118
3.7.4	Matching Actual Time.....	119
3.7.5	Delaying Time Zero	119
3.8	Applying Intervention Effects	120
3.8.1	Effects on Event Times.....	123
3.8.1.1	Using Kaplan–Meier Curves.....	123
3.8.1.2	Using Summary Measures.....	124
3.8.1.3	Dealing with Composite Outcomes.....	126
3.8.2	Changes in a Level	126
3.8.3	Unintended Effects.....	127
3.9	Recording Information	127
3.9.1	What to Record	127
3.9.2	How to Record	128
3.9.3	Discounting.....	130
3.10	Reflecting Resource Use	131
3.10.1	Implicit Handling Using Cost Accumulators.....	131
3.10.2	Explicit Representation.....	131
3.10.2.1	Capacity	133
3.10.2.2	Scheduling.....	134
3.10.2.3	Utilization.....	134
3.10.2.4	Queues	134
4.	A Simple Example	137
4.1	Design.....	138
4.1.1	Problem	138
4.1.2	Influence Diagram.....	139
4.1.3	Model Technique	140
4.1.4	Flow Diagram	141
4.2	Obtaining the Inputs.....	143
4.2.1	Patient Characteristics, Costs, and Quality of Life	143
4.2.2	Equations	145
4.3	Structuring the Model	150
4.3.1	Creating the Entities.....	150
4.3.2	Assigning Initial Attribute Values	151
4.3.3	Assigning Recurrence Event Time.....	154
4.3.3.1	For Standard of Care	155
4.3.3.2	Applying the Treatment Effect	158
4.3.4	Accruing Values Until Recurrence.....	162
4.3.5	Updating Attribute Values.....	166
4.3.6	Assigning the Time of Death.....	171
4.3.7	Accruals at the Second Event.....	174
4.4	Obtaining Results.....	177

5. Analyses	181
5.1 Base Case	182
5.1.1 Dealing with Chance (Stochastic Uncertainty)	182
5.1.2 Reflecting Uncertainty in Parameter Inputs	185
5.1.2.1 Deterministic Uncertainty Analyses	186
5.1.2.2 Probabilistic Uncertainty Analyses	187
5.1.3 Structural Uncertainty Analyses	190
5.2 Exploring Sensitivity to Input Values	193
5.2.1 Subgroups	194
5.2.2 Other Sensitivities of Interest	194
5.2.3 Threshold Values	195
6. Formulating the Required Equations	197
6.1 Requirements for the Equations	197
6.2 Selecting Data Sources	199
6.2.1 Interventional Data Sources	200
6.2.2 Observational Data Sources	201
6.2.2.1 Routinely Collected Data	201
6.2.2.2 Prospectively Collected Data	202
6.2.3 Considerations When Using Multiple Sources of Data	203
6.3 Taxonomy of Equation Types Commonly Used in DES	204
6.3.1 GLM-Based Equations	208
6.3.1.1 Continuous Response Variables	208
6.3.1.2 Categorical Data	210
6.3.1.3 Count Data	212
6.3.2 Handling Longitudinal Data	213
6.3.3 Time-to-Event Analyses	216
6.3.3.1 Deriving Equations	216
6.3.3.2 Incorporating Time-Dependent Predictors	220
6.4 Selection of Predictors	221
6.4.1 Role of Predictors in the Equation	222
6.4.2 Building the Equation	224
6.5 Validation of the Final Equation	225
6.6 Combining Inputs and Equations from Different Sources	226
6.6.1 Incorporating External Data on Intervention Effects	227
6.6.1.1 Considerations with Comparative Data on External Treatments	228
6.6.1.2 Considerations for Non-Comparative Data on Treatment Effects	231
6.6.2 Joining Time-to-Event Distributions and Predictive Equations	232

7. Efficiency and Variance Reduction	235
7.1 Reducing Unwanted Variance.....	236
7.1.1 Duplicating Entities.....	236
7.1.2 Duplication of Pathways	240
7.1.3 Synchronizing Entities.....	243
7.2 Other Efficiency Improvements	244
7.2.1 Time-to-Event Approach Instead of Periodic Checking.....	246
7.2.2 Simultaneous Inclusion of Entities.....	246
7.2.3 Using Super Entities	248
7.3 Settings Affecting Model Execution	251
7.3.1 Animation Settings.....	251
7.3.2 Speed-Destroying Leftovers.....	252
8. Validation	253
8.1 Face Validity.....	254
8.1.1 Problem Specification and Model Conceptualization	256
8.1.2 Is the Choice to Use DES Justified?.....	257
8.1.3 Is the Specification of Events Adequate?	259
8.1.4 How Will Time Be Advanced?.....	260
8.1.5 What Entities Will Be Simulated?.....	260
8.1.6 What Attributes Will Be Modeled?	261
8.2 Verification	262
8.2.1 Model Logic and Implementation	263
8.2.2 Equations.....	265
8.2.3 Code	265
8.3 External Validation	266
8.3.1 Dependent Validation	266
8.3.2 Independent Validation	268
8.3.3 Predictive Validation	270
9. Special Topics	273
9.1 Documentation.....	273
9.1.1 Design Stage	274
9.1.2 Input Data Stage.....	276
9.1.3 Implementation Stage.....	277
9.1.4 Analysis Stage	281
9.1.5 Validation	281
9.1.6 Reports.....	282
9.1.6.1 Non-Technical Documentation	282
9.1.6.2 Technical Report.....	283

9.2	Animation.....	283
9.2.1	Purpose of Animation.....	283
9.2.2	Difficulties with Animation	286
9.2.3	Components	286
9.2.4	How to Animate.....	289
9.3	Software	292
9.3.1	DES Software History	292
9.3.2	DES Software Future	294
9.3.3	Specialized for DES.....	295
9.3.4	General Programming Languages	296
9.3.5	Spreadsheets	299
9.3.6	Spreadsheets Plus.....	300
	9.3.6.1 Visual Basic for Applications.....	300
	9.3.6.2 Monte-Carlo-Simulation Extensions	300
9.3.7	TreeAge.....	301
9.3.8	R.....	302
9.4	Agent-Based Models.....	303
9.5	Hybrid Models	306
9.5.1	With Continuous Simulation.....	307
9.5.2	With State-Transition Models	308
9.5.3	With System Dynamic Models.....	309
9.5.4	With Decision Trees	309
10.	Case Study: Breast Cancer Surveillance	311
10.1	Background	311
10.2	Why DES?	313
10.3	Design.....	314
	10.3.1 Population	315
	10.3.2 Structure.....	315
	10.3.3 Interventions.....	317
10.4	Data Sources	317
10.5	Implementation.....	319
10.6	Analyses.....	320
10.7	Results	322
10.8	Comments.....	323
	References	325
	Index	343