Rolling the DICE: Discretely Integrated Condition Event Simulation for Health Economic Analyses

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As part of a health technology assessment (HTA), there is commonly an analysis of the economic and health implications of paying for a new technology. This analysis is nearly always based on a mathematical framework that provides for integrating information from the relevant clinical trials with data from other sources to forecast what will happen if the new technology is used in place of an existing one. These models are developed using some organizing constructs.

The technique most commonly used today organizes the model around the states that people can be in and transitions among them (i.e., a Markov model).[1] While Markov states can be applied to many aspects of a disease and its management, they are restricted by several strong requirements: any given group of people can be in only one state at a given time and that group must be homogeneous in terms of the transition probabilities. These make it difficult to properly capture our increasingly sophisticated knowledge about the factors that determine the course of illness and the characteristics (e.g., biomarkers) that imply a better response to an intervention in a given person. Moreover, HTA agencies and their expert advisers have become increasingly sophisticated and demanding.

One alternative to Markov models is discrete event simulation.[2] While this technique was developed for operations research and focuses on competition for resources and resulting queues, it has been adapted for use in HTA.[3] The technique organizes the model around events instead of states and offers multiple constructs, like entities, attributes, resources, queues, and an explicit clock. Many of these can be leveraged for economic analyses, but for most applications, they are unnecessary, and specialized software is required for implementation.

Modelers in our field view these techniques as distinct alternatives, and for most projects, an early decision is made on which approach to use, with the rest of the modeling exercise then closely tied to that choice. It turns out that this decision is detrimental to the conceptualization and largely unnecessary as the event and state constructs can be brought together into a single, unified approach, expressly developed for HTA. This approach, DICE simulation, integrates much more flexible states (called "conditions" to distinguish them from the constrained Markov variety) with events that correspond to the happenings of interest.[4] In this overview, the features of DICE are presented in a question and answer format. A demonstration model is available for download as well.

General

What is DICE?

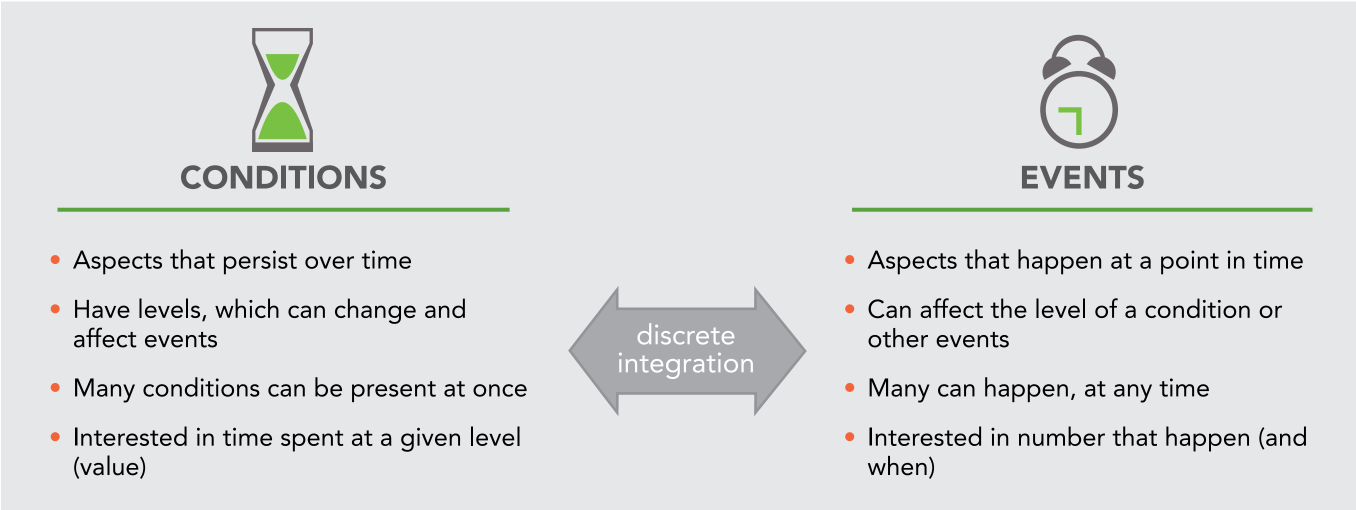
DICE stands for Discretely Integrated Condition Event simulation. It is a modeling technique specifically designed for decision-analytic modeling that conceptualizes a disease process and its management in terms of conditions and events.

Conditions

What are conditions?

Conditions are one of the two central features of DICE and represent any aspect of the problem that persists over time. Conditions have levels, which can change over time. A person can bear any number of conditions at the same time (e.g., age, body weight, glycemia, disease severity). The time spent in a condition can have value, measured in whatever units are of interest (utilities, quality of life score, costs, willingness-to-pay, weights for a multi-criteria decision analysis, etc.). This value may depend on the level of the condition.

Figure 1: The concepts that define a DICE



What can conditions be?

Conditions can characterize aspects of the disease (e.g., viral load, cancer stage, osteoporosis) or its consequences (e.g., renal impairment, pain, disability); features of the treatment (e.g., dose, compliance) or its unintended effects (e.g., neutropenia, weight change); or any other aspects that persist over time (e.g., costs, quality-adjusted life years [QALYs]). They can even pertain to the environment (e.g., analytic perspective, inflation rate, uptake).

Why "discretely integrated"?

Conditions can be changing continuously over time (e.g., tumor size, glycemia, body weight) but in a DICE these changes are evaluated at discrete points in time to avoid the mathematical complexity of simulating continuous interacting processes and to accord with our level of knowledge for most conditions, which is obtained at discrete time points. Thus, these conditions are integrated with (some of) the events, which are convenient time points for updating the conditions' levels.

Are conditions like Markov states?

A Markov state is a reduced form of a DICE condition. It is limited because a person can only be in one Markov state at a time, the state is static – it cannot change over time – and everyone in a state has to face the same consequences (i.e., transition probabilities). DICE conditions are not mutually exclusive and can evolve (e.g., viral load can decrease to below a threshold, stay below for some time and eventually rise above the threshold again; while CD4 count is increasing gradually; and other conditions, such as body weight, are changing as well). Thus, they provide much greater flexibility in representing the problem, without adding additional layers of complexity and leading to state explosion.

Are conditions like attributes in discrete event simulation?

A DICE condition is not restricted to information pertaining to an individual (e.g., the epidemic outbreak status in a given area is a DICE condition); any aspect that persists over time is represented as a condition. A DES attribute reflects any information that is personal to an entity.

Events

What are events?

Events are aspects of the problem that happen at a point in time. They have no duration but their time of occurrence is of interest. Events can happen at any time and several can occur simultaneously. Events can also have value, measured in whatever units are relevant (utility tariffs, quality-of-life score, costs, willingness-to-pay, etc.). This value may depend on when the event occurs, and on other factors such as the conditions that exist at that time.

What can events be?

Events can reflect what happens during the disease (e.g., progression of cancer, relapse, symptom relief, flare), or one of its consequences (e.g., fracture, death). Events can also represent aspects of the treatment (e.g., switch to another treatment, changes in dose or route of administration, start dialysis) or of its unintended effects (e.g., anaphylaxis, neutropenia). Events may also be used to reflect clinical activities (e.g., diagnostic testing, biopsy, surgery, admission to an emergency department or to hospital, discharge, admission to a nursing facility). Behaviors like non-compliance, stop smoking, work absenteeism, provide caregiving, and so on can be events.

Are events like Markov transitions?

A Markov transition can be represented as a DICE event (i.e., the event of transitioning from one state to another), but DICE events have many more features, including valuations such as costs and quality-of-life impacts, while Markov transitions are valueless. DICE events can even affect the entire context of the model (e.g., a new treatment entering the market). Moreover, they can occur at any point in time during the simulation (not just once during a cycle) and can coincide in time.

How do DICE events differ from DES events?

The events in a proper DES are occasions when one or more system variables change, whereas in DICE, events reflect what happens during the disease process and its management and the consequences can affect any aspect of the problem, not only the system variables.

Profiles

What are profiles?

A profile is a set of conditions that sufficiently characterizes a population of interest. Specific profiles are defined to represent the population adequately for the purpose at hand. Each profile denotes a "subgroup" of interest. Defining a single profile is tantamount to specifying a Markov cohort. There can be as many profiles as the analyst wants, including running all the profiles manifested in a particular population of patients (e.g., the participants in a clinical trial).

Is DICE an individual simulation?

Health economic analyses are always about a population specified by the user – never about individuals as such. The analyses for a population can be either deterministic or stochastic. If they are deterministic, it is convenient to consider the population as a cohort, while stochastic analyses require executing the model many times to fully reflect what happens in that population. Each replication does not, however, represent any particular individual – it is just one possible outcome in a population with the specified profile, but it has come to be known as "individual-level" simulation. DICE can run deterministic analyses; even a standard Markov model can be easily implemented with a single profile describing the cohort. Stochastic analyses following the Markov structure (so called "microsimulation") can be run as well as a time-to-event approach. DICE even has the flexibility to incorporate all three types of elements in a single model.

Using DICE

How is DICE specified?

A DICE simulation is specified using a set of tables that itemize all of the model's structure and workings. Only two sets of tables are required: one for Conditions and another for Events. An overall Events table lists all of the events, their initial time of occurrence and the name of their corresponding consequences table. This set of Tables is the full specification of the DICE simulation. In each Table, the applicable information is listed. For example, the table for an Event has a row for each consequence of that event and the columns contain the type of item affected (condition, event, output), the name of the item, and an expression that specifies what the consequence is. An Event can modify any of the Accumulators (e.g., QALYs) or Counters (e.g., is this event to be tallied); or even modify the model structure (e.g., acts as gate).

For the users' convenience and transparency, some of the specialized conditions can be put into their own tables; thus, there can be a Profiles table, and results can be stored in an Accumulators table if they are items that accrue (e.g., QALYs, costs) or in a Counters table if they are counted (e.g., hospitalizations, deaths, treatment switches).

Other helpful tabulations can list the features of the setting (e.g., discount rate) in a Context table, the particulars of a given analysis (e.g., time horizon) in a Scenario table, all the equations that may be used in an analysis in an Equations table. Other information needed for an analysis (e.g., equation intercepts, conversion factors) can go in a Constants table. Valuations (i.e., utilities, unit costs, etc.) can be specified in a Valuations table or can be incorporated directly into the Conditions and Events tables, as appropriate.

How does DICE work?

To execute a DICE, the selected software must read the Conditions table to establish the list of conditions to be considered during the simulation. Next, the Start Event table is read and its consequences are processed – each row in the table is an instruction that specifies a consequence. The occurrence of subsequent events is implemented by establishing an event schedule and maintaining it as events happen and conditions change. The consequences of each event are handled in the same way as for the Start Event.

What types of analyses can be done with DICE?

Since DICE can reflect any aspect of a disease and its management and apply whatever values matter, there is complete flexibility in terms of analyses - from the basic cost-consequences and budget-impact analyses, to cost effectiveness, cost utility, cost value, and even MCDA. These analyses can cover any period of interest, including lifetime. Any number of analytic types can be run simultaneously since they just require that the appropriate accumulators and counters be set up.

Table 1. Example of a Conditions Table

CONDITIONS		
Name	**Initial Value**	**Notes**
Sex	Pick from profile	
Age	Pick from profile	Depends on sex
Biomarker	Pick from profile	Distribution by age and sex
Utility		Select by age and sex
Current Treatment	Standard care	
Cancer Status	Remission	1=Remission 2=Progressed
Time Of Progression	Never	Never
Hazard ratio		Treatment Hazard Ratio

Table 2. Example of an Event Table (for a simple Start Event)

START EVENT			
Assignment Type	**Assigned Item**	**Expression**	**Notes**
Event	Progress	(-Ln (Rand ()/(0.000916* (if(Sex= "Female",-0.458,0)+Age*0.032 +Biomarker*0.003)))^(1/1.67)	Weibull using an embedded Cox proportional hazards
Condition	Utility	Vlookup(QoL,Age,Sex)	
Condition	Hazard Ratio	If(Tmt="New",0.42,1)	

Can DICE estimate QALYs?

In a DICE, QALYs are easily estimated. The accumulating QALY is a type of condition that accrues the time lived adjusted by its quality. Utility values are applied to any events that merit them and to the time spent in particular conditions, according to the level of the condition (as tariffs, percentage changes or whatever the analyst specifies).

What software is required?

There is no specific software requirement. The Tables specifying the DICE are conveniently entered on a spreadsheet (e.g., MS Excel®), and organized into corresponding worksheets. The handling of events is implemented using a very simple macro that reads each row in a Table and executes its instruction. This can be written as a Visual Basic for Applications (VBA) macro, thus keeping the entire DICE in Excel; or advantage can be taken of the tools provided in various simulation software that can accomplish these tasks efficiently. EviDICE™ is an Evidera tool that provides an efficient implementation of DICE in MS Excel, with built-in functions and other tools for the user.

How much time does a DICE model take to run?

The speed of the calculations depends on several factors, as well as the computer's processing capability – the choice of software, the complexity of the model structure, how many outcomes are to be produced, how uncertainty is handled, the number of profiles to be analyzed in a run, and whether the run is stochastic or deterministic. Running a single profile deterministically (i.e., similar to a cohort Markov model) is nearly instantaneous. By contrast, running in MS Excel a large quantity of profiles stochastically requiring complex calculations may take several minutes or even longer for the most elaborate analyses. Carrying out probabilistic uncertainty analyses will add time proportional to whatever a single run takes. The best way of limiting run times is to carefully choose which profiles to run and keeping the number down. Compiling the discrete integrator macro increases the speed substantially.

How does someone use a DICE?

After carefully conceptualizing the problem, designing the model, obtaining the data and deriving the equations, the simulation is implemented as a DICE by specifying the Conditions and Events tables. Reviewers can inspect all the DICE tables and easily see what the DICE is doing. A user can modify the rows in any table to make the model pertinent to their setting and analysis of interest.

Use of a DICE can be facilitated by constructing a user-interface that assists the user in making changes and protects the integrity of the model and inputs. The user-interface makes it easy to run analyses, collect and display the results. This user-interface can be developed within the same Excel workbook that contains the DICE or it can be a separate piece of software, web interface, or tablet app.

Dissemination

How transparent is a DICE?

A DICE is as transparent as a model can possibly be. The entire specification is contained in the set of Tables. There is nothing hidden from the reviewer and the macro that executes the events is generic and easily inspected. There is no "black box" whatsoever. (Of course, if a modeler uses obscure inconsistent labeling and does not adhere to the prescribed table structure, the model can lose transparency).

Will authorities accept a DICE?

DICE meets all the stated modeling requirements of all HTA agencies at present. It can be transparently specified and implemented in a spreadsheet; it can accommodate any type of model that uses either conditions (e.g., Markov "states"), events (e.g., Markov "transitions") or both. DICE simulations are readily reviewed and even modified. The DICE method has been presented to many of the leading HTA agencies and no objections have been raised.

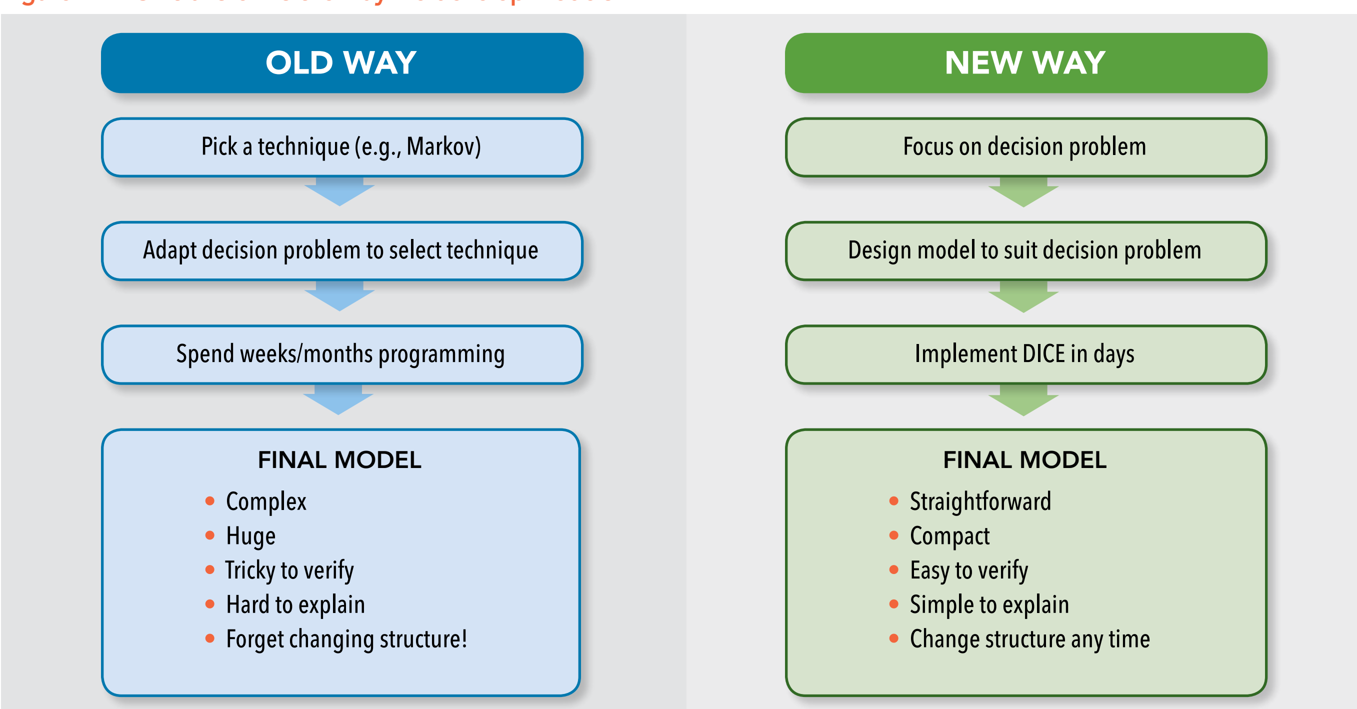
What is the experience with DICE?

Although the DICE specification is new (developed over the past two years), it is a formalization of techniques that draws from established methods that have been in use for more than 20 years (variously called semi-Markov, DES for HTA, etc.). Experience with it is growing rapidly as many companies are adopting it for disease models and health economic submissions.

Conclusion

The modeling techniques in use in our field today, even the relatively new discrete event simulation, date back to the 1950's and were developed to address different problems from those that face us today. They have not

Figure 2. DICE transforms the way we develop models



been updated to address evolving HTA requirements. DICE brings together the best of those techniques into a unified approach that is crystal clear, user friendly, and efficient. The two concepts (conditions, events) that define a DICE are straightforward and correspond directly to the disease and its management. Since DICE uses a standard framework, terminology, and a generic macro, users and reviewers need not "relearn" each new model. The disease-specific terms will change but the structuring and implementation remain consistent across models. The ability to fully program a DICE in familiar software (e.g., MS Excel) removes the need to purchase and learn new software and meets the requirement imposed by many agencies and other stakeholders. As the model is entirely specified by the Tables, there is no need to re-validate the macro (e.g., the VBA code in an MS Excel implementation) for each new model. Checking it once will suffice for all future models.

DICE is very easy to communicate and readily understood by clinicians, modelers, reviewers, decision makers, and other stakeholders. Even a person completely unfamiliar with modeling should be able to quickly understand the concept and review a model (the equations may require specialized statistical knowledge, but that is not specific to DICE). DICE simulation is very flexible. It can accommodate anything from very simple models to vast complex structures, all the while remaining very transparent and easy to debug. The technique does not introduce any awkward ideas (e.g., events represented as pre- and post-states) or impose unnecessary assumptions (e.g., memory-less states, single transitions per cycle).

DICE has been developed to meet the needs of the decision-analytic models commonly developed today. It is not meant for models that require explicit resources with capacities and queues (DES should be used in that case), nor for simulations that entail interactions with the environment or other people (agent-based should be used in that case). Nevertheless, it can be expected that DICE will transform how we develop models. DICE holds the promise of dispensing with the old way of modeling that starts with picking a technique, typically an oversimplified Markov, and forcing the decision problem to fit the technique, with one or more people spending weeks programming the model. Instead, research teams will focus on the decision problem, without wasting time thinking about the modeling technique, and designing a model that best fits the decision problem. This is possible because the DICE implementation is quick and straightforward so there is no need to worry about it from the beginning.

For more information, please contact Jaime.Caro@evidera.com.

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