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Modeling using Discrete Event Simulation: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-4

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A B S T R A C T

Discrete event simulation (DES) is a form of computer-based modeling that provides an intuitive and flexible approach to representing complex systems. It has been used in a wide range of health care applications. Most early applications involved analyses of systems with constrained resources, where the general aim was to improve the organization of delivered services. More recently, DES has increasingly been applied to evaluate specific technologies in the context of health technology assessment. The aim of this article was to provide consensus-based guidelines on the application of DES in a health care setting, covering the range of issues to which DES can be applied. The article works through the different stages of the modeling process: structural development, parameter estimation, model implementation, model analysis, and representation and reporting. For each stage, a brief description is provided, followed by consideration of issues that are of particular relevance to the application of DES in a health care setting. Each section contains a number of best practice recommendations that were iterated among the authors, as well as among the wider modeling task force.

Keywords: discrete event simulation, best practices, modeling, methods.

Background to The Task Force

A new Good Research Practices in Modeling Task Force was approved by the ISPOR Board of Directors in 2010, and the Society for Medical Decision Making was invited to join the effort. The Task Force cochairs and members are expert developers and experienced model users from academia, industry, and government, with representation from many countries. Several teleconferences and hosted information sessions during scientific meetings of the Societies culminated in an in-person meeting of the Task Force as a whole, held in Boston in March 2011. Draft recommendations were discussed and subsequently edited and circulated to the Task Force members in the form of a survey where each one was asked to agree or disagree with each recommendation, and if the latter, to provide the reasons. Each group received the results of the survey and endeavored to address all issues. The final drafts of the seven articles were available on the ISPOR and Society for Medical Decision Making Web sites for general comment. A second group of experts was invited to formally review the articles. The comments received were addressed, and the final version of each article was prepared. (A copy of the original draft article, as well as the reviewer comments and author responses, is available at the ISPOR Web site: http://www.ispor.org/workpaper/Modeling-Using-Discrete-Event-Simulation.asp.) A summary of these articles was presented at a plenary session at the ISPOR 16th Annual International Meeting in Baltimore, MD, in May 2011, and again at the 33rd Annual Meeting of the Society for Medical Decision Making in Chicago, IL, in October 2011. These articles are jointly published in the Societies' respective journals, *Value in Health* and *Medical Decision Making*. This article summarizes the value of discrete event simulation (DES) to inform health care decisions and presents guidance on best practices in the application of DES. Other articles in this series [1–6] describe best practices for conceptualizing models, building and applying other types of models, addressing uncertainty, and ensuring transparency and validity. Examples are cited throughout, without implying endorsement or preeminence of the articles referenced.

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Introduction

DES is a flexible modeling method characterized by the ability to represent complex behavior within, and interactions between individuals, populations, and their environments [7]. In health care, this means that events occurring to an individual and how that individual interacts with others, the health care system, and the general environment can be modeled simultaneously. The term "discrete" refers to the fact that DES moves forward in time at discrete intervals (i.e., the model jumps from the time of one event to the time of the next) and that the events are discrete (mutually exclusive). These factors give DES the flexibility and efficiency to be used over a very wide range of problems.

DES was developed in the 1960s in industrial engineering and operations research to help analyze and improve industrial and business processes. Applications in health care have increased over the last 40 years [8] and include biologic models [9,10], process redesign and optimization [11–13], geographic allocation of resources [14,15], trial design [16,17], and policy evaluation [18–20].

All DES represent an environment or a system, which may be a specific location (e.g., a hospital) or more generally, a particular disease in a defined population (e.g., persons with cardiovascular disease in Australia). A strategy is an alternative policy or configuration of the system, where the purpose of the model is to compare strategies to identify the one that best meets the decision-maker's criteria.

The core concepts of DES are entities, attributes, events, resources, queues, and time.

Entities are objects that have attributes, experience events, consume resources, and enter queues, over time. In health care models, they are typically patients, but they can be other people (e.g., caregivers) or items such as organs, or even signals (e.g., an e-mail) that can interact with other entities or the system itself. Entities can be created at the start or whenever it is appropriate to the problem (e.g., when a new patient arrives at a clinic, or develops a disease). The time of relevance to an entity may be a subset of the simulation time (i.e., individual entities can enter and leave a model between model start and end times).

Attributes are features specific to each entity that allow it to carry information (e.g., age, sex, race, health status, past events, quality of life, and accumulated costs). These values may be used to determine how an entity responds to a given set of circumstances (e.g., timing and type of past events may influence the likelihood and timing of subsequent events). Attribute values may be modified at any time during the simulation, may be aggregated with those of other entities, or analyzed further outside the simulation (e.g., to estimate mean cost and effect).

Events are broadly defined as things that can happen to an entity or the environment. An event can be the occurrence of clinical conditions such as onset of a condition (e.g., stroke), an adverse drug reaction, or progression of a disease to a new stage; resource use (e.g., admission to hospital); clinical decision (e.g., change in dose); or even experiences outside of health care (e.g., failure to show up at work). Events can occur, and recur, in any logical sequence.

A *resource* is an object that provides a service to an entity. This may require time. DES represents resource availability at relevant points in time (e.g., a clinic with three doctors is more likely to see a patient sooner than a one-doctor clinic). In representing resources, DES can capture spatial factors, such as the number of available consulting rooms or distance between a ward and an operating theatre (informing times to and from theatre).

If a resource is "occupied" when an entity needs it, then that entity must wait, forming a queue. Queues can have a maximum capacity, and alternative approaches to calling entities from queues can be defined: first-in-first-out (e.g., a typical waiting room queue); last-in-first-out, where entities get picked from the back of the queue; or based on some priority (such as emergency room triage).

A fundamental component of DES is time itself. An explicit simulation clock (initiated at the start of the model run) keeps track of time. Referencing this clock makes it possible to track interim periods (e.g., hospital length of stay, time spent with symptoms, and survival). The discrete handling of time means that the model can efficiently advance to the next event time, without wasting effort in unnecessary interim computations (e.g., a patient might have nothing happening for 2 years and then a myocardial infarction occurs, with ambulance, treatment, stroke, and other events occurring within minutes).

Other important concepts include interaction, which occurs whenever an entity competes with another over a resource, and emergent behavior, which is behavior that is characteristic of the system as a whole, such as spontaneous overcrowding in emergency rooms because elective surgeries are scheduled only once a week.

DES can be used to address a wide range of questions [21,22]. It allows for very flexible time management, events can occur anytime, without restricting occurrences to fixed time intervals [23]. DES is a particularly good choice when patients are subject to multiple or competing risks because its treatment of time allows for the optimal use of data describing the time to each event. Although this can be approximated in state transition models by using very short cycle lengths, this can lead to increased running times because the model has to check whether each event has occurred during every model cycle. DES is also a good choice when many patient characteristics must be taken into account, particularly if they change over time; when what happens next depends on what happened before; when the effects of decisions made along the way (rather than only at the start) are of interest; and whenever health care or disease processes involve a series of associated events (e.g., myocardial infarct to resuscitation to percutaneous coronary intervention (PCI) stenting to stroke).

There are two categories of DES applications in health care: non–constrained-resource [24–26] and constrained-resource models [27,28]. Non–constrained-resource models—although unusual in other fields that use DES—are required in our field to accord with the common structural assumption made in most health economic models today: that all required resources are available as needed, with no capacity limitations. In contrast, constrained-resource models incorporate these capacity limitations explicitly. They represent indirect interactions between individuals, generally involving multiple entities (e.g., patients) competing for access to resources (e.g., for clinic appointments or donor organs) and waiting in queues. Patients' demand for particular resources and their priority status in a queue may be influenced by their attributes. For such scenarios—the very problems for which it was developed—DES is clearly an appropriate choice.

DES can also be used to model more complex, direct interactions between individuals (e.g., transmission of disease). This "agent-based modeling [29,30]"—an extension of DES—provides more detailed representation of interactions between agents. An agent is an entity with embedded logic that determines how it responds to circumstances (e.g., will intimate interaction be accepted).

The remainder of this article covers design and structuring, estimation and specification of inputs, implementation, running and analyzing, and representation and reporting of DES models.

Structure and Design

DES design starts by defining the system to be represented and relevant events that can occur. Events need not be restricted to those that change an entity's health status; they can represent events that alter the likelihood of other outcomes (e.g., reperfu-

sion following myocardial infarction). In many cases, disease course can be represented as an event (e.g., occurrence of relapse or a bone fracture). Disease course can also involve a continuous variable (e.g., hemoglobin A_{1c} [Hb A_{1c}] level in diabetes). Such measures can be represented by using attributes, which can be updated during the simulation [31].

Time from an event (e.g., time since diagnosis) can be specified as an attribute to facilitate the estimation of costs and quality-of-life effects, and may also influence the likelihood of subsequent events. The choice of other attributes to be represented is informed by the events included in the model (e.g., patient characteristics that influence the likelihood, severity, priority ordering, and outcomes of the specified events).

Common outcomes for constrained-resource models include flow times, wait times, throughput, and resource utilization (costs). Changes in these variables may also affect health outcomes (morbidity and/or mortality) via changes in access to care and time to treatment. Given that the objective of health care systems is to improve outcomes, such effects are of interest to decision makers.

Best practices

IV-1 Discrete event simulation (DES) models should be used when the problem under study involves constrained or limited resources. DES is also an attractive option in non-constrained models when there are interactions between individuals, populations and/or their environment, when time-to-event is best described stochastically rather than with fixed time intervals and time dependencies are important, when individual pathways through the model are influenced by multiple characteristics of the entity, and when recording individual entity experience is desirable.

IV-2 Constrained resource models should consider the effect of alternative strategies on health-related outcomes, and not focus solely on measures of resource utilization and system capacity. The omission of health-related outcomes from a model should be justified.

IV-3 The need to model constrained resources should be carefully considered.

The effects of constrained resources should be modeled if

1. levels of access are altered (e.g., increased referral rates result in longer waiting times for a particular procedure) and
2. time to access has significant effects on costs or outcomes (e.g., surgery).

Events for which the representation of constrained resources is relevant should be identified, (i.e., those to which entities may not have immediate access and for which they queue). Most commonly, constrained-resource events are represented in models that evaluate alternative service pathways, though constrained-resource events have been used to evaluate alternative health technologies as well [27,28].

Best practices

IV-4 If downstream decisions can have significant effects on the differences in costs or outcomes, the model should be structured to facilitate analyses of alternative downstream decisions.

The conceptualization of the system to be modeled should identify decision points (e.g., at which treatment decisions are made). At each decision point, the analyst should consider whether the probabilities of alternative decisions should be represented (i.e., the likelihoods of alternative downstream decisions are parameters to be estimated) or whether the analysis seeks to evaluate combinations of decisions. The latter is clearly relevant to evaluating the organization of existing services. It is also potentially relevant to the evaluation of new technologies (e.g., the cost-effectiveness of screening may be greatly affected by the diagnostic and treatment decisions).

Parameter Estimation

DES can incorporate various parameter types, representing disease course, clinical and administrative decision algorithms, resource costs and constraints, health condition costs, and quality-of-life weights. Disease course parameters are commonly represented as time-to-event (i.e., the parameter describes the likelihood of subsequent event(s) occurring at various, often continuous, time points). Some disease parameters may be unobservable (e.g., preclinical disease stages in screening models requiring calibration for estimation [32]).

Algorithms describe decisions regarding treatment, prioritizing of patients, and implementation of clinical orders. Costs and quality-of-life weights are attached to events and time spent with different health conditions to estimate long-term costs and health outcomes (e.g., quality-adjusted life-years [QALYs]).

Trade-off between structure and parameter estimation

As DES facilitates complex structures, it often requires extensive data. There are several options when lacking data for some parameters. The most radical is to desist from building the model, which may be appropriate when missing information is extensive. Alternatively, the original model structure may be maintained and missing parameter values derived via calibration. Calibration is useful even when empirical estimates are available for all inputs, especially for complex models with many uncertain parameters. There is not a unique set of inputs, however, that reproduces a set of calibration targets, and the uncertainty around calibrated parameter values should be represented in sensitivity analysis [33]. Another option is to eliminate the sections of the model that require the parameters with missing information. This restructuring requires assessment of whether the revised model can provide sufficient insight into the problem. Ideally, the importance of the parameters to be excluded would be assessed by running the original model over a credible range of values for those parameters.

The use of expert elicited data as applied to DES

In the absence of data, inputs may be elicited from experts working in the system modeled. Expert elicitation is subject to a range of biases, both intentional and unintentional. The strength (or value) of elicited inputs will vary according to the complexity (or granularity) of the parameters and the experience of the experts. To increase confidence in values elicited from experts, it is important to validate their responses by asking additional questions from which elicited values can be compared with empirical data. For a DES, clinicians might be asked to estimate not only the missing frequency of referrals to another professional but also the empirically estimated frequency of surgical referrals. Their accuracy in estimating the latter provides some sense of their accuracy with respect to the unknown parameter. Elicited parameter values can also be cross-checked by comparing expert values from independent sources. It is also important to represent the certainty with which different parameters can be estimated by experts, for which established methods can be applied that also provide transparency [34].

Best practices

IV-5 If parameter values are elicited from experts, uncertainty around the elicited values should be represented, and the elicited values should be validated.

IV-6 If confidence in the elicited values is low, resulting analysis should be viewed only as a starting point for what-if analyses, and for estimating the value of collecting additional data.

IV-7 If the decision is made to modify the original structure due to data constraints, the new structure must be carefully analyzed to understand the effects of modifications so as to inform decision makers of the additional uncertainty introduced. Explicit considerations of the size and likely direction of the effects of the modification should be presented.

Clinical guidelines are not always implemented

DES often represents clinical and administrative decision-making algorithms (e.g., processes for assigning patients to clinics). Although clinical guidelines may specify resources that ought to be available and the decisions that clinicians ought to make, there is considerable evidence of variation in the uptake of guidelines [35]. Indeed, one of the purposes of the model may be to demonstrate the potential costs and benefits of adhering to published guidelines. The algorithms could be derived from analyses of patient records, though it is often more feasible to ask clinicians and administrators what decisions they make, given specified circumstances.

Best practices

IV-8 When modeling clinical practice, it should not be assumed that relevant guidelines are actually applied.

IV-9 Ideally, clinical and administrative decision algorithms should be based on analyses of observed decisions. If that is infeasible, algorithms should be developed with relevant personnel, and validated using routinely collected data (e.g., extracting data from patient records).

Assigning times-to-next-event

When analyzing patient-level data to estimate the time-to-next-event for two or more possible next events, competing risk models are not required unless the competing risks (i.e., events that preclude or alter the likelihood of another event occurring) are not represented in the DES, since a new time-to-event can be sampled for the events that are not the first to occur. Two approaches to analyzing time-to-event data are estimating [36].

1. separate times to each potential next event, with the entity moving to the event with the earliest sampled time, or
2. a single time to the next event, with a separate sampling process to determine the type of event that occurs (e.g., using multinomial regression analyses to define the relevant probabilities). The type probabilities may vary as a function of the sampled time to the next event.

Approach 1) is more straightforward to parameterize: survival data for each event can be used directly, or parametric curves can be estimated for each event, and so it is easier to achieve a good fit to observed data. Approach 2) uses a two-stage process to estimate time-to-event parameters for each event, and so it is more difficult to ensure a good fit between observed and estimated event rates. The latter approach, however, provides a more accurate description of the uncertainty around the mean time-to-event parameter values because the times to the different events are jointly estimated.

Best practices

IV-10 Where feasible, when estimating times to competing events, methods of analysis that estimate the timing of competing events jointly are preferred to approaches that estimate separate time to event curves for each event.

Representing continuous disease parameters

In some cases, the likelihood of discrete events is a function of the value of a continuous measure (e.g., diabetic complications are a function of Hb A_{1c}, or clinical presentation is a function of tumor size), as described in the model structure and design section. Time checks can be used to sample the likelihood of discrete events, conditional on the status of the continuous measure of disease progression (e.g., monthly time checks to update Hb A_{1c} levels and define related probabilities of complications).

Alternatively, it may be possible to define joint probability distributions that represent the combined likelihoods of disease progression and related events. In the diabetes example, we might sample the Hb A_{1c} level at which the first complication occurs, and then sample the time at which a patient reaches that level. This latter approach maintains a key asset of DES, namely, that time moves forward when the next event occurs, not in fixed time cycles.

Best practices

IV-11 Where possible, progression of continuous disease parameters and the likelihood of related events should be defined jointly to maintain the discrete event nature of DES (e.g., sample the continuous measure at which an event occurs, and then sample the time at which that level is reached).

Model Implementation

Implementation involves transferring a defined structure into a computer program, which can be populated and analyzed. DES generally represents complex systems, and their implementation requires some form of programming. It is important to ensure that the implementation promote transparency and efficient analyses. Implementations typically consist of Read Data, Create Entities (e.g., patients), Main Section, Remove Entities, and Present Results. The Main Section contains the logic for the events, resource utilization and queuing, risk updating, and anything else that happens during the simulation.

Consider using submodels

The use of submodels facilitates transparency by grouping related model logic (code), which can be reviewed sequentially. Examples include departments within a hospital (where the full system is the whole hospital) or the course of specific events such as myocardial infarction and stroke (where the full system is the course of cardiovascular disease).

The same model may be used to evaluate similar systems in different jurisdictions (e.g., different hospitals or countries), and data available to populate the different versions may vary (e.g., microcosting data may be available in one country, but only higher-level data in another). Separate submodels can be defined that facilitate the use of alternative forms of inputs.

Submodels also mean less code, making the model easier to debug (each submodel can be tested separately, and identical code does not need to be verified in multiple instances). They also ensure that changes to the model will be consistently implemented for all strategies and facilitate updating as new information becomes available.

Best practices

IV-12 To simplify debugging and updating, sub-models should be used to structure the model. When comparing strategies within the same system, sub-models common to all strategies should be defined once and called from each strategy.

Defining multiple model structures

Uncertainty around the model structure warrants implementation and analysis of alternative structures (i.e., structural sensitivity analysis). Rather than implementing separate models for each structure, alternative structures can be implemented within a single DES, reducing programming errors, as common code can be referenced by all structures. The use of a single model also reduces nuisance variance across model structures (e.g., through the use of common random numbers for shared submodels).

Best practices

IV-13 For structural sensitivity analyses, alternative structures should be implemented within a single DES.

Avoiding blocking events

A common implementation error is to inadvertently block the possibility of events occurring (e.g., patients at risk of stroke may have this "suspended" while in hospital following an admission for another event).

Best practices

IV-14 Analysts should ensure that ongoing risks remain active over the relevant time horizon.

Only collect outputs that are required

The manner in which a model is implemented determines the range and level of outputs that can be used in the validation and final analyses. If in modeling a clinic's operation, the interest is in the distribution of waiting times across individuals, it is necessary to implement the model so that each entity holds in its attributes a record of its waiting times. Individual-level recording is not required if the interest is only in the mean, and complexity can be reduced by using global variables to collect values.

Best practices

IV-15 Implementation should account only for the outputs required for validation and final analyses. If individual-level data are required, outputs should be stored as attributes; otherwise, aggregated values should be collected.

General programming or dedicated DES software

Most DES models are implemented by using either a general programming language (e.g., C++, R, or Fortran) or software developed specifically for DES. A general programming language provides increased flexibility, faster execution, and less dependence on proprietary software, but it requires writing code for basic functions (e.g., to administer the event list, run queues, manage resources, and sample from probability distributions), is more complex, requires extensive debugging, and lacks transparency. For many general programming languages, there are code libraries to assist with many basic functions, which can significantly improve coding efficiency and debugging.

Dedicated DES software is designed to overcome the limitations of general programming languages. They typically offer an attractive, easy-to-use interface that provides most of the required functions (i.e., entry points, queues, events, etc.) as modules readily incorporated in the model, with the code required to implement them integrated within. Time, event lists, and other basic tasks are taken care of automatically. Common graphical user interface conventions are utilized to ease use and transparency. Many of the software incorporate animation, which renders the model more visual and understandable. These features also facilitate debugging and greatly increase programming efficiency—the trade-off is somewhat reduced flexibility and calculation speed.

Spreadsheets are sometimes preferred because they are perceived to be widely understood and it is felt that this increases transparency. As a spreadsheet's core idea is to calculate everything simultaneously, implementing the sequential nature DES and recording the movement of time is awkward. Moreover, spreadsheets rapidly grow in complexity and diminish in transparency. They offer few ready-built tools for creating, running, or displaying a DES and programming in an accompanying language (such as VBA) defeats the purpose of using the widely understood spreadsheet format.

Best practices

IV-16 The choice between using general programming or dedicated DES software should be informed by the relative importance of flexibility and execution speed (the former) vs. modeling efficiency, automated structure and transparency (the latter).

Analysis

A single model run estimates the outputs associated with a single set of input parameters. Outputs may include mean values or distributions of values. The distribution of values within a model run may be of interest when evaluating systems such as a clinic, to estimate the proportion who waits more than a certain time before being seen. Mean values are commonly of interest for health technology assessments (HTAs), where interest is in mean costs and outcomes.

The stability of the means or output distributions can be improved by either running more entities or increasing the time horizon. In systems where the number of entities is sampled (e.g., patients presenting at a clinic) and the time horizon is fixed (e.g., daily operation of clinic), multiple replications using the same inputs can be run. Undertaking more replications will reduce variability. One model run can consist of multiple replications.

Best practices

IV-17 Analysts should test the stability of outputs generated by similarly specified model runs using alternative random number seeds to perform several independent runs and identify the number of entities, replication duration, or number of replications (using the same inputs) required to ensure that the distribution of outputs is stable (e.g. less than a 5% or 1% difference between output values across model runs).

Optimizing analyses

Multiple model runs, using alternative inputs, are undertaken to represent uncertainty around outputs. In addition, many runs will be undertaken during calibration or validation. These aspects of analyzing DES can lead to lengthy running times. A general option is to seek extended computing resources that facilitate parallel runs across multiple processors. Lacking sufficient computing resources, it is important to ensure the analytic efficiency of DES by using the following:

1. Variance reduction techniques
2. Planned or algorithmic search strategies to identify input values and a restricted set of strategies
3. The optimal balance between accuracy and number of runs
4. Meta-models to analyze the behavior of complex models

Model runs can be shortened by minimizing unwanted differences between alternative strategies being evaluated [7]. A good starting point is to use identical populations for each alternative. Despite starting with identical populations, nuisance variance is introduced by entities experiencing different pathways because of the divergence of selected random numbers. The application of separate streams of common random numbers to different events (e.g., one

stream for sampling an event occurrence and another for length of stay) helps reduce the possibility that different random numbers are selected for the same event by the same patient under different strategies. Using common random numbers is additionally useful in debugging: the analyst can check that the time to an event not influenced by the strategy is identical for the same simulated patient across strategies. Other more sophisticated techniques, such as signaling between populations to resynchronize their experience, can be implemented, thus further reducing the required computing time.

Best practices

IV-18 Use of variance reduction techniques is recommended. Balance should be sought between using simple techniques such as extending model runs or matching baseline characteristics, and more sophisticated methods available in dedicated DES software or requiring coding in more generic software. The balance trades-off coding time versus improvements in run times and results' accuracy.

Factorial design is recommended when there are multiple dimensions to each factor and one can reasonably conceive of "high" and "low" (or "on" and "off") values for each factor defining a strategy. If a DES is evaluating a continuum of options (e.g., the level of cholesterol above which an intervention might be utilized) or there are multiple dimensions to alternative options (e.g., several staffing options for many staff categories), then it can become infeasible to test every possible option [37]. The aim is to understand how the output is related to the multiple factors. Instead of using one-way sensitivity analysis on the k factors, the factorial approach runs the model with each factor at either its "high" or "low" level (i.e., a total of 2k model runs). This provides estimates of each factor's main effect and of interactions between factors. When k is large, this can become prohibitive (e.g., 215 = 32,768 runs), suggesting the use of "fractional factorial design," where only a subset of the 2k design points is used [38].

Optimum seeking approaches are useful when the decision maker is interested in identifying the optimal strategy across many options. This uses iterative algorithms to assess outputs for the current configuration of options relative to a previously analyzed set, which, in turn, informs the next set of options to evaluate [32]. This iterative process is continued until a specified "stopping rule" is achieved (e.g., a specific number of iterations or some "tolerance level" for improvement in output response). There are many methods that can be used to decide on the next configuration to evaluate, including moving a certain number of steps in the direction in which performance appears to be improving and using random jumps to avoid local optima. Such approaches are standard in the field of optimization and often save substantial analyst and computer time.

Handling uncertainty around inputs is an additional process that can be done by a series of runs by using alternative inputs (either deterministically or probabilistically). Running times for probabilistic sensitivity analysis can be large due to the combined requirement to reduce the variance around each run's outputs and to undertake multiple runs. Rather than abandon probabilistic sensitivity analysis altogether, formulae based on analysis of variance can be used to estimate the combined run size and the number of model runs required to optimize the precision of the outputs, given an available (or desired) analytic time [39].

Meta-modeling involves running a DES with different inputs and then using regression methods to obtain an equation estimating the outputs as a function of the inputs [40]. The selection of configurations to run can be informed by factorial design, and the meta-model can, in turn, be used to inform and speed up factorial design and optimum seeking approaches. Gaussian process emulators have been used in health economic simulations and have the advantage that output uncertainty can be represented for configurations not within the evaluated set, which enables quicker computation of probabilistic sensitivity analysis and expected value of information estimates.

Best practices

IV-19 If the number of strategies to compare is large or there are many structural assumptions to test, then factorial design and optimum seeking approaches should be used.

IV-20 When run times for probabilistic sensitivity analysis are constrained, the optimal combination of run size (per input parameter set) and numbers of alternative inputs tested should be estimated empirically to optimize the precision of the outputs of interest.

IV-21 When computing time precludes adequate representation of all potential strategies and parameter uncertainty, meta-modeling should be used.

Warm-up or preload

In some decision problems, the analysis does not start with an empty system (e.g., when simulating a hospital clinic that has been running for a number of years, the relevant starting point will be the current operation of the clinic, incorporating the patients currently booked or waiting). One option is to preload entities with existing attributes and history of events and start collecting results for analysis immediately. Preloading is appropriate if it is based on an empirical data set describing the current status of entities across the system. The alternative is to run the model for some time prior to starting the analysis—a "warm-up" period. From empty at the beginning of the warm-up period, the system is built up to the current state on the basis of inputs that will continue to be applied within the main analysis.

An important advantage of using a warm-up period is that it helps validate the model by testing whether it is able to create realistic starting conditions. The process of matching current conditions can be difficult, however, if inputs have changed over time (e.g., as a result of shifting referral patterns or the introduction of new technologies). In such cases, the application of constant values will misrepresent the values to be applied within the main analysis.

Outputs generated during the warm-up phase may vary from those in the main analysis, and these provide another opportunity for model validation.

Best practices

IV-22 If the system to be modeled is not empty at the start of the time horizon to be evaluated, a warm-up period should be used to build the system up to the starting point provided:

- ***it can be reasonably assumed that the key parameters have remained constant over time or***
- ***the history of the key parameters can be incorporated into the warm-up period.***

Otherwise, creating starting entities with ready-made histories ("preloading") is acceptable.

Representing and Reporting Des

Animation

Dedicated DES software often facilitates animated representation of models, where the key events are displayed with the passage of entities between them. Humans are better at recognizing pattern and problematic movement visually than via analysis of equations or data. Animation plays to this strength, enabling the identification of illogical movements in the model. It also provides for face validation, where content experts can review the structure of the model and the movement of entities.

Best practices

IV-23 Animated representation that displays the experience of events by individuals is recommended as a means of engaging with users and helping to debug through identification of illogical movements.

Diagrams

Reports of DES should include diagrams that help the readers understand their structure and function. Flow diagrams or state charts provide general frameworks for representing key elements, including possible pathways between events (logic and causal relationships) and presence of queues and decision points. More detailed representations of the structure should enable the readers to replicate the model (if they so wish). Module or event documentation figures can be used to describe the actions undertaken before, during, and after each event. Lists of variables and attributes used and when they are updated provide the user with a detailed understanding of the underlying process.

Best practices

IV-24 Both general and detailed representations of a DES structure and logic should be reported to cover the needs of different users. Detailed event documentation figures are also of benefit to the modeler when returning to the model after a period of absence.

Conclusion

DES provides a flexible framework that can be used to model a wide variety of health care problems. Since it facilitates the representation of complex systems, there are a range of issues along the model development, parameter estimation, implementation, analysis, and reporting spectrum that should be addressed to maximize the value of the final model and its associated outputs. This article has reviewed the main components of the modeling process and provided best practice recommendations that should, if followed, increase the validity, transparency, and value of DES applied in a health care context.

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REFERENCES

[1] Caro JJ, Briggs AH, Siebert U, Kuntz K. Modeling good research practices—overview: a report of the ISPOR-SMDM modeling good research practices task force-1. Value Health 2012;15:796–803.

[2] Roberts M, Russel L, Paltiel AD, et al. Conceptualizing a model: a report of the ISPOR-SMDM modeling good research practices task force-2. Value Health 2012;15:804–811.

[3] Siebert U, Alagoz O, Bayoumi AM, et al. State-transition modeling: a report of the ISPOR-SMDM modeling good research practices task force-3. Value Health 2012;15:812–820.

[4] Pitman R, Fisman D, Zaric GS, et al. Dynamic transmission modeling: a report of the ISPOR-SMDM modeling good research practices task force-5. Value Health 2012;15:828–834.

[5] Briggs AH, Weinstein MC, Fenwick E, et al. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM modeling good research practices task force-6. Value Health 2012;15:835–842.

[6] Eddy DM, Hollingworth W, Caro JJ, et al. Model transparency and validation: a report of the ISPOR-SMDM modeling good research practices task force-7. Value Health 2012;15:843–850.

[7] Pidd M. Computer Simulation in Management Science (5th ed). New York: John Wiley & Sons, 2004.

[8] Jacobson SH, Hall SN, Swisher JR. Discrete-event simulation of health care systems, patient flow: reducing delay in healthcare delivery. Int Ser Oper Res Manag Sci 2006;91:211–52.

[9] Figge MT. Stochastic discrete event simulation of germinal center reactions. Phys Rev E Stat Nonlin Soft Matter Phys 2005;71:1–9.

[10] Zand MS, Briggs BJ, Bose A, Vo T. Discrete event modeling of $CD4^+$ memory T cell generation. J Immunol 2004;173:3763–72.

[11] Coelli FC, Ferreira RB, Almeida RM, Pereira WC. Computer simulation and discrete-event models in the analysis of a mammography clinic patient flow. Comput Methods Programs Biomed 2007;87:201–7.

[12] Comas M, Castells X, Hoffmeister L, et al. Discrete-event simulation applied to the analysis of waiting lists: evaluation of a prioritization system for cataract surgery. Value Health 2008;11:1203–13.

[13] Stahl JE, Rattner D, Wiklund R, et al. Reorganizing the system of care surrounding laparoscopic surgery: a cost-effectiveness analysis using discrete-event simulation. Med Decis Making 2004;24:461–71.

[14] Clark DE, Hahn DR, Hall RW, Quaker RE. Optimal location for a helicopter in a rural trauma system: prediction using discrete-event computer simulation. Proc Annu Symp Comput Appl Med Care 1994;888–92.

[15] Chase D, Roderick P, Cooper K, et al. Using simulation to estimate the cost effectiveness of improving ambulance and thrombolysis response times after myocardial infarction. Emerg Med J 2006;23:67–72.

[16] Skolnik JM, Barrett JS, Jayaraman B, et al. Shortening the timeline of pediatric phase I trials: the rolling six design. J Clin Oncol 2008;26:190–5.

[17] Barth-Jones DC, Adams AL, Koopman JS. Monte Carlo simulation experiments for analysis of HIV vaccine effects and vaccine trial design. Winter Simul Conf Proc 2000;2:1985–94.

[18] Groothuis S, van Merode GG. Discrete event simulation in the health policy and management program. Methods Inf Med 2000;39:339–42.

[19] Mar J, Arrospide A, Comas M. . Budget impact analysis of thrombolysis for stroke in Spain: a discrete event simulation model. Value Health 2010;13:69–76.

[20] Stahl JE, Vacanti JP, Gazelle S. Assessing emerging technologies--the case of organ replacement technologies: volume, durability, cost. Int J Technol Assess Health Care 2007;23:331–6.

[21] Brennan A, Chick SE, Davies R. A taxonomy of model structures for economic evaluation of health technologies. Health Econ 2006;15:1295–310.

[22] Stahl JE. Modelling methods for pharmacoeconomics and health technology assessment: an overview and guide. Pharmacoeconomics 2008;26:131–48.

[23] Karnon J, Brown J. Selecting a decision model for economic evaluation: a case study and review. Health Care Manag Sci 1998;1:133–40.

[24] Karnon J, Czoski MC, Smith KJ, Brand C. A hybrid cohort individual sampling natural history model of age-related macular degeneration: assessing the cost-effectiveness of screening using probabilistic calibration. Med Decis Making 2009;29:304–16.

[25] Tosh JC, Wailoo AJ, Scott DL, Deighton CM. Cost-effectiveness of combination nonbiologic disease-modifying antirheumatic drug strategies in patients with early rheumatoid arthritis. J Rheumatol 2011;38:1593–600.

[26] Caro JJ, Ward A, Deniz HB, et al. Cost-benefit analysis of preventing sudden cardiac deaths with an implantable cardioverter defibrillator versus amiodarone. Value Health 2007;10:13–22.

[27] Jahn B, Pfeiffer KP, Theurl E, et al. Capacity constraints and cost-effectiveness: a discrete event simulation for drug-eluting stents. Med Decis Making 2010;30:16–28.

[28] Cooper K, Davies R, Roderick P, et al. The development of a simulation model of the treatment of coronary heart disease. Health Care Manag Sci 2002;5:259–67.

[29] Auchincloss AH, Diez Roux AV. A new tool for epidemiology: the usefulness of dynamic-agent models in understanding place effects on health. Am J Epidemiol 2008;168:1–8.

[30] Borshchev, A., and A. Filippov. 2004. From system dynamics and discrete event to practical agent based modeling: reasons, techniques, tools. The 22nd International Conference of the System Dynamics Society, July 25-29, 2004, Oxford, England.

[31] Crane G, Karnon J, Kymes S, et al. A discrete event simulation to optimise the allocation of constrained hospital resources for glaucoma. Value Health 2011;14:A55.

[32] Vanni T, Karnon J, Madan J, et al. Calibrating models in economic evaluation: a seven-step approach. Pharmacoeconomics 2011;29:35–49.

[33] Karnon J, Vanni T. Calibrating models in economic evaluation: a comparison of alternative measures of goodness-of-fit, parameter search strategies, and convergence criteria. Pharmacoeconomics 2011;29:51–62.

[34] O'Hagan A, Buck CE, Daneshkhah A, et al. Uncertain Judgements: Eliciting Expert Probabilities. Chichester: Wiley, 2006.

[35] Grimshaw JM, Thomas RE, MacLennan G, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. Health Technol Assess 2004;8:1–72.

[36] Barton P, Jobanputra P, Wilson J, et al. The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis. Health Technol Assess 2004;8:1–104.

[37] Law AM, Kelton WD. Simulation Modeling and Analysis 4th ed.). New York: McGraw-Hill, 2007.

[38] Duintjer Tebbens RJ, Thompson KM, Hunink MG, et al. Uncertainty and sensitivity analyses of a dynamic economic evaluation model for vaccination programs. Med Decis Making 2008;28:182–200.

[39] O'Hagan A, Stevenson M, Madan J. Monte Carlo probabilistic sensitivity analysis for patient level simulation models: efficient estimation of mean and variance using ANOVA. Health Econ 2007;16:1009–23.

[40] Stevenson MD, Oakley J, Chilcott JB. Gaussian process modelling in conjunction with individual patient simulation modelling: a case study describing the calculation of cost-effectiveness ratios for the treatment of osteoporosis. Med Decis Making 2004;24:89–100.