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4 Modeling Frameworks

Albert Wertheimer
PhD, MBA, Professor, Nova Southeastern University, Ft. Lauderdale, FL, USA

Lorenzo Pradelli
AdRes Health Economics and Outcomes Research, Torino, Italy

Chapter reviewed by

- Lucia Sara D'Angiolella. *Research Centre on Public Health (CESP), University of Milano-Bicocca, Monza, Italy*
- Fredrik Olof Laurentius Nillson. *Senior Health Economics Manager, Health and Value Sweden, Sollentuna, Sweden*
- Gabriel Tremblay. *Vice President, North American HEOR. Cytel/Purple Squirrel Economics. Québec City, Canada*

Abstract

Two types of simulation can be used in a model: cohort or patient-level simulation. In the latter, each patient has a set of characteristics and a number of iterations is run to calculate the outcomes.
The decision analysis usually follows a 5-step process: problem conceptualization; model conceptualization; model parameter estimation; run the model and interpretation; sensitivity analysis, transparency, and validation.
A step that sometimes is undertaken before building a detailed decision tree is drawing an influence diagram containing decision and chance elements and outcomes.
A particular model is generally used in case of diseases characterized by a gradual progression: Markov model. It considers several health states and transitions, to which probabilities are assigned. Time is divided into a series of sequential cycles; within each cycle, an individual must be in one state; transitions between the states occur at the end of each cycle.
Partitioned survival models are characterized by a series of health states: The proportion of patients in each health state at each time point does not depend on transition probabilities, but is determined by a set of non-mutually exclusive survival curves.
Discrete-event simulations are characterized by events that occur at an instant in time, resulting in a change of state in the system. The system is a chronological sequence of events.
In the Discretely Integrated Condition Event (DICE) model, diseases can assume different levels over time and patients have different conditions varying over time. Events occurring at a particular time point can change the disease level or affect the occurrence of other events. The levels of conditions may change the probability of an event or its consequences.
In agent-based models, individuals (agents) do not move between compartments, but change their internal state based on their interactions. Agents are characterized by activity, autonomy, and heterogeneity. Agents are active, while the environment (stage for agents' behaviors) is passive.

4.1 Introduction

Modeling is a tool for expressing the known, observed, or expected reality in mathematical terms allowing to simulate or estimate various scenarios and predict the future with a certain level of accuracy [OHE briefing]. The use of a mathematical model has several advantages:

1. A model can generalize data observed in a specific context (e.g., a RCT) to real-life or to a different geographic area;
2. A model can project data over a limited time window (e.g., fitting a parametric curve over the overall survival Kaplan-Meier curve);
3. A model can correlate the primary outcome of an RCT (e.g., the progression-free survival) with a more important clinical outcome (e.g., overall mortality).

On the contrary, some limitations should be highlighted: A model is a simplification of a real problem, thus some assumptions are necessary. As it is not an experimental study, model results should be validated using external sources.

As the use of models to inform policy decision about the use of health technologies has been increasing, the range of modeling techniques has advanced substantially [Caro, 2012]. The relative simplicity of cohort-based models is still an attraction for many modelers and decision makers; nevertheless, there are situations when the decision problem demands taking extensive history into account and patient-level simulation methods are required (see next section).

A major quandary in modeling is the choice of technique that will be used to structure and analyze the model. Many techniques and variations are available and, with sufficient effort, most problems can be structured in almost any of the techniques [Roberts, 2012]. However, this does not mean that the techniques are interchangeable, but the choice should be made carefully. Indeed, there is no reason to treat these as mutually exclusive alternatives: Hybrid models with some components from decision trees and other components from Markov models, for example, can be a very flexible and accurate approach [Caro, 2012]. At the same time, overly complex models should be avoided, if a simpler one accurately reflects all aspects of the decision problem.

4.2 Microsimulation or Cohort Modeling?

When we start to build a model, we have to decide if we want to simulate a cohort of patients globally or each patient individually [Brennan, 2006].

In the first approach, called "cohort model", the experience of each patient is not considered in detail but only the proportions of a population undergoing different health states or events is examined, e.g., "after one year of treatment 80% of patients are in remission". The cohort is considered as an aver-

Cohort model	Microsimulation
Easier to develop, less data intensive, and faster in computation	Time required for microsimulation runs, microsimulation generates stochastic uncertainty; many individual patients should be simulated to ensure expected values are stable
Allows almost instantaneous deterministic analysis and easy probabilistic analysis of parameter uncertainty	Deterministic sensitivity analyses require complete microsimulation runs while it could be computationally problematic to combine microsimulation with probabilistic sensitivity analysis (each iteration of probabilistic analysis must be replicated for each individual)
No memory of previous events since only the mean behavior of the cohort is simulated; it may compromise validity, especially in chronic disease progression with multiple lines of therapy	Model has "memory" because the path of each simulated individual is tracked; model switching through multiple lines of therapy can be easily simulated
Limited ability to model cohort heterogeneity*	Capturing heterogeneities, mimicking disease progression, and predicting clinical outcomes (but computational expensive)
Average characteristics for all cohort: 80% of patients in remission after one year, mean weight 70 kg	Can use empirical data or statistical distributions of individual subjects' baseline characteristics: After one year the probability to be in remission is 80% (i.e., the remission status is modeled as a Bernoulli variable with parameter 0.8), the weight for each patient is sampled from a statistical distribution (e.g., normal) with mean 70 kg and standard deviation 15
The model can predict only the mean behavior of the cohort, while extreme results (outliers) cannot be predicted	Complex outcomes can be calculated also in the base analysis (mean, median, standard deviation, interquantile range)

Table 4.1. Comparison between cohort model and microsimulation.

*Subgroups can be used to model heterogeneity, but only until the variety and level of patients' characteristics are few, as the number of subgroups increases exponentially

age entity with average characteristics, e.g., "60% are male" or "mean weight is 70 kg". In order to model a more realistic and heterogeneous population, subgroups are often considered to refine the analysis. The cohort is split into several subcohorts, characterized for example by age (older and younger than 65 years), prior disease course (presence of a complication or not), health behaviors (smokers vs. non-smokers), comorbidities (patients with and without diabetes), genetic predisposition, or family history.

The second approach is called "microsimulation" or "patient-level simulation"; each patient is created with a proper set of characteristics (sex, age, weight, events predisposition) and his/her disease history is evaluated and recorded until the end of the simulation. The process is then replicated for a suitable number of iterations (in general between 1,000 and 10,000) and the resulting outcomes are calculated as the mean of the outcomes of each patient.

Table 4.1 shows the generic differences between a basic cohort model and a microsimulation. However, it should be kept in mind that several limitations of cohort model may be overcome by increasing the complexity and introducing subgroups. Anyhow, the complexity that should be added to a cohort model to overcome its limitations may be greater than the complexity of microsimulations.

Example: Microsimulation Model in HIV

A patient-level simulation model was developed to evaluate the cost-effectiveness of different Highly Active AntiRetroviral Therapies (HAARTs) for the treatment of HIV patients in Italy [Pradelli, 2017]. The microsimulation approach has been chosen because the Markovian assumption (i.e., that the future position is entirely dependent only on the current position) was considered too restrictive. Specifically:

- All the treatment pathways should be recorded for each patient because future therapy was a function of the previous therapies, the classes of HAART which a patient is intolerant to, and the classes of HAART which a patient is resistant to;
- CD4 count at any given time was a function of the time patients have been virally suppressed and at what point in time they have been virally suppressed;
- Viral rebound depends on the number of times the patient has failed previously due to resistance;

- The rate of comorbidities (cardiovascular disease, chronic kidney disease, diabetes, and hypertension) was simulated using a series of multivariate linear regressions involving as covariates baseline characteristics, HIV treatment history, and CD4 evolution.

4.3 Steps in Decision Analysis

While the process may be broken down in a number of different ways, we will follow previous Authors and describe a decision analysis in terms of five steps [Roberts, 2012; Briggs, 2012; Eddy, 2012]:

- Problem conceptualization;
- Model conceptualization;
- Model parameter estimation;
- Run the model and interpretation;
- Sensitivity analysis, transparency, and validation.

Example: How to Develop a Model for Emergency Contraception and Pregnancy?

National survey data for 1994 indicate that 49% of all pregnancies were unintended and 54% of the unintended pregnancies ended in abortion [Henshaw, 1998]. About half of the women who unintentionally became pregnant had been using a regular method of contraception. Emergency contraception can prevent pregnancy if taken within 72 hours of unprotected sex. We can explore the consequences of a decision whether or not to use emergency contraception using decision analysis. If emergency contraception is used, the probability of pregnancy is reduced (but not eliminated). If pregnancy does occur, a predictable proportion of women will choose to terminate the pregnancy. Some women who continue their pregnancies will miscarry. For the sake of simplicity, we shall ignore the effects of nausea following the use of emergency contraception, and complications such as ectopic pregnancies.

Problem Conceptualization

The first step in a decision analysis is to identify the alternative courses of action. In the example we are using, the decision is whether or not to use emergency contraception following unprotected sex. The consequences of

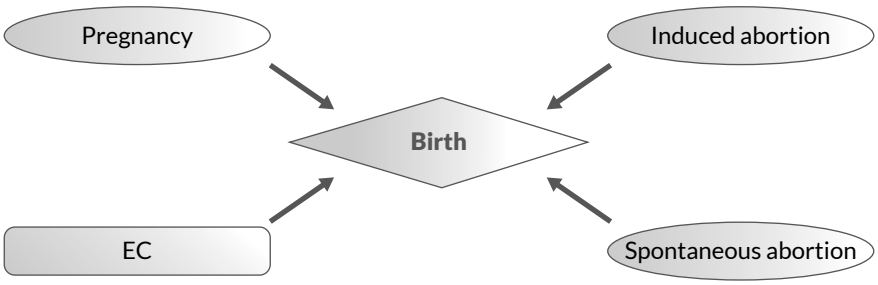

Figure 4.1. Influence diagram. This diagram represents the decision element and chance elements influencing the outcome of unwanted birth.

EC = Emergency Contraception

interest are the numbers of unwanted pregnancies, or, more specifically, the number of pregnancy terminations and live births that would be avoided through the use of emergency contraception. The endpoints of the analysis, therefore, are pregnancy terminations and live births. The time horizon will be limited to an episode of unprotected sex and its unintended consequences, i.e., nine months. The perspective is that of the society.

Influence Diagrams

It is sometimes useful to draw an influence diagram before constructing a detailed decision tree. An influence diagram makes specific the decision to be taken, the outcome of interest, and the chance elements that influence the outcome. Figure 4.1 shows an influence diagram corresponding to the decision tree in Figure 4.5.

The only outcome of interest in Figure 4.1 is live births following unprotected sex (induced abortion was also an endpoint in the decision analysis shown in Figure 4.1).

The outcome is affected by the chance occurrences of pregnancy, induced abortion, and spontaneous abortion. The decision, chance elements, and outcome are presented as a square, circles, and a lozenge shape, respectively.

Model Conceptualization

The appropriate model type is determined by purpose, level of detail, and complexity. In this example, it was decided to use a decision tree due to the limited time horizon (an episode of unprotect sex and its consequences, i.e.,

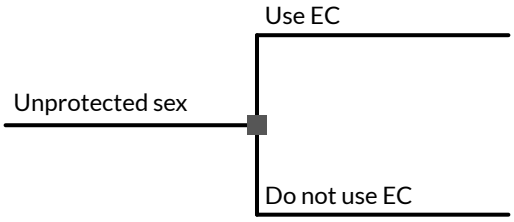

Figure 4.2. Partial decision tree with decision node. The decision is whether or not to use emergency contraception following unprotected sex.

EC = emergency contraception

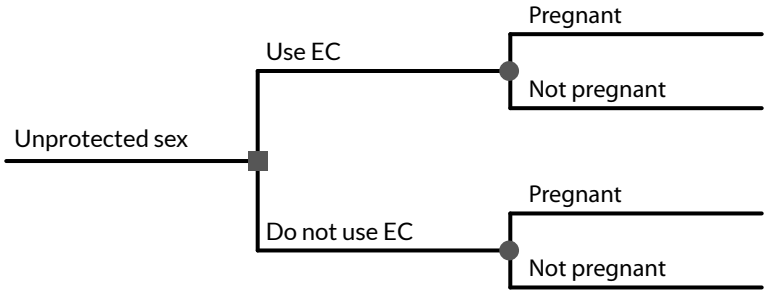

Figure 4.3. Partial decision tree with chance nodes. Chance nodes reflect the likelihood of pregnancy following unprotected sex.

EC = Emergency Contraception

nine months). The tree begins with the decision node and branches representing the alternative courses of action. Here, the decision is to use or not to use emergency contraception following unprotected sex (Figure 4.2).

Following the use (or not) of emergency contraception, pregnancy may or may not occur. A chance node reflecting these alternative outcomes is added to each branch emanating from the decision node (Figure 4.3).

If pregnancy occurs, some women opt for termination and others to continue their pregnancy to term. While for an individual woman this is a decision that must be made, from the perspective of an observer of a population of women, a measurable proportion of women will choose one option over the other. This proportion might vary according to the composition of the population of women and other factors. The node branching to either pregnancy termination or continuation is thus a chance node.

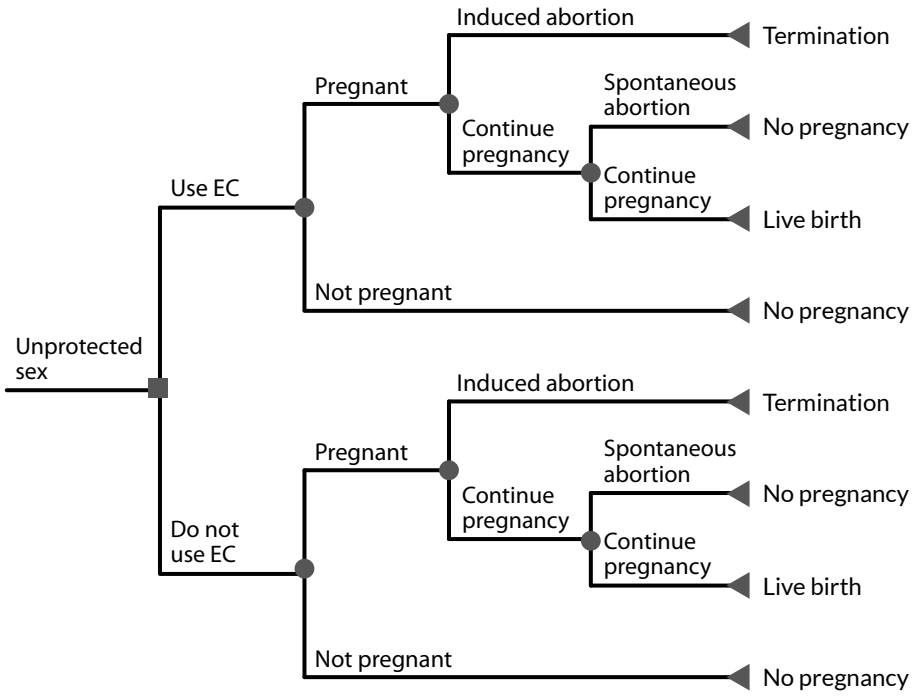

Figure 4.4. Complete decision tree for the decision of whether to use emergency contraception following unprotected sex.

EC = Emergency Contraception

A certain proportion of women continuing their pregnancies undergo spontaneous abortion; this is also reflected in a chance node. The branches now in the model lead to the endpoints that were decided on in Step 1—pregnancy termination, live birth, and no pregnancy. The last step in creating the decision tree, therefore, is to add the terminal nodes (Figure 4.4).

The decision tree describing the problem we identified and bounded in Step 1 is now complete.

Model Parameter Estimation

In the case of the decision tree in Figure 4.4, the information sought is a probability value for each chance node. The probability estimates are displayed beneath the branches of the decision tree, as seen in Figure 4.5.

In Figure 4.5, the probabilities of conception with and without emergency contraception are taken from a clinical trial of emergency contraception ver-

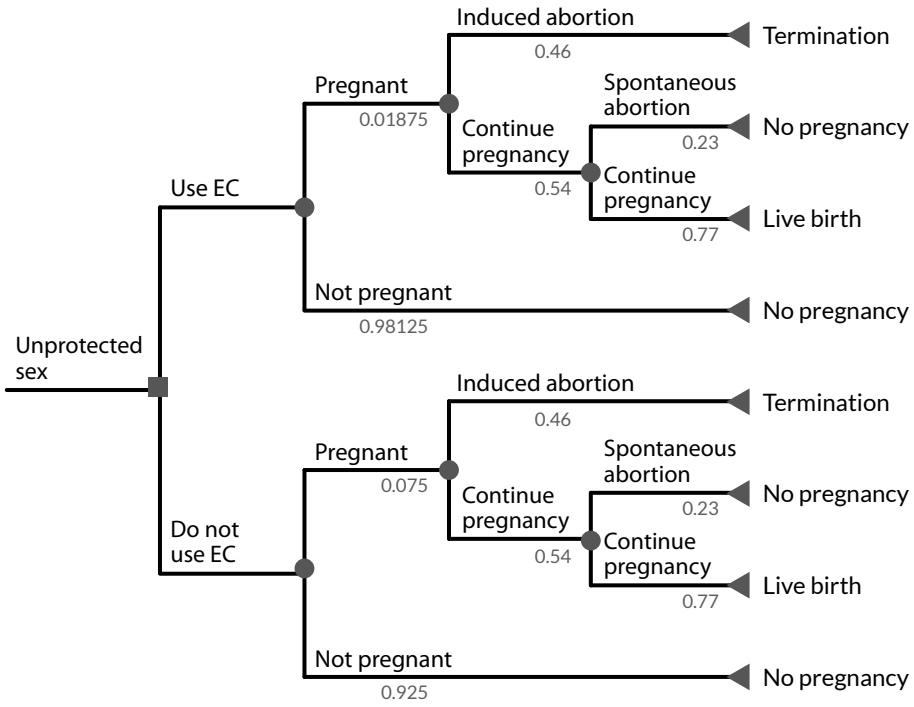

Figure 4.5. Decision tree (see Figure 4.4) with probabilities added.

EC = Emergency Contraception

sus a control group without emergency contraception. The probabilities of induced and spontaneous abortion are obtained from state statistics [Marciante, 2001]. A more extensive description of information sources is given in Chapter 7.

Run the Model and Interpretation

We will analyze the tree by calculating the probability of reaching the outcome represented by each of the terminal nodes. This is done by tracing the branches from each terminal node backwards to the beginning of the tree; the probabilities along these branches are multiplied together to produce the probability of the outcome. These calculations can be performed using a spreadsheet. The spreadsheet has a row for each terminal node and a column for each chance node plus a column for the calculated probability of the outcome.

Decision	Probability				
	Pregnancy	Induced abortion	Spontaneous abortion	Outcome	
EC	0.01875	0.46		0.0086	Termination
EC	0.01875	0.54	0.23	0.0023	No pregnancy
EC	0.01875	0.54	0.77	0.0078	Unplanned birth
EC	0.98125			0.9813	No pregnancy
				0.0164	SUM: Unwanted pregnancy*
No EC	0.075	0.46		0.0345	Termination
No EC	0.075	0.54	0.23	0.0093	No pregnancy
No EC	0.075	0.54	0.77	0.0312	Unplanned birth
No EC	0.925			0.9250	No pregnancy
				0.0657	SUM: Unwanted pregnancy*

Table 4.2. Analysis of decision to use emergency contraception (EC). Analysis of the decision tree shown in Figure 4.5 (see text).

* Sum of probabilities of pregnancy terminations and unplanned births. The value is 1 minus the sum of probabilities of "no pregnancy"

	Induced abortions	Unplanned births
EC	86	78
No EC	345	312
Difference	-259	-234

Table 4.3. Outcomes of decision to use emergency contraception (EC) per 10,000 women.

The spreadsheet corresponding to the decision analysis in Figure 4.5 is shown in Table 4.2.

The probability of an induced abortion if emergency contraception is used (corresponding to the top row of Table 4.2 and the uppermost branch line of Figure 4.5) is $0.01875 \times 0.46 = 0.0086$ (note that there are blank cells in the table where a particular chance node does not occur along the branch line). The outcome for the second and forth rows of Table 4.2 is the same ("No pregnancy") and the probabilities are added together: the probability of no pregnancy if emergency contraception is used is $0.0023 + 0.9813 = 0.9836$. Similarly, the probability of "No pregnancy" if emergency contraception is not used is: $0.0093 + 0.9250 = 0.9343$. The probability of an unwanted pregnancy (sum of

Example

In our decision analysis of the use of emergency contraception, the point estimate of the probability of spontaneous abortion was 0.23. The range of values for this probability is 0.17-0.29 [Marciante, 2001]. Inspection of the decision tree shows that changing the probability of spontaneous abortion does not affect the number of induced abortions but does affect the number of live births. Substituting first the upper limit estimate (0.29) and then the lower limit estimate (0.17) for the value 0.23 used in the initial calculation, we find that the difference in the number of unplanned births (without emergency contraception minus with emergency contraception) varies between 216 and 252 (the point estimate was 234). The spontaneous abortion rate, thus, does not critically affect the reduction in the number of unplanned births attributable to the use of emergency contraception.

pregnancy terminations and unplanned births) is 0.0164 if emergency contraception is used and 0.0657 if it is not (Table 4.2).

The consequences, in terms of induced abortions and unplanned births, of the decision to use or not to use emergency contraception for a hypothetical population of 10,000 women are shown in Table 4.3. The use of emergency contraception would prevent 259 induced abortions and 234 unplanned births per 10,000 women who had had unprotected sex.

Sensitivity Analysis, Transparency, and Validation

Any measurement should be expressed in terms of a point estimate and an indication of its reliability. For instance, in descriptive statistics a mean (point estimate) and 95% confidence interval may be provided. The decision analysis described above has yielded a point estimate of the number of unintended pregnancies prevented by emergency contraception. The reliability of such a point estimate is made difficult to calculate by the (usually) large number of probabilities involved in the model. A point estimate was used for each of the probabilities in the model, but of course there is a range of likely values for each of the probabilities.

Sensitivity analysis determines the effect on the result of varying the probability estimates through the range of their possible or likely values. In a one-way sensitivity analysis, the probabilities at each chance node in the decision tree are varied across their range of values one at a time. This process determines the sensitivity of the results to changes in the assumptions in the model and can identify the most critical assumptions in the model, i.e., those

that have the greatest effect on the results. The following is an example of one-way sensitivity analysis. Multiway (2- or more) and other forms of sensitivity analysis are discussed below. Sensitivity analysis will be further described in Chapter 7.

To increase model transparency, a nontechnical description—including model type, intended applications, funding sources, structure, intended uses, inputs, outputs, other components that determine function, and their relationships, data sources, validation methods, results, and limitations—should be made available to anyone. In the same way, technical documentation, should be made available (openly or under agreements protecting intellectual property). The latter should be written so as to enable expert readers to properly evaluate and potentially reproduce the model.

Finally, validation includes:

- Face validity (experts evaluate model structure, data sources, assumptions, and results);
- Verification or internal validity (check accuracy of coding);
- Cross validity (comparison of results with other models analyzing the same problem);
- External validity (comparing model results with real-world results); and
- Predictive validity (comparing model results with prospectively observed events).

The last two are the strongest forms of validation.

4.4 Markov Models

The decision analysis shown in Figure 4.5 represents a single, linear chain of events transpiring over a single time period. Some diseases, however, progress gradually over a period of years, while the risk of the outcome of interest, for instance, coronary death, increases with age. Markov analysis is appropriate for such problems.

Markov analyses use tree diagrams similar to those used in simple decision analysis. However, the elements of the problem are first mapped out in a Markov diagram similar to an influence diagram. Figure 4.6 shows a Markov diagram representing the progression of congestive heart failure. The Markov model consists of states (ovals) and transitions (arrows).

In Figure 4.6, there are four states: well, early-stage heart failure, late-stage heart failure, and dead from heart failure, where early- and late-stage heart

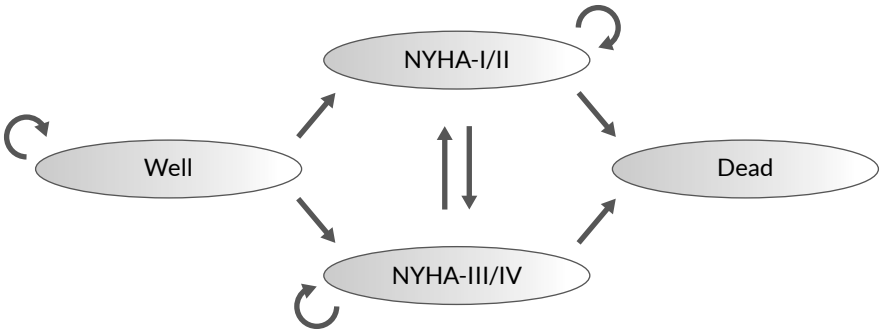

Figure 4.6. Markov transition state diagram for patients with heart failure. Markov diagram based on study by van Hout et al. [van Hout, 1993]. For simplicity, NYHA classes I and II have been combined, as have NYHA classes III and IV.

NYHA = New York Heart Association class for heart failure

failure are represented by New York Heart Association (NYHA) class I/II and III/IV, respectively. Time is broken down into a series of sequential periods or cycles; within each cycle, an individual must be in one of the four states; transitions between the states occur at the end of each cycle. Individuals in the "well" state can transit into either of the NYHA class states or remain in the well state (represented by an arrow exiting from and circling back into the well state). Similarly, individuals in the NYHA-I/II state can remain in that state, progress into the NYHA-III/IV state, or enter the "dead" state at the end of each cycle. Needless to say, individuals cannot exit the dead state. Probabilities must be assigned for each transition. Since time is modelled as a series of cycles of equal length, the probabilities can be different at each cycle, so that they can be made dependent on the age of individuals entering the model. Markov models in which probabilities are time-dependent are called semi-Markov model or Markov process models. Generally, the term "Markov model" indicates a cohort simulation; when the model is developed using a microsimulation approach, the term "individual state-transition model" is preferable.

Example: Markov Model in the Treatment of Secondary Hyperparathyroidism

An illustrative example of the application in pharmacoeconomics of a probabilistic, patient-level model based on Markov cycles is the economic evaluation of cinacalcet in the treatment of Secondary HyperParaThyroidism (SHPT) for chronic kidney patients in the Italian context [Eandi, 2010]. In di-

alysis patients considered in the study, the standard treatment, consisting of D vitamin sterols and phosphate binders, is compared with a new treatment where cinacalcet is included. This drug acts as a regulator of levels of plasma ParaThyroid Hormone (PTH), and indirectly of serum calcium (Ca) and phosphorus (P), by controlling the parathyroid activity, thus being associated with clinical benefit, in terms of CardioVascular (CV) and fracture protection. However, the cinacalcet regimen is more expensive than standard care and this creates the necessity for a comprehensive pharmacoeconomic evaluation about its possible adoption. For this purpose, the novel probabilistic model proposed by Eandi et al. [Eandi, 2010] simulates the effect of cinacalcet on the variation of PTH, Ca, and P levels on individual patients, and correlates these levels with main clinical endpoints like mortality and morbidity resting upon published evidence.

The model consists of a decision tree scheme (designed with the TreeAge 2009 software) with two independent arms representing the standard and the cinacalcet treatment course in Markov cycles: SHTP, SHTP with parathyroidectomy, and death represent the available states of the Markov chain where the main clinical events (CV event, fracture, parathyroidectomy) may be experienced. The simulation spans over a time horizon equal to the whole patients' lifetime, divided in 8-weeks cycles. The outcomes chosen to measure the effectiveness of the cinacalcet and standard treatment are the average time below the recommended KDOQI range (TiR) of PTH, Ca, P, Ca × P [Eknoyan, 2003]: PTH ≤ 300 pg/ml, Ca < 9.5 mg/dl, P < 5.5 mg/dl, and Ca × P lower than 55 $(mg/dl)^2$.

At each iteration one patient is created with his/her unique initial baseline attributes (gender, initial age, PTH, Ca, P level) and sent to both the standard and cinacalcet arm, so that the simulation runs on the very same cohort. During the iteration, patients' parameters may change in time, thereby affecting probabilities and event rates; the short-term variation (weeks) of PTH, Ca, P level of generated individuals with respect to the baseline values are assigned sampling the results of the European multicenter, randomized, open-label OPTIMA study [Messa, 2008] conducted on hemodialysis patients. The model then associates parameter concentrations to Relative Risk (RR) of events (e.g., mortality), also considering the dependence of subsequent events on prior event occurrence (in CV hospitalization or fracture) and the correlations between different events (the effect of parathyroidectomy on mortality and fracture rate). Mortality and morbidity rates are constantly updated by updating RR factors, in turn adjusted on current PTH and mineral levels, probabilistically sampled for each simulated patient on distributions, and

data extracted from literature. Internal and external validation of the model performed with data from literature confirms the reliability of the model.

Costs and outcomes predicted by the model, discounted at a 3.5% annual rate (Table 4.4) are obtained as summary statistics of 10,000 iterations.

Measure of effectiveness (TiR), utility (LE, QALE), and cost (€)	Cinacalcet group	Standard group	Differences
	Mean (SD)	Mean (SD)	Mean (SD)
TiR PTH < 300 pg/ml	5.45 (6.61)	0.19 (0.80)	5.26 (6.59)
TiR Ca < 9.5 mg/dl	6.89 (6.81)	3.26 (5.49)	3.63 (6.87)
TiR P < 5.5 mg/dl	5.86 (6.80)	4.16 (5.93)	1.70 (6.66)
TiR Ca x P < 55 $(mg/dl)^2$	6.96 (6.87)	4.60 (6.12)	2.36 (6.58)
TiR all	2.72 (5.57)	0.04 (0.34)	2.68 (5.55)
LE (LYs)	9.15 (6.33)	7.95 (5.9)	1.20 (3.75)
QALE (QALYs)	5.84 (5.04)	4.95 (4.54)	0.89 (2.59)
Costs (€) w/o dialysis	51,756 (52,481)	23,595 (25,142)	29,161 (47,277)
Costs (€) with dialysis	294,273 (210,108)	234,273 (177,400)	60,000 (127,831)

Table 4.4. Effectiveness, utility outcomes, and final discounted costs with 10,000 iterations, in terms of time in recommended KDOQI range.

LE = Life Expectancy; KDOQI = Kidney Disease Outcomes Quality Initiative; LY = Life-Years; PTH = Parathyroid Hormone;
QALE = Quality-Adjusted Life Expectancy; QALY = Quality-Adjusted Life-Year;
SD = Standard Deviation; TiR = Time in Range

	ICER (cost w/o dialysis)	ICER (cost with dialysis)
TiR PTH (pts-y)	5,354	11,407
TiR Ca (pts-y)	7,754	16,520
TiR P (pts-y)	16,556	35,275
TiR Ca x P (pts-y)	11,947	25,454
TiR all (pts-y)	10,525	22,425
LE (LY)	23,473	50,012
QALE (QALY)	31,616	67,361

Table 4.5. ICER values calculated for 10,000 iterations according to the various possible definitions of effectiveness and utility: Values expressed in Euro versus discounted patient-years (for TiR), Life-Years (for LE), or Quality-Adjusted Life-Years (for QALE).

ICER = Incremental Cost-Effectiveness Ratio; LE = Life Expectancy; LY = Life-Years; PTH = Parathyroid Hormone; QALE = Quality-Adjusted Life Expectancy; QALY = Quality-Adjusted Life-Year; TiR = Time in Range

The benefit of the health treatment is estimated also in terms of utility: Predicted Life Expectancy (LE) is weighted by the utility values of end-stage renal disease and dialysis (Table 4.4) obtained from published literature [de Wit, 1998].

Finally, in order to decide the possible adoption of the cinacalcet based treatment, the Incremental Cost-Effectiveness Ratio (ICER) has been calculated (Table 4.5). When considering LE, the average ICER of cinacalcet vs. standard treatment resulted 23,473€/LY, while if considering QALE, the average ICER was 31,616€/QALY (Table 4.4).

4.5 Partitioned Survival Models

Similarly to Markov models, Partitioned Survival Models (PSMs) are characterized by a series of health states. However, in PSM the proportion of patients in each health state at each time point does not depend on transition probabilities, but is determined from a set of non-mutually exclusive survival curves [Woods, 2017]. The way in which state membership is determined in PSM can be illustrated using a model structure commonly applied in economic evaluation of treatment for advanced or metastatic cancer [Woods, 2020]. This model included 3 states: progression-free, progressed (worsening or spreading of the cancer), and dead (Figure 4.7 A). The PSM derives state membership using two survival curves. The Progression-Free Survival (PFS) curve describes the time from model entry to exiting the progression-free state via progression or death (a composite outcome), whilst the Overall Survival (OS) curve describes the time from model entry to death. For each time t of simulation, PFS(t) provides the proportion of patients remaining in the health state "progression-free"; 1 – OS(t) is the proportion of dead patients; and the difference between OS(t) and PFS(t) provides the proportion of patients who are alive but not progression-free (Figure 4.7 B).

The approach can be applied to models with any number of states as long as patients only move progressively through health states (i.e., no backward transitions, such as from progressed to progression-free, are permitted).

Generally, survival curves are obtained from clinical trials, while parametric models are used to extrapolate beyond the time horizon of the original study.

Example: PSM in Advanced or Unresectable Hepatocellular Carcinoma

We refer to the cost-effectiveness analysis of atezolizumab plus bevacizumab (A + B) in comparison to sorafenib (S) in patients with advanced or

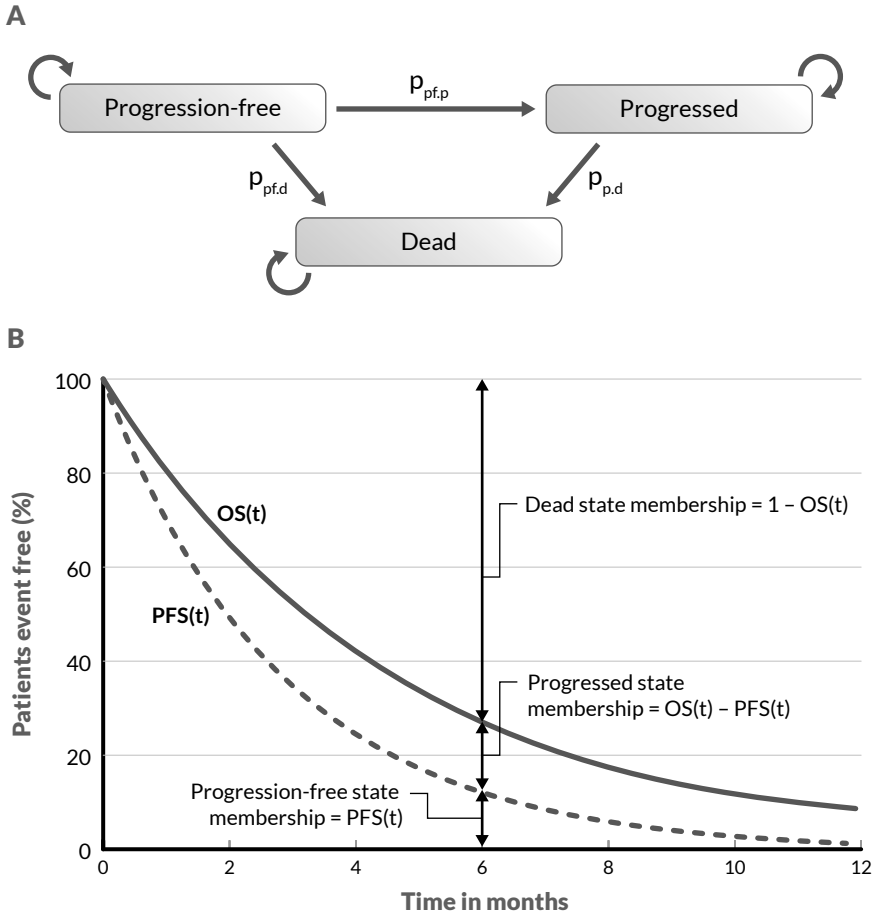

Figure 4.7. State transition model (A) in advanced or metastatic cancer and determination of state membership (B). Modified from [Woods, 2020].

OS(t) = Overall Survival curve at time t; PFS(t) = Progression-Free Survival curve at time t; $p_{p.d}$ = probability of death from the progressed state; $p_{pf.d}$ = probability of death from the progression-free state; $p_{pf.p}$ = probability of disease progression observed prior to death in a model cycle

unresectable HepatoCellular Carcinoma (HCC) in Italy [Pradelli, 2022] as an example of application of partitioned survival model. Disease evolution was modelled using OS and PFS curves estimated from the pivotal trial IMbrave150 for the clinical follow-up period (median 8.6 months). Subsequently, extrapolation was performed by fitting parametric distributions to the observed time

	A + B	S	Delta A + B vs. S	ICER/ICUR
Total LYs	**2.70**	**1.17**	**1.53**	**59,085 €/LY gained**
In PFS	1.58	0.51		
In progression	1.11	0.66		
Total QALYs	**2.29**	**0.98**	**1.31**	**68,896 €/QALY gained**
In PFS	1.36	0.43		
In progression	0.93	0.55		
Overall costs (€)	**135,907**	**45,643**	**90,264**	
Treatment	74,413	16,074		
Administration	661	0		
Adverse events	674	662		
Supportive care	1,712	742		
Post-discontinuation	55,408	24,937		
Terminal care	3,039	3,228		

Table 4.6. Summary results.

A = Atezolizumab; B = Bevacizumab; ICER = Incremental Cost-Effectiveness Ratio; ICUR = Incremental Cost-Utility Ratio; LY = Life-Years; PFS = Progression-Free Survival; QALY = Quality-Adjusted Life-Year; S = Sorafenib

to event data, independently for the two treatments compared (Gamma and Log-logistic distributions for A + B and Log-normal and Weibull distributions for S, respectively, for PFS and OS were used). Cost categories included were: Treatment, administration, adverse events management, supportive care, post-discontinuation therapies, and terminal care cost. Time spent pre- and post-progression was weighted for the utility values derived for the clinical trial in order to estimate the total quality of life associated with the two alternatives. Costs and health gains were discounted at an annual 3% rate, according to Italian guidelines on health economic evaluation, and a half-cycle correction was applied.

A + B is associated with an incremental survival (1.53 LYs), also after weighting for quality of life (1.31 QALYs), when compared with S and incremental costs (€ 90,264) are a consequence of longer survival (Table 4.6). The incremental cost-efficacy ratio is about € 60,000 per LY gained, while the incremental analysis for QALY showed a cost/utility ratio of approximately € 70,000 per QALY gained (Table 4.6), within the threshold for life-extending treatments in people with a short life expectancy in Italy.

4.6 Discrete-Event Simulation

In Discrete-Event Simulation (DES), the operation of a system is represented in the form of a chronological sequence of events. Each event occurs at an instant in time and results in a change of state in the system [Robinson, 2004].

The development of DES dates back to 1960s and belongs to the field of industrial engineering. However, ever since applications in healthcare have increased [Jacobson, 2006] (e.g., biologic models and physiology, process redesign and optimization, geographic allocation of resources, trial design, policy evaluation, survival modeling, and health technology assessments). Key points in discrete-event simulation are entities, events, and time:

- Entities are the objects that can experience the events defining the model structure (typically patients);
- Events are defined as things that can happen to an entity during the simulation. Events can be, for example, adverse drug reaction, occurrence of clinical conditions (e.g., a stroke) or progression of a disease to a new stage. Markov states can also be considered as events;
- Time does not flow continuously but is fixed when an event occurs. Events duration is simulated using probabilistic distributions fitted to set of real data (if available) or to mean ± SD.

Example: DES Model in TPN

The analysis of effectiveness and cost-effectiveness of supplemental glutamine dipeptide in Total Parenteral Nutrition (TPN) therapy for critically ill patients performed by Pradelli et al. [Pradelli, 2012] is a representative case of a pharmacoeconomic study where a DES model is developed. Several works (cited in [Pradelli, 2012]) show that alanyl-glutamine (Ala-Gln) in TPN therapy of critically ill patients reduce mortality, infection rate and shorten Intensive Care Unit (ICU) and hospital Lengths Of Stay (LOS) as compared to standard TPN regimens. The main aim of the simulation study was to investigate whether the Ala-Gln treatment cost is completely offset by the reduction of hospital and medical costs due to improvements in clinical outcomes. This evaluation is performed within a DES scheme with a patient-level approach. In this approach, every generated individual concurrently follows the clinical course of standard and supplemented Ala-Gln TPN treatment experiencing common events in each simulation step. The two simulated therapeutic arms differ only quantitatively for the probabilities characterizing events occurrence and duration. Each patient starts in ICU where he/she may, or may

not, develop a new nosocomial infection. In either case, the patient admitted to the ICU has three alternative possibilities: death in the ICU, or recovery and transfer to general ward, or recovery and discharge home. For patients transferred to general ward, there are two possibilities left: recovery and discharge, or death. Death and discharge represent the end of patient treatment. The time spent in each treatment arm is not discretized in cycles with fixed time intervals valid for the whole patients' cohort (as in case of Markov cycles), but is handled as a time-to-event, specifically sampled for every patient from Weibull distributions fitted to "Progetto Margherita" data, yielding a satisfying goodness-of-fit [GIVITI, 2009].

Patient pathways are shown in Figure 4.8: The time spent in each state depends on the outcome of the state itself, i.e., patients who die in ICU will spend less time in ICU than those who are discharged alive; mathematically, LOS in ICU will be sampled from two different distributions.

All the input values of characteristics and probabilities for every generated patient were randomly sampled (Monte Carlo method) from mathematical distributions fitting data concerning critically ill patients obtained from published works: The baseline outcome rates are extracted from 2007 edition of "Progetto Margherita" [GIVITI, 2007], that reports data regarding more than 60,000 inpatients of 200 Italian ICUs, while the efficacy of supplementation of Ala-Gln in the standard treatment are extracted from a systematically reviewed Bayesian meta-analysis of clinical trials [Pradelli, 2012].

The costs items yielding the overall treatments cost were calculated from the perspective of Italian hospital and were determined using various data sources actualized to the 2008 values according to the inflation index of ISTAT (the Italian National Institute of Statistics). The cost of Ala-Gln was calculated for every simulated patient on the basis of his/her body weight assuming a dose of 0.5 g/kg/day using the maximum price to Italian hospitals (2,107€/g). Body weight and TPN duration were sampled from the population data reported in the trials. Average daily cost to hospital of Italian ICUs (including variable, fixed ICU ward costs, and ancillary costs) results equal to €1,289 [Cavallo, 2001], while the average cost in Italian hospital ward is calculated as €707.64 [ASSR, 2003]. As for the cost of infections, only the extra anti-infective treatments cost, i.e., ICU-emerged blood stream infections [Orsi, 2002], is calculated (€1,034.6) because the reduction of cost infection in ICU due to the use of Ala-Gln is already counted for in the consequent reduction of LOS with respect to the standard TPN regimen.

In Table 4.7, the main clinical outcomes and the costs resulting from the Monte Carlo model simulation conducted for 10,000 patients are summarized.

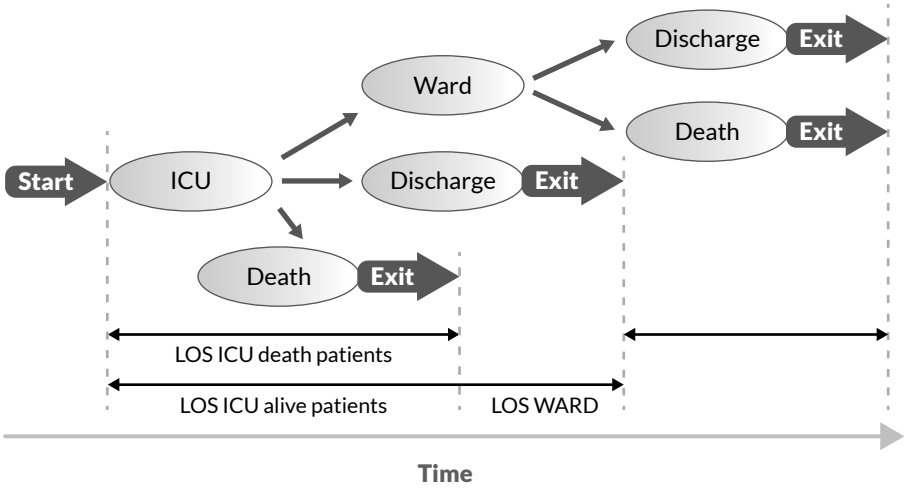

Figure 4.8. DES diagram based on a cost-effectiveness analysis by Pradelli et al. [Pradelli, 2012]. Simulated patients enter the model in the ICU and face three alternative outcomes: Transfer to a general ward, discharge directly at home, or death in the ICU. Those transferred or treated in the general ward are either discharged alive or die during the hospital stay. The latter two determine the end of patient treatment.

DES = Discrete-Event Simulation; ICU = Intensive Care Unit; LOS = Length Of Stay

Outcome	Standard TPN Mean (SD)	Standard + Ala-Gln TPN Mean (SD)	Difference Mean (SD)
LOS (days/patients)	25.99 (0.26)	24.91 (0.25)	-1.08 (0.10)
Deaths/10,000 pts	3,446 (208)	2,460 (159)	-986.01 (57.14)
Infections/10,000 pts	1,878 (391)	1,377 (287)	501.41 (106.71)
Overall costs (€/patient)	24,161 (3,523)	23,409 (3,345)	-752.08 (307.30)
ICU	12,925.48 (2,554.33)	11,669.13 (2,308.10)	-1,256.35 (255.08)
Antibiotics	193.73 (56.81)	142.00 (41.62)	-51.72 (15.36)
Supplementation	0 (0)	602.95 (175.79)	602.95 (175.79)
Ward (pre-ICU)	2,905.55 (612.67)	2,905.55 (612.67)	0 (0)
Ward (post-ICU)	8,136.51 (1,711.83)	8,089.56 (1,698.92)	-46.95 (65.05)
Overall costs/survivor (€)	36,905 (5,535)	31,061 (4,496)	-5,844 (1,162)

Table 4.7. Costs, effectiveness, and cost-effectiveness results for Ala-Gln + TPN versus TPN alone in critically ill ICU patients based on model simulation.

ICU = Intensive Care Unit; LOS = Length Of Stay; SD = Standard Deviation; TPN = Total Parenteral Nutrition

On average, Ala-Gln-based TPN therapy would prevent more than one-quarter of deaths and infections and reduce the overall mean LOS by 1.1 day, compared with standard TPN. Furthermore, these findings show that the cost of Ala-Gln nutrition is more than offset by the reduction of ICU and antibiotic costs, resulting in a mean net cost saving of €752 per patient. Therefore, it could be concluded that addition of Ala-Gln to standard TPN is expected to dominate standard TPN alone, presenting better clinical and economic outcomes. Internal validation of the model performed with observed clinical data strengthen the reliability of the model. The variation of input cost and clinical parameters in one-way sensitivity and in scenario analyses tested the robustness of the results.

4.7 Discretely Integrated Condition Event Simulation

In a Discretely Integrated Condition Event (DICE) model, the disease evolution and its management are conceptualized in terms of the conditions that patients can be in, integrated with the events they can experience [Caro, 2016].

A condition is something that persists or happens over time and can assume different levels, e.g., cancer status (levels: Cured, remission, progressive disease). Patients' characteristics are also conditions (sex, age, blood pressure, etc.). The sex condition is unchanging, while most of these conditions tend to vary over time.

Events are things that happen at particular points in time, e.g., death, detecting cancer progression, hospitalizations, or infections.

Events can initiate/terminate a condition, change its level, or affect the occurrence of other events. Conversely, the levels of conditions can change the likelihood of an event or its consequences. In reality, such interaction occurs continuously over time. For simplicity, in the majority of pharmacoeconomic evaluation, conditions and events are integrated at the discrete points in time when the events occur.

The design of the DICE model involves three steps:

1. Each component of the model is classified as an event or a condition, depending on whether it persists over time;
2. Each condition is specified together with its possible levels, and how these might change overtime;
3. Each event is described in terms of time of occurrence and its consequences.

Example: How to Develop a DICE Model in Cancer

We refer to the toy example developed by Caro [Caro, 2016]. Suppose to be interested in assessing the efficacy of a new treatment for a particular cancer with a poor prognosis that leads to premature death. Age, sex, and specific biomarker levels are included as patients' characteristics as strong predictors of both Progression-Free Survival (PFS) and post-progression survival.

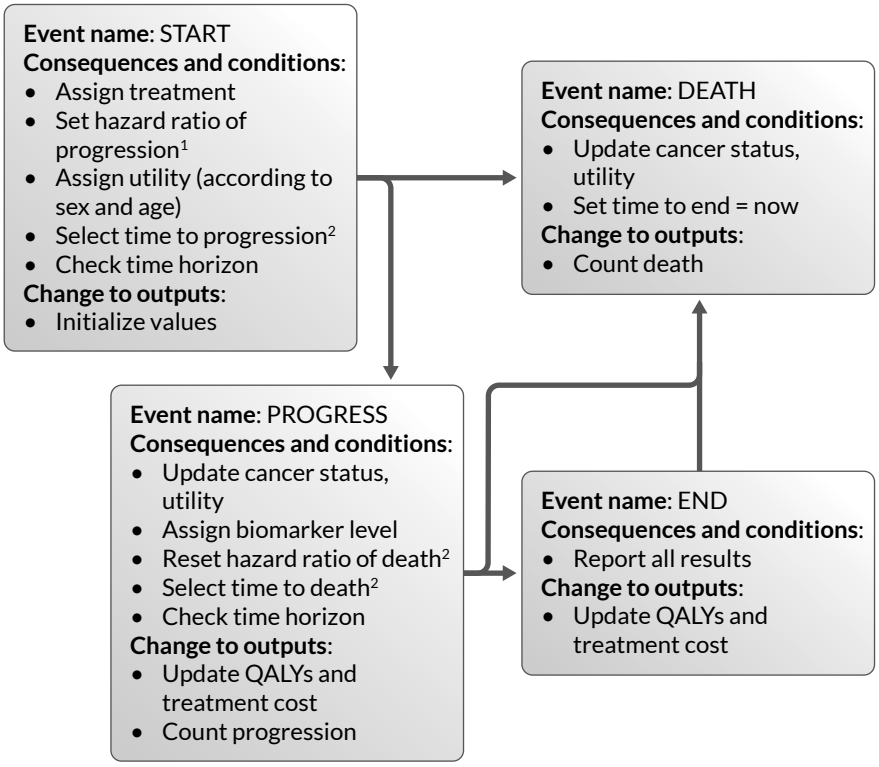

Figure 4.9. Illustrative representation of the events considered in the simplified DICE example (the boxes) and the connections among events (the arrows).

DICE = Discretely Integrated Condition Event; QALY = Quality-Adjuted Life-Year; RCT = Randomized Clinical Trial;

[1] 0.42 for antineoplastic intervention, 1 for standard of care according to RCT results

[2] Values are sampled from specific Weibull distributions adjusted for sex, age, biomarker, and treatment effect

[3] 0.73 for antineoplastic intervention, 1 for standard of care according to RCT results

Efficacy evidence for the new antineoplastic intervention, compared with standard of care, comes from a well-designed Randomized Clinical Trial (RCT) in terms of increasing in the time to remission and overall survival (Figure 4.9).

The simplified structure of the model is illustrated in Figure 4.9.

4.8 Agent-Based Models

In an individual or Agent-Based (AB) model the status of each individual is explicitly tracked over time. In this case, individuals are discrete entities who do not move between compartments, but rather change their internal state (e.g., susceptible, infected) on the ground of their interactions. Furthermore, AB models can incorporate population heterogeneity quite easily. Finally, they are flexible enough to assess complex interventions.

Individuals evolving in an AB model are called "agents". An agent is defined by the following characteristics [Niazi, 2011]:

- Activity: Each agent independently acts following the rules assigned in the simulation and its own pre-programmed behavior. Agents may interact or exchange information with other agents; these interactions may have particular effects on the agent, including its destruction or change in goal-seeking behavior;
- Autonomy: Each agent can make independent decisions in accordance with rules assigned in the simulation;
- Heterogeneity: Generally, each agent is created as a member of a limited set of common templates, but it develops individuality through interactions.

Stage for agents' behaviors is called "environment". Environment may change dynamically according to the actions of the agents, but these changes occur passively, rather than in the active fashion of agent evolution in time. The state of the environment evolves dynamically, but only in response to the actions of the agents; in sum, agents are active while the environment is passive.

Agent-based modeling allows to incorporate and evaluate complex behaviors and interactions and, as such, permits to effectively model complex phenomena [Miller, 2007]. Global system evolution is not modeled *a priori*, but depends on a "few" rules that are assigned to each agent (Figure 4.10).

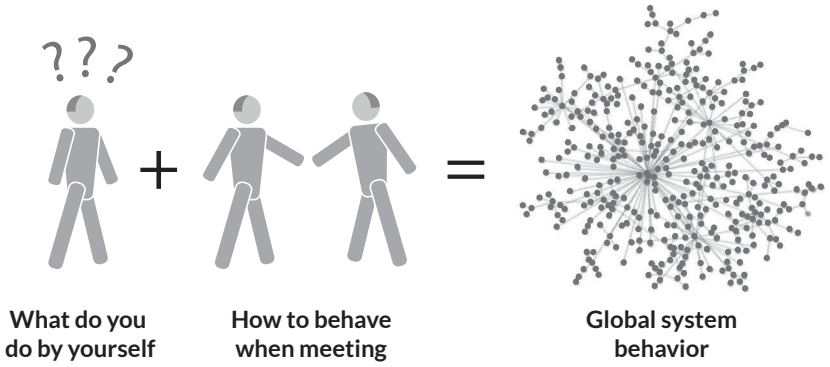

Figure 4.10. Illustrative representation of an AB model: Rules of conduct of a single agent when alone and when interacting with other agents that are assigned *a priori* (but may change due to interaction or learning). The global behavior of the whole population (framed network with dots corresponding to agents) naturally arises without external constraints.

Example: AB Model in Screening Program

This case study evaluated the impact of screening for hypothetical infectious disease [Chhatwal, 2015]. The Authors modelled the transmission of an infectious disease which progressed among an isolated population (Figure 4.11).

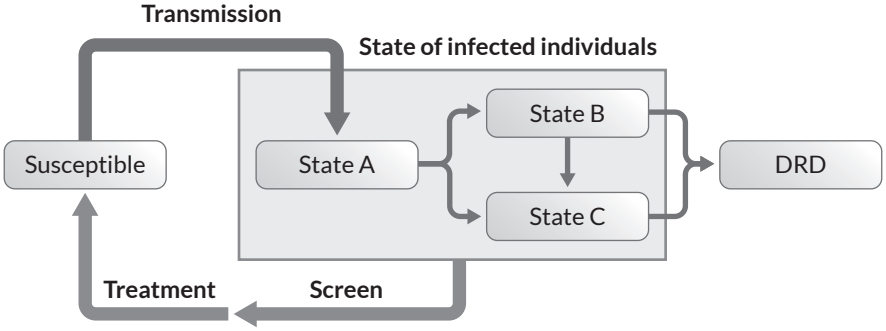

Figure 4.11. Illustrative representation of the transmission and progression of disease in the agent-based model. Modified from [Chhatwal, 2015].

DRD = Disease-Related Death

Infection radius	Screening	Cost per patient ($)	QALYs	Delta cost ($)	Delta QALYs	ICER ($/QALY)	DRDs averted	Infections averted
Small	No	966	25.20					
	Yes	1,438	25.20	472	0.01	60,504	0.08%	0.02%
Medium	No	2,209	25.08					
	Yes	2,824	25.10	614	0.02	29,258	0.18%	0.18%
Large	No	12,044	24.33					
	Yes	14,145	24.43	2,101	0.09	23,084	0.94%	1.46%

Table 4.8. Results of the case study comparing the cost-effectiveness of the screening program versus no-screening scenario for different values of infection radius.

DRD = Disease-Related Death; ICER = Incremental Cost-Effectiveness Ratio; QALY = Quality-Adjusted Life-Year

The agents were defined as people who can be susceptible, infected, or at the chronic stage. In each cycle, an infected person could come into contact with several susceptible persons in his/her radius and could probabilistically transmit disease to them (State A). In contrast to a Markov model, agents in the AB model change their attributes on the basis of their interactions with other agents. The infected agents, if screened and treated, can be cured and move to a susceptible state with a possibility of reinfection. Untreated infected agents can progress to advanced stages of disease (State B and C) and, eventually, experience a Disease-Related Death (DRD).

Results of the case study comparing the cost-effectiveness of the screening program versus no-screening scenario are reported in Table 4.8 for different values of infection radius.

4.9 Conclusions

During the process of converting the problem conceptualization into an appropriate model structure, several model types may be suitable (Table 4.9). However, some problems are more naturally represented in some types than others [Roberts, 2012].

Decision trees are useful for problems with short time horizons where the estimation of outcomes is straight-forward. Markov models or quasi-Markov models are useful for problems with longer time frame or when probabilities vary over time. DES and more sophisticated DICE models are useful for rep-

	Decision trees	Markov models	State transition models	PSM	DES	DICE simulation	AB models
Patients simulated as	Cohort	Cohort	Each patient individually	Cohort	Each patient individually	Each patient individually	Each patient individually
Time horizon	Short	Long	Long	Long	Long	Long	Long
Interaction between individuals	No	No	Yes	No	Yes	Yes	Yes
Interaction between patients and environment (e.g., resource constraints)	No	No	No	No	Yes	Yes	Yes
Software	TreeAge, MS Excel	TreeAge, MS Excel	TreeAge, MS Excel	TreeAge, MS Excel	MS Excel, specific software	Specific software	Specific software

Table 4.9. Comparison between the main simulation models.

AB = Agent-Based; DES = Discrete-Event Simulation; DICE = Discretely Integrated Condition Event; PSM = Partitioned Survival Model

resenting individual behavior under certain constraints or events that could change patients' pathway. AB models are suitable for model interaction between subjects and their impact on the results.

The model types presented in this chapter are not exhaustive and some healthcare problems are not easily represented with these commonly used techniques. Combinations of models or hybrid models (e.g., decision tree to simulate acute phase followed by Markov model in the chronic phase) could be more appropriate. Furthermore, model simplicity is desirable for transparency, validation, and description. However, the model must be complex enough to incorporate all aspects clinical experts feel are required.

Questions

1. **Tick the correct sentence**
   A. Patient-level simulation is easier to develop and faster in computation than cohort model
   B. In cohort model only mean results can be calculated
   C. Cohort model can mimic disease progression
   D. Microsimulation has no memory of previous events

2. **Tick all that apply to microsimulation**
   A. Each patient is created with a proper set of characteristics
   B. The experience of each patient is not considered in detail
   C. The process is replicated for a suitable number of iterations
   D. Can use empirical data or statistical distributions of individual subjects' baseline characteristics

3. **Tick all that apply to decision analysis**
   A. The first step is model conceptualization
   B. The decision tree is made by nodes and branches
   C. Further information is used to fill the decision tree
   D. Four steps are involved in the decision analysis

4. **Which is the right order of the step forming the decision analysis?**
   A. Problem conceptualization; model conceptualization; model parameter estimation; run the model and interpretation; sensitivity analysis, transparency, and validation
   B. Model conceptualization; model parameter estimation; problem conceptualization; run the model and interpretation; sensitivity analysis, transparency, and validation
   C. Problem conceptualization; model conceptualization; sensitivity analysis, transparency, and validation; model parameter estimation; run the model and interpretation
   D. Sensitivity analysis, transparency, and validation; problem conceptualization; model conceptualization; model parameter estimation; run the model and interpretation

5. **In influence diagrams**
   A. Decision elements are represented as squares
   B. Chance elements are represented as squares
   C. Outcomes are represented as squares
   D. Individuals are represented as squares

6. **Tick all that apply to Markov models**
   A. May be used in case of diseases gradually progressing over years
   B. Markov diagrams are similar to influence diagrams
   C. In each cycle, every individual must be in one state
   D. Individuals can exit the dead state

7. **In Markov models, when do transitions between the states occur?**
   A. Only in case of death
   B. No transitions occur in Markov models
   C. In the middle of each cycle
   D. At the end of each cycle

8. **Key points in discrete-event simulation are**
   A. Cycles, transitions, and periods
   B. Entities, events, and time
   C. Entities, events, and conditions
   D. Cycles, transitions, and states

9. **Tick all that apply to discrete-event simulations**
   A. The operation of a system is represented as a chronological sequence of events
   B. It was originally developed in the field of veterinary medicine
   C. Each event occurs at an instant in time
   D. Each event marks a change of state in the system

10. **DICE stands for**
   A. Different Iterations Condition Event
   B. Discretely Integrated Condition Event
   C. The plural of die, as the name of the technique reminds the randomness of the possible conditions a patient can be in
   D. Different Integrated Condition Event

11. **In the DICE model**
    A. Every condition is allowed to assume just one level
    B. The disease evolution and its management are conceptualized in terms of the conditions that patients can be in, integrated with the events they can experience
    C. All the conditions associated with patients vary over time
    D. Events do not interact with conditions

12. **Tick all that apply to agents in agent-based models**
    A. Agents are individuals
    B. Agents are events
    C. Agents have the following characteristics: entities, events, and time
    D. Agents have the following characteristics: activity, autonomy, and heterogeneity

13. **Tick all that apply to agent-based models**
    A. The status of each individual is explicitly tracked over time
    B. Individuals are discrete entities who move between compartments
    C. Individuals change their internal state based on their interactions
    D. Stage for agents' behaviors is called "cycle"

Answers

1. **B**
2. **A, C, D**
3. **B, C**
4. **A**
5. **A**
6. **A, B, C**
7. **D**
8. **B**
9. **A, C, D**
10. **B**
11. **B**
12. **A, D**
13. **A, C**

References

- ASSR. Agenzia Nazionale per i Servizi Sanitari Regionali. Ricoveri, personale e spesa delle aziende ospedaliere (2003). Available at: http://www.agenas.it/agenas_pdf/AO_2003.pdf [in Italian] (last accessed October 2012)
- Brennan A, Chick SE, Davies R. A taxonomy of model structures for economic evaluation of health technologies. *Health Econ* 2006; 15: 1295-310. https://doi.org/10.1002/hec.1148
- Briggs AH, Weinstein MC, Fenwick EAL, et al. Model parameter estimating and uncertainty: a report of the ISPOR-SMDM modeling good research practices task force-6. *Value Health* 2012; 15: 835–42. https://doi.org/10.1016/j.jval.2012.04.014
- Caro JJ. Discretely Integrated Condition Event (DICE) Simulation for Pharmacoeconomics. *Pharmacoeconomics* 2016; 34: 665-72. https://doi.org/10.1007/s40273-016-0394-z
- Caro JJ, Briggs AH, Siebert U, et al. Modeling good research practices-Overview: a report of the ISPOR-SMDM modeling good research practices task force-1. *Value Health* 2012; 15: 796–803. https://doi.org/10.1016/j.jval.2012.06.012
- Cavallo MC, Lazzaro C, Tabacchi M, et al. Cost of ICU in Italy. Results from an empirical study on a sample of 12 hospitals. *Minerva Anestesiol* 2001; 67: 41-53
- Chhatwal J, He T. Economic evaluation with agent-based modelling: an introduction. *PharmacoEconomics* 2015; 33: 423–33. https://doi.org/10.1007/s40273-015-0254-2
- de Wit GA, Ramsteijn PG, de Charro FT. Economic evaluation of end stage renal disease treatment. *Health Policy* 1998; 44: 215-32. https://doi.org/10.1016/S0168-8510(98)00017-7
- Eandi M, Pradelli L, Iannazzo S, et al. Economic evaluation of cinacalcet in the treatment of secondary hyperparathyroidism in Italy. *Pharmacoeconomics* 2010; 28: 1041-54. https://doi.org/10.2165/11538600-000000000-00000
- 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: 843–50. https://doi.org/10.1016/j.jval.2012.04.012

- Eknoyan GLA. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. *Am J Kidney Dis* 2003; 42(Suppl 3): S1-S201. https://doi.org/10.1016/S0272-6386(03)00905-3
- GIVITI. Progetto Margherita. Rapporto 2007. Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva (GIVITI), 2007
- GIVITI. Progetto Margherita. Report 2009. Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva (GIVIT), 2009
- Henshaw SK. Unintended pregnancy in the United States. *Fam Plann Perspect* 1998; 30: 24-9. https://doi.org/10.2307/2991522
- Jacobson SH, Hall SN, Swisher JR. Discrete event simulation of health care systems, patient flow: reducing delay in healthcare delivery (Ed. Hall RW). *International Series in Operations Research & Management Science* 2006; 91: 211-52. https://doi.org/10.1007/978-0-387-33636-7_8
- Marciante KD, Gardner JS, Veenstra DL, et al. Modeling the cost and outcomes of pharmacist-prescribed emergency contraception. *Am J Public Health* 2001; 91: 1443-5. https://doi.org/10.2105/AJPH.91.9.1443
- Messa P, Macário F, Yaqoob M. The OPTIMA Study: assessing a new cinacalcet (Sensipar/Mimpara) treatment algorithm for secondary hyperparathyroidism. *Clin J Am Soc Nephrol* 2008; 3: 36-45. https://doi.org/10.2215/CJN.03591006
- Miller JH, Page SE. Complex adaptive systems: an introduction to computational models of social life (Princeton Studies in Complexity). Princeton: Princeton University Press, 2007
- Niazi M, Hussain A. Agent-based computing from multi-agent systems to agent-based models: a visual survey. *Scientometrics* 2011; 89: 479-99. https://doi.org/10.1007/s11192-011-0468-9
- OHE Briefing. The Pros and Cons of Modelling in Economic Evaluation. Conference of the International Society for Technology Assessment in Health Care (ISTAHC), San Francisco 26th June 1996. Available at https://www.ohe.org/publications/pros-and-cons-modelling-economic-evaluation (last accessed September 2022)
- Orsi GB, Di Stefano L, Noah N. Hospital-acquired, laboratory-confirmed bloodstream infection: Increased hospital stay and direct costs. *Infect Control Hosp Epidemiol* 2002; 23: 190-7. https://doi.org/10.1086/502034
- Pradelli L, Bellone M, Sanchez Alvarez J, et al. POSB108 Cost-Effectiveness and Cost-Utility Analyses of Atezolizumab-Based Therapy in Patients with Advanced or Unresectable Hepatocellular Carcinoma in Italy. 2022; 25 (supplement): S82. https://doi.org/10.1016/j.jval.2021.11.381

- Pradelli L, Di Perri G, Rizzardini G, et al. A cost-effectiveness analysis of E/C/F/TAF vs three boosted regimens in the Italian context. *Farmeconomia. Health economics and therapeutic pathways* 2017; 18: 113-27. https://doi.org/10.7175/fe.v18i1.1312
- Pradelli L, Iannazzo S, Zaniolo O, et al. Effectiveness and cost-effectiveness of supplemental glutamine dipeptide in total parenteral nutrition therapy for critically ill patients: a discrete event simulation model based on Italian data. *Int J Technol Assess* 2012; 28: 22-8. https://doi.org/10.1017/S0266462311000705
- 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: 804–11. https://doi.org/10.1016/j.jval.2012.06.016
- Robinson S. Simulation. The practice of model development and use. London (UK): Wiley, 2004
- van Hout BA, Wielink G, Bonsel GJ, et al. Effects of ACE inhibitors on heart failure in The Netherlands: a pharmacoeconomic model. *Pharmacoeconomics* 1993; 3: 387-97. https://doi.org/10.2165/00019053-199303050-00006
- Woods BS, Sideris E, Palmer S, et al. NICE DSU Technical Support Document 19. Partitioned Survival Analysis for Decision Modelling in Health Care: A Critical Review. NICE Decision Support Unit; 2017. Available at https://www.sheffield.ac.uk/media/34205/download?attachment (last accessed September 2022)
- Woods BS, Sideris E, Palmer S, et al. Partitioned survival and state transition models for healthcare decision making in oncology: where are we now? *Value Health* 2020; 23: 1613–21. https://doi.org/10.1016/j.jval.2020.08.2094